Clinical trial design and cross-cultural issues for PROs

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Mapi Values

Objectives

- Trial design issues and potential solutions

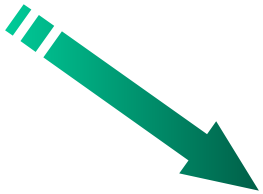
- Cross-cultural issues and potential solutions

List of Abbreviations

- QoL-Quality of Life
- HRQL=Health-related quality of life
- PRO=Patient reported outcomes
- QALY=Quality Adjusted Life Years
- MD=Missing data
- N=Sample Size
- BL=Baseline
- W1,W2,W3, etc=Week 1, Week, 2, Week 3, etc

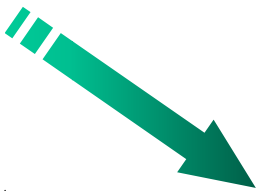
Progress in Defining Outcomes

QoL



HRQL

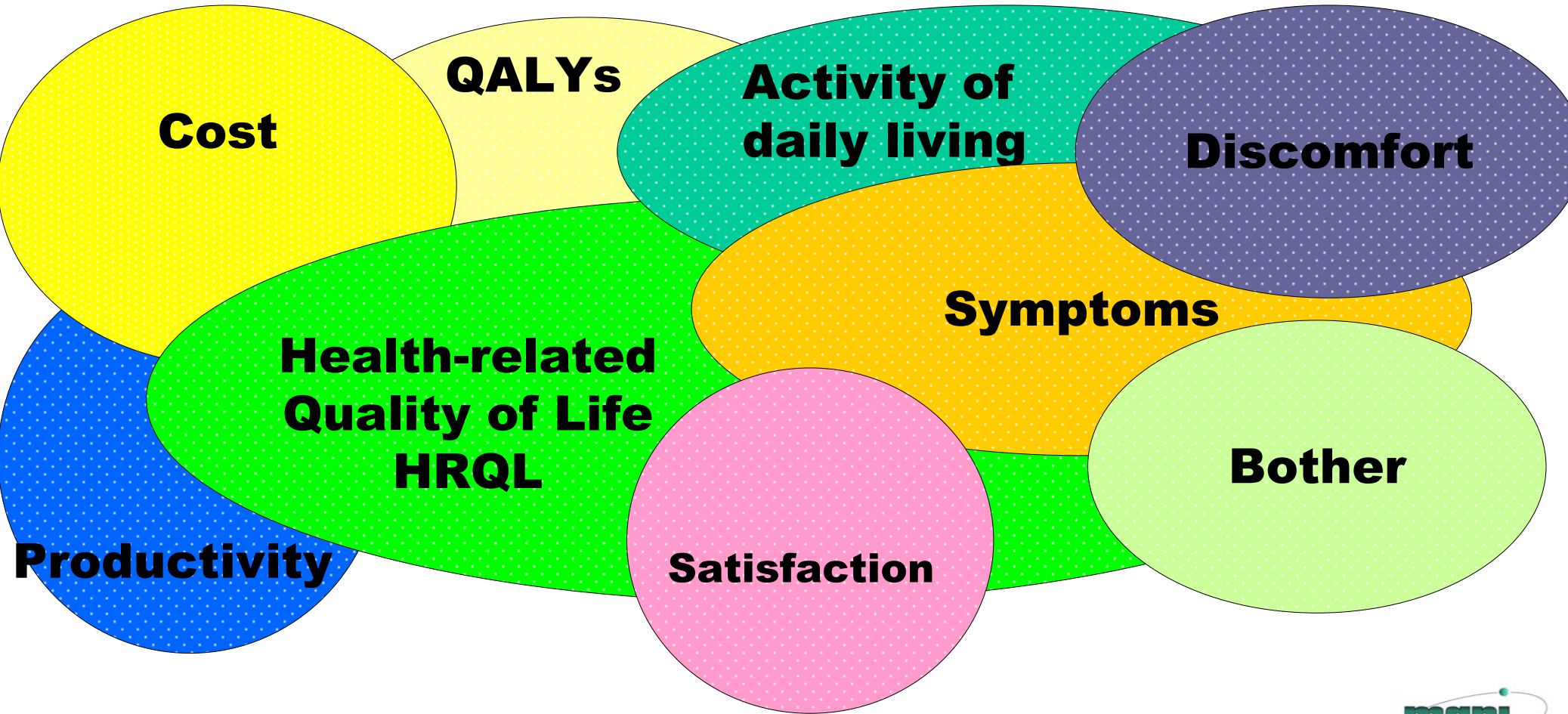
"Represents the patient's evaluation of the impact of a health condition and its treatment on relevant aspects of life"
"A multidimensional construct"



PRO

"The patient's report of a health condition and its treatment"

Patient Reported Outcomes: Concepts?

