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Contracting & Compliance Considerations in Clinical Trials

Celesq® AttorneysEd Center
www.celesq.com

5301 North Federal Highway, Suite 180, Boca Raton, FL 33487
Phone 561-241-1919 Fax 561-241-1969

Contracting & Compliance Considerations in Clinical Trials

Kyle Y. Faget, Esq.

FOLEY

FOLEY & LARDNER LLP

Overview

Conduct of Clinical Trials

- Commercial Sponsors
- Sponsor-Investigators
- Universities/Health Systems/Hospitals

Funding Sources

- Commercial Sponsors
- Foundations/Grants
- Government Funding (e.g. NIH)

Regulation – DHHS/OHRP

- The Office for Human Research Protections (OHRP) provides leadership in the protection of the rights, welfare, and wellbeing of human subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (DHHS).
- The Federal Policy for the Protection of Human Subjects or the “Common Rule”
- The Common Rule is a federal policy regarding Human Subjects Protection that applies to 17 Federal agencies and offices.
- An institution with a DHHS approved Federal Wide Assurance typically agrees to apply DHHS regulations to all research regardless of the funding source, including research that is internally funded and collaborative research across institutions.

Common Rule – 45 CFR Part 46

- The main elements of the Common Rule include:

- Requirements for assuring compliance by research institutions
- Requirements for researchers' obtaining and documenting informed consent
- Requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping.

- The Common Rule includes additional protections for certain vulnerable research subjects.

- Subpart B provides additional protections for pregnant women, in vitro fertilization, and fetuses
- Subpart C contains additional protections for prisoners
- Subpart D does the same for children.

FDA Regulation - 21 CFR, Part 50, and 21 CFR, Part 56.

- **FDA regulations governing the conduct of clinical trials describe good clinical practices (GCPs) for studies with both human and non-human animal subjects**
- Electronic Records; Electronic Signatures (21 CFR Part 11)
- Regulatory Hearing Before the Food and Drug Administration (21 CFR Part 16)
- Protection of Human Subjects (Informed Consent) (21 CFR Part 50)
- Financial Disclosure by Clinical Investigators (21 CFR Part 54)
- Institutional Review Boards (21 CFR Part 56)
- Good Laboratory Practice for Nonclinical Laboratory Studies (21 CFR Part 58)
- Investigational New Drug Application (21 CFR Part 312)
- Applications for FDA Approval to Market a New Drug (21 CFR Part 314)

FDA Regulation

- Bioavailability and Bioequivalence Requirements (21 CFR Part 320)
- New Animal Drugs for Investigational Use (21 CFR Part 511)
- New Animal Drug Applications (21 CFR Part 514)
- Applications for FDA Approval of a Biologic License (21 CFR Part 601)
- Investigational Device Exemptions (21 CFR Part 812)
- Premarket Approval of Medical Devices (21 CFR Part 814)

FDA Regulation – Clinical Investigators

- Part 54 of section 21 covers financial disclosure for clinical investigators. This regulation is intended to ensure that financial interests and arrangements of clinical investigators that could affect reliability of data submitted to FDA in support of product marketing are identified and disclosed by the sponsor.
- Part 312 of section 21 covers investigational new drug application regulations, including regulations for clinical investigators.

- 312.60 General Responsibilities of Investigators
- 312.61 Control of the Investigational Drug
- 312.62 Investigator Recordkeeping and Record Retention
- 312.64 Investigator Reports
- 312.66 Assurance of IRB Review
- 312.68 Inspection of Investigator's Records and Reports
- 312.69 Handling of Controlled Substances
- 312.70 Disqualification of a Clinical Investigator

NIH Grants

- Recipients of NIH grant funds must comply with all applicable Federal statutes (such as those included in appropriations acts) regulations, and policies. Additionally, they must also comply with their institutional requirements.
- Grant recipients must also comply with:

- Notice of Award (NoA).
- NIH Grants Policy Statement
- NIH Guide for Grants and Contracts
- Additional Regulations: 42 CFR Part 52 - Grants for Research Projects; 45 CFR Part 46 - Public Welfare, Protection of Human Subjects; 2 CFR Part 376 (2 CFR Part 180) –Debarment and Suspension; 42 CFR Part 50, Subpart F - Financial Conflict of Interests

