Session 1:
Advancing the Assessment of Outcomes Meaningful to Patients in Drug Development: A Brief History at the FDA and Beyond

FIFTH ANNUAL
PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP

April 29 - 30, 2014 ■ Silver Spring, MD

Co-sponsored by

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Session Overview

The overarching goal of this session is to reflect on where we are today in regard to the measurement of patient-centered outcomes **by considering how we got here**.

This year's workshop title:

HONORING THE PAST, NAVIGATING THE PRESENT, CHARTING THE FUTURE

Session Participants

Moderator

- *Stephen Joel Coons, PhD* – Executive Director, Patient-Reported Outcome Consortium, C-Path

Presenters:

- *Robert Temple, MD* - Deputy Center Director for Clinical Science and Acting Deputy Director of the Office of Drug Evaluation I, OND, CDER, FDA
- *Catherine Acquadro, MD* - Scientific Advisor at Mapi Research Trust and Coordinator of Patient-Reported Outcomes (PRO) Harmonization Group (2000-2002)
- *Donald L. Patrick, PhD, MSPH* – Professor and Director, Seattle Quality of Life Group and Biobehavioral Cancer Prevention and Training Program, University of Washington
- *Andrew E. Mulberg, MD, FAAP, CPI* – Deputy Director, Division of Gastroenterology and Inborn Error Products (DGIEP), OND, CDER, FDA
- *Tara Symonds, PhD* – Senior Director, Global Head PRO Center of Excellence, Pfizer
- *Laurie Beth Burke, RPh, MPH* – Founder of LORA Group, LLC and former Associate Director for Study Endpoints and Labeling, OND, CDER, FDA

PROs at FDA

Robert J. Temple, M.D.
Deputy Center Director for Clinical Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

PRO Consortium Workshop
April 29, 2014

Effects of Treatment

As Laurie said, a drug's effect is measured by how it affects how the patient "feels, functions, or survives." The first formal FDA use of that phrase was in the preamble to the accelerated approval rule (1992).

In any case, apart from survival, and some "functional" assessments we have standardized and refined (exercise tests, pulmonary function tests, cognitive function tests, neurological tests, etc.) all assessments of how a patient feels, and many of how the patient functions, referring to day to day activities, MUST come from the patient.

Who Says How a Patient Feels?

The ultimate source for these assessments must be the patient but the patient's state can be reported through a learned observer, doctor or other health professional. The report on the patient can involve specified questions or a structured report by the observer based on answers to either specific or general questions in an interview. It can be an assessment with multiple components, but where only the total score is considered, or a scale with defined components of the condition (each rated separately, then perhaps combined) or a rating of the condition as a whole (a "global" score) and FDA has certainly accepted all of them.

A concern of mine has always been that it seems probable that different raters might respond differently to the same patient response. It is, after all, the observer's "wisdom," judgment, etc. we are trying to incorporate. Given likely variability of such judgments, could we be adding "noise," or assuming uniform skill than is warranted. This seems a most obvious concern with a "global," but could effect other assessments.

Eliminate the Intermediary

For a number of reasons, interest has grown in using patient-based assessments of symptoms and function. This was partly philosophical (it's the patient who has the symptom), but also reflected the thought that identifying the consequences of symptoms (effects on work, relationships, mood, etc.) would be better identified by patients than by caregivers.

Apart from deciding who can best assess those features, it leads to a new interest in finding out, while developing PRO instruments, what those other (less obviously disease-related) effects are and asking about them.

A Concern: Could You Measure the Wrong Thing

Drugs, some drugs at least, do more than one thing. If a PRO has diverse elements, e.g., some clearly related to the disease (pain, depression, etc.) and others related to broader function (relationships, job performance), could an effect unrelated to the disease move the scale.

- Could an "activating drug" (amphetamine, caffeine) improve performance even without an effect on the disease of interest.
- Could an "anxiolytic" seem to affect function in a wide range of CNS conditions without affecting the underlying problem.

All this leads to some interest in the components and some anxiety about relying on a single general scale alone.

Whole Scale vs Components

Illustrations:

1. Alzheimer's Disease

Cognitive function alone has been considered not enough because of concern that the effect could be too small to matter (e.g., recall a few more numbers).

So we also want to see a broader measure, e.g., caregiver or physician global or an ADL assessment.

But would the latter alone do? I'd say probably not because improved ADL could relate to mood or other effects, not to an effect on cognition at all.

So we get BOTH.

A PRO or Caregiver's Scale would have similar problems. "Too global" hides the components, so an overall global is troublesome as a sole measure of effectiveness.

Whole Scale vs Components

There can be particular problems with broadly based scales like the SF-36, which we have not accepted as a sole effectiveness endpoint. Their attractiveness is their attempt to incorporate all aspects of health (physical function, perceived health, emotional status, social function). Certainly, even for a purely physical problem, e.g., back pain, it would be of interest to see how a treatment affected those aspects of life. You worry, though, that an effect unrelated to the pain could drive the score. So we usually think of these as an add-on, after clear effect on back pain and perhaps ADL is established.

2. Living with Heart Failure (1984)

Developed over many years by U of Minnesota (with NHLBI) and used in the AHEFT study of BiDil (of course that trial also showed an effect on mortality and hospitalization). It assesses the physical aspects of CHF

- SOB, fatigue, edema, difficulty sleeping

and psychological components

- Anxiety and depression

and ADL and other consequences

- Walking, climbing stairs, working, or going out of the house, sexual function, eating, mental status

and

- Side effects

Living with Heart Failure -2

Total of 21 aspects tested on a 6 point Likert Scale, 0-5.

CAN look at items individually, but total score is considered the best measure. However, it is recognized that looking at "physical" components and psychological components separately is attractive.

Testing showed good correlations with separate measures (dyspnea score, fatigue score, SF12 physical and emotional subscores, and NYHA classification (a sort of physician global with very long use).

Overall

We clearly are most comfortable with PROs that address specific critical aspects of disease (as determined through both patient and physician input) and I think the individual items going into the scale should have "face validity" and some quantitative aspect. Ideally there would be data on the components (treatments could affect different aspects differently) but this is plainly difficult and isn't done with physician scales either, usually.

As noted, there is reason to hope that measures specifically chosen to be broadly useable by patients could be less "noisy" than scales that depend heavily on physician skills.

Genesis of the PRO Harmonization Group

Catherine Acquadro, MD
Mapi Research Trust

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1997- ERIQA Group / The Genesis

- **November 4-5, 1997 (Vienna Austria)**
  Exploratory meeting organized by Mapi Research Institute on Quality of Life and Regulatory Issues
- **Gathering**
  - Representatives from regulatory bodies
  - Academics
  - Seven countries: France, Germany, Italy, Spain, Sweden, UK, USA
- **Objective**
  To enable regulators to express their thoughts and concerns about QOL assessment in the specific framework of registration and reimbursement of medicinal products
- **Conclusions**
  - There is a need to rationalize the field of HRQL research
  - This issue can only be resolved through a **collaborative effort** between key players: regulatory authorities, academics (HRQL researchers) and pharmaceutical companies

1997- ERIQA Group / The Genesis

PRO CONSORTIUM
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Special Issue — March 98

Quality of Life NEWS LETTER

Quality of Life and Regulatory Issues

Report of a Meeting Held in Vienna, Austria, November 4-5,1997

On 4 and 5 November last year, Mapi Research Institute organised a meeting on Quality of Life and Regulatory Issues, in Vienna, Austria. The main objective of this meeting was to bring together quality of life researchers and representatives of European regulatory agencies in order to allow the authorities to express their thoughts about QOL evaluation within the specific framework of registration and reimbursement of pharmaceutical drugs.

Health authorities from 6 European countries as well as European agencies (EMEA, EC), and the FDA were contacted. Eight members from European and US health authorities accepted to join the meeting (see list of meeting participants).

QOL experts from several European countries and from the USA were also invited, either as speakers or special guests (see list of meeting participants).

Prior to the meeting, a survey was sent to the health authorities in order to assess their level of knowledge in QOL issues as well as their expectations.

The results revealed a very mixed audience, whose preoccupations were nevertheless very similar: among the most cited issues were the definition of QOL concept and the interpretation of study results.

With these concerns in mind, the programme was structured into three sessions:

- Session I: Quality of Life Issues
- Session II: Regulatory Issues
- Session III: Workshops:
  1. Quality of Life and Registration Issues.
  2. Quality of Life and the Purchaser/ Payer's Perspective (includes reimbursement issues).

This special issue of the Quality of Life Newsletter takes up the programme's structure (see on page 2), introducing a summary of each presentation and of the 2 workshops, followed in some cases by comments or questions asked by the audience with corresponding answers. Otherwise the clarifications made by the speakers have been directly included in the summary.

At the end of the meeting, participants agreed on two main conclusions:

1. **there is a need to rationalise the field of quality of life and to make it credible as a criterion of evaluation to the health authorities;**
2. **this issue can only be resolved through a better collaborative effort between key players: mainly QOL researchers, health authorities, and pharmaceutical companies.**

Following up this last point, the Mapi Research Institute is prepared to promote and coordinate the efforts of a multiparty QOL working group. An exploratory meeting is planned in order to define and organise the tasks of such a working group. •

List of Meeting Participants

France:
- Prof. Jean-Pierre Bader, Excert - Agence du Médicament, Saint-Denis, France
- Dr Olivier Chassany, Rapporteur - Agence du Médicament, Saint-Denis, France
- Danielle Golinelli, Etudes et Information Pharmaco-Economiques, Agence du Médicament, Saint-Denis, France

Germany:
- Prof. Monika Bullinger, Universität Hamburg, Mezinische Klinik, Hamburg, Germany
- Prof. Dr. Gottfried Kreutz, Bundesinstitut für Arzneimittel und Medizinprodukte, Berlin, Germany
- Dirk Schleert, Bundesverband der Betriebskrankenkassen, Essen, Germany

Italy:
- Dr Giovanni Apolone[1], Laboratorio per la Ricerca Clinica Oncologica, Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy

Spain:
- Dr Jordi Alonso, Dpt d'Epidemiologia i Salut Publica, Institut Municipal d'Investigacio Medica, Barcelona, Spain

Sweden:
- Prof. Bjorn Beermann, Div. of Epidemiology / Inspection, Medical Products Agency, Uppsala, Sweden
- Prof. Marianne Sullivan, Health Care Research Unit, Institute of Internal Medicine, Sahlgrenska University Hospital, Göteborg University, Göteborg, Sweden
- Dr Sighild Westman Naeser, Medical Products Agency, Uppsala, Sweden
- Dr Ingela Wiklund, Dpt of Quality of Life Research, Astra Hassle, Mölndal, Sweden

UK:
- Dr Jeffrie Strang, North Yorkshire Health Authority, York, UK

USA:
- Laurie Beth Burke, Center for Drug Evaluation and Research, US Food & Drug Administration, Rockville, USA
- Prof. Donald L Patrick, Department of Health Services, University of Washington, Seattle, USA

Mapi-Adelphi team:
- Bernard Jambon, CEO, Mapi Group, Lyons, France
- Stuart Cooper, CEO, Adelphi Group, Bollington, UK
- Katrin Conway, Research Director, Mapi Research Institute, Lyons, France
- Dr Catherine Acquadro, Scientific Adviser, Mapi Research Institute, Lyons, France
- Dr Patrick Marquis, Scientific Director, Mapi Values, Lyons, France
- Clare McGrath, Development Director, Mapi Values, Bollington, UK
- Yolanta Buxton, Adelphi Group, Bollington, UK

[1] Dr Apolone from Italy is actually not a member of regulatory agency, but represented Pr Garattini, Director of the Mario Negri Institute and member of the CPMP of the EMEA.

