SECOND ANNUAL
PATIENT-REPORTED OUTCOME (PRO)
CONSORTIUM WORKSHOP

March 15, 2011 │ Silver Spring, MD

Co-sponsored by

CRITICAL PATH INSTITUTE

FDA
PRO Consortium
Working Group Updates

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PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP

March 15, 2011  ■ Silver Spring, MD

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FDA

collaborate  ·  innovate  ·  accelerate
Active Working Groups

Irritable Bowel Syndrome
• Co-chairs: Mollie Baird and Charlie Baum

Cognition
• Co-chairs: Christopher Leibman and Usha Mallya

Asthma
• Co-chairs: Linda Nelsen and Sulabha Ramachandran

Depression
• Co-chair: Nicholas Greco

Non-Small Cell Lung Cancer
• Co-chairs: Ben Gutierrez and Peter Trask

Functional Dyspepsia
• Co-chairs: Mollie Baird and Robyn Carson

Rheumatoid Arthritis
• Co-chairs: Enkeleida Nikai and April Naegeli
Irritable Bowel Syndrome (IBS) Working Group

Mollie Baird, MPH
Associate Director, Clinical Operations
Ironwood Pharmaceuticals
# IBS WG Participants

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<td><strong>Non-Member Participants</strong></td>
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<tr>
<td>Nancy Norton</td>
<td>IFFGD</td>
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<td>Lin Chang, Brennan Spiegel</td>
<td>UCLA</td>
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<td>Jeff Lackner</td>
<td>University at Buffalo</td>
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<td><strong>Vendor</strong></td>
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<tr>
<td>Sheri Fehnel, Claire Ervin, Allen Mangel, Diana Goss</td>
<td>RTI Health Solutions</td>
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</table>
Objective: Develop a PRO instrument that can be qualified by the FDA for use as a primary endpoint in clinical trials

Disease: IBS-subtype (constipation-predominant, mixed or alternating pattern, and diarrhea-predominant)

Target population: Adult males/females meeting Rome III criteria for IBS-subtype

Targeted labeling language: The IBS PRO instrument would provide an indication of improvement in symptom severity. The claim would be treatment of IBS-subtype supported by an improvement in both abdominal symptoms and bowel movement-related symptoms
Proposed Initial Conceptual Framework

- Abdominal Symptoms
  - Abdominal Pain
  - Abdominal Discomfort
  - Cramping/Pressure
  - Bloating/Distension

- Bowel Movement-Related Symptoms
  - Stool Consistency
  - Stool Frequency - Incomplete/Complete
  - Straining
  - Flatulence
  - Incontinence
  - Urgency
Status

News of interest since last report

• Qualitative research (concept elicitation) interviews are underway with RTI-HS
  • Round 1: Raleigh - Feb 28 – March 2
  • Round 2: San Antonio - March 7-9
  • Round 3: San Diego - March 16-18

Recent accomplishments

• Finalized IBS Concept Elicitation Protocol, Patient Interview Guide, and Targeted Review of the Literature

Next Steps

• Complete qualitative research
• Generate/revise item pool and draft instruments
• IBS WG Expert Panel meeting: June 10 in Raleigh, NC
Cognition Working Group

Christopher Leibman
Sr. Director, Health Economics/Market Access
Janssen Alzheimer Immunotherapy R&D, LLC
## WG Participants

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<td>Juergen Reess, Mark Gordon</td>
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<td>Bristol-Myers Squibb</td>
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<td>Mallik Angalakuditi</td>
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<td>Julie Chandler, Yi Mo</td>
<td>Merck Sharp &amp; Dohme Corp</td>
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<td>Novartis Pharmaceuticals</td>
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<td>Pfizer, Inc.</td>
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<td>Nina Hill, Judith Dunn, Todd Paporello, Glenn Morrison</td>
<td>Roche Laboratories</td>
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<td><strong>Vendor</strong></td>
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<tr>
<td>Kellee Howard, Leah Kleinman, William Lenderking, David Miller</td>
<td>United Biosource Corporation (UBC)</td>
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Introduction

Objective

• To develop a reliable, valid and FDA-qualified PRO to capture the patient’s perspective on outcomes which would contribute to detection of disease, description of disease progression, and the measurement of treatment effect

Target Population (and stage)

• Patients diagnosed with MCI due to AD age 45 years and older.

Role of PRO measure in endpoint hierarchy

• Co-Primary

Targeted Labeling Language

• Focus on claims related to Interpersonal Functioning (IF) and Complex Activities of Daily Living (complex ADLs)
Background

Submission feedback April, 2010:

• Concern about ability of patients (and caregivers) to report reliably even at early stages of AD
• Interpersonal functioning and complex ADLs are good targets for measurement
• Labeling will not be duplicative and will avoid implication of disease-modifying effects

Resubmission focus:

• Literature review on preservation of insight in MCI
• Revised endpoint model
• Conceptual Framework focusing on Interpersonal functioning and complex ADLs
Conceptual Framework - Core Concepts

Interpersonal functioning

- Interpersonal functioning is expressed as the ability to interact effectively and appropriately with other people across a wide range of relationships (e.g., as parent, spouse, employee).

