



# **PRO Consortium Working Group Updates**

Presented at:

***FIRST ANNUAL  
PATIENT-REPORTED OUTCOMES (PRO)  
CONSORTIUM WORKSHOP***

**March 23, 2010 – Bethesda, MD**

# Current Working Groups



- **IBS**
  - Co-Chairs: Charles Baum and Barbara Lewis
- **Cognition**
  - Co-Chairs: Usha Mallya and Marc Cantillon
- **Asthma**
  - Co-Chairs: Linda Nelsen and Sulabha Ramachandran
- **Depression**
  - Chair: Ken LaPensee
- **Non-Small Cell Lung Cancer**
  - Chair: Bhash Parasuraman
- **Advanced Breast Cancer**
  - Chair: Bonnie Teschendorf



# **Irritable Bowel Syndrome Working Group (WG)**

**Presenter: Charles Baum, MD, MS, FACG**

Executive Medical Director, GI and  
Internal Medicine, Global Medical Affairs  
Takeda Pharmaceuticals

# IBS WG - Participants



Company	Name
<b>CO-CHAIRS</b>	
Takeda	Charlie Baum
Ironwood	Barbara Lewis
<b>PARTICIPANTS</b>	
Takeda	Gale Kennedy
Forest	Robyn Carson
Ironwood	Jeff Johnston
<b>NONMEMBER PARTICIPANTS</b>	
UCLA/Rome Foundation	Lin Chang
SUNY Buffalo	Jeff Lackner
IFFGD	Nancy Norton

# IBS WG - Overview



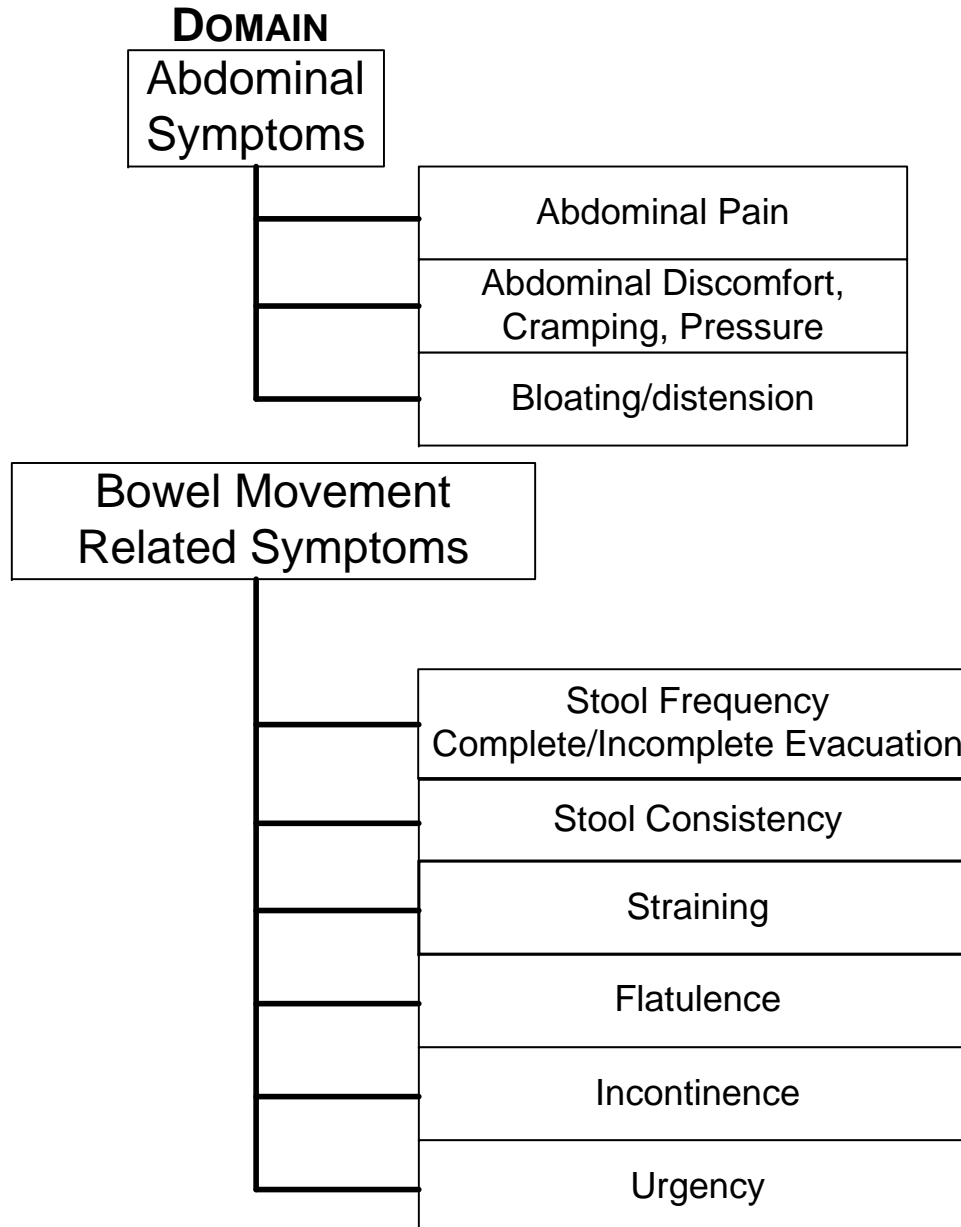
- Objectives
  - To replace non-validated PRO measures
- Target Population
  - Adults aged 18+
  - IBS subtypes (constipation, diarrhea, and mixed) diagnosed by Rome III criteria

# IBS WG - FDA Feedback



- After discussion with the GI Review Division and SEALD team, there was agreement on changes to the scoping document and agreement from the FDA to participate in the qualification process of the IBS Composite Symptom Severity Index
- Clarification was provided on future use of PRO instrument in drug development:
  - It remains an empirical question whether the same or different instruments can be used for each IBS subtype.
  - If an alternative indication is sought and a subset of symptoms is considered as the primary endpoint, all of the other clinically important symptoms which comprise the IBS Composite Symptom Severity Index would still need to be measured.

