ENGELBERG CENTER for Health Care Reform at BROOKINGS

FRIENDS of CANCER RESEARCH

Conference on Clinical Cancer Research

Panel Three:

Symptom Measurement in Clinical Trials

November 10, 2011 • Washington, DC

Panel 3:
Symptom Measurement in Clinical Trials
Introduction

Ethan Basch, M.D., M.Sc.
Memorial Sloan-Kettering Cancer Center

November 10, 2011

No Financial Disclosures

PANELISTS	AFFILIATIONS
Ethan Basch	Memorial Sloan-Kettering Cancer Center
Laurie Burke	Food and Drug Administration
Mark Gorman	National Coalition for Cancer Survivorship
Virginia Kwitkowski	Food and Drug Administration
Richard Levy	Incyte Corporation
Lori Minasian	National Cancer Institute
Brian Seal	Bayer HealthCare

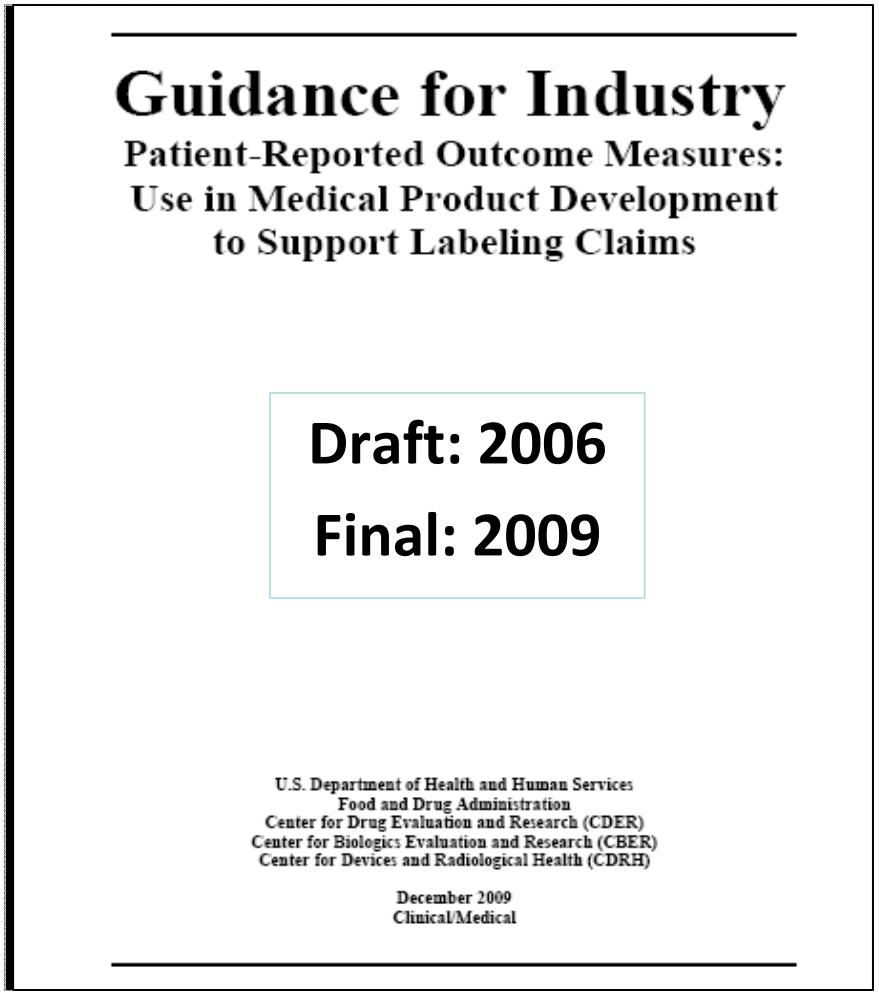
Symptoms in Oncology

- Common
- Important to patients and clinicians
- Important to payers
- Essential to understand in drug development
  - To adequately characterize benefits and harms
- Requires rigorous assessment

Standard Approach to Collecting Symptoms

- Patient-reported outcomes (PRO) measures

"Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else"



Guidance for Industry

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

Draft: 2006

Final: 2009

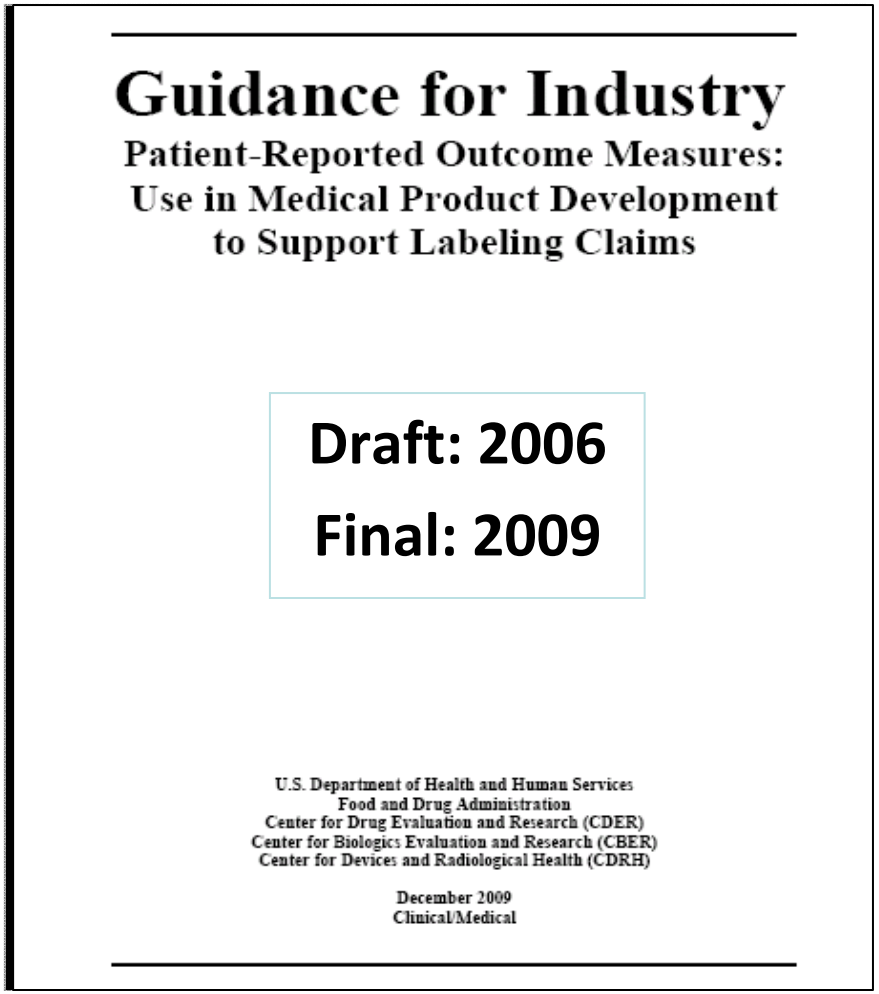
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

Standard Approach to Collecting Symptoms

- Patient-reported outcomes (PRO) measures

- Reflects FDA commitment to patient perspective
- Provides methodological standards for sponsors



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December 2009
Clinical/Medical

2006-2010

- More than 20% of labels overall included PROs
- None in anticancer drug labels

- Prior oncology PRO labeling claims:

DRUG	ENDPOINT	YEAR
Mitoxantrone	Pain in prostate cancer	1996
Gemcitabine	Symptoms in pancreas	1996
Topotecan	Symptoms in NSCLC	1998
Imatinib	Reduced interferon toxicity	2003

Drugs@FDA.gov; CenterWatch.com

What are the Barriers?

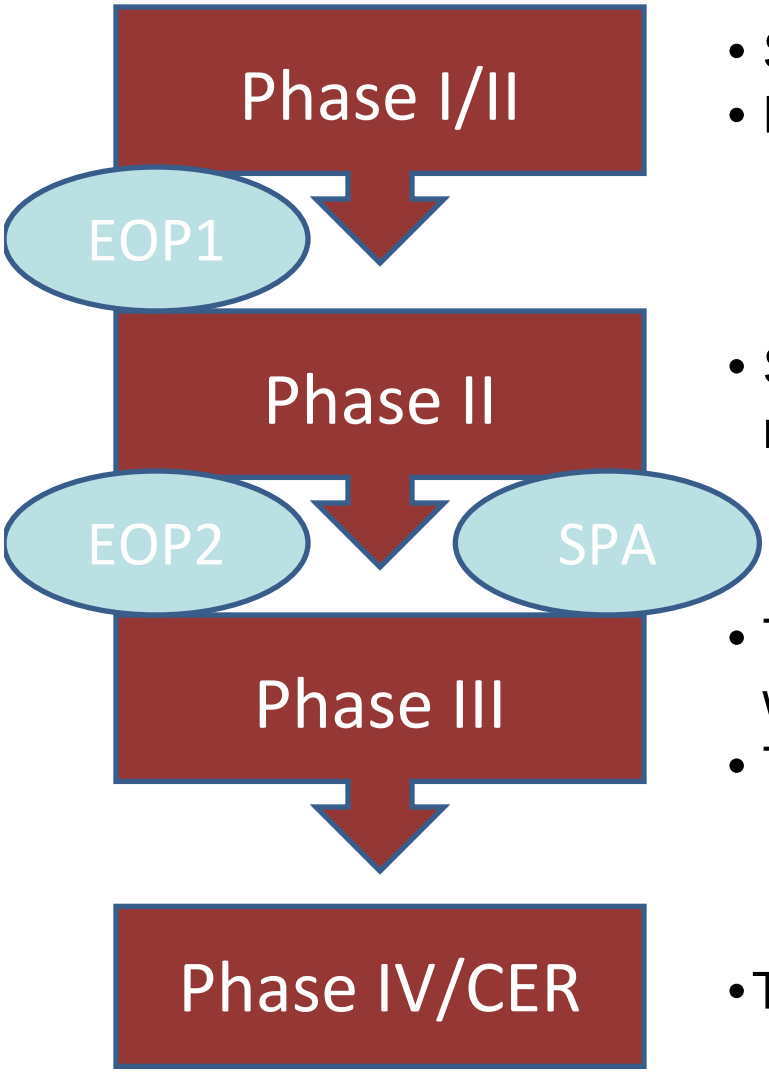
1. Cultural
2. Communication
3. Methodological
4. Logistical

