Patient Reported Outcomes

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Engaging with payers and physicians to support market access
The Goal of Development Program

- Provide added benefit for patients in terms of how they live their lives
  - Improved survival
  - Improved function in daily lives
  - Decreased symptoms

- Too much regulatory focus → possibility of missed opportunities
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PRO data can make all the difference

Hemoglobin A1c levels are not particularly meaningful to patients more interested in heading of hypoglycemia events. Panel votes to approve . . . and view that a hypoglycemia benefit was not shown.

Sue Sutter, Afrezza review shows need for patient driven endpoints in diabetes, The Pink Sheet, 1 April 2014
PRO data can make all the difference

“It was a secondary endpoint, but in our mind this is why we gave the application full approval. One could quibble about the importance of reduction in spleen size, but with reduction in all the symptoms, full approval was warranted”

Erin McCallister & Steve Usdin, A PROfessional trial, BIO Century, Dec. 5 2011
What is a Patient-Reported Outcome?

- A measurement of any aspect of a patient’s health status that comes directly from the patient without interpretation from anyone else
  - Can range from symptom frequency, duration, or severity to more complex issues of health-related quality of life, activities of daily living, etc.
  - Can be assessed through direct self-report or interview administration
  - Measured through individual items, subscales, or full questionnaires administered via electronic (e.g. handheld diary, IVRS, tablet) or paper/pencil format

Value of Patient-Reported Outcomes (PRO)

- Some treatment effects known only to patient
- Physiologic endpoints may not be the best predictors of treatment benefit
  - Sometimes poor correlations between objective and PRO measures (i.e., FEV1 and asthma symptoms; exercise capacity and activities of daily living) suggest we are capturing unique information
- Translate the patient's voice into scientific and commercial messages
- Better quantify how products benefit patients
- Compete on the basis of something other than price alone
- Improve medical outcomes from the patient's point of view
PROs and Related Measures

Clinical outcome assessments (COAs) measure a patient’s symptoms, overall mental state, or the effects of a disease or condition on how the patient functions.


- **Performance task outcome (PerfO)**
  - Defined task / quantification of performance is measurement (e.g., distance walked in 6 minutes)

- **Clinician-reported outcome (ClinRO)**
  - Assessment of patient’s health status based on clinician observation, reporting and / or interpretation

- **Observer-reported outcome (ObsRO)**
  - Observable concepts assessed by another person (e.g., a caregiver) when patient unable to self-report

- **Patient-reported outcome (PRO)**
  - Measurement based on a report that comes directly from the patient related to his/her health condition
Patient-Reported Outcomes Allow a Holistic View of Treatment Effects

Assessing disease activity and treatment outcomes

Physiological
- Biomarkers
  - Lab values & tests
  - Functional tests
  - Blood tests
  - Biopsies
  - Tolerance tests
  - Vital signs

Clinician
- Signs
  - Physical examination
  - Visual inspection
  - Palpation
  - Auscultation
  - Clinical impression

Patient
- Experience
  - Symptoms
  - Activity tolerance
  - Cognitive function
  - Physical function
  - Psych distress
  - Rx satisfaction

Caregiver
- Experience
  - Symptoms
  - Activity limitations
  - Cognitive function
  - Physical function
  - Psych distress
  - Burden