# IBS WG - Conceptual Framework



# IBS WG - Targeted Labeling Language



- Proposed labeling language:
  - As currently conceived, the IBS PRO instrument would provide an indication of improvement in symptom severity (composite score).
    - Treatment with product X results in a clinically meaningful improvement in the symptoms of IBS subtype.
  - Secondary labeling claims around individual concepts/items (e.g., abdominal pain) will require evidence that the concept is adequately measured



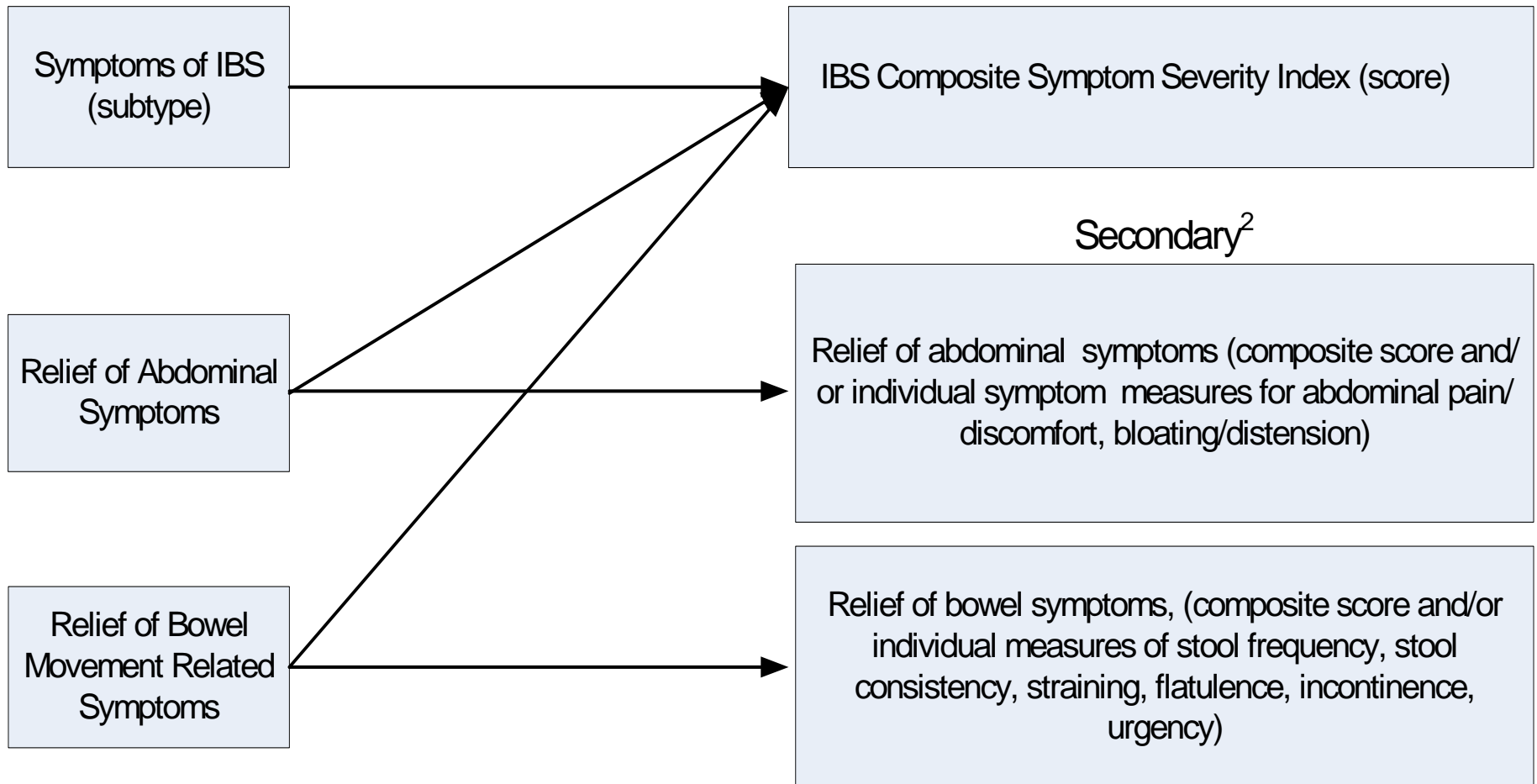
# IBS Endpoint Model



## Concept

## Endpoints

Primary<sup>1</sup>



# IBS WG - Status



- IBS Working Group to begin Vendor Selection Stage



# **Cognition Working Group (WG)**

**Usha Mallya, PhD**

Associate Director, Global Health Economics  
and Outcomes Research

Novartis Pharmaceutical Corporation

# Cognition WG - Participants



Company	Name
<b>CO-CHAIRS</b>	
Merck Sharpe & Dohme Corp.	Marc Cantillon
Novartis	Usha Mallya
<b>PARTICIPANTS</b>	
Abbott	Nicholas Greco, Steven Hass, Genevieve Laforet, Ramanuj Achari
Bristol-Myers Squibb	Leah Burns, Lucinda Orsini
Boehringer Ingelheim	Juergen Reess, Andrea Jung
Janssen Alzheimer's Immunotherapy R&D	Christopher Leibman, Trent McLaughlin
Eisai	Grant Maclaine
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Pfizer	Ming-Ann Hsu
Genentech	Nina Hill, Sarah Trease
Takeda	Stephen Sainati, Anuja Roy

