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Issues in Negotiating Clinical Trial Agreements

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Why Focus on Clinical Trial Agreements?

- Increasing scrutiny of relationships between academic medical centers and industry
- Conflict of interest issues
- Publication controversies
- Pressure from institutions to get a share of clinical trial dollars
- Increasing competition from non-academic sites and CRO's
- Government focus on clinical trial issues

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Purposes of a Clinical Trial Agreement

- Sponsor's Perspective
  - Ensure that trial results in data that can be used in FDA submission
  - Control quality of trial activities and protocol adherence
  - Maintain company investment in test articles through control over confidential information, data use and intellectual property
  - Financial terms

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Purposes of a Clinical Trial Agreement

- Site's Perspective
  - Limit sponsor's control of academic aspects of trial
  - Indemnification
  - Protect academic freedom
  - Financial terms

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General Negotiating Tips

- Understand your negotiating position
  - Is it a multi-center study?
  - Does the research involve a specific expertise of your institution?
  - How important is the study to the investigator?
  - Has the investigator already negotiated an agreement?
  - Have you been involved in a study with this sponsor/CRO before? If so, what did you agree to?
- Any preexisting agreements (e.g., confidentiality) that will supersede, affect, or apply to this one?

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Checklist of General Provisions

- Identity of the parties
  - Sponsor or CRO
  - Study site
  - PI endorsement?
- Recitals (the "whereas" clauses) -- purpose of the study; consideration for the Agreement; charitable mission of the Institution
- Scope of the work

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Checklist of General Provisions (continued)

- Principal investigator -- identity and responsibilities
- Supply of drug/device -- to be provided and shipped by sponsor, at sponsor's expense
- Study schedule -- including enrollment targets

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Checklist of General Provisions (continued)

- Compensation and budget
- Ownership issues
  - Study data
  - Intellectual property
- Confidentiality -- including sponsor information; study site information; and patient information

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Checklist of General Provisions (continued)

- Publication rights
- Use of name
- Representations and warranties
- Indemnification
- Injury compensation
- Insurance
- Term and termination
- Post-termination responsibilities

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Scope of the Work

- Define scope by the protocol, and attach it as an exhibit
  - If protocol conflicts with Agreement, Agreement governs
- Include IND or IDE status and FDA-assigned number, if possible
- Identify other study sites involved, if any
- Defining the scope becomes very important in determining intellectual property rights.

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Compensation and Budget

- Fair market value for services provided
- Avoid volume payments or bonuses
- Consider including IRB administrative expenses
  - Initial review of protocol
  - Continuing review
  - Amendments

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Compensation and Budget (continued)

- Review study design to determine what clinical care costs will be reimbursable
- Detail in the Agreement those treatments not reimbursable, but covered by the sponsor
  - Provide notice of costs not covered in informed consents
  - Any waiver of costs must satisfy OIG requirements
- OIG 2002 Annual Work Plan: focusing on whether Medicare payments related to clinical trials comply with program requirements

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Ownership Issues: Study Data

Study Site Position

- Data belongs to the generating party or, alternatively, joint ownership of all study data

Sponsor Position

- Sponsor solely owns case report forms and study data

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Ownership Issues: Study Data (continued)

Regardless, study site should . . .

- Always retain ownership of medical records and research notebooks
- Reserve the right to use the data for educational, research, patient care, and publication purposes, as well as to comply with federal, state, or local laws or regulations

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Ownership Issues: Intellectual Property

- The number of university patents and licensing agreements is on the rise
- University revenue from licensing increased from $186 million to $725 million between 1991 and 1997

Source: Annetine C. Gelijns, PhD, & Samuel O. Their, MD, "Medical Innovation and Institutional Interdependence," JAMA, Vol. 287, No. 1 (Jan. 2, 2002)

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Ownership Issues: Intellectual Property (continued)

Who owns new inventions?

