SEMINAR

May 23, 2003 – 09:00-16:45 pm

INAMI, 211 Tervueren Av, BRUSSELS

Educational Program on Patient-Reported Outcomes (PROs) in Clinical Trials

Facilitators

Catherine Acquadro, Olivier Chassany

Introductions

Objectives

- ✓ To help pharmaceutical companies, reviewers, and investigators of clinical trials acquire the skills needed to assess PRO included in regulatory files and publications
- ✓ To facilitate decisions made by health authorities and health-care providers
- ✓ To facilitate dialogue between regulators, members of pharmaceutical companies, and health-care providers through the same training

Background

- ✓ 1st version developed by Adelphi and Mapi Values in 1995 on model from airline industry
- ✓ Adaptation and development for a Program on HRQL/PRO in Clinical Trials in 2002, collaboration between:
  - **Mapi Research Institute, Lyon, France**
    Catherine Acquadro, MD
  - **The ERIQA Group**
    Olivier Chassany, MD, PhD
  - **and the Cochrane HRQL Methods Group**
    Donald L. Patrick, MSPH, PhD

Methods: Workmats

- ✓ **Interactive learning method**
- ✓ **Participants**
  - Small ***group discussions*** and interactions
  - To understand the new information
  - To complete the assignments through group discussions
  - Group answers have to be discussed by all participants to reach a consensus

Methods: Workmats

- ✓**Workmats (WM)**
  - Large worksheets
  - Contain concise information: background
  - Present various assignments
- ✓**Workbook**
  - Reference source
  - Additional information on PRO
  - Questionnaires and articles

Content

WM	
1	How do disease and treatment impact upon a patient – from the patient's perspective?
2	Deciding which PRO to assess the impact of disease and treatment
3	How is a new PRO questionnaire developed? 1st Steps: Development of items and item reduction
4	How is a new PRO questionnaire developed? 2nd Steps: Psychometric validation and cultural adaptation
5	Choosing an appropriate existing measure
6	Analysis of PRO data
7	Presentation and interpretation of PRO included in clinical trials

Facilitators

Europe

- Linda Abetz
- Catherine Acquadro
- Benoît Arnould
- Juliette Longin
- Elyse Trudeau
- Olivier Chassany
- Isabelle Girod
- Bernard Jambon
- Elaine McColl

USA

- Kathy Bungay
- Bruce Crawford
- Verne Kemerer
- Patrick Marquis
- Elisabeth Piault
- Donald Patrick
- Ann Skinner
- Claire Snyder
- Anita Wagner
- Albert Wu

Pilot training: 2002

Tests	Speakers
Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), May 15, 2002; Paris, France	Catherine Acquadro, MD; Olivier Chassany, MD, PhD; Juliette Longin, PhD
Food and Drug Administration (FDA), May 23, 2002; Washington, D.C., USA	Catherine Acquadro, MD; Olivier Chassany, MD, PhD; Bruce Crawford, MA, MPH; Patrick Marquis, MD, MBA
International Cochrane Colloquium, July 31 to August 3, 2002 Stavanger, Norway	Catherine Acquadro, MD; Olivier Chassany, MD, PhD; Elaine McColl, Msc; Donald L. Patrick, MSPH, PhD

Finalization of workmats

2003 Sessions

Health Authorities

- Jan. 24: **AFSSAPS**, Faculté Lariboisière, Paris, France
- April 8: **ANAES**, Paris, France
- May 23: **INAMI**, Brussels, Belgium

