ISPOR Educational Symposium

Tuesday, May 6, 2008

1:30PM-2:30PM

Obtaining a Patient-Reported Outcomes Label Claim: What Evidence Do You Need?

Moderator: **Sheri Fehnel PhD**, Global Head, Patient-Reported Outcomes, RTI Health Solutions, Research Triangle Park, NC, USA

WHAT IS A PRO LABEL CLAIM AND WHAT EVIDENCE DO YOU NEED?
Speaker: **Kati Copley-Merriman MS, MBA**, Global Head, Outcomes Research and Regulatory Strategy, RTI Health Solutions, Ann Arbor, MI, USA

PRO EVIDENCE TO SUPPORT LABEL CLAIMS
Speaker: **Julie Chandler PhD**, Senior Director, Epidemiology, Merck Research Laboratories, Blue Bell, PA, USA

CONCEPTUAL FRAMEWORK AND ENDPOINT MODELS TO SUPPORT LABEL CLAIMS
Speaker: **Diane Wild MS**, Director, Patient-Reported Outcomes, Oxford Outcomes Oxford, UK

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Questions or Comments? Please contact Kati Copley-Merriman at kcmerriman@rti.org.

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What is a Patient-Reported Outcome (PRO) Label Claim and What Evidence Do You Need to Support a PRO Claim?

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Topics

1. Background on Patient-Reported Outcome Label Claims
2. How to Get a Claim: What Evidence Do You Need?
   - Claim Language
   - Trial Design- Endpoints and Analysis Plan
   - Validated PRO Data Collection Instrument and Measurement Strategy

US Food and Drug Administration (FDA) Definition of a PRO

A PRO is a measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's response by a physician or anyone else)

- PRO
  - Element of feeling or function affected by disease
  - Reported directly by patients
- PRO instrument/measure
  - A tool for measuring function or feeling
- PRO concept
  - Notion of treatment benefit that is the goal of measurement
  - May be simple or complex
  - PRO ≠ a concept
  - Quality of life (QOL): weak concept for medical product development
  - Health-related quality of life (HRQL): multidomain concept representing patient's overall perception of the impact of a condition and its treatment

FDA (Laurie Burke, et al.). Patient-reported outcome instruments: overview and comments on the FDA Draft Guidance. Presented at the DIA 42nd Annual Meeting. Jun 2006.

What is a Product Label Claim?

- Statement or implication of treatment benefit that appears in any section of a product's FDA-approved labeling.
- Requires substantial evidence by regulation.
- PROs may relate to safety or efficacy claims.
- PRO claims normally appear in the Clinical Studies section of the Product Label.

Labeling or Advertising Claims

- Labeling (approved claims)
  - Indications must be in the label
  - Other information of clinical significance
  - Relevance for prescribing decision
  - Could be in the Product and/or Patient Label
  - The FDA decides (approves)
- Advertising (permitted claims)
  - Meet advertising substantiation and disclosure requirements
  - Must be consistent with and not contrary to Label
  - Company decides, the FDA reviews

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Claim Structure

- The claim language usually describes:
  - Trial Results
  - PRO endpoint measured
  - Comparator
  - Specific population for the claim
  - The instrument used is often included (e.g., "as measured by X [PRO instrument])

Example: Lotronex Label- 3/10/2006

- Clinical Studies Section:

Note: The pivotal trials were done in non-constipated women with IBS meeting ROME Criteria for 6 months.

- *"Compared with placebo, 10% to 19% more women with diarrhea-predominant IBS who received LOTRONEX had adequate relief of IBS abdominal pain and discomfort during each month of the study"*

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Orencia: December 2005 (Bristol-Myers Squibb)

Rheumatoid Arthritis Trials – Clinical Studies Section

Physical Function Response and Health-Related Outcomes

- **Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI). In Studies II-V, ORENCIA demonstrated greater improvement from baseline than placebo in the HAQ-DI....**During the open-label period of Study II, **the improvement in physical function has been maintained for up to 3 years.**
- Health-related quality of life was assessed by the SF-36 questionnaire 4 at 6 months in Studies II, III, and IV and at 12 months in Studies II and III. **In these studies, improvement was observed in the ORENCIA group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS).**

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Recent PRO Label Claims
Chantix: May 2006 (Pfizer)

Smoking Cessation: Clinical Studies Section

Urge to Smoke

- Based on responses to the Brief Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal scale "Urge to Smoke" item, CHANTIX **reduced urge to smoke compared to placebo in all studies.**

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Cymbalta: February 2007 (Eli Lilly)

Generalized Anxiety Disorder – Clinical Studies Section

Extent Emotional Symptoms Disrupt Functioning

- In all three studies, Cymbalta demonstrated superiority over placebo as measured by greater improvement in the Hamilton Anxiety Scale (HAM–A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score. **The SDS is a widely used and well-validated scale that measures the extent emotional symptoms disrupt patient functioning in the following three life domains: work/school, social life/leisure activities, and family life/home responsibilities.**
- Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