# Cognition WG - Overview



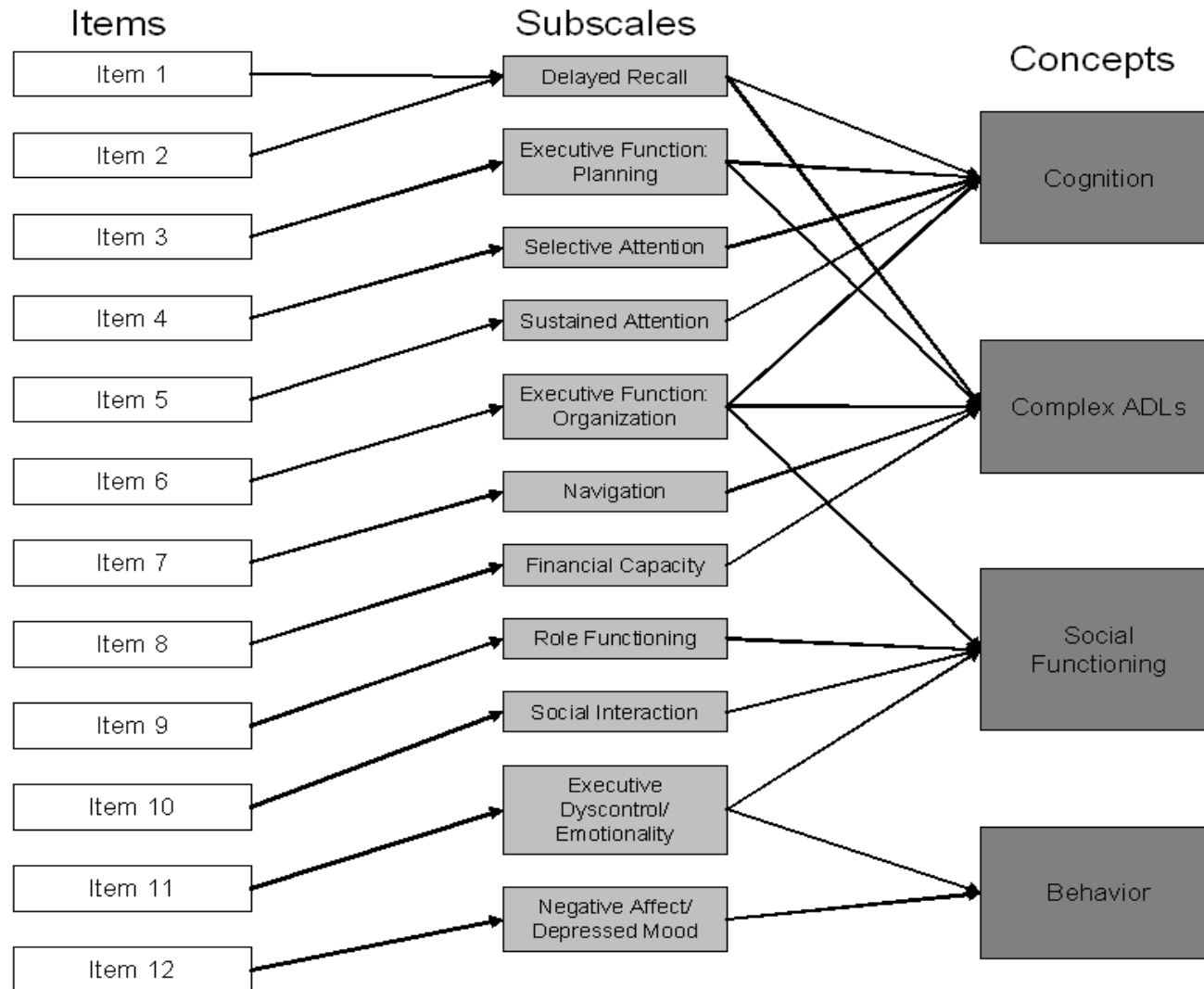
- **Objectives**

- The Cognition Working Group seeks to develop outcome measures that improve upon the measurement of mild levels of cognitive impairment and capture the patient's and informant's perspectives on relevant outcomes.

- **Target Population**

- A continuum of patients aged  $\geq 50$  years, meeting inclusion/exclusion criteria, diagnosed with MCI, amnesic subtype, and mild to moderate probable AD and without a diagnosis for Major Depressive Disorder as well as any clinically relevant condition
- Informant: Family member or friend of a patient meeting inclusion criteria and who has familiarity with the patient's basic and complex Activities of Daily Living

