Industry Perspective: PROs in Oncology Trials

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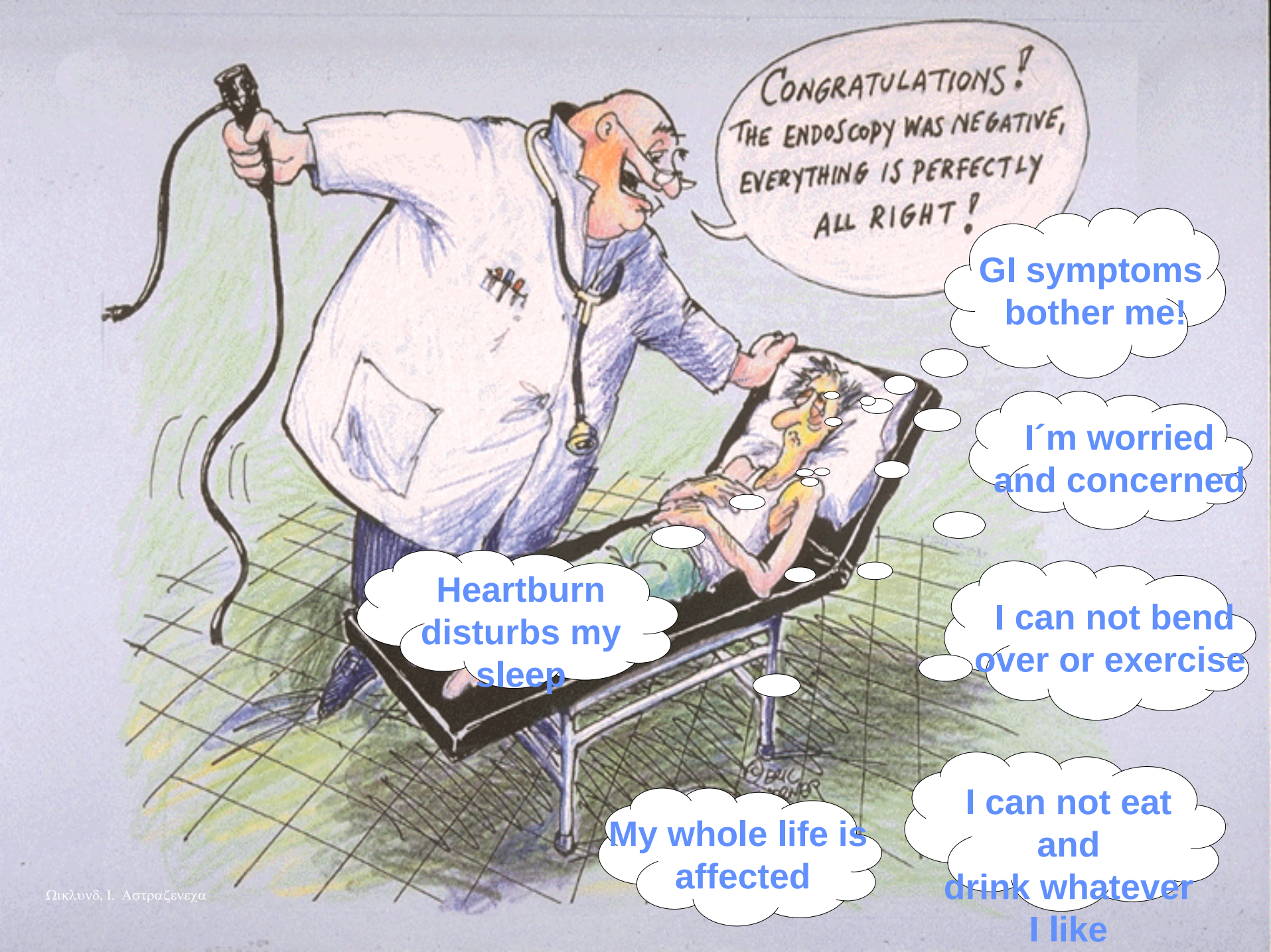
Agenda

- Industry's Interest
- Status of PROs in industry sponsored trials
  - Current studies
- Study Conduct
- Drug Product Labels
- Communication of Results


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

Why do Outcomes Research in Oncology?

- Frequently, the result of treatment is to achieve palliative benefit in metastatic disease
- PRO data may complement and enhance clinical efficacy and safety data
- Physicians and patients are interested in the nature of clinical benefits and tradeoffs
- Baseline PRO measures have been shown to predict overall survival

Why do Outcomes Research in Oncology?