Culture

- Treatment benefit: “Impact on how a patient *survives, feels, or functions*”
- Measuring patient experience not at forefront of sponsors’ or regulators’ minds during development
- Rarely primary or key secondary endpoint
  - Inadequate statistical power
  - HRQL and health state may be evaluated

57 Federal Register 13234;1992

Missed Opportunities



- Sponsors do not screen for salient symptoms
- FDA does not encourage such characterization

- Sponsors do not identify or evaluate PRO measures and approaches early enough

- Too late to rigorously evaluate or comply with FDA PRO Guidance
- Too few “off-the-shelf” endpoint models

- Too late to evaluate in controlled trial

~Result: inadequate understanding of patient experience~

Methodological

- Most common reasons for rejection of PRO claims:
  1. Inadequate blinding/inadvertent unblinding by toxicities (without sufficient effect size) → bias
  2. Measure not “fit for purpose”
  3. Missing data

Panel Draft Recommendations

1. FDA should routinely review drug development plans for potential role of symptom endpoints
   - Sponsor should provide rationale when *not* including PROs
2. Sponsors should integrate symptom PRO assessment throughout drug development with sufficient rigor
   - Include broader screening in early-phase
   - Consider as key secondary or primary endpoint in phase III
3. Mechanism should be standardized for continuous communication and agreement between FDA and sponsors around symptom assessment and endpoints

Scenarios When Symptoms Are Particularly Valuable

Can be Basis of Labeling or Approval

1. Disease with a symptom burden that may be improved by an active anticancer agent
   - B-symptoms in lymphoma; tiredness in metastatic kidney cancer; dyspnea/tiredness in metastatic lung cancer; abdominal bloating/pain in advanced ovarian carcinoma
2. Product with similar efficacy but less toxicity than an existing product ("comparative tolerability")
   - Less sensory neuropathy vs. a taxane; less nausea vs. a platinum-based regimen; less tiredness vs. interferon

~When might a "second" trial with PRO endpoint be merited?~

3. PFS endpoint with OS not likely to be

Entering a Patient-Centered Era

Subtitle D—Patient-Centered Outcomes Research

SEC. 6301. PATIENT-CENTERED OUTCOMES RESEARCH.

(a) IN GENERAL.—Title XI of the Social Security Act (42 U.S.C. 1301 et seq.) is amended by adding at the end the following new part:

"PART D—COMPARATIVE CLINICAL E

"COMPARATIVE CLINICAL EFFEC

"SEC. 1181. (a) DEFINITIONS.—In th
"(1) BOARD.—The term 'Boar
ernors established under subsectio
"(2) COMPARATIVE CLINICAL
RESEARCH.—
"(A) IN GENERAL.—The
effectiveness research' and 're
ating and comparing health
effectiveness, risks, and benefi

Patient-Centeredness in Policy and Practice: A conference on evidence, programs, and implications—Agenda

Overview | Organizers | Agenda | Speakers | CME/CLE Credits | Registration | Logistics | Contact

A Free Live Conference at FDA's White Oak Campus

Tuesday, November 29, 2011

7:00 AM	**Registration Opens**
7:00 - 8:30 AM	**Complimentary Continental Breakfast**
8:15 AM	**Welcome and Introduction**

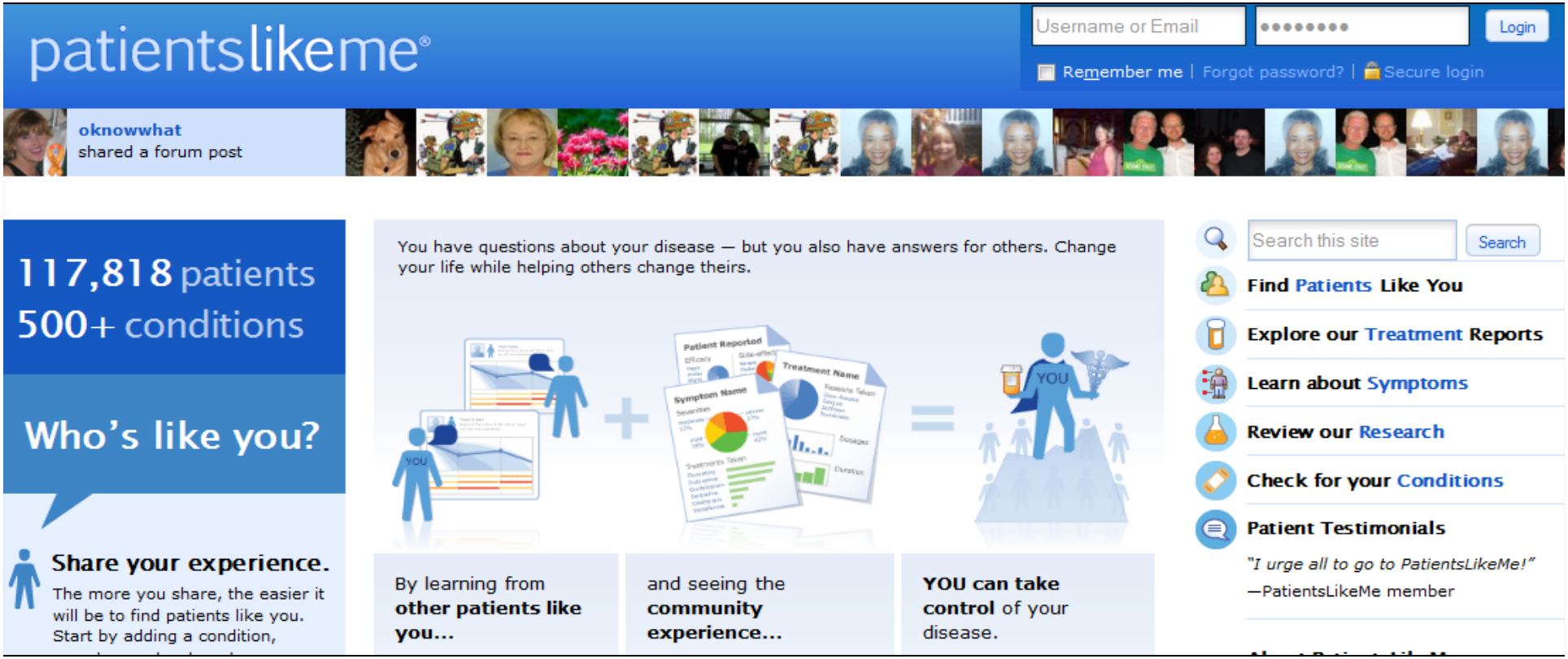
- **Margaret A. Hamburg, MD,** Commissioner, Food and Drug Administration
- **Jeffrey C. Lerner, PhD,** President and Chief Executive Officer, ECRI Institute

8:30 - 9:45 AM

Session 1
Policy Discussion – Researching and Regulating for Patient-Centeredness
This policy discussion among the leaders of key Federal agencies addresses their perspectives as well as the programs they are implementing to research and regulate a healthcare system that values and seeks to implement patient centeredness. This discussion is designed to probe lynchpin issues so that we can increase our collective understanding of what we know and do not know about patient centeredness, and how we can give it practical expression after proper evaluation.

- **Margaret A. Hamburg, MD,** Commissioner, Food and Drug Administration
- **Carolyn M. Clancy, MD,** Director, Agency for Healthcare Research and Quality
- **Joe V. Selby, MD, MPH**, Executive Director, Patient-Centered Outcomes Research Institute
- *Moderator:* **Susan Dentzer,** Editor-in-Chief, *Health Affairs*

Patients Are Exchanging Symptom Information



- *Suggests we are not providing adequate symptom information to patients*

Conclusions

- Essential information about the patient experience is missing in oncology drug development research and in product labels

- It is our responsibility as a scientific and regulatory community to strive to overcome barriers which prevent patients from understanding the experiences of their peers with approved products

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Symptom Measurement in Clinical Trials

Mark Gorman
National Coalition for Cancer Survivorship

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National Cancer Institute:

Perspective on Patient Reported Outcomes in Cancer Clinical Trials

Lori Minasian, MD
Acting Deputy Director
Division of Cancer Prevention

Clinical Trial Outcome Assessments

- Treatment Efficacy Endpoints
  - Mostly, Objective Assessments
  - Primary Endpoints
- Treatment Toxicity
  - Clinician Reported CTCAE
  - Collected, Analyzed with Treatment Efficacy

- HRQOL, Symptoms, Functional Status

Health Related Quality of Life

- HRQOL Rigorously Developed for General Use
  - Reliable, Validated, for Collection of Information
    - Disease Specific
    - Multi-Dimensional
  - Not Evaluated for Specific “Context of Use”
  - Not Developed for use as Primary Efficacy Endpoints

PROs as Clinical Outcome Assessments

- Patient's Perspective Valuable to:
  - Refine Toxicity Assessments
  - Identify Superior Tolerability
  - Support Primary Indication with Secondary Symptom Endpoint

- "Context of Use" Requires Understanding Natural History of Disease, Effects of Therapy

PROs as Clinical Outcome Assessments

- How to Capture Sufficient Information to Evaluate Context of Use Given Changing History of “Natural History of Disease?”

