Assessing and reporting outcomes important to patients in clinical trials and Cochrane reviews

XV Cochrane Collaboration

25 October 2007

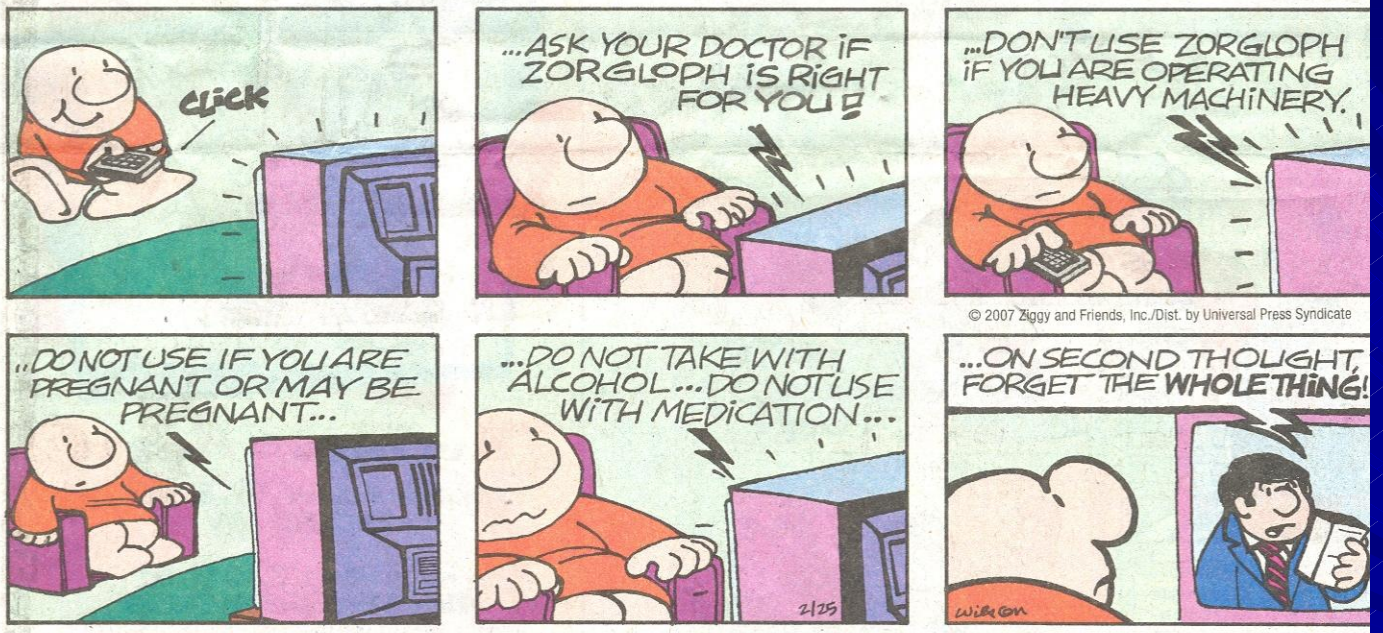
09:00 am -10:30am

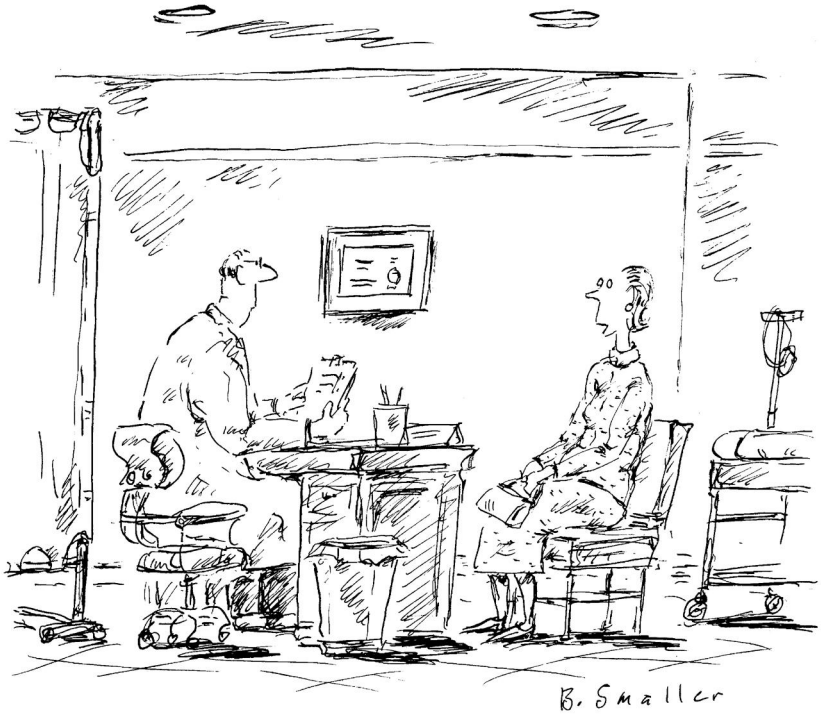
Donald L. Patrick

University of Washington

Co-Convenor, Patient Reported Outcomes Methods Group

ZIGGY/ by Tom Wilson





"I think the dosage needs adjusting. I'm not nearly as happy as the people in the ads."