PROs
Concept and Definition

Array of Effectiveness Measures

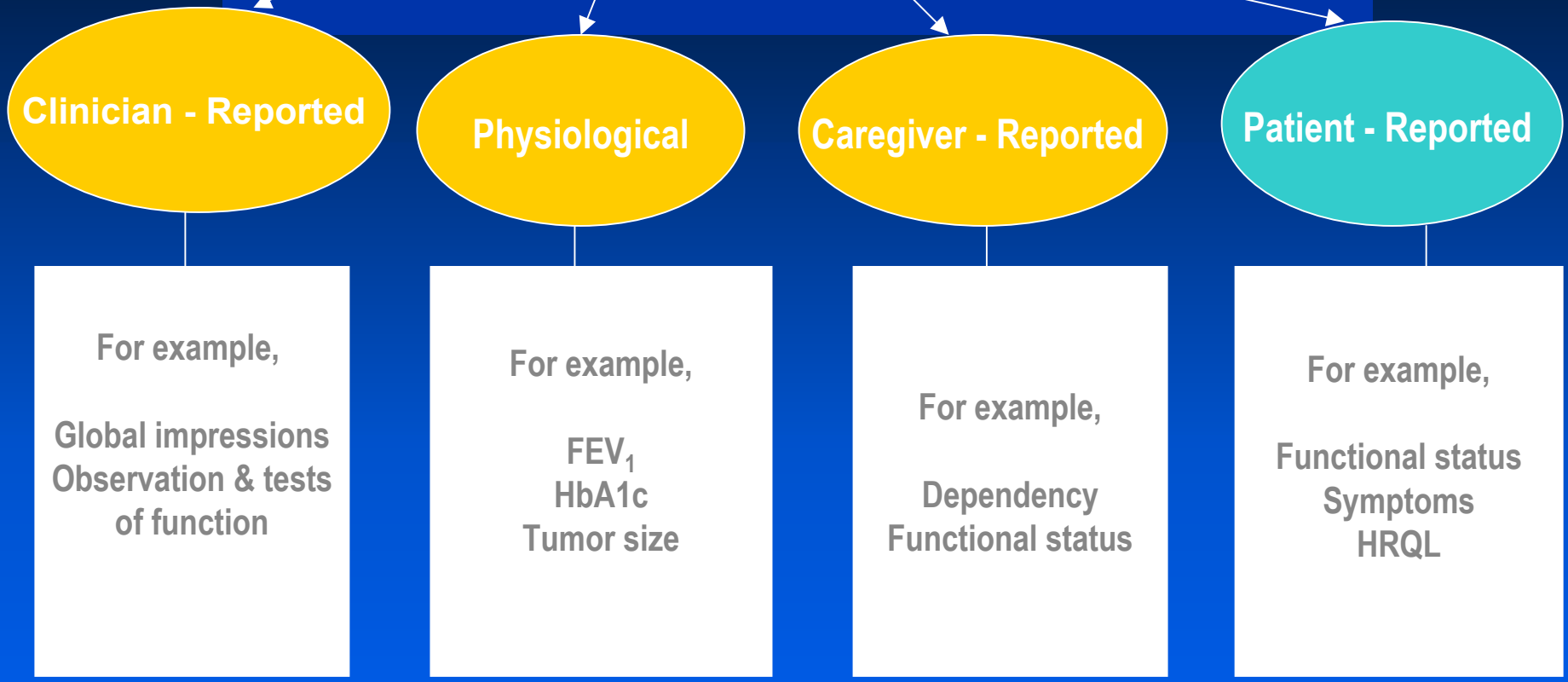
- **Surrogate endpoints, e.g., mm Hg blood pressure reduction**
- **Endpoints such as number of heart attacks prevented**
- **Survival, e.g., lives saved, number of life-years gained**
- **Patient Reported Outcomes, including symptoms, health status, quality of life, and HrQoL**
- **Others include: cost, productivity, satisfaction with treatment, QALYs and their variants**

