The Mechanics Of Clinical Trial Agreements

Veronica Legg, M.S., FNP, APRN-BC
Ann Mooney, MSN, RN, CNN
Brigid Flanagan, BA, RN, CCRC
C. Elizabeth O’Keeffe, JD, MPH, LLM

This Presentation Is Not Intended To Provide Legal Advice.
Global Conference & Exhibition
In conjunction with the APPI Program for pharmaceutical physicians and investigators
April 25–29, 2008 • Boston, MA, USA • www.acrp2008.org
Introduction

I. Ethical issues and background
II. Regulatory environment
III. Clinical trial agreement components
IV. Administration and finance
V. Auditing and monitoring
I. Ethical issues and background

Presented by:

Brigid Flanagan, BA, RN, CCRC
Ethical issues and background

• Contemporary landscape
  ▪ Tales of conflict of interest
  ▪ Misrepresented data
  ▪ Poor oversight of human subject research
Doctor Accused of Leak to Drug Maker

By STEPHANIE SAUL
Published: January 31, 2008

A leading member of the Senate said Wednesday that a prominent diabetes expert had leaked an unpublished and confidential medical journal article to GlaxoSmithKline last year, tipping the company to the imminent publication of safety questions involving the company’s diabetes drug Avandia.
Heart Surgery Drug Pulled From Market

By CARDINER HARRIS
Published: November 6, 2007

Pressured by regulators, the German pharmaceutical giant Bayer AG announced Monday that it had agreed to withdraw the controversial heart surgery drug Trasylol after a Canadian study suggested that it increased death rates.
January 30, 2008

Financial Ties Are Cited as Issue in Spine Study

By REED ABELSON

Some of the nation’s most prominent spine surgeons hailed it as a medical breakthrough.

In a study of nearly 240 patients with lower back pain, the doctors said that the ProDisc, an artificial spinal disk, had worked much better than conventional surgery in which patients’ vertebrae were fused.

As it turns out, Dr. Zigler had more than a medical interest in the outcome. So did doctors at about half of the 17 research centers involved in the study. They stood to profit financially if the ProDisc succeeded, according to confidential information from a patient’s lawsuit settled last year.
Ethical issues and background

Why do Investigators do research?

• Publication in prestigious medical journals
• Enhancement of academic reputation
• Access to further research grant money
• Important university faculty appointments
Ethical issues and background

Why does the private-practicing physician do research?

• Allows them to keep abreast of the most current treatments and offer them to their patients
• Allows them to fulfill personal academic goals
• Additional source of revenue in a climate of declining reimbursement rates
Ethical issues and background

• Nuremberg Code
• National Research Act (1974)
• The Belmont Report (1979)
• International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002.)
Ethical issues and background

• Additional Guidance and Requirements:
  - Clinical Trial Agreement
  - Federal-Wide Assurance (FWA)
  - Institutional Policies
  - Private Accreditation Organizations (AAHRP)
  - International Committee of Medical Journal Editors
The Nuremberg Code

• Person should have “sufficient knowledge…to make an understanding and enlightened” about participation.
The Jewish Chronic Hospital Disease Case (1963)

- “Live cancer cells” were injected sq into 22 chronically ill and debilitated patients.
- The Principal Investigator argued that informing the patients would have caused them needless psychological distress.
Willowbrook

- Researchers deliberately exposed children and adolescents to hepatitis
- The protocol had been reviewed by various university and state entities, as well as by the Armed Forces Epidemiological Board, which funded the study.
The Tuskegee Syphilis Study

- Initiated in 1932. Over 400, mostly illiterate men were recruited.
- They were not informed of the true nature of the study, or about their condition, nor were their partners informed of the risk.
- PCN publicly available in the late 1940s.
The National Research Act (1974)

• National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

• The Belmont Report:
  – Respect for Persons
  – Beneficence
  – Justice
45 CFR 46

• Known as the Common Rule
• FDA requirements are largely in agreement with the Common Rule
• The Common Rule
  – Establishes standards for the operation and use of IRBs
  – Requires oversight of research by participating institutions
  – Establishes requirements related to recordkeeping
  – Lays out the basic structure for obtaining and documenting the valid informed consent of voluntary research subjects.
II. Regulatory Environment

Presented by:

Brigid Flanagan, BA, RN, CCRC
II. Regulatory Environment

Increasing scrutiny of clinical trials
From multiple sources:

- DOJ
- OIG
- FDA
- Subjects
- HHS

- OHRP
- ORI
- Qui tam relators
- Researchers
- States

Balancing interests of stakeholders:

- Researcher
- Sponsor
- Subject/Public

- Institution
- Government
Who are the Players?

- Department of Health and Human Services (HHS)
  - Office of Human Research Protection (OHRP)
    - Informed Consent, Recruitment Issues, Financial Relationships, Conflicts of Interest, Scientific Integrity, Adverse Event Reporting, and Other Issues
Who are the Players?

• HHS
  – Office of the Inspector General for the Department of Health and Human Services (OIG)
    • Enforcement
    • 2008 Workplan includes Investigator Financial Disclosures as an area of interest and Grantee Management of Financial Conflicts of Interest in Research.
Who are the Players?

- HHS
  - National Institutes of Health (NIH)
- Grant Administration, Cost Reporting, Scientific Integrity
  - Office of Research Integrity (ORI)
- Scientific Misconduct
- Food and Drug Administration
- Research on Humans (21CFR Parts 312, 314, 600, 812 and 814)
Who are the Players?

Office of Research Integrity

- Falsification is the most frequently reported type of research misconduct (36%)
- Serious deviations from accepted practices (25%)
- Fabrication (24%)
- Plagiarism (15%)
What Is The Regulatory Landscape?

OIG compliance program guidance for pharmaceutical manufacturers:

Is any one purpose of a financial relationship intended to reward or induce referrals or recommendations of business payable under a federally-funded program?

Concern that funding research conducted by customers can be used to induce or reward purchase of sponsor’s products.

Post-marketing research particularly suspect, due to greater perception that the objective is to generate sales.
What Is The Regulatory Landscape?

PhRMA code on interactions with health care professionals

Research should be conducted under a bona fide 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
What Is The Regulatory Landscape?

AdvaMed code on interactions with health care professionals:

- Written signed agreement specifying services to be performed (purpose of the research funding must be clearly documented)
- There should be a written research protocol
- Compensation should be consistent with FMV
- Need for the research should be based on legitimate criteria established in advance
- Selection should be based on qualifications and expertise
What Is The Regulatory Landscape?

• The Association of American Colleges (AAMC) and the Association of American Universities (AAU) issued guidelines in February 2008 on institutional conflicts of interest and conflict management programs.

• [www.aamc.org](http://www.aamc.org)
What are the Regulatory Risks?

483 Notice of Inspection
- Can raise issues that complicate the review process
- Sometimes given considerable weight by third parties e.g. the media
- Immediately disclosable through FOI requests
- A good response, accompanied by documentation of corrective actions, can head of a warning letter
- Potentially useful for plaintiffs in product liability litigation
What are the Regulatory Risks?

