ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Addressing Methodological Challenges in International CNS Clinical Trials

ISCTM AUTUMN CONFERENCE WORKSHOP

Boston Park Plaza

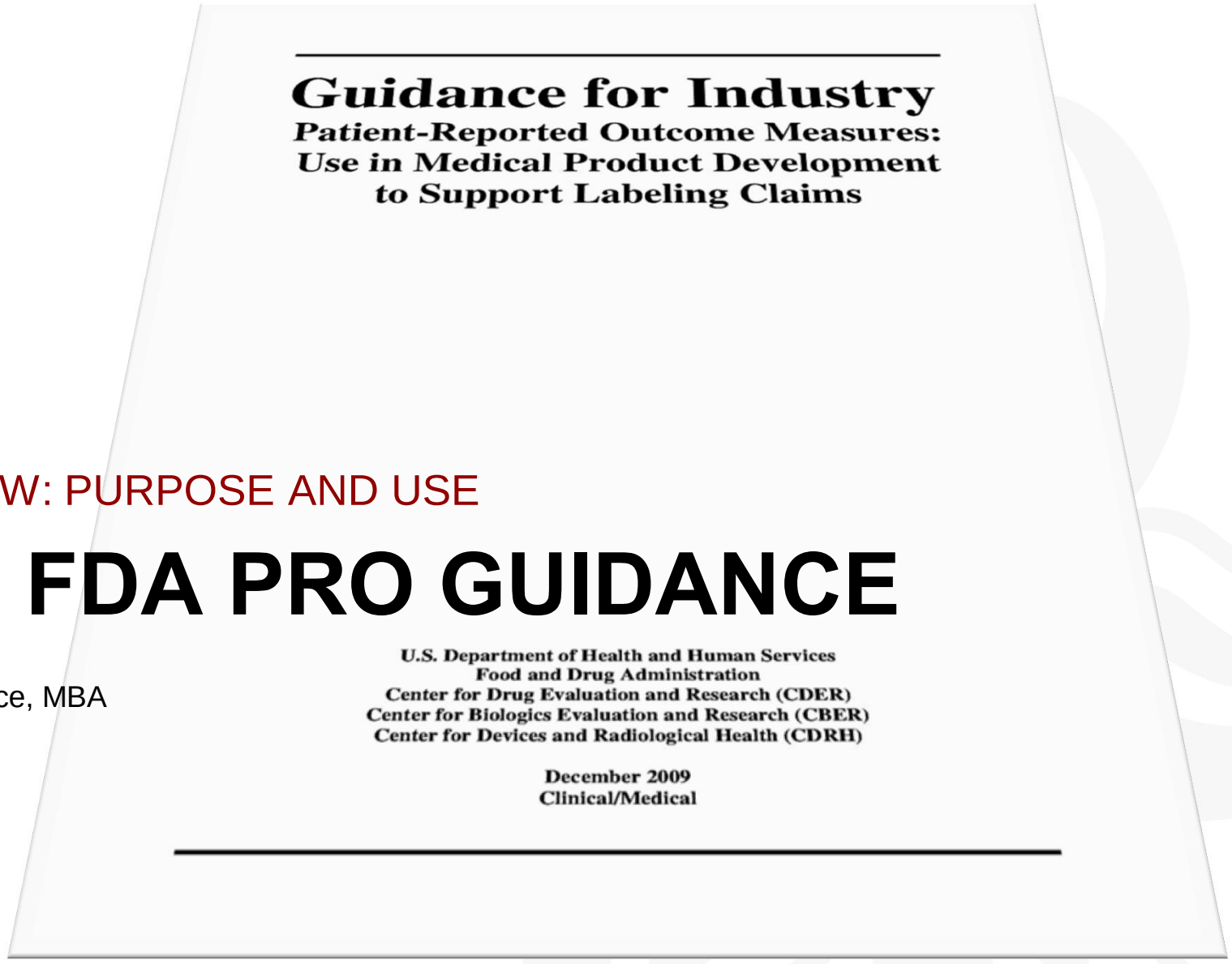
October 6, 2014

Working Group Chairs: Richard Keefe, PhD; Amir Kalali, MD

A REVIEW: PURPOSE AND USE

THE FDA PRO GUIDANCE

Monika Vance, MBA



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Presenter Disclosure

Monika Vance - *Founder & President, Santium*

I have relevant financial relationships with the concepts described, reviewed, evaluated, or compared in this presentation.