PROs: Concept and Definition

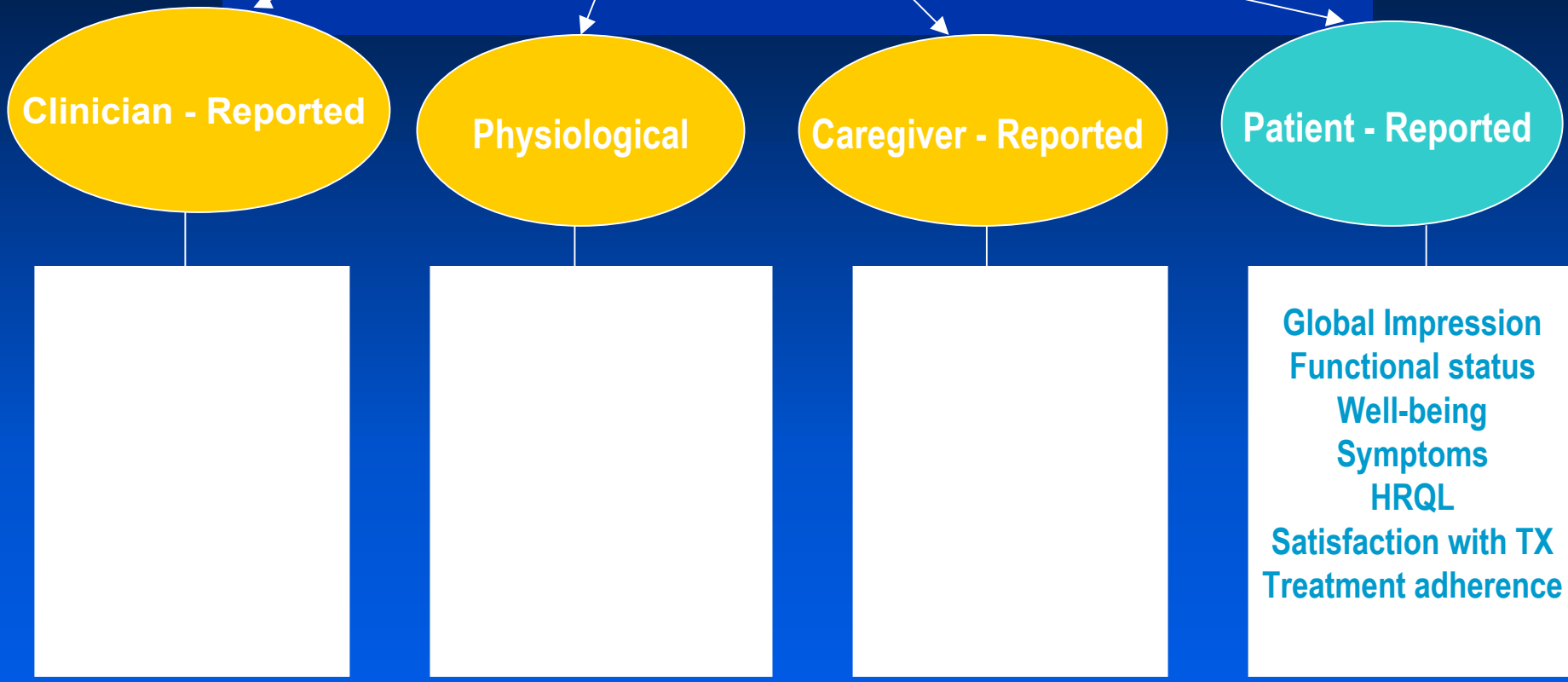
- ✓ **Patient-reported Outcomes**

The patient's report of a health condition and it's treatment

Patient Outcomes Assessment Sources and Examples



Patient Outcomes Assessment Sources and Examples



Health-Related Quality of Life

One Type of PRO

Health-Related Quality of Life

One Type of PRO

- ✓ Represents the patient's evaluation of the impact of a health condition and its treatment on relevant aspects of life

Health-Related Quality of Life

Essential Elements

- ✓ Represents the patient's *evaluation* of the impact of a health condition and its treatment on relevant aspects of life
  - The evaluative component can be measured by
    - *severity*
    - *bothersomeness*
    - *importance or*
    - *satisfaction*

Health-Related Quality of Life

Essential Elements

- ✓ Represents the patient's evaluation of the impact of a health condition and its treatment on *relevant aspects* of life
  - The relevant aspects of life are measured as domains, e.g.,
    - *physical*
    - *psychological*
    - *social*
    - *symptoms*

Health-Related Quality of Life

Essential Elements

- ✓ Represents the patient's evaluation of the impact of a health condition and its treatment on *relevant aspects* of life
  - Domains are selected to be relevant to patients and their significant others, e.g.,
    - *focus groups*
    - *cognitive interviews*
    - *literature reviews*

Patient Satisfaction with Treatment and Care

One Type of PRO

Why Assess Patient Satisfaction?

