Phase II Design

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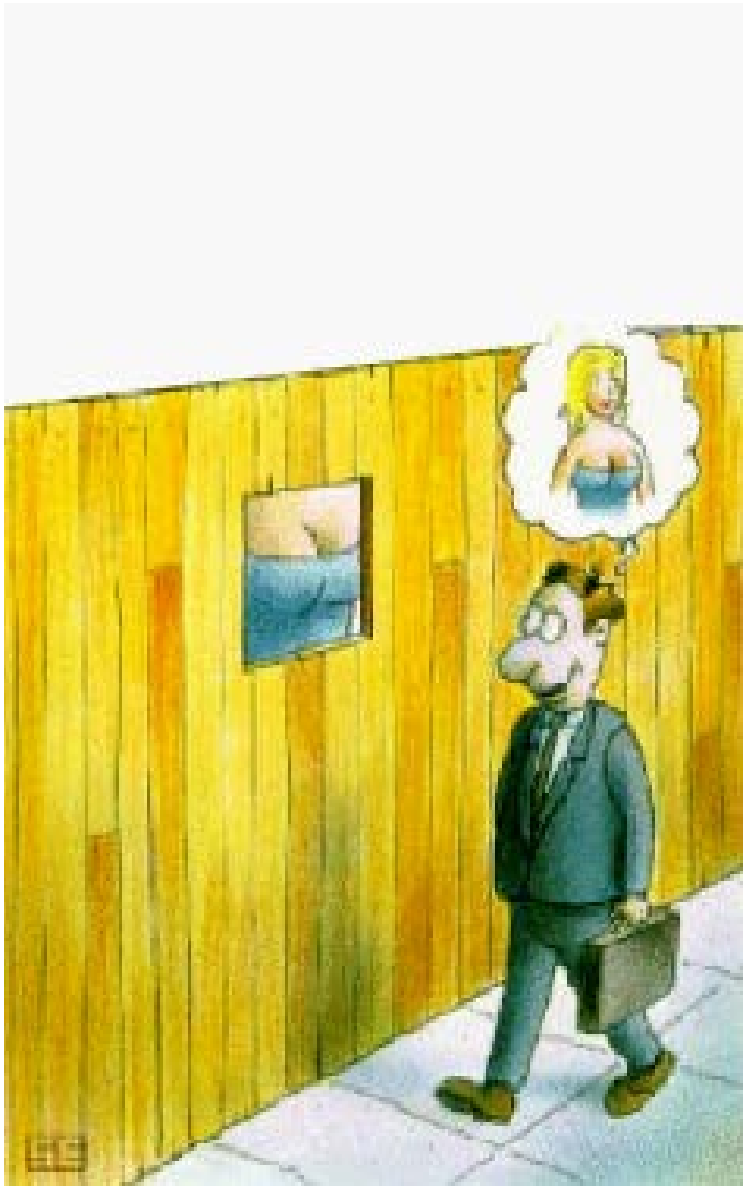
Phase II Study Results



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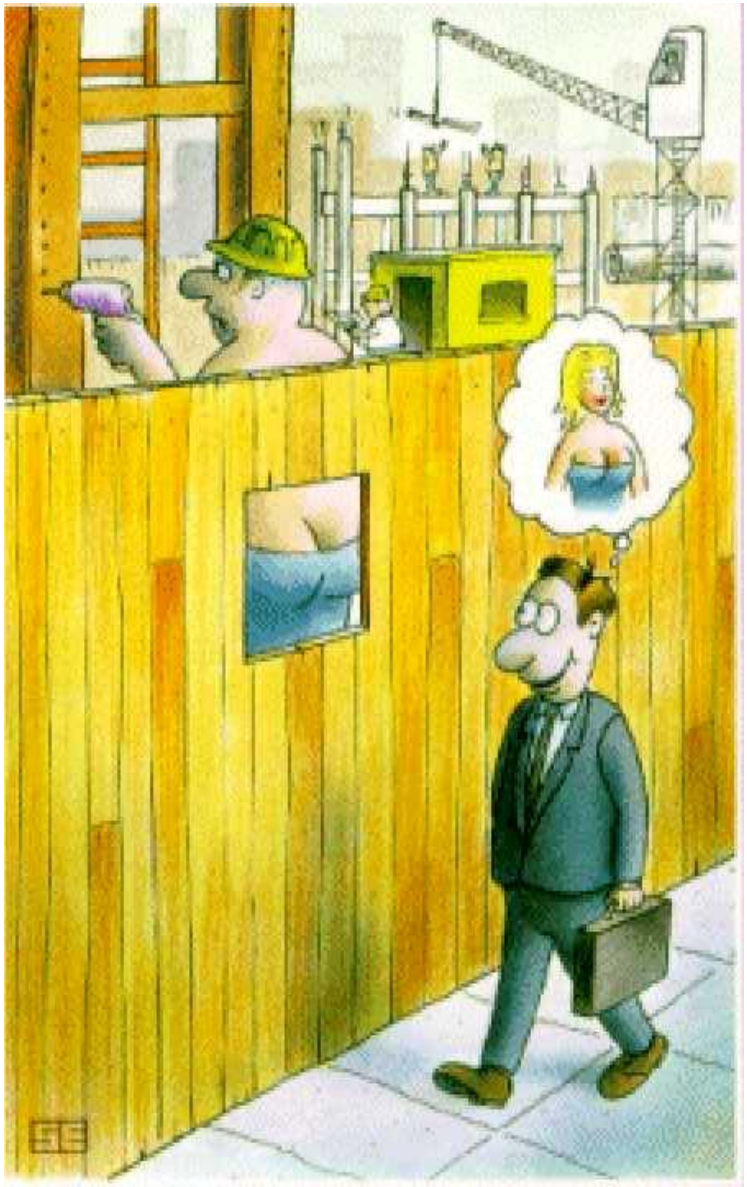