- Further Complicated by Unknown Long-term Side Effects of Targeted & Co-morbidities

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Symptom Measurement in Clinical Trials

Brian Seal
Bayer Health Care

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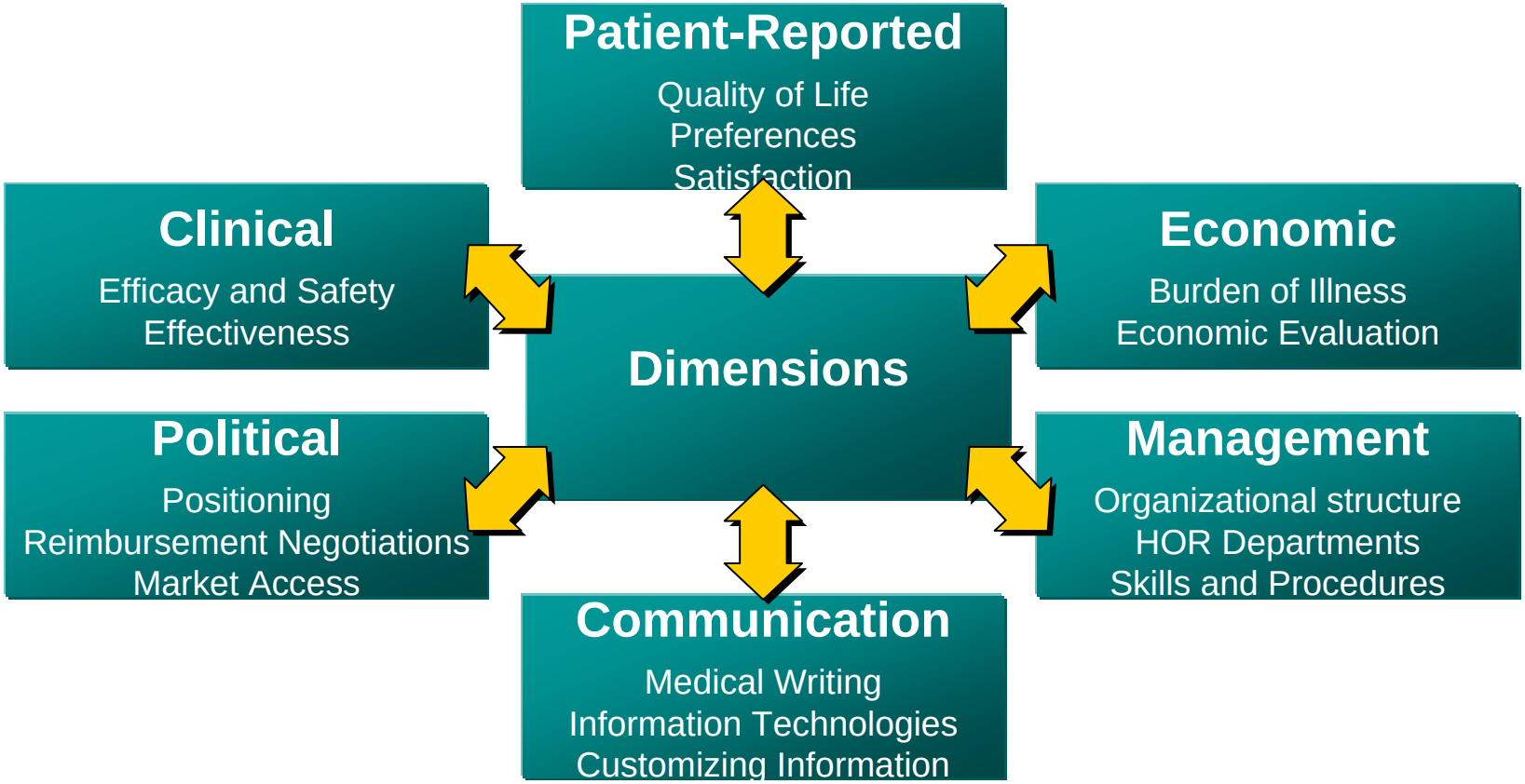
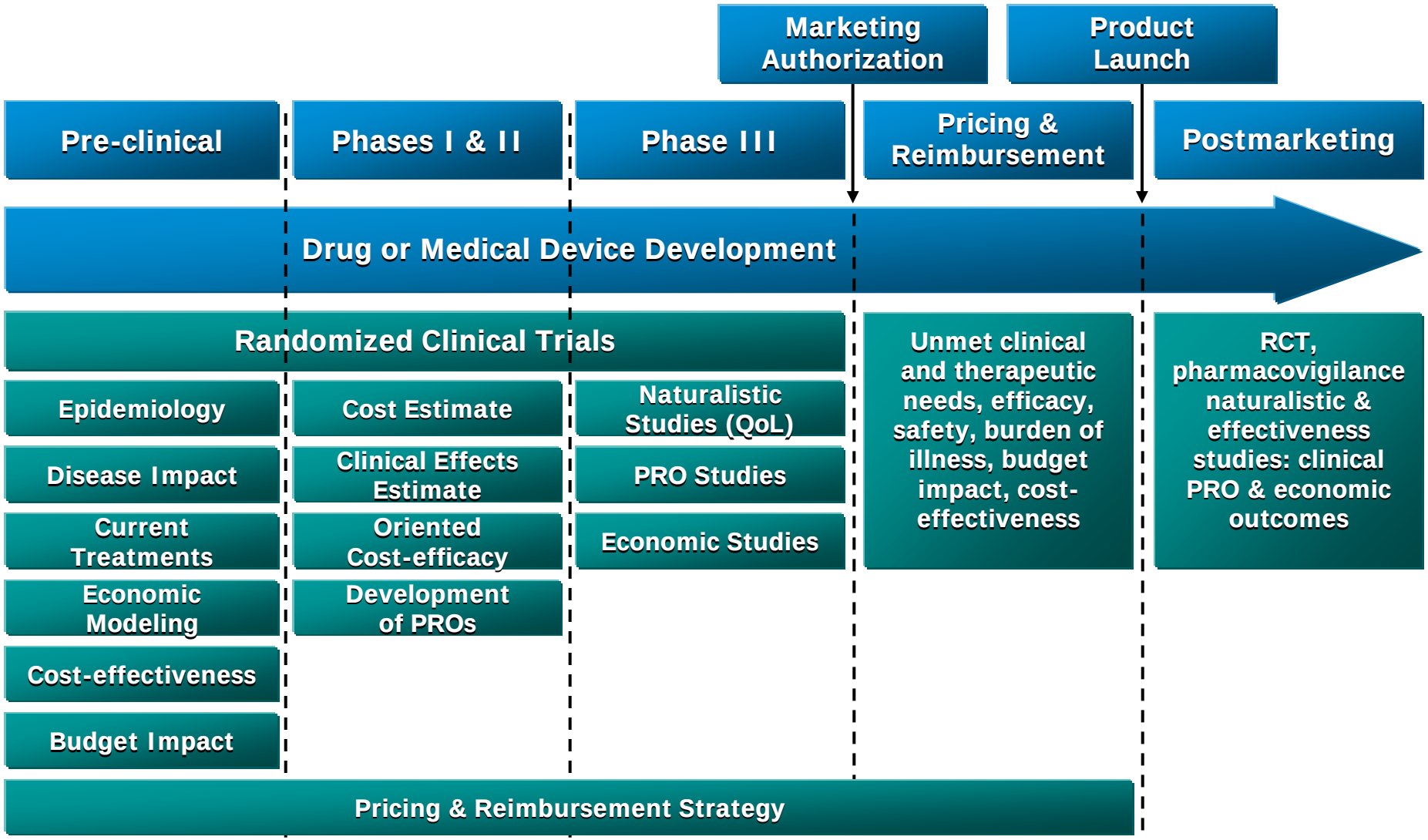
Dimensions of Health Outcomes Strategy Development



Health Economic Strategies Must be Developed Throughout The Development Process



Case Study

Development and Use of a Symptom Assessment Instrument to Support Registration of Ruxolitinib for the Treatment of Myelofibrosis

Richard S. Levy, MD
Executive Vice President
Chief Drug Development and Medical Officer
Incyte Corp.

Background on Myelofibrosis (MF)

- MF is a clonal bone marrow malignancy with activation of the JAK – STAT pathway resulting in:
  - Progressive bone marrow dysfunction (cytopenias)
  - Extramedulary hematopoesis (including massive splenomegaly)
  - Severe constitutional and other symptoms associated with elevated inflammatory cytokine burden
  - Shortened survival associated with infections, bleeding, thrombosis, cachexia and increased risk of transformation to AML

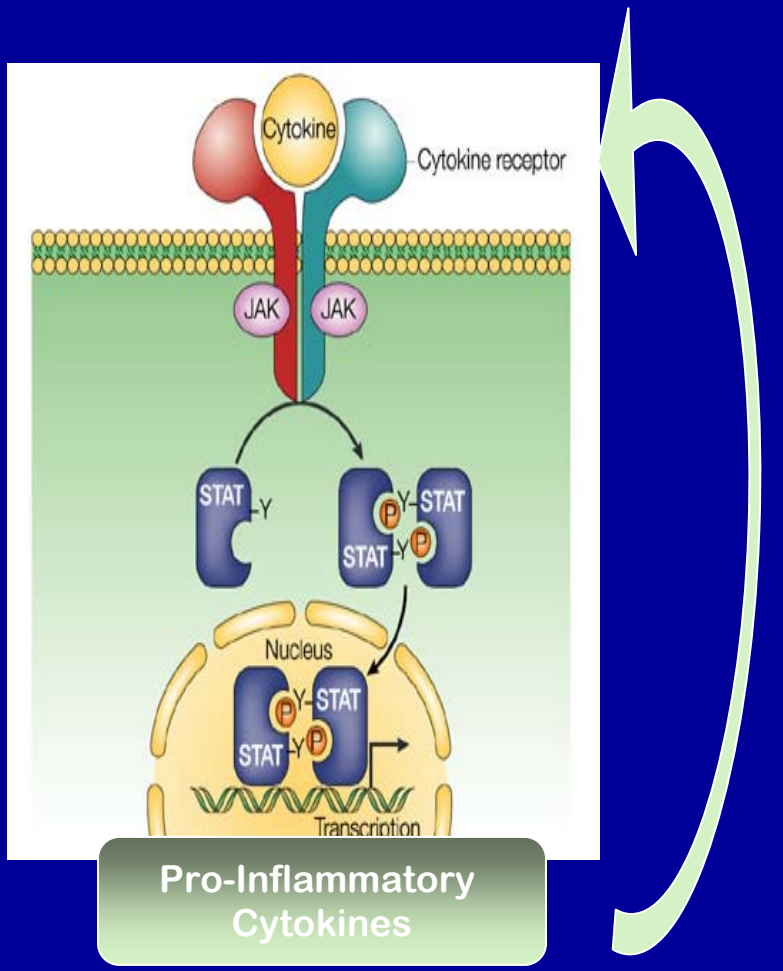
Patient Reported Symptoms of MF

- Internet survey of 1179 patients with myeloproliferative disorders
  - 458 patients with myelofibrosis
- Fatigue - 84%
- Night Sweats - 56%
- Symptomatic splenomegaly - 54%
- Pruritus (itching) - 50%
- Bone pain - 47%
- Weight loss (>10% body weight) - 20%
- Fevers - 18%

