

Biostat 226 (TICR Biostat V) Winter 2010 Current Issues in Randomized Clinical Trials Joan F. Hilton, Sc.D., UCSF Division of Biostatistics Copyright, January 1, 2010
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Outline of Course

Lecture 1: An Introduction to Clinical Trials

- Phase I, II, III, and IV trials
Therapeutic mechanism of action → Choice of endpoint → Study design → Analysis method
- FDA resources & opportunities for involvement in decision-making:
Guidance documents; Advisory Committees
- Congress: *Senate Bill 1956*

Lecture 2: Phase III Study Designs: Superiority, Noninferiority, Other

Lecture 3: Phase III Outcome Monitoring: Efficacy & Safety

Lectures 4-6: Introduction to Bayesian Methods

**Figure 6. Ronald Fisher
(1890 - 1962)**



*Father of Modern
Statistical Analysis of
Experiments*

**Figure 10. Thomas Bayes
(1702 -- 1761)**



*Father of Bayesian
Statistics*

BACKGROUND READING: Textbooks I like

Friedman LM, Furber CD, DeMets DL. Fundamentals of Clinical Trials, 3rd edition. Springer, 1998.

Green S, Benedetti J, Crowley J. Clinical Trials in Oncology, 2nd edition. Boca Raton: Chapman & Hall, 2003.

Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian Approaches to Clinical Trials and Health-Care Evaluation. Wiley, 2004.

Definitions of Phase I, II, III, and IV Trials

Most clinical trials are designated as phase I, II, III, or IV, based on the study objectives.

Phase I trials: Test a new drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

Phase II trials: Give the study drug or treatment to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

Phase III trials: Give the study drug or treatment to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

Phase IV trials: Conduct post-marketing studies to obtain additional information about the drug's risks, benefits, and optimal use.

Source: Food and Drug Administration in the Code of Federal Regulations.

Regardless of the study objectives, the methodology must be sound.

Topic	Over-Arching Question	Key Components	Where Addressed
What?	What research questions are being addressed in the trial, and how important are they?	<ul style="list-style-type: none"> • Historical Context • Clinical Importance 	Aims
Why?	Why should the trial be conducted — i.e., does the scientific rationale adequately support the research question?	<ul style="list-style-type: none"> • Pre-trial Data • Biologic Processes 	Background
Who?	Who will support the trial and how likely are they to embrace it?	<ul style="list-style-type: none"> • Physician's Perspective • Clinical Sites • Patient Accrual • Patient Retention 	Appendix
How?	How well designed is the trial to answer the research questions it addresses?	<ul style="list-style-type: none"> • Patients • Intervention • Comparison or Control • Outcome 	Method

PICO: Patient Issues

- *Are the eligibility requirements optimal?*

Heterogeneity vs. homogeneity?

Inclusion of patients from underserved populations?

Relative to likely clinical use of the intervention?

Is adequate, timely accrual feasible?

- *Does this design make the most efficient use of patients?*

Could the primary questions be answered with fewer patients?

Could fewer patients be exposed to the less effective intervention?

Could results could be achieved more rapidly?

Could additional questions be addressed without compromising the study?

Can the study determine not only whether the intervention is beneficial, but also which patients are most likely to benefit?

Will patients who participated in the trial but did not receive the experimental treatment have subsequent access to the experimental treatment if it is found to be effective?

Will the experimental intervention be made available to patients who did not receive it, if it is found to be effective? What long-term follow-up is planned?

Will patients be informed about the results of the trial?

PICO: Intervention Issues

From a practical point of view, aspects of the intervention that may have limited relevance to the disease (e.g., number of clinic visits), are important to patients and may impact trial accrual and retention, both of which are crucial for the success of trials.

- *Why was the experimental intervention selected?*

If this is a drug trial, what drug, dose, and schedule of administration will be used? Were alternatives considered?

If this is not a drug trial (e.g., radiation, surgery, psycho-social, quality of life, correlative science intervention) what variations on the interventions were considered?

What supportive therapies (i.e., drugs provided to counteract side effects) will be provided and under what circumstances?

Under what circumstances will the drug dose or other aspects of the intervention be modified?

