RTI HEALTH SOLUTIONS®

Date

Patient Reported Outcomes

Presented by: Ari Gnanasakthy
RTI Health Solutions
9th Feb 2015

Engaging with payers and physicians to support market access

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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

Patrick D. Aging in Motion. March 28, 2014.

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.

afrezza

Sue Sutter, Afreeza 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

Source: FDA Guidance, 2009. http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf.

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

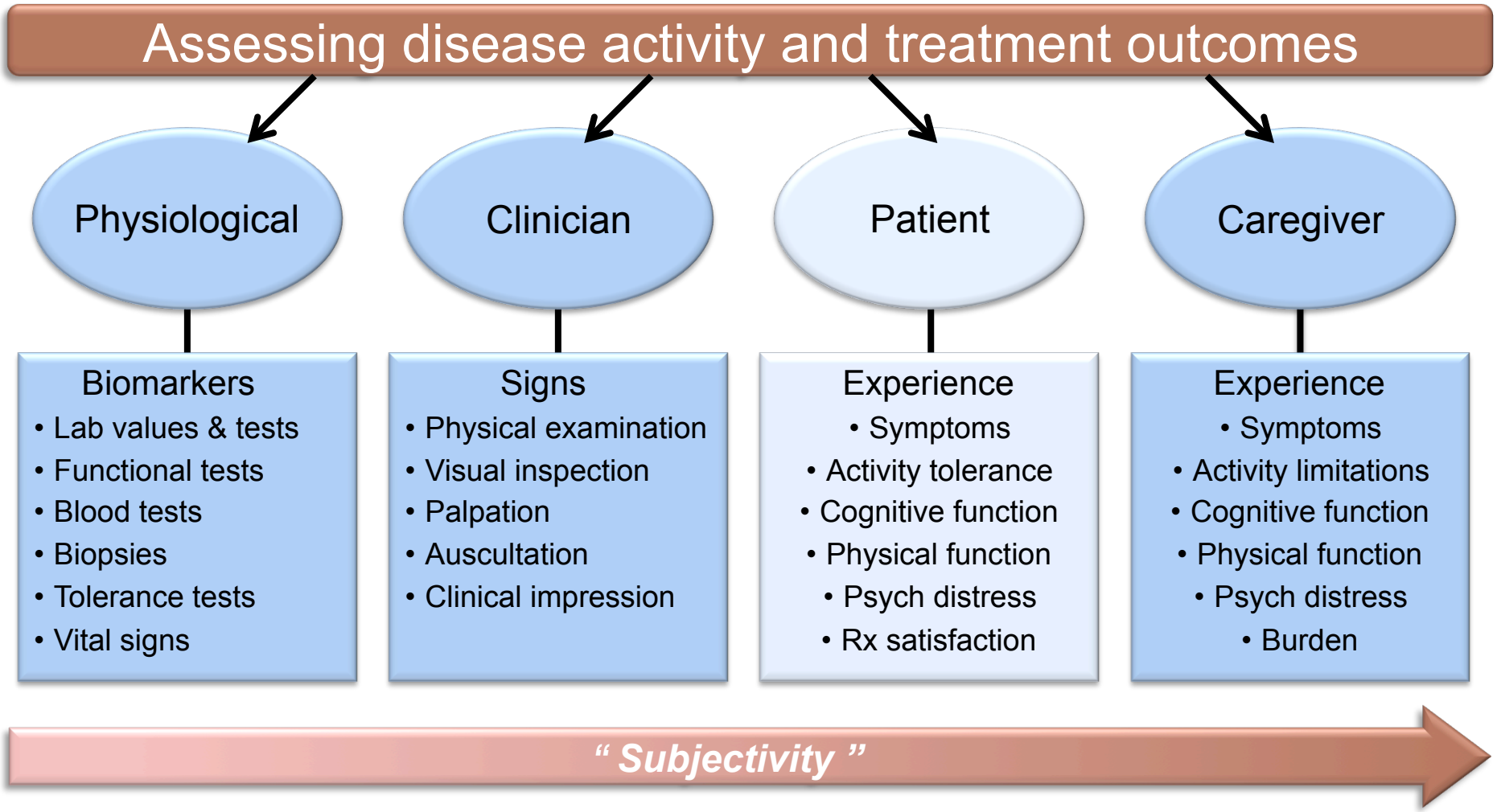
PROs and Related Measures

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

FDA http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm

Performance task outcome (PerfO)	Clinician-reported outcome (ClinRO)	Observer-reported outcome (ObsRO)	Patient-reported outcome (PRO)
Defined task / quantification of performance is measurement (e.g., distance walked in 6 minutes)	Assessment of patient's health status based on clinician observation, reporting and / or interpretation	Observable concepts assessed by another person (e.g., a caregiver) when patient unable to self-report	Measurement based on a report that comes directly from the patient related to his/her health condition

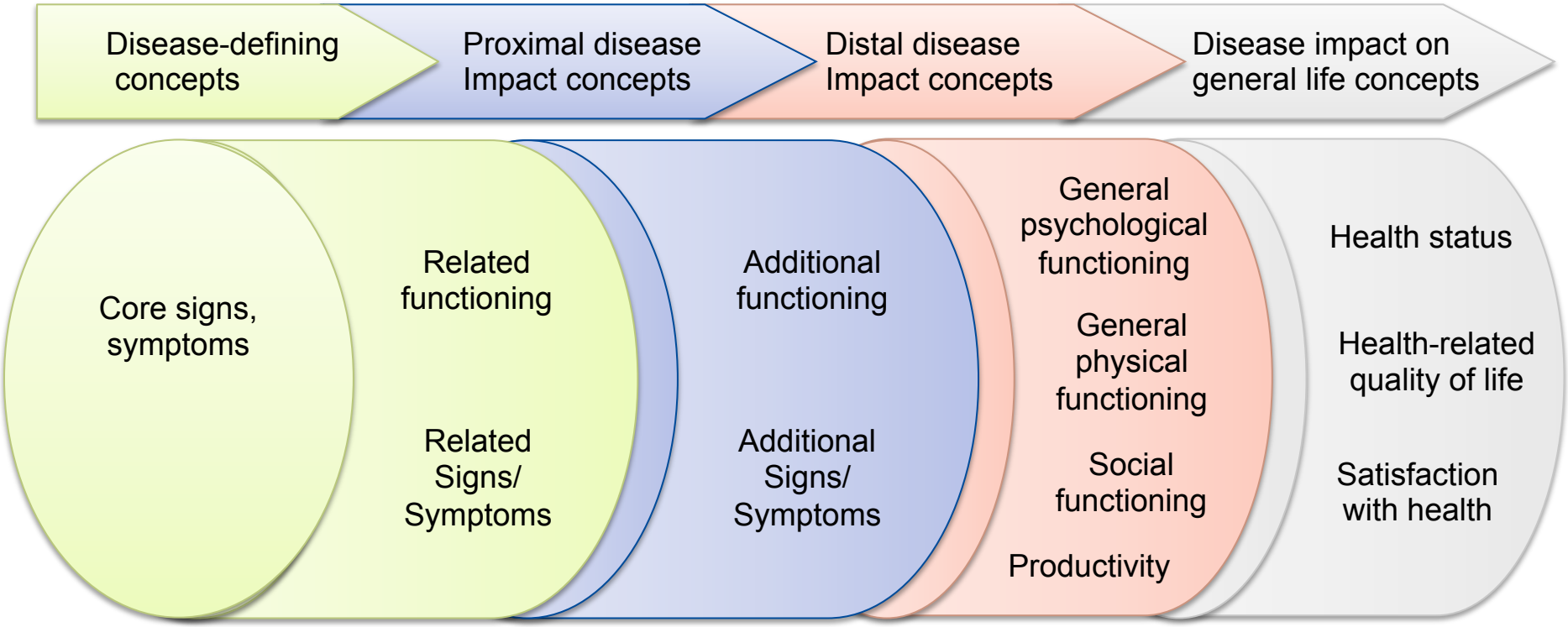
Patient-Reported Outcomes Allow a Holistic View of Treatment Effects



Common Types of Patient-Reported Outcome Measures

Type of PRO Measure	Example Coverage/Domains	PRO Measures
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