- More oral products becoming available
  - Patients more accountable for adherence and outcomes and will weigh benefits/ AEs/ cost
  - Home vs hospital/clinic may lead patients may be more active
- Critical for reimbursement (QALYs)

Why do Outcomes Research in Oncology?

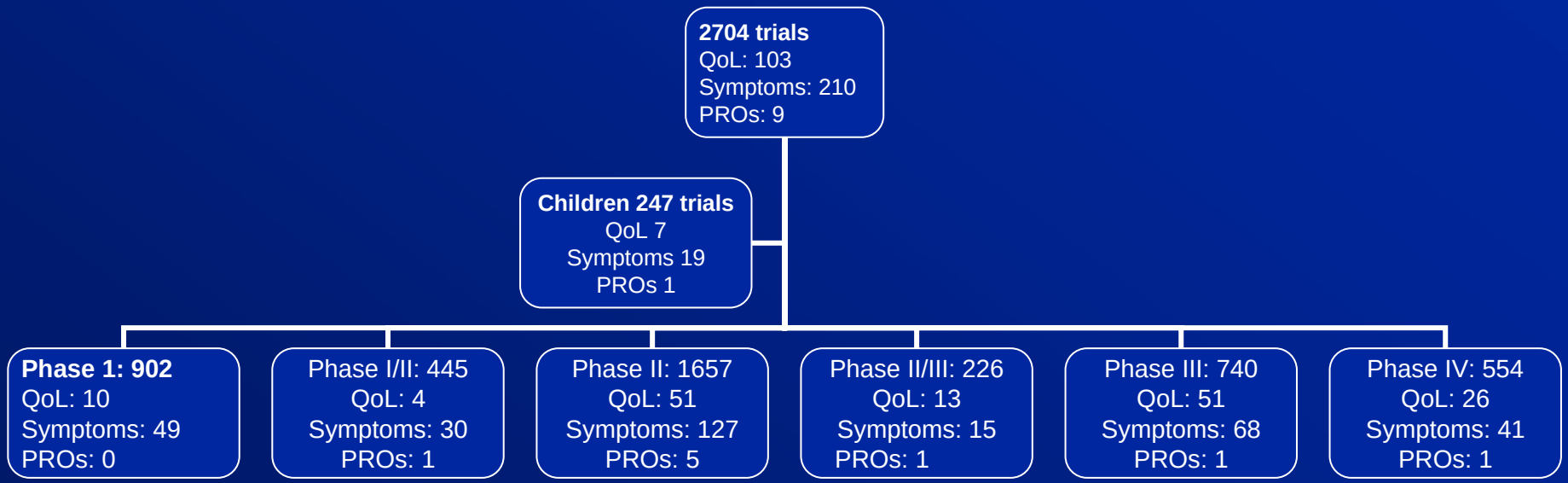
- Decision Makers are interested and engaged
  - US Managed Care survey- 52% indicated the importance of patient-reported outcomes (PRO) data for formulary decisions
  - Oncologists survey- 51% said PRO study findings had influenced their recommendations for treatment

Crawford et.al., 2001 and Bezjak et.al., 2001

What does industry want to achieve with PRO measures?

- To understand the burden of disease to the patient
- To identify theoretical and empirical relationships between treatment, clinical endpoints, AEs and PRO
- To consider the relevance to patients by reflecting their perspectives and values
- To provide evidence of cost-effectiveness