Financial ï financial compensation from Santium, with 100% ownership interest and income generated from government, healthcare and pharmaceutical industries; providing services centered on psychological assessment instrumentation, including management of psychometric and linguistic validations, and health outcomes research.

Non-financial - No relevant non-financial relationships to disclose.

FDA PRO GUIDANCE

A POSITION DOCUMENT

It's *only* a **RECOMMENDATION**

FDA's current thinking and attitude to dominant research trends in the pharma industry.

FDA's expectations for:

- alignment in information exchange
- optimal turn-around timeline

Think of it as a **communication guide** for the type of information FDA expects to see in your submissions.

Do NOT think of it as a methodology manual.

Draft: February 2006; Final: December 2009

REMEMBER:

The Guidance could never be a set of concrete requirements that pharma must follow line-by-line to ensure approval from FDA. That is why the guidance is not overly specific. If it were, even if only interpreted as such, it would limit progress in CNS drug development, your scientific and medical objectivity and judgment, and also disregard a monumental volume of psychometric research.

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PRO GUIDANCE

INTENDED PURPOSE

To accelerate evaluation of claims for medical product labeling.

When…

PROs are used as clinical trial endpoints, and patientsô voice is important in approval process.

Claim ï statement or implication of treatment benefit

Labeling ï packaging insert; description and summary of use, safety, and effectiveness of the medical product (i.e. drug, device, biologic etc.)

- Aimed at confirmatory trials
- Emphasizes need for supporting documentation:
  - PRO development
  - nature of modification
  - psychometric properties and scoring
  - statistical analysis and interpretation
- Supports industryôs view that PROs are important for insights into unobservable symptoms, and relevant patient experiences without clinical interpretation by observing physicians.
- Explains FDAôs SEALD divisionôs logic and process when evaluating PRO label claims
- Passively implies application to ClinROs and ObsROs

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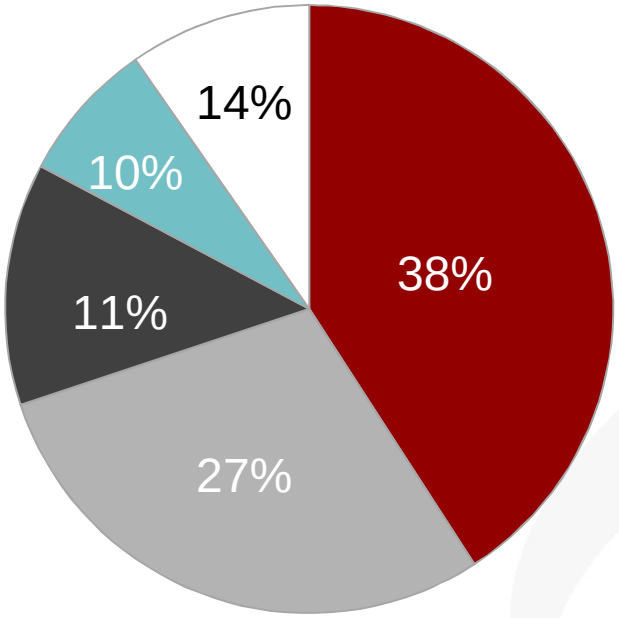
WHY A GUIDANCE FOR PROs?

HISTORY: DENIALS OF CLAIMS

FDA 2006 - 2010
116 unique new brand drugs approved
52 with PRO label claims (44.8%)
26 denied (22%)



- **PRO Fit for Purpose**
- **Study Design, Data Quality & Score Interpretation**
- Statistical Analysis Issues
- Test Administration & Training Quality
- No Rx Benefit

FDA: 213 PRO Violation Notices

- Use of individual items: 45%
- Insufficient evidence of content validity: 36%
- Broadening claim beyond PRO construct: 27%

- Design & data interpretation: 49%
- Broadening claim beyond trial scope: 55%
- No PRO used: 50%

Rejection rates for PRO claims remain high across therapeutic areas.