Complex activities of daily living (ADL) task performance

- Everyday functioning is expressed by the ability to complete Complex Activities of Daily Living which are activities requiring cognitive skills beyond those required for Instrumental Activities of Daily Living.
Conceptual Framework - Interpersonal Functioning

Conversational Skill  “...ask you a question and you go ‘duh,’ ...can’t think how to answer” [pt]

Dysnomia  “I don’t remember names” [pt]

Executive Functioning to Maintain Social Relationships  “We used to pick up our grandchildren a lot...I would say, ‘Go write it down’ because he wouldn’t want to miss it.” [cg]

Maintaining Social Roles  “I’m not as interested in seeing people.” [pt]

Social Use of Language  “I purposely don’t ...try to tell them something that’s important to me because I’m not going to get the words right.” [pt]

Working Memory  “Sometimes you don’t know what you’ve already said.” [pt]
Conceptual Framework - Complex ADLs (CADLs)

**Household Management** “...now I ...lock the burners so he can’t turn them on.” [cg]

**Managing Finances** “One day I started comparing the checkbook with the bills, and was I in for a shocker.” [cg]

**Navigating** “He wants to go a different direction than before, even some older places.” [cg]

**Need for support** “He just doesn’t remember. So I am forced into the whole mother thing again.” [cg]
Conceptual Framework - Complex ADLs (CADLs)

Organizing Information and Materials for Task Completion “That’s what he really gets a lot frustrated with is trying to find the pots and pans that he wants and everything in the cupboards and-so.” [cg]

Planning Skills Required for Hobby and Task Completion “Instructions are like the last thing he wants to deal with.” [cg]

Praxis “I can answer it, and I can make calls...That’s about all I can do.” [pt]

Using Memory in the Process of Task Completion “…he’ll even call me from the grocery store at times you know...” [cg]
Conceptual Framework

Figure 1. Conceptual Framework

- Assessment of Complex ADL Task Performance
- Assessment of Interpersonal Functioning
Status

News of interest since last report
• FDA Review of ‘revised’ SSSD – Response Received!
• ICAD 2011 Submission: Focused Research Symposium on “Measuring the Earliest Symptoms of Mild Cognitive Impairment”

Recent accomplishments
• Validity and Reliability of Patient Self Report in Early AD – ‘Insight’
• Revised conceptual framework – focus on patient-report and core symptoms of IF and CADLs
• Completed individual interviews focusing on patient insight and concept elicitation
• Solicited Core Expert Feedback on Item Pool
Challenges

Field is evolving quickly
• This group is developing information at the same time the field is struggling with lexicon and population characterization, i.e., diagnostic criteria and terminology are changing

Sustained advocacy for current effort
• We are one of many prodromal AD workstreams in the competition of ideas

Measurement target is complex
Next Steps

- Analyze latest wave of qualitative data
- Summarize expert opinion on the item pool and conceptual framework
- Evaluate FDA feedback and prepare response
- Plan 3\textsuperscript{rd} Expert Panel to Review
- Draft Instrument
- Cognitive Debriefing of Draft Instrument
- Dissemination efforts
Asthma Working Group

*Linda Nelsen, MHS*
Associate Director, Epidemiology
Merck, Sharp & Dohme Corp
# WG Participants

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<td>Darren Talbot, Elke Hunsche</td>
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<td>Novartis Pharmaceuticals</td>
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Introduction/Background

Objective
• To develop a daily diary of asthma symptoms

Target population
• Adolescents and adults aged 12 and older with a clinical diagnosis of mild to persistent asthma with:
  • Lung function impairment but without fixed airway obstruction
  • Requirement for asthma controller therapy based on current asthma management guidelines
## Endpoint Hierarchy: Role of PROs

### Co-primary or key secondary endpoints

<table>
<thead>
<tr>
<th>Efficacy Endpoint</th>
<th>Measure</th>
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<tr>
<td><strong>Co-Primary Endpoints</strong></td>
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<tr>
<td>Improvement in airflow obstruction</td>
<td>Trough FEV1</td>
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<tr>
<td>Reduction in asthma symptoms</td>
<td>Asthma symptom score from Asthma Symptom Diary</td>
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<tr>
<td><strong>Secondary Endpoints</strong></td>
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<tr>
<td>Symptom Free Days</td>
<td>Proportion of days without symptoms based on Asthma Symptom Diary</td>
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<tr>
<td>Nighttime symptoms</td>
<td>Reduction in nights with asthma symptoms based on Asthma Symptom Diary</td>
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Examples of summary statements to describe effect of treatment on symptom severity (e.g., frequency, intensity, and/or duration) include:

