What are the regulatory issues that impact endpoints for prevention trials?

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United Goal

• Development of safe and effective treatments for prevention/reduce the risk of acute graft versus host disease
Basis for NDA Approval

• Demonstration of efficacy with acceptable safety in adequate and well-controlled studies

• Ability to generate product labeling that
  – Defines an appropriate patient population for treatment with the drug
  – Provides adequate information to enable safe and effective use of the drug
Requirements for Drug Approval

- Safety (FDAC, 1938)
- Efficacy demonstrated in adequate and well controlled studies (1962)
NDA - Efficacy Requirement

- Regular approval
  - clinical benefit or established surrogate

- Accelerated Approval
  - uses a surrogate endpoint reasonably likely to predict clinical benefit
  - requires subsequent confirmation of benefit
Accelerated Approval
Regulatory Basis

- For serious or life-threatening diseases
- Where the drug appears to provide benefit over available therapy
- Approval based on a surrogate that is reasonably likely to predict clinical benefit
Accelerated Approval (continued)

• Subject to the requirement that the applicant verify and describe benefit
• Post-marketing studies would usually be underway
• The applicant shall carry out such studies with due diligence
Accelerated Approval

- Trial designs to demonstrate benefit over available therapy
  - In refractory settings: single arm trials
  - In available therapy settings: comparative trials

- Post-approval confirmation of benefit
  - related (less refractory) population
  - could use same trial/population (HIV example)
Evidence for Accelerated Approval

- **Substantial evidence** from well controlled clinical trials regarding a surrogate endpoint
- **NOT:** Borderline evidence regarding a clinical benefit endpoint
Clinical Benefit

• Improvement in quantity of life
• Improvement in quality of life
How many trials?

• Usually more than one trial is needed. **Substantial evidence:** “Adequate and well-controlled investigations”

• Sometimes a single trial may suffice.
  – FDAMA (1997) single trial plus other supportive evidence
  – 1998 FDA Effectiveness Guidance:
    • Multicenter trial
    • Statistically strong evidence
    • Important clinical benefit
    • Additional trials not ethical
Established Surrogates Supporting Regular Approval in OODP

• Disease-free survival (selected settings)
• Durable complete response rates in some settings (e.g., acute leukemia)
• Partial response rates in some settings (e.g., hormonal treatment of breast cancer)
Biomarkers

• Useful for diagnosis of disease, prognosis for outcome, predictive of response, or monitoring during therapy

• Useful for measure of disease process or the drug activity on disease process
Biomarkers continued

• As a study endpoint, the effect of the drug on the clinical endpoint is reliably predicted by the effect of the drug on the surrogate biomarker (Fleming TR, 2003)
“Prevention” Trials

• Link between putative mechanism of action and disease?

• Consider what you are really able to show (what does the agent really do)
  – sufficient evidence from non-clinical or early clinical testing?
“Prevention” Trials

• Randomized, double-blind if possible, comparator trials -- not single arm trials
  – Historical controls problematic
  – Need to provide patient and physician with an accurate understanding of risks and benefits
“Prevention” Trials continued

- Claim sought influences enrollment population
- Patient population
  - At risk (reasonably)
  - Well-defined
- Stratified randomization between treatment and placebo arms
- Balanced arms for known and unknown factors
“Prevention” Trials continued

• Endpoint is the prevention of the disease (not an aspect of disease)

• Endpoint chosen
  – what is known scientifically
  – study drug administration

• Absence of disease
  – Use established criteria if possible (or likely to be accepted by a majority)
  – If cannot double blind trial– consider blinded assessors
“Prevention” Trials continued

• Novel endpoints and development plans – FDA may get outside external consultants

• Statistical Analysis Plan
  – Well thought out ahead of time
  – Hierarchical testing for primary and secondary endpoints
  – Intention to Treat analysis

• One trial or more than one? – Supportive evidence
“Prevention” Trials

• Consider the impact of protocol amendments on outcome

• Ensure enrolled subjects are not taking part in another trial

• Adhere to established guidelines for clinical research (institutional and US government)
Relevant Guidances
http://www.fda.gov/opacom/morechoices/industry/guidedc.htm

• Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products
• Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics
• E6 Good Clinical Practice: Consolidated Guideline
• E8 General Considerations for Clinical Trials
• E9 Statistical Principles for Clinical Trials
• E10 Choice of Control Group and Related Issues in Clinical Trials
• Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (Draft)
• Formal Meetings With Sponsors and Applicants for PDUFA Products
Issues Regarding GVHD Prevention Trials

• What are the sources of heterogeneity in the transplant population that impact the risk of acute GVHD and how do we manage these?
• Are the diagnostic criteria for acute GVHD suitably established?
• How long should the patients be monitored for acute GVHD?
• What endpoints denote clinical benefit?
• What endpoints are reasonably likely to predict clinical benefit?
• How do we assess clinical benefit endpoints statistically in the face of competing risks?
Speakers for Morning Session

**GVHD Prevention Trial Design and Endpoints**
Paul Martin, MD, Fred Hutchinson Cancer Research Center, Seattle, WA
Mary Horowitz, MD, MPH, CIBMTR, Milwaukee, WI

**Statistical Considerations**
Eric Leifer, PhD, NHLBI, Office of Biostatistical Research, Bethesda, MD
Brent Logan, PhD, CIBMTR, Milwaukee, WI

**Biomarkers**
John Hansen, MD, PhD, Fred Hutchinson Cancer Research Center