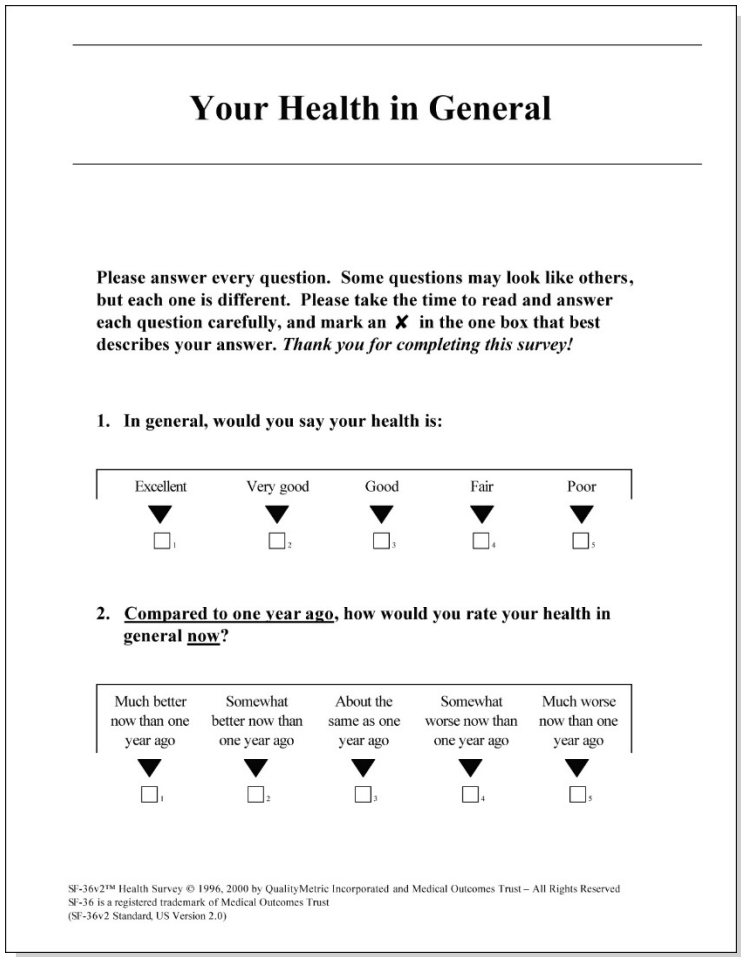


Two General Types of Patient-Reported Outcome Measures

- 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

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 ✘ in the one box that best describes your answer. ***Thank you for completing this survey!***

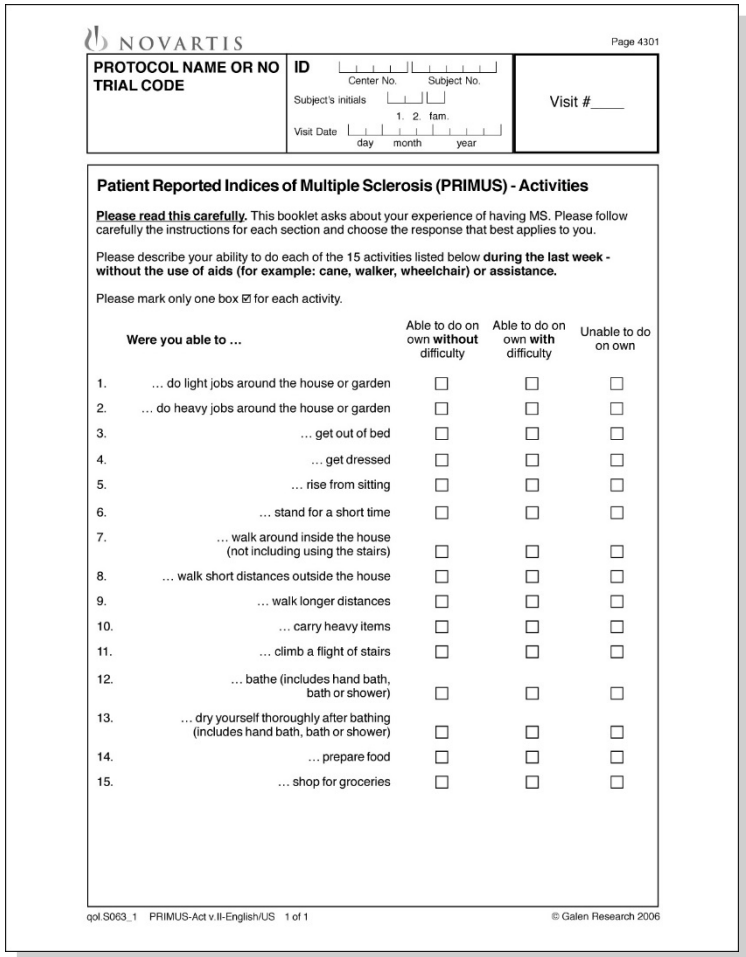
1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Generic