Industry sponsored cancer trials
www.clinicaltrials.gov 8/14/06



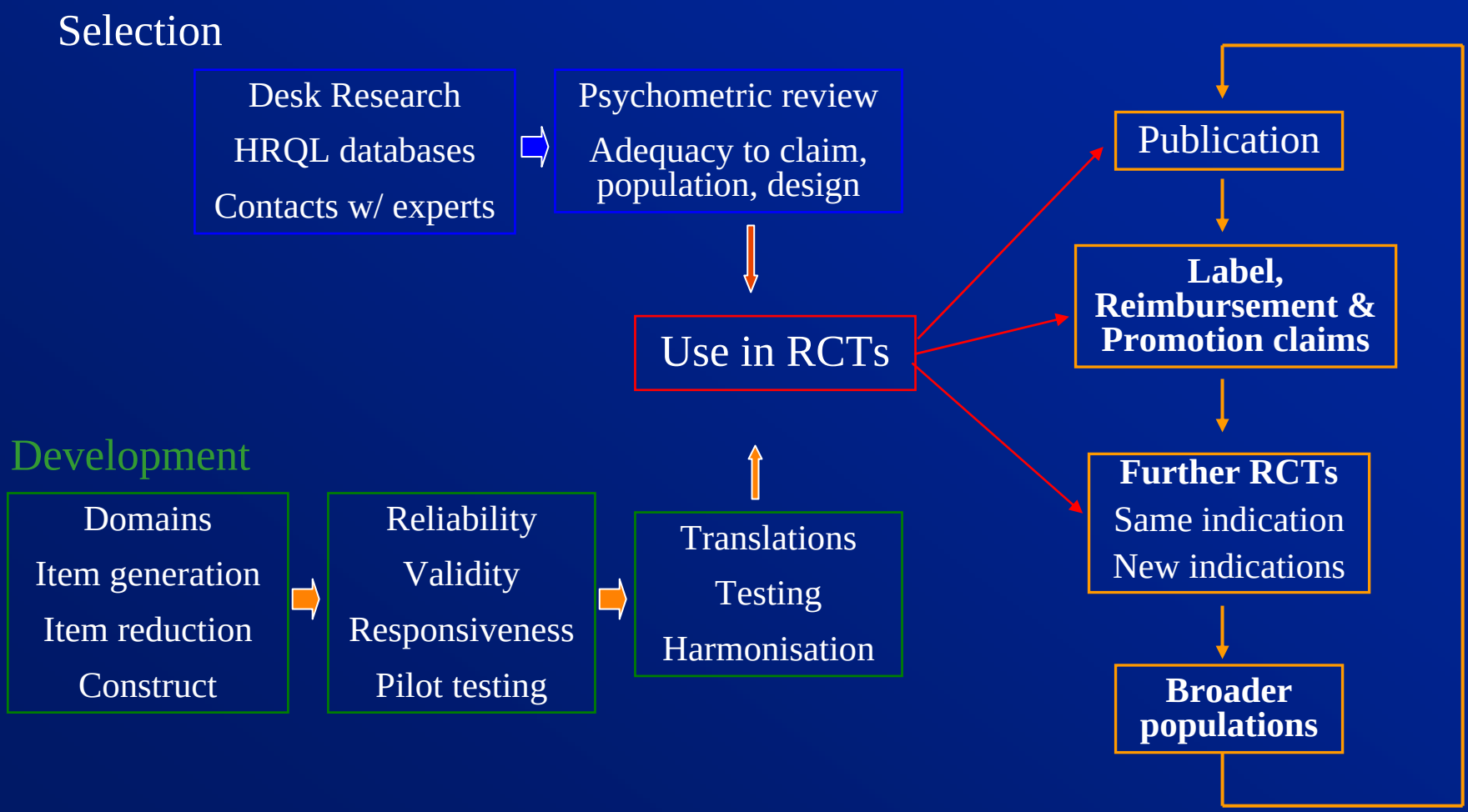
Cancer Trials by Disease with QoL, Symptoms or PROs www.clinicaltrials.gov

Cancer/# Trials	Quality of Life	Symptoms	PROs
Breast 436	24	49	2
Lung 404	19	32	3
Lymphoma 332	8	8	0
Leukemia 233	7	6	0
Prostate 218	16	18	2
Colorectal 205	2	28	2
Bone 200	9	22	0

Cancer Trials by Disease with QoL, Symptoms or PROs www.clinicaltrials.gov

Cancer/# Trials	Quality of Life	Symptoms	PROs
Kidney 132	4	16	0
Head & Neck 121	7	7	1
Ovarian 116	8	2	1
Melanoma 93	2	14	0
Pancreas 86	5	9	0
Brain 81	7	10	0
Liver 71	3	7	0
Sarcoma 71	4	3	1