- ✓ **Patient satisfaction affects**
  - Use of services
  - Maintenance of relationships with providers
  - Adherence to treatment regimens
- ✓ **Patient satisfaction contributes to the evaluation of**
  - Health care: organizational and individual
  - Specific aspects of treatment

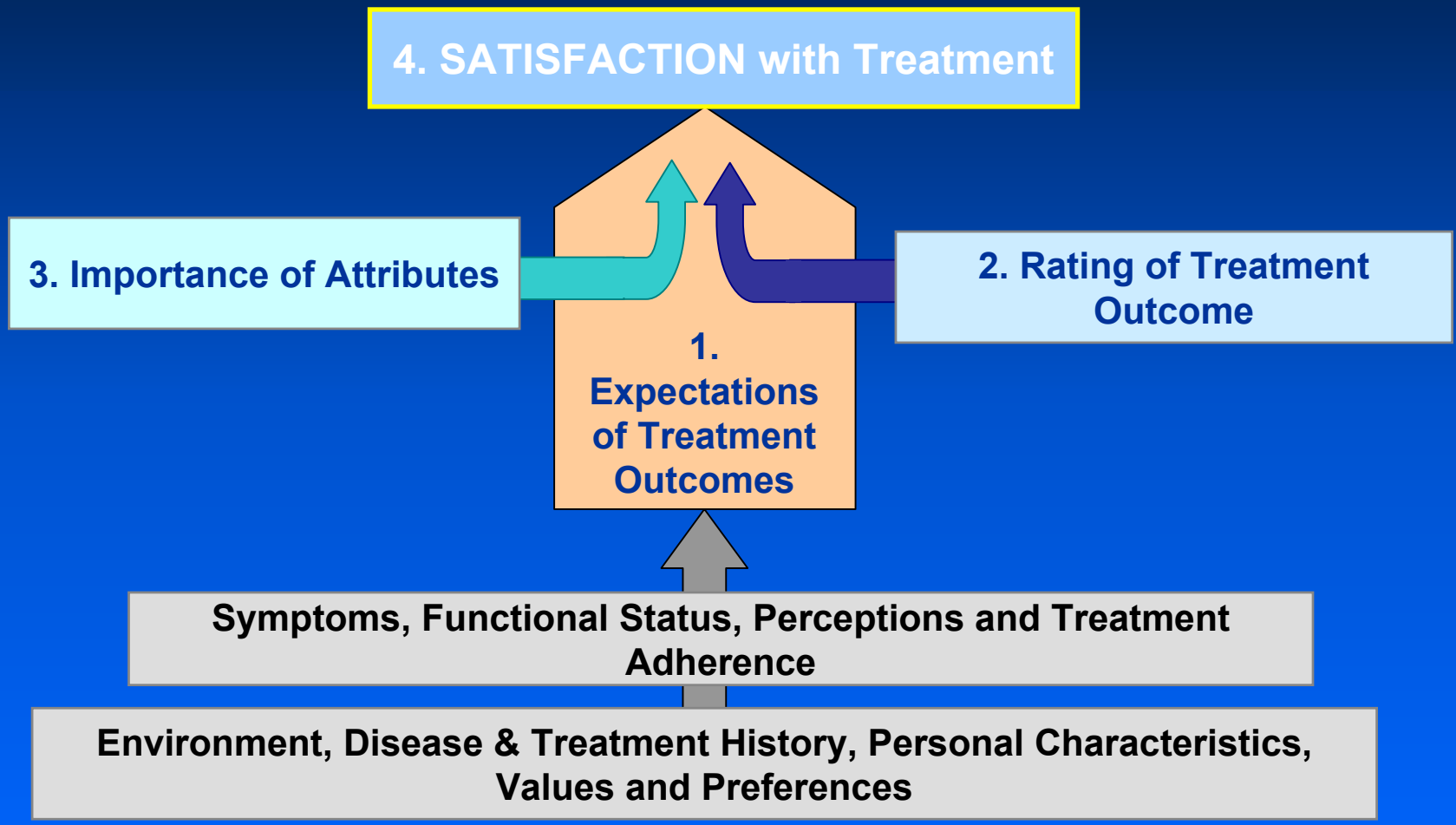
Patient Satisfaction with Treatment

One Type of PRO

- ✓ Represents the patient's evaluation of salient aspects of the treatment and overall evaluation of treatment experience

