Supporting Product Label Claims in Drug Development: A Framework for Integrating Patient Reported Outcomes and Health Economic Concepts and Endpoints

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Objective
To introduce, define and differentiate between conceptual models, endpoint models and conceptual frameworks, and to discuss how they fit together in the context of supporting product claims in drug development.

In addition, to explore the potential added benefit of including health economic concepts and endpoints within the same framework.

Background
- Conceptual models, endpoint models and conceptual frameworks are research tools used by PRO researchers.
- There is a lack of understanding regarding their definition and utilisation.
- The FDA draft guidance suggests that for successful treatment benefit claims using PRO endpoint models and conceptual frameworks are essential components of the dossier.

Conceptual Model
- A conceptual model:
  - Clearly defines the outcomes of interest and their interrelationships and possible determinants.
  - Provides the rationale for and specification of the PRO outcomes of interest in the population of interest for a particular decision to be made.
  - In the context of FDA regulatory decision-making, a conceptual model identifies and describes the PRO concepts and hypotheses that underlie a PRO-based labelling claim.
- Why develop a conceptual model?
  - Provide the rationale for and specification of the PRO endpoints.
  - Focus groups/interview data.
  - In the current FDA environment the labelling of a domain has to be meaningful with respect to all of the items within the domain and this has to make sense in the endpoint model and the wording of the claim.

Hypothetical Conceptual Model for Alcohol Dependency

Endpoint Model
- Early in product development sponsors are encouraged to identify all measurement concepts (PRO and non-PRO) that may be appropriate for endpoint definition.
- The endpoint model:
  - Ties together natural history, treatment goals, and the instruments intended to demonstrate treatment benefit.
  - Specifies the hierarchy and hypothesized relationships among all treatment benefit endpoints.
  - Describes measurable concepts of a specific disease state, including the spectrum of both prominent symptoms and expected clinical course.
  - Additional treatment-specific concepts relevant to the patient population are incorporated.
  - Why develop an endpoint model?
    - To facilitate communication with the FDA a preliminary endpoint model can be developed.
    - The endpoint model provides a context to show how multiple end points fit together to support the primary hypothesis in a clinical study supporting product approval.
    - When to develop an endpoint model?
      - Recommend development at pre-phase II.
      - Revised through life-cycle of product development.

Proposed Simplified Endpoint Model for Alcohol Dependency Reduction Drug X

Conceptual Frameworks
- Alternatively referred to as a content map/measurement model.
- Maps the expected relationships of items within a domain and of domains within a PRO concept.
- Specifies how items in an instrument fit together in a domain and how domains fit together in a total score (as appropriate).

Development
- Literature review.
- Focus groups/interview data.
- Timing
  - It is developed during the development of the PRO and validated during the process of psychometric validation.

Validation
- Assess measurement properties.
- Inform how many items are grouped together in sub-domains.
- Scale development without a priori thought about domain structure can be problematic.
- In the current FDA environment the labelling of a domain has to be meaningful with respect to all of the items within the domain and this has to make sense in the endpoint model and the wording of the claim.

Interrelationships between Conceptual Models, Endpoint Models and Conceptual Frameworks including Economic Evaluation

Conclusion
Each of the models discussed are useful in supporting product claims in drug development, and from a PRO perspective endpoint models and conceptual frameworks are essential.

From a health economics perspective, employing a similar framework encourages scientific rigour, facilitates communication, and could help design of appropriate data collection in clinical trials.