NOVARTIS

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PROTOCOL NAME OR NO TRIAL CODE	ID (Center No. / Subject No.) Subject's initials (1. 2. fam.) Visit Date (day / month / year)	Visit #____

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	☐	☐	☐

qol.S063_1 PRIMUS-Act v.II-English/US 1 of 1

Disease-Specific

Generic vs. Disease-Specific Instruments

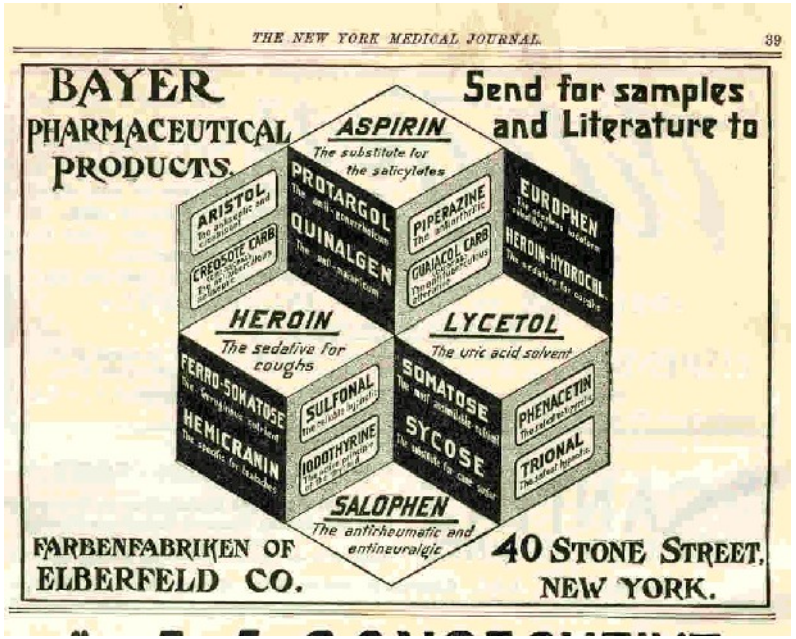
Instrument	Advantages	Disadvantages
Generic	• Investigators and other key stakeholders (e.g., clinicians) may be familiar with instrument • Competitors may have used instrument in their trials • Can be used to compare one population to another or to compare scores in a specific population to normative 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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Wherever you go, carry PHILLIPS' TABLETS
"ON THE SPOT" RELIEF FROM UPSET STOMACH
PHILLIPS' MILK OF MAGNESIA 30 TABLETS 30
FAST RELIEF FROM UPSET STOMACH INDIGESTION HEARTBURN
Wherever you go, upset stomach, gas, heartburn or other symptoms of acid indigestion are liable to cause distress. So for on-the-spot relief carry delightfully flavored Phillips' Tablets with you. Phillips' Tablets will make you feel better—*almost instantly*—because they contain one of the world's *fastest* antacids. Pack several pocket-size tins—as well as a bottle of 75 or 200 tablets—in your suitcase!
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Easy To Swallow!
No Ill Effects!
PRUNES
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SEND NO MONEY
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will be yours if you will
"Pull the Cords"
Gives the Flesh the Resiliency and Freshness of Youth
Prevents Double Chins
Effaces Double Chins
Reduces Enlarged Glands
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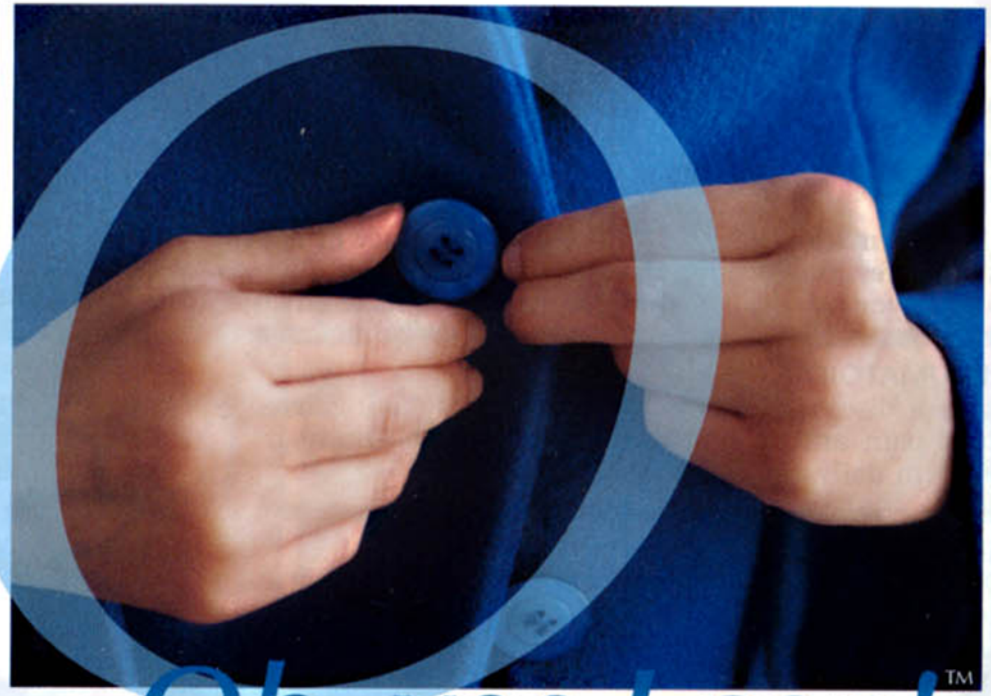
Chin Reducer
and
Beautifier
The only mechanism producing a concentrated, continuous massage of the chin and neck, dispelling flabbiness of the neck and throat, restoring a rounded contour to thin, scrawny necks and faces, bringing a natural, healthy color to the cheeks, effacing lines and wrinkles. Price only $10. What better investment could be made? Sent postpaid immediately.
Free Booklet
—giving valuable information on how to treat double chin and enhance facial beauty will be sent on request. Write at once to
Prof. Eugene Mack
507 Fifth Ave. Suite 1004 New York