(continued on p 2)

INTRODUCTION

Quality of Life and Regulatory Issues

(continued from p 1)

Programme of the November 4-5, 1997 Meeting — *Page*

I- November 4, 1997 - 14:00 to 18:45
Session I: Quality of Life Issues

14:00 - 14:10	1st Welcome ! - Presentation of the Institute - The problems regarding Quality of Life Evaluation Bernard Jambon, CEO Mapi Group	
14:10 - 14:20	2nd Welcome ! - The logic of this meeting - Results of the Authorities Quality of Life Survey Catherine Acquadro, MD, Scientific Advisory Committee, Mapi Research Institute	*1-2*
14:20 - 16:15	Strategies for interpreting Quality of Life Questionnaires Patrick Marquis, MD, Mapi Values, France Discussion	*3-4*
16:15 - 16:30	*Break*	
16:30 - 17:30	Examples of Quality of Life Studies and Discussion - In Sweden: Marianne Sullivan, PhD, Health Care Research Unit, Göteborg University, Sweden - In Spain: Jordi Alonso, MD, PhD, Health Services Research Unit, Institut Municipal d'Investigacio Medica, Barcelona, Spain	*5* *7*
17:30 - 18:45	Quality of Life and PharmacoEconomic Evaluation Donald Patrick, PhD, University of Washington, Seattle, USA Discussion	*6-7*

II-November 5, 1997 - 9:00 to 17:15
9:00 - 12:00 Session II: Regulatory Issues

9:00 - 9:30	Quality of Life: A Pharmaceutical Industry Perspecti Ingela Wiklund, Astra Hassle, Sweden Discussion	
9:30 - 10:15	Quality of Life Evaluation: the FDA experience Laurie Burke, RPh, MPH, FDA, Rockville, USA Discussion	
10:15 - 10:45	*Break*	
10:45 - 11:15	Role of Quality of Life Studies in the Reimbursement Danielle Golinelli, MSc, BSc, Agence du Médicament Discussion	
11:15 - 11:45	Quality of Life Measures in Italy: Regulatory Perspec Giovanni Apolone, MD, Mario Negri Institute, Italy Discussion	
12:00 - 13:15	**Lunch**	
13:30 - 17:15	**Session III: Workshops**	
13:30 - 15:15	1. Quality of Life and Registration Issues (Mediator: Clare McGrath, Mapi Values, UK) 2. Quality of Life and the Purchaser/Payer's Perspe (includes reimbursement issues) (Mediator: Yo Buxton, Adelphi Communication, UK)	
15:15 - 15:30	*Break*	
15:30 - 17:15	Presentation of the results of the Workshops/Discussion	
17:15:	**End of sessions**	

About the speakers — *16*

1999 - HRQL/PRO Harmonization Group
The Genesis

- **In 1999**, **four organizations/societies** had produced supporting guidance documents on the use of HRQL evaluation in drug development:
  - European Regulatory Issues on Quality of Life Assessment (ERIQA) Group
  - International Society for Quality of Life Research (ISOQOL)
  - International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
  - Health Outcomes Committee (HOC) of the Pharmaceutical Research and Manufacturers of America (PhRMA HOC)
- These documents provided suggestions, recommendations, opinions on important topics and issues

1999- HRQL/PRO Harmonization Group
The Genesis

- At the initiative of PhRMA HOC, and Mapi Research Institute, a comparison of the four documents was undertaken
- The idea was to compare all recommendations and explore the differences, and points of controversy
- And to present findings to the FDA
- The questions were:
  - How to present these findings?
  - And to whom?
- **How?** Through a **collaborative effort** between ERIQA, PhRMA HOC, ISOQOL and ISPOR

1999- HRQL/PRO Harmonization Group
The Genesis

ISOQOL Annual Meeting
Satellite Symposium on HRQL and Regulatory Issues
November 30th - December 2th, 1999

Jean-Paul Gagnon
PhRMA HOC
Aventis

Bernard Jambon
ERIQA
Mapi Research Institute

Catherine Acquadro
ERIQA
Mapi Research Institute

To whom?

Laurie Burke
DDMAC/CDER/FDA

HRQL/PRO Harmonization Group Meetings

- The overall objectives of the HRQL/PRO Harmonization Program were:

  1. **To clarify** areas of concern or confusion about HRQL/PRO evaluation;
  2. **To explain** the added value of HRQL/PRO outcomes among all key players, i.e., academics, regulators, industry researchers, and prescribers;
  3. **To open and maintain** communication between key players;
  4. **To disseminate** meeting outcomes, i.e., to publish papers, to participate in international conferences

HRQL/PRO Harmonization Group Meetings

- **Four meetings were organized from March 2000 to March 2002**
- **HRQL/PRO Harmonization Meetings Coordination Committee**
  - Bernard Jambon, Patrick Marquis (ERIQA)
  - Paul Kind, Nancy Kline Leidy (ISPOR)
  - Ivan Barofsky, Dennis Revicki (ISOQOL)
  - Margaret Rothman, Nancy Santanello (PhRMA HOC)
- **With the support of**
  - Laurie Beth Burke (FDA Advisor)
  - Catherine Acquadro (Coordinator)
  - Jean-Paul Gagnon (Moderator)

HRQL/PRO Harmonization Group Meetings

- **March 31, 2000 (Ritz Carlton Hotel, Pentagon City)**:
  "Comparison of Health-related Quality of Life and Regulatory Initiatives in Europe and in the USA -- selection of problematic issues and possible solutions"

➔ **Meeting outcomes**

- Consensus and areas of disagreement were identified in four areas: Concept, Study Design, Interpretation and Conditions for Claims*
- Group agreed to continue discussion and form a coordination group with representatives from the four organizations to organize future meeting
- ***Real issue "does outcomes research provide added value?"***

- **September 14, 2000 (FDA, Rockville)**:
  "The Added-Value of HRQL Outcomes: Preliminary Conclusions"

➔ **Meeting outcomes**

- Conceptual framework was broadened to Patient-Based Assessment (PBA) which was changed to **Patient-Reported Outcomes (PRO)** for clarity
- Decision made to continue discussions and schedule meeting with FDA and EMA representatives

PRO Harmonization Group Meetings

- **February 16th, 2001 (FDA, Rockville)**:
  *"Important Issues in **Patient Reported Outcomes** Research"*

➔ **Take Away Points**

- *Patient has a unique voice and valuable perspective* that should play a role in medical decision making
- *PROs can be measured in reliable and valid ways*

- **September 21st, 2001 (FDA, Rockville)**:
  "Important Issues in Patient Reported Outcomes Research: Continued Discussion"
  Meeting postponed March 1st, 2002

PRO Harmonization Group Meetings

02/14/2001 meeting Audience (60)

FDA: Tom Abrams, Mark Askine, Julie Beitz, Laurie Burke, Judy H. Chiao, Jean-Ah Choi, Sarah Dawisha, Hung Du, Mary Furucker, Donna Griebel, Tarek Hammad, Lisa Kammerman, Peter A. Lechedbmuch, Marianne Mann, Kate Meaker, Bob Meyer, Robert O'Neil, R. Pazdur, Leah Palmer, Rupa Shah, Dan Shames, Jay Siegel, Jeff Siegel, Robert Temple, Grant Williams, Deborah Wolf

NCI: Joseph Lipscomb, Bryce Reeve, Claire Snyder. AHRQ: Stephen Byron, Yen-pin Chiang Carolyn Clancy, Joanna Siegel

Coordinators: Catherine Acquadro (ERIQA), Marguerite Barberan (Mapi Research Institute), Bernard Jambon (Mapi Research Institute)

Representatives of ERIQA, ISOQOL, ISPOR, PhRMA HOC not involved in Working Groups:

PhRMA HOC Chair: Catherine Copley-Merriman (Pfizer), ISPOR: Marylin Dix Smith, ERIQA: Bruce Crawford (Mapi Values)

ORGANISATION	REPRESENTATIVES (involved in Working Groups)
ERIQA	Olivier Chassany, Hôpital Lariboisière, France; Dominique Dubois, Janssen, Belgium; Asha Hareendran, Pfizer, UK; Patrick Marquis, Mapi Values, France; Ingela Wiklund, AstraZeneca, Sweden; Rhys Williams, Knoll-BASF, USA
PhRMA HOC	Haim Erder, Amgen, USA; Jean-Paul Gagnon, Aventis, USA; Joe Jackson, BMS, USA; Charlotte McMillan, AstraZeneca LP, USA; Margaret Rothman, Janssen Research Foundation, USA; Nancy Santanello, Merck, USA; Richard Willke, Pharmacia, USA
ISPOR	Joyce Cramer, Yale University School of Medicine, West Haven, CT, USA; Pennifer Erickson, Pennsylvania State University, PA, USA; Paul Kind, University of York, UK; Nancy Kline Leidy, MEDTAP International, Bethesda, MD, USA
ISOQOL	Ivan Barofsky, Johns Hopkins University, Baltimore, MD, USA; Rick Berzon, Boehringer Ingelheim, Ridgefield, CT, USA; Donald Patrick, University of Washington, Seattle, WA, USA; Albert Wu, Johns Hopkins University, Baltimore, MD, USA

PRO Harmonization Group Outcomes

- The **Study Endpoint and Label Development (SEALD)** Team (FDA, CDER, OND)
- **The FDA PRO Guidance:**
  - Draft published in February 2006
  - Final version published in December 2009
- **A key meeting (02/22-24, 2006) - Chantilly, VA, USA**
  - Organised by the Mayo Clinic to discuss the FDA Guidance for Patient-Reported Outcomes, with over 400 attendees, and experts from around the world.
  - FDA representatives answered over 300 questions over the three days of the meeting regarding the content of the guidance document and implications for discussion, dissemination, and operationalization.
- **An example for other initiatives:** ISPOR PRO Task forces, PRO Consortium *[The Critical Path Institute (C-Path)]*, etc.

Conclusion

- Thanks to a **fantastic** collaborative effort…
- …and the **pioneer** spirit of Laurie…
- …the **patient's perspective** is now officially taken into consideration in the evaluation of medicines in the USA and in Europe

References

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Trials, Tribulations, Triumphs and Tributes *in Ten*

Donald L. Patrick, PhD, MSPH
University of Washington

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In Tribute: Captain, Colleague, Sage, …and Friend

I.

