TWIST: Formalizing Study Design & Writing Your Protocol

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The Basics

Types of Research
Laboratory Research

- Applies knowledge of basic sciences towards development of procedures and strategies to prevent, control and understand mechanisms of health-related phenomena
- Genes, proteins, molecules
- Human and non-human tissue
- **Wet** - on the bench with test tubes
- **Dry** – on a computer – eg. computational or large database
Epidemic and Population Research

- **Epidemic investigations**: study of outbreaks, in local populations, to identify agent(s), transmission mode(s), and possible control measure(s)

- **Population-based (field) research**: study of distribution, determinants, control measures of health-related phenomena in chosen populations, followed by application of suitable biostatistical techniques which may allow generalization of results
Clinical Research

• Research that directly involves a particular person or group of people to better understand some aspect of health.

• *Clinical trial* : prospectively planned experiment for the purpose of evaluating potentially beneficial therapies or treatments
Why Clinical Trials?

1. Most definitive method to determine whether a treatment is effective.

   - Other designs have more potential biases
   - One cannot determine in an uncontrolled setting whether an intervention has made a difference in the outcome.
   - Correlation versus causation
Examples of False Positives

1. Vasectomy and prostate cancer
2. Drinking water frequently and bladder cancer
3. Not consuming olive oil and breast cancer

Replication of observational studies may not overcome confounding and bias
Why Clinical Trials?

2. Help determine incidence of side effects and complications.

Example: Coronary Drug Project - for patients with documented MI, does taking lipid modifying drugs reduce mortality?

A. Detection of side effect (other arrhythmias)
   Clofibrate  33.3%
   Niacin      32.7%     p<.05
   Placebo    28.2%

B. Natural occurring side effect (nausea)
   Clofibrate  7.6%
   Placebo    6.2%     p>.05
Why Clinical Trials?

3. Theory not always best path

- Intermittent positive pressure breathing (IPPB) $\Rightarrow$ reduced use, no benefit
- Tonsillectomy $\Rightarrow$ Reduced use
- Bypass Surgery $\Rightarrow$ Restricted use
What’s The Question?

What is the study hypothesis?
What’s The Question?

- What’s the outcome?
- What’s the intervention?
- When and for how long?
- For whom?
- How many participants are needed?
- How can we optimize potential benefit (and what we learn) while minimizing potential harm?
Primary vs. Secondary Questions

• **Primary**
  – most important (i.e., central question)
  – ideally, only one
  – stated in advance
  – basis for design and sample size calcs

• **Secondary**
  – related to primary
  – also stated in advance
  – limited in number but usually more than 1
Examples

- **Physicians Health Study (PHS)** (phs.bwh.harvard.edu)
  - risks and benefits of aspirin and beta carotene in the prevention of cardiovascular disease and cancer
  - started recruitment of US male physicians in 1982
  - conducted entirely by mail (much cheaper!!)
  - 2x2 factorial structure
  - **Primary endpoint**: total mortality
  - **Secondary endpoint**: myocardial infarction

\[
\begin{array}{c|cc|cc}
\text{2 x 2 Design} & \text{Beta Carotene (Y)} & \text{Beta Carotene (N)} \\
\hline
\text{Aspirin (YES)} & Y & Y & N & Y \\
\text{Aspirin (No)} & Y & N & N & N
\end{array}
\]
Examples

- Eastern Cooperative Oncology Group (ECOG)
  - Information available at [www.ecog.org](http://www.ecog.org)
  - multicenter cancer clinical trial
  - Elderly women with stage II breast cancer
  - tamoxifen vs placebo
  - Double blind study
  - **primary**: tumor recurrence/relapse, disease-free survival
  - **secondary**: total mortality
Response Variables

• Biologic activity
• Biomarker
  – Understand mechanism
  – Surrogate outcome
• Toxicity
• Condition/vector/gene interaction
• Feasibility for larger study
• Clinical outcome
Response Variable Criteria

- Well defined
- Stable
- Reproducible
- Unbiased
- Ascerttainable in all participants
- Adequately address study hypothesis
Answering the Question