VERAMYST: April 2007 (GlaxoSmithKline)

Seasonal Allergic Rhinitis Trials – Clinical Studies Section

Rhinoconjunctivitis Overall Quality of Life (RQLQ)

- ...For the RQLQ in all three seasonal allergic rhinitis trials, VERAMYST Nasal Spray 110 mcg demonstrated **greater decrease from baseline in the overall RQLQ than placebo, and the difference from placebo was statistically significant.** The difference in the overall RQLQ score mean change from baseline between the groups treated with VERAMYST Nasal Spray and placebo ranged from -0.60 to -0.70 in the three trials, **meeting the minimally important difference criterion.**

VERAMYST (cont'd)

Perennial Allergic Rhinitis Trials – Clinical Studies Section

Rhinoconjunctivitis Overall Quality of Life (RQLQ)

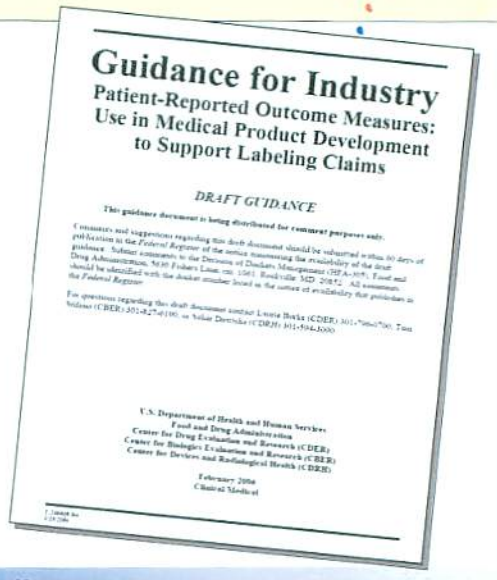
- ....However, unlike the trials in patients with seasonal allergic rhinitis, **patients with perennial allergic rhinitis who were treated with VERAMYST Nasal Spray 110 mcg did not demonstrate statistically significant improvement from baseline in total ocular symptom scores (rTOSS) or in disease-specific QOL as measured by the RQLQ compared with placebo.** In addition, the **overall RQLQ score mean change from baseline difference between the group treated with VERAMYST Nasal Spray and the placebo group was -0.23, which did not meet the minimally important difference of ≥ 0.5.**

Topic 2: How to Get a Claim: What Evidence Do You Need to Support a PRO Claim?

- General Process
- Evidence Elements
  - Claim Language
  - Trial Design- Endpoints and Analysis Plan
  - Validated PRO Data Collection Instrument and Measurement Strategy

How to Get a Label Claim

- PRO Guidance: Published February 2, 2006, in draft as a level 1 guidance according to the FDA's Good Guidance Practices



Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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

February 2006
Clinical Medical

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Substantial Evidence: FDA Act 505

- Adequate and well-controlled investigations…
- By experts qualified to evaluate therapy effectiveness…
- Can be concluded that the drug has the effect it purports…
- Under the conditions of use, prescribed, or recommended in the label.

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General Process to Prepare for Obtaining a Label Claim

- Understand the impact of the disease on patients
- Start with the desired claims
- Develop with patient input
- Integrate with the clinical program
- Validate with clinical trial experience
- Get FDA buy-in early

Elements of PRO Evidence Needed

- **Claim specification** (in the context of the PRO, disease/condition, population, treatment)
- **Endpoint model** (specific to the protocol)
- **Conceptual framework** (for the PRO)
- **Instrument development** (item generation with patient input, item reduction, and scoring methods justified)
- **Instrument validation** (validity, reliability, internal consistency, responsiveness to change)
- **Interpretation of scores** (benchmark change scores)
- **Translation process and questionnaire administration**
- **Data analysis plan** (integrated with primary endpoint analysis plan, plan for multiple comparison adjustment)

Endpoint Structure

- Distinguish the:
  - Concept/outcome one is attempting to measure (e.g., decrease in pain intensity),
  - From the instrument (10-cm VAS from M-BPI) used to make the measurement,
  - From the endpoint used in the statistical analysis plan (e.g., change over a certain time interval in pain intensity)
  - For responder analysis, the response criteria should be defined and justified (e.g. change in score which = response)

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Instrument Development: Identify Concepts and Develop Conceptual Framework

Identify concepts and domains that are important to patients.
Determine intended population and research application.
Hypothesize expected relationships among concepts.

II Create Instrument

Generate items.
Choose administration method, recall period, and response scales.
Draft instructions.
Format instrument.
Draft procedures for scoring and administration.
Pilot test draft instrument.
Refine instrument and procedures.