Key Contracts

- Master Services Agreement (MSA) with Contract Research Organization (CRO)
- Clinical Trial Agreements (CTA)
- Informed Consent Form (ICF)
- Investigator Initiated Study Agreements
- Collaboration Agreements

I. Master Services Agreement (MSA) with Contract Research Organization (CRO)

Contract Research Organization (CRO)

- CROs provide support to pharmaceutical and medical device companies by performing research services on an outsourced basis, e.g., clinical trial management.
- Many companies contract with CROs because CROs can reduce costs, increase efficiency, and provide skillsets that a sponsor company may not have in-house.
- CROs vary dramatically in size, footprint, experience, and price, e.g., IQVIA, PAREXEL, Halloran.

CRO Master Services Agreement

- Delegation of authority results in loss of control, some of which can be managed through contract terms.
- Sponsor may delegate regulatory responsibility to CRO, but the sponsor remains accountable for any violations of good clinical practices (GCPs), human subject protections, safety reporting requirements, protection of patient privacy and other laws.

CRO Master Services Agreement

- Key Provisions:
  - Confidentiality:
    - Do you need the CRO's confidential information?
    - Will the CRO contract out work? If so, will the CRO remain liable for a subcontractor breach?
  - Ownership:
    - Does CRO condition work product on payment?
    - Is there explicit language re: Sponsor owning all deliverables and or an assignment provision?

CRO Master Services Agreement

- Key Provisions:
  - Termination:
    - Is there a termination penalty? Is it commercially reasonable? Is there another way to solve for the CRO's concern, e.g., unassigned staff.
    - Will the CRO be able to termination without cause? Not recommended due to sunk costs.
    - Is there a provision for close-out services?
  - Indemnification:
    - Does the MSA provide indemnification to the Sponsor for IP, illegal actions, negligence? Is the indemnification clause carved out of the limitation of liability?

CRO Master Services Agreement

- Key Provisions:
  - Clinical Trial Agreement:
    - Will the CRO be negotiating CTAs? Whose interest does the CRO truly have?
    - If so, does the MSA contemplate Sponsor having final approval of key terms, e.g., subject injury, indemnification, confidentiality, IP?
  - Local Representative:
    - Will the trial occur in countries that require a local representative? Does the MSA contemplate the CRO providing such a service?

CRO Master Services Agreement

- Key Provisions:
  - Non-conforming Services:
    - Will the CRO remedy the issue at no cost?
  - Local Representative:
    - Will the trial occur in countries that require a local representative? Does the MSA contemplate the CRO providing such a service?
  - Compliance:
    - Is the CRO willing to represent that it has not been debarred?
    - Are anti-bribery representations required?

CRO Master Services Agreement

- Key Provisions:
  - Data Protection:
    - Will the CRO represent compliance with privacy laws, including obtaining all required licenses and permits?
  - Audits:
    - Will the CRO allow Sponsor to audit its books and records? Its facilities?

II. Clinical Trial Agreements

Clinical Trial Agreements

- Key Provisions:
  - Subject injury:
    - reimburse Institution, at usual and customary rates, for the reasonable and necessary out-of-pocket medical expenses in excess of a Study Subject's commercial medical or hospital insurance, that are incurred by Institution for the diagnosis and treatment of (i) adverse reactions directly resulting from use of the Study Drug in accordance with the Protocol; and (ii) injuries arising directly from a procedure that the Study Subject would not have undergone but for such Study Subject's participation in the Study; provided, that such adverse reactions or injuries are not attributable to (1) an Institution Indemnitee's negligence, willful misconduct or failure to adhere to the Protocol; or (2) a pre-existing medical condition of the Study Subject or his/her underlying disease; and
    - Sponsor will reimburse a Study Subject for any injuries sustained as a direct result of Study Subject's participation in the Study in accordance with the terms of the Informed Consent Form.-

    - ***Need to consider secondary payor rule implications***…..