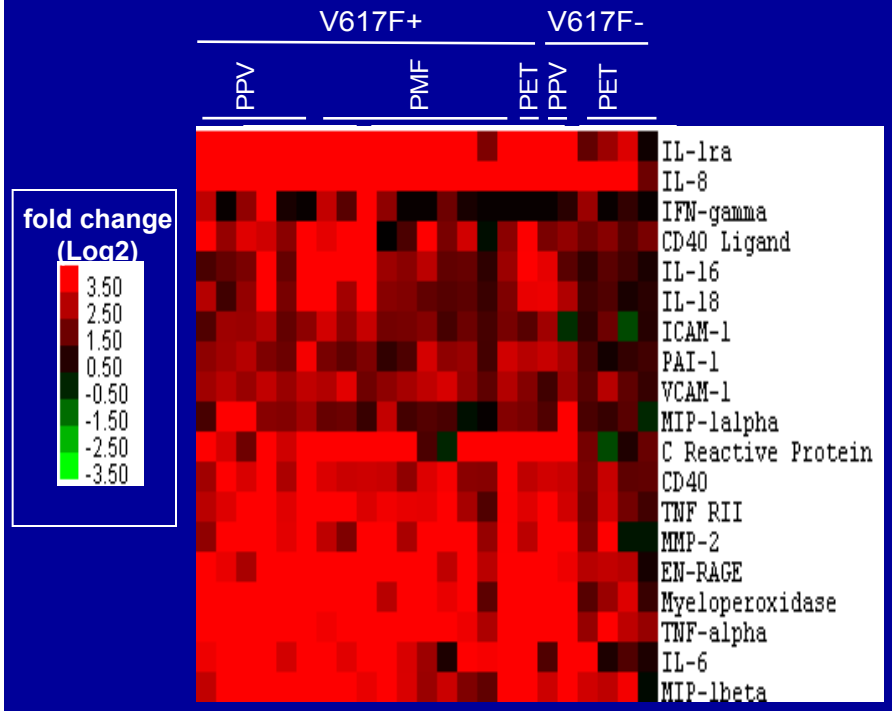
Source: Mesa RA et al, *Cancer*, 2006

JAK1 and JAK2 Inhibition and Their Role in Myelofibrosis

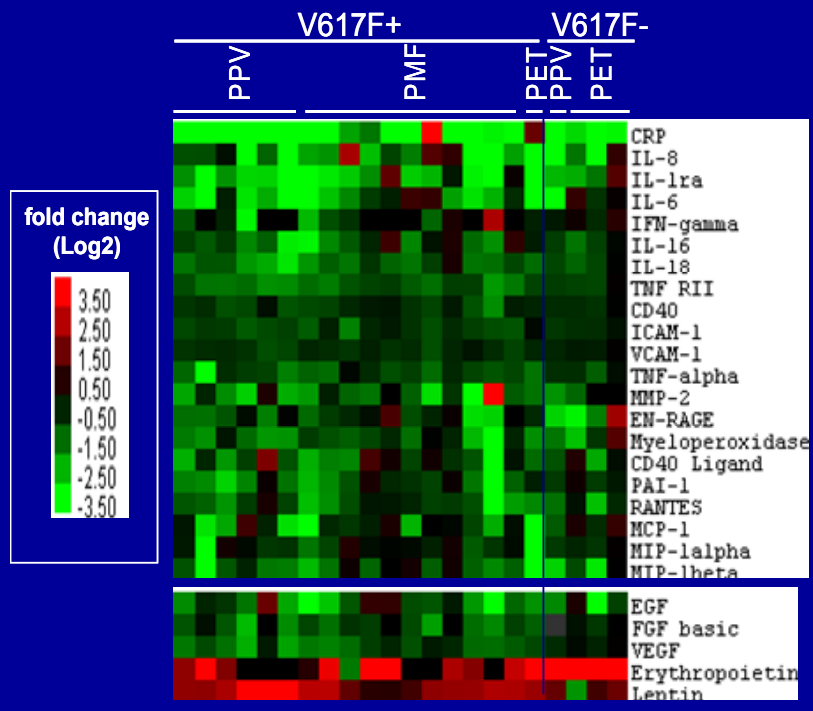
- JAKs mediate signaling of cytokines and growth factors by intracellular phosphorylation of cytokine receptors and subsequently STATs
- Most patients with MF have JAK 1 AND JAK2 activation
- Ruxolitinib is a potent inhibitor of JAK 1 and JAK 2 and a potential new treatment for MF



Aberrant JAK Signaling Results in Elevated Cytokine Levels that Respond to a JAK Inhibitor



Levels of cytokines in MF patients relative to healthy volunteers



Levels of cytokines in MF patients treated with ruxolitinib relative to pre-dose

Development of the MFSAF Tool

- 19-item questionnaire developed at Mayo Clinic ('MFSAF')
- 15-item modified version ('modified MFSAF') included in first clinical trial with ruxolitinib
- Preliminary discussion with FDA about inclusion of patient reported symptom assessments in registration trials – 1H 2008
- Conducted qualitative patient interviews: Defined and characterized most important and relevant concepts related to MF from the patient perspective
- Conducted cognitive debriefing patient interviews to assess readability and understanding of proposed questions
- Developed MF Symptom Diary ('MFSD') and discussed with FDA DDOP and SEALD – 2H2009
  - 46 items assessing symptom frequency, duration, degree of bother and severity
  - FDA provided guidance to simplify the tool and focus on symptoms at their worst severity with short recall period (24 hrs)
- Developed final 7-item modified MFSAF v2.0 diary which was accepted by FDA as part of an SPA for the registration trial (COMFORT I)

Modified MFSAF v2.0

1. During the past 24 hours, how severe were your worst night sweats (or feeling hot or flushed) due to MF?
2. During the past 24 hours, how severe was your worst itchiness due to MF?
3. During the past 24 hours, how severe was your worst abdominal discomfort (feel uncomfortable, pressure or bloating) due to MF?
4. During the past 24 hours, how severe was your worst pain under the ribs on the left side due to MF?
5. During the past 24 hours, what was the worst feeling of fullness (early satiety) you had after beginning to eat due to MF
6. During the past 24 hours, how severe was your worst bone or muscle pain due to MF (diffuse not joint or arthritis pain)?
7. During the past 24 hours, what was the worst degree of inactivity (including work and social activities) you had due to MF?

Each question answered with 0-10 point scale:

0 (Absent)	1	2	3	4	5	6	7	8	9	10 (Worst Imaginable)

Demonstration of a 'Fit for Purpose' Tool

- FDA's PRO Guidance states that results generated by a well-defined and reliable PRO tool used in a well-designed clinical trial could support labeling language
- Determined that the tool measured what is important to patients through qualitative patient interviews
- Demonstrated that the questions were interpretable and meaningful to the patient through cognitive debriefing interviews
- Demonstrated reliability of the test by assessing internal consistency and test-retest correlations
- Demonstrated construct validity by correlations with change in other established measures (eg, EORTC QLQ30, BPI)
- Demonstrated the tool can detect change
- Determined that definition of response is clinically important to the patient

Phase 3 Registration Studies

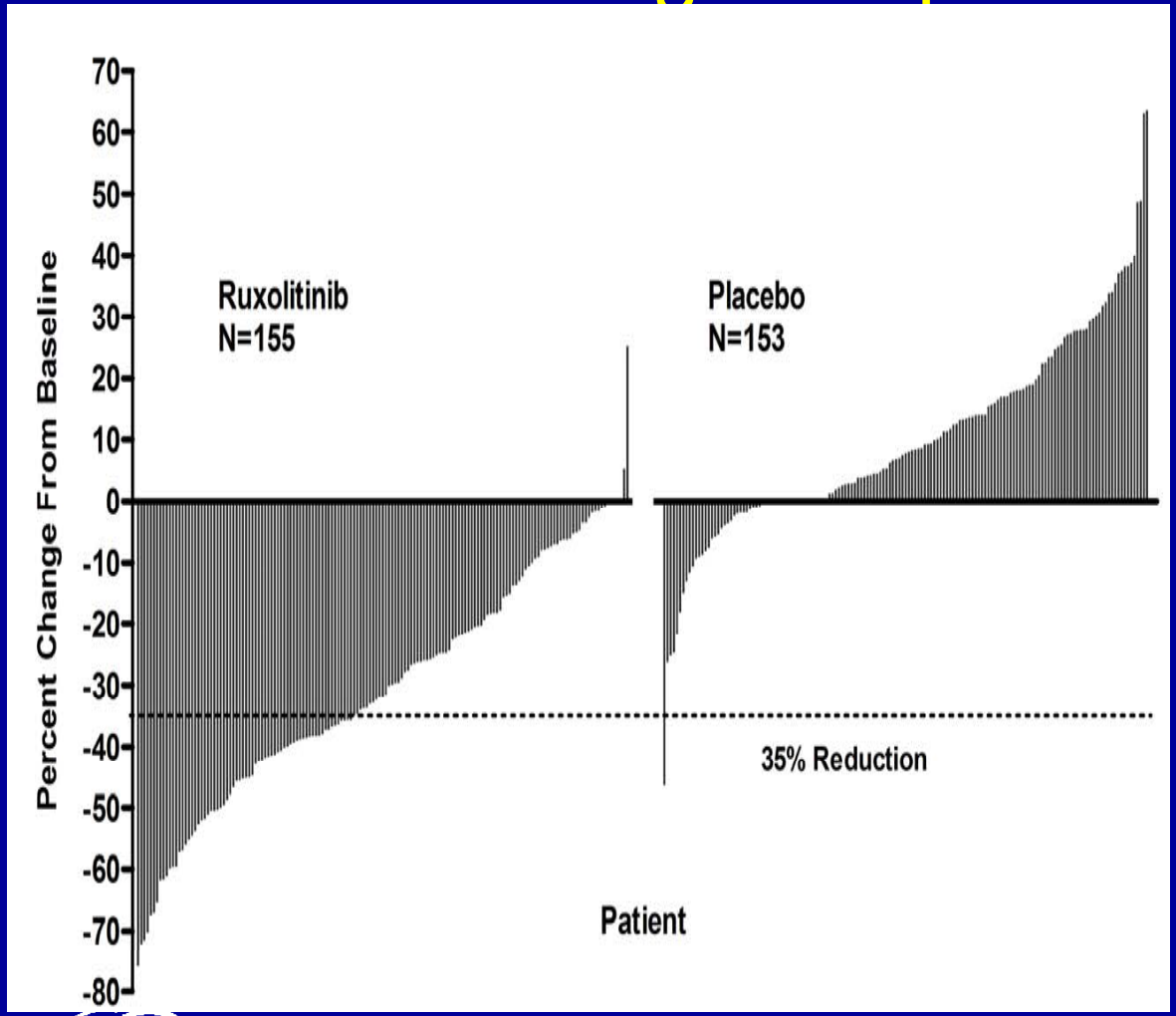
COMFORT I (US, Can, Aus)