III Assess Measurement Properties

Assess score reliability, validity, and ability to detect change.
Evaluate administrative and respondent burden. Add, delete, or revise items.
Identify meaningful differences in scores. Finalize instrument formats, scoring, procedures, and training materials.

IV Modify Instrument

Change concepts measured, populations studied, research application, response options, recall period, or method of administration.

From Guidance for Industry, Feb 2006

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Small Changes in an Instrument That May Affect Measurement Properties

- Change in instructions or format
- Administration of only a subset of items/domains
- Administration in combination with new items/domains (e.g., new composite)
- Change in scoring algorithm
- Change in recall period
- Applied to new patient population
- Never before applied to clinical trial

NOTE: Existing instruments may need further validation due to development issues or population application.

FDA. Presented at the DIA Workshop on Assessing Treatment Impact Using PROs, Paris, France. May 2004.

Translation Issues in Clinical Trials

- More non–United States trials and more PROs increase translation issues; More mixed populations within a country (e.g. Latino and Asian in U.S.)
  - Concept varies by population
    - Normal
    - Severity
  - Diagnosis varies by population
    - Endometriosis
    - Depression
    - Obesity
  - Language limitations, particularly in the expression of feelings

General Statistical Considerations

- Design and analysis considerations
  - Same as for any other endpoint
  - Multiplicity considerations
  - Consistency with study objectives
  - Missing data considerations
  - Interpretation of findings
    - Analysis of means
    - Analysis of proportions (of responders)

FDA (Laurie Burke, et al.). Patient-reported outcome instruments: overview and comments on the FDA Draft Guidance. Presented at the DIA 42nd Annual Meeting. Jun 2006.

Interpretability

- Minimum important difference (MID)
  - Interpretation will be based on MID, Effect Size, p-values, etc. depending on the type of analysis
  - Provides confidence in the treatment benefit (e.g. a statistical significance found meets a minimal threshold for a clinically meaningful difference to the patient)
  - Based on mean population changes
- Responder Analysis
  - Defines a treatment benefit for a patient (minimal score change for improvement)
  - Can use traditional statistics to compare responder rates between groups (p-values)

Plan for Multiplicity Issues

- Integration of all assessments according to a planned procedure
  - Win on both clinician assessment and PRO?
  - Win on objective measure first, then PRO?
  - Closed testing procedure?
- Include all endpoints that might constitute a claim (and that exclude exploratory endpoints)
- Don't duplicate data collection by asking the same question in multiple questionnaires

Tips

- Industry and CROs are finding FDA requirements for instrument development and validation to be very strict
  - Consider the entire trial design and population- not just the instrument selection
  - Positive psychometric properties do not trump patient input even for well-established instruments
  - Recall period should be as short as possible

Ultimate Goal: Promotional Claim

Do you suffer from fibromyalgia? The real, widespread pain condition that also makes daily activities difficult. Well, until recently, there were no medicines approved by the FDA specifically for the management of fibromyalgia. Today there's prescription Lyrica (LEER-I-kah). The first and only FDA-approved treatment that can help relieve the pain associated with fibromyalgia and **can help improve function.** So if you have fibromyalgia, ask your doctor about the first and only FDA-approved treatment by name. Lyrica.

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PRO EVIDENCE TO SUPPORT LABEL CLAIMS

Strategy for Assembling a PRO Evidence Dossier

ISPOR

Toronto, May 6, 2008

Julie Chandler, PhD
Senior Director, Epidemiology, Merck and Co, Inc
Chair, PRO subcommittee, PhRMA HOTG
in collaboration with
Laurie Burke, SEALD, FDA

FDA/Industry Interactions regarding PRO use for label claims

DRAFT PRO Guidance: Development/Validation components needed to support PRO use in labeling