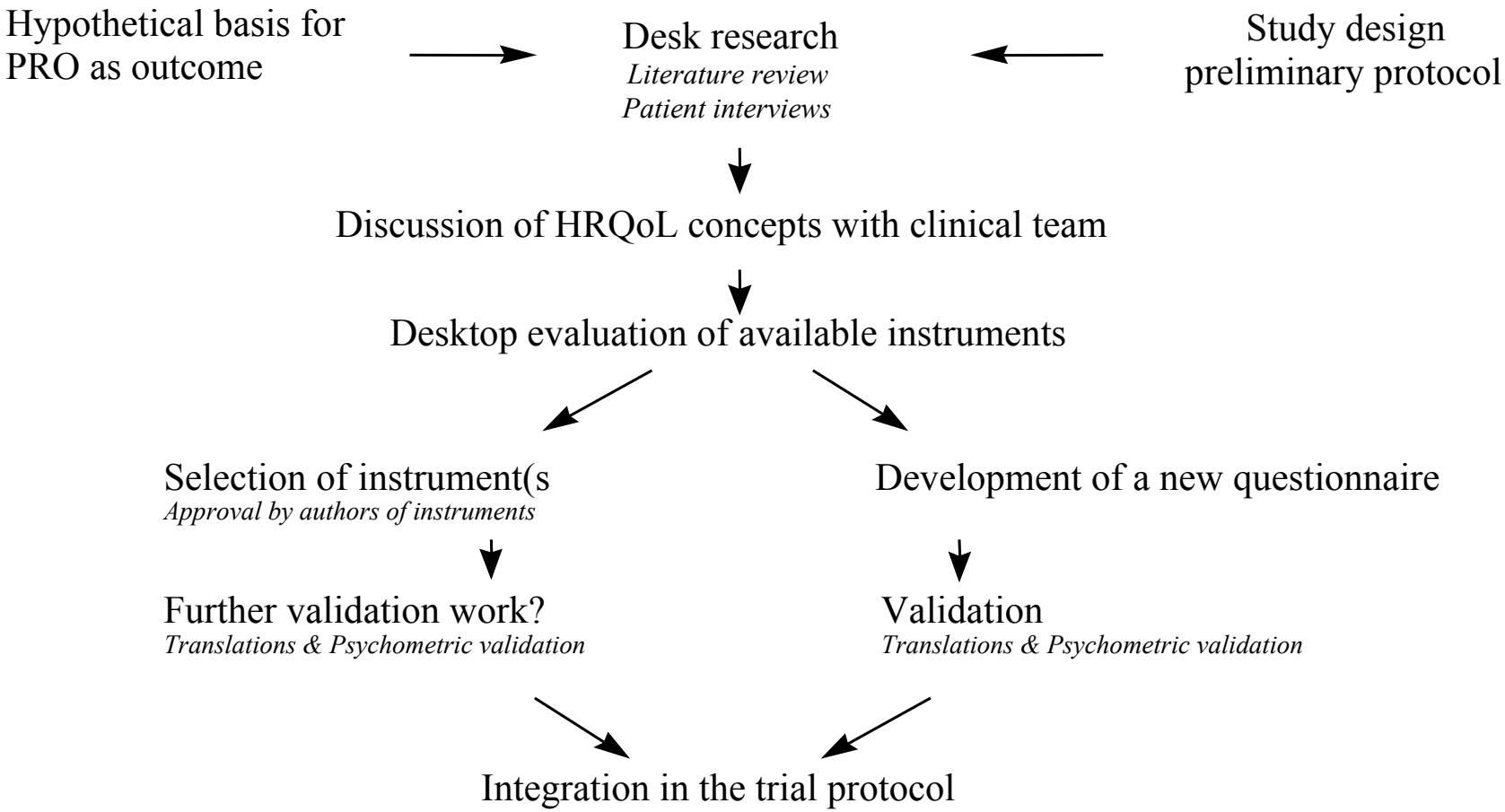


From Laurie Burke, Evidence Review Branch, DDMAC, FDA

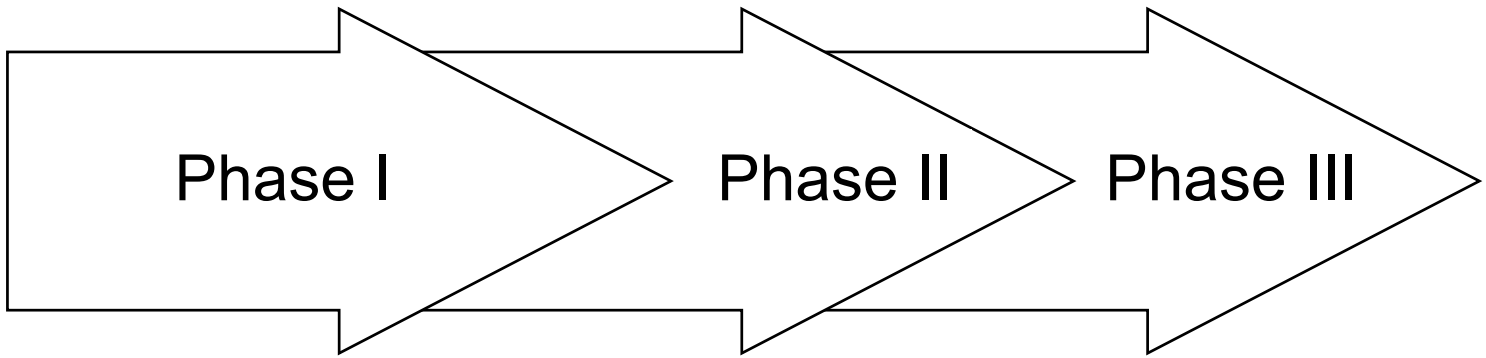
Reasons for Conducting PRO Studies

- Improved PRO benefits over alternative treatment may assist regulatory strategies
- Demonstrates value in patient outcomes for treatment expenditures
- Provides clinicians and patients with more complete product information

Steps in the development of PRO strategy



An 'Integrated' approach incorporating the design and validation of PRO measures into overall clinical development activities



PRO Program

Instrument Development
- literature review
- patient interviews
- expert opinions/inputs
- clinical hypotheses

Instrument Validation
- cross sectional study
- longitudinal study
- phase III feasibility ("Go/No-Go") and strategy
- publication strategy

Phase III PRO Program
- sub-study
- stand alone

Clinical Trial Design

How it can impact results

Things to consider

- PRO hypotheses
- Chosen questionnaires
- Modes of administration
- Timing of assessments
- Training of investigators
- Incorporation into protocol
- Development of analysis plan

PRO hypotheses

- PRO domains impacted by disease
- PRO domains impacted by product
  - positive/negative effects
  - equivalence
- Keep in mind the inclusion/exclusion criteria
- Hypotheses will aid in the selection of an appropriate questionnaire

Chosen patient-reported questionnaires should be

- Relevant to the patient trial population
- Clear and easy to understand
- Reliable, valid and responsive
- Have a relevant recall period
- Available in local languages (or can be translated appropriately)
- Easy to interpret

Developing or Adapting an instrument: Prerequisites

- Relevance of quality of life to clinical scenario
- Absence of existing valid and appropriate measures
- Feasibility/favourable logistics of qualitative research

Psychometric Analysis

- **Acceptability**
  - missing data
  - descriptive statistics
- **Scaling assumption**
  - item-item correlations
  - item-scale correlations
  - factorial/multitrait analysis
- **Reliability**
  - reproducibility
  - internal consistency (Cronbach's alpha)
- **Validity**
  - content validity
  - criterion/construct validity
  - clinical validity
- **Sensitivity**
  - discriminative power
  - responsiveness over time

Modes of Administration

- Respondent
  - Patient
  - Proxy (spouse, carer, parent, clinician, nurse)
- Type of questionnaire
  - Self-administered
    - Paper/pen (self-administered)
    - Palm-pilot and other computer administered
  - Interview-administered
    - By phone
    - Face-to-face