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

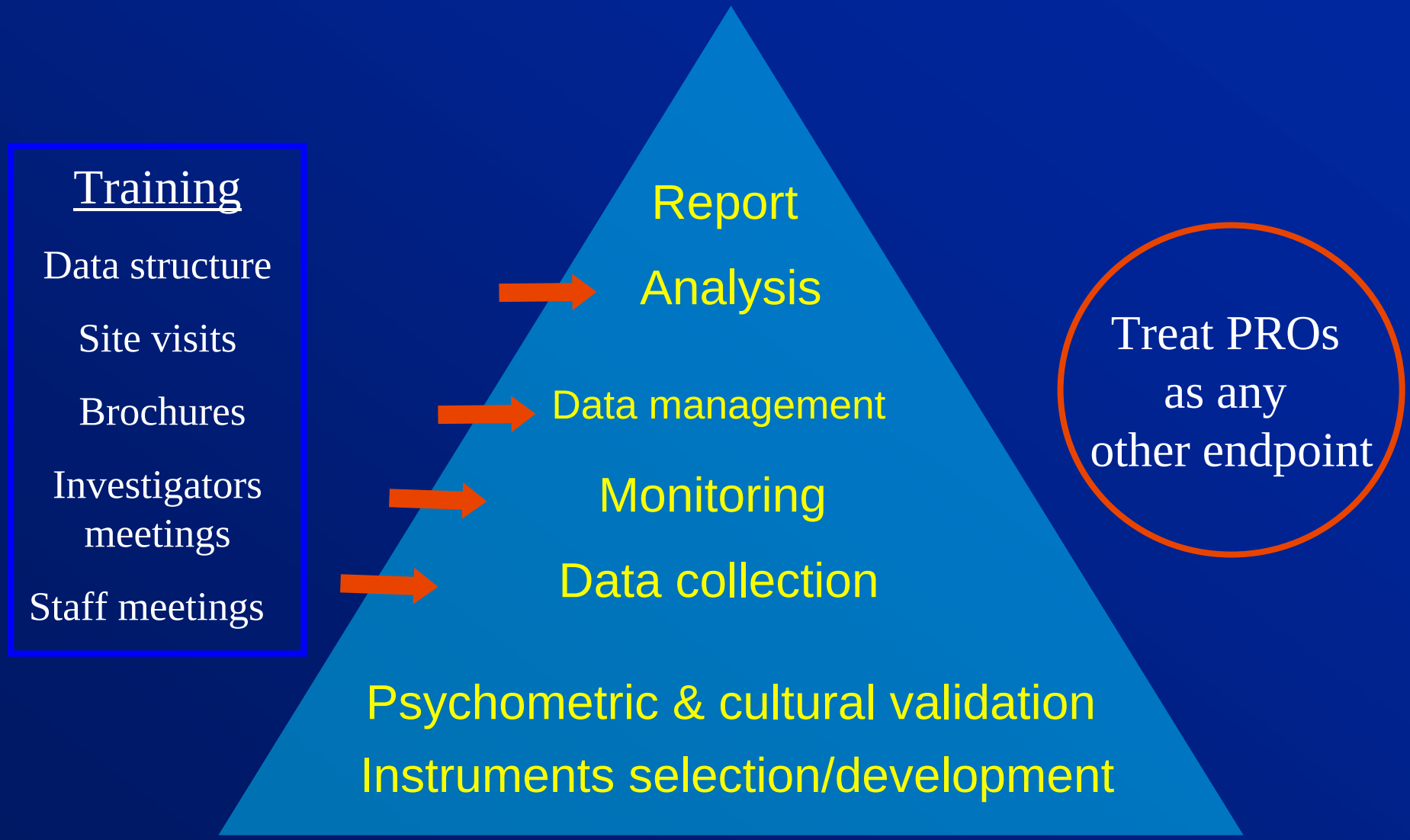


Time is the essence: need to plan backwards

In Industry the PRO Agenda Needs to be Front-loaded: Early Planning Is Key

Goal: No compromise on quality, nor on development timelines

Quality of processes - Quality of data



Challenges: Systematically Collect PRO Data

- Assessment of burden to investigator, sites and patients critical first step
- Cost

Protocol needs to specify

- Why PRO endpoint is important (rationale)
- What concept each PRO measures
- When, where, and how PROs will be assessed
- Data entry, data management, and PRO scoring procedures
- Primary and subgroup comparisons of PRO data
- Inclusion of all PRO instruments included in protocol
- How the PRO instrument will be evaluated within the study population

What are the Challenges to Study Design

- Sample Size: Estimate of effect sizes and if the study has enough power to measure PRO differences
  - Take into account adjustment for multiplicity
  - Estimate power for detecting clinically significant changes

- Site Selection: Translation of surveys for a small number of patients in a given country; training if study is very multi-national

Challenges to Study Design

- Study Population: Very late stage patients
  - Improvements with therapy possible
  - Stay in the study longer than a few months

- Trial Length: Measurement of PRO endpoints after treatment is completed (when patients aren't undergoing toxic treatment)