Agenda

- Objectives of phase II trials
- Endpoints of phase II trials
- Statistical designs of phase II trials
- Group exercise

Phase II Trials

- Purpose
  - Primary
    - To determine activity or “response” of a new treatment in a particular patient population
    - Should the treatment be tested in a 1000+ patient phase III study?
  - Secondary
    - Larger population to explore
      - Acute and cumulative toxicity
      - Optimal schedule and dose
      - Pharmacokinetics
      - Biological effectiveness

Structure of Phase II Trials

- Protocol specifies:
  - Patient population
  - Intervention
  - Outcome(s) of interest
    - What will be used to decide whether the intervention is “effective”
  - Decision rules
    - What level of outcome will determine whether treatment is worthy of further evaluation

Patient Population

- Specific cancer and stage of disease
  - Important to define inclusion/exclusion clearly as patient selection plays a significant role in response
  - Typically, patients have exhausted the currently established standard therapies
  - Phase II “window” studies
    - New treatment is given prior to standard therapy
    - More patients available, greater chance of response, risk of toxicity less
    - Ethical issues
  - For targeted therapies: specific molecular marker enriched or at least with some power to evaluate in a subset
    - Does it really matter? Need to recognize the limitations of the assessment of the particular marker and its relation to the mechanism of action of a particular drug

Intervention

- Recommended phase 2 dose (RP2D) may be based on a limited number of patients treated on the phase I trial
- Cumulative effects may not be known
- “Optimal” dose/schedule may not be well defined
  - e.g. antibodies

Outcomes

- Should “unambiguously be associated with clinical improvement”
  - Measurable disease
    - RECIST criteria
  - Disease specific criteria
    - e.g. PSA and prostate cancer
  - Symptoms
    - Validated symptom scoring
  - Survival
    - Progression and overall survival at a particular time-point

Decision Rules

- Classically tests a binary outcome
  - Null hypothesis: response (or outcome) rate is “low” and no further evaluation is warranted
  - Alternative hypothesis: response (or outcome) rate is “high” warranting further evaluation
- Need to really consider the question if results would really lead to a go/no-go decision for phase III
  - ambiguous endpoints and decision rules lead to ambiguous drug development
  - If a phase II trial cannot answer the question - then why do it?
    - Other primary endpoints: toxicity, surrogate/biologic markers

Phase II Designs

- Fixed sample size (single stage)
- Two-stage
- Randomized phase II

Single Stage: Fixed Sample Size

- Study parameters
  - Set null hypothesis (H_0) where response rate (p_0) considered not “interesting” based on literature and historical data
  - Set the alternate hypothesis (H_1) where response rate (p_1) would be considered interesting for further study
- Treat N patients, Observe X responses
- Decision rule
  - If $X < a$, then no further testing
  - If $X \geq a$, then further testing indicated
- Select an N and a so that
  - False positive rate is $\leq \alpha$
    - Generally set at 0.05 or 0.10
  - True positive rate (power) is $\geq 1-\beta$
    - Generally set at 0.8 to 0.9 - False negative rate 0.2 to 0.1