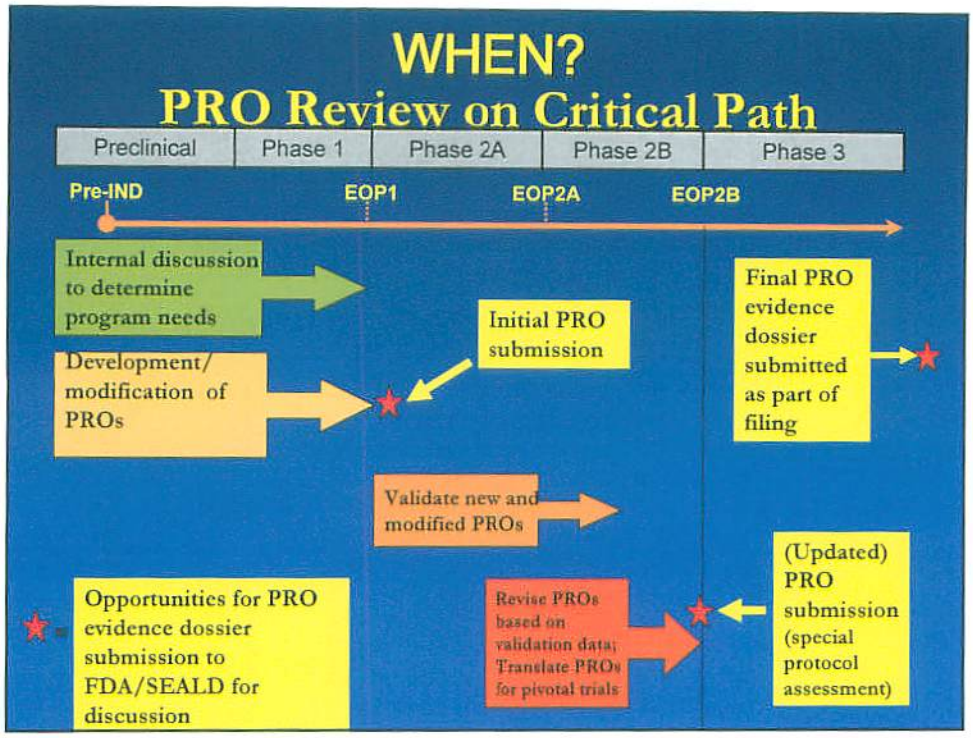
Recommendation: 'early' contact with Review Division/ SEALD to discuss adequacy of PRO validation

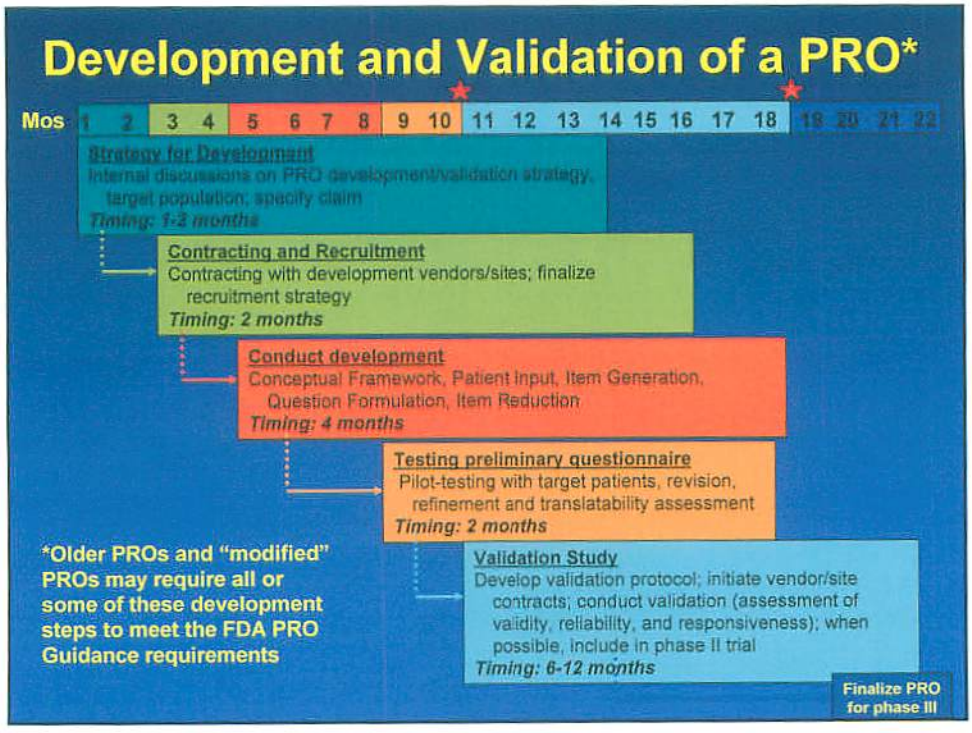
NEED Submit PRO evidence dossier for review by FDA/ SEALD

When? To enter PRO discussions With FDA

What? Elements to include in evidence dossier

How? To organize the elements


WHEN?
PRO Review on Critical Path
Preclinical
Phase 1
Phase 2A
Phase 2B
Phase 3
Pre-IND
EOP1
EOP2A
EOP2B
Internal discussion to determine program needs
Development/ modification of PROs
Initial PRO submission
Final PRO evidence dossier submitted as part of filing
Validate new and modified PROs
(Updated) PRO submission (special protocol assessment)
Revise PROs based on validation data; Translate PROs for pivotal trials
Opportunities for PRO evidence dossier submission to FDA/SEALD for discussion


Development and Validation of a PRO*
Mos 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Strategy for Development
Internal discussions on PRO development/validation strategy, target population, specify claim
Timing: 1-3 months
Contracting and Recruitment
Contracting with development vendors/sites; finalize recruitment strategy
Timing: 2 months
Conduct development
Conceptual Framework, Patient Input, Item Generation, Question Formulation, Item Reduction
Timing: 4 months
Testing preliminary questionnaire
Pilot-testing with target patients, revision, refinement and translatability assessment
Timing: 2 months
Validation Study
Develop validation protocol; initiate vendor/site contracts; conduct validation (assessment of validity, reliability, and responsiveness); when possible, include in phase II trial
Timing: 6-12 months
*Older PROs and "modified" PROs may require all or some of these development steps to meet the FDA PRO Guidance requirements
Finalize PRO for phase III

WHAT?