Conceptual Model for Treatment Satisfaction

Patrick et al, forthcoming



Types of Assessments

- ✓ **Satisfaction with care**
  - Very satisfied to Very dissatisfied
- ✓ **Beliefs about care**
  - Strongly agree to Strongly disagree
- ✓ **Ratings of care**
  - Excellent to Poor
  - 0 - 10
- ✓ **Reports about Care**
  - Yes/No
  - Never to Always

Attributes of MigraineTreatment

Patrick et al, forthcoming

To have *total relief* from my migraine pain

To have my migraine pain *relieved quickly*

During a migraine, to be *free of pain for a long time*

Other than pain, to have *no additional migraine symptoms* that bother me

To have *confidence* this treatment will work

To have migraines cause *less disruption* in my life

To have my migraine relieved with *just one dose of medication*

As the medication wears off, to have *freedom from migraine pain returning*

To have a treatment that is *easy to use*

Pitfalls in Measuring Satisfaction with Health Care

- ✓ Patients report high levels of satisfaction with treatment
  - – Occurs even in the face of other negative information
  - – Global measures particularly suffer + bias

Why is Satisfaction Positively Biased?

- ✓ Low expectations – consider intent and effort of medical providers
  - Pain management
- ✓ If negative experience, assume outside provider's area of responsibility
- ✓ Patients take the blame
- ✓ Patients want physicians to like them
- ✓ Need to justify time/effort spent on tx

Why is Satisfaction Positively Biased?

- ✓ Tendency to give socially desirable response – reluctant to say dissatisfied
- ✓ Fear poor treatment in future if complain
- ✓ Perceive service as positive because asking about their satisfaction
- ✓ Questionnaires don't always tap complaints of patients

Adherence to Treatment Recommendations

One Type of PRO

Terminology

ADHERENCE vs. COMPLIANCE

- ✓ Adherence is the preferred term

- ✓ Adherence: active, choice, interactive
- ✓ Compliance: passive, non-selective, not balanced with shared decision making

Adherence

One Type of PRO

- ✓ Represents the patient's report of behaviors that coincide with medical or health advice to take medications, follow diets, use devises, or execute life-style changes

Adherence Measurement

- ✓ PRO assessment complements unobtrusive measures like MEMSCAP, pill counts
- ✓ May reflect patient evaluation of HRQL and satisfaction
- ✓ May determine patient evaluation of HRQL and satisfaction
- ✓ Intermediate outcome and not end-result

INSTRUMENT DEVELOPMENT

From: Patient Reported Outcomes Harmonization Meeting
Food and Drug Administration
Rockville, Maryland, March 1, 2002