- Randomized, blinded (placebo controlled)
- 1º EP: % of patients with ≥ 35% reduction in spleen volume (week 24)
- 2º EPs:
  - ≥ 50% reduction n MFSAF total symptom score (TSS)
  - Others
- Other symptom and QOL measures

COMFORT II (Europe)

- Randomized, open-label compared to best available therapy
- 1º EP: % of patients with ≥ 35% reduction in spleen volume (week 48)
- 2º EPs:
  - MFSAF not included in open label study
  - Others
- Other symptom and QOL measures overlapping with measures in Comfort I

COMFORT I: Primary Endpoint Analysis: Change in Spleen Volume

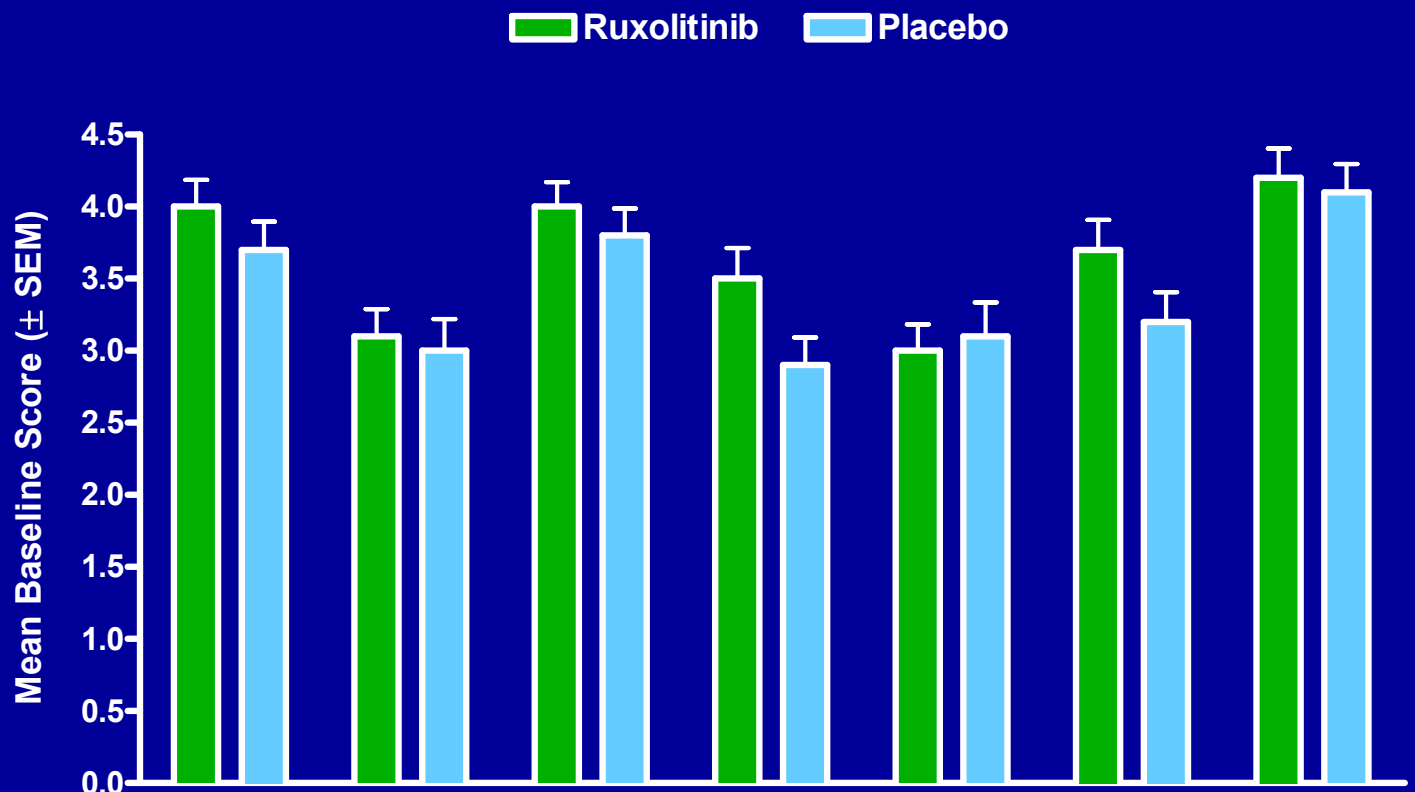


Responder Analysis

Proportion with ≥35% Reduction	
Ruxolitinib 41.9%	PBO 0.7%
P<0.0001	

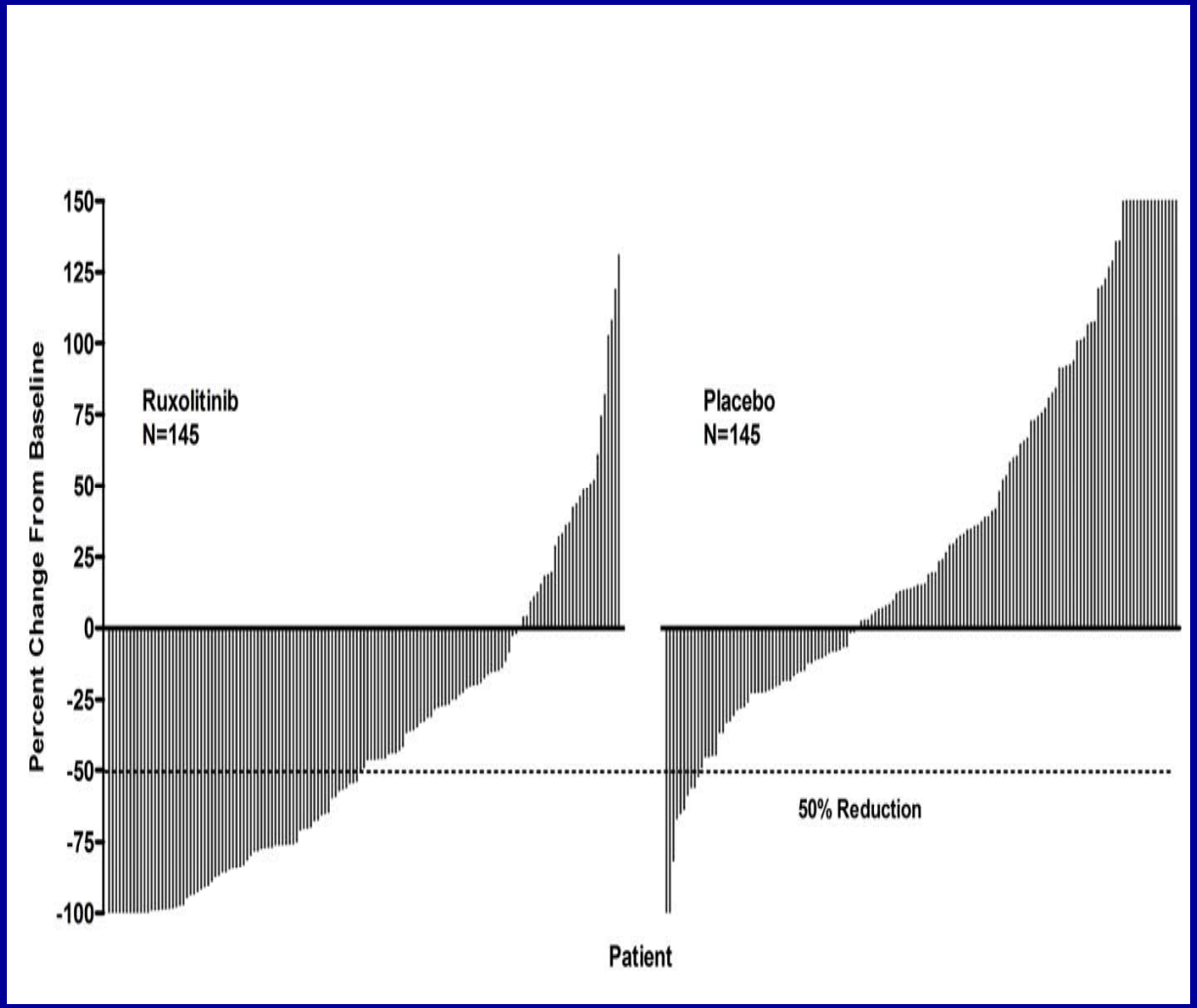
- Similar results were seen in COMFORT II

Baseline Prevalence and Severity of MF Symptoms in COMFORT-I



% With Symptom at Baseline	Abdominal Discomfort	Pain Under Left Ribs	Early Satiety	Night Sweats	Itchiness	Bone/ Muscle Pain	Inactivity
Rux	95.3	83.9	94.0	80.5	75.8	81.9	91.9
PBO	94.1	80.9	91.4	83.6	74.3	82.9	92.8