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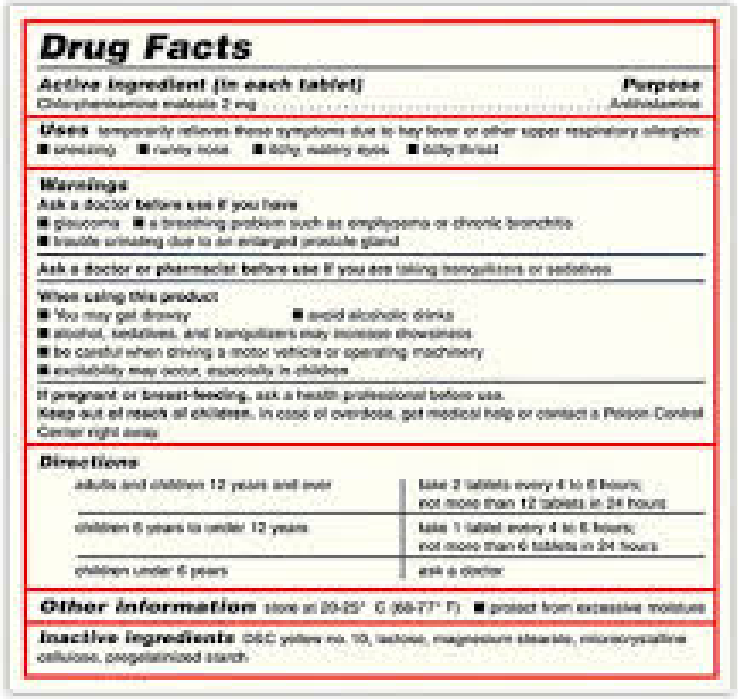
LAURIE BURKE

1. Remembering the Regulatory Context



Drug Facts

Active ingredient (in each tablet) — **Purpose**

Chlorpheniramine maleate 2 mg — Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
- sneezing
- runny nose
- itchy, watery eyes
- itchy throat

Warnings

Ask a doctor before use if you have
- glaucoma
- a breathing problem such as emphysema or chronic bronchitis
- trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product
- you may get drowsy
- avoid alcoholic drinks
- alcohol, sedatives, and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery
- excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor

Other information store at 20-25° C (68-77° F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

The context:
Adequate and well-controlled efficacy (A&WC) studies

- Studies that provide:
  - Evidence to support drug marketing authorization
  - Substantial evidence of effectiveness
    - Required by law to support a conclusion that a drug is effective
      - See 21 CFR 314.126
- " The methods of assessment of subjects' response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and the criteria used to assess response." 21CFR314.126(b)(6) Feb. 22, 1985

The Context:

Target Product Profile

A Strategic Development Process Tool

DRAFT GUIDANCE
March 2007

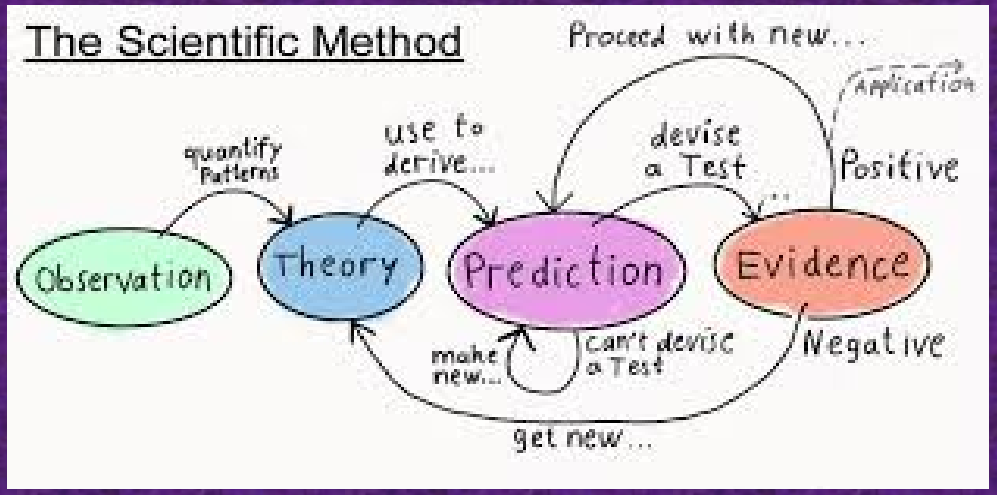
For questions regarding this draft document contact Jeanne M. Delasko at 301-796-0900.

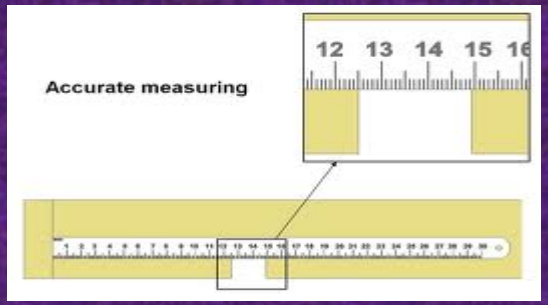
2. In the best interest of patients

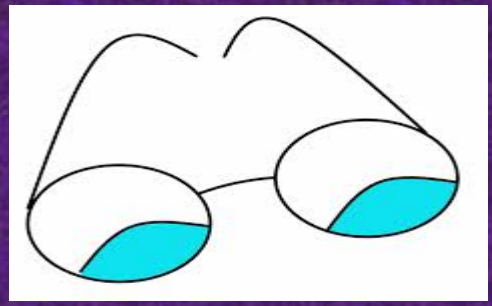
It's All

About People

3. Practicing good measurement science





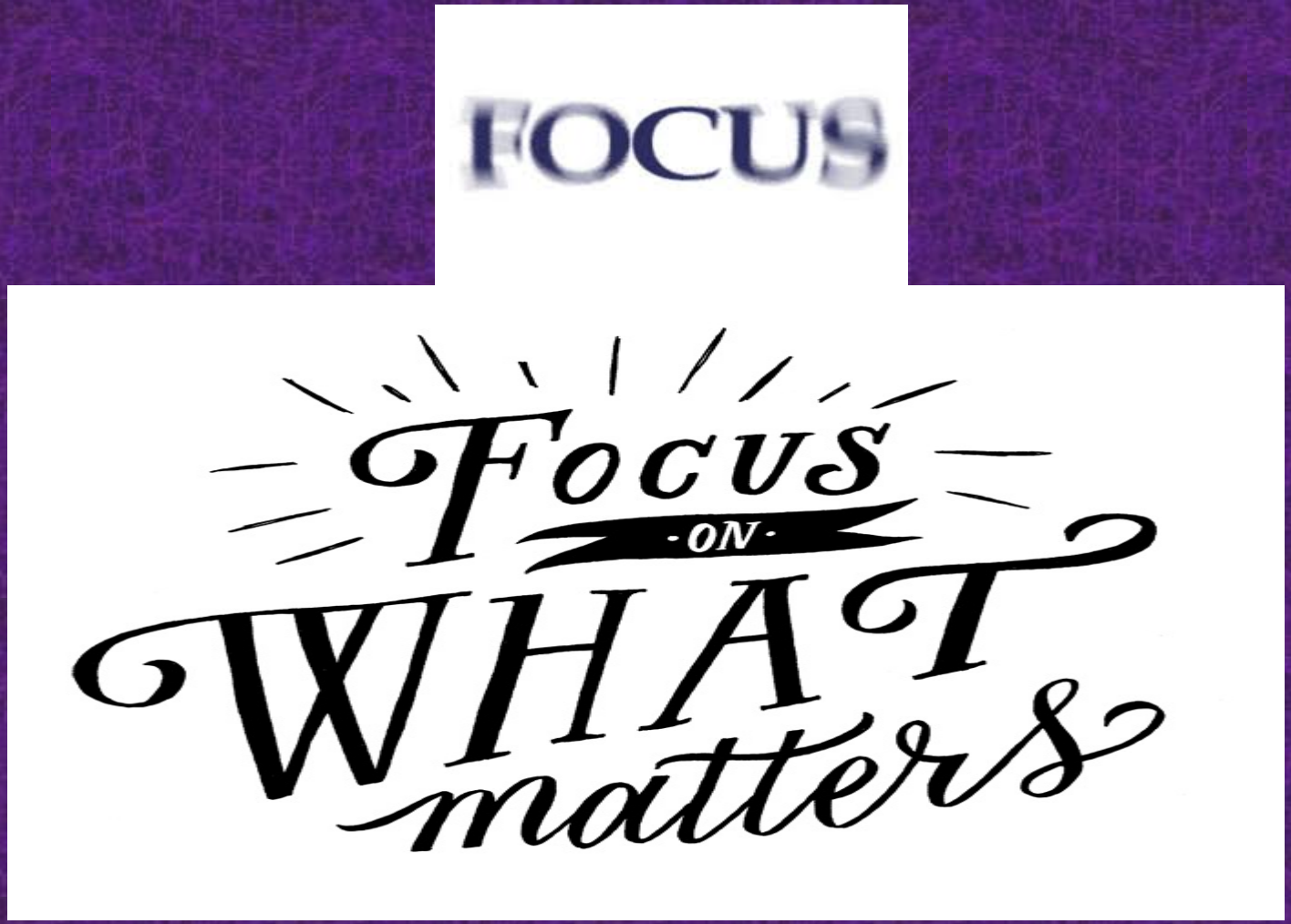


Archie Cochrane: The WHY of good measurement

- **Be delightfully surprised when any treatment at all is effective**
- **Always assume a treatment is ineffective unless there is evidence to the contrary**

Effectiveness and Efficiency, 1971

4. The HOW of good measurement: Focus on *what* is being measured before *how* to measure



I wonder who reminded us almost daily?

- "It is often much worse to have good
- measurement of the wrong thing—especially
- when, as is so often the case, the wrong thing
- will in fact be used as an indicator of the right
- thing—than to have than to have poor
- measurement of the right thing."

- John Tukey

5. Putting it into one figure

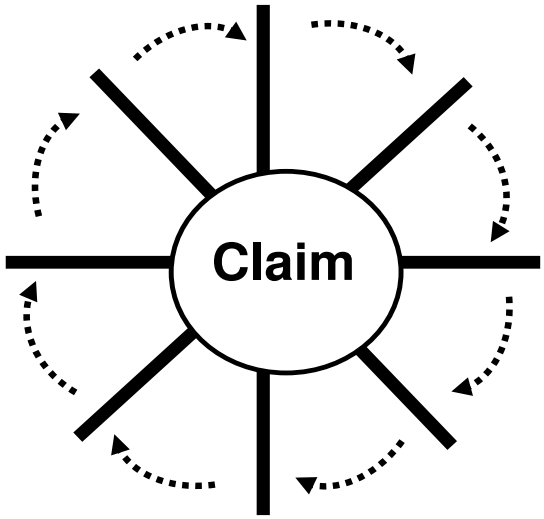
i. Identify Concepts
- Identify claims
- Identify relationships among all endpoints
- Identify concepts relevant to patients
- Determine intended population
- Develop expected relationships among items & concepts/domains

ii. Create Instrument
- Generate items
- Choose administration method, recall period & response scales
- Draft instructions
- Format instrument
- Draft procedures for scoring & administration
- Pilot test draft instrument
- Refine instrument & procedures

iii. Assess Measurement Properties
- Assess score reliability, validity, & ability to detect change
- Evaluate administrative & respondent burden
- Add, delete, or revise items
- Confirm conceptual framework
- Finalize instrument formats, scoring, procedures & training materials

iv. Collect, Analyze, & Interpret Data
- Prepare protocol & statistical analysis plan
- Identify responder definition
- Evaluate cumulative distribution curve
- Present interpretation of treatment benefit

v. Modify Instrument
- Change concepts measured, populations studied, research application, response options, recall period, or method of administration
- Translate & culturally adapt to other languages



SO what is new?