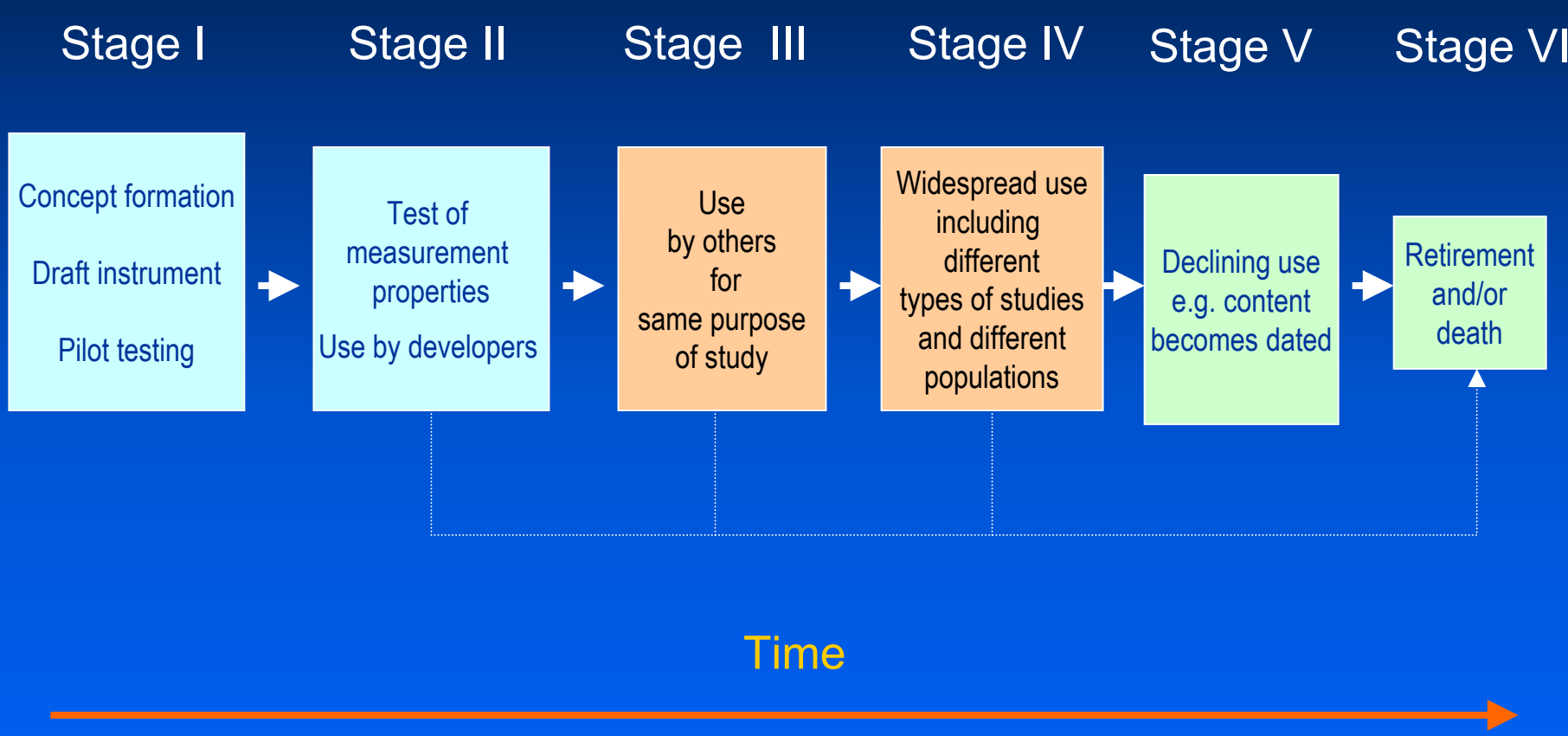
What is a PRO Instrument?

- ✓ A PRO instrument is comprised of one or more self-reported items that reflect some underlying concept
- ✓ Items must provide good coverage of the concept
  - Comprehensiveness of coverage is a qualitative determination, but instrument should:
    - *Include* items that are relevant and important to the patient
    - *Exclude* items that are not relevant to the patient
    - *Not* be overly weighted toward less important concepts

PRO Instruments: Selection or Development

- ✓ Instruments to meet development criteria: Harmonization
- ✓ Use of instruments to meet study design and analysis criteria: CONSORT
- ✓ Instruments to meet psychometric criteria: established by testing experts, psychological associations, health outcomes experts

