

Controlled Clinical Experiments ***A Brief Introduction***

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***Experience is the name everyone gives
to their mistakes.***

Oscar Wilde

A Selective History of Clinical Research

Who	When	What
Frederick II	1200 C.E.	Effects of exercise on digestion
van Helmont	17 th Century	Effects of bloodletting on fever
Billroth	Late 1800s	Value of simple mastectomy in treatment of breast cancer
Various Frei	1940s-50s	Tuberculosis trials 6-MP and childhood ALL
Doll Wynder	1950	Link between smoking and lung cancer

The Modern Clinical Trial

What is a controlled clinical trial?

- A clinical experiment in which the treatment assignment is by design
 - May or may not contain a “control” group
- Investigator decides to evaluate an intervention (compare with observational studies)

Phase I Trials

- Dose-finding
 - Begin to define toxicity profile
 - Define dose(s) to be subsequently evaluated
- Pharmacokinetics
 - relationship between time and plasma concentration of a drug
 - what the body does to the drug
- Pharmacodynamics
 - relationship between drug concentration and effect
 - what the drug does to the body/target

Phase II Trials

- Safety
 - More precisely define toxicity profile and tolerability of an intervention
- Efficacy
 - Estimate the clinical effectiveness of an intervention

Phase III Trials ***(Randomized Clinical Trial)***

- Comparative safety
 - Compare safety of experimental intervention to standard treatment (standard of care)
- Comparative efficacy
 - Evaluate effectiveness of experimental intervention in comparison to standard treatment (standard of care)

Phase IV Trials

- Post-marketing
- Determine long-term effectiveness and safety
 - May be mandated by regulatory authorities
- Quality of life information
- Cost-effectiveness

Clinical Research What You Want

- High-quality science
- Rapid accrual
 - Access to patients
 - Adequate research network
- Unimpeachable data

Clinical Research

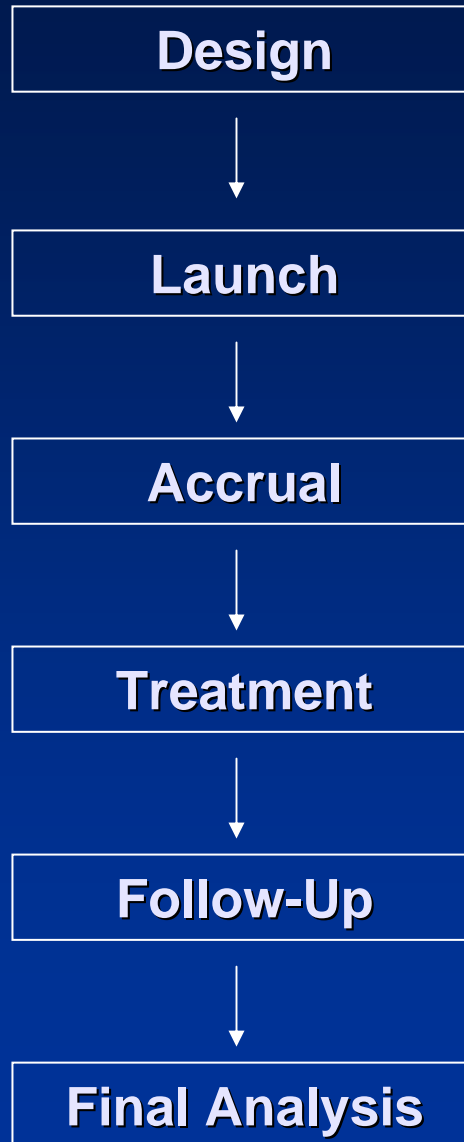
The Modern Problem

- Exponential increase in number of new drugs
- Limited number of patients
- Limited number of clinical investigators

Types of Research Organizations

- Single institution/investigator
- Study Group
 - Industry- or NIH-funded
- Traditional Cooperative Group (NCI Model)
 - Government-funded
- Contract Research Organization (CRO)
 - For-profit
 - Often division of larger entity (contract labs, practice management, etc)

The Six Ages of a Clinical Trial



Critical Components of the Clinical Trial

- Protocol
 - Fundamental guide to the conduct of the trial
 - “User’s manual”
 - Required for any clinical experiment
- Institutional Review Board (IRB) oversight
 - Independent regulatory authority responsible for safeguarding the rights and safety of research subjects
 - All research involving humans or human tissue must be approved by an IRB

Critical Components of the Clinical Trial (II)

- Study Monitoring
 - Auditing site(s) performing the trial
 - Quality Assurance
 - Data and Safety Monitoring Board (DSMB)

- Trial/Data Management
 - Trial oversight (medical supervision)
 - Case Report Forms
 - Databases

Critical Components of the Clinical Trial (III)

- Regulatory Compliance
 - Federal, state, and local guidelines
 - FDA/other regulatory authority guidelines

- Economics
 - Is the trial affordable?
 - Is the trial worth it?