<table>
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<tr>
<th>Overall</th>
<th>Patients treated with X reported significant reduction in asthma symptom severity</th>
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<tr>
<td>Daytime Symptoms</td>
<td>Significantly more patients treated with X reported improvements in daytime asthma symptom severity</td>
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<tr>
<td>Nighttime Symptoms</td>
<td>Patients treated with X reported significantly fewer nights with asthma symptoms</td>
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<tr>
<td>Individual Symptoms</td>
<td>Product X reduces the severity of wheeze</td>
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**Targeted Labeling Language**
RFP Responses indicated that while the conceptual framework is a good working model, it will be important to clarify the scope of the measure and confirm the proposed conceptual framework.
News of Interest Since Last Report

• Scoping document led to discussion of need for an Asthma Symptom PRO:

  “asthma... a priority area as it lacks a standard PRO instrument that is fit for the purpose of measuring important patient-experienced aspects of asthma...mission of the Asthma WG is to address this unmet need in close collaboration with regulatory agencies by evaluating and developing PRO instruments for use in clinical trials in accordance with the FDA PRO Guidance”

• Led to a productive discussion with FDA regarding need for asthma symptom diary as key first step in development of appropriate PRO instruments for use in asthma clinical trials
• Areas for future focus include pediatric asthma symptoms, exacerbations & control
Status: Recent accomplishments

- Qualitative Research RFP
  - Released January 25, 2011
  - Seven proposals were received by the deadline, February 16, 2011

- Asthma WG has reviewed the proposals and is in the process of finalizing the selection of a vendor for the qualitative research

- Ten member firms have confirmed support for the qualitative research
Next Steps

- Finalize vendor selection
- Execute an agreement with selected vendor for the proposed scope of work
- Schedule the Project Kick-off meeting
  - Anticipated April 2011
- Conduct qualitative research
Depression Working Group

Nicholas Greco IV, M.S., BCETS, CATSM
Clinical Research Manager - Psychometrics and Assessment, Global Pharmaceutical Research & Development
Abbott Laboratories
# Working Group Participants

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<td>Lucy Abraham, Zoe Kopp, Philip Ninan</td>
<td>Pfizer, Inc.</td>
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<td>Omar Olhaye, Glenn Phillips</td>
<td>Sunovian Pharmaceuticals</td>
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Numerous patient-reported depression symptom inventories exist

- However, no existing instrument has been used consistently in clinical development programs
- A well-developed, patient-reported depression symptom inventory provides a basis for potential future development of other patient-reported aspects of depression and treatment

Existing inventories vary on

- Response options
- Anchoring, scoring algorithms
- Recall period
Introduction/Background

Objectives

- Assess adequacy of PRO instruments currently used in depression studies regarding the capture of important symptom information from the patient’s self-report
- If the above assessment reveals there is an unmet need, either modify an existing instrument or develop a new depression symptom inventory

Target Population

- Male & female subjects aged 18-65 who have experienced a Major Depressive Episode within the last 6 months
- Ham-D-17 score >18
- Sponsors may target segments of the depression population based on proposed labeling claim and mechanism of action (e.g., “severe” or “treatment-resistant” depression)
Proposed Conceptual Framework

Sadness → Dysphoria
Suicidality → Dysphoria
Worthlessness → Dysphoria
Anhedonia → Dysphoria
Appetite change → Dysphoria
Body pain → Physical/Somatic Symptoms
Low energy → Physical/Somatic Symptoms
Insomnia → Physical/Somatic Symptoms
Somnolence → Sleep-Related Symptoms
Restlessness → Cognitive Symptoms
Slowed thinking → Cognitive Symptoms
Difficulty concentrating → Cognitive Symptoms

Depression Symptoms
Proposed Endpoint Model

Concept

**Indication**
- Treatment of symptoms of major depressive disorder

**Supportive concept**
- Improvement in signs of major depressive disorder

Endpoints

**Primary**
- Depression Symptom Inventory score (PRO assessment)

**Secondary**
- e.g., Affect (ClinRO)
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 ZZ 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 ZZ 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 ZZ 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 ZZ symptom inventory
Feedback from the FDA

- The FDA cautioned on the use of redundant measures of the same concepts
- Symptoms related to cognition in depression have not been well-defined and may present a measurement challenge
- Empiric evidence is needed to define terms such as symptom onset and symptom resolution
- A specific methodology may be needed for selecting and modifying an existing depression PRO instrument

Recent accomplishments

- Depression WG’s RFP was released on Friday, February 18, 2011
- Proposals were to be submitted by Friday, March 11, 2011
Next Steps