Clinical Trial Agreements

- Key Provisions:
  - Sponsor Indemnification:
    - Sponsor agrees to indemnify, defend and hold harmless Institution, its trustees, directors, officers, employees (including Investigator), Study Personnel and agents (collectively, the "**Institution Indemnitees**") against any third party claims, including reasonable attorney's fees for defending those claims (each, a "**Claim**"), to the extent a Claim arises out of or relates to (a) any theory of product liability concerning the Study Drug; or (b) any side-effect or adverse reaction, illness or injury directly resulting from (i) use of the Study Drug in the Study, or (ii) a procedure specified in the Protocol that the Study Subject would not have undergone but for such Study Subject's participation in the Study. The foregoing indemnity will not apply to the extent a Claim arises out of or relates to (1) an Institution Indemnitee's (A) negligence or willful misconduct or (B) failure to adhere to the terms of the Protocol or any written instructions from Sponsor or its designee; (2) a claim related to a drug or product other than the Study Drug; or (3) Institution's or Investigator's failure to adhere to the terms of this Agreement.

Clinical Trial Agreements

- Key Provisions:
  - Site Indemnification:
    - Institution agrees to indemnify, defend and hold harmless Sponsor and its directors, officers, employees and agents (collectively, the "**Sponsor Indemnitees**") against any Claim to the extent such Claim arises out of or relates to (a) an Institution Indemnitee's (i) negligence or willful misconduct or (ii) failure to adhere to the terms of the Protocol, or any written instructions from Sponsor or its designee; or (b) Institution's or Investigator's failure to adhere to the terms of this Agreement.
      - Sites are now refusing to indemnify sponsors. Some sites will claim that they are a state agency, and the state constitution and/or state tort claims act limit institution's ability to indemnify another party.
      - Instead, ask sites to be financially responsible for any third-party claim (to the extent permitted by applicable law).

Clinical Trial Agreements

- Key Provisions:
  - IP:
    - Materials: All documentation, information, equipment or materials furnished by or on behalf of Sponsor including Study Drug (collectively, together with all associated intellectual property rights, the "**Materials**") will remain the exclusive property of Sponsor. Institution and Investigator will use Materials only as necessary to conduct the Study. Institution and Investigator will not analyze Materials except as necessary to conduct the Study and will not transfer or make the Materials available to third parties, without the prior written consent of Sponsor.
      - It is important to claim all materials as Sponsor's property.

Clinical Trial Agreements

- Key Provisions:
  - IP:
    - Study Drug Inventions: Inventions that relate to (i) the Study Drug, including without limitation, a method of predicting responsiveness to Study Drug (and any diagnostic method or product related thereto), compositions or formulations comprising Study Drug, a new method of manufacturing, administration or dosing scheme for Study Drug, or new uses, enhancements or improvements of Study Drug, or (ii) Sponsor's Confidential Information will be the sole and exclusive property of Sponsor (collectively, the "**Study Drug Inventions**").
    - Inventions that are not Study Drug Inventions (the "**Other Inventions**") will be owned in accordance with inventorship as determined under U.S. patent law.
      - Other inventions will be a very small universe of inventions. Nonetheless, it is important to spell out an option right for Sponsor.

Clinical Trial Agreements

- Key Provisions:
  - Confidentiality:
    - “Confidential Information” means (a) any and all scientific, technical, business, regulatory, or financial information in whatever form (written, oral, electronic or visual) that is delivered or otherwise disclosed to Institution or Investigator, by or on behalf of Sponsor or its affiliates, including the Protocol, the Investigators’ Drug Brochure, information contained in or comprised of Materials, and the financial terms of this Agreement; (b) all approvals and correspondence with or from an IRB or other entities with oversight responsibilities for the Study, including ethics committees or data safety monitoring committees, all Study correspondence, all Study Drug and Study Drug accountability forms, and all CRFs (collectively, the “**Study Documentation**”); and (c) all Study Data; provided, however, that Institution and Investigator may use Study Data (for the purposes of the study and for non-commercial research purposes) and publish the data (in accordance with the publication provisions of the CTA).
      - Sites will want two-way confidentiality, but it does not benefit Sponsor to accept confidential information from Site. The information could corrupt the Sponsor.