Can you open this?

Fasten this?



Oh, yes I can!™

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.

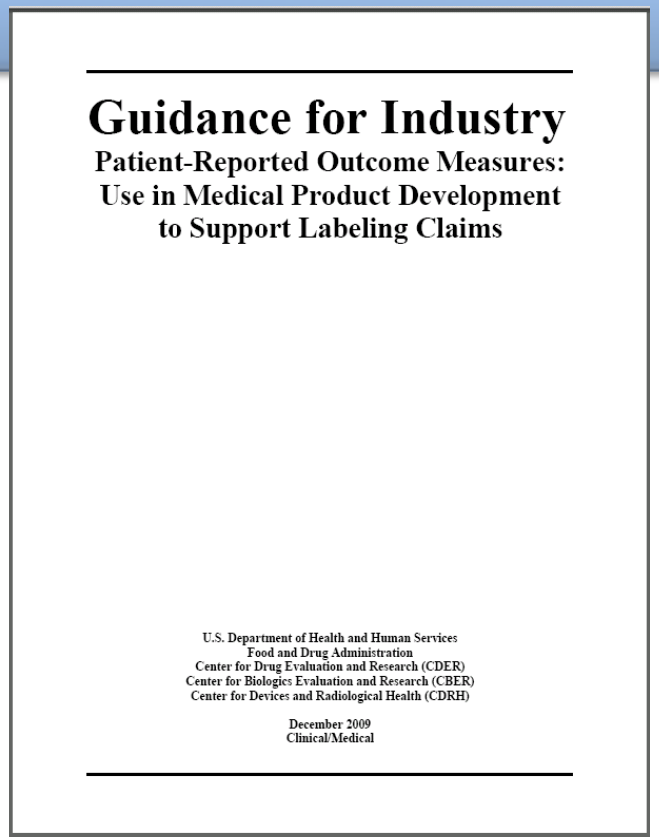
What Constitutes a Label Claim in the US?