Sample Size Requirements: Fixed Sample Size

p_0	p_1	α	1-β	N	a
.05	.20	.10	.80	21	2
.05	.20	.05	.80	27	3
.05	.20	.05	.90	38	4
.10	.25	.05	.90	55	9
.25	.45	.05	.90	49	17
.40	.60	.05	.90	56	28

- Example: p0=.40, p1=.60, then N=56 and 28 responses needed to declare drug “interesting”
- Problem: What if in the first 30 patients only 6 responses?
  - Response rate .20 with (95% CI .10,.39)

Two-Stage Phase II Design

- 2-stage designs allows for early stopping for an observed low response rate
- Can also stop for high response rate
- Study parameters
  - Set null hypothesis (H_0) where response rate (p_0) considered not “interesting”
  - Set alternate hypothesis (H_1) where response rate (p_1) would be considered interesting for further study
  - First stage: Treat N_1 patients, Observe X_1 responses
  - Decision rule
    - If $X < a_1$, then H_0 is accepted and trial stopped
    - If $X \geq a_1$, then additional accrual to N (total)

Sample Size Requirements

- α=0.10, power (1-β)=0.9

p_0	p_1	Reject Drug if a_1/N_1	Reject Drug if a/N
.05	.20	0/12	3/37
.10	.25	2/21	7/50
.20	.35	5/27	16/63
.30	.45	9/30	29/82
.40	.55	16/38	40/88

- Example: p0=.05, p1=.20, then 12 patients accrued to first level
  - If 0 responses – trial stopped
  - If 1 or more responses, accrue 37 patients

Biometric Research Branch

Division of Cancer Treatment and Diagnosis

Optimal Two-Stage Phase II Design Software

Download

This file provides an easy to use, fast compiled C program that runs in a DOS window for computing optimal and minimax two-stage designs for phase II clinical trials. The program is based on the paper by R. Simon: "Optimal two stage designs for phase II clinical trials", Controlled Clinical Trials 10:1-10, 1989. To use the program, open a DOS window using the command prompt menu item in your start menu. CD to the directory into which you have put the file, and execute it.

Please send comments and suggestions to brb@linus.nci.nih.gov

last updated: Feb. 25, 2004

Find Optimal/MiniMax Phase Two

This program loops through all Phase II Two-Stage designs for testing:

H_0: $p=p_0$

H_1: $p=p_1>p_0$

subject a fixed maximum sample size, N, and finds all the designs that satisfy Type I & II error criteria.
[see Simon, Controlled Clin Trials, 10:1-10,1989]

p0	.05	This is the "bad" response probability
p1	.30	This is the "good" response probability
power	0.90	Set the power of the design
alpha	0.05	Set the alpha level of the design
N	40	All designs <= N are searched
Type of result:	graphics and text	
Type of graphic to return:	JPEG	