# Cognition WG - Proposed Conceptual Framework for the Patient- and Informant-reported Instrument

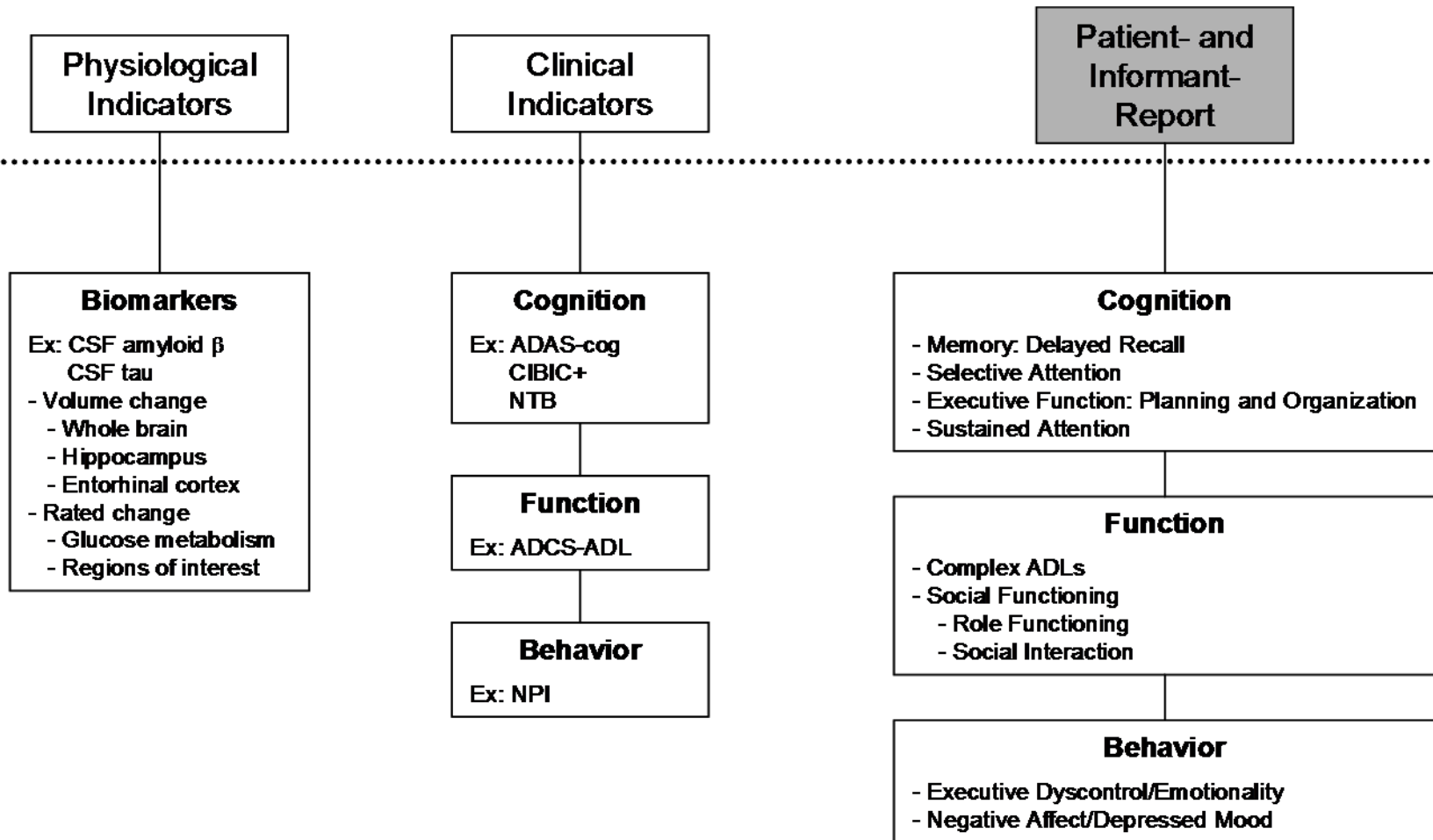


# Cognition WG - Targeted Labeling Language



- Cognition:
  - Treatment slows the progression of memory impairment in patients with mild cognitive impairment.
- Functioning:
  - Treatment reduces worsening of Complex Activities of Daily Living functioning in patients with mild cognitive impairment.
- Behavior:
  - Treatment reduces worsening of executive dyscontrol and emotionality in patients with mild cognitive impairment.
  - Treatment reduces worsening of negative affect in patients with mild cognitive impairment.
  - Treatment reduces worsening of emotional dyscontrol as it affects social functioning, represented by appropriate interpersonal interactions and social role functioning and/or occupational functioning, in patients with mild cognitive impairment.

# Cognition WG - Endpoint Model





# Cognition WG - Status



- Cognition Scoping Stage Summary Document submitted to the FDA and EMA on December 22<sup>nd</sup>, 2009



# **Asthma Working Group (WG)**

**Presenter: Linda Nelsen, MHS**

Associate Director, Epidemiology

Merck Sharpe & Dohme Corp.

# Asthma WG - Participants



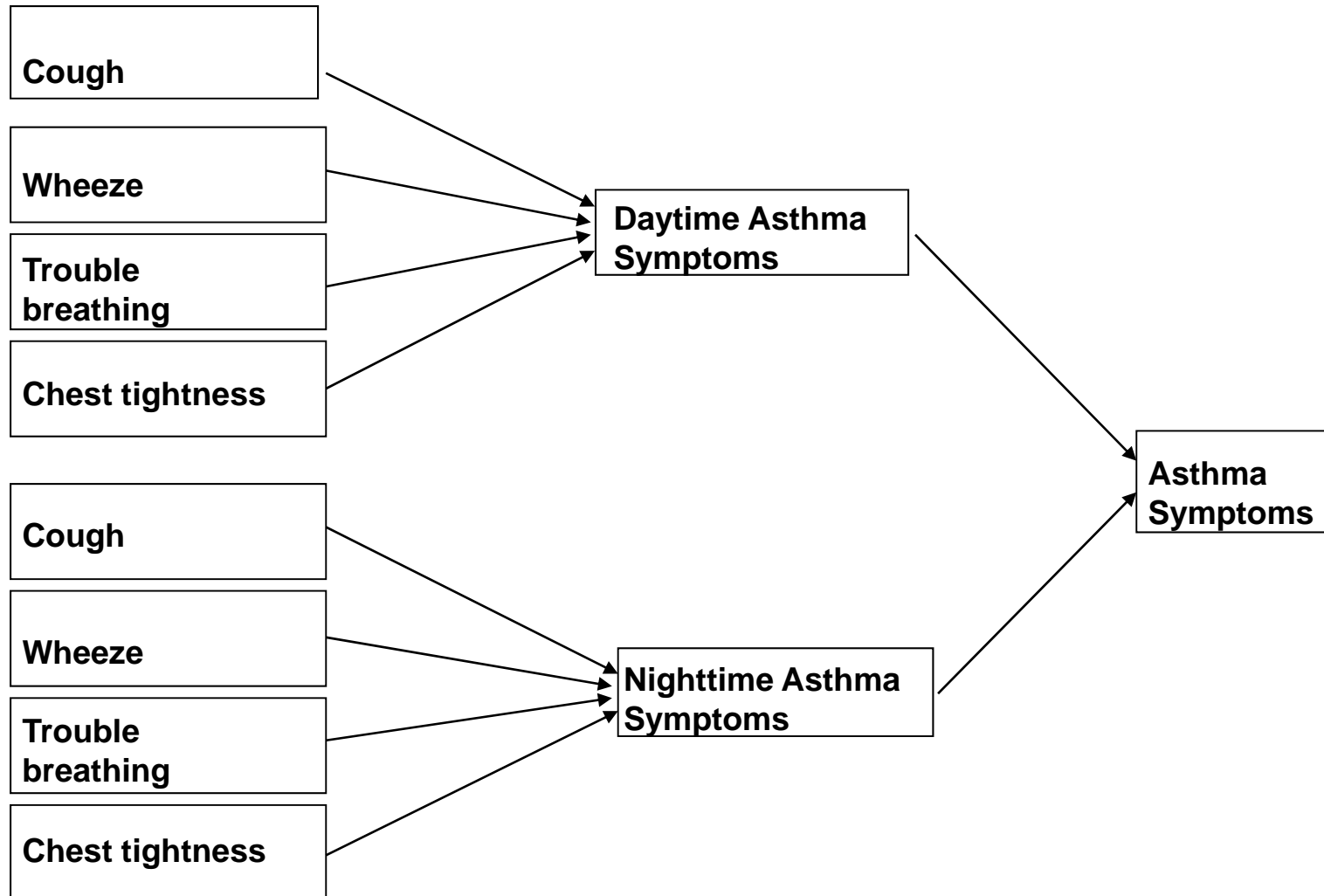
Company	Name
<b>CO-CHAIRS</b>	
AstraZeneca	Sulabha Ramachandran
Merck Sharpe & Dohme Corp.	Linda Nelsen
<b>PARTICIPANTS</b>	
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Actelion	Elke Hunsche
Amgen	Fang Chiou, Vasily Belozeroff
AstraZeneca	Kim Gilchrist, Niklas Karlsson
Boehringer Ingelheim	Michael Engel, Rozsa Schlenker-Herceg
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GlaxoSmithKline	Priti Jhingran, Richard Stanford, Margaret Tabberer
Ironwood Pharmaceuticals	BJ Lavins, Barbara Lewis
Novartis	Andrine Swensen, Jie Zhang, Cat Bui
Pfizer	Tara Symonds, Claire Gilbert
UCB	Dorothy Keininger, Enkeleida Nikai

