Clinical Trial Agreements and Research Agreements: How They Differ?

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Key Take Away Points:

• Why are clinical trial agreements treated differently from other industry research

• Terms and conditions that are unique to clinical trials

• Negotiation tips
Research and Clinical Trials

Human Research

Clinical Research

Clinical Trials

Investigator Initiated Protocol

Sponsor Initiated Protocol
What is a “Clinical Trial”? 

• The controlled, clinical testing in human subjects of investigational new drugs, devices, treatments, or diagnostics, or comparisons of approved drugs, devices, treatments, or diagnostics, to assess their safety, efficacy, benefits, costs, adverse reactions, and/or outcomes.

• Such studies may be conducted under an industry-authored protocol or an investigator-authored protocol.

• Financial support for a clinical trial must be provided by a for-profit entity.
What is Not Considered a Clinical Trial?

- Retrospective chart reviews
- Testing of an investigational drug or device in animals
- Laboratory Research (i.e. bench and basic science studies)
- Run specialized tests on samples obtained in a clinical trial
- Analyzed data of existing medical data/records
- Data collection for registry purposes
- Federally funded clinical research
CT Specific Terms and Conditions – Top 10

• Budget/Payment
• HIPAA & Access to Study Records
• Ownership of Study Data
• Inventions
• Confidentiality
• Compliance
• Good Clinical Practices
• Debarment
• Indemnification & Subject Injury
• Publications with respect to multi-center trials
• Record Retention
Where do you start....... 

Scope of Work
• Research- defined scope of work
• Clinical Trial-defined protocol narrative (provided by sponsor for sponsor initiated trials)

Budgets
• Templates are different
Clinical Trial or Research??

University receives a contract from a pharmaceutical Company ABC. Company ABC will provide financial support for the study. The scope of work involves a long-term longitudinal living donor follow up to specifically assess patients for known risk factors of chronic liver disease through blood and urine analysis in an ethnically, diverse patient population. Data obtained will be analyzed.
Budgets (research)

• More simple (i.e. salaries, supplies, travel, equipment)
• Scheduled payments (i.e. payments made upon execution then quarterly)
• Payment terms are more simplified - tied to deliverables
• Different F&A rate
• Cost reimbursement vs. fixed priced contracts
• No IRB fees assessed
• No cost sharing allowed
Budgeting & Payment Terms

• Structured very differently than a Research budget

• Clinical Trial payments are generally associated with the completion and acceptance by an independent trial monitor of the CRFs

• Types of costs that make up a CT budget:
  • Initial Start-up cost
  • There are per patient costs
  • There are contingency costs (i.e. “invoiceables”)
  • There are set one time fees (i.e. IRB, pharmacy Set-Up and Radiology Set-Up fees)
Budgeting & Payment Terms

• **Coverage Analysis** develop an internal budget that lays out costs based on visits/procedures + fixed fees + contingent fees, then development payment schedule. PERFORM a coverage analysis to support billing research guarantor and insurance to avoid fines and penalties
HIPAA and Access to Study Records

PATIENT PRIVACY LAWS:

• HIPAA – “Health Insurance Portability & Accountability Act” (Federal Law)

• CMIA – “Confidentiality of Medical Information Act” (California Law)

• Regulates who can access personally identifiable information of a study subject from a medical record

• Of note the sponsor and its representatives should not have access to patient personally identifiable information when the study is Investigator-Initiated. It is not permitted unless the sponsor holds an IND or IDE. Unless your consent AND HIPAA authorization provide for access to the pharmaceutical or device company.
Study Data (research)

• University owns all data generated
• Sponsor may use copies of data and information delivered under contract for research and evaluation purposes
• Same position as with Clinical Trials
  - to promote open exchange of ideas
  - to use for further research
Ownership of Study Data

Study Data is:

• The data generated in the conduct of the study as compiled on the case report form (“CRF”); and

• Any reports (including but not limited to written reports, x-rays, lab reports) required to be generated and delivered to the sponsor pursuant to the protocol.
Ownership of Study Data