A Warning Letter
- Posted on the FDA’s website
- Often issued even if corrections implemented
- Threatening tone
- Negative publicity-media paying much more attention
- Can be useful to plaintiff’s lawyers
- Sarbanes-Oxley-shareholder litigation
- Can cause stock to drop
What are the Regulatory Risks?

Criminal Prosecution and Loss of Livelihood

• All violations of the FDC Act are, in theory, criminal violations

• Felony if attempt to “defraud” FDA-this can include attempting to conceal information

• Penalty : Fine, imprisonment for not more than 5 years or both.
III. Clinical Trial Agreements

Presented by:

C. Elizabeth O’Keeffe, JD, MPH, LLM
Agenda

- Anatomy of a contract
  - Standard sections
  - Recommended language
  - Practical, operational and legal perspectives
  - Compliance
  - Indemnification, insurance, and subject injury
  - Confidentiality
  - Publication
  - Representations & Warranties
  - Data Collection and Intellectual property
  - Compensation
What Are The Regulatory Risks?

• Withdrawal of site’s assurance under 45 C.F.R. Part 46- subject protections
• FDA holds or rejection of data
• False claims act liability
  granting agency and relators based on certifications
  Medicaid drug rebate reporting
  “Off-label” marketing
• Anti-kickback law violations
• Private litigation
  Personal injury, intellectual property
• Secondary effects
  Capital markets, securities
Why Is It Important To Have CTA?

- Allocation of
  - Risk
  - Responsibility
  - Money
  - Obligations

- Protection of
  - Rights
  - Compliance with local laws, applicable regs, protocol
“Ventriloquists make great salesmen, I can make a customer say ‘yes’ while I drink a glass of water!”
What Is A Clinical Trial Agreement?

- A legally binding agreement that manages the relationship
- Between the **sponsor** who may be providing:
  - Study drug or device
  - Financial support
  - Capital equipment
  - Proprietary information
- And the **institution** who may be providing:
  - Investigator
  - Data and/or results
  - Publication, input into publication
  - Input into further intellectual property
General Negotiation Issues

- Is the study a single-site or multi-center study?
- Does the institution have special human or physical assets that are needed for the research?
- Are there any other agreements with terms that could bar or limit the scope of the research (e.g., confidentiality, exclusivity)?
Things To Consider When Drafting CTAs

- Structure of agreement
  - Parties
  - Exhibits
  - Separate budget

- Geographic locations of sites
  - US and/or international
  - Local, state and national law

- Input from appropriate parties
  - Project management
  - Regulatory
  - IP group
  - Finance
Clinical Trial Agreements: The Sponsor’s Objectives

- Ensure that trial generates data that can be used in FDA application
- Control the quality of trial conduct and adherence to the protocol
- Maintain the sponsor’s investment in the research through control of confidential information and IP
- Lay the groundwork for introducing the product into the market (coverage, coding, payment)
Clinical Trial Agreements: The Institution’s (“Sites”) Objectives

- Limit the sponsor’s control over the researchers
- Maximize the economic benefit to the institution
- Limit or insulate the institution from liability
- Enhance the institution’s reputation
What Does The Institution Want?

- Protection—subject, investigator, institution
- Fairness & accuracy—in support of investigator & institution
- Compliance—support of mission
  - Publication/access to data/dissemination of information
  - Access to research at the bedside
  - Intellectual property
  - Indemnification
  - Liability
  - Injury compensation
“And no ‘Beware of Dog’ sign. Just goes to show you, you can’t trust anyone.”
Why Does The Institution Need To Worry?

- Investigator will sign a CDA without review
- Investigator will sign a CTA without review
- Investigator will blindly trust that sponsor has done everything correctly and in their best interest
- Investigator will accept improper content, e.g., enrollment or performance incentives
- Investigator does not think about fraud and abuse
  - I’m too busy saving lives
  - I’m too busy doing my other research
  - I’ve been doing research for 20 years ….
Why Does The Institution Need To Worry? (Cont.)

- Budget issue in CTA
  - Budget created and negotiated before review or consultation from budget, legal, or compliance
  - Investigator did not budget correctly
  - Work done prior to the contract
  - Will budget/language pass government scrutiny?
What Does The Investigator Want?

- Why did they get involved in doing research?
  - Self promotion– career path
  - Opportunity to offer alternative therapy for their patients
  - Opportunity to make money
  - Required by superior/mentor/division
What Does The Investigator Want? (Cont.)

- Speed in starting up project
- Accuracy
  - Not at expense of speed
  - Satisfactory accuracy from PI viewpoint, but not institution
- Protection
  - Publication rights
  - Data access
  - Legal
- Depending on you to inform them of fraud and abuse issues relating to language, budget, etc.
“Driving to work while shaving, eating, texting, dialing, dressing and tapping my foot to the radio. That counts as 30 minutes of cardio!”
Introductory Provisions

- *The parties:*
  - Identify and name all “participating” entities
  - Parties include individuals, such as the investigator, the corporate sponsor, an SMO or educational institution
  - State the complete, correct *legal* name of the parties, being sure to include jurisdiction of formation (existence) information and primary business address
Cautions/Reminders For Listed Parties

- Use defined terms diligently
- Include all parties in the indemnification
- Person signing must have authority to bind the entity
Recitals

- Recitals (a/k/a “WHEREAS clauses”) supply helpful context.
- Describe the who, why and how.
  - A very high-level synopsis of the agreement and provide a framework for interpretation of the agreement by the parties and/or the court.
- Recitals are non-binding, unless specifically incorporated.
  - “The recitals shall be incorporated by reference in this agreement as if full set forth herein.”
Scope Of Services

- Identify contracting parties.
  - Two-way: CTA between sponsor and investigator only. Ensure PI meets the requirements of an independent contractor (e.g., Financial disclosure, insurance).
  - Two-way: CTA between sponsor and institution only. Typical when institutional policy precludes investigator from being a party to the CTA.
  - Three-way: CTA between sponsor, investigator and institution. Most common; jointly and severally binds both the investigator and institution to the terms of the CTA.

- Clearly specify roles and responsibilities of each party/individual conducting study.
Scope Of Services (Cont.)

- Specifically delineate to the extent possible mutual assent, performance requirements, standards and timelines – offer, acceptance, remuneration.
  - Include exhibits: budget, protocol, informed consent, incorporated by reference to agreement.
- One party cannot bind a third party without being an agent of the third party – CRO/Site – may need to obtain separate letter of indemnification (sample attached).
Scope Of Services (Cont.)

- Site, investigator and sponsor have regulatory obligations, and protocol specific obligations; clearly define roles and relationship of each.

- One party’s *promise* to act or refrain from acting in a certain way in exchange for an act, inaction or promise from the other party. Typical terms:
  - “Best efforts” – use all available resources – pt enrollment, never commit to a set number of subjects.
  - “Time is of the essence” – on time is material, specify timelines to the extent possible.
  - “Satisfactory acceptance” – highly subjective (use caution).
Scope Of Services (Cont.)