- *Are all of the test procedures (e.g., blood draws, scans, biopsies) necessary?*

Are less intrusive procedures available?

How time consuming will these procedures be?

Must all of the procedures be completed at the research center?

Can the procedures be scheduled in a way that minimizes the number of trips a patient must make to the research center?

PICO: Comparison Issues

- *Is the control intervention appropriate?*

Will clinicians be allowed to choose among interventions?

Will researchers, health care providers, or patients know to which intervention arm patients were assigned (i.e., triple blinding)?

Will tests be performed on patients in both the experimental and control arms, even if they are not part of standard care? (Note: This provision is typically necessary to ensure blinding.)

- *How will patients be allocated among intervention arms?*

Are there ways in which patients assigned to different interventions arms may systematically differ (e.g., demographics, stage of disease)?

What, if any, patient attributes (e.g., gender, disease site or stage) will be stratified? How were these factors chosen?

What demographic and baseline variables will be measured to ensure that all groups were indeed equivalent?

- *How will data be analyzed when the standard protocol is not followed?*

If patients do poorly in the group to which they were assigned, will they be allowed to crossover?

How will the statistical analysis deal with patients who crossover or drop-out of the trial? (i.e., question whether analysis is intent-to-treat or what was actually received.)

PICO: Outcome Issues

The choices of outcomes or endpoints typically involve trade-offs that reflect priorities concerning speed, completeness, and clinical value; thus they vary across phase I, II, III, and IV. Secondary endpoints may be specified in the protocol (e.g., side-effect profile, quality of life) without the trial being powered to assess them.

- *What is the primary endpoint?*

Is it important to patients?

Will it lead to definitive results?

Will it be measured in a reliable and valid manner?

What alternatives were considered and why was this one chosen?

- *If the primary outcome is a surrogate endpoint:*

Why was this surrogate endpoint selected?

What clinically relevant outcomes are correlated with the surrogate?

What is the evidence that impacting the surrogate endpoint will also impact the clinical outcome that is of primary interest?

- *Many clinical trials collect and analyze a host of demographic and biomarker measures in the hope of identifying questions worthy of future study.*

If biomarkers will be measured from bi-specimens (e.g., blood, tumor tissue), how will the bio-specimens be collected and handled? How will the biomarkers be assayed?

How will these data be analyzed and used?

Phase I trials

Objectives:

- To determine the recommended phase II dose of a new agent using a particular dosing schedule. Initial dose & schedule guesses are based on preclinical (animal) studies.
- To characterize the toxicity profile of an agent (expected and unintended consequences).

Patients:

Typically have advanced disease; have exhausted available treatment options; hope an investigational therapy will work.

Disadvantages:

- Therapy may be effective at early but not late stage disease
- Effectiveness may take time to show up
- Patient's health declining: too late to interrupt disease course; may be lost to follow-up

Intervention: non-specific, cytotoxic anti-tumor agents:

- Safety: Administered at relatively high doses; Toxicity can be acute, severe (e.g., grade 3-4)
- Efficacy: Tumor regression (shrinkage) in proportion to dose; short-term response
- **Outcome:** Enroll cohorts of 3 – 6 patients at escalating doses until MTD is identified. What proportion, p , experience dose limiting toxicity (DLT)? (Fibonacci scheme)
 - $p_i < 1/3$: Increment dose; evaluate.
 - $p_i = 1/3$: Treat 3 more patients at current dose.
 - * $p_{i+1} < 2/6$: Increment dose; evaluate.
 - * $p_{i+1} \geq 2/6$: Define current dose as MTD. Stop.
 - $p_i > 1/3$: Define current dose as MTD. Stop.

- Diminishing increments between successive doses: D_1 (initial dose) = 10% of animal LD_{10} . $D_2 = 2.0 \times D_1$, $D_3 = 1.67 \times D_2$, $D_4 = 1.5 \times D_3$, $D_5 = 1.4 \times D_4$.
- Alternative schemes: Designed to speed up identification of target dose. [Ref: Storer, *Biometrics*, 45:925-38, 1989.]

Intervention: targeted, cytostatic agents:

Many new therapeutic targets (aberrant genes and signaling pathways) are being identified.