Life Cycle of a PRO Instrument



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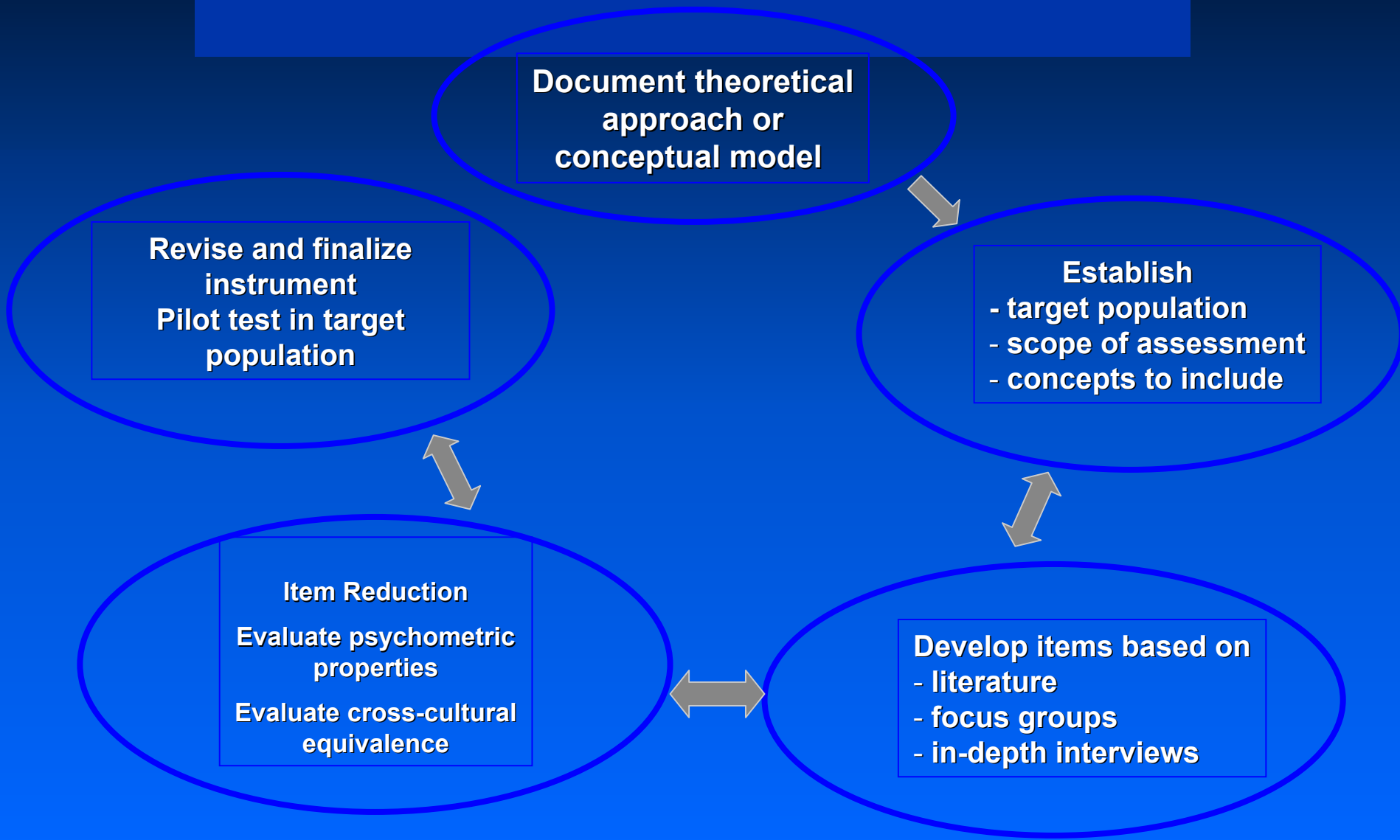
PRO Instrument Development

- ✓ Patient involvement required at multiple points in development of instrument
- ✓ Involvement may be:
  - Direct
    - E.g., focus groups, cognitive debriefing
  - Indirect
    - E.g., response to instrument (to provide data for psychometric assessment)

Development of a PRO Instrument an Iterative Process



Steps in Developing a PRO Instrument

1

- ✓ **Identify theoretical approach or conceptual model** (drives development of items)
  - Needs based model
  - Functional assessment
  - Preference based assessment
  - Behavioral dysfunction
- ✓ **Identify measurement model** (drives scoring)
  - Index vs. profile
  - Domain structure

Steps in Developing a PRO Instrument

2

- ✓ **Identify**
  - Target population
    - E.g., age, condition severity, cognitive capability
  - Concepts to be included in PRO assessment
    - E.g., symptoms, HRQL, functional status
  - Scope of assessment
    - E.g., single vs. multiple domains
- ✓ **Item generation and selection**
  - Review literature (including similar instruments), focus groups, in-depth interviews
  - Identification of response options, recall period

Steps in Developing a PRO Instrument

3

- ✓ **Pilot**
- ✓ **Generate data for item reduction**

  in target population

  - Consider generalizability

- ✓ **Item reduction**

  E.g., importance ratings, item analysis, factor analysis

Steps in Developing a PRO Instrument

4

- ✓ **Evaluation of cross cultural equivalence**
  - Current effort to identify best practices
- ✓ **Cognitive debriefing**
  - Ensure that respondent understands the intent of items and instructions

Steps in Developing a PRO Instrument

Example from WM4

Assignment 2:
The cultural adaptation of a PRO measure is a rigorous and complex process (see workbook).

Its main objective is to obtain a conceptual equivalence between the source and target versions, allowing, among other things, a « pooling » and comparison of international studies data.