Timing of assessments

- Don’t expect QoL improvement if there is no clinical improvement or if major AE
- Is trial long enough to see PRO improvement?
- Timing of when benefits and AE occur should be taken into account
  - If AE occur in W4 and dissipate followed by benefits by W6, when should you assess?
- Recall period in questionnaire vs timing of assessments
  - Avoid overlap: BL, 2W, 4W - 4W recall…

Training of investigators

- Essential to train investigators and CROs on:
  - importance of PRO data capture
  - how questionnaire was selected/developed and what it contains
  - how to administer the questionnaire and what it will be used for
- Without their buy-in, risk of missing data is high

Collection and Management of PRO in clinical trials

- No queries
- Quality checks on identification between questionnaires and CRFs only

Implementing PRO into the protocol

- **Introduction & justification of choice of the questionnaire(s)**
- **Objectives: Primary or secondary?**
- **Timing of assessments-CRUCIAL**
  - Based on clinical, symptom and side effect hypotheses: don't expect improvements if no clinical or symptom improvements are expected or if major side effects are expected
  - Is the trial long enough to detect PRO improvements?
  - At a minimum, baseline and endpoint, though one mid-point is recommended
- **Analysis plan (usually very brief/provided as separate)**
- **Integrate into investigator/monitor meeting**
  - 15-20 minutes of instructions on how to implement questionnaires

Analysis of PROs

Main Issues to consider

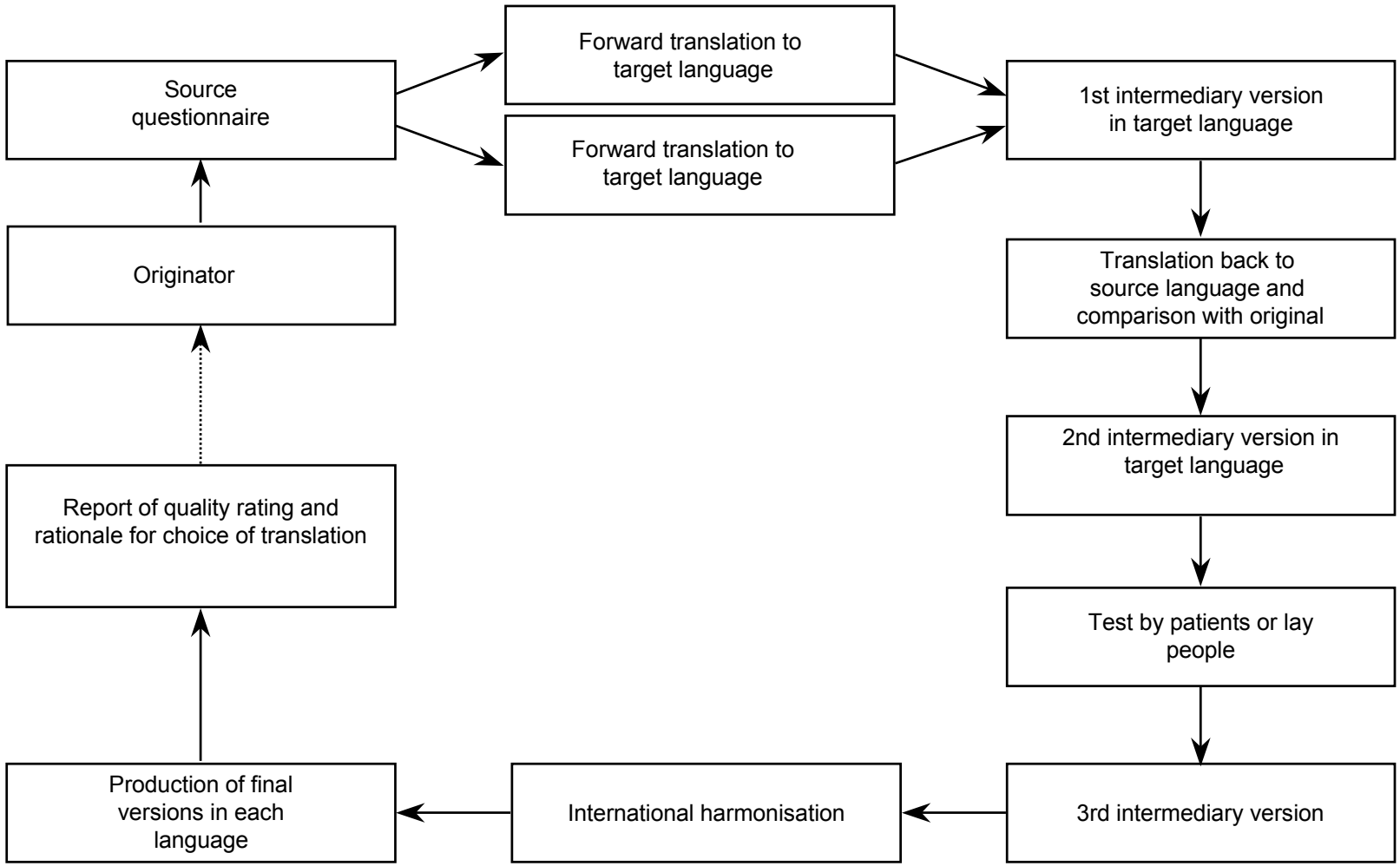
- Power calculations
- Write analysis plan prior to analysis
- Get scoring documentation ASAP
- Treatment of missing data
  - item level
  - questionnaire level
- Multiple testing
- Size of differences in scores over time
  - not just statistical significance