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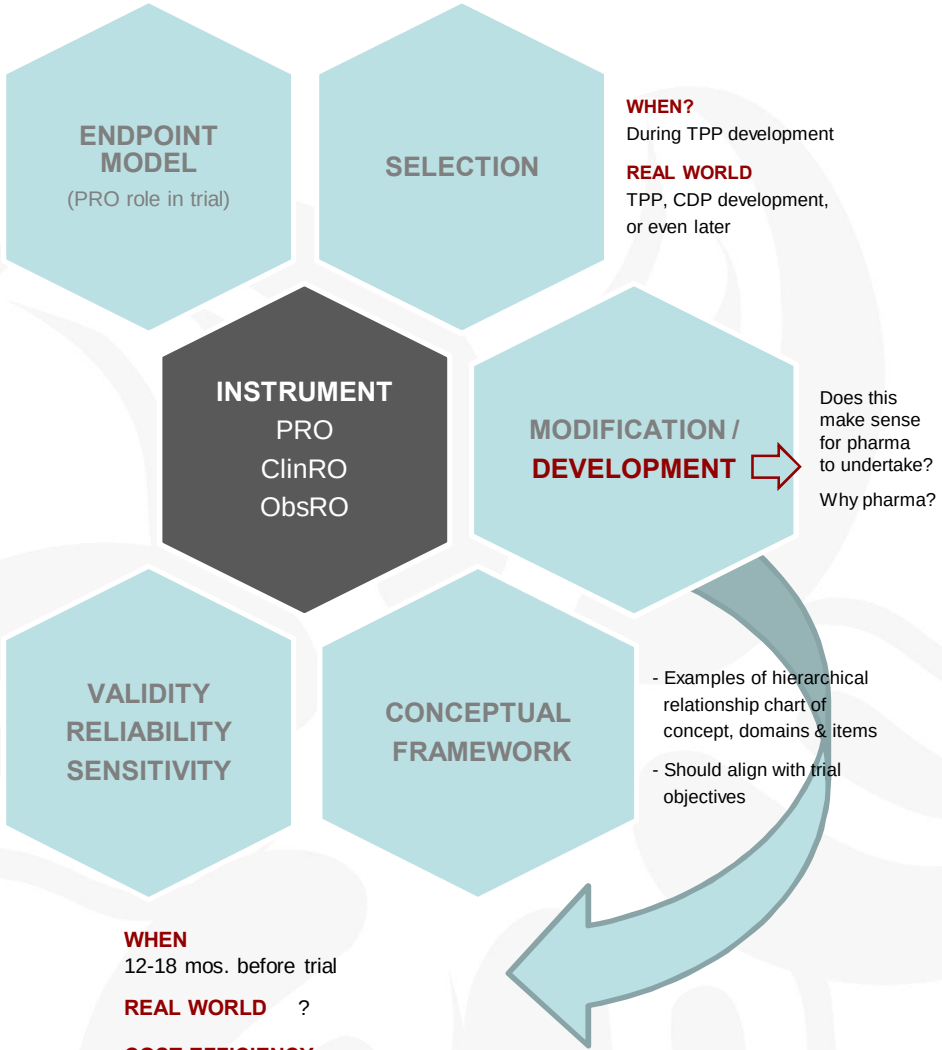
DeMuro C, Clark M, Mordin M, Fehnel S, Copley-Merriman C, Gnanasakthy A. Reasons for rejection of patient-reported outcome label claims: a compilation based on a review of patient-reported outcome use among new molecular entities and biologic license applications, 2006-2010. Value Health 15, 443-448 (2012).

Symonds T, Hackford C, Abraham L. A Review of FDA Warning Letters and Notices of Violation Issued for Patient-Reported Outcomes Promotional Claims between 2006 and 2012. Value in Health, Vol. 17, Issue 4, p433ï 437 (2012).

PRO GUIDANCE
CONTENT

1. EVALUATION OF A PRO INSTRUMENT
2. CLINICAL TRIAL DESIGN
3. DATA ANALYSIS & INTERPRETATION
4. GLOSSARY
5. APPENDIX: DOSSIER TEMPLATE