PRO Evidence Dossier: Key Elements

- Proposed claim based on the PRO
- Endpoint Model (endpoint relationships- *PRO, non-PRO)*
- Rationale for PRO selection
- Description of the conceptual framework
- PRO Development
  - content validity, patient input early in D/V process
  - Scoring, recall period
  - construct validity and measurement properties
  - Mode of administration, translation
- Statistical Analysis Plan
- References
- Appendices
  - Instrument, User Manual, Target Product Profile

HOW?

Template for PRO Evidence Dossier submissions

Standard organizational structure for critical PRO information to support labeling

Increase efficiency of providing relevant PRO information to FDA Review Division /SEALD

Increase efficiency of FDA/SEALD review of PRO information

PRO Evidence Dossier: Principles

1. Extent of background information provided depends upon the PRO instrument
2. Some sections may be less relevant for a particular PRO instrument application, or less complete for early discussions; subsequent submissions should be completed on same template
3. When submitted electronically, place PRO Evidence Dossier in section 5.3.5.3 of The Electronic Common Technical Document (eCTD)
4. PRO evidence dossiers can contain more than 1 PRO; Include all PROS in trial program

PRO Evidence Dossier: Table of Contents

1. Dossier Objective
   - 1.1 Claim structure
2. Endpoint Model
   - 2.1 Efficacy Endpoint Model
   - 2.2 Endpoint Relationships
3. Rationale for Instrument selection
4. Conceptual Framework
5. Development of PRO
   - 5.1 Content validity
   - 5.2 Scoring of instrument
   - 5.3 Recall Period
   - 5.4 Psychometric Properties
   - 5.5 Interpretation of Scores
   - 5.6 Mode of PRO administration
   - 5.7 Translation/Cultural Adaptation
6. Statistical Analysis Plan
7. References

Appendix A: Instrument
- -proposed instrument
- -prior versions, if relevant

Appendix B: User Manual

Appendix C: Target Product Profile

Appendix D: Other, as needed

PRO Evidence Dossier: Table of Contents (>1 PRO)

1. **Dossier Objective**
   1.1 Claim structure
2. **Endpoint Model**
   2.1 Efficacy Endpoint Model
   2.2 Endpoint Relationships
3. **Rationale for Instrument selection**
   3.1 Instrument X
   3.2 Instrument Y
4. **Conceptual Framework**
   4.1 Instrument X
   4.2 Instrument Y
5. **Development of PRO**
   5.1 Instrument X
      5.1.1 Content validity X
      5.1.2 Scoring instrument X
      5.1.3 Recall Period X ....
   5.2 Instrument Y
      5.2.1 Content validity Y
      5.2.2 Scoring instrument Y
      5.2.3 Recall Period Y....

6. Statistical Analysis Plan
7. References

Appendix A: Instrument
- -proposed instrument X
- -prior versions X, if relevant
- -proposed instrument Y
- -prior versions Y, if relevant

Appendix B: User Manual
- - User manual X
- - User manual Y

Appendix C: Target Product Profile
Appendix D: Other, as needed

1. Dossier Objective

1.1 Claim Structure
- – Language targeted by PRO instruments
- – Specific disease/condition/symptoms
- – Intended population
- – Treatment benefit

2. Endpoint Model

2.1 Efficacy Endpoint Model
- Hierarchy of all PRO, non-PRO endpoints intended to support claims

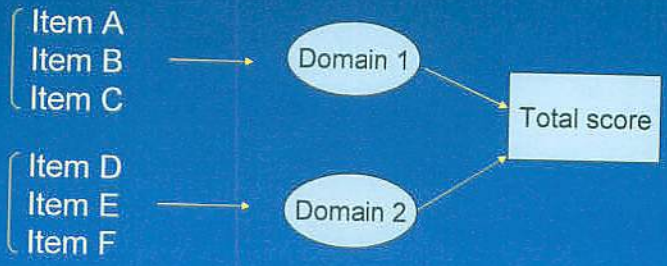
2.2 Endpoint Relationships
- Relationships (known and hypothesized) between PRO, non-PRO endpoints

3. Rationale for PRO instrument Selection

4. Conceptual Framework

- Diagram of PRO instrument conceptual framework showing relationship of items to domains and domains to total score

E.g.