# Asthma WG - Overview



- Objectives
  - To develop a new asthma symptom diary
- Target Population
  - Adolescents and adults aged 12 and older with a clinical diagnosis of persistent asthma with lung function impairment but without fixed airway obstruction

# Asthma WG - Proposed Conceptual Framework for Asthma Symptom Diary



# Asthma WG - Targeted Labeling



## OVERALL

- Patients treated with X reported significant reductions in asthma symptom [frequency; severity; duration]
- Significantly more patients treated with X reported improvements in asthma symptoms
- Patients treated with X reported significantly fewer days with asthma symptoms

## DAYTIME

- Patients treated with X reported significant reductions in daytime asthma symptom [frequency; severity; duration]
- Significantly more patients treated with X reported improvements in daytime asthma symptoms
- Patients treated with X reported significantly fewer days with asthma symptoms

## NIGHTTIME

- Patients treated with X reported significant reductions in overnight awakenings with asthma symptoms
- Patients treated with X reported fewer nights with awakenings with asthma symptoms

## INDIVIDUAL SYMPTOMS

- Product X improves [intensity, frequency, duration] of cough associated with asthma
- Patients treated with X reported significant improvements in shortness of breath
- Product X reduces the [frequency, intensity, duration] of wheeze

# Asthma WG - Endpoint Model



<u>Efficacy Endpoint</u>	<u>Measure</u>
<b>Co-Primary Endpoints</b>	
Improvement in airflow obstruction	Trough FEV1
Reduction in asthma symptoms	Asthma symptom score from Asthma Symptom Diary
<b>Secondary Endpoints</b>	
Symptom Free Days	Proportion of days without symptoms based on Asthma Symptom Diary
Nocturnal awakenings	Number of nights with nighttime awakenings due to asthma symptoms measured in Asthma Symptom Diary
Asthma exacerbation	Number of exacerbations

# Asthma WG - Status



- Asthma Scoping Stage Summary Document submitted to the FDA and EMA on March 2, 2010





# Depression Working Group (WG)

Presenter: Ken LaPensee, PhD, MPH

Director, Health Economics and Outcomes Research

Forest Research Institute

# Depression WG - Participants



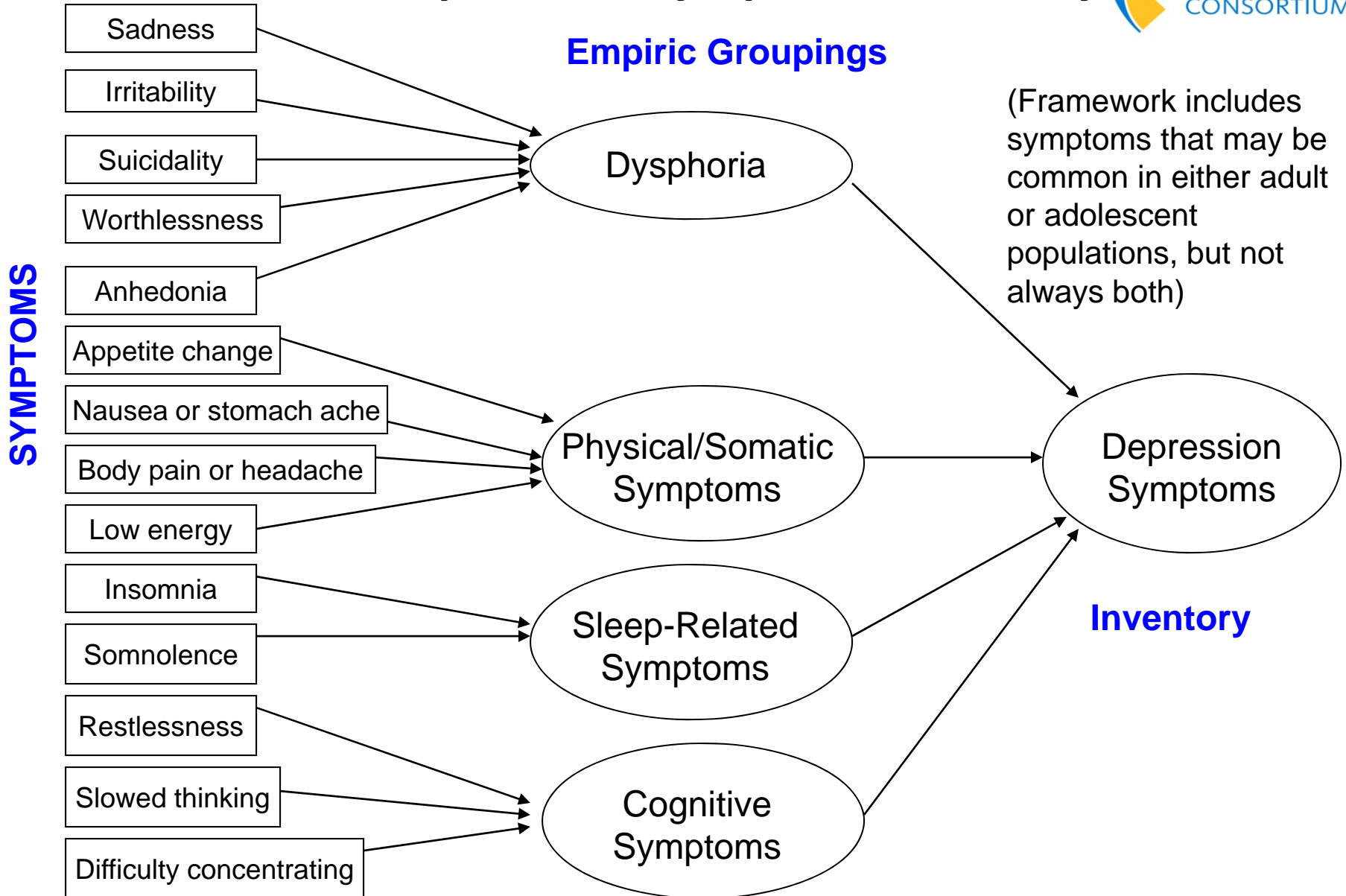
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Forest Research Institute	Ken LaPensee
<b>PARTICIPANTS</b>	
Abbott	Nicholas Greco, Steven Hass
AstraZeneca	Mariam Hassan
Dainippon Sumitomo Pharma America	Omar Olhaye, Vincent Chia
Eisai	Grant Maclaine
Eli Lilly & Co	Glenn Phillips
Forest Research Institute	Abhilasha Ramasamy, Steven Blum
GlaxoSmithKline	Brian Bowers, Sunny Mahajan
Ironwood Pharmaceuticals	BJ Lavins
Merck Sharpe & Dohme Corp.	Jaime Barnes
Sanofi-Aventis US, Inc	Daryl DeKarske
Takeda	Stephen Sainati, Anuja Roy