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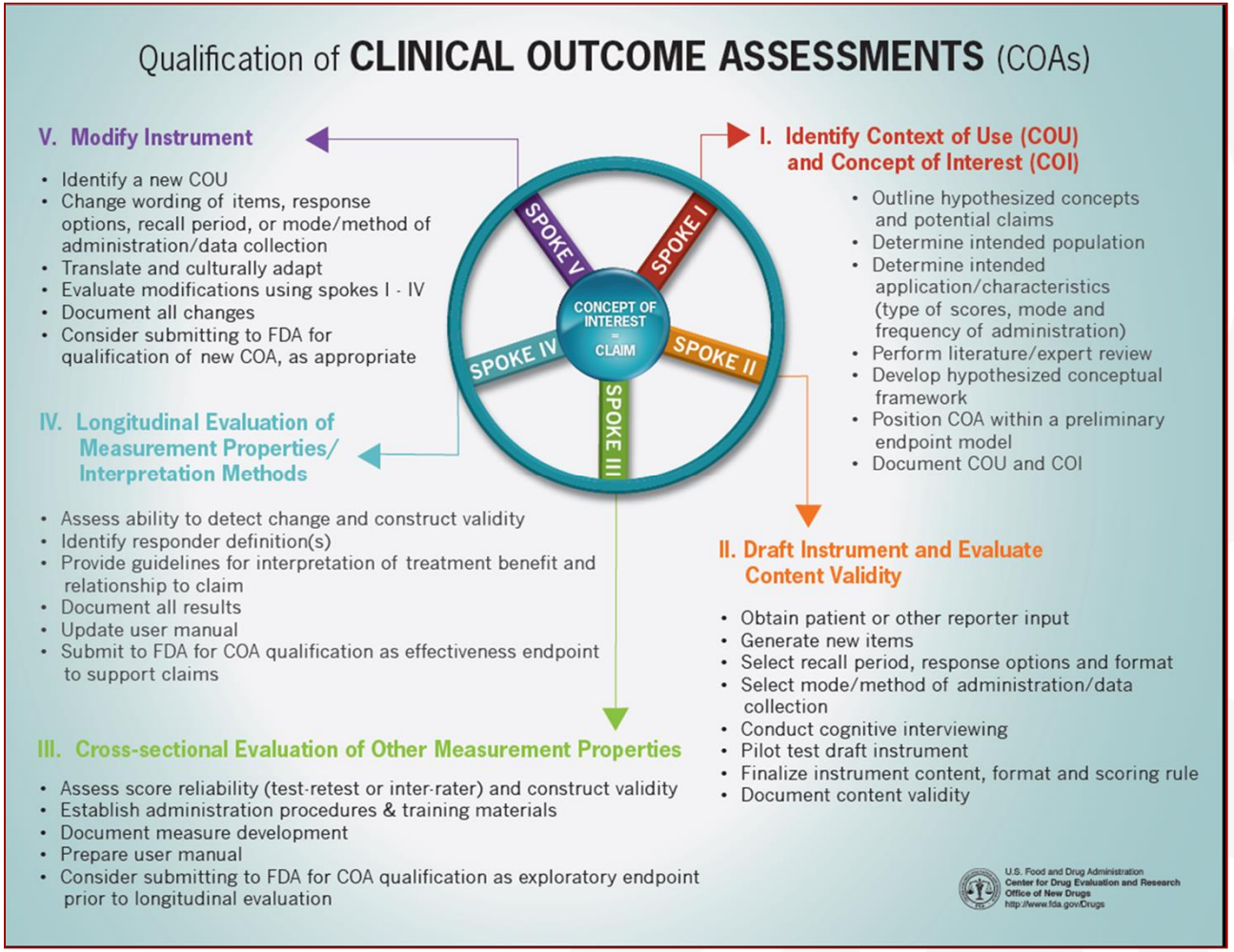
* Reference for breakdown of pharma cost:
Hayes, R. (2011). Road Less Traveled: the Pharmaceutical Perspective of the PRO Consortium. [PowerPoint Presentation] *C-Path PRO Consortium*. Retrieved from: http://goo.gl/DOdBQ2

INSTRUMENT MODIFICATION & DEVELOPMENT:
The Agile Way

LINGUISTIC VALIDATION

SPOKE I - V



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FDA, DHHS, CDER, CBER, CDRH. (2009) Qualification of Clinical Outcome Assessments (COAs). [image*Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Industry Guidance; December 2009. Retrieved from: www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf

PRO GUIDANCE

SOURCES OF CONFUSION RE: LINGUISTIC VALIDATION

- **Inconsistency in detail across guidances**
- **Lack of specificity in method**
- **Scientifically compromising**

DHHS / FDA GUIDELINE (1988)

Guideline for the Format and Content of the Clinical and Statistical Sections of an Application

vs.

FDA PRO GUIDELINE (2009)

USE THE *SPOKE WHEEL* !

DHHS / FDA GUIDELINE (1988)

Modifications of existing or new instruments

1. For language translations and cultural adaptation processes, include:
   a. Description of the expertise of the translators
   b. Description of procedures used (forward, back, reconciliation, harmonization, assessment of measurement properties)
   c. Description of patient testing
   d. Results of translation / adaptation including clear description of all translation issues and how they were resolved
2. **For content, wording, format, or mode of administration changes, describe results from studies conducted to evaluate modification, or rationale for not conducting studies.**
3. **For use in a new indication or new population, document instrument development and assessment of measurement properties as described above.**

FDA PRO GUIDELINE

VIII. Language Translation and Cultural Adaptation

?