- Study site's ability to obtain IP rights may depend on . . .
  - Structure of the study (e.g., multi-center)
  - The nature of the institution involved
  - How much the institution contributed to the study design or protocol
  - Whether negotiating with CRO or sponsor

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Ownership Issues: Intellectual Property (continued)

- Strong study site position:
  - If study site personnel make an invention constituting a new use of or modification to the drug/device study site retains ownership of the invention
  - Study site will license the invention to the sponsor on a right-of-first-refusal basis
  - Time in which sponsor can exercise option to license is limited (e.g., six months)
  - Terms of the license are to be negotiated in good faith

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Ownership Issues: Intellectual Property (continued)

- Sponsor position:
  - All rights to inventions created as a result of the performance of the clinical trial belong to the sponsor
  - Study site agrees to assign exclusive ownership to the sponsor

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Ownership Issues: Intellectual Property (continued)

Possible middle ground:

- Inventions made by sponsor personnel belong to the sponsor
- Inventions conceived and reduced to practice as a direct result of the performance of the clinical trial according to the protocol belong to the sponsor
- Inventions made by the study site that extend beyond the description in the protocol belong to the study site

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Ownership Issues: Intellectual Property (continued)

- Possible middle ground (continued):
  - Study site will grant sponsor an option to negotiate an exclusive, royalty-bearing license to the inventions it owns
  - Term of the option is limited (e.g., six months)
  - Negotiations must be made in good faith

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Ownership Issues: Intellectual Property (continued)

General Tips

- Preserve preexisting IP rights
- Define what constitutes an “invention”; refer to federal patent law
- Include provision that all IP rights are subject to any rights of the U.S. government
- Identify which party bears filing costs
- Specify consequences if licensing negotiations break down (e.g., study site has no obligations to the sponsor)

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Hypothetical on Data/IP Ownership

- Multi-center trial of possible new indication for approved drug (10 sites)
- Scientist at AMC participated, as member of scientific advisory board, in review of protocol
- Study involves unusual patient population, and AMC has clinic for the disease

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Confidentiality

- Narrow the definition of “confidential information”
  - Attempt to limit sponsor confidential information to that marked as “confidential,” or, for visual or oral information, request that the sponsor verify confidentiality in writing within short time period (e.g., 30 days)
  - Avoid expansive definition of sponsor confidential information; can affect publication rights

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Confidentiality (continued)

- Sponsor confidential information should be limited to information provided by the sponsor
- It generally should not include study data, research results, or other information generated from the study by the study site
- If the definition includes study data, study site should reserve the right to publish information that it generated
- Establish a time limit (e.g., 3 to 5 years) in which each party agrees not to disclose confidential information

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Confidentiality
(continued)

Standard Exclusions

- The information was publicly available prior to the date of the Agreement or becomes publicly available through no wrongful act of the recipient
- The information was known to any recipient prior to the date of disclosure or becomes known to any recipient from a third party having an apparent bona fide right to disclose the information

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Confidentiality
(continued)

Standard Exclusions (continued)

- The information is disclosed by any recipient with prior written approval
- The information is independently developed by any recipient

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Confidentiality
(continued)

Standard Exclusions (continued)

- A recipient must produce the information pursuant to a court order or subpoena, provided that . . .
  - The recipient promptly notifies the other party
  - The recipient reasonably cooperates with the other party's efforts to oppose or limit the scope of the court order or subpoena

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Confidentiality
(continued)

- Study site should reserve the right to disclose information to third party payors or government agencies in order to obtain reimbursement for medical services provided to study enrollees that are not otherwise reimbursed by the sponsor

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Confidentiality
(continued)

The Health Insurance Portability and Accountability Act of 1996 (HIPAA)

- Protects the privacy of individually identifiable health information and prohibits use or disclosure of such information except as required or permitted by HIPAA
- All agreements must contain provisions that comply with HIPAA
- Coordinate with authorization/IRB issues relating to use of information

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Confidentiality
(continued)

Sample HIPAA-Compliant Provision

"Notwithstanding anything to the contrary in this Agreement, all individually identifiable health information shall be treated as confidential by the parties in accordance with all applicable federal, state, or local laws and regulations governing the confidentiality and privacy of individually identifiable health information, including, but . . .

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Confidentiality
(continued)

. . . without limitation, the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") and any regulations and official guidance promulgated thereunder, and the parties agree to take such additional steps and/or to negotiate such amendments to this Agreement as may be required to ensure that the parties are and remain in compliance with the HIPAA regulations and official guidance."