- Safety: Toxicity can be chronic, moderate (e.g., grade 2); late; intermittent
- Efficacy: Biologic or pharmacologic endpoints
 - Target inhibition:
 - * requires known target, specific to agent (ideally, 1:1 association)
 - * logistical issues: access to tissue (biopsy), technical skill (protein expression level), cost
 - Pharmacology: Preclinical data correlate systemic exposure levels (dose) with extent of anti-tumor activity (response), suggest target AUC or steady-state concentration. Assumes plasma concentration equals tumor concentration.
- Study design:
 - Dose escalation beyond some threshold may increase toxicity without increasing efficacy (saturable target): Less steep dose-response curve implies larger sample size.
 - Biologic markers to guide dose levels: Do changes in markers imply clinical response?
 - Outcomes may occur over a long time-frame.
 - Consider toxicity plus other endpoints in recommending phase II dose

Outcome: Modify the conventional dose escalation schemes to use biological endpoints plus toxicity

- Define a target AUC using a model; from preliminary data
- Continual reassessment model: 1 patient per dose level; larger overall N (dose:response curve shallower)

Examples / Phase I: Search criteria = dose, open studies, heart, child, phase I

- Erythropoietin for Brain Protection in Neonatal Open Heart Surgery:
www.clinicaltrials.gov/ct2/show/NCT00513240
Notes: $N = 240!$ Phase 1?
 - Three doses per person (active versus placebo), all delivered within a few days.
 - Final short-term outcome measure collected on day 7 post-op.
 - would allow for adaptive randomization.
- Inhaled Iloprost as an Adjunct to Inhaled Nitric Oxide in Pediatric Critical Care Patients:
www.clinicaltrials.gov/ct2/show/NCT00981591
Notes: $N = 40$. Active versus placebo – ethical?
 - Dose = 0.5 mcg/kg every 2 hours; Maximum dose = 30 mcg every 30 minutes.
 - Final outcome measure collected soon after randomization (? time-frame not provided)
 - would allow for adaptive randomization.

Phase II trials

Objectives:

- To screen agents for efficacy
- To further define short- and long-term toxicity
- To refine dose & schedule
- To determine if efficacy varies by risk group, cancer type, etc

Patients: Want to select the most promising candidates

- Homogeneous targeted group, if mechanism well defined and patients who will benefit can be identified.
- Heterogeneous group, otherwise. Quicker recruitment; results generalizable to larger target.

Intervention: non-specific, cytotoxic anti-tumor agents:

- Efficacy: Ordinal response, extent of tumor shrinkage
 CR, Complete regression
 PR, Partial regression
 SD, Stable disease
 PD, Progressive disease
- Study design: Typically two stages. Stop early only for lack of efficacy. Short-term endpoint. (Study duration precludes more stages: Between stages: complete stage-1 treatment, await patient responses and staff data reviews; process opening of Stage 2.)
 - 1st Stage: Enroll n_1 patients; count successes, r_1 . Proceed to 2nd stage if $r_1 \geq X\%$. (Avoid treating patients with ineffective agents; “type I error”.)
 - 2nd Stage: Enroll n_2 more patients. Proceed to phase-III trial if $r_2 \geq X\%$.

– **Example 1:** $H_0 : p = 0.10$ and $H_A : p = 0.30$; **power**= 0.90.

Stage	Cumulative n	Cumulative CR required	Cumulative α
I	20	2+	0.02
II	35	8	0.05

– **Example 2:** $H_0 : p = 0.20$ and $H_A : p = 0.40$; **power**= 0.90.

Stage	Cumulative n	Cumulative CR required	Cumulative α
I	25	4+	0.02
II	45	14	0.05

Intervention: targeted, cytostatic agents:

- Efficacy: Now expect SD, not CR+PR.
- Safety: Best dose & schedule? Combine with another agent?
- Study design issues:
 1. **Comparison group:**
 - One-arm trials: Relative to historical control group; Relative to own prior experience (sequential design): $TTP1/TTP2 > 1.33$
 - Multi-arm trials: Relative to control group; random allocation to groups
 2. **Outcomes:**
 - Single measure: SD rate; PD rate; T-T-progression (TTP); symptomatic response; QOL. Use “randomized discontinuation design.” At Stage 1,
 - * CR/PR → continue Rx until PD or toxicity,
 - * SD → randomize to continue/stop Rx,
 - * PD → stop Rx. (Biased?)
 - Multiple measures (“multinomial design”) – for example, Phase II/III trial:
 - * Stage 1: Phase II trial (tumor response = shorter-term). Must meet pre-defined survival threshold for arm to proceed to Stage 2; requires N typical for Phase II.
 - * Stage 2: Phase III trial (patient response = longer-term). Continue accrual to remaining arms; requires N typical for Phase III.
 - Survival outcome is suitable if late Rx effect.
 - Phase I ⇒ Phase III trial: Risky! (*See Senate Bill*)

Examples of Phase II Studies:

Search terms: MRSA — Open Studies — Interventional Studies — Adult — Phase II

- Clinical Trial on the Reduction of Methicillin Resistant Staphylococcus Aureus (MRSA):
www.clinicaltrials.gov/ct/show/NCT00790608
- Strategies Using Off-Patent Antibiotics for Methicillin Resistant S. Aureus “STOP MRSA”:
www.clinicaltrials.gov/ct/show/NCT00729937

Search terms: dental — Open Studies — Interventional Studies — Phase II → 36 hits on 1/4/10

- Effectiveness of Dental Brushing for Preventing Ventilator-Associated Pneumonia:
www.clinicaltrials.gov/ct/show/NCT00842478

Phase III trials

Objectives: To assess relative efficacy.

- Subgroups: To determine if efficacy varies by risk group, cancer type, etc
- Safety: To further define short- and long-term toxicity

Patients:

- Homogeneous target group: Select patients with the highest chance of responding to the agent.
 - Exclude patients who lack the agent’s molecular target!

Intervention: targeted, cytostatic agents:

- Study design issues:
 1. Random allocation: to ensure groups differ by Rx alone. (*Balanced?*)

2. Blinding: to ensure outcome is assessed without bias. (*Single, Double, Triple? Evaluated?*)
3. **Outcomes:** Clinical endpoint vs. Surrogate marker
4. **Comparison:** “Group Sequential Design:” Monitor outcome over time by arm. Consider stopping early
 - if there is evidence of strong positive or negative effect, or
 - if there is no chance of showing a positive effect (“futility”).

Example of Phase III Trial

Search terms: nursing — Open Studies — Interventional Studies — Phase III

- A Trial to Reduce Pneumonia in Nursing Home Residents (PRIDE):
www.clinicaltrials.gov/ct/show/NCT00975780

Example of Phase II-III Trial

Search terms: prostate — Open Studies — Interventional Studies — Phase II III

- Ablatherm Integrated Imaging High Intensity Focused Ultrasound for the Indication of Low Risk, Localized Prostate Cancer:
www.clinicaltrials.gov/ct/show/NCT00295802

Reporting results: CONSORT Guidelines,
www.consort-statement.org

Phase IV trials

- Phase 4 Efficacy and Safety Study of Cubicin With and Without Combination Therapy in S. Aureus Infective Endocarditis: www.clinicaltrials.gov/ct/show/NCT00638157

- Aripiprazole + Lamotrigine in Patients With Bipolar I Disorder:
www.clinicaltrials.gov/ct/show/NCT00277212

FDA: Resources, and Opportunities for Involvement in Decision Making

www.fda.gov/SiteIndex/ucm148495.htm

- Guidance documents
- Advisory Committees

Congressional Involvement

Access Act

- S.1956: *Access, Compassion, Care, and Ethics for Seriously Ill Patients Act*
Introduced 11/3/05, by Sen. Brownback (Rep, KS) and Sen. Inhofe (Rep, OK)
<http://thomas.loc.gov/cgi-bin/query/z?c109:S.1956>:
- Expanded Access to Investigational Drugs for Treatment Use
- Power SH. The right of privacy in choosing medical treatment: should terminally ill persons have access to drugs not yet approved by the Food and Drug Administration? *John Marshall Law Rev.* 1987 Summer;20(4):693-714. No abstract available. PMID: 11650094 [PubMed - indexed for MEDLINE]

Public Law 110-85