Total Symptom Score (TSS) Response



Responder Analysis

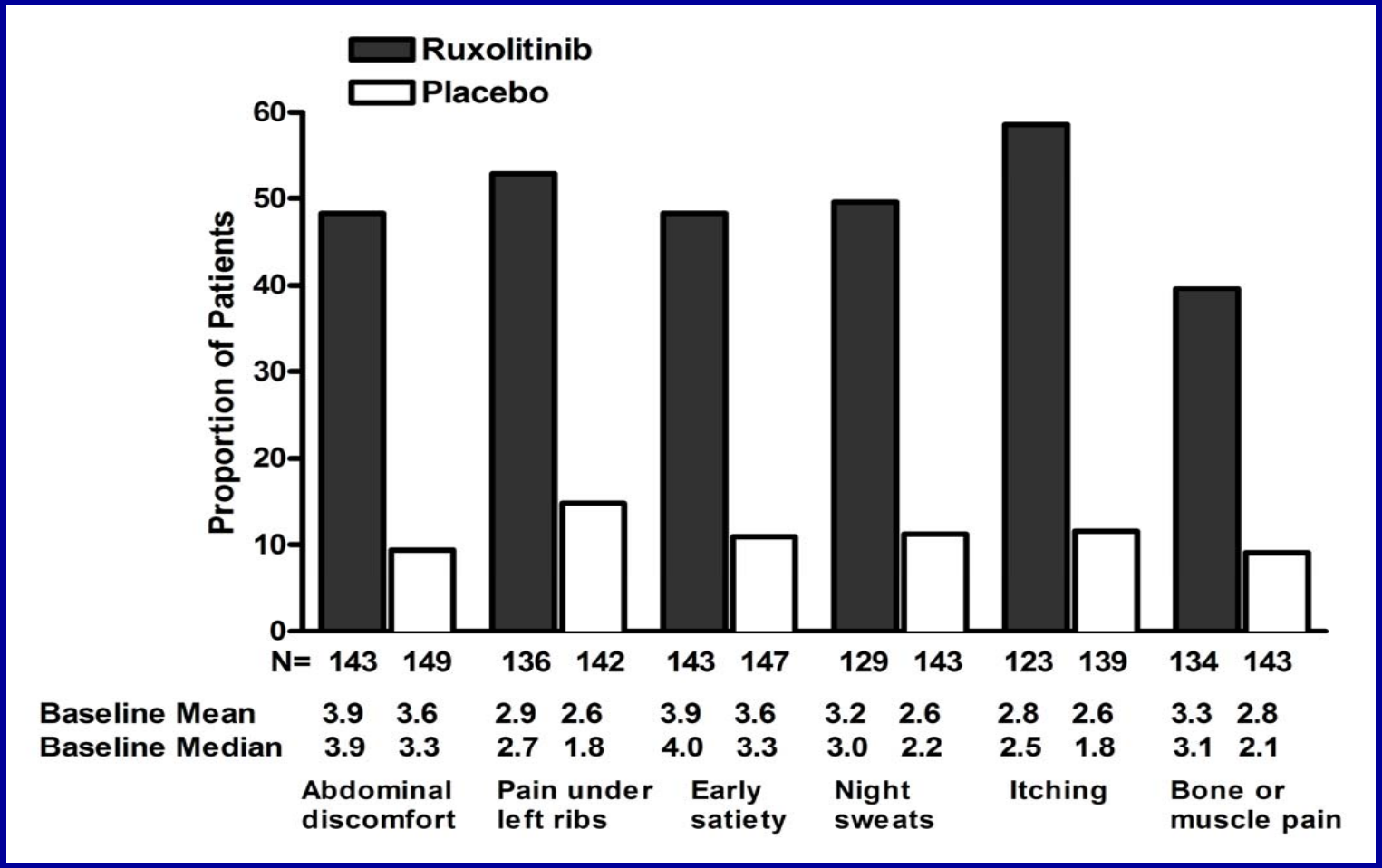
Proportion with ≥50% Reduction	
Ruxolitinib 45.9%	PBO 5.3%
P<0.0001	

12

Differential Improvement in TSS Response Rates Were Seen Prior to First 'On Treatment' Visit at Week 4

13

Individual Symptom Scores: Proportion of Patients with 50% or Greater Improvement



Individual score range = 0 to 10

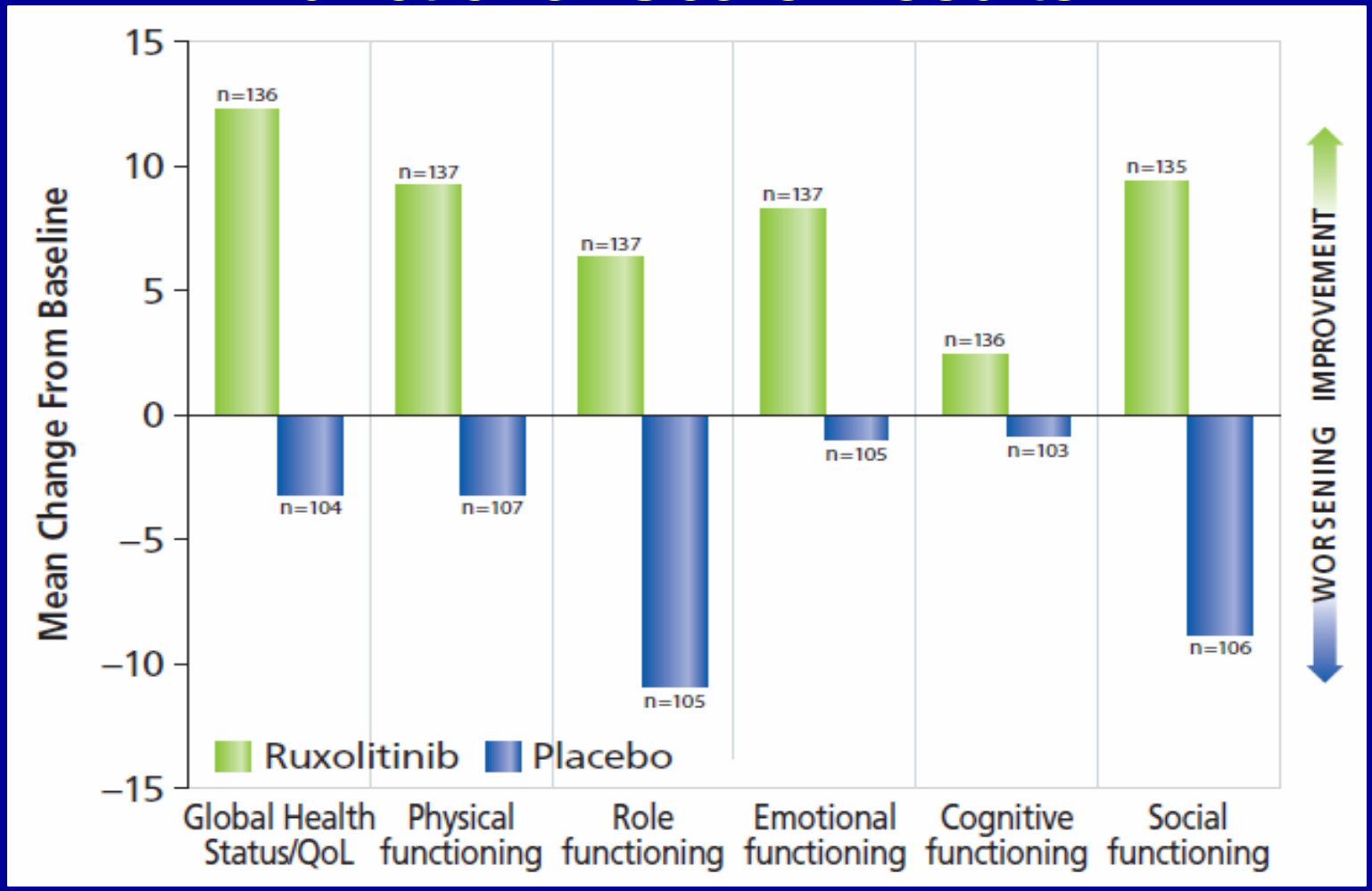
Associations Between modified MFSAF v2.0 TSS and Patient Global Impression of Change (PGIC)

	Ruxolitinib (n=127)				Placebo (n=100)			
TSS Score →	Responder (n=68)		Non-Responder (n=59)		Responder (n=9)		Non-Responder (n=91)	
PGIC Response ↓	n	%	n	%	n	%	n	%
Very much improved	35	51.5	8	13.6	1	11.1	0	0.0
Much improved	27	39.7	19	32.2	3	33.3	7	7.7
Minimally improved	3	4.4	22	37.3	3	33.3	17	18.7
No change	0	0.0	6	10.2	2	22.2	30	33.0
Minimally worse	2	2.9	3	5.1	0	0.0	19	20.9
Much worse	1	1.5	0	0.0	0	0.0	14	15.4
Very much worse	0	0.0	1	1.7	0	0.0	4	4.4