Clinical Trial Agreements

- Key Provisions:
  - Publication:
    - “Neither Institution nor Investigator will submit for publication or public disclosure any publication or disclosure based on the results of the Study until after the first to occur of (a) publication of the Multi-Center Clinical Trial results; (b) notification by Sponsor that the Multi-Center Clinical Trial submission is no longer planned; or (c) the eighteen (18) month anniversary of the completion or early termination of the Multi-Center Clinical Trial. After such event, Institution and Investigator may publish or publicly present the Study Data; provided, that (i) the Study was conducted at Institution in compliance with the Protocol (it being understood that emergency treatment of a Study Subject will not be deemed non-compliance with the Protocol); (ii) such publication or presentation (x) is made in a recognized medical or scientific journal or at a recognized scientific conference; (y) makes use of all Study Data and not subsets of Study Data; and (z) is made in accordance with the provisions of subsections (1- Review Period) and (2 – Patent Filings) below.
      - Sites will balk at any limitations placed on publication, but it is important to ensure that any publication reflects the overall study data so that results are not skewed.
      - It is also important to allow Sponsor time to file a patent application should a publication contain Sponsor Confidential Information.
  - **Termination: Note that many sites will want the ability to terminate without cause.**

Clinical Trial Agreement Considerations

- Clinical Trial Budgets may not exceed Fair Market Value or Sponsor risks violating the Anti-kickback Statute (42 CFR 1320a-7b(2))
  - Research Funding Principle:
    - Payments for research services should be fair market value for legitimate, reasonable, and necessary services
    - Many Sponsors rely on commercial databases for FMV benchmarking, e.g., Metidata Grants Manager & IMS Health Plan
  - Start-up Costs

Clinical Trial Agreement Considerations

- Should FMV be viewed on a per visit basis or per procedure basis? Or should the budget in its entirety be analyzed only?
- Line items that perpetually generate protracted negotiation and can present risk to the company include:
  - Indirect Costs (IDC) or costs not tied to a specific budget line item, e.g. administrative support
  - Screen Failures

III. Informed Consent Form (ICF)

Informed Consent Form (21 CFR 50.20)

- . . . no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.
- Required Elements found in 21 CFR 50.25 for FDA studies.
- Required Elements found in 45 CFR 46, Subpart A (the “Common Rule”) for HHS studies.

ICF Considerations

- Information that is given to the subject (not “patient”) should be in language understandable to the subject or their representative (6th – 8th grade level).
- Must not contain exculpatory language; consider specifically stating that a subject is not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the clinical study.
- Confidentiality: Must inform subject that the FDA may inspect their records without gaining their permission.
- Compensation for Injury: clearly state if and to what extent a subject will be compensated in the event of an injury & match the CTA subject injury term.

Deficient ICF and Process

- Loss of data from subject, site, or entire study
- Regulatory Citation: Form 483 or Warning Letter from FDA
- Tort/Battery claim
- Negligence claim
- Criminal Liability
- ICFs are part of GCP requirements, so GCP has not been satisfied if an ICF is deficient

IV. Investigator Initiated Studies

Investigator Initiated Studies

- Why do pharmaceutical and medical device companies support/engage in Investigator Initiated Studies?
  - IIS are often a more efficient and less costly way for manufacturers to obtain data about their product(s).
    - The risk for industry is becoming too involved in a study that is not their study.
    - Kickback Risk: If the financial sponsor funds research that lacks scientific merit, the funding could be viewed as a kickback being provided to the recipient investigator.

Investigator Initiated Studies

- Definitions:
  - *Investigator*: the individual actually conducting the clinical investigation – the person actually administering or having oversight of administration of an investigational drug or device to a subject.
    - In the event an investigation is conducted by a team of individuals (sub-investigators and/or research nurses), the investigator is the responsible leader of the team.
  - *Sponsor*: "a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators." (21 C.F.R. § 312.3(b))
  - *Sponsor-Investigator*: "an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor." (21 C.F.R. § 312.3(b)). See 21 C.F.R. § 812.3 for similar definition applicable to devices.

Investigator Initiated Studies (IIS)

- Sponsor Types:
  - *Regulatory Sponsor*: the agency, organization, company or person primarily responsible for initiating and overseeing the research and ensuring the study complies with federal regulations, typically the IND holder for drugs and biologics studies and the IDE holder for device studies.
    - For industry-sponsored trials, the regulatory sponsor is typically a pharmaceutical, medical device, or biotechnology company.
    - For non-industry sponsored trials, the regulatory sponsor is typically the PI.
  - *Financial Sponsor*: the agency, organization, company, or person that financially supports the trial.