- Conceptual framework should correspond to study endpoint concept(s) proposed as labeling claim(s)

5. Development of PRO Instrument

5.1 Content validity
- items, response options relevant, understandable, clinically important, important to patients, complete
- Qualitative study protocols, interview guides
- Item tracking matrix
- Evidence of saturation

5.2 Scoring of Instrument

5.3 Recall Period

5.4 Psychometric Properties
- Construct validity, reliability, responsiveness

5.5 Interpretation of scores
- Responder definition
- Method for benchmarking change

5.6 Mode of PRO administration
- Patient v. interviewer, paper v. e-format

5.7 Translation/Cultural Adaptation
- Translation of PRO
- Harmonization, expert review process
- Cognitive debriefing
- Qualifications of those who completed translations /cultural adaptation

6. Statistical Analysis Plan:

PRO-specific plans related to data analysis plans for:

- multiplicity adjustment
- missing data
- between group differences, e.g. cumulative distribution function

7. References

APPENDIX A: Instrument

- Proposed instrument, including instructions
- Prior version(s) of instrument (if relevant)

APPENDIX B: User Manual

- Timing, method, mode of administration
- Scoring Algorithm
- Training method, materials used for questionnaire administration
  - Patient training
  - Investigator training
  - Other training

APPENDIX C: Target Product Profile*

- Include specific labeling targets
  - (e.g. disease/condition with stage, severity, or category, if relevant)
- Intended population
  - (e.g. age group, gender, other demographics)

*** Draft Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool**
http://www.fda.gov/cder/guidance/6910dft.pdf

Summary: PRO Evidence Dossier

- **When** to engage FDA/SEALD in PRO discussions ?
  - Ideal: early in development (end of Phase 1) and pre-Phase III
- **What** to include?
  - Key elements of PRO Guidance, as relevant
- **How** to assemble?
  - Template provides consistent and efficient structure for submission and review of evidence through course of PRO development

Conceptual Models, Endpoint Models and Conceptual Frameworks to Support Label Claims

Diane Wild, MSc
Director, Oxford Outcomes

Oxford Outcomes

Topics

- Conceptual models
- Endpoint models
- Conceptual frameworks

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Conceptual Models

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Conceptual Model:Definitions

- '…a taxonomy of patient outcomes according to the underlying health concepts they represent and proposes specific causal relationships between different health concepts'

  Wilson and Cleary, JAMA, 1995

- 'Provides the rationale for and specification of the PROs of interest in the population of interest that will result in a specific treatment decision'

  Rothman et al, Value in Health, 2007

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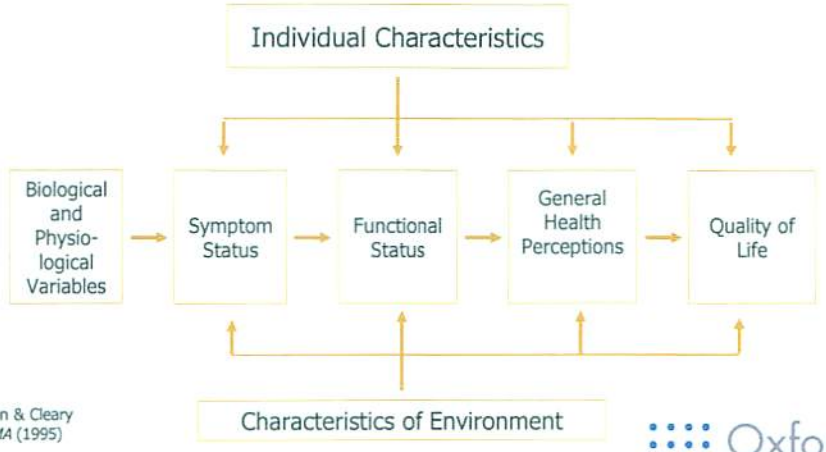
Conceptual Model Example (I)

- *Integrates biological and psychological aspects of health outcomes*
- *5 Level continuum of increasing biological, social and psychological complexity*



Wilson & Cleary
JAMA (1995)

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Why Develop a Conceptual Model?

