Importance of PRO Guidance: PRO'S and CON'S

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Why PRO Guidelines?

- Need for formal recognition of added value of Patient Reported Outcomes:
  - Only measure that directly reflects the patient's own viewpoint on impact of disease and its treatment
  - Only measure that makes trade-off between efficacy and tolerability

Why PRO Guidelines?

- Need for informed health care decision making:

"The only way to find out what patients want, is to ask them."

Source: Wennberg

Why PRO Guidelines?

- Need for scientific quality and rigor:
  - Methodological standards
  - Good Clinical Practice principles also applicable to Patient Reported Outcomes

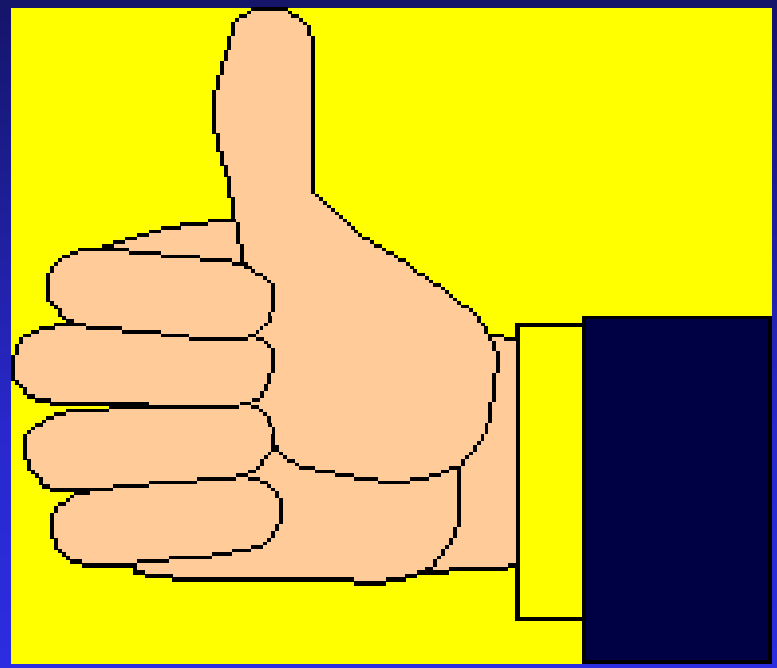
Why PRO Guidelines?

- Need to convince regulatory agencies that PRO/HRQL:
  - Are key patient outcomes
  - Are a reliable criterion for evaluation of medicines

Important to whom?

- Patients!
- Regulatory Agencies
- Pharmaceutical Industry
- Researchers
- Clinicians

