Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

- If sharing any data or information from these slides generated by the REiNS International Collaboration, please acknowledge the authors, group chairs, and specific working group.
- If using any information presented with a citation, please reference the primary source.

FDA Perspective: Approach to Rare Diseases and Use of Natural History Studies

REiNS Winter Meeting

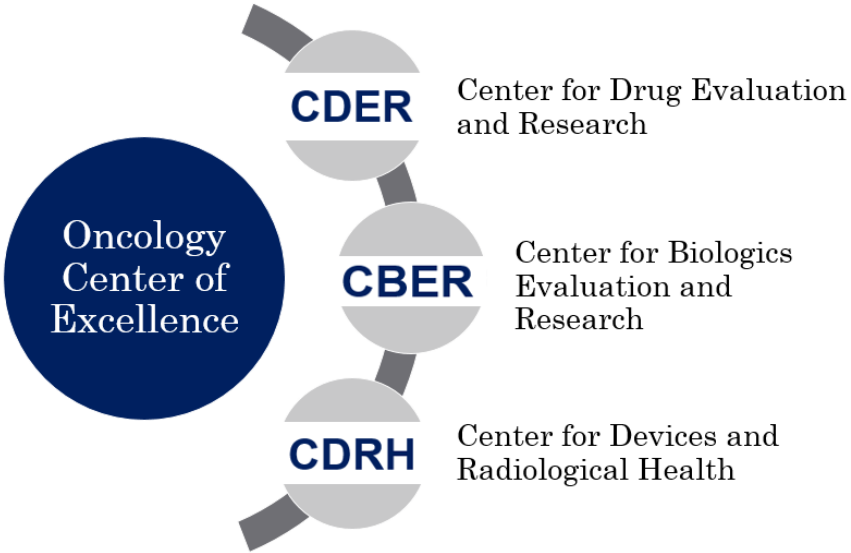
December 5, 2022

Diana Bradford, MD
Cross-Disciplinary Team Leader, Division of Oncology 2
Office of Oncologic Diseases (OOD)
Center for Drug Evaluation and Research (CDER)
U.S. Food & Drug Administration

Outline

- FDA Review of Rare & CNS Tumor Submissions
- Regulatory Requirements for Approval
- Natural History Studies and Considerations for Drug Development
- Opportunities for Formal Advice

Review of Rare Submissions



CDER Office of Oncologic Diseases: Clinical Divisions

– Clinical review teams includes Medical and Pediatric Oncologists, Neurologists, Neurosurgeons, Radiation Oncologists

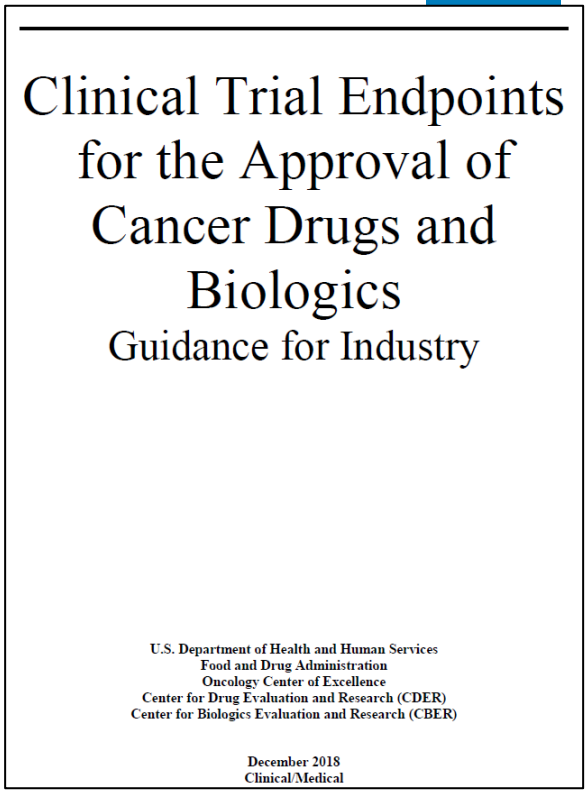
Requirements for Drug Approval

- Substantial evidence of effectiveness with acceptable safety in adequate and well-controlled studies
- FDA examines the evidence in the context of the disease, study design, endpoints selected, and strength of the evidence
- Ability to generate product labeling that:
  - Defines an appropriate patient population
  - Provides adequate information to enable safe and effective use

Federal Food, Drug, and Cosmetic Act, Section 505(d)

Clinical Trial Endpoints in Oncology

- Primary efficacy for **anti-cancer agents** is typically demonstrated by objective tumor measures or survival
  - For anti-cancer indications, mechanism of action is reduction or control of malignancy
  - Does the drug shrink or delay progression of an inexorably progressive cancer?
- Has the drug been shown to be **safe and effective**?
- Is the overall **benefit:risk assessment** favorable?


Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2018
Clinical/Medical

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics

Drug Approval in Rare Diseases

- Requirement for substantial evidence regardless of disease rarity
- Trial design, endpoint specific to disease
- Sufficient safety evaluation

Rare Diseases: Common Issues in Drug Development
Draft Guidance for Industry, February 2019

Potential Roles of Natural History Studies in Drug Development

- Patient selection
- Clinical outcome assessment selection
- Biomarker selection
- Use as external control

Rare Diseases: Natural History Studies for Drug Development Guidance for Industry
Draft Guidance for Industry, March 2019

Patient Selection

- Understand phenotypic/genotypic heterogeneity
- Identify sub-populations who may benefit from a given therapy

Clinical Outcome Assessment Selection

- Inform selection of traditional endpoint
- Inform identification of additional clinical outcomes assessments
  - Clinician-reported outcome
  - Observer-reported outcome
  - Patient-reported outcome
  - Performance outcome

Biomarker Identification

- Diagnostic
- Prognostic
- Predictive
- Guide patient selection

External Controls

Context for Use

- Feasibility Challenges
- Ethical Concerns
- Questionable Equipoise

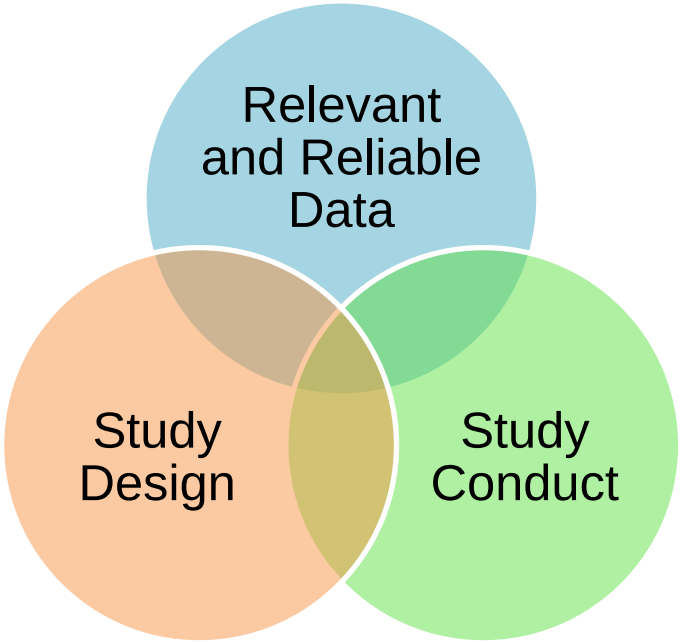
Potential Applications

- Pediatrics
- Rare Diseases
- Significant unmet medical need
- Molecular subgroups
- Underrepresented populations

Potential Regulatory Objective for External Controlled Designs

What are the primary purposes for use of an external control?

- As benchmark, baseline, or natural history study [**epidemiology**]
- As individual patient-level matched data for formal comparative study [**effectiveness**]



Challenges for External Controls

Concern for bias in absence of randomization

- External control needs to be similar to treated group
- Evolution in disease definition, diagnosis, treatment and monitoring over time
  - e.g., evolution in definition of brain tumors diagnoses with WHO criteria
- Well-defined and reliable outcome assessments
- Data collection (i.e., intervals and quality)

Rare Diseases: Natural History Studies for Drug Development Guidance for Industry
Draft Guidance for Industry, March 2019

Appropriateness of External Control Design

May be appropriate when…

1) Natural history of disease well-defined
2) External control population similar to treatment group
3) Concomitant treatments that affect the primary endpoint not substantially different between external control and trial
4) Results provide compelling evidence of a change in established progression of disease

Design Considerations

- ✓ Trial design alone does not determine whether evidence is sufficient to establish substantial evidence of effectiveness
- ✓ Poor execution can render a trial of any design to be not adequate or not well-controlled and unable to provide substantial evidence of effectiveness

FDA guidance for industry, *Rare Diseases: Common Issues in Drug Development* (2019)

Opportunities for FDA Advice

- Formal Meetings with Review Divisions
  - Associated with an IND / drug development program (Types A – D)
    - New: Type D meeting with shorter timeline on focused set of issues
  - New: Initial Targeted Engagement for Regulatory Advice (INTERACT) – intended to facilitate IND-enabling efforts, when there is a novel, challenging issue
- Critical Path Innovation Meetings (CPIM)

Recently Published RWE Guidances

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Draft Guidance for Industry, September 2021

Data Standards for Drug and Biological Product Submissions Containing Real-World Data

Draft Guidance for Industry, October 2021

Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry

Draft Guidance for Industry, November 2021

Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products

Draft Guidance for Industry, December 2021

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products

Guidance for Industry, September 2022

Select FDA Guidances Relevant to Externally Controlled Studies

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

Draft Guidance for Industry, December 2019

Rare Diseases: Natural History Studies for Drug Development Guidance for Industry

Draft Guidance for Industry, March 2019

Rare Diseases: Common Issues in Drug Development

Draft Guidance for Industry, February 2019

Acknowledgements

- Catherine Lerro
- Donna Rivera
- Elizabeth Duke
- Harpreet Singh
- Paul Kluetz
- Rick Pazdur


FDA
U.S. FOOD & DRUG
ADMINISTRATION

BACK-UP

External Control Characteristics

***Selected* characteristics of the disease setting that should be met for EC use**

Characteristic
1. The natural history of disease is **well defined**
2. EC population is **very similar** to treatment group
3. Concomitant treatments that affect the primary endpoint are **not substantially** different
4. Evidence of change in the established progression of disease (e.g. **tumor shrinkage**)

FDA guidance for industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,* (2019) and *Rare Diseases: Common Issues in Drug Development* (2019)

Data must be Fit-for-Purpose

Relevance

includes the availability of key ***data elements*** (exposure, outcomes, covariates) and sufficient numbers of representative patients

Reliability

includes data ***accuracy***, **completeness. provenance,** and ***traceability***

TTE should be evaluated in randomized studies

- ECs can have reliability and interpretability challenges
- Apparent differences in outcome may arise from factors other than the investigational drug
- Randomized studies minimize the effect of known and unknown differences between populations

FDA Guidance, Clinical study Endpoints for the Approval of Cancer Drugs and Biologics (December 2018)