



CLINICAL TRIALS: FROM NEGOTIATION TO TERMINATION

Presented by

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Definition Of A Clinical Trial

- Experiment, involving patients, designed to find the most appropriate treatment of future patients with a given medical condition
- Essential characteristic: results from a limited sample of patients are used to determine treatment in the general population

2

FDA Clinical Trial Phases

Testing in Humans				
	Number of Patients	Length	Purpose	% of Drugs Successfully Tested
Phase 1	20 – 100	Several Months	Mainly safety	70%
Phase 2	Up to several hundred	Several months to 2 years	Some short-term safety, but mainly effectiveness	33%
Phase 3	Several hundred to several thousand	1 – 4 years	Safety, effectiveness, dosage	25% – 30%


For example, of 100 drugs for which investigational new drug applications are submitted to FDA, about 70% will successfully complete Phase 1 and go to phase 2; about 33% of the original 100 will complete phase 2 and go to phase 3; about 20-30% of the original 100 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).

3

The Development of A Clinical Trial

- Planning of trials
- Objectives
- Patient selection
- Phase I trials
- Phase II trials
- Phase III trials

4




The Investigator

- An investigator is a medical provider with full responsibility for the treatment and evaluation of patients on research protocols, as well as the integrity of the research data

(continued)


5



The Investigator (2)

- Investigator must ensure:
 - Protocol is followed, and
 - The data are collected promptly and accurately, *EVEN* if treatment and drug administration is delegated to another

6



The Planning And Execution Of a Clinical Trial

- Drafting of a protocol
- Patient eligibility criteria
- Pharmaceutical information
- Treatment plan
- Monitoring of patients
- Statistical considerations
- Records to be kept

7



Participation By Additional Researchers/Institutions

- All protocol treatments and observations will be made by affiliated investigators
- Other medical providers
- Multi-center trials
- Ancillary studies

8




The FDA Commitment

- **Investigator** assures that trial will be conducted according to ethically and scientifically sound principles
- Statement of the education and experience
- IRB

(continued)

9



The FDA Commitment (2)

- Maintain adequate drug accountability records
- Prepare and maintain adequate and accurate case histories
- Reports to sponsor
- Promptly reports any ADR

10




Investigational New Drug (IND) Application Process

- Information for clinical investigators
- Institutional Review Boards
- Manual of Policies and Procedures (MaPPs)

(continued)

11



Investigational New Drug (IND) Application Process (2)

- Emergency use issues
- Targeted Product Information (TPI) Project
- Drug Development and Review Definitions
- <http://www.fda.gov/cder/regulatory/>


12



Monitoring and Quality Assurance

- Protocol compliance
- Data accuracy
- Informed consent
- IRB approval
- Drug accountability

13




Important Issues in Negotiating the CTA

[Taken from the Clinical Trials and Tribulations Workshop held at UCLA on March 25, 1998, by Mr. Phil Costic in the Office of Sponsored Research
<http://www.ora.med.ucla.edu/issuesclintrial.htm>]

- Publication rights
- Confidential information
- Patent rights

(continued)


14



Important Issues in Negotiating the CTA (2)

- Subject injury
- Payment
- Indemnification
- State law

15



Clinical Research Agreement Clinical Study Protocol

- Protocol will be provided by ??
- Protocol will specify:
 - The principal investigator
 - The Study design
 - Information desired
 - Estimated duration of the Study
 - Estimated charges
 - Institution(s) involved

16

Additional Protocol Requirements

- Required language for informed consent
- Adverse experiences which must be reported
- Grounds for stopping the study or participation in the study

(continued)

17

Additional Protocol Requirements (2)

- Release of patient/subject information to Company, FDA and other governmental agencies
- Medical records and patient privacy
 - *Health Insurance Portability and Accountability Act of 1996 (HIPAA)*

18

Clinical Research Agreement: Scope of Work

- Best efforts or completion?
- Phases included (single phase, multiple or options)
- Who is "Investigator"?
- Who provides the IRB, etc.?
- Reporting, data and document management and treatment responsibilities

19

**Clinical Research Agreement:
Term**

- Completion or period of time
- Extensions
- Delays
- Force majeure

20

**Clinical Research Agreement:
Payment**

- Method(s) of payment (e.g. per procedure; per patient; cost reimbursement)
- Time of payment(s)
- Amounts
- Exclusivity of payor (i.e., are multiple sponsors allowed?)

21

**Clinical Research Agreement:
Other Cost Issues**

- Costs incurred and associated with the diagnosis of an adverse reaction involving the Study Drug
- Costs for treating the adverse reaction
- Other payments (e.g., other compensation from Company if any injury occurs)
- Routine medical care costs
- Referral fees

22

**Clinical Research Agreement:
Principal Investigator**

- Can Sponsor approve the Principal Investigator (PI)?
- PI's commitment to conduct the Study
- If the PI becomes unable to complete the Study, must Sponsor consent to a new PI?
- Can Sponsor follow PI?
- Multiple PIs?