- Audits and inspections.
  - Specify site’s obligations with regard to government, regulatory and sponsor inspections.
  - Access to records/facilities at study site.
  - Conduct of audit; reasonable notice and during normal business hours.
Term & Termination

**Term:**

**Effective date**
- As of a specified date or
- Upon execution by last party to sign

**Automatic termination (a.k.a. “Expiration”)**
- Specific date
- Completion of all study related activities
- “End of study” needs to be clarified
- IRB closure at site?
- Sponsor close out visit?
- Data analysis from all sites in multi-center study?
Term & Termination (Cont.)

*Initiated termination:*

- **Sponsor:**
  - Generally 3-5 different ways for sponsor to terminate
  - Includes a ‘no cause’ out for sponsor
- **Site:**
  - Usually a way for site to terminate to ‘protect the safety of subjects’
- **Termination for breach:**
  - Material breach of agreement
  - Provide opportunity to cure
Term & Termination (Cont.)

- **Effects:**
  - **Subjects:**
    - Cease enrollment and withdraw subjects from treatment
    - Transfer subjects to another investigation site
  - **Compensation**
    - If breach by site or investigator, sponsor may request return of payments
    - If breach by the sponsor or early termination, sponsor should pay for services provided to date
Record Retention

- Obligation to “maintain” and “retain” records.
  - During the study.
  - Post-closure.

- Obligation is contractual or statutory.
  - Contract references statutes.
    - HIPAA and state privacy laws.
    - Medicare and Medicaid regulations.
    - FDA regulations.

- Contract references parties expectations.
  - Monitoring purposes.
  - Statute of limitations for product or tort liability.
  - Intellectual property rights.
Record Retention

- FDA requirement:
  - Two (2) years following the latter of:
    - (1) the date the study is terminated or completed.
    - (2) the date such records are no longer required to support PMA.
  - Require sponsor to provide notice of the disposal date.

- Medicare requirement:
  - Four (4) years following the claim date.
  - Applies to primary payee.
  - Applies to any subcontractor if paid over $10,000 or a duration over one (1) year.
Use Of Name/Publicity

- “Publicity” is not “publication”

- Limitation on use of names, symbols marks, logos/logotypes of one party by another party

- Consider needs for advertisements, press release, promotional, recruitment activities
  - Sponsor/site website
  - Publications, marketing materials
  - Clinical trial information registries
  - Internal reports
  - Federal grant applications

- Require prior written consent unless specified
Compliance

- Obligation for all parties to the agreement
- Board provision covers all applicable laws, regulations, guidance, and/or policies:
  - FDA, OHRP, ORI
  - Medicare, Medicaid
  - HIPAA and state privacy
  - Anti-kickback statute, Stark law
  - Tax-exemption regulations
  - Ethical and religious directives
UNETHICAL? WHAT DO YOU MEAN, UNETHICAL?

© Original Artist
Debarment

- Each party must certify that no debarred person is participating in the study.

- FDA rules on debarment:
  - Section 306(k)(1) of the act states “…any application for approval of a drug product shall include a certification that the applicant did not and will not use in any capacity the services of any person debarred…in connection with such application.”
  - *Person* includes an individual, partnership, corporation, and association.
  - Any use of conditional or qualifying language such as “to the best of knowledge” is unsatisfactory.

- List of disqualifiers: http:\firstclinical.com/actions/.
Exclusion

- Medicare provider exclusion rules states:
  - No Medicare provider shall contract with any person or entity who has been excluded from participating in the Medicare or other government health care program.

- Person includes an individual, partnership, corporation, and association.

- Each party certifies that:
  - Neither it nor any of its affiliates is excluded from participation in a federal healthcare program;
  - It has not knowingly contracted with any excluded employee, contractor, agent, vendor or vendor's affiliate; and.
  - No final adverse action, as defined in 42 USC section 1320a-7e(g)(1) and 42 USC section 1320a-7a(g), has occurred or is pending against it or its affiliates or contractors.
Relationship Of The Parties

- Clearly state the parties will be acting as INDEPENDENT CONTRACTORS.

- Clarifies and avoids potential tort, tax, liability and authority implications.

- Neither party is an agent or employee of the other, because:
  - An agent might be deemed authorized by “the principal” to take action on its behalf and cause a party to be responsible or liable for their actions.
  - No partnership is deemed to exist.
  - No employment relationship is deemed to exist.
  - MAGI sample: “site is an independent contractor to sponsor, and not a partner, agent, employee, representative or JV of sponsor. Investigator is site’s (insert applicable capacity). Except as set forth in this agreement, no party, or its employees, agents or subcontractors, has any right or authority to bind or act on behalf of another party.”
Freedom To Contract

- Each party represents and agrees that it is party to no agreement that conflicts with any obligations or provisions to the CTA.

- **MAGI** sample: “the parties represent that they have the right to enter into this agreement, that existing obligations do not materially interfere with their duties and responsibilities under this agreement, and that the terms of this agreement are valid and binding. During the term of this agreement, the parties will not enter into other obligations that materially interfere with their duties and responsibilities under this agreement”
Notices

- Address and parties to be notified upon occurrence of certain events affecting the contract.
  - (Force majeure, breach, termination, amendment).

- The contract must state that the other party must provide notice – a defined process must be followed to be “official notice.”

- Be clear on where notices should be sent – especially for record destruction – it may be necessary to delineate study related v. administrative, legal or payment issues.

- Note ability to document delivery.
  - (Certified mail, fax confirmation page, etc.).
Severability

- Court or other determination that certain provisions are not legally enforceable
- Allows remainder of the contract to remain in effect
- Non-enforceable provisions may
  - Be removed in its entirety
  - Be revised to extent necessary to comply with law
- Important to include language that specifies:
  - Parties will negotiate replacement provision to approximate original intent/economic benefits
  - Court to apply “blue pencil” provision if applicable under state law
Governing Law/Venue

- Choice of law determines which state or country’s law should govern the contract.
- Choice of venue determines where disputes are resolved.
- State institution limited to their state laws.
- Use: “without regard to its conflict of laws provisions.”
- Silence – remove the clause.
  - Where is the work being done? Many states will apply this.
Force Majeure

- What is it?
  - Circumstances/events that “should” excuse performance.
  - Acts of god.
  - Events beyond reasonable control of parties.

- Including:
  - Hurricanes, earthquakes, etc.
  - Terrorism; bioterrorism.
  - Work force stoppage/strikes.
  - Facility destruction.

- Options to the parties?
  - Define a period of time.
  - Right for unaffected party to terminate.
  - Suspend payments.
Survival

- What is it?
  - Ensures that certain contractual terms “survive” the contract when the contract ends.

- Issues:
  - Indemnification.
  - Confidentiality.
  - Intellectual property.
  - Payment terms.