“Subjectivity”
## Common Types of Patient-Reported Outcome Measures

<table>
<thead>
<tr>
<th>Type of PRO Measure</th>
<th>Example Coverage/Domains</th>
<th>PRO Measures</th>
</tr>
</thead>
</table>
| **Symptoms**        | • Pain  
                      • Fatigue  
                      • Wheezing  
                      • Depression | 0 – 10 numeric rating scale  
                      Fatigue Severity Scale  
                      Asthma Symptom Diary  
                      Beck Depression Inventory |
| **Functioning**     | • Emotional functioning  
                      • Productivity  
                      • Activities of daily living | Hospital Anxiety and Depression Scale  
                      Work Productivity and Activity Impairment Questionnaire  
                      Katz ADL |
| **Health status**   | • Multiple domains of functioning | SF-36  
                      Sheehan Disability Scale |
| **Health-related quality of life** | • Impact of health on a patient’s subjective sense of well-being | Cystic Fibrosis QoL Questionnaire |
| **Treatment satisfaction** | • Satisfaction with medication | Treatment Satisfaction Questionnaire for Medication |
| **Utility**         | • Health status for the purpose of computing QALYs | EQ-5D |
Patient-Reported Concepts of Interest
Proximal to Distal Impacts on Treatment Benefit

Disease-defining concepts

Proximal disease impact concepts

Distal disease impact concepts

Disease impact on general life concepts

Core signs, symptoms

Related functioning

Related Signs/ Symptoms

Additional functioning

Additional Signs/ Symptoms

General psychological functioning

General physical functioning

Social functioning

Productivity

Health status

Health-related quality of life

Satisfaction with health
Two General Types of Patient-Reported Outcome Measures

- **Generic PRO measures**
  - Designed to be used by any population
  - Intended to cover a broad aspect of the concept being measured
  - Can be used to compare one population to another or to compare scores in a specific population to normative scores

- **Disease-specific PRO measures**
  - Designed to assess concerns that are most important for a given population
  - May be more sensitive and therefore more likely to detect differences and changes in scores when they occur in response to interventions
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Example of Each Questionnaire Type

Your Health in General

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully, and mark an X in the one box that best describes your answer. Thank you for completing this survey!

1. In general, would you say your health is:

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
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<td>□</td>
</tr>
</tbody>
</table>

2. Compared to one year ago, how would you rate your health in general now?

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
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</tbody>
</table>

Generic

Disease-Specific

Patient Reported Indices of Multiple Sclerosis (PRIMUS) - Activities

Please read this carefully. This booklet asks about your experience of having MS. Please follow carefully the instructions for each section and choose the response that best applies to you.

Please describe your ability to do each of the 15 activities listed below during the last week - without the use of aids (for example: cane, walker, wheelchair) or assistance.

Please mark only one box # for each activity.

Were you able to ... | Able to do on own without difficulty | Able to do on own with difficulty | Unable to do on own

1. ... do light jobs around the house or garden
2. ... do heavy jobs around the house or garden
3. ... get out of bed
4. ... get dressed
5. ... rise from sitting
6. ... stand for a short time
7. ... walk around inside the house (not including using the stairs)
8. ... walk short distances outside the house
9. ... walk longer distances
10. ... carry heavy items
11. ... climb a flight of stairs
12. ... bathe (includes hand bath, bath or shower)
13. ... dry yourself thoroughly after bathing (includes hand bath, bath or shower)
14. ... prepare food
15. ... shop for groceries
## Generic vs. Disease-Specific Instruments

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Generic          | • Investigators and other key stakeholders (e.g., clinicians) may be familiar with instrument  
                    • Competitors may have used instrument in their trials  
                    • Can be used to compare one population to another or to compare scores in a specific population to normative scores | • May miss important aspects of experience  
                    • More likely to ask questions that are irrelevant to group under study  
                    • Potential to alienate respondents  
                    • Greater potential for missing data  
                    • Generally less sensitive to treatment effects |
| Disease-specific | • Highly relevant to patient group under study  
                    • Content more likely to cover all important aspects of patients’ experience  
                    • Less like to pose irrelevant questions  
                    • Respondents feel that their experience is valued  
                    • Reduced potential for missing data  
                    • Likely to have greater responsiveness | • Where new instruments are needed, they may be time consuming and costly to develop  
                    • Key stakeholders may be unfamiliar with new instruments |
What is a Label Claim?

