Statistical Considerations in Study Development:
How to write good objectives!

Emily Van Meter, PhD
Assistant Professor, Division of Cancer Biostatistics
University of Kentucky Markey Cancer Center

UK Center for Clinical and Translational Science (CCTS)
Biostatistics, Epidemiology, and Research Design (BERD)
Pizza and Pilots
October 29, 2012
The process for statistical design and development

- Statistical considerations permeate both the design and analytic plan
- Requires interaction with your statistician

- *Really, we are here to make your life easier!!*

Portions of this presentation adapted from: Garrett-Mayer E, 2012 ASCO/AACR Clinical Cancer Research Methods Workshop
Statistical Considerations: 5 part process

I. Stating research aims
II. Determining your outcome measures
III. Choosing the experimental design
IV. The analytic plan
V. Sample size justification
Statistical Considerations: 5 part process

I. Stating research aims
II. Determining your outcome measures
III. Choosing the experimental design
IV. The analytic plan
V. Sample size justification
Research Aims: Always Starts with a Question!

- All studies will have multiple questions
  - Primary
  - Secondary
  - Exploratory

- The **primary** question drives the study design
  - Sample size
  - Study population
  - Study procedures
  - Data analysis

- More than whether A is “better” than B!!!
Basic Research Aims

• Common goals of any study:
  • Determine safety
  • Determine dosing/administration
  • Determine feasibility
  • Determine signal of efficacy
  • Determine efficacy
  • Determine clinical benefit

• However, the goals above are vague...

• SO how do we accomplish these things?!?!
1. Stating Research Aims

• Authors devised a protocol, beginning with research aims
• Aims should be concrete and include measurable outcomes
• Bad examples:
  – To evaluate the effect of flavopiridol on cancer
  – To see if flavopiridol improves cancer outcomes
  – To determine the safety profile of flavopiridol
• What is wrong with these aims?
  – what does “effect” mean? what kind of cancer, in what patients?
  – “Improves” compared to what? what is the outcome of interest?
  – what does “safety profile” mean?

• Think about how you are going to determine if this treatment works or not!!
1. Stating Research Aims

• Better examples:
  – **To evaluate the efficacy of flavopiridol** administered by two different schedules followed by ara-C and mitoxantrone in adults with newly diagnosed AML with poor-risk features
  – **To evaluate the toxicities** of flavopiridol administered by two different schedules followed by ara-C and mitoxantrone in adults with newly diagnosed AML with poor-risk features

• **Keywords for primary objective:**
  – determine, estimate, evaluate, describe, identify
  – efficacy, safety
Devising your aims

• Generally, there is ONE primary aim and your study is designed to address the primary aim

• Very often:
  – Phase I: primary aim is finding the “recommended” dose
  – Phase II: primary aim is determining if there is sufficient efficacy

• Secondary aims:
  – Important, but do NOT drive the design
  – Examples in Phase I:
    • describe pharmacokinetics
    • describe pharmacodynamic (e.g., methylation)
    • describe clinical responses
  – Examples in Phase II:
    • determine/describe/compare overall survival
    • describe safety
    • evaluate changes in biomarkers
Aims and Hypotheses

• Aims are often accompanied by hypotheses
• Stating the hypothesis to be tested can be a useful guide for the analytic plan:
• Examples of clinical research hypotheses:
  – The complete remission rate of patients in the *bolus infusion* arm will be at least 55%
  – The complete remission rate of patients in the *hybrid-bolus infusion* arm will be at least 55%
  – The median disease-free survival time across both arms will be at least 14 months
II. Determining your outcome measures

• The outcome measure will depend on the parameter of interest (Based on your aims!)
• Examples of possible parameters of interest in phase II:
  – response rate
  – complete remission rate
  – 6 month progression-free survival
• Synonyms: outcome, endpoints
• **Aim ≠ endpoint**
• What is an endpoint or outcome?
  – patient-level measure of “effect” of interest
  – measured on each patient in the study
  – it is QUANTIFIABLE
## Parameter of interest vs. outcome

<table>
<thead>
<tr>
<th>Parameter of interest</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate: proportion of patients with CR or PR</td>
<td>Response (CR or PR)</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>Time from enrollment to death (or last follow-up)</td>
</tr>
<tr>
<td>6 month overall survival</td>
<td>Time from enrollment to death (or last follow-up)</td>
</tr>
<tr>
<td>Successful completion of intervention</td>
<td>Proportion of subjects that took at least 90% of trial medication AND 90% of all required visits, etc</td>
</tr>
<tr>
<td>Mean change in quality of life</td>
<td>Difference in quality of life scores from baseline to follow-up</td>
</tr>
</tbody>
</table>
Q2: An investigator wrote a trial with the following primary aim:

To goal of this study is to define the presence or absence of malignancy in mediastinal lymph nodes of patients with known or suspected lung cancer, who undergo endobronchial ultrasound with fine needle aspiration for staging purposes.