- Trend: continuing obligation to report debarment.
  - Sponsors certify no debarred persons with submissions after study completion.
  - Post termination debarment may be an issue.
Assignment

- What is it?
  - Ability to assign contract to another party
  - May be prohibited or limited to written consent

- Issues:
  - By institution/investigator
    - Qualifications of new investigator/staff
    - Indemnification, confidentiality and IP provisions enforceable against all parties
  - By sponsor/CRO
    - Continuity of obligations

- Overall, ensure full assignment of responsibilities:
  - Payment
  - Study completion and reporting
Prevailing Agreement Provision

- Conflict of terms: indicates the documents that control the relationship and indicates the priority of control in the event of conflict.
  - Clinical trial agreement (CTA), protocol, informed consent form (ICF), budget may have inconsistent provisions.
  - CTA & ICF: subject compensation.
    - CTA – contractual legalese.
    - ICF – 8th grade level.
  - CTA & protocol: procedures, timelines, budget
    - IRB approves protocol – takes precedence with respect to study.
    - CTA could specify language to address inconsistencies between CTA and documents attached by reference to the CTA.
  - MAGI model CTA sample: protocol prevails regarding medicine, science and conduct of the study – CTA for everything else.
Entire Agreement/Modification

- What is it?
  - Ensures that the contract represents the entire understanding of the parties with respect to the subject matter.
    - Must incorporate protocol, exhibits, schedules, addendum, etc.
  - Assures that assurances outside the contract are not enforceable.

- Issues with modifications:
  - Must be in writing.
  - Must be signed by proper parties.
  - Must properly integrate with core agreement.
Contract Logistics

- Proof before you send/sign
- Copy/paste errors
- Templates getting switched

- Emails vs. Hard copy
- Paper versions can be changed just as easily as electronic ones

- Who keeps signed originals?
Contract Signature

- Authority to sign.

- Expediting Contract Execution.
  - Counterparts Clause.
  - Facsimile signature clause.

“This Agreement may be executed in one or more counterparts by signature of a person having authority to bind the party, which may be facsimile signature, each of which when executed and delivered, by facsimile transmission or by mail delivery, will be an original and all of which will constitute but one and the same Agreement.”
Indemnification - The Basics

- “Indemnify” means “to pay.”
- An obligation to indemnify is an obligation to pay for losses incurred if a specified risk occurs.
  - In a contract, the obligation shifts responsibility for the specified risk from one party to the other, like insurance.
- “Hold harmless” means “to assume liability.”
  - One party agrees to hold the other without responsibility for damage or other liability.
- “Defend” means “to defend.”
- All are subject to a party’s ability to pay. (Thus, the need for insurance.)
Clinical Study Agreements

- Indemnification is a critical issue because humans are involved, not only subjects in the study itself, but also future users of the drug/device being tested.
- Potential liability extends far beyond personal injury claims by study subjects.
Indemnity Considerations – Clinical Study Agreements

- Who is being indemnified?
- How and why does scope of indemnification vary?
  - Sponsor designed protocol
  - Investigator designed protocol
- What if agreement is with CRO?
- Which exclusions are appropriate?
Who Should Sponsor Indemnify?

- Indemnified parties
  - Principal investigator
  - Institution
- Officers, directors, agents, employees, heirs, assigns of institution
- Affiliated hospitals (if applicable)
- Faculty medical practices (if applicable)
- Subcontractors
What About Indemnification Of Sponsor By Institution?

- State institutions cannot legally provide indemnification.
- Most private institutions would prefer not to have indemnification obligations…but may agree to limited indemnification for claims arising from their (1) negligence/willful misconduct; (2) failure to adhere to the protocol; (3) failure to comply with applicable rules, regulations and laws.
Sponsor’s Indemnification Obligations

A. Sponsored designed protocol

Provide indemnification for claims, damages, etc. arising from:

- Illness or injury to study subject;
- Sponsor’s use, non-use, interpretation, or publication of study data or results;
- The design, production, manufacture, sale, use in commerce, lease or promotion by sponsor or its sublicensee of any product, process or service relating to the agreement;
- The negligence or willful misconduct of sponsor.

(Note: if sponsor disclaims patent infringement, then Sponsor must indemnify for such claims.)
Sponsor’s Indemnification Obligations

B. Investigator designed protocol.

- Scope is much less broad.
- Some sponsors refuse to provide any indemnification but there are certain risks that should be covered depending on the circumstances.
- If sponsor is granted ownership of or rights to study data, results or inventions then it is reasonable for sponsor to indemnify for its use, non-use, interpretation or disclosure of such.
- If sponsor is supplying a drug or device, then sponsor should indemnify for defective design or manufacture and sponsor’s negligence/misconduct.
Clinical Study Agreements With CRO’s

- Generally sponsors are not a party to such agreements.
- Sponsor must sign a separate letter of indemnification (otherwise sponsor has no legal obligation).
- Letter of indemnification must specifically identify the study, protocol and investigator.
- The letter of indemnification should be an exhibit to the agreement with CRO or at least be referenced in such agreement.
Acceptable Exclusion Criteria

- Sponsor's indemnification obligations shall apply except if the claim is a result of....

Unacceptable exclusion criteria.

- Sponsor’s indemnification obligations shall apply only if ....
Exclusions To Indemnification Obligations

- Read them carefully!!

- Slight changes in the language can make a significant difference.

- Potentially acceptable exclusions:
  - Claims resulting from failure of investigator or institution to comply with (a) the protocol; or (b) applicable rules, regulations, or law;
  - Claims resulting from the negligence or willful misconduct of investigator or institution; and
  - Claims resulting from a material breach of the clinical study agreement.
Acceptable Indemnification Language

Sponsor agrees to indemnify, defend, and hold harmless the principal investigator, institution, its officers, directors, trustees, employees and agents from any losses, damages or claims (including attorneys’ fees and costs of litigation) (“claims”) arising out of the performance of the study or this agreement, except when such claims are due to the university's negligence or failure to comply with the study protocol or any applicable laws or regulations.
Unacceptable Indemnification Language

Sponsor shall defend, indemnify and hold harmless investigator, institution and its officers, directors, agents and employees from any and all liability, claims, losses, damages and expenses (including lawyers’ fees) (“losses”) incurred by them in connection with any and all suits, claims or demands by or on behalf of subjects taking part in the study (or their dependants) against any indemnified party for personal injury or death to study subjects to the extent arising out of or relating to (a) the administration of the study drug in accordance with the protocol, this agreement and any written instructions of sponsor or (b) the performance of any test or procedure that is required by the protocol to which subjects would not have been exposed, but for their participation in the study, provided that institution and investigator (i) used reasonable judgment in the conduct of the study; (ii) otherwise acted in conformity with generally accepted standards of the medical community in which they practice; and (iii) notified the sponsor of such loss within ten (10) days.
Terms Of Confidentiality Agreements

- Establishing the term of years
- Considering whether to allow oral disclosures
- Establishing the extent of liability for disclosure
- Requiring personnel to sign NDAs and invention assignment documents
Terms Of Confidentiality Agreements

- Establishing the term of years:
  - Typical term of years: 3, 5, 7, 10
  - Term may extend from:
    - Date of disclosure
    - During the term of the study and for “X” years after close of study
    - From effective date of the agreement
- Important considerations:
  - Strength of intellectual property position
  - Phase of study (phase I and II studies may require longer terms)
  - Internal policies
  - State laws
Terms Of Confidentiality Agreements