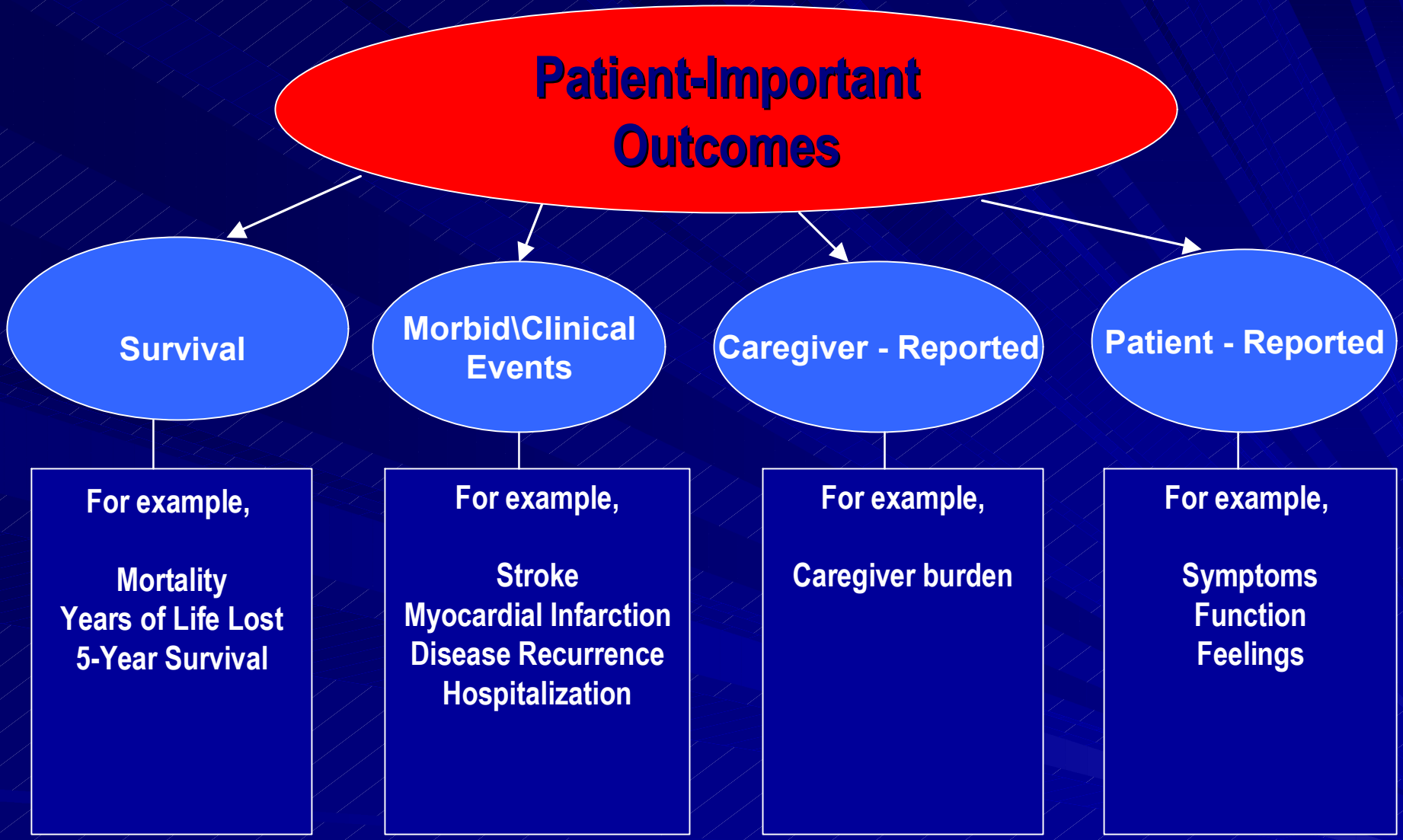
"In your case, Dave, there's a choice—elective surgery, outpatient medicinal therapy, or whatever's in the box that our lovely Carol is holding."