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Publication Rights

Uniform Requirements for Manuscripts Submitted to Biomedical Journals

- Joint standards of International Committee of Medical Journal Editors (JAMA, NEJM, etc.)
- Amended September 2001
- New requirements regarding conflicts of interest and publication
- All agreements must be consistent with new requirements in order to preserve publication rights

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Publication Rights (continued)

Uniform Requirements for Manuscripts Submitted to Biomedical Journals

- Must disclose all relationships that may present a conflict of interest
  - Conflict of interest exists if author (or author's institution) has financial/personal relationship with other persons or organizations that inappropriately influence the author's actions

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Publication Rights (continued)

Uniform Requirements for Manuscripts Submitted to Biomedical Journals

- Authors must disclose details of their role and sponsor's role in study
- Editors are encouraged to review protocols and/or contracts before accepting study for publication

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Publication Rights (continued)

Uniform Requirements for Manuscripts Submitted to Biomedical Journals

- Authors may be required to certify in writing that they . . .
  - Accept responsibility for the integrity of the data and the accuracy of data analysis
  - Had full access to the data
  - Controlled the decision to publish

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Publication Rights (continued)

Uniform Requirements for Manuscripts Submitted to Biomedical Journals

- Sponsor can review manuscript prior to submission in order to file additional patent protection, if necessary
- But sponsor may not be allowed to impede publication of study results, even if data may be detrimental to product development

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Publication Rights (continued)

Key Provisions in Clinical Trial Agreements

- Sponsor may have right to review, but not to approve, manuscript
- Eliminate all provisions requiring sponsor consent to publication

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Publication Rights (continued)

Key Provisions (continued)

- Sponsor may have right to object to publication, but only to the extent that . . .
  - The manuscript contains sponsor confidential information (unless would prevent publication)
  - Sponsor is seeking to protect patent or other intellectual property rights with respect to a sponsor-owned invention under the Agreement

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Publication Rights (continued)

Key Provisions (continued)

- Study site's right to publish when sponsor has objected . . .
  - Parties will use best efforts to agree on a mutually acceptable format for using confidential information
  - If parties cannot agree, (1) study site has right to proceed with publication, or (2) parties will submit matter of whether confidential information exists to mediator/arbitrator

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Publication Rights (continued)

Key Provisions (continued)

- In multi-center trial, study site may agree to delay publication until . . .
  - Submission of all multi-center results for publication
  - Sponsor notification that multi-center submission is no longer planned
  - Some limited time period (e.g., six months) after termination of study at all sites

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Hypothetical on Confidentiality/Publication

- Phase I study, 3 sites
- New investigational cancer drug, never before used in humans
- Sponsor developed protocol and has IND
- Pre-existing confidentiality agreement protecting protocol as confidential

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Use of Name

- Restrictions on use of a party's name
  - Restriction limited to use of name as part of an advertising campaign, promotional or sales literature, or publicity?
  - Permitted upon prior written approval?
- Exception: use of sponsor name permitted as necessary for publication purposes and for grant applications

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Representations and Warranties

- Possible representations and warranties :
  - Party and persons involved with study have not been debarred by FDA
  - A party's applicable employees have not been found to have violated any laws, rules, or regulations related to clinical investigations
  - Party complies with all applicable laws and regulations

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Representations and Warranties (continued)

- Sponsor should warrant:
  - That it and its employees are not under investigation by a government enforcement agency in connection with the research study
- Study site should not provide warranty of merchantability or fitness for a particular purpose with respect to its research activities, work product, or other activities or services provided pursuant to the Agreement

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Indemnification

- Study site's position:
  - Broad indemnification by the sponsor alone
  - Covering the study site, its officers, directors, trustees, employees, representatives, affiliated medical, research, and professional staff
  - Applying to all claims, damages, liabilities, costs, losses and expenses (including attorneys' fees)

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Indemnification (continued)