- Considering whether to allow oral disclosures.
  - **Clarity**: written disclosures provide greater clarity about what is covered under the agreement.
  - **Fluidity**: the clinical setting is fluid; compliance with a requirement for written disclosures within a prescribed time period may be difficult.
  - **Middle ground**: the parties shall use reasonable efforts to reduce confidential information disclosed orally to writing. The writing may be in summary format.
Terms Of Confidentiality Agreements

- Establishing the extent of liability for disclosure
  - Money damages
  - Specific performance
  - Injunctive or other equitable relief
- Disclosures required by law
  - Require notification
  - Request assistance in seeking a protective order
  - Limit disclosure to the minimum required to be disclosed
Terms Of Confidentiality Agreements

- Requiring personnel to sign NDAs and invention assignment documents
  - Confirm policies at clinical site with respect to NDAs and invention disclosures
  - Limit disclosures to individuals with a “need to know” who are bound by similar terms of confidentiality
- Assess the role of non-employees (volunteers, contractors) and their status with respects to NDAs and invention disclosure requirements
Agreeing On Publication Rights

- Determining the scope of the sponsor’s rights to pre-publication review
- Considering first publication rights when the trial is part of a multi-center trial
- Negotiating a reasonable publication strategy with academic sites
Agreeing On Publication Rights

- Determining the scope of sponsor’s rights to pre-publication review

- Sponsor needs
  - To remove confidential information
  - To identify and protect new intellectual property
  - Opportunity to comment on site conclusions and provide perspective

- Site needs
  - Academic freedom
  - Freedom to publish study results (local data)
Agreeing On Publication Rights

- Considering first publication rights when part of a multi-center trial.
  - Sponsors generally want the first right to publish.
  - Sites request permission to publish local data following first publication by sponsor or when notified by sponsor that there will be no multi-center publication.
  - Consider what access, if any, local sites may have to multi-center data.
Agreeing On Publication Rights

- Negotiating a reasonable publication strategy with academic sites
  - Establish reasonable time frames for review of manuscripts and abstracts (30, 45, 60 days)
  - Establish reasonable time frames for intellectual property protection (45, 60, 90 days)
  - Respect institutional needs to ensure academic freedom
PI/Site’s Obligations

- IRB approval(s)
- Obtaining proper informed consent
- Conduct research in compliance with good clinical practices
- Responsible for compliance with FDA regulations
- Responsible for compliance with HIPAA privacy and security standards
- Timely completion of case reports
- Immediate notice of adverse events
Institution And PI Performance Standards

- Strictly follow protocol
- Protocol vs. Clinical trial agreement
- US federal Food Drug and Cosmetic Act
- ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH GCP)
- Declaration of Helsinki World Medical Association recommendations
- IRB/ethics committee requirements
PI/Site’s

Representatives And Warranties

- No party has been excluded from participation in Medicare or Medicaid
- No party debarred from participation in federal grants and contracts
- No party debarred by the FDA
- No party subject to professional discipline
- No party subject to adverse decisions by agencies overseeing research (ORI or OHRP)
PI/Site’s Representations And Warranties

- No conflicts with other existing contracts (ex: sponsor’s competitors)
- Site will comply with good clinical practices
- PI and staff have completed training in responsible conduct of research
Insurance

Sponsor insurance.
- Sponsor is responsible for the primary burden of risk, therefore sponsor needs to have adequate coverage.
- Self insurance.
- Specify amounts.
  - $1, $3, $5 million per occurrence.
  - $3, $5, $10 million in the annual aggregate.
Insurance— Cont.

- **Institution insurance.**
  Institutions need insurance for injuries that occur to patients at their premises.
  Institutions should ensure that their coverage extends to their institutional review board in relation to its oversight duties in the conduct of any clinical trials that take place on its premises.

- **Investigator insurance.**
  The investigator needs to procure insurance to provide protection in the event of potential liability arising out of direct patient care issues involving the human subjects in the trial.
Compensation For Injuries

- Study site wants broad indemnification from sponsor to cover all of the costs for care and treatment of any injury related to the study.

- Sponsor wants to limit costs to:
  - Injuries sustained by subject if site acted in strict accord with the protocol.
  - Costs of care and treatment that are not covered by subject’s health care benefits program.
  - CMS’s position on subject injury, compensation is an “insurance plan” therefore Medicare is secondary.
Compensation For Injuries

- Compromise language:

  Sponsor agrees to assume responsibility for the direct costs of medical care required by a subject as an immediate and direct result of an injury due to participation in the study and in full compliance by the site with the study protocol, to the extent that these costs are not covered by any health care benefits program, including hospital or medical insurance or any government-funded program providing such coverage.
Subject Injury

- Starting position
- Sponsor may agree to reimburse institution reasonable costs incurred by institution and associated with the diagnosis and treatment of an injury involving the study drug/device or protocol but ensure that:
  A. Costs are not covered by the subject’s medical or hospital insurance or by a governmental program providing such coverage
  B. The injury is not attributable to investigator’s negligence or misconduct
  C. The injury is not attributable to any underlying illness
  D. The protocol was followed
Subject Injury—Cont.

- Requires careful drafting in order to.

- Prevent false claims (determine what will be paid upfront and communicate this clearly to institution in CTA to avoid double billing); and

- Avoid interpretation of sponsor as primary payor.

- NOTE: remember that language in the informed consent form must mirror the language in the CTA’s subject injury section.
Ownership Issues: Study Data

Study site:
Data belongs to
The party that
Developed the
Data, or
Ownership must
Be equitably
Allocated

Sponsor:
Site already
compensated at
fair market value
for work
performed, so
sponsor owns the
study data and
takes the
entrepreneurial risk.
Data Collection & Reports

- Case report forms
- Adverse events
- Provisions for future use of data
  - HIPAA authorization can be combined with informed consent form
Ownership Issues: Study Data

- IP ownership issues if sponsor and site collaborate:
  - Inventions by sponsor personnel belong to the sponsor
  - Inventions conceived and reduced to practice as a result of conducting the clinical trial according to the protocol belong to the sponsor
  - Inventions made by the study site that extend beyond the scope of the protocol belong to the study site
Ownership Issues: Study Data

- Sponsors may condition funding on:
  - All rights to inventions created as a result of the study protocol
  - Site agrees to assign exclusive ownership to the sponsor
Ownership Issues: Study Data

- Site may want IP rights, which may be affected by:
  - Location(s) of the study
  - Nature of the study
  - Contribution to the study protocol (ex: new developments)
  - Interests of the sponsor
  - Mission of the site (public or private institution)
Ownership Issues: Study Data

- Study site should maintain adequate records to substantiate work done and to comply with any laws affecting medical records.
- Seek to use data for educational, research, patient care, and publication purposes.
Ownership Issues: Study Data

- Study site will grant sponsor an option to negotiate an exclusive, royalty-bearing license to the inventions it owns
- Limits to the term of the option
- Negotiations in good faith
Post-termination Obligations

- Return/destruction of confidential information
- Safeguarding PHI
- Return of case report forms, unused drug/device and related equipment and supplies
- Surviving obligations (e.g., IP, use of name, confidentiality, indemnification)
“I don’t know why you’re upset with us. Didn’t we provide you with excellent excuses?”
Focus Area: Stark Law

- Stark Law—General Rule
  - If physician-investigator makes referrals to facility for designated health services (“DHS”), financial relationship must comply with Stark exception
  - Failure to comply means DHS referrals are prohibited; facility can’t bill Medicare/Medicaid for services provided pursuant to prohibited referral
  - Civil monetary penalties, possible False Claims Act Liability
- Primary exceptions for arrangements involving payments to investigators
  - Bona fide employment relationships
  - Personal Service arrangements
  - Fair market value compensation
- Other potential financial relationships
  - Rental of office space or equipment to investigator
  - Provision of staff or support services to investigator
Focus Area: Stark Law (Cont.)