Challenges: Analyze PRO Data

Statistical analysis plan prespecifies analysis of PRO data

- To determine objectives in measuring PRO within clinical trials
  - Adequately powered trials are important
- Compare treatments
  - Primary analyses, subgroup comparisons, exploratory analyses
  - Missing data
  - Multiple comparisons
  - Pooling data from multiple translations
  - Statistical differentiation versus clinical differentiation
  - Interpret results

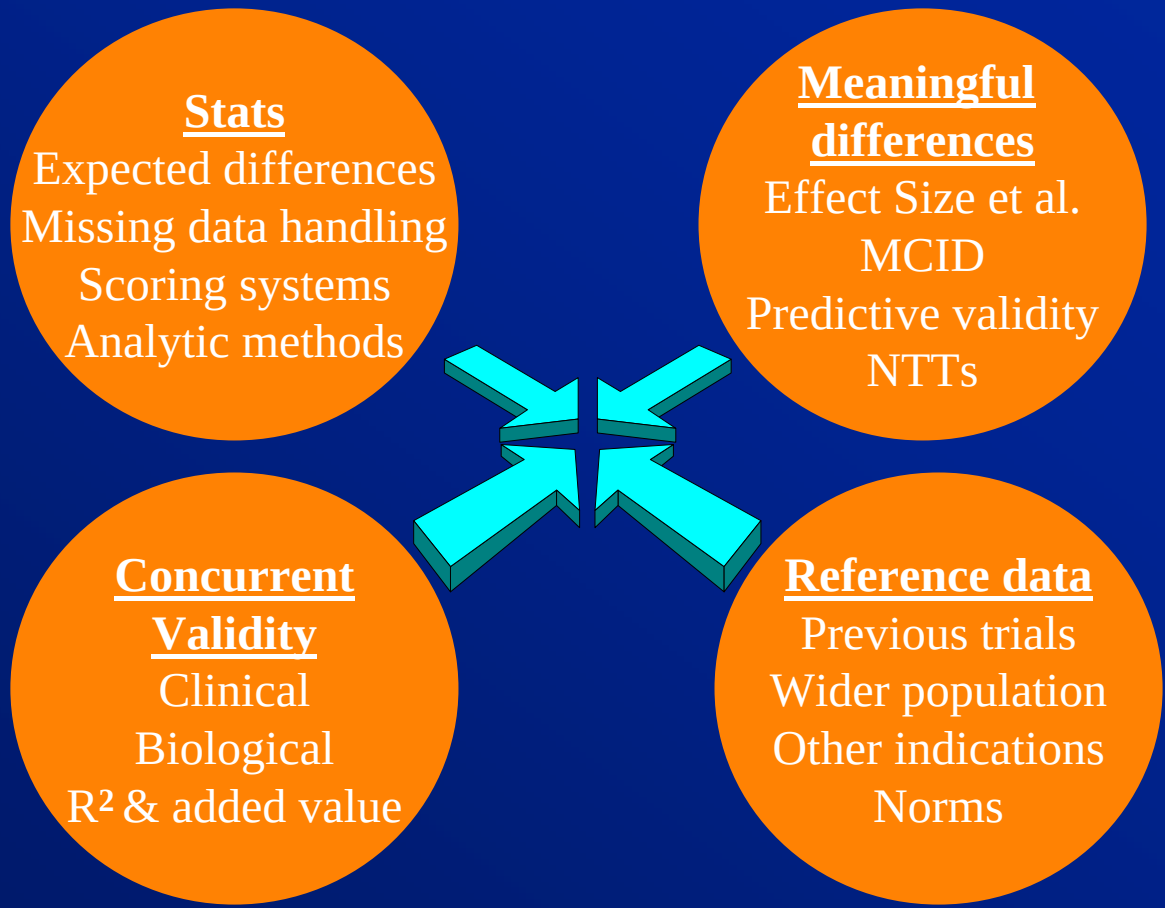
Types of Analyses Employed in Clinical Trials for PROs

- Change from baseline
  - Mean change, shows overall treatment impact in patient population
- Responder analysis
  - Demonstrates percentage of patients who improve, worsen or remain the same
- Time to symptomatic progression
  - Similar analysis to OS, demonstrates symptom impact over time

What are the challenges to interpretation of results

- Relevance to individual patient/subgroups
- Clinical significance versus statistical significance of results
- Interpretation of failure to detect change
- PROs relative to medical outcomes

Interpretation: the operational view



Cast fair balance between known instruments (easy interpretation) and new kids on the block (possible higher responsiveness)