Revised aim:

To goal of this study is to determine if there are factors that can predict the presence of malignancy in mediastinal lymph nodes of patients with known or suspected lung cancer, who undergo endobronchial ultrasound with fine needle aspiration for staging purposes.
An Ideal Endpoint

• Valid and reliable
• Easy to observe
• Free of Measurement Error
• Capable of being observed independent of the treatment assignment
• Clinically relevant
Ideal Endpoint differ by trial type

• Oncology Studies
  – Time to Event
    • Overall survival
    • Time to tumor progression
    • Time to relapse

• Cardiovascular Disease Trials
  – Total mortality
  – Non-fatal MI
  – Combined events

• Spinal Cord Injuries
  • ASIA (Motor and Sensory)
  • Functional Improvement
  • Pain Score
  • Time to movement
  • AIS
Endpoints by CT Phase

- **Phase I (Dose-finding, safety)**
  - Toxicity outcomes

- **Phase II (Hint of efficacy)**
  - RECIST Criteria
  - Percentage of patients w/ Complete, Partial Response, or Stable Disease
  - Surrogates Endpoint

- **Phase III (BIG Trial, Effectiveness, Clinical Benefit)**
  - Time to progression, overall survival, etc
Response Variables
(Often Phase II Endpoints)

• Potential Response Variables
  – mortality, death from a specific cause
  – incidence of a disease
  – a complication or specific adverse effect of disease
  – symptomatic relief
  – a clinical finding
  – a laboratory measurement
  – the cost and ease of administering the intervention
  – RECIST criteria – complete/partial response, stable/progressive disease

• In general, a single response variable should be identified to answer the primary question. If more than one are used, the probability of getting a nominally significant result by chance alone is increased!!!
Secondary and Subsidiary Questions

• Secondary Questions: the response variable is different from that in the primary question
  – Safety (often primary in phase I)
  – Quality of Life measures

• Subsidiary Questions: relates to subgroup hypothesis:
  (1) specified before data collection begins
  (2) based on reasonable expectations
  (3) limited in number!!!
Additional aims (correlatives, etc.)

• VERY important aims!
• Same principles apply for stating aims, determining outcomes, writing analytic plan
• Usually power/sample size is less of a concern for secondary aims
• “correlative” does not mean you can be vague!
  – these need to be well-conceived
  – often on biopsy tissue, pre post design
  – will you really learn anything?
  – Is it worth the time and effort?
Surrogate Endpoints

• An endpoint that is measured in place of the “true” or “final” biological or clinical outcome

• Expected to predict clinical benefit, lack of benefit, or harm

• **NO** surrogate for safety
Surrogate Endpoints

• A surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives.

• Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.
Surrogate Endpoints

• Examples of Surrogate/Outcome Pairs?
  – BP/MI for clinical hypertension
  – MRI/Relapse lesions for MS
  – PSA/Dx progression (time to event) for prostate cancer
  – Tumor growth/Mortality for cancer
  – Intraocular pressure/Vision loss for glaucoma
Why use surrogate endpoints?

- Can be measured earlier
- Easier and more convenient to measure
- Observed more frequently
- Less affected by other factors than the “true” endpoint
- True endpoint does not happen often, i.e. mortality or progression (depends on disease setting)
A Good Surrogate

• Strongly associated with the definitive outcome
• Part of the causal pathway
• Yield the same inference as the definitive endpoint
• Responsive to the treatment
• Short latency
III. Choosing the experimental design

• Based on the aims and the outcome, a design can be identified

• Other considerations
  – patient population
  – accrual limitations
  – previous experience with the treatment of interest in this or other populations
  – results from earlier phase studies
Types of Endpoints

- Continuous/Dichotomous
- Count, Ordinal
- Nominal
- Time to Event
- Composite or Global

- There are pros and cons to each type!!!
- Statistical analysis plans **COMPLETELY DEPEND** on type of endpoint!!!
Things to consider: Categorizing Data

• Attractive for descriptive purposes
• Impression that categorization makes it easier for clinical interpretation and avoids complex statistical assumptions... not really!
• Difficult to interpret across studies
• Loss of information, increased chance of misclassification error (correct cutpoint?)
• Loss of power - if there really is a difference to detect, categorized endpoints often require a larger sample size to be able to detect it
IV. Analytic Plan

• Do you want to compare?
• Do you want to estimate?
• Do you want to test a hypothesis?
• These questions, in regards to your stated aims, will determine your analytic plan
IV. Analytic Plan

• Depends on the design and the goals
• Example is a Phase II trial
  – single arm approach to analysis
  – compare to historical CR rate (e.g., 0.30)
• Phase I studies
  – often the analysis plan is descriptive
  – rare to see hypothesis testing (for primary aim)
• Phase III studies
  – head to head comparison of two groups
  – more common to see overall survival as the outcome of interest. (time to event methods are required)
V. Sample Size

- Must be based on primary objective!
- Also depends on the analytic plan...
  - Hypothesis testing?
  - Estimation?
Take home message...

• It is easy to write aims. It is more challenging to show that you can actually achieve your aims!

• Your aims (and corresponding outcome measurements) COMPLETELY drive the study design, statistical analysis plan, and sample size!

• So choose wisely! 😊
Feedback loop

- The process is actually not completely linear as stated
- Examples:
  - Design issues may cause you to change your outcome or restate your aim
  - Accrual limitations may cause you to change the design
- “Dynamic process”
How can we help you!?

• We can help turn your aims into feasible and appropriate endpoints!
  – Also assist with study design, analysis plans, sample size, etc

• BERD Core
  – Drs. Richard Kryscio, Heather Bush, Richard Charnigo, Emily Van Meter, Mary Kay Rayens

• Website:
  – [http://ccts.uky.edu/BERD/default.aspx](http://ccts.uky.edu/BERD/default.aspx)

• Email contact: Catherine Starnes
  – Catherine.starnes@uky.edu