

# **Symptoms as Outcome Measures in Cancer Clinical Trials**

## **FDA Perspective**

Edwin Rock, MD, PhD  
Medical Officer  
Division of Drug Oncology Products

# Cancer Drug Approval Endpoints

Historical Order	When Introduced	Effect Measured	Benefit Measured	Need for Blinding
Tumor Shrinkage	1950s	Drug	Surrogate	No
Overall Survival	1980s	Drug plus natural history	Direct	No
Symptom Palliation	1980s	Drug in disease setting	Direct	Yes
Time to Event (PFS, TTP)	1990s	Drug plus natural history	Surrogate	Yes

# Endpoint Model → Conceptual Framework

## ➤ Endpoint model

- Identifies appropriate endpoint concepts
- Relates such concepts to one another
- Points to appropriate trial designs to support claims

## ➤ Conceptual framework

- Defines each endpoint measure
- Maps items of measurement to domains of interest
- May evolve in an iterative process of validation

# Example: Primary Brain Tumors

- January 2006 AACR/FDA/NCI Public Workshop: Clinical Trial Endpoints in Primary Brain Tumors

## Nature of Benefit

## Measured Concepts / Domains

Absence of tumor

MRI Imaging

Physical Function

PRO: activities of daily living

Neurologic Function

Standardized neurologic exam

Cognitive Function

- Learning/memory
- Speech
- Executive functions

Potential Confounders

Steroid Use

# PROs in Cancer Drug Approvals: 1995-2004

<b>Product</b>	<b>Year</b>	<b>Domains</b>	<b>N</b>
Photofrin	1995	Dysphagia	1
Gemzar	1996	Pain/PS/Weight	2
Novantrone	1996	Pain	1
Topotecan	1998	Symptoms (9)	1
Amifostine	1999	Xerostomia	1
Palifermin	2004	Mucositis	1

# Summary and Discussion

- Benefit → Claim → Endpoint Model → Conceptual Framework
  - Guidance addresses medical product development, not other settings
  - Conceptual development requires patient input
  - Documentation of content validity is a review issue
  - Measurement properties hinge on content validity
- Study Design → Data Analysis → Interpretation Issues
  - Blinding and randomization
  - Multiplicity and likelihood of false positive errors
  - Missing data and the risk of biased results
  - Mean vs. responder analyses