# Depression WG - Overview



- Objectives
  - Assess adequacy of PRO instruments currently used in major depressive disorder (MDD) studies regarding capture of important symptom information from the patient’s perspective
  - If there is an unmet need, either modify an existing instrument or develop a new depression symptom inventory
- Target Population
  - Male & female adolescents and adults aged  $\geq 12$  with MDD including patients of all levels of severity from “mild” to “severe” requiring ambulatory or inpatient pharmaceutical, somatic, or cognitive therapy
  - Sponsors may target segments of the depression population based on proposed labeling claim and mechanism of action (e.g., “severe” or “treatment-resistant” depression, adolescents)

# Depression WG - Proposed Conceptual Framework for Depression Symptom Inventory



# Depression WG - Targeted Labeling Language



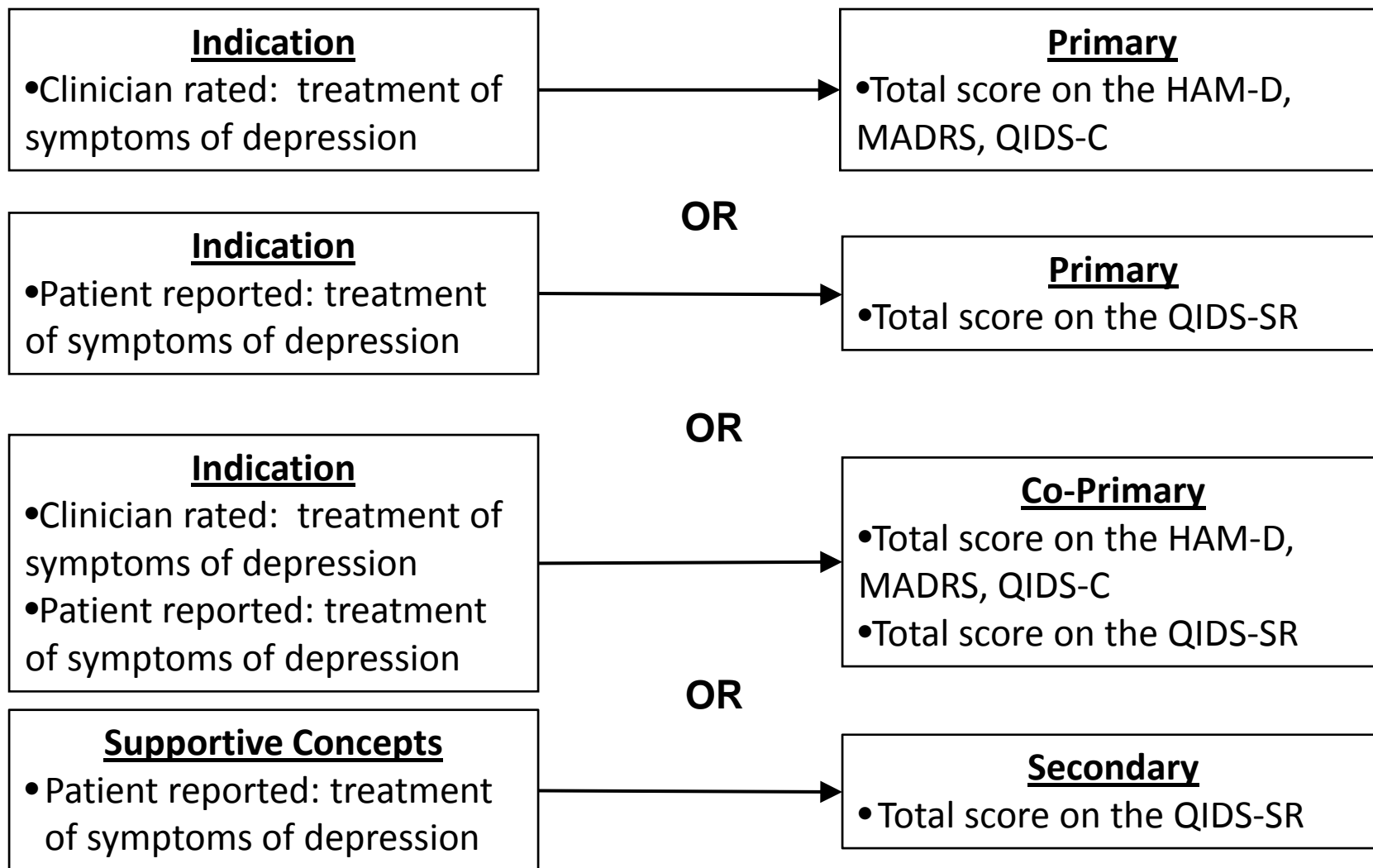
- **Based on group comparison using mean values:**
  - Patients treated with XX reported clinically meaningful reductions in depression symptom [frequency; severity] compared with treatment YY, as assessed by the symptom inventory
- **Based on group comparison using responder analysis:**
  - Compared with YY, significantly more patients treated with XX reported meaningful reductions in depression symptoms as assessed by the symptom inventory
- **Based on group comparison of number of days with symptoms**
  - Compared with YY, patients treated with XX reported significantly fewer days with depression symptoms as assessed by the symptom inventory.
- **Based on group comparison of number of days to meaningful clinical response**
  - Compared with YY, patients treated with XX reported significantly faster resolution of depression symptoms as assessed by the symptom inventory