A. Process used to translate and culturally adapt the instrument for populations that will use them in the trial.
B. Description of patient testing, language- or culture-specific concerns, and rationale for decisions made to create new versions.
C. Copies of translated or adapted versions.
D. Evidence that content validity and other measurement properties are comparable between the original and new instruments.

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FDA , DHHS (1988). *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application*. Industry Guidance; July 1988. Retrieved from: www.fda.gov/downloads/Drugs/Guidances/UCM071665.pdf

FDA, DHHS, CDER, CBER, CDRH. (2009) *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Industry Guidance; December 2009. Retrieved from: www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf

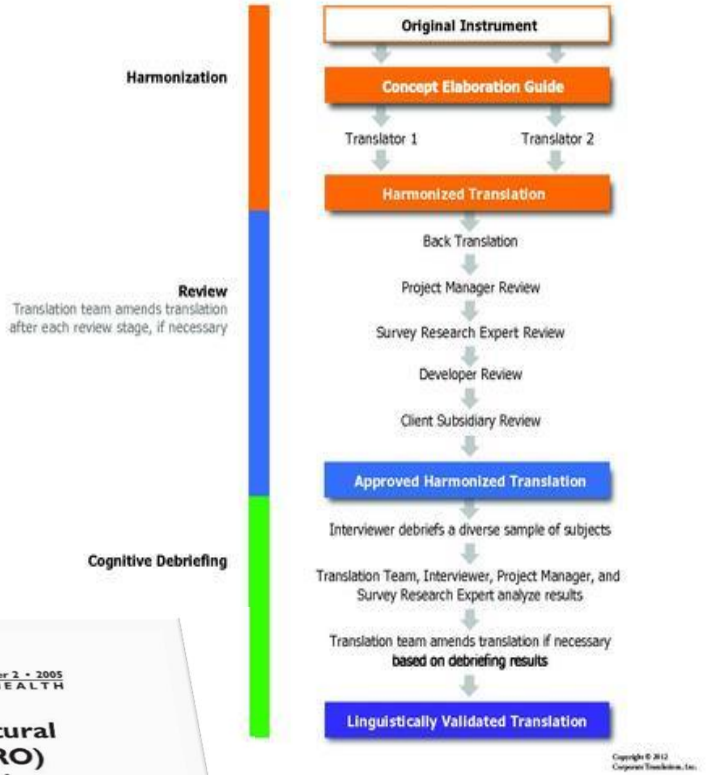
PRO GUIDANCE

LINGUISTIC VALIDATION METHODOLOGY

Where is it??

It's <u>not</u> in the PRO Guidance;
or in the DDT Guidance,
or in the 1988 Content/Format Guidance….

THE ñ*WILD PAPER*ò from ISPOR



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Wild D, Grove A, Martin M, et al. *Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translating adaptation.* Value Health 2005;2:94-104.

Graphic by Corporate Translations. Retrieved from: http://www.corptransinc.com/Services/Linguistic-Validation.aspx

PRO GUIDANCE

IMPACT

Has it made a difference?

- ñAdmirable intent with recommendations based on sound scientific principles.ò*
- Inconsistent implementation of guidance within SEALD and across other FDA reviewing divisions
- Some FDA reviewing divisions appear to prefer claims based on specific PROs (usually primary endpoints)

YES, SOME, BUTÉ

ñEvidence suggests that since the release of the Draft PRO Guidance, many PRO claims continue to be approved by FDA reviewing divisions; however, the reviewing divisions are not always adhering to the current standards when assessing PRO data for a claim.ò

Mordin, M., Clark, M., Siersma, C., Copley-Merriman, K., & Gnanasakthy, A. (2009). *Impact of the FDA draft guidance on Patient Reported Outcomes (PRO) label claims for approved drug products in the US: Has it made a difference?*, Value in Health, 12 (3):A29-A29.

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Additional resource: * Fehnel, S., DeMuro, C., McLeod, L., Coon, C., Gnanasakthy, A. (2013). *US FDA patient-reported outcome guidance: great expectations and unintended consequences.* Expert Review of Pharmacoeconomics & Outcomes Research, August 2013, Vol. 13, No. 4 : Pages 441-446.