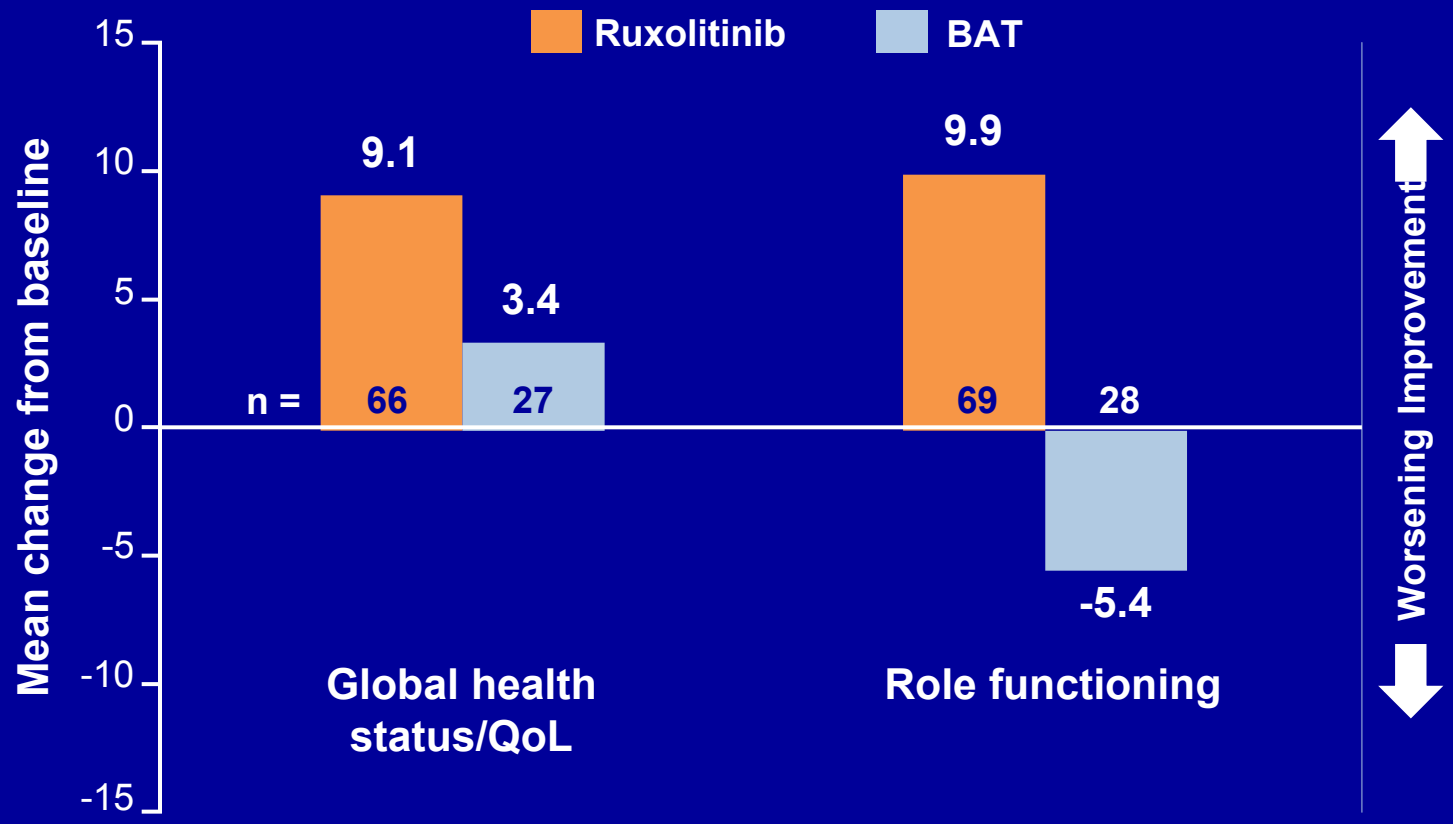
Modified MFSAF v2.0 Data Collection Metrics

- Compliance with data entry
  - 96% of all expected data entered
  - 98% completed minimum requirement of 4 out of 7 baseline days
  - 95% completed minimum requirement of 20 out of 28 days during Month 6 of the trial
  - 94% completed the daily assessment in 1 minute or less
- Test- retest reliability correlation coefficient from Week 7 to Week 8 of 0.97 with placebo and 0.98 with ruxolitinib
- Correlation with pain items in MFSAF with pain scores in EORTC QLQ C30 and Brief Pain Inventory (BPI) of approximately 0.6

Mean Change From Baseline to Week 24 in EORTC QLQ-C30 Global Health Status and Functional Scale Results

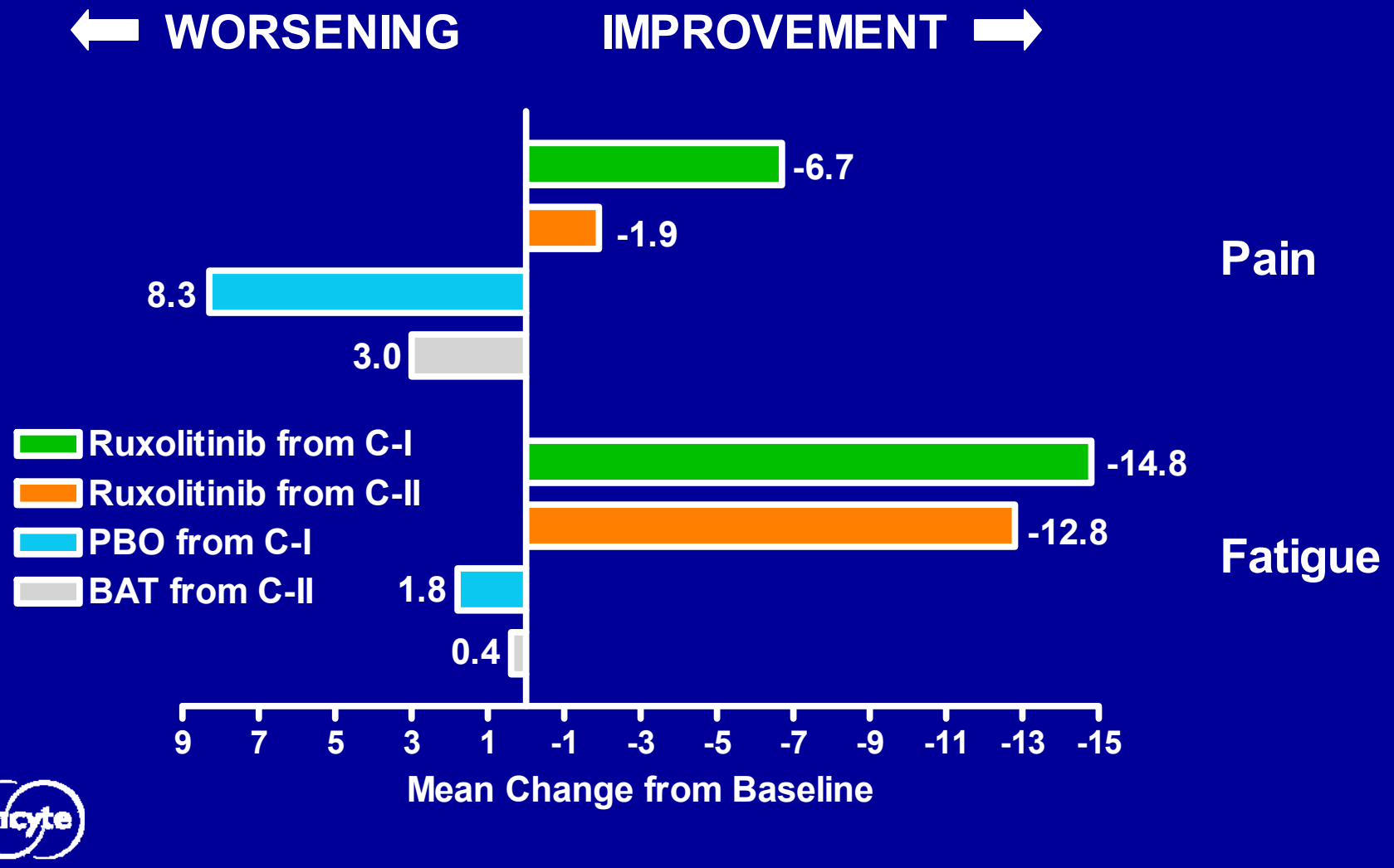


Change in EORTC QLQ-C30 In COMFORT II vs. Best Available Therapy (unblinded)



- Improvements were seen by Week 8 and continued through Week 48

Change in EORTC Fatigue and Pain Scores in Comfort-I (C-I) and Comfort-II (C-II)



Ruxolitinib Fair Balance Summary

- The most common hematologic adverse reactions were thrombocytopenia and anemia
- The most common non-hematologic adverse reactions were bruising, dizziness and headache
- Serious infections should have resolved before starting therapy and patients should be monitored for signs and symptoms of infection during therapy
- Lower starting doses are recommended for patients receiving strong CYP3A4 inhibitors and patients with renal and hepatic impairment who have lower platelet counts

Symptom Data Displays Proposed for the Package Insert

- Total symptom score response rates with p-value
- Waterfall plot showing range of changes in total symptom score for ruxolitinib and placebo treated patients
- Response rates of individual symptoms improving by at least 50% - no p-values (individual symptom analyses were not alpha controlled but all were nominally significant)

Strategies for Potential Success

- Understand the most important and relevant concepts from the patients' perspective
- Ask simple, understandable and unambiguous questions which have been endorsed by the patient
- Enroll only symptomatic patients
- Assess for introduction of bias, even in blinded trials
- Focus on methods to help ensure patient compliance to complete the selected tool
  - Electronic diaries (provided by invivodata inc.) and low burden to complete the diary help ensure necessary compliance
- Involve the FDA/SEALD in discussions about the development of a PRO tool and obtain SPA agreement for trials using a PRO tool (especially a newly created or modified one)
- Have a drug with a robust treatment effect

Measuring Treatment Benefit: Regulatory Perspective

Conference on Clinical Cancer Research

Washington DC – November 10, 2011

Laurie Beth Burke

Associate Director for Study Endpoints and Labeling

Office of New Drugs

CDER-FDA

The views expressed are those of the author, and do not necessarily represent an official FDA position

Treatment Benefit

- The impact of treatment on how patients survive, feel, or function in their daily lives
  - Measured as effectiveness or comparative safety
- Can be measured directly (eg, symptoms) or indirectly (eg, tumor burden)
- Indirect assessment needs empiric justification for its value as a replacement for how patients survive, feel or function
- Described in labeling as a claim using words that represent the concept measured by the COA.

Clinical Trial Outcome Assessment Primer

- Clinical trial outcome assessments (COAs) are critical to understanding drug benefits and harms.
- All COAs require rigorous development before we can adopt them in clinical trials to support product approval and treatment benefit claims
  - Survival, Biomarkers, Patient-reports, Clinician-reports, Other
  - To reduce scientific uncertainty AND regulatory uncertainty, we need COAs that are “well-defined and reliable” in the clinical trial context of use.