- Concentration on content validity within context of use
  --validity not a property of the instrument; it has to be evaluated within target population and actual application (context of use)
  --"*it depends*" becomes operationalized
- Separation of ability to detect change from interpretation of change
  --*responsiveness* NOT a characteristic of the instrument but instrument in context of use

….but one morning the phone rang

6. All those sponsors, all those drugs, all those diseases, all those pathways to approval

PRO CONSORTIUM
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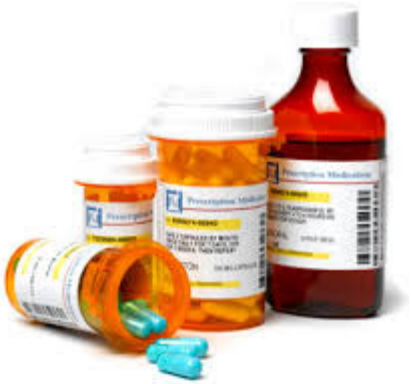
"The" FDA: 3 Centers, 13 divisions in CDER alone

Browse by Drug Name

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z 0-9



Claudette

COLBERT

in

I COVER THE WATERFRONT

with

BEN LYON

ERNEST TORRENCE

Presented by

JOSEPH M. SCHENCK

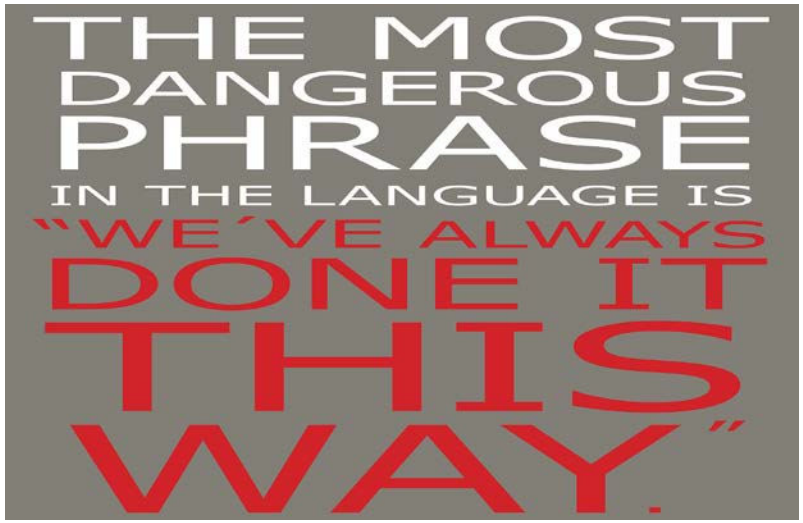
Produced by

EDWARD SMALL

RELEASED THRU UNITED ARTISTS

8. The legacy of the past

Respecting the past



But Forging the Future

9. Identifying the essential, not the perfect


KEEP
CALM
AND
Don't get
DISTRACTED

….adequate not perfect

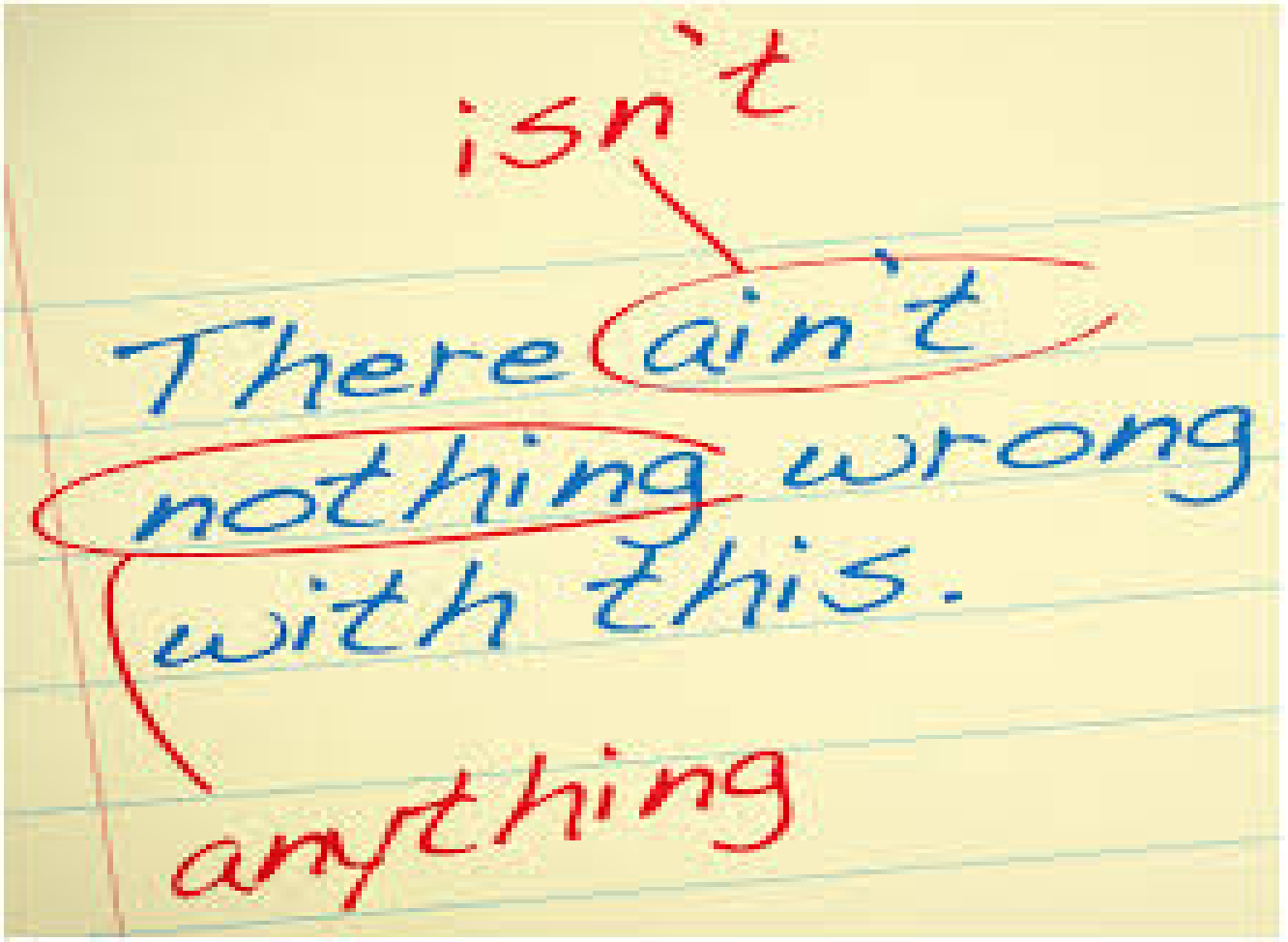
10a. The practical: Finding the right language

Avoiding the word “should”

Getting the right content and tone

PRO ≠ QOL ≠ HRQL

1000 drafts and Dee Kennedy



10b. The practical: technology, security, and bureaucracy

And if it weren't for…

It was the water


IPA
Bass
IPA
Budweiser
BUD LIGHT


WE DID IT...

Advancing the Assessment of Meaningful Patient Outcomes in Drug Development: A Brief History at the FDA and Beyond

Andrew E. Mulberg, MD, FAAP
Deputy Director
Division of Gastroenterology and Inborn Errors Products, CDER/FDA

FIFTH ANNUAL
PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP

April 29 - 30, 2014 ■ Silver Spring, MD

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FDA

Advancing the Assessment of Meaningful Patient Outcomes in Drug Development

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Kudos to our friend, expert and colleague,

Laurie Burke for being a pioneer, leader and expert in this arena

FDA's Mandate from Congress

- For approval drugs must:
  - demonstrate substantial evidence of effectiveness and clinical benefit
    - i.e. the impact of treatment on how a patient feels, functions, or survives
  - through adequate and well-controlled clinical studies

Path Forward: Disease Specific Clinical Trials

- Need well-defined patient population
  - to control variation in response to study drug
  - to better isolate clinical benefit of drug
- Need to exclude overlapping diseases that mimic:
  - Gastroparesis, such as functional dyspepsia, Gastroesophageal reflux disease (GERD) or Irritable Bowel Syndrome (IBS)
- Outcome measures should be appropriate for the intended concept of interest and context of use, and clinically meaningful

Path for developing new drugs

- Need to accurately identify patient population
- Need to identify key symptoms and disease definition
- Need to be able to measure clinically meaningful change

What are particular challenges for Gastroparesis trials?

Gastroparesis: characterized by delayed gastric emptying and Gastrointestinal (GI) symptoms

Gastric emptying test (GET)

- a laboratory measurement of gastric transit time
- not a measure of how a patient feels, functions, or survives
- does not always correlate with the clinical outcome
- delayed or rapid gastric emptying may produce same symptoms

Relationship between delayed gastric emptying and symptoms

- symptoms of gastroparesis are not solely related to delayed gastric emptying
- other etiologies may explain symptoms (independent of gastric emptying time)
  - visceral hypersensitivity
  - defective accommodation
  - gastric distension

Challenges for GP trials

- GET needs to be standardized
  - protocols
  - technologies (software & hardware)
- need to determine what constitutes a clinically meaningful change
  - outcome measures should be appropriate for the intended concept of interest and context of use, and clinically meaningful

IBS-Constipation

Proposed Primary Endpoints

Patient should be a weekly responder in BOTH pain severity AND stool frequency

- **Pain Severity Responder**
  - Decrease in weekly average of "worst pain in past 24 hours" score of $\geq$ 30%
- **Stool Frequency Responder**
  - An increase of at least 1 complete spontaneous bowel movement (CSBM) per week from baseline

IBS-Diarrhea

Proposed Primary Endpoints

Patient should be a weekly responder in BOTH pain severity AND stool consistency

- **Pain Severity Responder**
  - Decrease in weekly average of "worst pain in past 24 hours" score of $\geq$ 30%

- **Stool Consistency Responder**
  - Patient who experiences a $\geq$50% reduction in the number of days per week with at least one stool which has a consistency of $\geq$ type 6 compared with baseline

Guidance for Industry

Irritable Bowel Syndrome — Clinical Evaluation of Products for Treatment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Ruyi He at 301-796-0910 or Ann Marie Trentacosti at 770-716-9984.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2010
Clinical/Medical

Advancing the Assessment of Meaningful Patient Outcomes in Drug Development

PRO CONSORTIUM
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- **Alternate Endpoints and Clinical Outcome Assessments in Pediatric Ulcerative Colitis Registration Trials. J Pediatr Gastroenterol Nutr 2014**
  - Haihao Sun, Jessica J. Lee, Elektra J. Papadopoulos, Catherine S. Lee, Robert M. Nelson, Hari C. Sachs, William J. Rodriguez, and Andrew E. Mulberg

Advancing the Assessment of Meaningful Patient Outcomes in Drug Development

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

- **Cross-sector sponsorship of research in eosinophilic esophagitis: A collaborative model for rational drug development in rare diseases. J Allergy Clin Immunol 2012**
  - Robert Fiorentino, MD, Gumei Liu, MD, PhD, Anne R. Pariser, MD, and Andrew E. Mulberg, MD

Advancing the Assessment of Meaningful Patient Outcomes in Drug Development

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- Other disease areas currently under focus in DGIEP with SEALD
  - Functional Dyspepsia
  - PRO Development in Pediatric and Adult UC and Crohn's
  - Inborn errors of Metabolism

Acknowledgments

- Laurie Burke, RPh, MPH
- Ann Marie Trentacosti, MD
- Elektra Papadopoulos, MD
- Ashley Slagle, PhD
- Paivi Miskala, PhD
- Ruyi He, MD
- Nancy Snow
- Donna Griebel, MD

Discussion and/or Questions?