• Response variable –
  – selection and measurement
• What is the intervention
• Study design
• Eligibility criteria
• Sample size estimate
• Patient management procedures
• Monitoring for safety and benefit
• Data analysis approaches
Defining the Intervention

- Dose/dosing schedule
- Route of delivery
- Method of preparation
Types of Clinical Trials

- Randomized
- Non-Randomized
- Single-Center
- Multi-Center
- Phase I, II, III, IV Trials
Phase I Trial

- Objective: To determine an acceptable range of doses and schedules for a new drug
- Usually seeking **maximum tolerated dose**
- Participants often those that have failed other treatments
- Important, however, that they still have "normal" organ functions
Phase II Trial

- Objective: To determine if new drug has any beneficial activity and thus worthy of further testing / investment of resources.
- Doses and schedules may not be optimum
- Begin to focus on population for whom this drug will likely show favorable effect
Phase III Trial

- Objective: To compare experimental or new therapies with standard therapy or competitive therapies.
- Generally large, expensive studies
- Required by FDA for drug approval
- If drug approved, usually followed by Phase IV trials to follow-up on long-range adverse events – concern is safety
<table>
<thead>
<tr>
<th>Preclinical Research (in vitro and in vivo)</th>
<th>Clinical Studies</th>
<th>FDA Review</th>
<th>Post-Marketing Surveillance</th>
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</thead>
<tbody>
<tr>
<td>Short-term testing in animals</td>
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<tr>
<td>Long-term testing in animals</td>
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<tr>
<td>Phase 1</td>
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<td>Small trials studying safety and toxic effects in healthy volunteers</td>
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<td>Phase 2</td>
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<td>Trials of safety and efficacy in patients with the condition to be treated</td>
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<td>Phase 3</td>
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<tr>
<td>At least 2 larger, randomized &quot;pivotal&quot; trials of efficacy and safety</td>
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<td>Phase 4</td>
<td>FDA Office of Drug Safety monitors reported adverse reactions</td>
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- Usually 2000 to 5000 patients are exposed to a drug during clinical studies before FDA approval.
- FDA cannot mandate further safety studies.

- Company obtains FDA permission for trials in humans
- Application for new drug approval
- FDA approval
Study Design

• Uncontrolled
• Controlled
  – Before/after
  – Historical
  – Concurrent, not randomized
  – Randomized
Non-randomized Trials May Be Appropriate

• Early studies of new and untried therapies

• Uncontrolled early phase studies where the standard is relatively ineffective

• Investigations which cannot be done (no “clinical equipoise”)

• Truly dramatic response
Comparing Treatments (Randomized Trials)

• Fundamental principle
  • Groups must be alike in all important aspects and only differ in the intervention each group receives
  • In practical terms, “comparable treatment groups” means “alike on the average”

• Randomization
  • Each participant has the same chance of receiving any of the interventions under study
  • Allocation is carried out using a chance mechanism so that neither the participant nor the investigator will know in advance which will be assigned

• Blinding
  • Avoidance of conscious or subconscious influence
  • Fair evaluation of outcomes
Advantages of Randomized Control Clinical Trial

1. Randomization "tends" to produce comparable groups

2. Randomization produces valid statistical tests
Disadvantages of Randomized Control Clinical Trial

1. Generalizable Results?
   - Participants studied may not represent general study population.

2. Recruitment
   - Hard

3. Acceptability of Randomization Process
   - Some physicians will refuse
   - Some participants will refuse

4. Administrative Complexity
Study Population

Subset of the general population determined by the **eligibility criteria**

- **General population**
  - Eligibility criteria

- **Study population**
  - Enrollment

- **Study sample**
  - Observed
Sample Size (1)

- The study is an experiment in people
- Need enough participants to answer the question
- Should not enroll more than needed to answer the question
- Sample size is an estimate, using guidelines and assumptions
Sample Size (2)

• Approaches for early phase studies
  – Dose escalation schemes
  – Decision that intervention is unlikely to be effective in x% of participants
  – Decision that intervention could be effective in x% of participants

• Standard ways of estimating for phase III
Sample Size (3)