- Compliance Tips
  - Identify all financial relationships between sponsor and investigator
  - Review terms of each financial relationship (as reflected in a written agreement, where required) for compliance with a Stark exception
  - Review payments to investigators to confirm they are consistent with the terms of the Stark-compliant agreements
  - Promptly fix any arrangements that have fallen out of compliance (or that didn’t comply in the first place) with Stark
    - Stark regulations have exception for temporary noncompliance
      - Must have been in compliance for 180 days
      - Noncompliance no within entity’s control
      - Relationship doesn’t violate anti-kickback statute; bill/claim complies with all other laws/regulations
      - Only applies for first 90 days after noncompliance starts; can only use once every 3 years for a particular investigator
  - If exception isn’t available, don’t submit claims during period of noncompliance
Focus Area: Anti-Kickback Statute

- Prohibits, among other things, soliciting, receiving, offering or paying any remuneration in return for referring a patient or to induce the referral of a patient to any person for any item or service for which payment may be made under a federal health care program
- Safe harbors are available
  - Bona fide employment relationships
  - Personal services and management contracts
  - Space and equipment rentals
- Compliance Tips
  - Review all financial relationships with investigators who make or can influence referrals
    - Fit within safe harbor where possible
    - In all cases, ensure compensation paid by either party with fair market value
    - Ensure that there is not intent to induce referrals of the statute
Focus Area: Stark and Anti-Kickback Auditing

- Key Elements for Relationships
  - Written agreements
  - Signed by the parties
  - Fair market value compensation set in advance
  - No services for payment until agreement is signed
  - Minimum term of one year
  - Compensation does not vary by value/volume of referral
Focus Areas: Stark and Anti-Kickback Contract Review

- Possible Approach:
  - Review accounts payable ledger for all physician payments
  - Check for contract to support each payment
  - Evaluate payments for consistency with contract terms and required elements
  - Review time logs where appropriate
  - Types of contracts for possible consideration:
    - Space Rentals
    - Equipment Rentals
    - Medical Director Agreements
    - Call Coverage Agreements
Compensation

- OIG fraud alert (1994): unrestricted “grants” for research may violate anti-kickback statute if the intent is to induce or reward business billable to Medicare
- Establish a budget to determine the fair market value for the services performed
- Avoid linking remuneration to any other business between the sponsor and the site or researcher
- Avoid volume payments or bonuses
- Establish time and effort reporting system
Compensation (Cont.)

- Determine responsibility for administrative costs (initial and subsequent IRB interviews)
- Establish milestones for progress payments
- Determining which costs will be covered by the sponsor
  - Any waiver of costs must avoid beneficiary inducement penalties
  - Coordinate with any private insurance to avoid “double dip”
“Your ALTITUDE is determined by your ATTITUDE, not your APTITUDE. I’ll never forget the day I gave that speech to a group of student pilots!”
Administrative and Financial Considerations of a Clinical Trial Agreement

Ann Mooney, MSN, RN, CNN
Director of Clinical Studies
Fresenius Medical Care
Waltham MA
IV. Administrative and Financial Considerations of a Clinical Trial Agreement

Objectives:

• To understand how the contract is operationalized in the research setting

• To identify components of the contract that will assist your site with:
  – Appropriate allocation of resources
  – Maximize revenues
  – Ensure compliance with Medicare rules and federal guidelines

• To identify measures your site can take that will enhance the implementation of the contract.
IV. Administrative and Financial Considerations of a Clinical Trial Agreement

Think of the contract as the protocol for the business side of the study.

The protocol is to the clinical implementation of the study as the contract is to the business implementation of that project.
IV. Administrative and Financial Considerations of a Clinical Trial Agreement

To make the contract “come alive” and do good work for you in the clinical setting it must be:

1. Clearly written

2. Comprehensive in scope and detail

3. Supported by an Infrastructure at the site level that fosters all aspects of implementation
Elements of the Agreement

1. Scope of work
2. Roles
3. Payment
4. Subject injury
5. Warrantee
6. Insurance Coverage
Clearly Written Contract

Identification of the parties:

- Not always as simple as it appears

- PI, Academic Institution, Business entities, Sponsor and CROs, JVs

- Make sure they have the legal authority to bind the agreement

- Make sure that ALL necessary parties are part of the agreement
Clearly Written Contract

Scope of work:
• Make sure it parallels the protocol and schedule of assessments and is within usual scope of practice.

• Revisit this part of the contract with each protocol revision

• Make sure it is in alignment with duties of all parties involved in the project

• Make sure it parallels CFR, GCP and ICH Guidelines
Payment

How clearly the contract defines what is being paid for, is as important as how much is being paid.

Make sure the contract clearly defines:

- Consented, screened, enrolled, randomized, re-screens, screen failures, lost to follow-up, etc.
- These can vary among protocols
Payment

Frequent bone of contention in contracting: **Screen failures**

- **Pro**– creates incentive to conduct wide screening.
- **Con**– Sponsor concerned that it creates incentive to conduct inappropriate screening.

Some options:

- **Cap**: total number per site, paid according to procedures completed.
- **Ratio**: a screen failure for every X number of patients enrolled. Typically this is also capped but in terms of x screen failures for every completed study subject– up to a maximum of y screen failures.
- **Payment**: sometimes at end of study. If long study or large enrollment target, propose payment in groups of 2-3 pts.
Payment

Make sure the contract clearly states:

- How Much
  - Per patient (how much and how many)
  - Completers
  - Early term
  - Screen failures (how much and how many)
  - Re-Screens (how much and how many total or per patient)
  - Following for endpoints post removal from study (rescue therapy) or withdrawal of consent
Payment

• Beyond the Budget:
  – Number of patients (min and max)
  – Start-up fees (refundable vs. non-refundable)
  – Line Items
  – Penalty clause for non-payment (think of a parallel for enrollment penalty which some sponsors are now starting to seek).
Payment

- Make sure that schedule of assessments matches the protocol and that they both match the budget

- Repeat this review with each protocol amendment and amend your contract accordingly

- Review the CRFs (even if only draft) before agreeing to the budget. Can be lengthy and complicated and take more time than anticipated.