23

**Clinical Research Agreement:
Records**

- Records retention
 - Time for retention
 - Completion or termination of the Study
 - Marketing application approval
 - Discontinuation of the IND
- Maintenance of Study records for the period

(continued)

24

**Clinical Research Agreement:
Records (2)**

- Transfer of Study records
- Ownership of documents
 - *Health Insurance Portability and Accountability Act of 1996 (HIPAA) and State laws on Patient Records*

25

**Clinical Research Agreement:
Confidentiality**

- Information which is disclosed by Sponsor to the Institution
- Information which is disclosed by Institution to Sponsor
- Third-party information
- Patient/Subject information
- Obligations of Investigator, staff and students

26

**Clinical Research Agreement:
Promotional Activities**

- Use of name of Sponsor/Institution
- Use of PI's name
- Trademarks
- Publicity
- Advertisement for patients
- Press releases
- Inquiries from media and financial analysts

27

**Clinical Research Agreement:
Publications and Scientific
Communications**

- Right to publish the results of the Study
- Other rights to discuss Study (e.g. conferences – where and when)
- Notification to Sponsor
 - Prior to submission

(continued)

28

Clinical Research Agreement: Publications and Scientific Communications (2)

- Notice if publication contains patent information
- Right to delay
- Nonscientific journals, newspapers, radio or television

29

Clinical Research Agreement: Intellectual Property Rights

- Inventions
 - Ownership
 - Licensing
 - Joint inventions

(continued)

30

Clinical Research Agreement: Intellectual Property Rights (2)

- Data
 - Copyright
 - Databases
- Administration of Intellectual Property
- Biological materials

31

**Clinical Research Agreement:
Indemnification**

- Who indemnifies and who is indemnified?
- From what?
- Expenses of claims and suits related to what injuries?

(continued)

32

**Clinical Research Agreement:
Indemnification (2)**

- Caused by – IN WHOLE OR IN PART?
- By any substance studied or any procedure performed in accordance with the provisions of the protocol

(continued)

33

**Clinical Research Agreement:
Indemnification (3)**

And

- For use by Sponsor of the results of the Study
- Product liability
- Indemnification without prior payment by Institution

(continued)

34



**Clinical Research Agreement:
Indemnification (4)**

- Exclusions from obligation to indemnify
 - Failure of the Institution to comply with any applicable governmental requirements or to adhere to the terms of the protocol?
 - Negligence of the Institution, officers, agent or employee, subcontractors?
- Some states will not allow indemnification of negligence or failure to comply with law

35



**Clinical Research Agreement:
Conditions to Indemnification**

- Notice of any claim or lawsuit
 - Right to defend the lawsuit
 - Subject to Institution's right to retain the counsel of its choice?
- Right to settle the claim
- Right to require the indemnified party to cooperate fully in the investigation and with defense of any such claim or lawsuit

36



**Clinical Research Agreement:
Additional Indemnification Issues**

- Costs of extra unanticipated tests, treatments, and hospitalizations of patients required as a result of adverse events
- Costs covered by the subject's or patient's medical or hospital insurance or by governmental programs providing such coverage

(continued)

37

**Clinical Research Agreement:
Additional Indemnification Issues (2)**

- Non-medical indemnification (e.g., worker's compensation, third-party injuries, public health costs)
- Insurance

38

**Clinical Research Agreement:
Compliance with Law**

- Debarment Certification (FDA certification)
- Conflict of interest
- Integrity in science
- Misconduct
- UBIT
- State laws
- Foreign countries

39

**Clinical Research Agreement:
Additional Topics**

- Independent contractor status
 - Should Institution ever act as joint venturer?
- Notices
 - To whom, where, and for what?
- Modifications and amendments
 - Who has the right to require, when and what if required by Government or science?

40

**Clinical Research Agreement:
Inspections and Access**

- May Sponsor inspect Institution's procedures, facilities and Study records?
 - May information obtained from such inspections be shared?
 - With whom and for what purposes?
- Access to patients, records, data, faculty, treatment facility, etc.

41

**Clinical Research Agreement:
Study Drug/Device**

- For what purpose(s) may Drugs furnished for Study ("Study Drugs") be used?
- When and how is Study Drug provided?
- Storage and accounting for Drug
 - DEA registration
- Derivative compounds, by-products and waste disposal

42

**Clinical Research Agreement:
Disputes**

- Method(s) of dispute resolution
- Costs and attorney's fees
- Jurisdiction and venue
- Right to jury
- Subcontractor disputes

43

Clinical Research Agreement: Termination

- Reasons for termination
- Payment on termination
- Responsibility for patients/subjects on termination
- Students and other personnel
- Close-out

44

Clinical Research Agreement: Additional Sources of Information

- www.clinicaltrials.gov
- www.fda.gov/cder/about/whatwedo/testtube.pdf (FROM TEST TUBE TO PATIENT:IMPROVING HEALTH THROUGH HUMAN DRUGS)
- www.utsystem.edu/OGC/ University of Texas Office of General Counsel
- www.fda.gov/oc/oha/default.htm#clinical Food & Drug Administration Clinical Trials site
- www.aamc.org/advocacy/issues/research/start.htm Association of American Medical Colleges site

45

Questions and Answers



46