- Statement or implication of treatment benefit
  - Evidence that the treatment has a positive impact on a concept of interest
    - How a patient feels or *functions* in daily life
    - How long a patient *survives*
  - May relate to safety or efficacy
Cough Suppression

Heroin was commercially developed by Bayer Pharmaceutical and was marketed by Bayer and other companies (c. 1900) for several medicinal uses including cough suppression.
The Pope approved!

In addition to endorsements from celebrities, physicians, and scientists, Pope Leo XIII also endorsed the popular product for its beneficial effects.
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Can you open this?

Fasten this?

Still having trouble with everyday things?

Maybe it’s time for a change in treatment.

ORENCIA is an RA treatment that works differently. It’s a prescription medication used to treat adults with moderate to severe RA who have not been helped enough by other medications for RA. It’s been shown to:

- Relieve the pain, swelling, and fatigue of RA
- Control the advance of joint damage
- Help improve physical and emotional health-related quality of life
Fran’s ADHD symptoms weren’t controlled during her day. She had trouble focusing and finishing her work.

In a clinical study of adults with ADHD, once daily Vyvanse significantly improved symptoms of inattention (e.g. lack of focus), hyperactivity, and impulsivity within one week.
What Constitutes a Label Claim in the US?

- May appear in any section of a product’s FDA-approved labeling
  - Typically appears in the Indication or Clinical Studies section of the product label
  - May appear in product advertising
- Requires substantial evidence by regulation

PROs appearing in the label can be used for promotion
Guidance for the industry

- Draft PRO Guidance: published December 2006
- Final FDA PRO Guidance: published December 2009
- Guidance developed by the SEALD group within the Office of New Drugs (OND) at FDA
- SEALD serves as an advisory group to all reviewing divisions

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

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)

December 2009
Clinical/Medical
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Regulatory challenges

A Review of Patient-Reported Outcome Labels in the United States: 2006 to 2010
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1Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 2RTI Health Solutions, Durham, NC, USA

ABSTRACT

Reasons for Rejection of Patient-Reported Outcome Label Claims: A Compilation Based on a Review of Patient-Reported Outcome Use among New Molecular Entities and Biologic License Applications, 2006–2010
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ABSTRACT

Objectives: Previous analyses of patient-reported outcome (PRO) label claims concentrated only on successful label claims. The goal of this research was to explore the reasons why PRO label claims were denied, and to compile regulatory feedback regarding the use of PROs in clinical trials. Methods: By using the Food and Drug Administration’s Drug Approval Report Web page, all new molecular entities and biologic license applications approved between 2006 and 2010 included PROs in the clinical trials supporting their approval, yet this rate is not regulatory guidance to support more widespread use of PROs in clinical trials. There were 158 PRO label claims in the clinical trials, and the reason for rejection was only mentioned for 31%. Results: Of the 158 PRO label claims, 31% were unrelated to the drug’s use, 24% were concerns with the reliability of the PROs, 15% were related to patient populations, 12% were related to the PRO instruments, and 6% were related to the PRO interpretation. Conclusion: These results underscore the need for further research on PROs in clinical trials to improve their reliability and validity, and to ensure that PROs are used in a manner that is meaningful and relevant to patients.

Patient-Reported Outcomes
Assessment of PRO Label Claims Granted by the FDA as Compared to the EMA (2006–2010)
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ABSTRACT

Background: The US Food and Drug Administration (FDA) provides formal guidance for the use of patient-reported outcomes (PROs) in clinical trials. Few (≤12%) were granted the same label claims. Despite this, FDA-granted claims were more likely to include higher order concepts. Few (≤12%) were granted the same label claims. Despite this, FDA-granted claims were more likely to include higher order concepts.
Four important takeaways . . .

- Sign and symptoms are the most likely candidates for PRO labels
- PRO labels are more likely for primary endpoints
- There are noticeable differences between the FDA and EMA
- Regulatory agencies are not the sole guardians of patients’ voice
Patient reported outcomes

- Enable sponsors to understand what matters to the patient
- Enables stakeholders to evaluate new technologies in a holistic manner
That’s all Folks!