FDA PRO Guidance: An Industry Perspective

Tara Symonds, PhD
Pfizer, Inc

FIFTH ANNUAL
PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP

April 29 - 30, 2014 ■ Silver Spring, MD

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FDA

First things first…..

- I would personally like to acknowledge Laurie's leadership in driving the development and implementation of the PRO Guidance over these many years and her professional dedication to assisting industry sponsors and other stakeholders committed to recognizing, amplifying and including the patient's voice in appraising treatment benefit.

Past

- Draft Guidance in 2006 and Final Guidance in 2009
  - Timely document to increase quality of PRO assessment and labeling in the FDA context of a regulated claim
  - Documents good guide to measurement science
    - Implementation also included, which is very useful
  - Has led to more collaborative efforts between industry sponsors and the FDA to engage development of gold standard measures where needed

Present

- Guidance has not moved things forward as quickly as we may have hoped
  - Reduced PRO measurement claims currently than previously
    - Gnanasakthy et al (2012) Value in Health
  - Pursuit of perfection
  - Open interpretation of the guidance
    - Qualitative nature of the research
  - Years to formally qualify a measure
    - EXACT-PRO only to date, and that not fully qualified

Future

- Continuously improve swift and clear communication between FDA Review Division Staff, SEALD and sponsors on technical discussions and agreements to accelerate PRO measure development
- Identify and implement ways to ensure consistent application and interpretation of the PRO Guidance across review divisions without entirely subverting reasonable clinical judgment to measurement perfection
- Identify ways to expedite the DDT qualification process for PRO measures

Finally…just to reiterate

- I would like to again acknowledge Laurie's considerable contribution to this field
  - Also her staff and the review divisions' efforts at improving PRO measurement science.
- We must continue to push forward and work out ways to expedite the qualification process.

Thank-you

History of Patient Reported Outcome Measurement at FDA: My Perspective

Laurie Burke, RPh, MPH

Founder of LORA Group, LLC and former Associate Director for Study Endpoints and Labeling, Office of New Drugs, CDER, FDA

FIFTH ANNUAL
PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP

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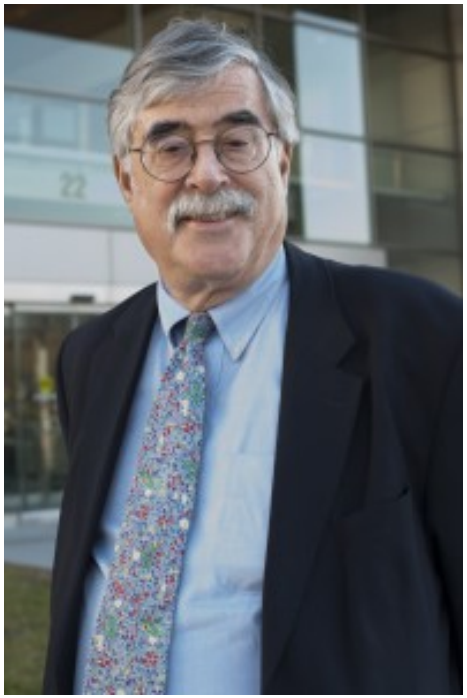
FDA

1962: Substantial Evidence of Effectiveness

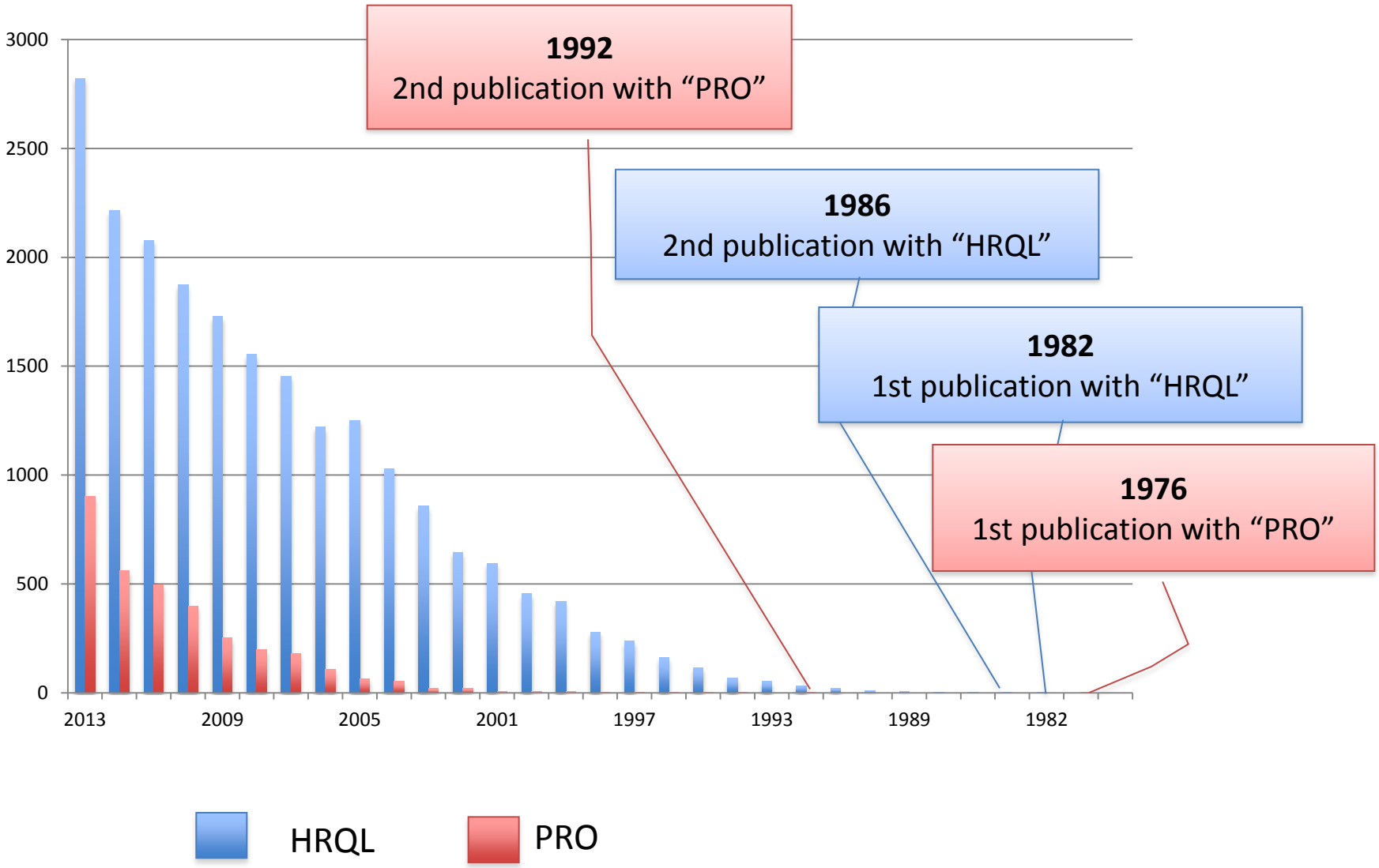
- *Kefauver-Harris Drug Amendments to the Federal Food, Drug, and Cosmetic Act*
  - Mandated that FDA must determine that a drug product is both safe and effective before it may be approved for marketing
  - Substantial evidence defined as *evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.*
  - Process of FDA oversight eventually evolved into the Investigational New Drug (IND) process

1970s: New Bureau of Drugs Staff

- 1972: Bob Temple
- 1975: Dee Kennedy
- 1976: Laurie Burke



HRQL and PRO Publications 1976-2013



PubMed search: 11 April 2014

1976: 1st PRO Publication

MEDICAL CARE
April 1976, Vol. XIV, No. 4

The Role of New Health Practitioners in a Prepaid Group Practice:

Provider Differences in Process and Outcomes of Medical Care

DAVID M. LEVINE, M.D., SC.D.,* LAURA L. MORLOCK, PH.D.,**
ALVIN I. MUSHLIN, M.D.,*** SAM SHAPIRO, B.S.,†
AND FAYE E. MALITZ, B.S.‡

Practice patterns and patient-reported outcomes of care are compared in detail for ten physicians and 12 new health practitioners delivering ambulatory care in two departments of a prepaid group practice, the Columbia Medical Plan (CMP). All providers completed questionnaires for a 50 per cent random sample of patients seen during a two-week period. Patients completed questionnaires prior to receiving care and were interviewed one week and one month after their clinic visits.

New health practitioners deliver approximately 75 per cent of well-person care, 56 per cent of problem-oriented care in adult medicine, and 29 per cent of problem care in pediatrics. They have become increasingly involved over time in the treatment of acute conditions and injuries while physicians have retained their predominant role in treating patients with chronic conditions.

1982: 1st HRQL Publication

MEDICAL CARE
May 1982, Vol. XX, No. 5

Communications

"Counterintuitive" Preferences in Health-Related Quality-of-Life Measurement

JAMES W. BUSH, M.D.,* JOHN P. ANDERSON, PH.D.,†
ROBERT M. KAPLAN, PH.D.,‡ AND WALLACE R. BLISCHKE, PH.D.§

The published preferences for scale steps in a health-related quality-of-life scale have been noted to be contrary to some prior assumptions about their rank ordering. The differences noted are actually statistically nonsignificant, and the observed ordering has a clear intuitive explanation. Several alternative explanations, including vagueness in the case descriptions, inaccuracy in the scaling method, the presence of interactions in the subjects' cognitive integration rules and chance inversions in the presence of the flat response surface characteristic of linear models, are all shown to be impossible or unlikely contributors to the empirical results. The implications of the "negative preferences" for other measurement approaches are discussed, as well as the role of separate attribute coefficients in health policy analyses.