- Explore a disease area
- Identify potential treatment benefits
- Guide the selection of endpoints and outcome measures

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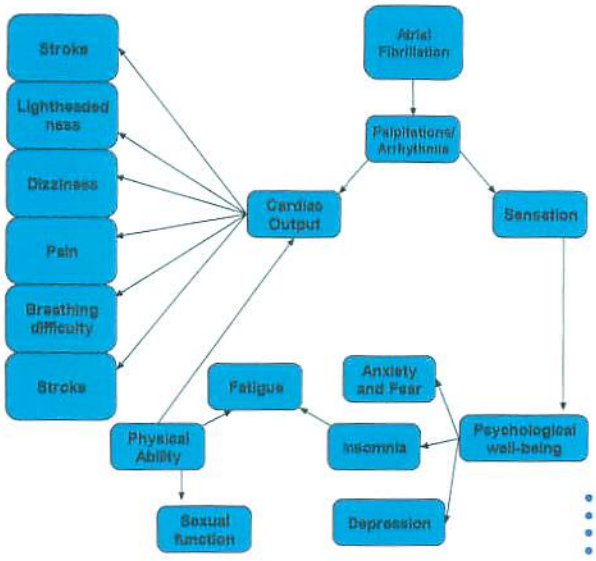
Conceptual Model Example (II): Atrial Fibrillation



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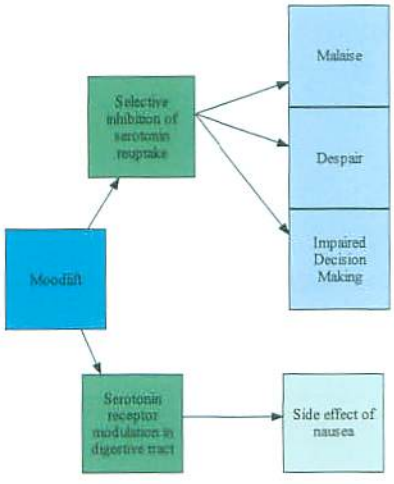
Conceptual Model Example (III): Product Claim Analysis (Rothman et al 2007)



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Methods

- Development
  - Literature review
  - Interviews with patients and clinicians
  - Primary quantitative data
- Validation
  - Patient interviews/focus groups
  - Clinician review
  - Psychometric validation

Oxford Outcomes

Endpoint Models

Oxford Outcomes

Endpoint model - Definition

- A representation of the relationships between all measures that may be defined as endpoints (primary or supportive) in a clinical trial or validation study....

  Burke 2006

- Describes how the end points in a study are expected to interact and justifies the need for their assessment

  Rothman et al, Value in Health, 2007

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Endpoint Model: Description

- Identifies all measurement concepts (PRO and non PRO) that may be appropriate endpoints
- Specifies the hierarchy and hypothesizes relationships among all treatment benefit endpoints

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Endpoint Model: Description

- Ties together natural history, treatment goals and the measures intended to measure treatment benefit
- Provides context to show how multiple endpoints fit together to support the trial hypotheses

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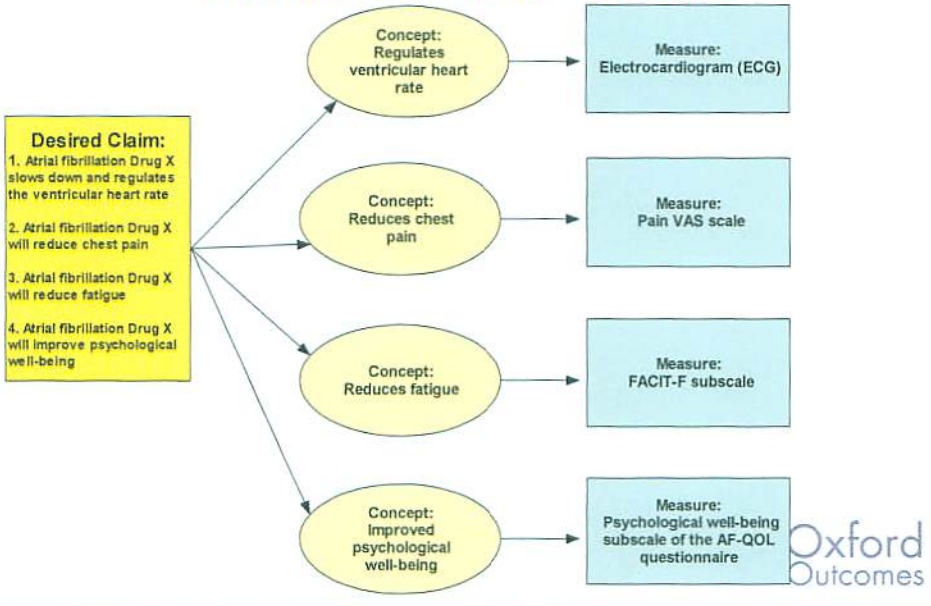
Simplified Endpoint Model: Treatment for Arterial Fibrillation



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Example Endpoint Model: Head and Neck Cancer

Concept/ Outcome	Measurement Tool	Endpoint	Hierarchy for Drug Approval*
Longer life	Date of death	Overall survival from baseline	1
Absence of disease progression	Radiographic and clinical assessments	Progression free survival from baseline	1
Clinician-reported function	Karnofsky Performance Status scale	Change from baseline to XX timepoint (TBD) in Clinician-rated performance status score	2
Patient-reported function	Swallowing diary	Change from baseline to XX timepoint (TBD) in Swallowing diary score	2
Patient-reported symptoms	Conversation diary	Change from baseline to XX timepoint (TBD) in Conversation diary score	2
Patient-reported function	Daily activities diary	Change from baseline to XX timepoint (TBD) in Daily activities measure score	2

*1 = By itself sufficient; 2 = If overall survival and progression-free survival are not in the wrong direction, acceptable as a component of a time-to-event progression metric with swallowing, speaking, and activities. Patrick et al 2007.