IIS Risks

- Control: IIS studies utilize a manufacturer's products, but the manufacturer necessarily ceded control of the study to the investigator. Any wrongdoing will always be tied back to the manufacturer's product.
- Sponsor-in-Fact:
  - FDA regulations require that each clinical study have a sponsor who is responsible for fulfilling the various regulatory requirements set forth in 21 C.F.R. Part 812 (devices) or 21 C.F.R. Part 312 (drugs).
  - While parties are free to contractually divide study responsibilities as they see fit from a legal perspective, FDA regulatory obligations cannot be transferred by contract.

IIS Risks

- When determining the true sponsor of a study conducted under a collaborative agreement, FDA will consider whether a company has exercised control over the study. Indicia of control include the following:

  - Study initiation;
  - Funding of the study through direct payments or grants;
  - Proprietary rights to utilize the study results for product approval or clearance;
  - Involvement in the design of the study or development of the study protocol;
  - Responsibility for the monitoring of the study;
  - Involvement in the analysis of the results of the study;
  - Involvement in the choice of sub-investigators; and
  - Involvement in the selection of study sites.

V. Collaboration Agreements

Collaboration Agreements

- Collaboration agreements in the pharmaceutical industry usually involve an agreement between a biotechnology company or an academic medical center (AMC) partner and a pharmaceutical or medical device company where the two entitles agree to share intellectual property, resources, and scientific and regulatory expertise in an effort to develop a new drug or device and bring it to market.
- Collaboration agreements are used in the pharmaceutical industry because large pharmaceutical companies may need the scientific knowledge and experience that a smaller company or AMC possesses. Also, small firms and AMCs may lack the experience and capital to take a new drug through the process of obtaining FDA approval and commercially market the drug.

Collaboration Agreements

- Industry License Agreement: The most common type of collaborative arrangement is a license agreement. The biotech company grants the pharmaceutical company a license to proprietary technology and patent rights in exchange for funding. The funding may take various forms, including an initial up-front payment, milestone payments and royalties.
  - The initial up-front payment often provides the biotech company with a quick infusion of capital.
  - Milestone payments are often triggered by the completion of one or more stages in the R&D or commercialization process – and thus if the milestone is not achieved, the milestone payment does not become due by the pharmaceutical company.
  - Royalty payments are generally calculated as a percentage of net sales of the final product. Also, the pharmaceutical company may receive equity in the biotech company.

Collaboration Agreements

- AMC License Agreement: AMCs have a unique interest and mission to preserve academic freedom and increase their reputation in the academic community, whereas industry's interest is to maximize profit.
  - AMC and industry often have competing interests with respect to the publication of results of academic research activities related to licensed technology. The AMC will want to publish explicit results of the research and specific details regarding the underlying laboratory testing, data and intellectual property. Industry, however, will want to preserve the confidentiality of these activities.
    - The parties will need to agree to delay publication in order to provide industry with the opportunity to obtain appropriate patent or other intellectual property protection.

Regulatory Issues with Collaboration Agreements

- FDA regulations do not provide specific definitions or considerations for determining “sponsor” in the context of collaboration agreements between two or more parties.
- FDA regulations require that each clinical study have a sponsor who is responsible for fulfilling the various regulatory requirements set forth in 21 C.F.R. Part 812 (devices) or 21 C.F.R. Part 312 (drugs).
- Collaboration agreements may pose unique challenges to determining the true sponsor of a study.
- For NDA and IDE studies, the sponsor is typically the applicant, but that is not always true.
- While parties are free to contractually divide study responsibilities as they see fit, from a legal perspective, FDA regulatory obligations cannot be transferred by contract.
- Should FDA determine that company X is the sponsor of an investigational study that is being conducted under a collaboration agreement, the agency will hold company X responsible for ensuring that all applicable regulatory obligations are met, regardless of any contractual agreements in place.
- Thus, there exists regulatory risk that company x could be held responsible by FDA for regulatory compliance, even if another party agreed to fulfill those requirements under the contract.

Questions?

Thank You

Contact Information:

Monica Chmielewski, Esq.

Foley & Lardner LLP

321 North Clark Street, Suite 2800

Chicago, IL 60654

mchmielewski@foley.com

(312) 832-4556

Kyle Faget, Esq.

Foley & Lardner LLP

111 Huntington Ave., Suite 2500

Boston, MA 02199

kfaget@foley.com

(617) 502-3292