1984: Adequate and well-controlled (A&WC) studies defined (21 CFR 314.126)

- Bureau of Drugs promulgated regs to explain the *substantial evidence of effectiveness* standard
- Studies are deemed A&WC based on multiple features of a clinical study design including:
  - Nature of the primary endpoint
    - Well-defined and reliable
  - Rigor of control of the Type I error rate
  - Prospectively planned analyses designed with rigor
- Treatment benefit = “feels, functions, survives”

1986: 2nd HRQL Publication

MEDICAL CARE
May 1986, Vol. 24, No. 5

Classifying Function for Health Outcome and Quality-of-life Evaluation

Self- Versus Interviewer Modes

JOHN P. ANDERSON, PHD, JAMES W. BUSH, MD, AND CHARLES C. BERRY, PHD

Validity assessment and the underreporting of dysfunction have been major problems in health-related quality-of-life measurement, including collecting data for analysis by the General Health Policy Model, using the Quality of Well-being scale (QWB). This analysis compares the results of self- versus interviewer modes of measurement and short, direct-answer questions versus probing algorithms in the QWB. The comparisons are made in terms of 1) correlations; 2) aggregate frequencies; 3) individual subject classifications; and 4) the actual state, established using evidence from multiple sources. Despite extremely high correlations between QWB scores from the two modes (>0.98), the lowest interviewer mode sensitivity (0.86) and predictive value dysfunctional (0.91) were substantially superior to the highest self-classification characteristics (0.66 and 0.73). In the populations studied, specificities and predictive values functional were equivalent (>0.94) for the two modes. The probe pattern of the

1989: Epoetin Alfa Approved for Tx of Anemia with Chronic Renal Failure

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APPROVED LABELING:

Once the target hematocrit (32% to 38%) was achieved, statistically significant improvements were demonstrated for most quality of life parameters measured, including energy and activity level, functional ability, sleep and eating behavior, health status, satisfaction with health, sex life, well-being, psychological effect, life satisfaction, and happiness. Patients also reported improvement in their disease symptoms. They showed a statistically significant increase in exercise capacity (VO2 max), energy, and strength with a significant reduction in aching, dizziness, anxiety, shortness of breath, muscle weakness, and leg cramps.

(This language was revised in 2007.)

1992: 2nd PRO Publication

Am J Cardiol. 1992 Jul 1;70(1):60-4.

Comparison of patient-reported outcomes after elective coronary artery bypass grafting in patients aged greater than or equal to and less than 65 years.

Guadagnoli E[1], Ayanian JZ, Cleary PD.

Abstract

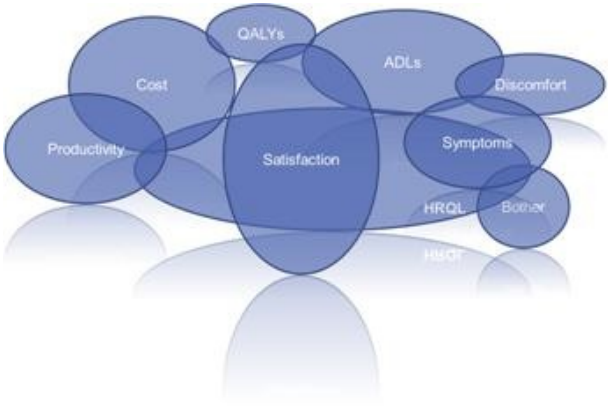
Older patients represent a growing proportion of patients undergoing coronary artery bypass grafting (CABG). Although functional benefits after CABG have been demonstrated, most assessments of outcomes have involved patients aged less than 65 years. Therefore, little is known concerning the impact of CABG on older patients compared with that on younger ones. A number of postsurgical (6 months) health-related quality-of-life outcomes (e.g., symptoms, cardiac functional class, instrumental activities of daily living, and emotional and social functioning) reported by patients aged less than 65 (n = 169) and greater than or equal to 65 (n = 99) years who underwent elective CABG at 4 major teaching hospitals in Massachusetts and California were compared. The proportion of patients reporting cardiac-related symptoms after surgery did not vary by age, and quality-of-life outcome scores of younger and older patients did not differ even after adjustment for clinical and demographic characteristics. The exception to this was mental health status, an outcome for which older patients reported better functioning than did younger ones. On average, patients in the 2 age groups reported equivalent improvement over preadmission status in instrumental activities of daily living, and emotional and social functioning. The independent relation of clinical and sociodemographic factors to quality-of-life outcomes was also investigated. Patients who functioned better before admission, those with less severe co-morbid disease, and married patients reported better functioning after discharge. In general, older patients who underwent elective CABG reported functional benefits similar to those reported by younger ones, and the factors associated with better functioning did not vary by age group.

20th Century Academic Activities that Provided the Foundations for the PRO Guidance

- 1932—Likert technique for measurement of attitudes
- 1949—Karnofsky performance measure
- 1969—Katz activities of daily living scale
- 1980s—Growth of psychometrics in health measurement
  - 1980—Health Insurance Study
  - 1987--McDowell and Newell
  - 1989—Streiner and Norman
- 1980s—New health status measures
  - 1973—Quality of Well-Being Index
  - 1979—Sickness Impact Profile
  - 1988—RAND MOS Short Form (SF-36)

1990s: Rise of Managed Care and Changes in Promotion in the US

- 1994—DDMAC/Lucy Rose
  - Laurie Burke recruited by DDMAC to review promotion evidence
  - Establishes HRQL and pharmacoeconomic working groups to address "new" claims
- 1995—DDMAC/Minnie Baylor Henry
  - Cost-effectiveness White Paper
  - Managed Care, Outcomes, and Labeling Staff (MOLS)
- 1997--PBM guidance
- 1998--Evidence Review Branch
  - Consults on HRQL measurement
    - CDER/CBER/CDRH
  - Elaine Hu Cunningham joins ERB



Draft - Not for Implementation

Guidance for Industry

Promoting Medical Products in a Changing Healthcare Environment; I. Medical Product Promotion by Healthcare Organizations or Pharmacy Benefits Management Companies (PBMs)

1999-2001: HRQL Harmonization Group Becomes the "PRO" Harmonization Group

- ISPOR
  - Nancy Kline Leidy
  - Paul Kind
  - Pennifer Erickson
  - Joyce Cramer
- ISOQOL
  - Dennis Revicki
  - Rick Berzon
  - Albert Wu
  - Donald Patrick
  - Ivan Barofsky
  - Charlotte McMillan
- PhRMA HOC
  - Nancy Santanello
  - Joe Jackson
  - Jean-Paul Gagnon
  - David Miller
  - Dick Willke
  - Rhys Williams
  - Haim Erder
  - Greg Boyer
- ERIQA
  - Catherine Acquadro
  - Ingela Wiklund
  - Dominique Dubois
  - Asha Hareendran
  - Olivier Chassany
  - Patrick Marquis
  - Bernard Jambon

- FDA
  - Bob Temple
  - Bob Meyer
  - Laurie Burke
  - Others

Volume 6 • Number 5 • 2003
VALUE IN HEALTH

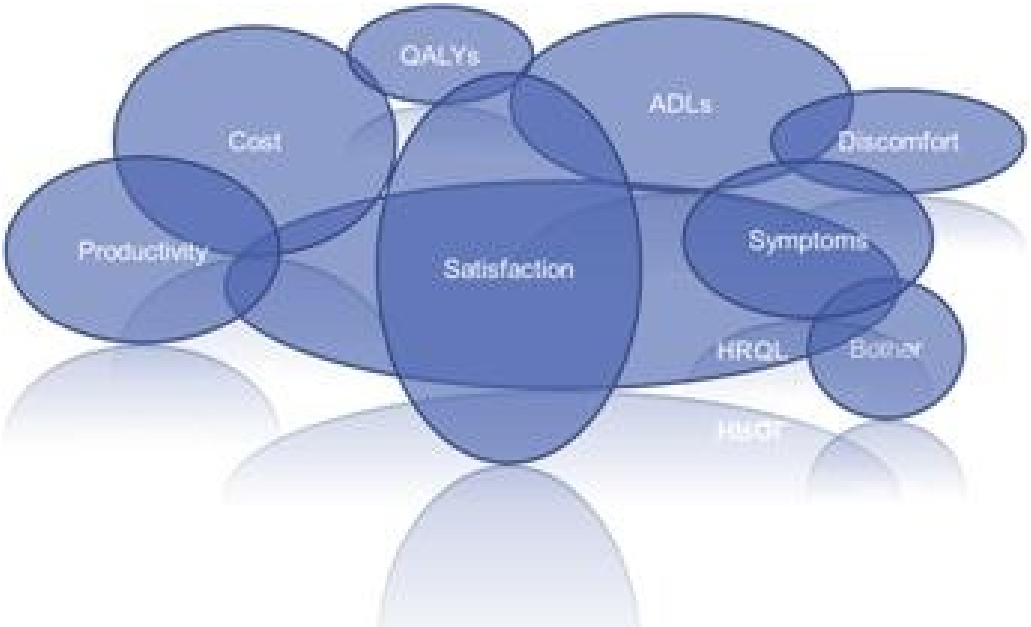
Incorporating the Patient's Perspective into Drug Development and Communication: An Ad Hoc Task Force Report of the Patient-Reported Outcomes (PRO) Harmonization Group Meeting at the Food and Drug Administration, February 16, 2001

Catherine Acquadro, MD,[1] Rick Berzon, DrPH,[2] Dominique Dubois, MD,[3] Nancy Kline Leidy, PhD,[4] Patrick Marquis, MD,[5] Dennis Revicki, PhD,[4] Margaret Rothman, PhD,[6] for the PRO Harmonization Group

[1]MAPI Research Institute, Lyon, France; [2]Boehringer Ingelheim GmbH, Ridgefield, CT, USA; [3]Janssen Pharmaceutica, Beerse, Belgium; [4]MEDTAP, Bethesda, MD, USA; [5]MAPI Values, Boston, MA, USA; [6]Johnson & Johnson, Raritan, NJ, USA

2000: "Patient Reported Outcomes" Introduced and Defined

- 3 October 2000, Drug Information Association, New Orleans
  - Includes HRQL, satisfaction, preference, symptoms, and anything else reported directly by the patient without interpretation or filtering



2002: Study Endpoints and Labeling Development (SEALD) Staff Formed

- John Jenkins and Sandy Kweder named OND Directors
  - Dan Shames, MD, former Director of Reproductive an Urologic Drug Products and visionary for study endpoint measurement

- SEALD began with staff of 1 plus a French intern (Elisabeth Piault)

  - 2003: Jane Scott
    - Wheel and spokes
  - 2004: Jeanne Delasko
    - Draft TPP guidance
    - Labeling review tool
  - 2005: Donald Patrick
    - Special Government Employee

2002: EMEA/FDA Interaction on HRQL/PRO

2002: Paris

Journee de therapeutique de Lariboisiere Staint-Louis, Paris, 25 octobre 2002

Olivier Chassany, Chair

Eric Abadie, CPMP/EMEA

2005: Reflection Paper

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 27 July 2005
Doc. Ref. EMEA/CHMP/EWP/139391/2004

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON THE REGULATORY GUIDANCE FOR THE USE OF HEALTH-RELATED QUALITY OF LIFE (HRQL) MEASURES IN THE EVALUATION OF MEDICINAL PRODUCTS