Study Data is **NOT:**

- Everything generated in the course of the study
- Patient Medical Records
- Source documents (e.g. as defined in ICH E6 Guidelines)
Inventions (research)

- Definition of Invention
- University retains ownership of inventions
- Grants sponsor time limited option to negotiate license
- Nonstandard Terms- work with Tech Transfer office
Inventions

Inventions –

• For sponsor initiated clinical trials (means pharmaceutical or device manufacturer has authored the protocol) standard for Academic Medical Centers (AMCs) to assign title to inventions pursuant to sponsor initiated clinical trials.

• For investigator initiated clinical trials- position is same as for “research”, negotiate license
Confidential Information (research)

- Confidential Disclosure Agreements
- Include “mark”, if oral, disclose to writing
- Do not accept “all information”
- Agreement cannot be confidential
- Data cannot be confidential
- Include the usual carve outs (i.e., prior known, disclosed from third party)
- Sometimes sponsor may include publication limitations in this section
- Time limit- Usually 7 years max
Confidentiality

– Terms and conditions very similar to your standard research agreement, but added consideration for
  • Disclosure of information in informed consent
  • Ability to disclose information in the event adverse event treatment to the treating physician
  • Certain documents may be deemed confidential
    – Protocol
    – Investigator’s brochure
    – Study Data, but only time its time to publish

** Can not agree to keep terms and conditions of Agreement confidential
For industry sponsored clinical trials and research, which of the following is correct?

a) Data generated are owned by the sponsor
b) Cost sharing is allowed in the budgets
c) Inventions are owned by the sponsor
d) Reports delivered are owned by the sponsor
Compliance

Good Clinical Practices “GCP”:

• Generally GCP is an internationally accepted ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials

• We adhere to FDA – GCP as codified in various sections of 21 CFR (i.e. parts 50, 54, 56, 312, & 812)
Compliance – Good Clinical Practices

• Clinical trials are subject to various Code of Federal Regulation provisions including but not limited to:
  – 21 CFR 50 (Protection of Human Subjects);
  – 21 CFR 54 (Financial Disclosure by Investigators);
  – 21 CFR 56 (IRBs);
  – 21 CRF 312 (Investigational New Drug Application);
  – 21 CFR 314 (Applications for FDA Approval to Market A New Drug); and
  – 21 CFR 812 (Investigational Device Exemptions).
Compliance

GCP Continued – ICH

• Watch out for adherence to ICH guidelines
• ICH’s mission is to make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines.
Compliance

GCP Continued – ICH:

• There are four distinct parts to the guidelines (Quality, Efficacy, Safety & Multidisciplinary)

• The one that is applicable to drug trials is Part E 6 and is the part recognized as “GCP”

• ICH is not a legal requirement it is merely a guideline.

• When you agree to be bound by it in the contract you are creating a contractual obligation that you otherwise don’t have a legal obligation to adhere to
Debarment / Exclusion / Disqualification

• Debarment:
  – Basically a “good standing” requirement, which if a person or entity has been debarred then any data submitted in support of a New Drug Application (“NDA”) may not be acceptable and could jeopardize the sponsor’s right to market their product.
  – Applies to anyone providing services on the trial so could expand to more than our agents and employees.
  – Of note only required to certify to the FDA not warrant

• Excluded:
  – An excluded party can not participate in Federal Healthcare Program
  – The effect would be that an excluded person or entity could not be reimbursed for services or items furnished

• Disqualification:
  – 21 CFR 312.70 (drugs) or 21 CFR 812.119 (devices) – Allows the FDA to disqualified from receiving an investigational drug or device
Indemnification (research)

• One party assumes financial responsibility in the event of a specified loss
• Transfer the risk of damages or loss from one party to another
• Limit negligent acts of omission of University’s employees, officers, agents
• Usually see reciprocal indemnification
• No third party liability
Indemnification

• Standard University considerations for indemnification (e.g. “...in proportion to and to the extent that...”)