Run Analysis

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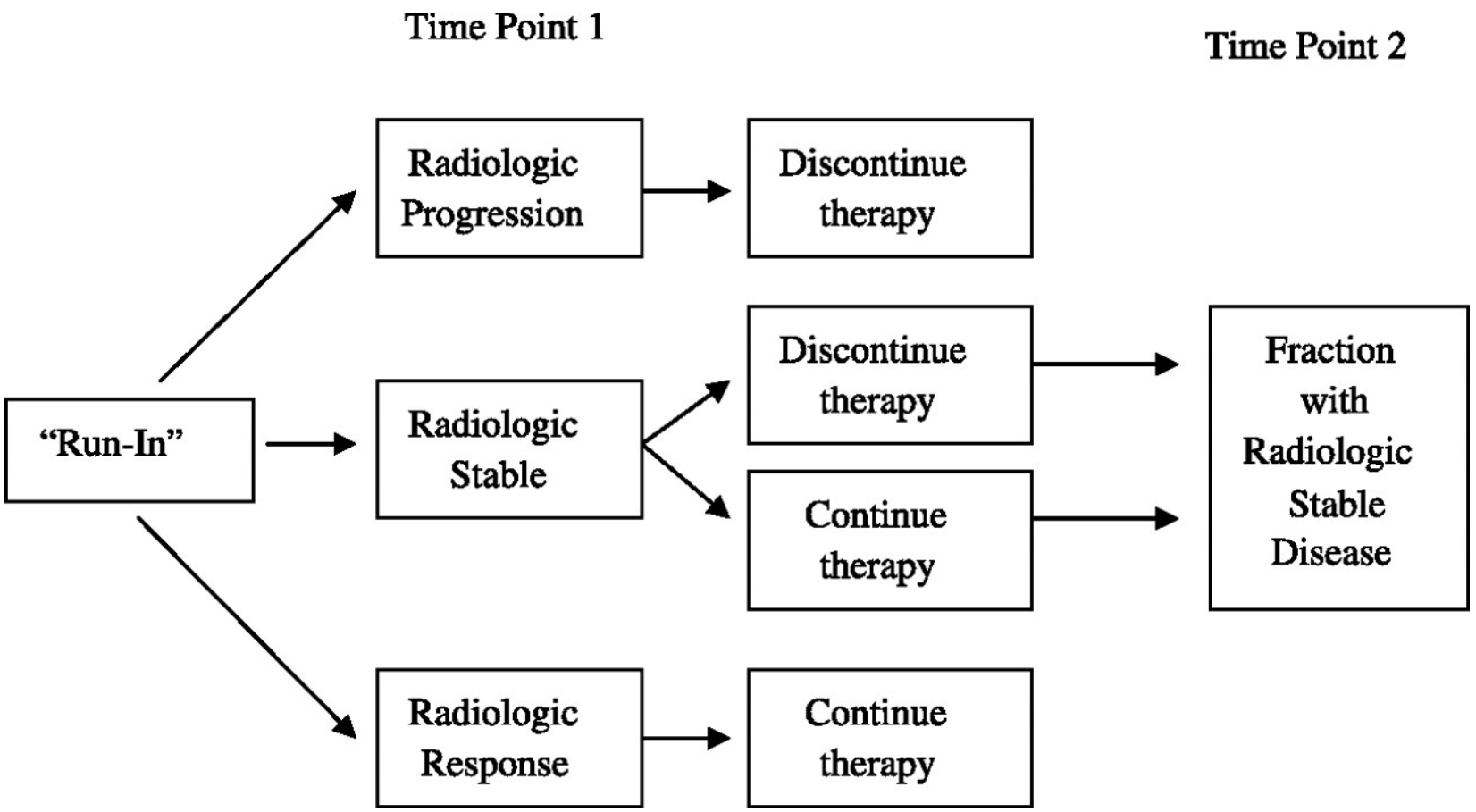
Some good advice…

- Work with a statistician

Randomized Phase II Design

- Goal is to balance treatment groups for prognostic factors
- In the classical sense
  - Random assignment to two different treatments
    - Two different doses
      - e.g. Iressa 250mg vs. 500mg
    - Two different drugs
  - Not a formal comparison but a “horse race”
  - Not ideal to test standard vs. experimental because of power
- Commonly used scenario
  - Internal control with standard therapy to assess the generalizability of the results in the “experimental” arm (e.g. combination studies)
  - Formal comparison of two groups with a non-survival primary endpoint
    - e.g. PSA response rate of Docetaxel + Calcitriol vs. Docetaxel in patients with HRPC

Randomized Discontinuation Trial Design



Stadler W M Mol Cancer Ther 2007;6:1180-1185

Randomized Discontinuation Trial Design

- Pro
  - All patients initially receive active drug
  - Fewer patients randomized to placebo
  - Assess effect of drug related growth inhibition vs. natural history of a cancer
- Cons
  - Large trials
  - Still requires phase III evaluation

Summary

- Objectives of phase II trials
  - Screening trials to determine whether or not to study a new treatment in phase III
- Endpoints of phase II trials
  - Endpoint associated with clinical benefit
  - Toxicity, correlative
  - Decision rules
- Statistical designs of phase II trials
  - Single stage: fixed sample size
  - Two stage
  - Randomized

Example

- RTK-223 is a novel small molecule inhibitor of a newly discovered oncogenic growth factor pathway present in 50% of all cancers. Pre-clinical models show single agent activity, and synergistic activity with chemotherapy.
- Phase I trials are completed:
  - Single agent daily
    - RP2D based on toxicity (DLT=fatigue) is 1000 mg/day
    - PK levels associated with preclinical effect seen at 200 mg/day
    - Evidence of biologic effect in surrogate tissues (skin biopsies) starting at 300 mg/day but no clear dose response
    - No PR/CR but a minor response in a patient with kidney cancer and several stable disease > 3 months at dose levels from 200 to 1000 mg/day in patients with prostate, colorectal and lung cancer.
  - Phase I with docetaxel
    - RP2D is 1000 mg/day with 75 mg/m2 of docetaxel
    - Responses are seen in patients with prostate and lung cancer.
- Because of these results, the company wants to develop the drug in lung cancer - you are charged with designing a phase II trial

Questions

- What’s your patient population?
- What’s your intervention?
- What are the endpoints?
- What design would you use?
- What’s your decision rule?