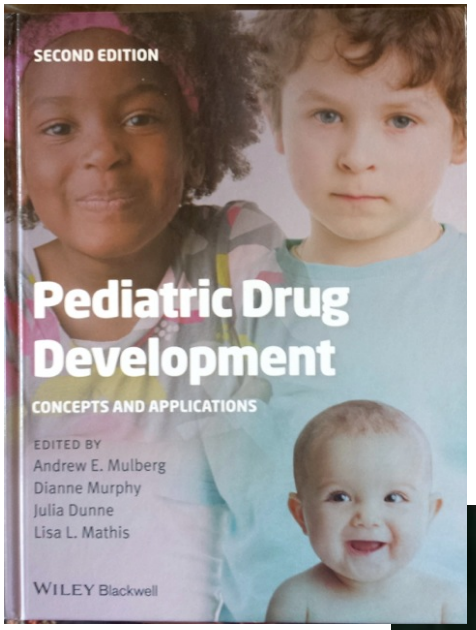
2012: Quarterly FDA/EMA meetings initiated with visit to FDA by Maria Isaac, MD

EMA Perspective on PRO Instrument Qualification and Harmonization

Maria Isaac, Spiros Vamvakas, Mira Pavlovic
Scientific Advice Section

2002: Increased Regulatory Focus on Pediatrics and Maternal Health

- 2002: BPCA
- 2003: PREA
- 2011: Mulberg, et al
- 2012: FDASIA



Guidance for Industry

Pediatric Study Plans:

Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans

2005: ISPOR PRO Good Research Practices Task Forces

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- 2005: Translation and Cultural Adaptation of PRO Instruments
- 2009: Using Existing PRO Instruments and Their Modification
- 2011: Content Validity: Eliciting Concepts for a New PRO Instrument
- 2011: Content Validity: Assessing Respondent Understanding
- 2009: Changing the Mode of Administration: Measurement Equivalence between Electronic and Paper-Based PRO Instruments
- 2013: Developing and Implementing PRO Instruments for Assessment of Children and Adolescents
- 2013: Validation of Electronic Systems to Collect PRO Data
- 2014: Developing and Implementing Clinician Reported Outcome Measures to Assess Treatment Benefit (in development)
- 2014: PROs in Rare Disease Clinical Trials (in development)

2005: PRO Qualification Program

2005: PhRMA/FDA workshop on vasomotor symptoms

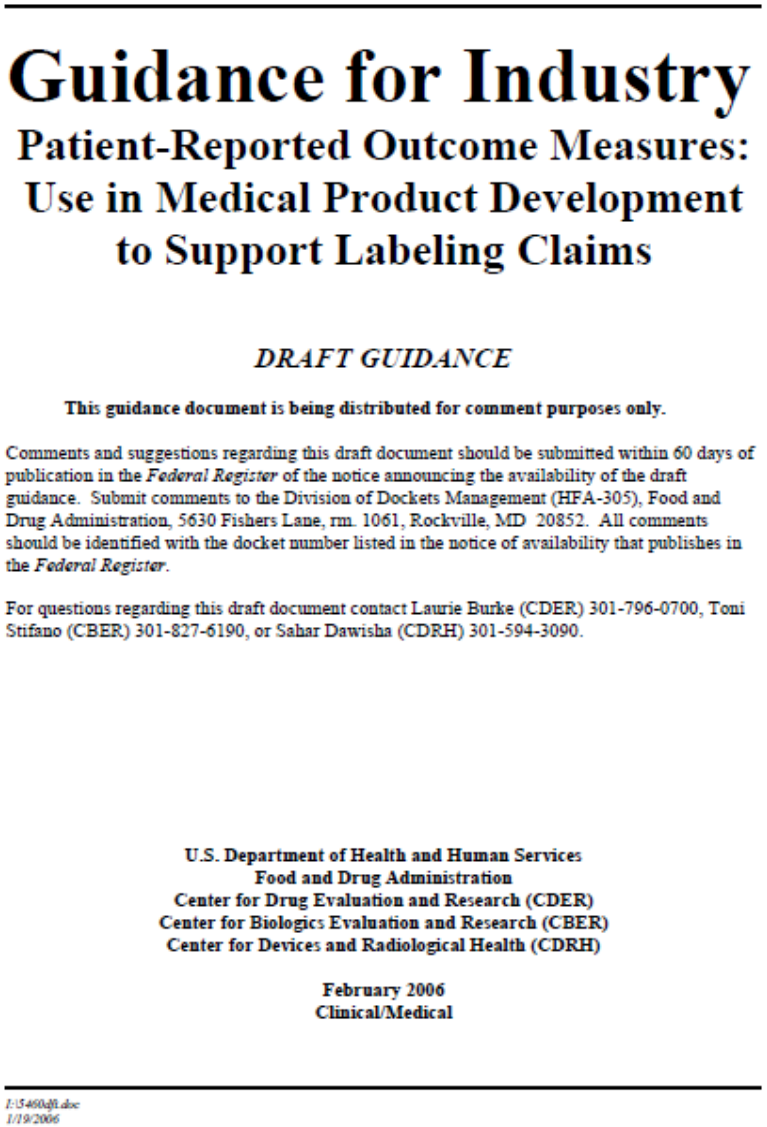
2006: PhRMA PPP proposal

2008: PRO Consortium formed

- CDER identified a list of PROs in search of a measure

2010: Draft DDT Qualification Guidance

2006: Draft PRO Guidance



Guidance for Industry

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

DRAFT GUIDANCE

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For questions regarding this draft document contact Laurie Burke (CDER) 301-796-0700, Toni Stifano (CBER) 301-827-6190, or Sahar Dawisha (CDRH) 301-594-3090.

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

1:\5460dft.doc
1/19/2006

- Defined how FDA interprets "well-defined and reliable" (21 CFR 314.126) for PRO measures intended to provide evidence of treatment benefit
  - Content validity
  - Construct validity
  - Reliability (particularly test-retest)
  - Ability to detect change
    - Information to support interpretation of change

2006: Chantilly Conference

- Organized jointly by the Mayo Clinic College of Medicine and CDER
- Intended to facilitate review and discussion of the draft guidance document among diverse stakeholders and FDA representatives
- Meeting titled “FDA Guidance on Patient-Reported Outcomes: Discussion, Dissemination, and Operationalization”
- Held during February 23–25, 2006, Chantilly, VA, USA (the same month the draft guidance was published)

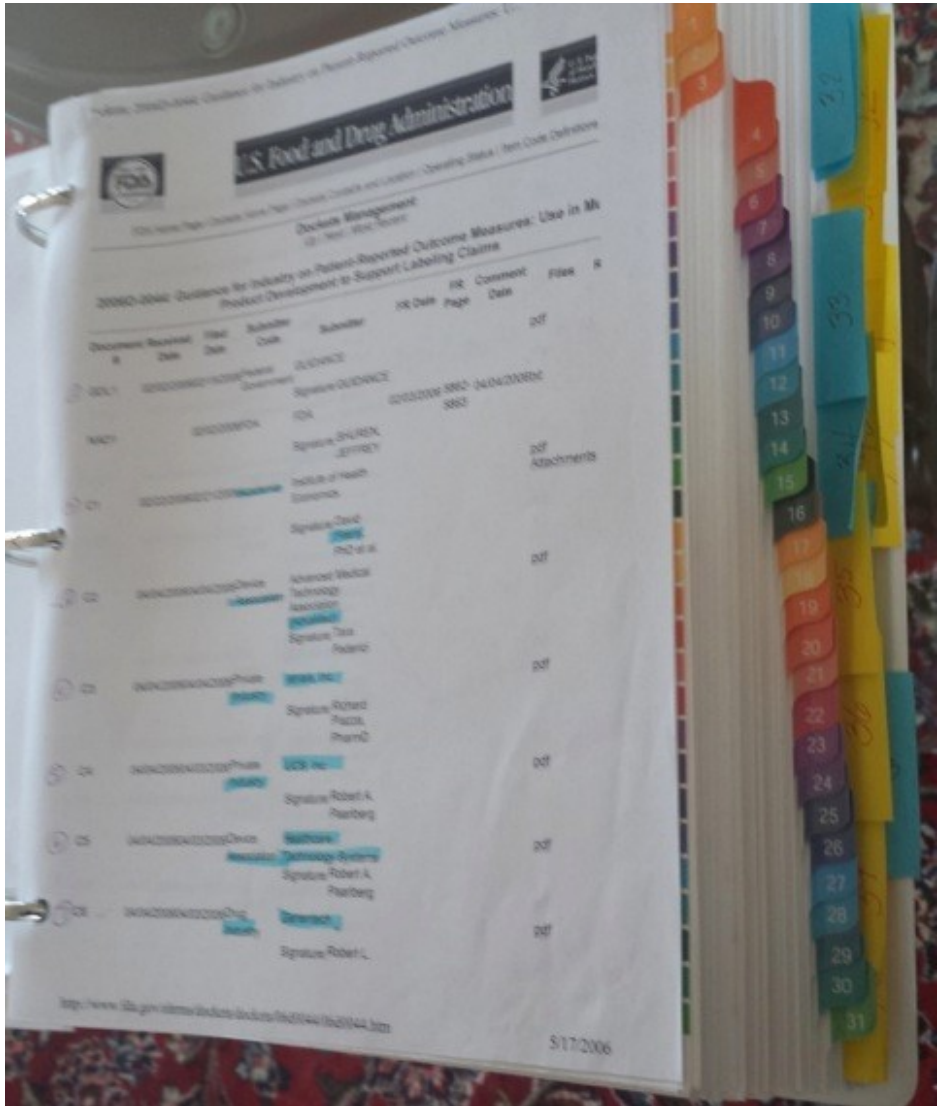
Volume 10 • Supplement 2 • 2007
VALUE IN HEALTH

Meeting on the FDA Draft Guidance on Patient-Reported Outcomes

Amylou C. Dueck, PhD, Jeff A. Sloan, PhD

Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

2007: Guidance Comments



2008: EMA Qualification Program

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 January 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

2009: Clinician and Caregiver Reported Outcomes

PRO CONSORTIUM
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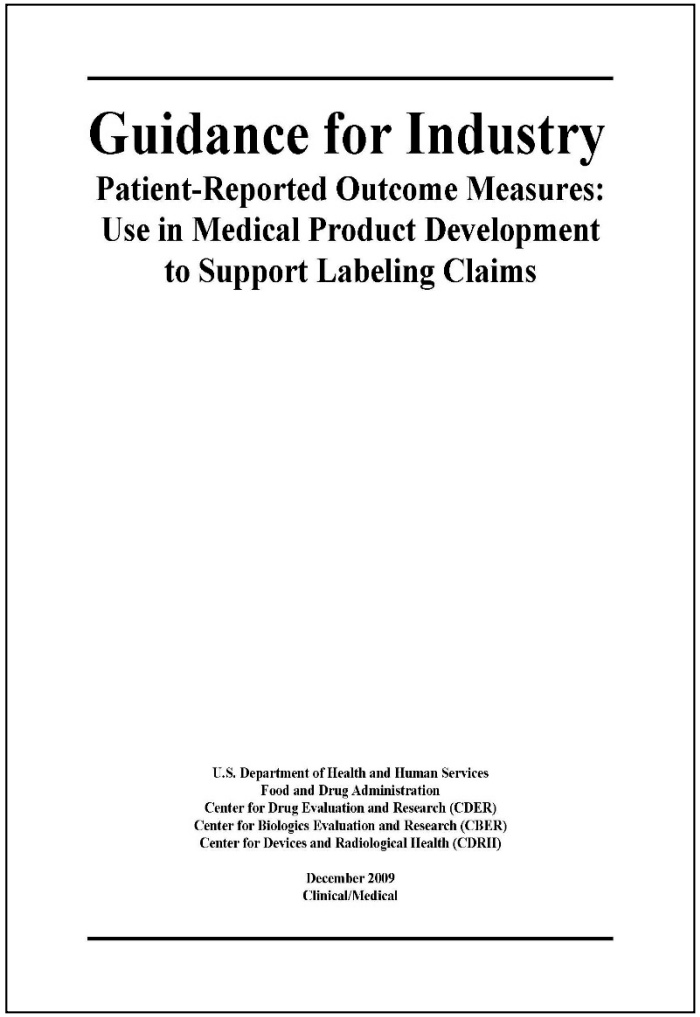
2009: Final FDA PRO Guidance