- Study site's position (continued):
  - Including the sponsor's material breach of the Agreement or its warranties under the Agreement; and the sponsor's negligent or wrongful acts or omissions, including those arising from the design, development, distribution, use or sale of any product or services derived from or related to the study
  - May want indemnification by sponsor even if negotiating with CRO

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Indemnification (continued)

- Possible exceptions to sponsor liability:
  - An indemnified party acts outside the scope of the Agreement, unless if necessary to protect patient welfare
  - An indemnified party engages in gross negligence or willful misconduct

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Indemnification (continued)

- Sponsor's position: study site should at least indemnify it from damages arising from . . .
  - The negligence, recklessness, or willful misconduct of the study site and its agents or employees in conducting the study
  - The study site's material breach of its warranties under the Agreement
- Sponsors may push for broader indemnification by study site

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Injury Compensation

If a research subject suffers an injury as a result of participation in the study . . .

- Study site: Sponsor fully reimburses costs of care and treatment
- Sponsor: Sponsor reimburses costs of care and treatment to the extent that costs are not covered by the subject's medical/hospital insurance or governmental programs providing coverage

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Hypothetical on Indemnification and Injury

- Phase III, multi-center, placebo-controlled trial of blood pressure medicine
- Patients in both arms have high blood pressure and, as part of routine care, would have stress EKG, chest x-rays and physical exams
- Study will use data from those tests/exams
- Extra overnight monitoring in hospital and additional imaging studies

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Termination

Allowed under what circumstances?

- Immediately, upon written notice to the other party, in order to protect patient safety
- For cause
- Without cause, as long as the right belongs to both parties?
- But any enrolled patient can complete study if completion is in the patient's best interests

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Post-Termination Responsibilities

- Payment for work performed and non-cancelable commitments
- Return of case report forms, unused drug/device, equipment
- Certain provisions in the Agreement survive (e.g., IP, publication, use of name, confidentiality, and indemnification provisions)

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Clinical Research Organizations: Competition

- In 2000, academic health centers received 40% of research grants from drug companies; CROs received 60%
  – Editorial, "Sponsorship, Authorship, and Accountability," New. Eng. J. Med, Vol. 345, No. 11 (Sept. 13, 2001)
- 2001 JAMA study: 48% of academic health centers surveyed feel pressure from competition with CROs
  – Eric G. Campbell, Ph.D., et. al, "Status of Clinical Research in Academic Health Centers," JAMA, Vol. 286, No. 7 (Aug. 15, 2001)

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Clinical Research Organizations: Competition (continued)

Effects of competition:

- Negotiating leverage
- Forcing some academic health centers to form own CRO

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Clinical Research Organizations: Contracting

- FDA permits transfer of any or all sponsor obligations to CROs (21 CFR § 312.52)
  - Monitoring investigation
  - Compliance with protocol
  - Adverse event reporting, etc.
- CROs that assume sponsor obligations must comply with applicable regulations and are legally liable for failing to comply

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Clinical Research Organizations Contracting (continued)

Requirements for transfer:

- Must be in writing
- If all sponsor obligations are transferred, general statement of transfer is sufficient
- If only some obligations are transferred, must describe each obligation being transferred; otherwise the sponsor remains obligated

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Clinical Research Organizations Contracting (continued)

- Determine which sponsor obligations CRO has assumed
- Clearly identify in the Agreement the obligations that the CRO has assumed and the obligations that the sponsor has kept

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For more information:

Government web sites:

- Food & Drug Administration: www.fda.gov
- Office of Inspector General: www.oig.hhs.gov

Organization web sites:

- Association of American Medical Colleges: www.aamc.org
- Association for the Accreditation of Human Research Protection Programs: www.aahrpp.org
- International Committee of Medical Journal Editors (Uniform Requirements for Manuscripts Submitted to Biomedical Journals): www.icmje.org

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For More Information (continued)

For sample clauses and agreements:

- www.radiology.ucsf.edu/academics/grants/docs/clinical_agree.pdf
- www3.utsystem.edu/ogc/IntellectualProperty/clinical%20trials.htm
- www.med.upenn.edu/ohr/services.html
- www.ahc.umn.edu/rso/rso_stdindagree.html
- http://research.louisville.edu/p-and-p/uofl-industry.htm

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