- If a multi-year study, calculate increases in cost of living (supplies) and personnel wages.

- Before the start of the study, define your “break even” point. Make sure the min/max enrollment numbers in the contract are aligned with what your business needs are.
Payment

- Know your patient population, if possible, gather statistics/data.
  - Will help to identify the best studies for you to conduct
  - Will help you contract for achievable enrollment numbers
  - Will demonstrate to Sponsor your value as a site

- Define the criteria you will use to close a study at your site and include this in the agreement.
  - This is a business decision
  - Will it be once X number of patients enrolled
  - Will it be once all patients at a particular study location have been screened/consented
  - Will it be at the end of a particular time period?
Payment

Make sure the contract clearly states:

– How Often: Payments
  • Quarterly
  • Upfront
  • Milestone
  • With Monitoring Visits

– Who is paying…. And are they a party to the agreement?
  • Is it the CRO
  • Is it the Sponsor
Payment

Contract must spell out what generates a Payment:

– Data received at Sponsor following monitoring visits
  • Push to get language regarding visit frequency in the contract
  • Or language regarding payment absent a visit
– Data entered into an E-CRF
  • Find out or set “data download” dates so that you will know when your data will be counted and your payment calculated. Add this to the contract.
– Invoice from site
  • Include language regarding format, frequency, contact individual at both site and sponsor
Payment

– What if:
  • Slow to pay
    – No pay
    – No study
    – Difference of Opinion
When I asked for funding of my rooster egg laying research, I was told the chick is in the male.
Payment
WHAT HELPS:

• Make sure all site information in contract is correct:
  – Payee name, business entity name, address, tax id
  – Payee info may be different from contracting entity

• Contract should clearly state site responsibilities with regards to getting payment information to Sponsor or CRO (dates, format, to whom)

• Assign a designated person within your site to chase the money.

• Consider contract language that requires payment be made within a specific timeframe after trigger is met
Payment

WHAT HELPS

• Invoices to Sponsor AND payment to site should be sent to an individual’s attention via a carrier service rather than regular mail or to an entity.

• Request backup detail of how payment was calculated so that you can track what has/has not been paid.

• Incentives should be based on non-enrollment aspects of performance i.e.; start-up time, query resolution, other matrix.
Subject Injury

• Make sure that language in the informed consent parallels what is in the contract and agreed to between Sponsor and Site

• Make sure that the subject injury cost/coverage language in the contract is in line with the National Coverage Decision
Debarment and Exclusion

Contracts contain debarment/exclusion requirements.

Each party must certify that no debarred person is participating in the study.

FDA rules on debarment:

- Section 306(k)(1) of the act states “…any application for approval of a drug product shall include a certification that the applicant did not and will not use in any capacity the services of any person debarred…in connection with such application.”

- *Person* includes an individual, partnership, corporation, and association.

- Any use of conditional or qualifying language such as “to the best of knowledge” is unsatisfactory.
Debarment and Exclusion

FDA guidance at

List of debarred providers:

List of disqualifiers: http:\firstclinical.com/actions/.
Debarment and Exclusion

Medicare provider exclusion rules states:

- No Medicare provider shall contract with any person or entity who has been excluded from participating in the Medicare or other government health care program.

*Person* is/can be defined as:

- an individual
- a partnership
- a corporation
- an association.

OR, an employee of the above
Debarment and Exclusion

Each party certifies that:

1. Neither it nor any of its affiliates is excluded from participation in a federal healthcare program

2. It has not knowingly contracted with any excluded employee, contractor, agent, vendor or vendor's affiliate; and

3. No final adverse action, as defined in 42 USC section 1320a-7e(g)(1) and 42 USC section 1320a-7a(g), has occurred or is pending against it or its affiliates or contractors.
Debarment and Exclusion

To meet these contractual requirements, make sure:

• Policies and Procedures for your site must be in place to meet these aspects of the contract which are tied to federal regulations.

• Suggest policies/procedures include:
  – Regular check for all associated MDs, vendors
  – Re-check at start of any contract negotiation
  – Identify key individual responsible for completing task
  – Communication of info:
    • Documentation of results
    • Method to convey positive findings
Infrastructure at site supports terms of the contract

- Site specific policies and procedures should be in place for the following study activities and the P&P should parallel how these activities are influenced by or in the contract:
  - Contracting
  - Budgeting
  - Accounting
  - Matrix tracking
  - Debarment/exclusion
  - Time and Effort Reporting
  - Compliance/Self-Monitoring program

- All should be reviewed and updated regularly
Infrastructure at site supports terms of the contract

Contracting

• Use templates when possible
• Should have templates for the following documents: CDA, MSA/CTA, LOI, ICF, HIPAA Auth
• SOP should address:
  – Define process of contract development
    » If possible, state a timeframe
  – Identify individuals permitted to negotiate terms and conditions
    » Identify signatories ahead of time
  – Require review of contract by legal and business prior to execution (both legal and business)
  – Consider developing a database/catalogue of contracts
Infrastructure at site supports terms of the contract

Budgeting

- Should have a policy and procedure on how it is done at your site and who can draft/negotiate

- Use a template

- Develop a price list: identify site costs for procedures ahead of time and compare that to the budget the sponsor presents for review.
Infrastructure at site supports terms of the contract

- Based on overall study accounting, review and update pricing list regularly.

- Aim to charge same procedural fees across all studies to all sponsors. “Equal pay for equal work” will help document FMV and avoid sense of impropriety in the case of an audit.

- Budget must be specific to the protocol to avoid impression of a “kickback”
Infrastructure at site supports terms of the contract

Accounting

- Keep each project distinct
- Avoid linking remuneration to any other business between the sponsor and the site or researcher
- Provides valuable documentation on time and effort, FMV, profitability
- Can be used as a feedback loop on budgeting process as well as price list
- Ideal is to have individual associated with accounting not be the same as the person who is doing the budgeting
Infrastructure at site supports terms of the contract

- Develop a QA program/policy

- Performance matrix: consider some of the following:
  - Contract turn around time
  - Time to project start-up
  - Targeted vs. achieved enrollment
  - Screen failure rates
  - Patient retention

- Matrix can be used as a negotiation tool to:
  - justify expenses
  - demonstrate site quality
Federally funded projects

With federal grants there are requirements pertaining to:
1. Administrative Requirements or Standards

2. Cost Compliance Principles

3. Audit requirements

www.whitehouse.gov.ombcirculars/
Federally Funded Projects

• Funds must be spent/dispersed in accordance with specific project

• Site must have the following systems in place
  – Financial management
  – Procurement systems
  – Time and effort reporting system
  – Monitoring activities
  – Ability to document adherence to terms and conditions of award
Federally Funded Projects

Time and Effort Reporting:

- Site specific tools can be used provided it captures all the necessary information.

- See 45 CFR 74.21 or 92.20

- Reports are subject to federal audit
Federally Funded Projects

Here are the principles that determine the bonafides in the contract:

• **REASONABLENESS**: if nature of goods/services applied and the cost reflect the action of a prudent person would have taken.