FDA Review of Clinical Trial Outcome Assessments (COAs)

- Regulatory standard: "well-defined and reliable"
  - Evidence guidance: FDA PRO Guidance summarizes good measurement principles applicable to any PRO, ClinRO or ObsRO assessment used for the following purposes:
    - Substantiate treatment benefit claims
    - Define primary or key secondary endpoints (NOT EXPLORATORY)
    - Represent clinical trial objectives

Instrument Development Begins with Defining the "Context of Use"

- The manner and purpose of use of a COA
  - Targeted population
    - Important areas of heterogeneity identified
    - Inclusion/exclusion criteria for study entry determined
  - Type of trial
    - Study objectives and design (BLINDED???)
    - Type of analysis (superiority or non-inferiority?)
    - Clinical trial endpoint model (critical in oncology)
  - Other
    - Drug: MOA, mode of administration, onset of action

Targeted Clinical Trial Endpoint Model

The role and hierarchy of all measures used as endpoints in the targeted clinical trials

Endpoints		Concepts	Clinical Trial Outcome Assessment
Primary	→	Concept A	COA 1
Secondary with Hierarchy	→	Concept B	COA 2
	→	Concept C	COA 3
	→	Concept D	COA 4
	→	Concept E	COA 5
Exploratory	→	Other concept	Other COA

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf

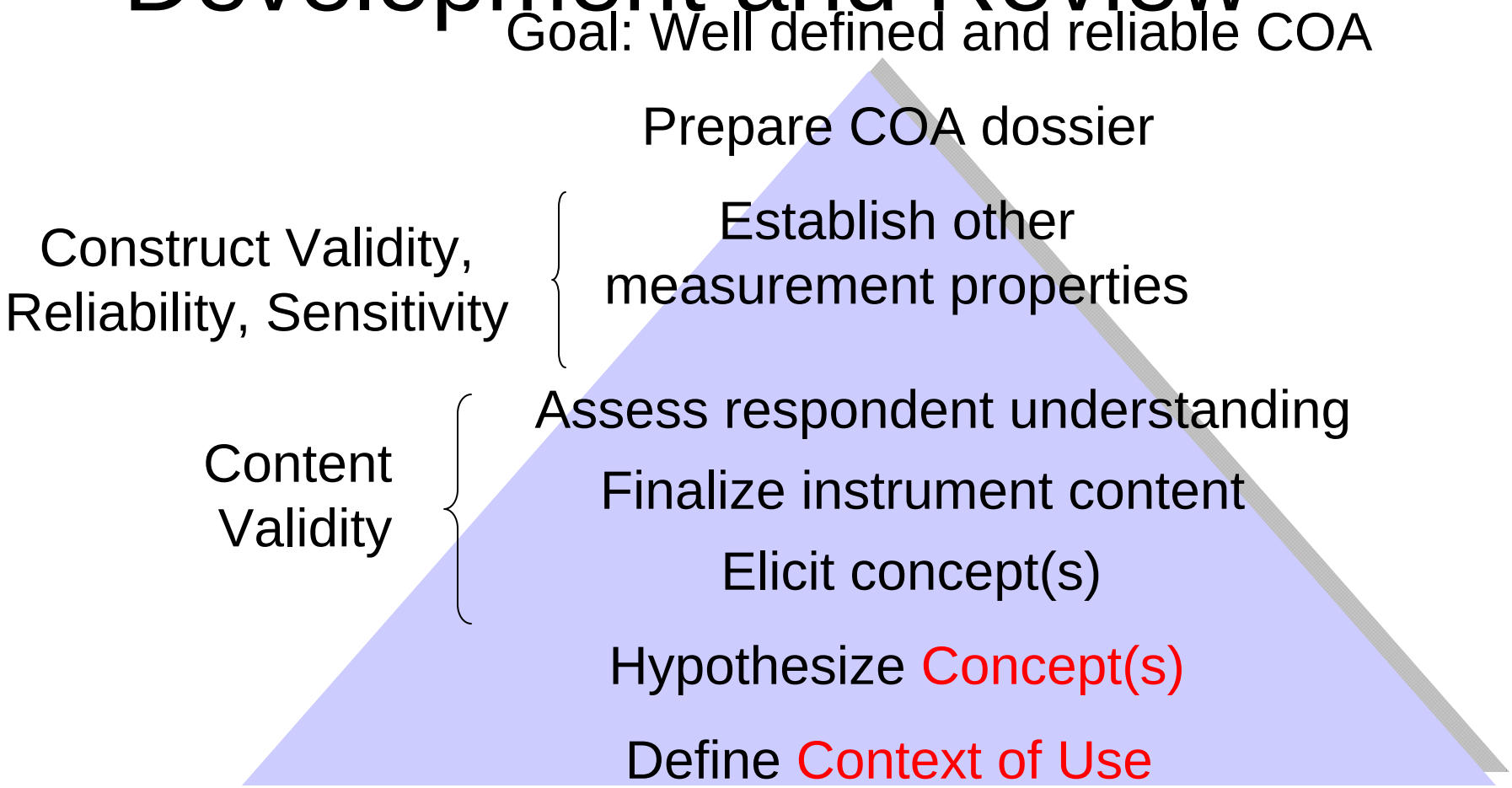
Establishing Content Validity: New COA Development or Review of Existing COA

- Begins after confirmation that the concept and the context of use are appropriate
- Empiric evidence that the instrument measures the targeted concept in the context of use
  - If existing instrument is used for a new context of use, additional content validity evidence may need to be developed
- Content validity must be established before other evidence of construct validity, reliability or sensitivity to change can be interpreted

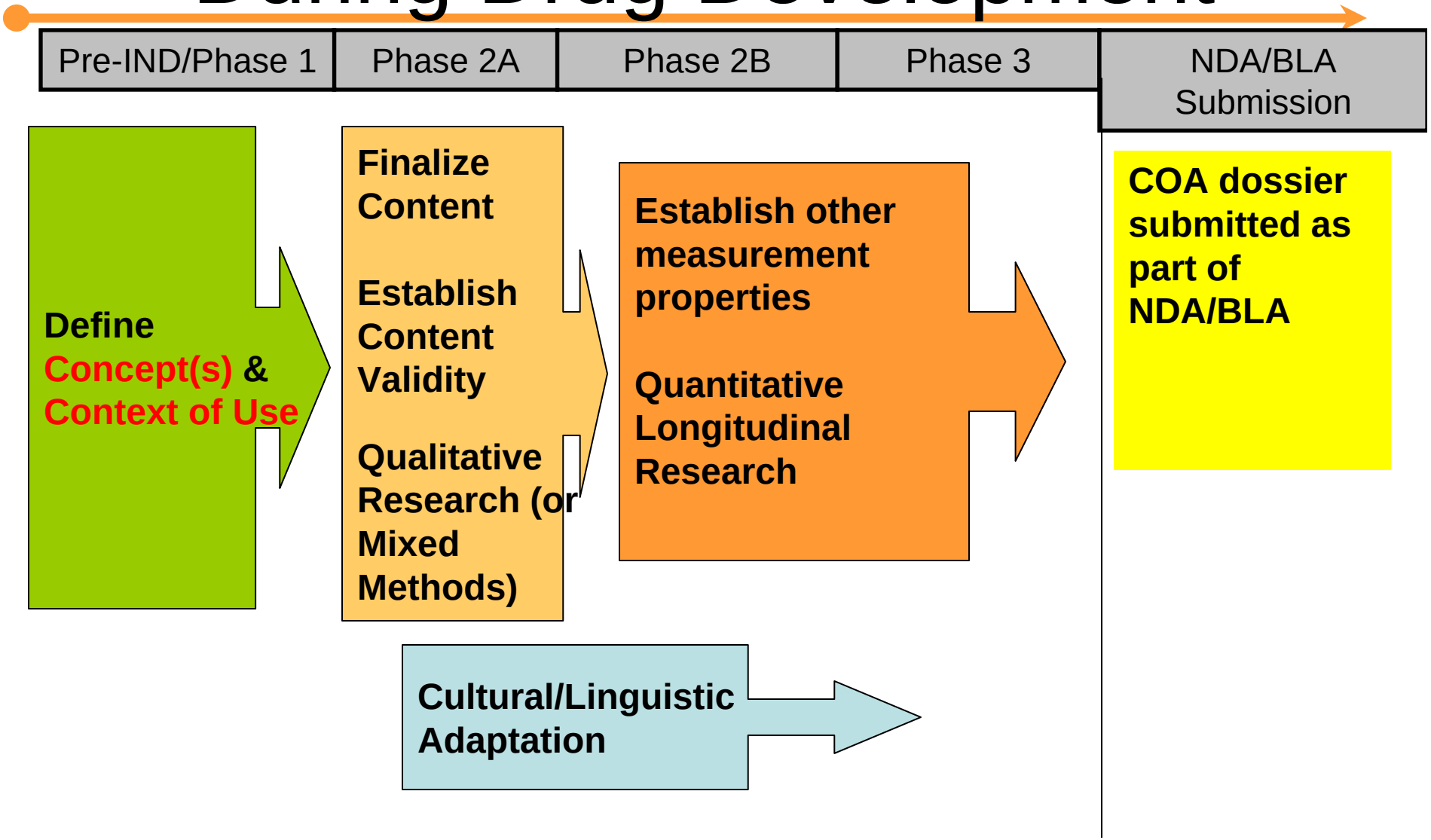
Methods to Establish Content Validity Are Iterative

- Literature review
- Expert opinion
- Qualitative Research: Critical
  - Input from target responder population to document understandability and comprehensiveness
    - PRO: target population of patients
    - ObsRO: target population of respondents
    - ClinRO: target population of clinicians
- Quantitative Analyses (Rasch, IRT)
  - Recommended for efficiency in instrument

Clinical Trial Outcome Assessment Development and Review



Optimal Timeline for COA Development During Drug Development



ENGELBERG CENTER for Health Care Reform at BROOKINGS

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