Clinical Trials
Drug Development

- Drug Discovery (Chemical)
- Pre-Clinical Studies
  - Laboratory Studies (In Vitro)
  - Animal Studies
  - These Provide Pharmacology And Toxicology Information
- Investigational New Drug (IND)/Investigational Device Exemption (IDE)
  - For Promising Drugs or Devices
  - Food and Drug Administration (FDA)
FDA

- 6 Centers
  - Food Safety and Applied Nutrition
  - Biologics Evaluation and Research (CBER)
  - Devices and Radiologic Health
  - Toxicological Research
  - Veterinary Medicine
  - Drug Evaluation and Research (CDER)
Clinical Trials

- Prospective human studies
- Well-controlled, monitored, and regulated
- Often characterized by “phases”
- The studies conducted companies to demonstrate that a drug is safe and efficacious (i.e., to get drugs approved)
Clinical Trials

- A lot of $ is spent conducting clinical trials
- More biostatisticians work on clinical trials than any other area
Explanation of Results

- Critical idea:
  - Isolate the effect of a treatment
  - Rule out things that can lead to misleading findings:
    - Bias and confounding (or at least minimize as much as possible)
    - Randomness
  - Rule in:
    - Cause and effect
Types of Studies

- Observational
  - Case report
  - Case series
  - Survey
  - Ecological study
  - Natural experiment
  - Case-control study
  - Cohort studies
Types of Studies

- Experiments
  - Clinical Trials
  - Laboratory Studies
    - Cell culture
    - Path specimens
    - Animal models
Validity vs. Ease of Conduct: Hierarchical order of studies

- High Validity: randomized trials, cohort studies, case - control studies
- Low Validity: ecologic studies, case reports

High Ease of conduct

Low Ease of conduct
Advantages of Clinical Trials

- Permits manipulation and measurement of exposure (treatment)
- In principle, provides the best means of avoiding bias and confounding, minimizing randomness, and quantifying the uncertainty in a statistical procedure
- High likelihood of valid results if properly designed and conducted
Disadvantages of Clinical Trials

- Costly and time consuming
- Infeasible in many instances because of ethical concerns
- Many questions of medical interest cannot be addressed by clinical trials
Phase I

- Assess tolerance of drug
- Find Maximum Tolerated Dose (MTD)
- May be dose-escalating
- Assess toxicity
- Identify AEs
- Small sample sizes
- Often performed on healthy people
Phase I

- Evaluation of efficacy is secondary
  - Gain preliminary data on therapeutic activity
- Pharmacokinetics (PK)
  - Effect of body on the drug
    - ADME (absorption, distribution, metabolism, elimination)
- Pharmacodynamics (PD)
- Effect of drug on the body
Phase II

- Performed on people with disease
- Homogeneous population
- Small N
- May be dose-ranging
- Find “optimal dose”
- Assess safety
  - Adverse Events (AEs)
  - Toxicities
Phase II

- Efficacy is secondary
- Assess short-term therapeutic activity
- More PK/PD
- Frequently employs surrogate endpoints
Phase III

- Large N
- Evaluation of efficacy and effectiveness relative to a CONTROL Group (placebo or active control)
- Randomization
- Will also assess safety and perhaps QOL
Phase III

- Uses intended target population (often heterogeneous)
- Multicenter
- Possibly “Blinded”
Phase III

- Usually need 2 consecutive trials significant at the "=$0.05 to file a New Drug Application (NDA) with FDA.
  - Exceptions made for orphan drugs and drugs with no cure, epidemics, rescue, and emergency medications
NDA

- Called Premarket Approval Application (PMA) in the device world
- Submission of all results from all studies to FDA. FDA review includes:
  - Chemistry
  - Pharmacology
  - Biopharmaceutics
  - Microbiology (for anti-infectives)
  - Clinical
  - Statistical
Phase IV

- Large N
- Drug is already approved (i.e., post-marketing studies)
- Investigate long-term effects w/long-term follow-up of subjects
Phase IV

- Observational (observe effects in the settings where the drug is actually used in practice)
- Surveillance
- Marketing tool – may expand the label to new populations
Some Statistical Issues

- Choice of Design
- Choice of Endpoints
- Multiple endpoints
- Randomization
  - Dynamic randomization (minimization)
  - Stratification
  - matching
Some Statistical Issues

- Sample-size and power
- ITT vs. PP (Intent-to-treat vs. per protocol, evaluable) populations
- Interim analyses/monitoring (safety vs. Efficacy; stopping rules)
  - Data Monitoring Committees (DMCs)
- Missing data
- Informative censoring
Randomization

- Allocation of treatments to patients is carried out using a chance mechanism such that neither the patient nor the physician know in advance which therapy will be assigned.
- Randomized clinical trials are regarded as the best way to carry out clinical trials.
Randomization

- Groups are alike “on average” (particularly when sample sizes are large)
- A foundation for statistical inference
Randomization: Advantages

- Eliminates conscious bias
  - Physician selection
  - Patient self selection
- Balances unknown biases among treatment groups
  - Unknown factors affecting outcome
  - Factors that cannot be measured or stratified upon
- Assures the expectation of balanced groups
Randomization: Disadvantages

- Patient or physician may not care to participate in experiment involving a chance mechanism to decide treatment.
- Does not ensure balance
Dynamic Randomization

- Minimization
- A method of further assuring balance between groups, by adjusting the probability that an individual is randomized to the treatments based on the individual’s baseline characteristics and the distribution of characteristics of individuals already randomized.
- Not universally accepted yet.
Stratification

- Stratified randomization can ensure balance with respect to known and measurable variables.
  - But not for unknown or immeasurable variables
- If randomization or design is stratified then analyses should be as well.
Stratification

- In general is a good idea.
- Limitations due to small sample size or large number of strata.
Blinding

- Process of hiding data (usually treatment) to people involved in the study in an effort to avoid bias.