# Depression WG - Endpoint Model



## Concept

## Endpoints



# Depression WG - Status



- **Completed:**
  - Surveys of depression-related endpoints used in trials (e.g., symptom inventories, HR-QOL, life satisfaction), current PRO labeling language
  - Group consensus that a currently used symptom inventory shows promise as PRO instrument
    - Both PRO and clinician assessments are based on DSM-IV symptom lists
  - Selection of the QIDS-SR<sub>16</sub> as a candidate for modification to comply with FDA guidance
- **Next steps:**
  - Determine how the patient perspective was incorporated into:
    - QIDS-SR<sub>16</sub> development
    - DSM-IV/DSM-V diagnostic criteria development
  - Conduct qualitative/quantitative research to support validity and reliability of modified instrument

# **Non-Small Cell Lung Cancer (NSCLC) Working Group (WG)**

**Presenter: Bhash Parasuraman, PhD**

Senior Director, Health Economics and Outcomes Research

AstraZeneca



# NSCLC WG - Participants



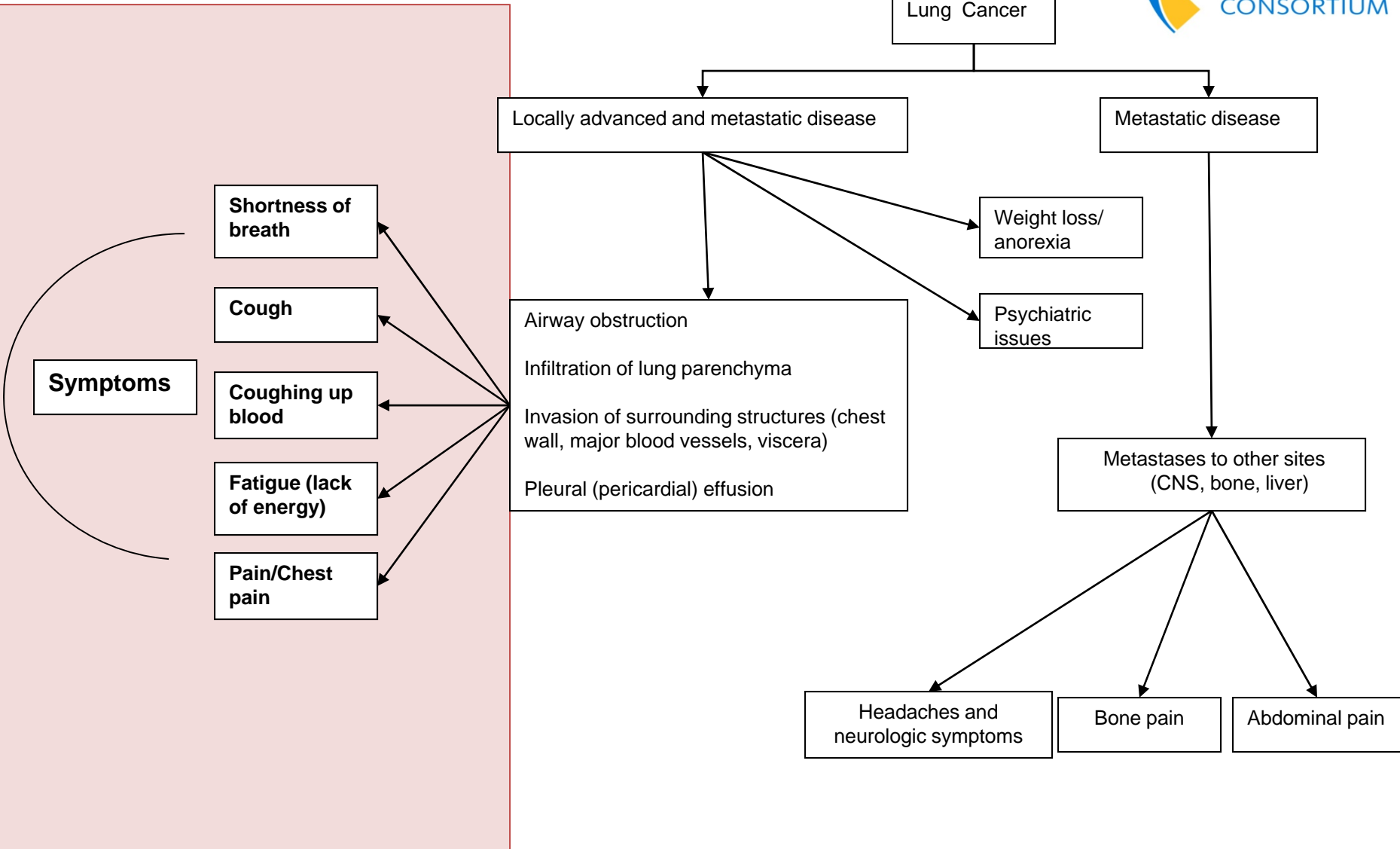
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AstraZeneca	Bhash Parasuraman
<b>PARTICIPANTS</b>	
Boehringer Ingelheim	Henrik Finnern
Bristol-Myers Squibb	Ben Gutierrez
GlaxoSmithKline	Maureen Neary
Pfizer, Inc.	Peter Trask
Eli Lilly & Company	Astra Liepa
Genentech	Sarah Trease
Merck Sharp & Dohme Corp.	Jean Marie Arduino

# NSCLC WG - Overview



- Objective
  - To develop a symptom measure for advanced, metastatic NSCLC, to be included in RCTs for pharmaceutical product development
- Target Population
  - Patients 18 and older with advanced stage (Stage III/IV) NSCLC and with performance status 0-2, regardless of line of therapy

# Lung Cancer WG - Proposed Conceptual Framework for NSCLC



# NSCLC WG - Targeted Labeling Language



Patients treated with Product X reported...