ADVANTAGES



Advantage #1

- Guidelines facilitate planning & integration of PRO's into clinical trials

The evolution of the use of PROs in clinical trials yesterday and today

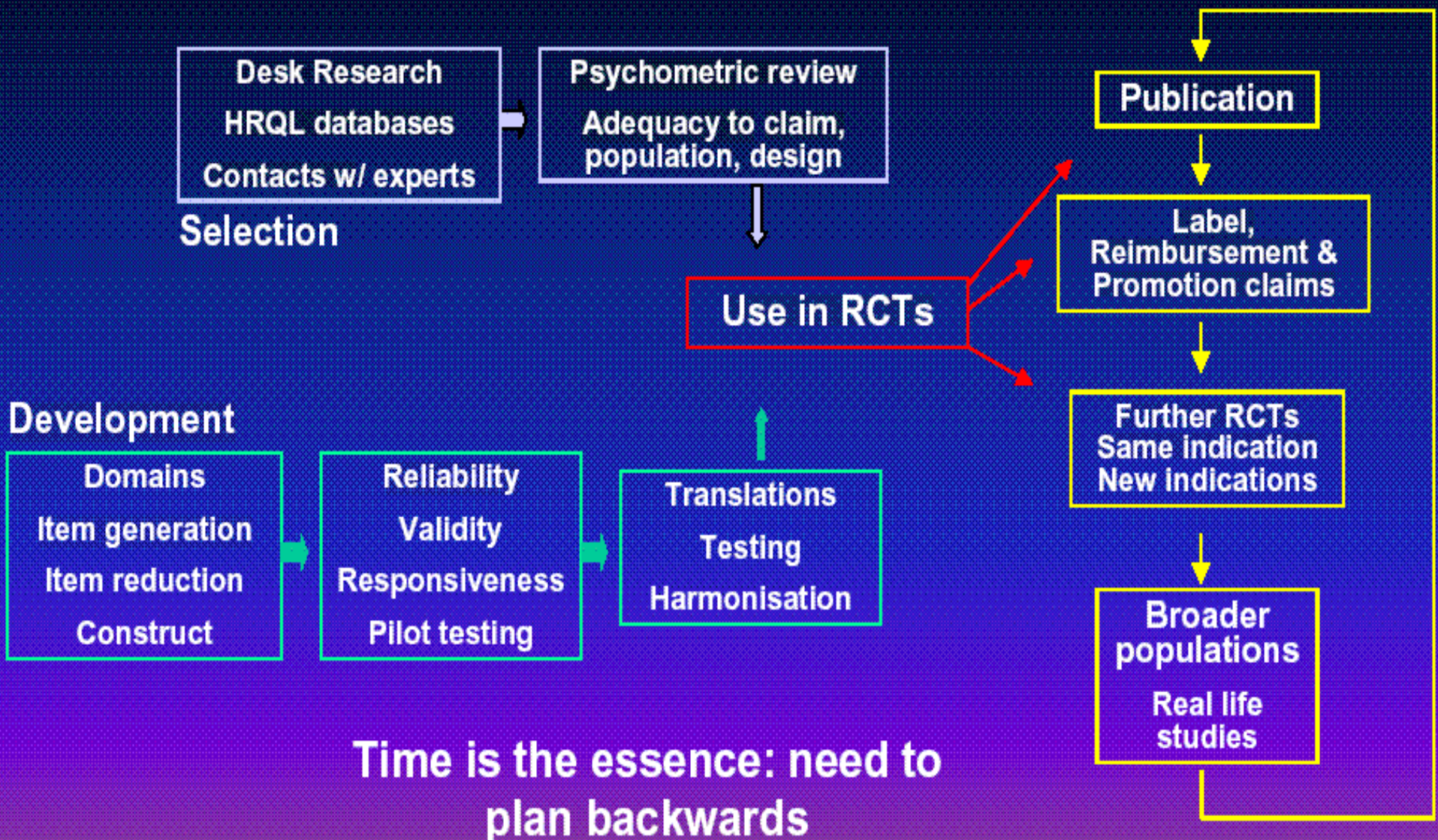
Yesterday

- Investigator compiled ad hoc tools
- No or poor validation
- ”Fishing expedition”
- PROs thrown into the study as an afterthought

Today

- Items derived from patients directly
- Psychometrically well validated scientific tools
- Clear hypothesis
- Well-integrated into the study protocol from the start

Processes for the selection, development and validation of PRO measures are well standardised



Time is the essence: need to plan backwards

Advantage #2

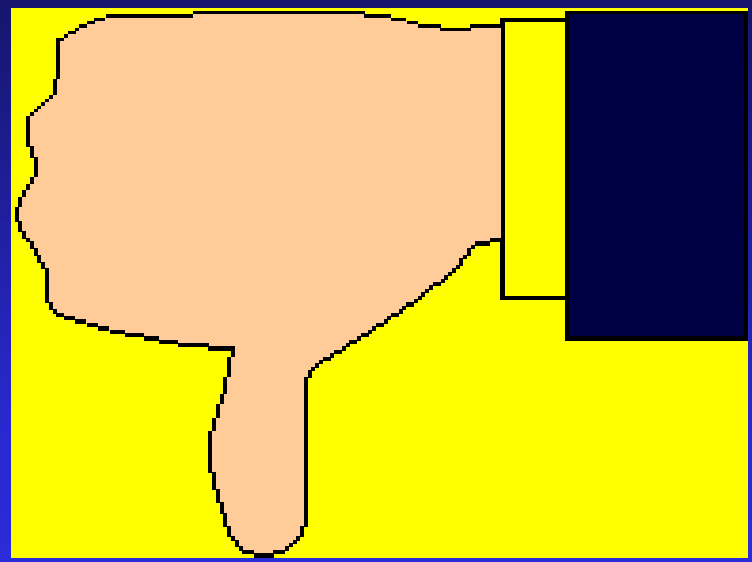
- Guidelines are useful to the extent that they reflect accepted requirements on methodological areas for which there is a broad consensus

Evidentiary requirements for PRO outcomes

- Well-documented rationale for the outcome and measure
- Clear objectives and hypotheses
- Reliable and valid instruments
- Appropriate observation intervals
- Adequate sample size
- A priori data analysis plan (statistical & clinical significance)
- Careful implementation
- Interpretable results relative to clinical parameters
- Full and honest disclosure
- ***No more and no less than the requirements for clinical efficacy endpoints***

Adapted from Leidy et al., Value in Health, 1999; ISOQOL, 2000; Harmonization Meeting, 2002