The Patient and Consumer Voice

- Information on effectiveness of treatments through accessible Cochrane reviews
- Preferences about outcomes and treatments – which side effects are best for me?
- Decision-making with clinicians in evidence based medicine
- How to get the patient voice into Cochrane reviews?

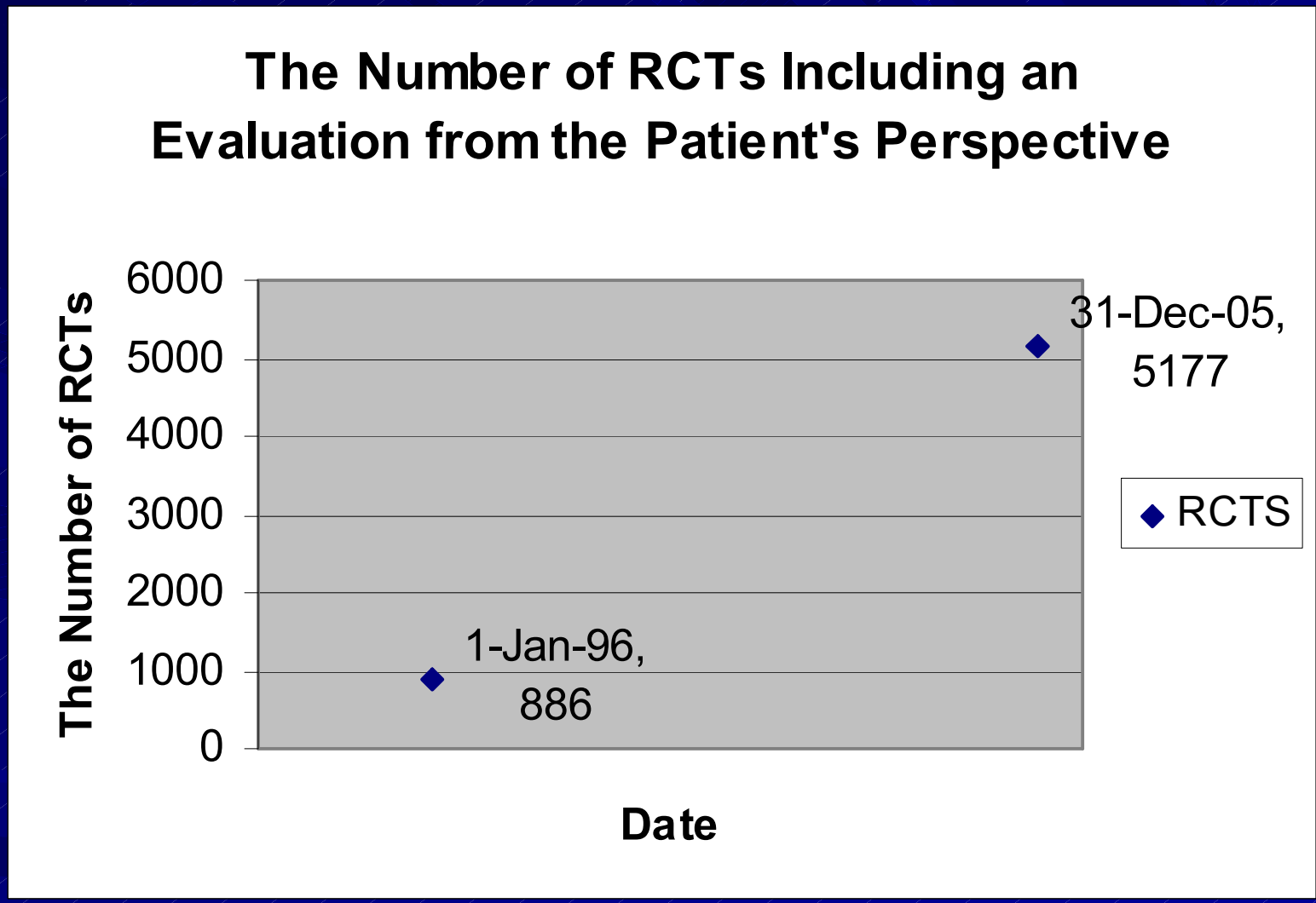
After this session, you will be able to:

- Define Patient Reported Outcomes (PROs)
- Explain why PROs are important in clinical trials
- Describe how PROs are currently being incorporated into Cochrane reviews
- Identify key methodological and practical issues


Patient-Important Outcomes
Survival
Morbid\Clinical Events
Caregiver - Reported
Patient - Reported
For example,
Mortality
Years of Life Lost
5-Year Survival
For example,
Stroke
Myocardial Infarction
Disease Recurrence
Hospitalization
For example,
Caregiver burden
For example,
Symptoms
Function
Feelings

What is a Patient-Reported Outcome (PRO)?

