Session 1: Complex Issues for Trial Design: Endpoints

Public Workshop on the Complex Issues in Developing Drug and Biological Products for Rare Diseases
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Discussion Questions 1 & 2

1. Discuss the role of information on the natural history of disease, effects of treatment, and patient benefits, in development of endpoints for clinical trials.

2. Discuss possible sources of information to characterize the natural history of disease and the effects of treatment.
Discussion Questions 3 & 4

3. Discuss what mechanisms and approaches could be utilized to facilitate endpoint development.

4. Discuss ways in which endpoint development efforts might be organized.
Clinical Endpoint

- A characteristic or variable that reflects how a patient feels, functions, or survives. Clinical endpoints are distinct measurements or analyses of disease characteristics observed in a study or a clinical trial that reflect the effect of a therapeutic intervention. Clinical endpoints are the most credible characteristics used in the assessment of the benefits and risks of a therapeutic intervention in randomized clinical trials.

Surrogate Endpoint

- A surrogate endpoint, or "marker," is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy.

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Attributes of Endpoints

• Should be clinically meaningful
• Should reflect how a patient feels, functions, or survives
• Should be reliably measured
• Showing an effect on the course of disease is dependent on
  - the disease and its manifestation(s)
  - the course of disease over time
  - what is being assessed and when assessed
  - the effect of the drug
Endpoint

• Well defined and reliable endpoints can help facilitate development of new drugs
  – Capture clinically meaningful effect(s) of the drug being studied
  – Impacts on key design elements for clinical trials
Endpoint Development & Improvement

- Approaches from the area of antibacterial drug development
- Understanding the natural history of disease
- Antibacterial drug therapy is standard of care for the treatment of patients with a number of different types of bacterial infections
- Approaches to understanding what the effect of treatment is on the course of disease – how does treatment change the natural history of untreated disease
Endpoint Development - Potential Resources - 1

- Published literature on the natural history of disease from the “pre-antibiotic” era
- Published trials from the time period when antibacterial drugs were first becoming available/studied evaluating antibacterial drug treatment vs. non-antibacterial drug treatment
  - Difference in more effective treatment over less effective treatment
- Information on what clinical effects are observed and when they occur
Endpoint Development - Potential Resources - 2

• Recent published literature on differences in clinical response in patients that inadvertently receive less effective or ineffective treatment for their disease

• Analysis of recently conducted clinical trials to evaluate patient response to treatment

• Prospective further development of an endpoint for a particular condition
Endpoint Development – Potential Mechanisms

Public-Private partnerships

• Foundations for the National Institutes of Health Biomarkers Consortium
  – participants from academia, industry, government to work on endpoint development for several conditions
  – provides a workspace to analyze and learn from previously conducted clinical trials
  – has made important contributions to endpoints for antibacterial drugs
Evaluating New Endpoints

• Use of existing information to inform endpoint selection and/or development

• Collaborative approach
  – Example of the FNIH biomarkers consortium
  – The work on endpoint development may be relevant to each of several different drug development programs

• If possible, consider piloting a new endpoint before entering into a phase 3 trial
  – Evaluate in a phase 2 trial
  – Evaluate using existing data
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