• Assumptions depend on
  – Nature of condition
  – Desired precision of answer
  – Availability of alternative treatments
  – Knowledge of intervention being studied
  – Availability of participants
Specific Clinical Trial Types

The Details
Phase I Design Strategy

- Designs based largely on tradition
- Typically do some sort of dose escalation to reach maximum tolerated dose (MTD)
- Has been shown to be safe and reasonably effective
- Dose escalation often based on Fibonacci series
  - 1 2 3 5 8 13 . . .
Typical Scheme

1. Enter 3 patients at a given dose
2. If no toxicity, go to next dosage and repeat step 1
3. a. If 1 patient has serious toxicity, add 3 more patients at that dose (go to 4)
   b. If 2/3 have serious toxicity, consider MTD
4. a. If 2 or more of 6 patients have toxicity, MTD reached
   b. If 1 of 6 has toxicity, increase dose and go back to step 1
Summary of Schemes
(Storer, Biometrics 45:925-37, 1989)

A. “Standard”
– Observe group of 3 patients
– No toxicity $\rightarrow$ increase dose
– Any toxicity $\rightarrow$ observe 3 or more
  • One toxicity out of 6 $\rightarrow$ increase dose
  • Two or more toxicity $\rightarrow$ stop

B. “1 Up, 1 Down”
– Observe single patients
– No toxicity $\rightarrow$ increase dose
– Toxicity $\rightarrow$ decrease dose
Summary of Schemes

C. “2 Up, 1 Down”
- Observe single patients
- No toxicity in two consecutive $\rightarrow$ increase dose
- Toxicity $\rightarrow$ decrease dose

D. “Extended Standard”
- Observe groups of 3 patients
- No toxicity $\rightarrow$ increase dose
- One toxicity $\rightarrow$ dose unchanged
- Two or three toxicity $\rightarrow$ decrease dose
Summary of Schemes
(Storer, Biometrics 45:925-37, 1989)

E. “2 Up, 2 Down”
- Observe groups of 2 patients
- No toxicity → increase dose
- One toxicity → dose unchanged
- Both toxicity → decrease dose

B, C, D, E - fixed sample sizes ranging from 12 to 32 patients
Can speed up process to get to target dose range

F. Bayesian sequential/adaptive designs
Phase II Designs

References:
  Gehan (1961) *Journal of Chronic Disorders*
  Fleming (1982) *Biometrics*
  Storer (1989) *Statistics in Medicine*

• Goal
  – Screen for therapeutic activity
  – Further evaluate toxicity
  – Test using MTD from Phase I
  – If drug passes screen, test further
Phase II Design

- Design of Gehan
  - No control (is this wise?)
  - Two-stage (double sampling)
  - Goal is to reject ineffective drugs ASAP

Decision I: Drug is unlikely to be effective in $\geq \underline{x}\%$ of patients

Decision II: Drug could be effective in $\geq \underline{x}\%$ of patients
Phase II Design

- Example: Gehan Design
  - Let $x\% = 20\%$ : want to check if drug likely to work in at least 20% of patients

1. Enter 14 patients

2. If 0/14 responds, stop and declare true drug response $\leq 20\%$

3. If 1+/14 respond, add 15-40 more patients

4. Estimate response rate & C.I.
**Phase II Design**

- Stage I Sample Size - Gehan

**Table I**

<table>
<thead>
<tr>
<th>Error</th>
<th>5%</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
<th>25%</th>
<th>40%</th>
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<tbody>
<tr>
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<td>19</td>
<td>14</td>
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<td>10%</td>
<td>45</td>
<td>22</td>
<td>15</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>
Phase III Trial Design

• The foundation for the design of controlled experiments established for agricultural experiments
• The need for control groups in clinical studies recognized, but not widely accepted until 1950s
• No comparison groups needed when results dramatic:
  – Penicillin for pneumococcal pneumonia
  – Rabies vaccine
• Use of proper control group necessary due to:
  – Natural history of most diseases
  – Variability of a patient's response to intervention
Phase III Design

- Comparative Studies
- Experimental Group vs. Control Group
- Establishing a Control
  1. Historical
  2. Concurrent
  3. Randomized
- Randomized Control Trial (RCT) is the gold standard
  - Eliminates several sources of bias
Goals of Phase III Clinical Trial