- Types
  - Single – subject (i.e., patient)
  - Double – subject and investigator (physician)
  - Triple – subject, investigator, DMC
  - Open-label – no blinding

- Can be impractical
  - Side effects may be obvious
    - Example: swelling or irritation at an injection site
Some Statistics

- 1 in 10,000 compounds reach Phase I
- 8% in Phase I get to market (decreasing)
- Synthesis to market:
  - ~17-20 years
  - 0.8-1.7 billion dollars
    - One key to profitability is to find drugs that do NOT work as quickly as possible
- IND → NDA: ~5 years
Some Statistics

- FDA is trying to speed things up and find more effective processes for developing medical treatments.
  - Critical Path Initiative
  - Accelerated approval for drugs treating diseases with no cure.
- Companies may also get incentives from the government for orphan drugs (i.e., for rare diseases with a smaller market, e.g., Ebola virus)
Monitoring Plan

- Devise plan on how the study is monitored
  - Use of DMCs
  - Interim analyses
- Interact with medical monitor on particular safety concerns
Statistical Analysis Plan (SAP)

- SAP finalized well before analysis
  - Preferable before trial begins
- Outline tests, handling of missing data, etc.
Design – Single Arm Pilot Study

- Administer drug to a group of patients and see if they improve or are cured
  - When measuring improvement, then we often use a “change from baseline” (a continuous variable) as an endpoint.
    - Analysis – calculate change over time to see if there is evidence of improvement (i.e., $\Delta > 0$) using 1-sample t-test
Design – Single Arm Pilot Study

- One may power such a study:
  - Sample size
    - Analyses envisioned as a T-test (1 sample)
    - Adjust for use of non-parametric test
    - Adjust for missing data
    - Need “minimum clinically relevant difference” to power the study
    - Get estimates of variability from literature (prior studies, historical data)
Design – Single Arm Pilot Study

- May also use "cure" or "response" as the endpoint in this study.
  - Analyses will consist of estimating the response rate (proportion) and perhaps testing if this rate is significantly high.
  - Example: ACTG 269
Design – Single Arm Pilot Study

- Problems:
  - Cannot control for “natural history” (people may have improved anyway)
  - Placebo-effect (or Hawthorne effect): patients/doctors believe that they are getting better because of treatment; manifesting itself in better scores
  - Miss a “good result” when you observe no change but patients would have gotten worse if left untreated.
Design – 2-Arm Placebo Controlled

- Randomization – expectation of balance of known and unknown factors
  - Stratification – can only be used for known factors that could potentially bias/confound the study
    - Example: sex
- Analyses may compare the change from baseline in the two groups or compare the response rates in the two groups.
Design – 2-Arm Placebo Controlled

- Consider:
  - Blinded study to avoid bias
  - Design study to avoid noncompliance and missing data.
  - Interim analyses?
Schematic – 2-Arm Placebo Controlled

Eligible patients → Sample → Intervention
  - Treatment
  - Control

Response:
- Yes
- No

Adapted from Clinical Epidemiology: The Essentials, 3rd ed. © Scott Evans, Ph.D.
Design – 2-Arm Placebo Controlled

- **Analysis for the continuous variable, “change from baseline”:**
  - calculate confidence interval for the difference between groups and see if zero (or some other meaningful predefined number) is included in the interval.

- **Analysis for the binary variable, “response”:**
  - calculate confidence interval for the difference between group proportions and see if zero (or some other meaningful predefined number) is included in the interval.
Design – 2-Arm Placebo Controlled

- **Problem:**
  - If treatment exists then randomization to a placebo arm may not be ethical
  - In order to get drug approved, a company does not necessarily need to show better than another drug. Instead they need to show that the new drug is at least as good as the standard of care (SOC).
Design – 2-Arm Non-inferiority Study

- Use of “active control” (a “standard of care” (SOC) usually already approved
- 2-arms (new drug and SOC)
- Need to show new drug is “no worse” than SOC drug
- Randomization
- Decide on “maximum difference that is clinically irrelevant” (this defines “practical equivalence” or the “noninferiority margin”)
Design – 2-Arm Non-inferiority Study

- Analysis – get CI for the difference between groups and note if CI is within the bounds of practical equivalence.
  - Or at least the lower bound of the CI is greater than -noninferiority margin
Superiority:
\( H_0: \text{diff} = 0 \)
\( H_A: \text{diff} \neq 0 \)

Equivalence:
\( H_0: \text{diff} \neq 0 \)
\( H_A: \text{diff} = 0 \)

Noninferiority Margin ( )
Noninferiority Study: Example

- A randomized, double-blind, multicenter study comparing the efficacy and safety of Piperacillin/Tazobactam (4G/500MG) and Imipenem/Cilastatin (500MG/500MG) administered intravenously every six hours to treat nosocomial pneumonia in hospitalized patients.
Noninferiority Study: Example

- **SOC: Imipenem/Cilastatin (IC)**
  - 60/99 cured
- **New drug: Piperacillin/Tazobactam (PT)**
  - 67/98 cured
- **Lower bound of 95% CI for the difference in response rates (PT-IC) is –0.066 which is greater than –0.20 (i.e., 20% was chosen as the noninferiority margin)**
- **Thus PT was shown to be noninferior to IC and was approved by the FDA**
Some Useful Websites

- National Institutes of Health
  - www.clinicaltrials.gov
- Food and Drug Administration
  - www.fda.gov
- International Conference on Harmonization
  - www.ich.org