Interpretation Recommendations

- Planned analysis by subgroups
- Use of group data for individual patient
- A-priori determination of clinically significant change
- Examine and rule out alternate explanations of failure to detect change
- PROs assume importance in context of study objectives, patient population etc

Providing evidence

Labels in Oncology

ELIGARD ® Sanofi-Aventis

- **Palliative treatment of advanced prostate cancer**. Other secondary efficacy endpoints evaluated included WHO performance status, **bone pain, urinary pain, and urinary signs and symptoms.** At Baseline, 94% of patients were classified as "fully active" by the WHO performance status scale (Status=0) and 6% as "restricted in strenuous activity but ambulatory and able to carry out work of a light or sedentary nature" (Status=1). At Month 6, these percentages were changed to 96% (Status=0) and 4% (Status=1). At Baseline, patients experienced little bone pain, with a mean score of 1.20 (range 1-9) on a scale of 1 (no pain) to 10 (worst pain possible). At Month 6, the mean bone pain score was essentially unchanged at 1.22 (range 1-5). Urinary pain, scored on the same scale, was similarly low, with a mean of 1.02 at Baseline (range 1-2) and 1.10 at Month 6 (range 1-8). Urinary signs and symptoms demonstrated a mean score of 1.09 at Baseline (range 1-4) and increased to 1.18 at Month 6 (range 1-7). In addition, there was a reduction in patients with prostate abnormalities detected during physical exam from 96 (82%) at Screening to 76 (65%) at Month 6.

Labels in Oncology

Plenaxis™ - Praecis

- **Advanced Symptomatic prostate cancer** Plenaxis™ is indicated for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metatases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) **severe bone pain** from skeletal metastases persisting on narcotic analgesia.
- Although the study was not designed to assess specific clinical outcomes, the following were observed: **None (0) of 8 patients with vertebral or epidural metastases and without neurological symptoms developed neurological symptoms.** Ten of 13 patients with bladder outlet obstruction and a bladder drainage catheter had the catheter removed by 12 weeks. **Eleven of 15 patients with pain due to skeletal metastases were able to reduce the potency, dose and/or frequency of narcotic analgesia at 12 weeks.**

Labels in Oncology

Gleevec ® -- Novartis

Chronic myelogenous leukemia

- Physical, functional, and treatment-specific biologic response modifier scales from the FACT-BRM (Functional Assessment of Cancer Therapy - Biologic Response Modifier) instrument were used to assess patient-reported general effects of interferon toxicity in 1,067 patients with CML in chronic phase. After one month of therapy to six months of therapy, there was a 13%-21% decrease in median index from baseline in patients treated with interferon, consistent with **increased symptoms of interferon toxicity**. There was no apparent change from baseline in median index for patients treated with Gleevec.

Labels in Oncology

Kepivance™ Amgen

- **Oral mucocitis** In Study 1, patients used a daily diary to record the amount of mouth and throat soreness. Compared with placebo-treated patients, Kepivance™-treated patients reported less Kepivance™.**mouth and throat soreness**. Study 2 was a randomized, multi-center, placebo-controlled study comparing varying schedules of Kepivance™. All patients received high-dose cytotoxic therapy consisting of fractionated TBI (12cGy total dose), high-dose etoposide (60 mg/kg), and high-dose cyclophosphamide (75-100 mg/kg) followed by PBPC support for the treatment of hematological malignancies (NHL, Hodgkin's disease, AML, ALL, CML, CLL, or multiple myeloma). The results of Study 1 were supported by results observed in the subset of patients in Study 2 who received the same dose and schedule of Kepivance™ as given in Study 1. Compared with placebo, there was a reduction in median days of WHO Grade 3/4 oral mucositis (4 vs. 6 days), lower incidence of WHO Grade 3/4 oral mucositis (67% vs. 80%) and lower incidence of WHO Grade 4 oral mucositis (26% vs. 50%) for Kepivance™.

Using Outcomes Data

Audiences	Opportunities
• Patients and Family/Caregivers • Clinicians • Payers • Regulators • Industry • Accrediting Organizations • Researchers	• Enhance understanding of cancer burden and implications of interventions • Facilitate communication • Inform decisions • Improve quality of care

General Recommendations

- Recognize that most challenges in analyzing PROs are not different than for other endpoints.
- Treat like other endpoints in terms of training
- Choose simple, robust analytical methods
- Use graphical analysis of data as first step followed by more rigorous statistical approaches
- Pay attention to subtle patterns of variation in underlying data
- Ensure transparency in assumptions and justify choice of models/methods