The Research Protocol

- Title page
- Table of Contents
- Study Summary
- Background
 - Review of scientific literature
 - Rationale for trial
- Objectives (Endpoints)
 - Clear formulation of goals of trial
 - Based on scientific hypothesis (hopefully)
 - Regulatory issues

The Research Protocol

- Study Design
 - Trial methodology
 - Treatment allocation
- Patient eligibility
 - Define population based on inclusion/exclusion criteria
- Study Assessments and Procedures
 - Baseline
 - During active intervention phase
 - Follow-up

The Research Protocol

- Investigational Products
 - Complete description of experimental drugs/devices, including potential side effects
 - Packaging, handling, special instructions
- Statistical Considerations
 - Statistical hypotheses and assumptions
 - Sample size calculation/justification
 - Description of statistical methodology
- Adverse Events
 - Definitions
 - Instructions on reporting

The Research Protocol

- Regulatory and Ethical Issues
- References
- Appendices

Getting Started

- Regulatory Approval
 - FDA
 - Other pertinent regulatory authorities (e.g., gene therapy)
- IRB approval
 - Protocol
 - Site(s)

Investigational New Drug Application (IND)

- Required for studies of investigational (not commercially marketed) drugs
- FDA must approve IND prior to initiation of a clinical study with an unapproved agent
- http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm

Types of INDs

- Investigator-initiated
 - Must be submitted by a physician who will supervise and/or conduct the investigation
- Emergency Use IND
- Treatment IND
 - For conduct of clinical trials using experimental drugs
 - Typically held by commercial sponsor

Components of IND

- Animal pharmacology and toxicology studies
 - May include data from previous human clinical studies
 - Investigational Drug Brochure (IDB)
- Manufacturing information
- Clinical Protocol(s) and Investigator Information

Filing an Initial IND

- FDA Form 1571
 - Identifies sponsor and responsible individual(s)
 - Checkboxes for type of filing/enclosures
 - Must accompany (serially numbered) all submissions to FDA for an IND
- Minimum components of initial filing
 - Form 1571
 - Protocol
 - Form 1572(s) for investigator(s)
 - Cross-reference letter or
Manufacturing/pharmacology/toxicology data

Wait 30 days. . .

Where to Send Your IND

For a Drug:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

For a Therapeutic Biological Product:

(<http://www.fda.gov/cber/transfer/transfer.htm>)

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

FDA Form 1572

“Statement of Investigator”

- Legal document
- Must be on file for every principal investigator (PI) participating in a clinical study
- Components
 - Investigator information (qualifications, e.g. CV)
 - Site Information (location, labs/other facilities)
 - Attestation

A Word About Regulations

- Code of Federal Regulations (CFR)
 - Interprets the Federal Food, Drug, and Cosmetic Act
 - 21 CFR contains most regulations pertaining to clinical studies
- Good Clinical Practice (GCP)
 - a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials
 - International Conference on Harmonisation (ICH)
 - Common international set of guidelines to provide standardized guidance on complying with GCP

Basic Site Regulatory Documents (I)

- Investigator CV's
- Certifications
 - Board certification
 - Clinical research training (NIH, commercial courses, HIPAA, GCP)
- FDA Form 1572
- Financial Disclosures (study-specific)

Basic Site Regulatory Documents (II)

- Lab Normals/Certifications
 - CLIA
 - ACP
- IRB approval letter
- IRB-approved informed consent
- Pharmacy/drug supply documents
- Copy of current protocol (with amendments)
- Investigator's brochure

Study Launch

- Investigators' Meeting
- CRA Training
- Site Initiation
 - Drug supply
 - Data collection
 - IRB submissions

Accrual/Treatment Phase

■ Data collection

- Protocol deviations → amendments
- Site monitoring (CRAs)
- Audits

■ Problem-shooting

- Slow accrual
- Adverse events
- Geographic variation

Treatment/Follow-Up

- Safety
 - Adverse event monitoring
 - Reporting of SAEs
 - DSMB
- Data validation
 - Review of source documents
 - Data “cleaning”
- Interim analyses
 - Timing
 - Release of data

Other Issues

- Central laboratory
- Tissue/body fluid collection and storage
 - IRB requirements
 - International regulatory rules (unclear)
- Central review of endpoints (scans, other tests)

***There are three kinds of lies: lies, damn lies,
and statistics.***

- Disraeli

“To call in the statistician after the experiment is done may be no more than asking him to perform a post-mortem examination: he may be able to say what the experiment died of.”

Ronald Fisher, 1938

Hypothesis Testing

- Null hypothesis: no difference between treatments

$$H_0 = H_1$$

- Research hypothesis: there is a difference

$$H_0 \neq H_1$$

Type I (α) Error

Reject the null hypothesis and it is true
(you think there is a difference between
treatments but there really is not)

Type II (β) Error

Accept the null hypothesis and it is false
(you do not think there is a difference
between treatments but there really is)

Types of Error

		Null Hypothesis	
		True (no diff)	False (difference)
Decision	Accept (no diff) $p > 0.05$	Correct	Type II Error
	Reject (difference) $p < 0.05$	Type I Error	Correct

Power

- Definition: likelihood study will detect a treatment difference for a given number of subjects if such a treatment difference actually exists
- Power = probability of rejecting a false null hypothesis
- Power = $1 - \beta$
- Usually set at 80% or 90% for phase III trials

Increasing Power

- Increase the number of subjects
- Detect large treatment differences
- Increase α

Q: So what's this got to do with conducting a clinical trial?

A: Statistical tests/procedures help us to accept or reject the null hypothesis!

***Statistical tests are used to determine
the probability that an observation
occurred by chance.***

p-value = probability of obtaining your results
assuming the null hypothesis is true

A Word About p-Values

- The p-value indicates the statistical likelihood that our results could have arisen due to random variability in the data, i.e. by chance
- The p-value tells you **NOTHING** about the absolute benefit (magnitude of effect) of a particular treatment

A Hypothetical Example

Treatment	Survival (N = 100,000)	Survival (N = 100,000)
Drug	50%	50.5%
Superdrug	51%	50%
	$p = 0.000000079$	$p = 0.025$

Statistically significant \neq Clinically relevant

I'll no more on't: it hath made me mad.

- Hamlet