- **PRO**: Any report directly from patients, without interpretation by physicians or anyone else, about how they function or feel in relation to a health condition and its therapy (from diaries, questionnaires, interviews, etc.)
- **PROs developed with patient input using qualitative methods a guiding principle**
- **PRO term requires concept purported to be measured be specified**
- **PRO ≠QoL≠HrQoL**


The Number of RCTs Including an Evaluation from the Patient's Perspective
The Number of RCTs
6000
5000
4000
3000
2000
1000
0
1-Jan-96, 886
31-Dec-05, 5177
RCTS
Date

Why PROs?

- Some treatment effects known only to the patient, i.e. pain, symptoms, feelings
- Small changes in survival further informed by symptoms, function, and feelings
- Survival not only outcome of interest for many interventions
- Physiologic measures often do reflect how patient functions or feels
- Well-developed assessment by patients is as reliable if not more reliable than ratings of patient's condition by clinicians

Relationship between Airway Obstruction and Respiratory Symptoms

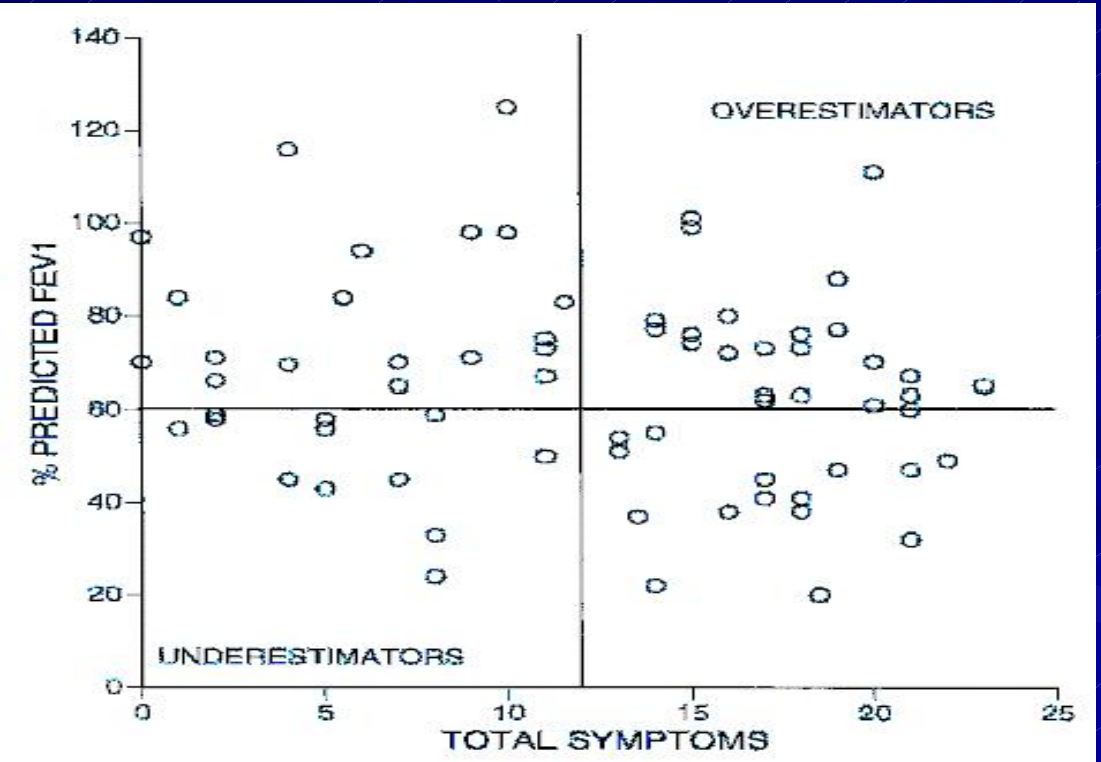
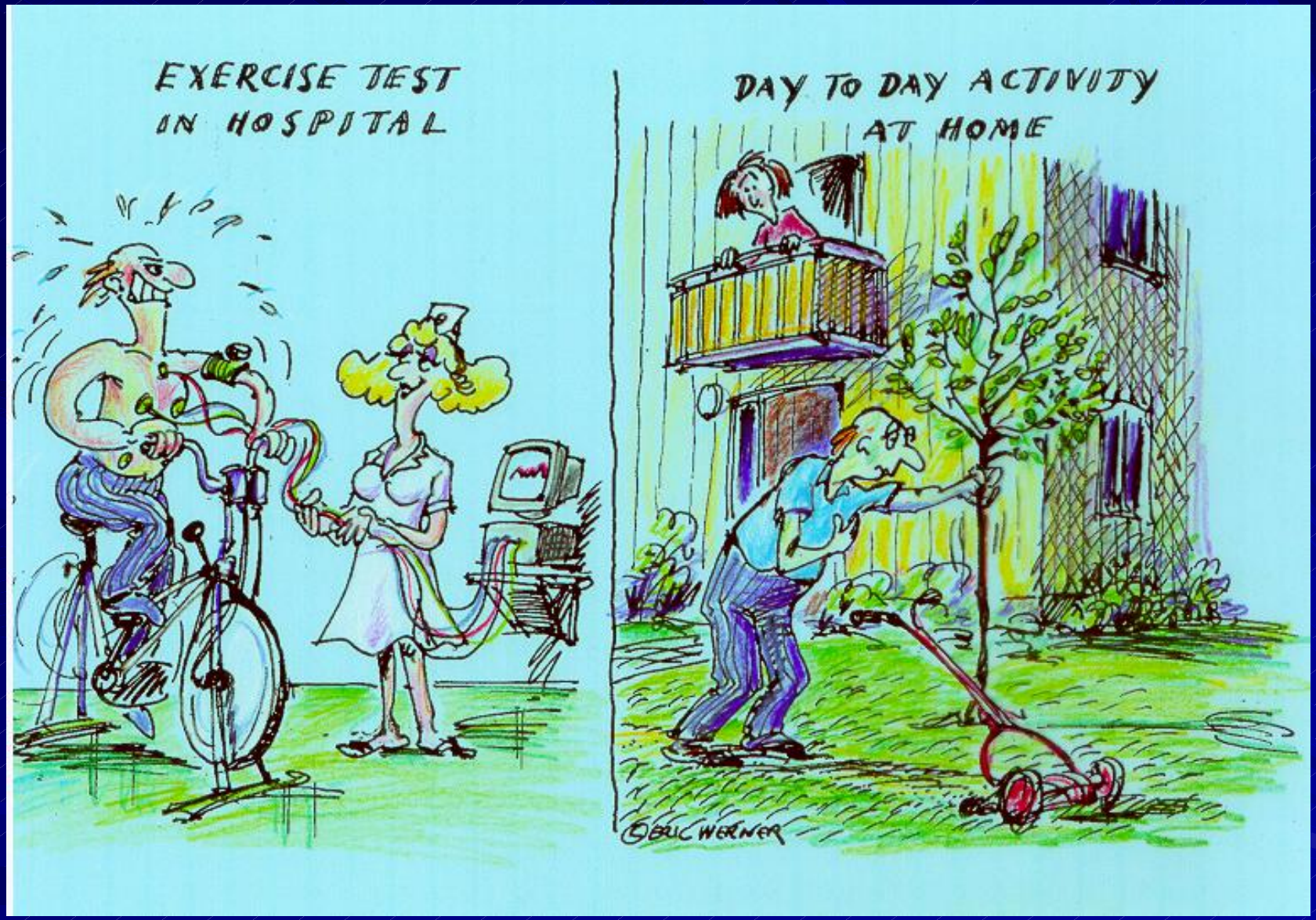