What do I need to know to analyse results?

- What are the PRO hypotheses?
- What type of questionnaires did we choose?
  - What are the scoring methods?
  - Are there reference scores available to help in interpretation?
- Is the questionnaire psychometrically valid in our clinical trial population?
- What type of missing data do we have (by treatment)?
  - How will we handle missing data?
- How are we controlling for multiple endpoints/tests?
- What were the clinical results?
  - Do your results make sense in line with clinical findings?

Cultural adaptation of PRO Questionnaires

Cross-cultural Adaptation



Proposed check list for psychometrics

	Mandatory for the original version	*For translated version*	
		Mandatory	*Recommended*
▪ Construct Validity	+		
▪ Internal consistency relia.	+		
▪ Score distribution	+		
▪ Clinical validity			+
▪ (Concurrent validity)			+
▪ Test-retest reliability	(+)		+
▪ (Responsiveness over time)			(+)

Pooling Data

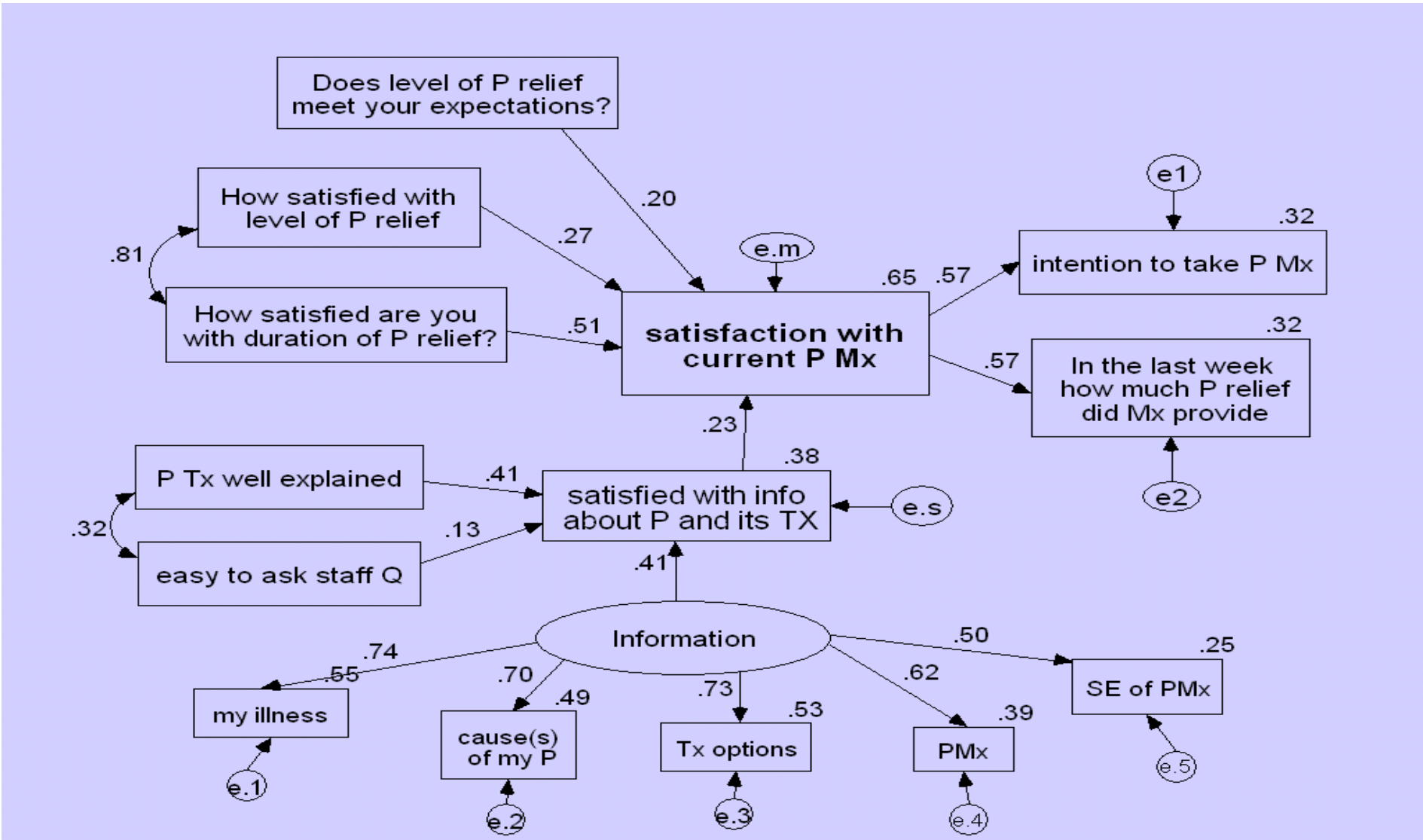
Patient Reported Outcomes (PRO) questionnaires in international trials : key questions