• Superiority Trials
  - A controlled trial may demonstrate efficacy of the test treatment by showing that it is superior to the control
    • No treatment
    • Best standard of care
Goals of Phase III Clinical Trials

• Non-Inferiority Trials
  – Controlled trial may demonstrate efficacy by showing the test treatment is similar in efficacy to a known effective treatment
  • The active control has to be effective under the conditions of the trials
  • New treatment cannot be worse by a pre-specified amount
  • New treatment may not be better than the standard but may have other advantages
    – Cost
    – Toxicity
    – Invasiveness
Ethics of Randomization

- Statistician/clinical trialist must sell benefits of randomization

- **Ethics** ⇒ MD should do what he thinks is best for his patient
  - Two MD's might **ethically** treat same patient quite differently

- Chalmers & Shaw (1970) *Annals New York Academy of Science*
  1. If MD "knows" best treatment, should not participate in trial
  2. If in doubt, randomization gives each patient equal chance to receive one of therapies (i.e. best)
  3. More ethical way of practicing medicine

- Bayesian Adaptive designs ⇒ More likely assign “better” treatment
Purpose of Control Group

• To allow discrimination of patient outcomes caused by test treatment from those caused by other factors
  – Natural progression of disease
  – Observer/patient expectations
  – Other treatment

• Fair comparisons
  – Necessary to be informative
Significance of Control Group

- Inference drawn from the trial
- Ethical acceptability of the trial
- Degree to which bias is minimized
- Type of subjects
- Kind of endpoints that can be studied
- Credibility of the results
- Acceptability of the results by regulatory authorities
- Other features of the trial, its conduct, and interpretation
Use of Placebo Control

- The “placebo effect” is well documented
- Could be
  - No treatment + placebo
  - Standard care + placebo
- Matched placebos are necessary so patients and investigators cannot decode the treatment assignment
- E.g. Vitamin C trial for common cold
  - Placebo was used, but was distinguishable
  - Many on placebo dropped out of study – not blinded
  - Those who knew they were on vitamin C reported fewer cold symptoms and duration than those on vitamin who didn't know
Regular Follow-up

• Routine Procedures (report forms)
  – Interviews
  – Examinations
  – Laboratory Tests
• Adverse Event Detection/Reporting
• Quality Assurance
Contingency Plans

- Patient management
- Evaluation and reporting to all relevant persons and groups
- Data monitoring plans
- Protocol amendment or study termination
Data Analysis (1)

- Occurrence of event
- Time to event
- Mean level of response
- Duration of response
Data Analysis (2)

- Intention-to-treat
- Explanatory
- Subgroups
- Adjusted vs. Unadjusted
Data Analysis (3)

• Specify in advance
  – Primary
  – Secondary
  – Other
  – Statistical approach

• Exploratory
Clinical Protocols

The Basics
Clinical Protocol (1)

• Background/Justification
  --Where we are in the field
  --What the study will add that is important

• Objectives
  --Primary hypothesis
  --Secondary hypotheses
  --Other
Clinical Protocol (2)

• Study Design and Methods
  --Type of study, comparison
  --Inclusion and exclusion criteria
  --Description of intervention (what, how)
  --Concomitant therapy
  --Examination procedures (baseline, follow-up, outcome assessment)
  --Intervention assignment procedure
Clinical Protocol (3)

• Monitoring and Management
  -- Data and safety monitoring
  -- Adverse event assessment, reporting
  -- Contingency procedures
  -- Withdrawal criteria
Clinical Protocol (4)

• Statistics
  --Sample size
  --Stopping guidelines
  --Analysis plans

• Participant protection issues
Summary

• Protocol lays out who, what, why, when, where, how
• Safeguards participants
• Safeguards study integrity
• Midcourse changes are often appropriate (even necessary)
Clinical Research

• To research on patients is a privilege.
• Need to provide excellent care
• Need to know what is standard and what is unknown
• Need to document and be responsible
• Get to improve patient outcomes.
Questions?

Please feel free to e-mail any questions or comments to JCTOQAU@med.cornell.edu