FIGURE 1. Relationship between total asthma symptoms and FEV_1 (r=0.143; p=0.237; n=70). Lines are drawn at a total asthma symptom score of 12 and FEV_1 of 60% predicted (see text).

r = 0.143 (p N.S.)

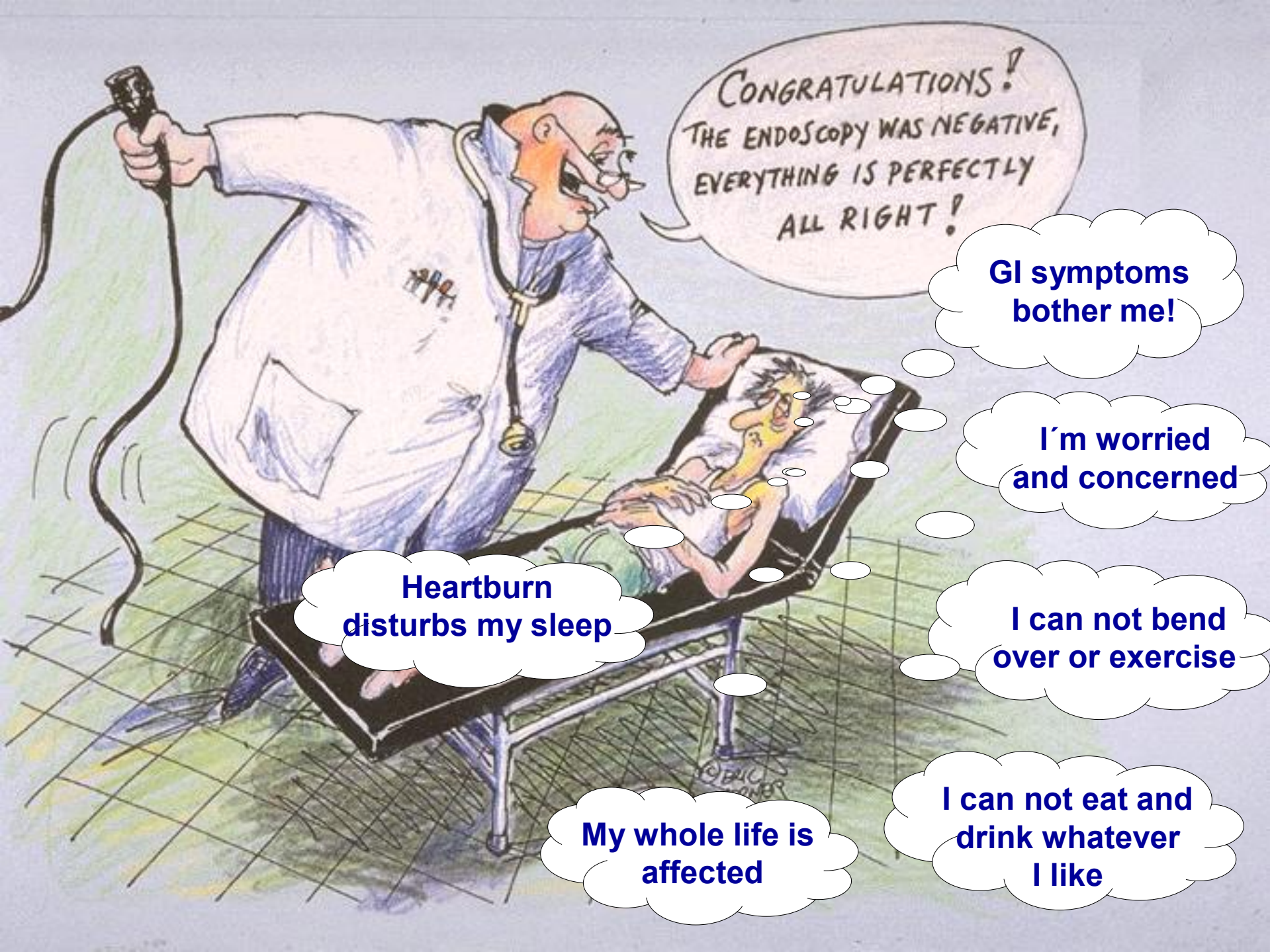
Teeter J. Chest 1998; 113:272-77



“Objective” **“Subjective”**

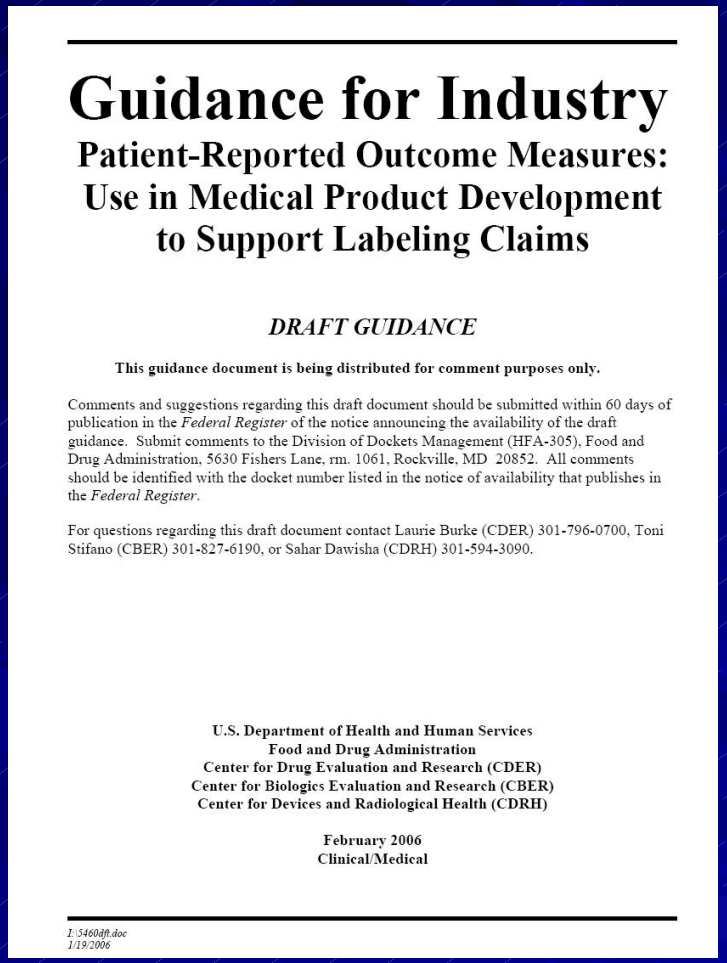
Exercise test versus physical functioning, r = 0.40