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Methods

- Systematic/comprehensive review of disease literature
- Clinical experts
- Clinical development team
- Conceptual model
- Target Product Profile (TPP)

Oxford Outcomes

Conceptual Frameworks

Oxford Outcomes

Conceptual Framework - Definition

- The diagram of relationships between the questionnaire items in a PRO and the concepts represented by items and represented as scores (Rothman et al 2007)

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Methods

- Development
  - Literature review
  - Focus groups/interview data
- Timing
  - Development of a PRO and validated during the process of psychometric validation
- Validation
  - EFA and CFA and SEM to confirm hypothesized conceptual framework

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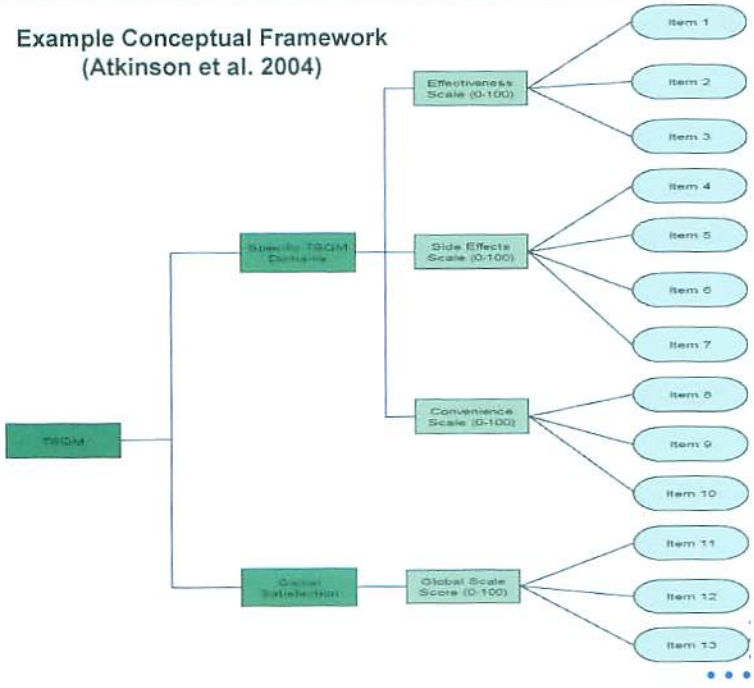
Example Conceptual Framework (Atkinson et al. 2004)



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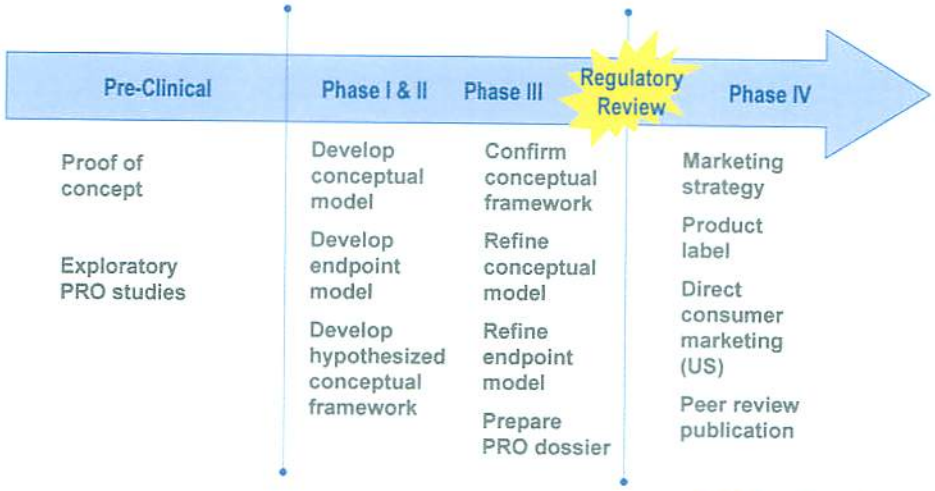
PRO Strategic Planning



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Conclusions

- Conceptual models:
  - Useful tools in PRO research for labelling claims and for broader use
  - Can be developed as early endpoint models
- Conceptual frameworks:
  - Need to be consistent with endpoint model and targeted claim
- Conceptual and endpoint model should be developed early in the drug development process

Oxford Outcomes

References

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