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

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf

2011: FDA "Clinical Outcome Assessment" Workshop

Measurement in Clinical Trials: Review and Qualification of Clinical Outcome Assessments; Public Workshop
October 19, 2011—White Oak, MD

Agenda

Welcome and House-keeping Considerations	5 min	Co-Chairs: **Laurie Burke, Marc Walton**	8:30 am 8:35 am
Introduction: Why Good Measurement Principles Matter	20 min	CDER perspective, measurement, and public-private partnerships; **Janet Woodcock**	8:35 am 8:55 am

Also starring: Tom Fleming, John Powers, Nat Katz, Jeremy Hobart, Nancy Kline Leidy, Todd Edwards, ShaAvhree Buckman, David Wholley, Stephen Coons, Patrick Marquis, Maria Isaac

Discussion Panel: John Alexander, Julie Beitz, Edward Cox, Sharon Hertz, Lisa Kammerman, Elektra Papadopoulos, Anne Pariser, Richard Pazdur, Bob Rappaport, Bob Temple, Ellis Unger, Josef Toerner, Maria Issac

2012: White Oak Meeting to Discuss Mixed Methods for Content Validity

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Qualitative Research

Quantitative Research

Concept elicitation study; draft instrument; cognitive debriefing to refine item content

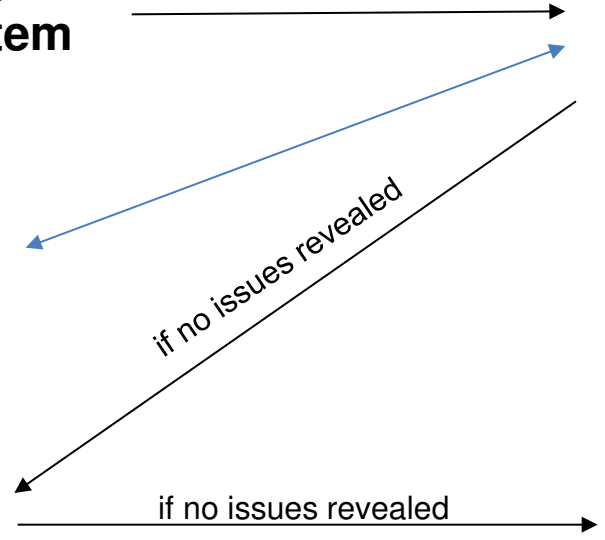
Address issues (e.g., range, gaps, response options)

Cognitive debriefing of final instrument

Administer draft questionnaire and explore using new psychometric methods

Administer revised questionnaire and analyze again

Content validity is established in the COU studied; proceed with further validation



2012: FDASIA/PDUFA V

Advancing Development of Patient-Reported Outcomes (PROs) and Other Endpoint Assessment Tools

1. Develop clinical and statistical staff capacity to more efficiently and effectively respond to submissions that involve PROs and other outcomes assessment tools. These staff will advance the development of these tools by providing IND and qualification consultations and through promoting best practices for review and qualification of outcomes assessment tools. The additional capacity includes staff who will focus on review and qualification of endpoint assessment tools, including IND consultations with sponsors, as well as staff who will be integrated into the review divisions to facilitate evaluation of these tools and improve familiarity and understanding of assessment tools among review staff. These activities will allow for greater understanding of challenges that arise during development of outcomes assessment tools, potential strategies to overcome these challenges, and greater consistency in FDA's approach to review, qualification, and usage of these tools as part of the drug development process.
2. By the end of FY 2014, hold a public meeting to discuss FDA's qualification standards for drug development tools, new measurement theory, and implications for multi-national trials.

2013: "Patient Centered Outcomes"

- 20 May 2013, ISPOR, New Orleans
  - ***Those outcomes important to patients' survival, function, or feelings as identified or affirmed by patients themselves, or judged to be in patients' best interest by clinicians and caregivers when patients cannot report for themselves***
    - ***Donald Patrick***

Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

1 Understanding the Disease or Condition

A. Natural history of the disease or condition
- Onset/Duration/Resolution
- Diagnosis
- Pathophysiology
- Range of manifestations

B. Patient subpopulations
- By severity
- By onset
- By comorbidities
- By phenotype

C. Health care environment
- Treatment alternatives
- Clinical care standards
- Health care system perspective

D. Patient/caregiver perspectives
- Definition of treatment benefit
- Benefit-risk tradeoffs
- Impact of disease

2 Conceptualizing Treatment Benefit

A. Identify concept(s) of interest (COI) for meaningful treatment benefit, i.e., How a patient:
- Survives
- Feels (e.g., symptoms)
- Functions

B. Define context of use (COU) for clinical trial:
- Disease/Condition entry criteria
- Clinical trial design
- Endpoint positioning

C. Select clinical outcome assessment (COA) type:
- Patient-Reported Outcome (PRO)
- Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- Performance Outcome (motor, sensory, cognition)

3 Selecting/Developing the Outcome Measure

A. Search for existing COA measuring COI in COU:
- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

B. Begin COA development
- Document content validity (qualitative or mixed methods research)
- Evaluate cross-sectional measurement properties (reliability and construct validity)
- Create user manual
- Consider submitting to FDA for COA qualification for use in exploratory studies

C. Complete COA development:
- Document longitudinal measurement properties (construct validity, ability to detect change)
- Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- Submit to FDA for COA qualification as effectiveness endpoint to support claims

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
http://www.fda.gov/Drugs

Qualification of **CLINICAL OUTCOME ASSESSMENTS** (COAs)

I. Identify Context of Use (COU) and Concept of Interest (COI)

- Outline hypothesized concepts and potential claims
- Determine intended population
- Determine intended application/characteristics (type of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework
- Position COA within a preliminary endpoint model
- Document COU and COI

II. Draft Instrument and Evaluate Content Validity

- Obtain patient or other reporter input
- Generate new items
- Select recall period, response options and format
- Select mode/method of administration/data collection
- Conduct cognitive interviewing
- Pilot test draft instrument
- Finalize instrument content, format and scoring rule
- Document content validity

III. Cross-sectional Evaluation of Other Measurement Properties

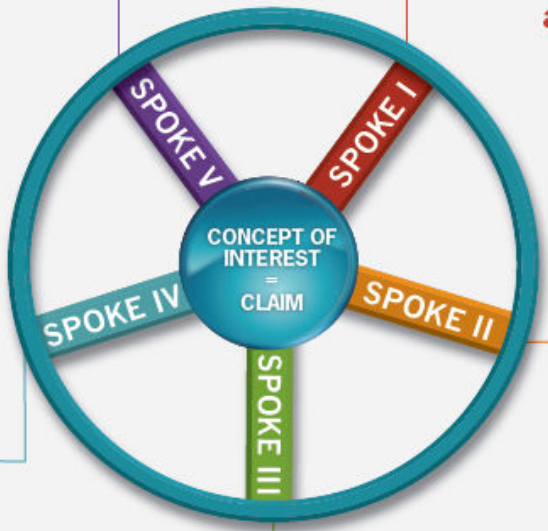
- Assess score reliability (test-retest or inter-rater) and construct validity
- Establish administration procedures & training materials
- Document measure development
- Prepare user manual
- Consider submitting to FDA for COA qualification as exploratory endpoint prior to longitudinal evaluation

IV. Longitudinal Evaluation of Measurement Properties/ Interpretation Methods

- Assess ability to detect change and construct validity
- Identify responder definition(s)
- Provide guidelines for interpretation of treatment benefit and relationship to claim
- Document all results
- Update user manual
- Submit to FDA for COA qualification as effectiveness endpoint to support claims

V. Modify Instrument

- Identify a new COU
- Change wording of items, response options, recall period, or mode/method of administration/data collection
- Translate and culturally adapt
- Evaluate modifications using spokes I - IV
- Document all changes
- Consider submitting to FDA for qualification of new COA, as appropriate



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2013: SEALD Staff

SEALD Staff, September 2013

2014: Final Qualification Guidance

- Outcome nomenclature clarified
  - Survival
  - Clinical outcome assessments (COAs)
    - Performance outcomes (PerfOs)
    - Clinician reported outcomes (ClinROs)
    - Observer reported outcomes (ObsROs)
    - Patient reported outcomes (PROs)
  - Biomarkers
- First qualification decision as an Attachment:

Attachment to

Guidance on Qualification Process for Drug Development Tools

Qualification of Exacerbations of Chronic Pulmonary Disease Tool for Measurement of Symptoms of Acute Bacterial Exacerbation of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease

DRAFT GUIDANCE

2014: More PRO-Related Guidances

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Guidance for Industry

Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway

Guidance for Industry

Analgesic Indications: Developing Drug and Biological Products

Guidance for Industry

Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis: Developing Drug Products for Treatment

Conclusions

- We've come a long way
- Patients have a loud voice in clinical trial outcomes
- The science of measurement continues to evolve
- Best practices in labeling continue to evolve
- There's a lot more to do!

Discussion and/or Questions?

Session Participants

Moderator

- *Stephen Joel Coons, PhD* – Executive Director, Patient-Reported Outcome Consortium, C-Path

Presenters:

- *Robert Temple, MD* - Deputy Center Director for Clinical Science and Acting Deputy Director of the Office of Drug Evaluation I, OND, CDER, FDA
- *Catherine Acquadro, MD* - Scientific Advisor at Mapi Research Trust and Coordinator of Patient-Reported Outcomes (PRO) Harmonization Group (2000-2002)
- *Donald L. Patrick, PhD, MSPH* – Professor and Director, Seattle Quality of Life Group and Biobehavioral Cancer Prevention and Training Program, University of Washington
- *Andrew E. Mulberg, MD, FAAP, CPI* – Deputy Director, Division of Gastroenterology and Inborn Error Products (DGIEP), OND, CDER, FDA
- *Tara Symonds, PhD* – Senior Director, Global Head PRO Center of Excellence, Pfizer
- *Laurie Beth Burke, RPh, MPH* – Founder of LORA Group, LLC and former Associate Director for Study Endpoints and Labeling, OND, CDER, FDA