Wiklund I et al.
Clin Cardiol 1991;14


CONGRATULATIONS! THE ENDOSCOPY WAS NEGATIVE, EVERYTHING IS PERFECTLY ALL RIGHT!
GI symptoms bother me!
I´m worried and concerned
I can not bend over or exercise
I can not eat and drink whatever I like
My whole life is affected
Heartburn disturbs my sleep

PROs communicate value of a treatment to…

- Patients\Consumers…who ask for and experience the treatments
- Families, caregivers, loved ones…who want the best for patients\consumers
- Providers...who decide with patients on prescribing of treatments
- Payers...who reimburse for treatments
- Regulatory authorities…who evaluate new products for approval and promotion
- Technology assessors, i.e., NICE in UK



Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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 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)

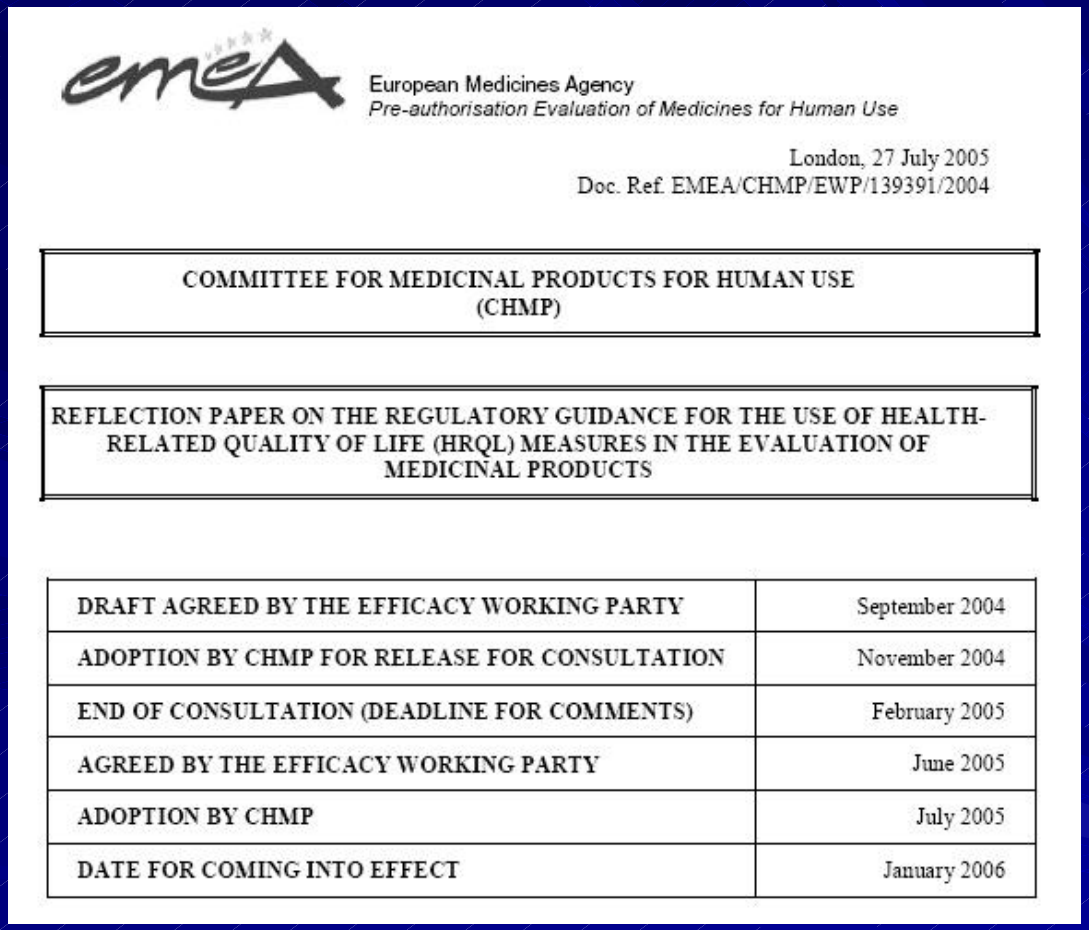
February 2006
Clinical/Medical

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

A little help from US drug regulators
Published Feb 2, 2006

www.**fda**.gov/cder/**guidance**/5460dft.pdf

EMEA



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

DRAFT AGREED BY THE EFFICACY WORKING PARTY	September 2004
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	November 2004
END OF CONSULTATION (DEADLINE FOR COMMENTS)	February 2005
AGREED BY THE EFFICACY WORKING PARTY	June 2005
ADOPTION BY CHMP	July 2005
DATE FOR COMING INTO EFFECT	January 2006