- 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

Regulatory challenges

VALUE IN HEALTH XX (2012) XXX

Available online at www.sciencedirect.com

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ELSEVIER

A Review of Patient-Reported Outcome Labels in the United States: 2006 to 2010

Ari Gnanasakthy, MSc[1,*], Margaret Mordin, MS[2], Marci Clark, PharmD[2], Carla DeMuro, MS[2], Sheri Fehnel, Phi
Catherine Copley-Merriman, MS[2]

[1]Novartis Pharmaceuticals Corporation, East Hannover, NJ, USA; [2]RTI Health Solutions, Durham, NC, USA

ABSTRACT

VALUE IN HEALTH XX (2012) XXX

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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

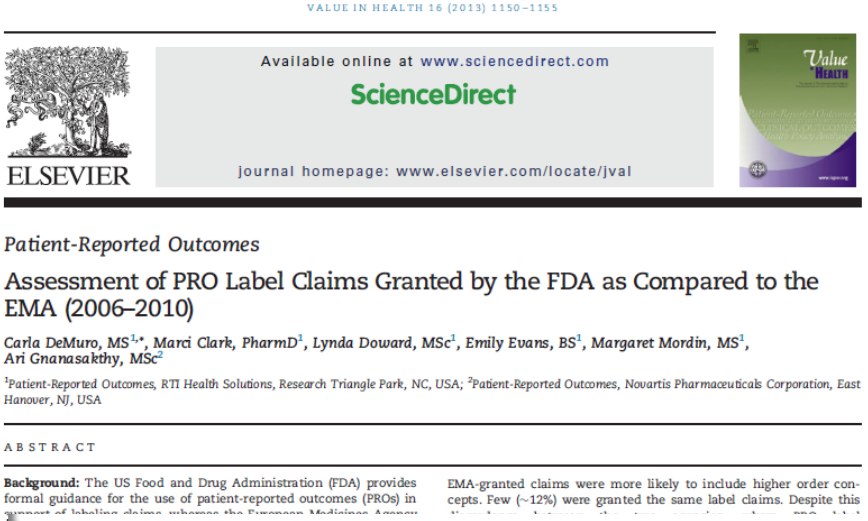
Carla DeMuro, MS[1,*], Marci Clark, PharmD[1], Margaret Mordin, MS[1], Sheri Fehnel, PhD[1], Kati Copley-Merriman, MS[1], Ari Gnanasakthy, MSc[2]

[1]RTI Health Solutions, Research Triangle Park, NC, USA; [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

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

issues of fit for purpose, issues of study design, data quality or interpretation, statistical issues, administrative issues, and lack of demonstrated treatment benefit. **Conclusions:** Based on drug approval packages, nearly half (45%) of new molecular entitity/biologic license application products in the years 2006 to 2010 included PROs in the clinical trials supporting their approval, yet this rate is not



VALUE IN HEALTH 16 (2013) 1150–1155

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Patient-Reported Outcomes

Assessment of PRO Label Claims Granted by the FDA as Compared to the EMA (2006–2010)

Carla DeMuro, MS[1,*], Marci Clark, PharmD[1], Lynda Doward, MSc[1], Emily Evans, BS[1], Margaret Mordin, MS[1], Ari Gnanasakthy, MSc[2]

[1]Patient-Reported Outcomes, RTI Health Solutions, Research Triangle Park, NC, USA; [2]Patient-Reported Outcomes, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

ABSTRACT

Background: The US Food and Drug Administration (FDA) provides formal guidance for the use of patient-reported outcomes (PROs) in

EMA-granted claims were more likely to include higher order concepts. Few (~12%) were granted the same label claims. Despite this

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!