• Certain carve outs generally allowed:
  – Claims arising out of University’s negligence or willful acts;
  – University’s failure to follow the protocol or written instructions of the sponsor; and
  – University’s failure to comply with applicable federal, state and local laws.

• Certain carve outs NOT allowed:
  – We do NOT bill the subject’s insurance – the primary payer must be the trial sponsor.
  – We do NOT carve out for Subjects inability to follow the protocol when not under the PI’s supervision.
Subject Injury

• University policy requires that a sponsor reimburse the university for the reasonable necessary costs associated with the medical care provide when a clinical trial subject is injured as a result of their participation in the study.

• For a Sponsor-Initiated Trial this requirement is absolute unless the Chancellor has provided a waiver.

• For Investigator-Initiated Trials, subject injury may not be required from the funding sponsor if the study drug/device is FDA approved. Check your institutional policy.
Subject Injury

- Sponsor shall not be obligated to reimburse the Institution for such costs to the extent the injury is caused by:
  - (i) a deviation from the Protocol by Institution or Investigator;
  - (ii) the negligence or intentional malfeasance of the Investigator or the Institution; or
  - (iii) the natural progression of the underlying disease of the Trial patient
Publication (research)

- No restriction/approval on publication
- Allow for short delay for review and comment, for disclosure of sponsor’s confidential information, for potentially patentable inventions
- 120 days max- same as Clinical trial
Publications

Multi-Center Publications:

• Later stage trials are conducted at multiple sites and many times the trials are also international.

• University will agree to a reasonable delay - “holdback” period to allow the sponsor to publish the multi-center results first.

• However, if no multi-center publication within 12 months (maximum w/o approval 18, anything longer requires VCR approval) then University can publish its data subject to normal review and request to delete sponsor Confidential Information or an additional time limited delay to file patents.

• Of note:
  – Trial registration is now a legal requirement.
  – For multi-center trials, authorship usually conditioned on size of enrollment and other considerations.
Record Retentions

• Of note because a sponsor may need to check source/patient medical records to validate/verify information.

• 21 CFR 312.62(c) or 21 CFR 812.140 (d) specifically outlines the investigator’s responsibility, which is for 2 years following the date a marketing application is approved or if no application filed, then 2 years after the investigation is discontinued

• Not appropriate to “turn-over” records to a sponsor – instead we would require the sponsor pay us a per subject fee to store the records

• Electronic Records and eCRFs – It is the Investigator’s responsibility to maintain “case histories” which include CRFs. The recommendation is that the Investigator maintain paper copies or have the sponsor continuously send copies of the eCRFs. This is an FDA audit issue
Which of the following is not correct?

a) Prior approval of publication is allowed.
b) For sponsor initiated trials, Sponsor is responsible for paying all subject injury costs.
c) According to 21 CFR 312, University must retain records for 5 years following the date a marketing application is approved or if no application filed, then 5 years after the investigation is discontinued.
d) All of the above
Negotiation Tips

• Develop a clause checklist
• Clinical Research Organizations (CROs) common with Clinical Trials (challenges)
• If sponsor does not accept language- Ask Why???
• Teleconference call to discuss clause
• Get the right folks on the call (decision makers)
Benefits of learning the “language of clinical trials”:

• More accurate and effective communication with sponsor
• Increased efficiency of finalizing contract negotiations and thus study start-up
• Fewer misunderstandings due to misuse of dual-use terminology
• Know the players in your institution (ie compliance, billing, IRB, etc.)
Resources – Clinical Trials

• **FDA Guidelines on Clinical trials**

• **FDA Warning letters**
  – [http://www.fda.gov/ICECI/EnforcementActions/ucm250720.htm](http://www.fda.gov/ICECI/EnforcementActions/ucm250720.htm)

• **Clinicaltrials.gov**

• **Disqualified and Debarment lists**

• **AAHRPP – Association for the Accreditation of Human Research Protection Programs**
Questions??????