Symptoms as Outcome Measures in Cancer Clinical Trials

FDA Perspective

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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

Product	Year	Domains	N
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