… from European Drug Regulators

Took effect: January 2006

Outcomes measured with PROs

- Direct assessment of treatment benefit
  - Not a surrogate
  - Elicited without clinical interpretation
  - Part of a general movement toward the patients participation in decisions about their health
  - Patients are the best source of information about how they feel and function as a result of treatment
  - Best PROs are those developed with patients

PRO Methods Group
Finding PRO studies for Reviews

- Reviewers cannot rely on single index term, medical subheading (MeSH or MeSH check words) or search term to identify trials incorporating PROs or PROs in trials.
- There are differences in index or search terms used to denote data on PROs in the major databases, i.e., MEDLINE, EMBASE, PsycINFO, etc.
- Apply standard search strategy recommended by the author's Collaborative Review Group (CRG). Check all retrieved studies to identify those that include the PROs of interest.
- Conduct a separate, additional PROs search to supplement the standard strategy.

Common Terms

- Quality of life
- Health status
- Psychosocial
- Functional status
- Symptoms (specific)
- Health-related quality of life
- Well-being
- Questionnaire
- Diary

Identifying Concepts in Existing PROs

- PRO concepts can be determined ONLY by examining the actual content of items or questions included in instrument *claiming* to measure quality of life or health-related quality of life or pain, etc.
- Read what developer says the instrument measures
- List the concepts you think are measured
- Compare with what patients might think is important
- Ideally you would have qualitative study to support patient voice

PROs in Cochrane Reviews: Cognitive Behavioural Therapy in Tinnitus

Martinez DP, Waddell A, Perera R, Theodoulou M. Cognitive behavioural therapy for tinnitus. *Cochrane Database of Systematic Reviews* 2007, Issue 1.

- Tinnitus is a condition where the patient consistently experiences sound within the ear or head. Currently there is no treatment specifically targeting this condition.
- This article presents Cognitive Behavioural Therapy as a treatment method for patients experiencing either unilateral or bilateral tinnitus.
- CBT is generally prescribed for patients suffering from depression, anxiety or insomnia, however the positive psychological outcomes that often accompany CBT suggest it would be effective for Tinnitus also.
- Six trials reviewed, composed of 285 participants.

Cognitive Behavioural Therapy in Tinnitus

- The primary outcome for this review was subjective tinnitus loudness.
- The secondary outcomes were
  - Depression
  - QoL
- No significant results were found for either the loudness (SMD = 0.06, 95% CI -0.25 to 0.37) or the depression (SMD = 0.29, 95% CI -0.04 to 0.63).
- **However, for QoL, there was a significant difference for those in CBT treatment, and patients reported a decrease of global tinnitus severity (SMD = 0.7, 95% CI 0.33 to 1.08).**

Cognitive Behavioural Therapy versus control (waiting list): Quality of Life

Martinez DP, Waddell A, Perera R, Theodoulou M. Cognitive behavioural therapy for tinnitus. *Cochrane Database of Systematic Reviews* 2007, Issue 1.

Cognitive Behavioural Therapy versus control (other intervention): Quality of Life

Martinez DP, Waddell A, Perera R, Theodoulou M. Cognitive behavioural therapy for tinnitus. *Cochrane Database of Systematic Reviews* 2007, Issue 1.

Many practical and methodological issues

- But nothing particularly special about missing data, reporting bias, heterogeneity, etc.
- Main issues are selection of PROs that reflect what is important to patients and
- Including PROs in evaluation of treatments
- One perhaps special issue…

Interpretation of Treatment Effects

- Degree to which one can assign easily understood meaning to observed score changes on a PRO measure at the end of the trial
- Prior experience with change scores often best guide
- Change in scores from new PRO instruments often translated to qualitative category or other external measure with more familiar meaning
- Saturday special session with Gord Guyatt

Quote from J. Tukey

- "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 poor measurement of the right thing."

Measuring the “right thing”?

- Ask patients\consumers and then
- Include patient-important outcomes in reviews and summary of findings tables


STAHLER
IRAQ
IT'S OBVIOUS... AFTER CONNECTING THE DOTS.