- an improvement in shortness of breath.
  - a delay in the time to deterioration of shortness of breath.
- an improvement in fatigue/lack of energy.
  - a delay in the time to deterioration of fatigue/lack of energy.
- an improvement in chest pain.
  - a delay in the time to the worsening of chest pain.
- an improvement in cough.
  - a delay in the time to the worsening of cough.

# NSCLC WG - Endpoint Model



<u>Efficacy Endpoint</u>	<u>Measure</u>
<b>Primary Endpoints</b>	
Delay in disease progression	Progression free survival as determined by RECIST criteria
Longer life	Overall survival from baseline
<b>Secondary Endpoints</b>	
Improvement or delay in the time to deterioration of shortness of breath	Shortness of breath scale score
Improvement or delay in the time to deterioration of fatigue or lack of energy	Fatigue scale score
Improvement or delay in the time to deterioration of chest pain	Chest pain scale score
Improvement or delay in the time to deterioration of cough (including hemoptysis)	Cough scale score

# NSCLC WG - Status



- Scoping Stage Summary Document under development



# **Advanced Breast Cancer Working Group (WG)**

**Presenter: Bonnie Teschendorf, PhD**

Director, Patient Reported Outcomes

Johnson & Johnson

# Breast Cancer WG - Participants



Company	Name
<b>CHAIR</b>	
Johnson & Johnson	Bonnie Teschendorf
<b>PARTICIPANTS</b>	
Boehringer Ingelheim	Gerlinde Maas
Bristol-Myers Squibb	Lisa Melilli
Eisai	Thomas Tencer
Eli Lilly & Company	Greg Price, Mark Boye
Genentech	Elaine Yu, Sarah Trease
GlaxoSmithKline	Mayur Amonkar
Merck Sharp & Dohme Corp.	Greg Reardon, Prakash Navaratnam
Pfizer, Inc.	Connie Chen
sanofi-aventis	Brian Seal, Lei Chen



# Breast Cancer WG - Overview



- **Objective** - To prepare a scoping document using state of the science information to guide development of a PRO instrument
- **Breast Cancer PRO target population**
  - Female breast cancer patients diagnosed with advanced (Stage IIIB or IV) disease. Approximately 99% of breast cancers are diagnosed in females. Male gender or patients with stage I thru IIIA disease are excluded from the target population.
  - May incorporate breast cancer patients with Stage I-III who progress from baseline with tumor induced symptoms
  - Other important planning considerations for subject recruitment in qualitative research
    - Subject characteristics and representativeness: age, ethnicity, socioeconomic groupings
    - Geographic distribution of subjects
    - Disease Characteristics/Classification: Pathology, Histology, disease symptoms, Family history, Genetic profile
    - Treatment History: Type of current therapy, prior therapy type, number of prior therapies, prior therapy side effects, comorbidities, history of adverse events

# Breast Cancer WG - Proposed Conceptual Framework for Symptoms/Side Effects of Treatment



## Items

### **Pain**

Pain at worst  
Pain right now  
Pain...



## Concepts

### **Pain**

Severity/Frequency



## Subscales

Pain

### **Tiredness**

Tired at worst  
Tired all time



### **Tiredness**

Severity/Frequency



Tiredness

### **Sleep Loss**

Can't go to sleep  
Restless sleep



### **Sleep Disturbance**



Sleep

### **Appearance**

Alopecia  
Weight



### **Appearance Change**



Appearance

### **Depression**

Lack motivation  
Feel disengaged



### **Mood/Disposition**



Mood

### **Arm Swelling**

Large in size  
Indentation



### **Lymphedema**



Lymphedema

# Breast Cancer WG - Targeted Labeling Language



1. Subjects treated for advanced breast cancer with Product X demonstrate clinically meaningful delay in time to worsening of pain (e.g., cancer-related; treatment-related, bone pain)
2. Subjects treated for advanced breast cancer with Product X demonstrate clinically meaningful stabilization in symptoms of tiredness (e.g., energy level, sleepiness)
3. Subjects treated for advanced breast cancer with Product X demonstrate clinically meaningful delay in time to worsening of distressing side effects (e.g. alopecia, neuropathy, lymphedema, sleep disturbance)
4. Subjects treated for advanced breast cancer with Product X demonstrate clinically meaningful stabilization in body weight (e.g., appetite)

# Breast Cancer WG - Endpoint Model for the Treatment of Advanced Breast Cancer



## Concept

## Endpoints

### Indication:

Treatment  
of Advanced Breast Cancer

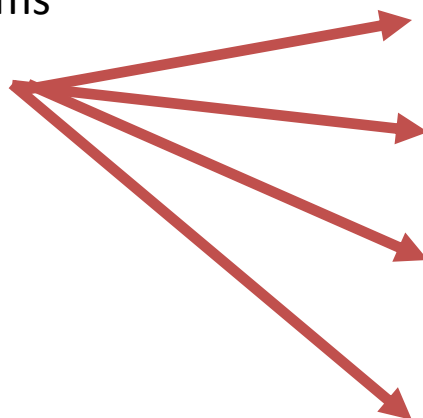


### Primary:

Stable Disease Progression  
(non-PRO assessment)

### Supportive Concepts:

Stable signs & symptoms  
Breast cancer



### Secondary (ordered):

- Stable/controlled pain  
(PRO assessment)
- Improved /No worsening sleep  
(PRO assessment)
- Improved /No worsening mood/disposition  
(PRO assessment)
- Stable body weight  
(non-PRO assessment)

# Breast Cancer WG - Status



- Scoping Stage Summary document in progress
  - Critical concepts identified from literature
  - Further deliberation on symptoms at diagnosis and side effects/symptoms post-treatment
  - Summary tables are complete:
    - PRO-Related Concepts in Current Labeling
    - PRO Measures used in Advanced Breast Cancer
  - Conceptual framework to be refined
  - Endpoint model in progress