- Are the different linguistic versions conceptually and linguistically equivalent and are they applicable to each target country?
- Can I analyse treatment effect on PRO using pooled data?
- How cultural differences impact analyses?
- How can one address the appearance of a strong “response signal” in one region and the absence of any signal in another region within the same multinational trial?
- What are Health authorities requirements?
- What is accepted?

Available methods to assess structural validity

- "Classical" psychometric methods
  - Principal Components Analysis (with factor rotation)
  - Multi-trait analyses (based on item-scale correlations)
- Modern psychometric methods
  - Confirmatory Factor Analysis / Structural equation modeling
  - Rasch model / Item Response Theory (probabilistic approach)

Indicators of satisfaction with medication and intention to comply with treatment



Analysis of international CT PRO data: Recommendations

- Describe acceptability (MD) and score distribution at country level
- Test structural validity at country/language version level using ad-hoc or baseline CT data (prior unblinding)
- Address cross-cultural equivalence: Rasch and CFA
- Assess criterion (clinical/known groups/concurrent/ predictive) validity and responsiveness to change over time at country level
  - may be problematic due to small sample sizes

Analysis of international CT PRO data: Recommendations

- Analyse treatment effect on PRO on pooled data if at least structural validity in each language version is satisfactory.
  - If not, analysis at country level should be considered.
- The analysis plan (finalised prior unblinding) should describe how data are going to be analysed and specify the decision rules to include (or not) a country in the pooled analysis

Prerequisites for a successful international trial using a PRO measure

- Clearly identifiable original instruments
- Cross-culturally acceptable concepts/Cross-culturally valid language versions
- Psychometrically comparable data
- Consistent understanding of PRO evaluation by users (drug companies, regulatory authorities, clinicians)

Criteria for success

- Choose a specific instrument
- Set up clear PRO hypotheses
- Involve the clinical/marketing teams in the definition of PRO assessment strategy
- Integrate clinical and QoL monitoring
- Relevant timing of assessments and relevant reporters/modes
- Set your objective and stick to it when publishing the results

Concluding Remarks (1)

- Start to think about PRO **early** in the drug development process in order to budget resources (time/money).
- Go to the patients to find out if PRO is affected before deciding to assess PRO. Go to clinicians to find out if patients' PRO will sway treatment decisions.
- Assess product/competitor profiles and trial protocol when making decisions
- Assess available instruments for reliability, validity, responsiveness. If acceptable, try to use an available instrument to maximize resources.
- A generic/disease specific approach is often the best method to

Concluding remarks (2)

- Ascertain comprehensiveness, responsiveness & interpretability.
- Keep interpretation in mind when designing the assessment strategy
- Remember audience needs when reporting results.