DISADVANTAGES



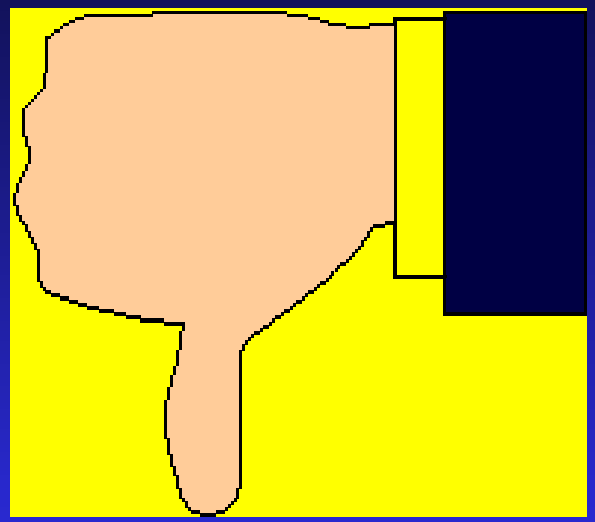
#1 Risk of being too specific

- Primary focus: Guidance on requirements for appropriate & meaningful PRO
- Outcomes Research is an evolving science:
  - Areas of consensus and areas of debate
  - No answers to all questions

#2 …or not specific enough?

- Use of proxies to identify drug benefits?
- Minimum coverage of multidimensionality?
- What constitutes sufficient evidence for validation of a new scale?
- Should power calculation be universally provided?
- Item banks and computerized adaptive testing during clinical trials; acceptable for product registration?

Where do we go from here?



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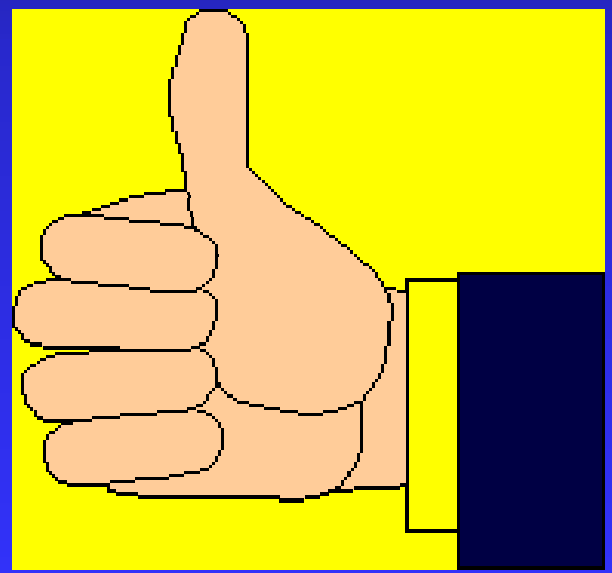
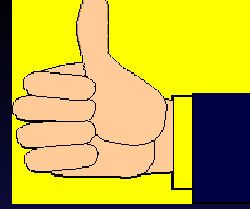


Business Case Pro



- Saves time and money
- Provides uniform basis for evaluation
- Establishes minimum reliability and validity norms for:
  - PRO instruments
  - Cultural adaptations
- More likely acceptance by Regulatory Agencies

Business Case Contra

- Costs additional time and money
- Provides too restrictive basis for evaluation
- Establishes excessive reliability and validity norms for:
  - PRO instruments
  - Cultural adaptations
- No guarantee for acceptance by Regulatory Agencies

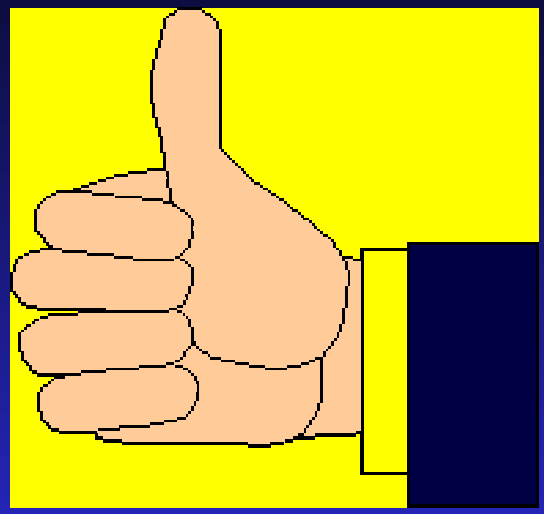
Regulatory Situation

- Despite wide differences across diseases, PRO claims for label and/or promotion are gaining momentum
- For pricing & reimbursement claims, PRO measures have long been included in assessment of added value by pricing & reimbursement authorities
- Support from multi-disciplinary groups (PRO Harmonisation, ERIQA, PhRMA-HOC) and Societies (ISPOR, ISOQOL) and DIA has proven important in bringing stakeholders together. Should be pursued and extended

Conclusions

- Creation of the SEALD Office at the FDA, and increased interest at EMEA and other regulatory agencies mark a turning point in the development of PRO measures
- Recent and ongoing regulatory developments will boost the acceptability of PRO endpoints

Where do we go from here?



Thank You !