Clinical Trials for Oncology for Scientists

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How Do We Learn That An Exposure Alters Risk, or That an Intervention Decreases it, is Efficacious?

Celecoxib, colon cancer and chd (Bertagnoli et sl)

Continuum: identification of approaches:

Cell lines,	most often used in therapy
Animal models,	most often used in therapy
Phase 1,2,3 clinical trials	
Epi in progression to trials?	

Why Do We Need Clinical Trials? Make It As Difficult as Possible to Get Wrong Answer

- Criteria for validity of treatment or prevention finding
  - Bias defined: wrong answer. Bias means we would get the wrong answer *in spite of sample size.*
  - Internal vs external validity
  - Information bias----
    - Misclassification, mismeasurement of exposure
    - Misclassification, mismeasurement of outcome
- Sample bias—probably greatest threat to case-control method
- Confounding bias—this is what clinical trial addresses most directly, Thomas et al, Marshall et al
- Statistical power and bias.
- Inadequate power: imprecision not the same as bias

Importance of Change, as Opposed to Long-term Level of Exposure

- Defined end points vs unlimited “mapping”
  - Nutritional Prevention of Cancer trial
  - ATBC trial: vitamin E and prostate cancer
- What can be studied by clinical trial
- Expense of prevention clinical trials
  - WHI: 800M
  - PPT: 40M
  - SELECT: 180-140M
  - CALGB 70807 (MEAL): 2.5M (under-funding)

Design of Clinical Trials

- Randomization
- Blinding: single, double
  - Sclerotherapy trial
  - CALGB 70807 request to unblind
- Statistician blinding
- Behavior change: can't blind subjects: try to blind evaluators
  - Polyp Prevention Trial
  - WHI diet intervention
  - WHEL
  - CALGB 70807 (MEAL)

Analysis of Clinical Trial Data

Simple

Confounding addressed by study construction

Endpoints specified and limited in number: cure, response, partial response….

Confounding by smoking in Wheat Bran Fiber trial

Randomization ratio changed in Wheat Bran Fiber trial—experimental subject dropout

PPT: “I can’t have this…”

Event occurs or does not

Chemotherapeutic Trial as Model: Chemotherapeutic vs Chemoprevention Trials

Compliance, side effects:

SWOG 9917: Dr. Crawford
Crossover, effects: Dave Byar
Blinding:

Beta Carotene trials: orange skin
Wheat Bran fiber trial (Alberts et al, 2000, NEJM): weight of boxes
Olestra sucrose polyester: anecdotes (David Hunter) vs theater experiment

Threat
Likelihood of patient benefit
Human trial phases

Phase 1: safety, activity
Phase 2: activity against a specified biomarker
Phase 3: disease endpoint

Screening Trials

Shapiro et al: HIP study of mammographic screening.

Mandel et al: FOBT
David Thomas: BSE(Huge sample in low-risk region)
Observational epidemiologic evaluation of screening

Prognostic bias: patients who did well would have done better anyway.

Lead-time bias: you have caught the disease earlier in its course. You just gave them the bad news earlier.

Single pertinent criterion of effect: survival

Catching the disease earlier, disease-specific mortality.

Intent-To-Treat Analysis

Study population (population from which *sample* of subjects is selected). We study samples, in almost every case. If we are studying populations, we do not need sampling statistics, because we are not generalizing from sample to population.

Study Power

Higher risk, more likely outcome (up to 50%)= more power for small study

Schatzkin et al (NEJM 342, April 20, 2000: pp1149-55): adenoma study can be smaller, shorter

Marshall et al (Cancer Prev Research Nov 4, 2011) SWOG 9917: higher risk patients. Believed to be higher risk…PCa looking for a place to land…

Parsons et al CALGB 70807 patients at higher risk yet: Cancer patients, development of progressive disease. Unfolding understanding of clinical course

Small Percentage of Eligible Patients Who Participate in Trials

PPT: around 5%; samples selected from colonoscopy/pathology logs, letters sent by researchers or by drs.

SWOG 9917: to look at those whose second biopsy was negative…clinical protocol

MEAL: As of October 1, 2014: 370 randomized, 88 not eligible, 11 withdrew during run-in. No idea how many patients were approached by their doctors, declined to consider. Some doctors—no idea how many--declined to offer the trial to their patients.

Sample Size Determination: Feasibility, Plausibility, Clinically Meaningful Outcome: 5 Years, Generally, to Get answer

SWOG 9917: likelihood of 50% drop in progression to PCa.

MEAL: same likelihood issue, but likelihood of getting answer in reasonable time. And 50% drop would be “clinically meaningful”.

Multiple dose trial of MSC vs SEMET: early phase trial: outcomes preliminary to disease outcomes study—contract canceled to assess highest dose

Protocol Development: Protocol as The Rule Book, Must be Followed. Changes Possible, But Are a Big Deal

MEAL: timeline

Pilot study proposal and funding: 2006-7
First RO1 submission2009
Notice of Grant award 2010
Submission of protocol to CALGB 2010
CALGB approval 2011
Division of Cancer Prevention Approval 2012
Release to CALGB sites 2013
First patient randomized: 2014
Last patient randomized 2016

Eligibility, Ineligibility Spelled Out

Data collection, key data elements

Adverse events
Outcomes assessment

Adherence, exclusion of noncompliant subjects (PCPT: pre-rand compliance)

Stopping rules: PCPT (outcome achieved); SELECT (futility)

MEAL: DSMB allowed continuation

Compliance, Crossover

Study attrition: SWOG 9917; if no rise in PSA. MEAL: awaiting outcome

Protocol violation

Closeout, manuscript preparation

Data Analysis

Survival analysis: stat approach outline

Intent to treat
- WHI
- PPT
- WHEL, MEAL

Evaluation of additional endpoints
- Interaction assessment
- Prespecified
- Power

Multicenter Trials

PPT—agreement not to publish

PPT—Request to question subject diet prior to enrollment

Control: study homogeneity

Conflict of interest: PI wants study to “work”

Statisticians as guardians of the data

Robert Sandler, CALGB protocol on ASA and colorectal cancer: action of stat center

Obtaining funding: be at right place, at right time, with right idea…

MEAL

Window of legitimacy

Omenn: criticized for doing the trial when… "it is clear that beta carotene is protective…"

Spiral CT: "too late"

People can be awfully sure of what is "known", lack of knowledge notwithstanding. Prior to SELECT: suggestion that MDR for vitamin E should be 400 IU. In early 1994, way prior to PPT, WHI results coming out, NCI, AICR, were issuing dietary guidelines. It is one thing to lean on the best information we have, another to pretend it is accurate.

Thank You