In this assignment, you will define the concepts behind several items, find appropriate equivalents of a same item in different languages and finally explore the relevance of patients' testing.

ASSIGNMENT 2

Cultural adaptation

B) Disease: Asthma -- Original version developed in Canada

Item: shoveling snow

➔ *The questionnaire had to be translated into Japanese, and Norwegian*

1) What is the concept explored?

2) Do you think that the team has chosen the literal translation?

✎ **Give your suggestions for the Japanese and Norwegian versions.**

Steps in Developing a PRO Instrument

5

- ✓ **Evaluation of feasibility and psychometric properties**
  - Feasibility (e.g., missing data, time to complete)
  - Reliability (alpha, test-retest, IRR)
  - Construct, cross-sectional and longitudinal validity (e.g., convergent, responsiveness)
  - Interpretation (e.g., distribution, anchor, experience)
  - Alternate methods of data collection

- ✓ **Specification and justification of scoring algorithm**
  - E.g. Index, subscale scores

Steps in Developing a PRO Instrument

Example from WM4

C) RESPONSIVENESS

- Within-subject difference (6 wk minus baseline) in salmeterol group divided by the pooled within-subject SD of change
- R - DB - PG - MC - 6-wk
- Salmeterol 50 µg or Salbutamol 400 µg bid
- 120 patients randomized
- FEV_1 % predicted : 59%

	*Effect size**
AQLQ (32)	0.820
Activities (11)	0.860
Symptoms (12)	0.723
Environment (4)	0.550
Emotions (5)	0.302
	Effect size
LWAQ	0.694
Health know ledge	0.625
Health appraisal	0.333
	Effect size

Van Mölken MP et al. Eur Resp J 1995; 8: 888-98.

O. Chassany

1

ASSIGNMENTS

Assignment 1:

This assignment presents several different validation steps.

Please comment each of them.

This is the comparison of 2 instruments used to evaluate the effects of salmeterol on patient's life. Give your comments.

AQLQ: Asthma Quality of Life Questionnaire; LWAQ: Living With Asthma Questionnaire

How do we know when we have enough evidence to support a claim?

- ✓ PRO instruments intended for use in labeling based on trial data should show
  - Evidence of reliability and validity *in the target population* studied independent of the trial on which claim is based
  - Additional validity support should be obtained from trials on which claims are based
  - Sponsor should provide full evidence of development and assessment upon request

Conclusions

- ✓ Instrument development is an iterative process
- ✓ No single *right* way to develop an instrument although best practices available for steps in the process
- ✓ Cannot tell by looking at items in an instrument whether it is an appropriate and unbiased measure of concept
  - Must look at process of development
  - Reasonable to request description of development process

WORKMAT 1

How do disease and treatment impact upon a patient from the patient's perspective?

Learning objectives

- To identify the impact of health conditions and treatment from a patient's perspective
- To distinguish the different ways diseases and treatment may affect a patient
- To create an awareness that treatments can affect patients

WORKMAT 2

Deciding which PRO to assess the impact of disease and treatment

Learning objective

To define the relevant domains and items depending on the conditions studied

WORKMAT 3

How is a PRO questionnaire developed?

1st Steps: Development of items and item reduction

Learning objective

To describe the process of item generation and item reduction

WORKMAT 4

How is a PRO questionnaire developed?

2nd Steps: Psychometric and linguistic validation

Learning objectives

- To describe the evaluation of psychometric properties: reliability, validity, and responsiveness
- To describe the process of linguistic validation

WORKMAT 5

Choosing an appropriate existing measure

Learning objectives

- To explore the process for selecting appropriate health status instruments for use in specific clinical trial scenario
- To examine the trade-offs in the selection process
- To review the criteria necessary for appropriate evaluation of a PRO instrument
- To identify and evaluate established questionnaires for use in a specific patient group

WORKMAT 6

Analysis of PRO data

Learning objectives

- To identify the issues and potential problems in designing a statistical analysis plan for PRO data
- To understand the different methods of treating missing data
- To gain the knowledge and skills needed to analyze differences in PRO between two or more treatments

WORKMAT 7

Presentation and interpretation of PRO included in clinical trials

Learning objectives

- To critically evaluate published literature describing PRO surveys data
- To interpret PRO data that are reported in the published literature