• **ALLOCABILITY**: cost can be allocated to a specific grant, function, or department

• **CONSISTENCY**: items charged either as a Direct or F&A in a consistent manner across all projects regardless of funding source

• **CONFORMANCE**: fits within the terms of the award.
Federally Funded Projects

(5) documents to guide your Time and Effort P&P and contractual obligations:

- **OMB Circular A-21**: cost principles for educational institutions
- **OMB Circular A-87**: cost principles for state, local, and Indian Tribal governments
- **OMB Circular A-122**: cost principles for non-profit institutions
- **24 CFR Part 74, Appendix E:**
- **48 CFR Subpart 31.2** (Federal Acquisition Regulation: Contracts with Commercial Organizations.)
Federally Funded Projects

• The fact that a cost requested in a budget is awarded as requested DOES NOT ensure a determination of reasonableness.
Infrastructure at site supports terms of the contract:

Compliance/Self-Monitoring program

• A must-have for federally funded projects

• Consider this for all projects, regardless of sponsor

• Should have a policy regarding self-monitoring:
  – to make sure no inappropriate billing of study related items or services
  – To document compliance with federal funding requirements
  – Makes good business sense too, nothing like bad press to ruin your bottom line
Infrastructure at site supports terms of the contract:

OIG work plan for 2008 targeting:

- NIH grant contracting procedures
- Administrative and clerical salaries charged to federally funded grants and cooperative agreements with academic institutions

- You may feel your site is too small to be audited but the trigger may be who you contract with.
Infrastructure at site supports terms of the contract

Insurance Coverage

- Sponsor is responsible for the primary burden of risk, therefore sponsor needs to have adequate **products liability** coverage with a clinical testing endorsement. You should ask about this!

- Self insurance: verify that your site/company/institution has the coverage Sponsor is requesting in the contract.
Infrastructure at site supports terms of the contract

• Be specific about the amounts and verify with your site:
  - $1, $3, $5 million per occurrence.
  - $3, $5, $10 million in the annual aggregate.

• Workman’s comp

• Know your State’s research specific regulations and indemnification limitations
Summary: What did she say????

- A well-written, comprehensive contract is well worth the time, effort, expense it takes to create it.
- Use templates when possible
- Make sure your site policies and procedures cover all aspects of the study process and are parallel with the contract and other federal regulations
- The principles behind the guidelines for federally funded research make good business sense so consider incorporating these into industry sponsored agreements.
- Know your State’s specific laws pertaining to research
Audits and Monitoring

Presented by

Veronica Legg, M.S., FNP, APRN-BC
Director of Clinical Studies
Fresenius Medical Care
Waltham MA
What is Monitoring?

• “The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirements”  (Source, Code of Federal Regulations, ICH Guidelines)
Guidelines for Monitoring

• U.S. Department of Health and Human Services
  Food and Drug Administration
  Office of Regulatory Affairs
  January 1988

• http://www.fda.gov/ora/compliance_ref/bimo/clinguid.html
Guidelines for Sponsor

1. Appropriately trained and qualified individuals to complete monitoring

2. Have written procedures for monitoring clinical investigations

3. Pre-study: Ascertaining investigator clearly understands and accepts the obligations incurred in undertaking a clinical investigation.
Guidelines for Sponsor (con’t)

4. Periodic Study Visits
5. Review Subject Records
6. Record On-site Visits
Contractual Language for Monitoring

• **Body of contract:** “Sponsor or its representatives, may visit Institution’s facilities to observe the progress of the Study and the Services, and any and all information and results derived there from or relating thereto.”
Better

• “Sponsor or its representatives, may, “upon its reasonable request, during normal business hours and after reasonable advanced notice and at a time mutually convenient to both Institution and Sponsor,” visit Institution’s facilities to observe the progress of the Study and the Services, and any and all information and results derived there from or relating thereto.
Contractual Language for Monitoring

• Budget & Disbursement Sections:
  – Often “hidden cost” in budget
  – May impact timeliness of payments:
    • “Payment will be made to Institution after each calendar quarter work is performed, based upon the number of Completed Case Report Modules, as defined in Section 2(C) of the Agreement, that Sponsor receives during such calendar quarter.”
Better

• “If payment schedule is based upon the collection of CRFs by Sponsor or monitoring visits conducted by Sponsor or CRO, payments must be made at least quarterly, regardless of the frequency of monitoring visits or collection of CRFs.”
What is an Audit?

• “A systematic examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded and analyzed, and accurately reported according to the protocol, sponsor’s SOPs, good clinical practice, and the applicable regulatory requirements” (Source, Code of Federal Regulations, ICH Guidelines)
What’s the Difference?

- **Monitoring** is conducted *while* the action is taking place.
- **Auditing** occurs *after* the action has taken place.
- **Monitoring** is a routine *ongoing process*.
- **Auditing** is a *point-in-time* systematic and independent review of the raw data.
What’s the Difference?

• **Monitoring** usually done by CRO or Sponsor
  – Cooperative effort with site personnel
  – Often develop an ongoing relationship

• **Auditing** performed by an independent auditor not affiliated with the study
  – Less potential for bias
Types of Audits

• GCP Audit

• Environmental Audits (chemical and hazardous waste management)
GCP Compliance Audits

• Conducted by:
  – Sponsors
  – CROs
  – FDA
  – IRBs
Audit Checklist

- Regulatory Documentation
- Randomization
- Consent Process
- Clinical Documentation (source vs. CRF)
- CRF Corrections
- AE Documentation
- Drug Accountability logs
Contractual Language for Auditing

- Usual Sponsor language: “Sponsor shall have the right to (a) monitor and audit the activities of the Principal Investigator in the conduct of the Study, and (b) monitor and audit the collection of data from the Study.”
Better

• “Sponsor, upon its request, but no more than once every six (6) months, during normal business hours, after reasonable advance notice by Sponsor, and at a time mutually convenient to both Institution and Sponsor, inspect Institution’s facilities for Study quality assurance purposes and inspect, copy, and audit the Records. Sponsor shall compensate Institution for such audits at a rate of $2,000 for each audit.”
Variations

• For Cause Audits- payable only if no cause found

• FDA Audit
  – Sponsor has right to conduct pre-FDA audit at no charge
  – Institution charges Sponsor if FDA audit occurs related to Sponsor’s study
In Conclusion

• Brigid Flanagan discussed the regulatory history and climate that impacts your clinical trial agreements

• Elizabeth O’Keeffe dissected the clinical trial agreement and how provisions vary based on Study, Institution and Viewpoint (Sponsor, CRO, Institution)
In Conclusion

• Ann Mooney talked about Operationalizing your contract-
  – Contractual provisions, Protocol elements and your study site operations integrated.

• Discussed Auditing vs. Monitoring and reflection in contractual language
Take Home Points

• Read your contract!
• Verify that the provisions support your individual or institutional needs.
• Determine that the budget reflects work required
• Be sure that the PI and coordinator are familiar with the contractual obligations.
There is no such thing as a “Standard Contract”