• Select vendor for the qualitative research

• Conduct qualitative research

• Prepare & submit *Qualitative Research Summary Document*, including draft instrument
Non-Small Cell Lung Cancer (NSCLC) Working Group

Ben Gutierrez, PhD
Director, Global HEOR
Bristol-Myers Squibb
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<td>Yasuhiro Torigoe</td>
<td>Roche Laboratories</td>
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Introduction/Background

Objective
• To develop a patient reported symptom inventory for NSCLC for use in as a secondary endpoint in clinical trials

Disease
• Advanced Stage (Stage III/IV) NSCLC

Target population
• Patients aged 18 and older with advanced stage NSCLC and ECOG status 0-2, regardless of line of therapy

Targeted Labeling Language
• Patients treated with Product X reported an improvement in the symptoms of NSCLC or delay in the time to deterioration of the symptoms if NSCLC
Conceptual Framework

- Cough
- Shortness of breath
- Chest pain

Pulmonary Symptom Score

- Appetite Loss
- Sleep Disturbance
- Lack of energy
- Pain (non-Chest)

Non-pulmonary Symptom Score

NSCLC Symptom Inventory Score
## Endpoint Model

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<tr>
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<tr>
<td>Delay in disease progression</td>
<td>Progression-free survival as determined by RECIST*</td>
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<tr>
<td>Longer life</td>
<td>Overall survival</td>
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<tr>
<td><strong>Secondary Endpoints (PRO-based)</strong></td>
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<tr>
<td>Improvement in the symptoms of NSCLC OR a delay in the time to deterioration of the symptoms of NSCLC</td>
<td>NSCLC Symptom Inventory Score</td>
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*Response Evaluation Criteria in Solid Tumors*
Status

- Received preliminary comments from FDA on the first draft of the NSCLC WG SSSD on September 1, 2010.
  - NSCLC WG reviewed the comments and drafted additional queries and replies.

- Changes in the revised SSSD
  - Addition of non-pulmonary symptoms to conceptual framework
  - Retained focus on advanced disease with ECOG 0-2
  - Requests clarification of initial responses regarding individual versus summary scoring

- Revised Scoping Stage Summary Document submitted to FDA Dec 13, 2010
Next Steps

• Awaiting feedback from FDA on revised SSSD

• Upon feedback, will review, with anticipated action being to submit RFP to vendors to begin the process of creating new NSCLC symptom measure.
Functional Dyspepsia Working Group

Robyn T. Carson, MPH
Assistant Director, HEOR
Forest Research Institute
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Introduction/Background

Objective: To develop a PRO instrument that is intended as a primary endpoint in support of the proposed indication of treatment of functional dyspepsia

• Disease: Functional dyspepsia (subtypes - epigastric pain syndrome and postprandial distress syndrome)

• Target population: Adult males/females that meet Rome III criteria for functional dyspepsia

• Targeted labeling language: Treatment of FD subtype (epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS))
Conceptual Framework

- **Condition**: Functional Dyspepsia
- **Domain**: Meal-Induced Dyspeptic Symptoms
  - Physical Discomfort
  - Postprandial Fullness
  - Early Satiation
  - Postprandial Nausea
  - Excessive Belching
  - Epigastric Pain/Discomfort
  - Epigastric Burning
  - Upper Abdominal Bloating
Status

News of interest since last report
• Draft 1 of scoping stage summary document under review by WG members
• Discussing WG member comments 3/21

Recent accomplishments
• Established WG with 4 member companies
• First draft of scoping document under review

Next steps
• Finalize scoping stage summary document and circulate for coordinating committee approval
• Develop scientific data disclosure plan
• Develop timeline
Rheumatoid Arthritis Working Group

Enkeleida Nikai, MSc Psych, M.B.
Senior Health Outcomes Manager,
Global Market Access
UCB Pharma S.A.
## Working Group Members

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<td>Linda Deal</td>
<td>Johnson &amp; Johnson</td>
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<tr>
<td>Dena Ramey, Douglas Watson</td>
<td>Merck Sharp &amp; Dohme Corp</td>
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<td>Lewis Pollack, Lois Kotkoskie</td>
<td>Novo Nordisk</td>
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<td>Alison Greene, Sarah Trease</td>
<td>Roche Pharmaceuticals</td>
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<td>Paulo Carita</td>
<td>sanofi-avantis</td>
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<td>Charles Baum, Ulrich Thienel</td>
<td>Takeda Pharmaceuticals</td>
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<tr>
<td>Christine De la Loge</td>
<td>UCB Pharma</td>
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Introduction/Background

Objective

- Develop a new PRO instrument for assessing rheumatoid arthritis (RA)

Target population

- Adult patients with RA of all severities (i.e., mild to severe) and duration (i.e., early to late)
- The clinical trial population will include patients 18 years and older, males and females, with a diagnosis of adult-onset RA.
Development of an **adequate measure of symptoms and physical function could be useful** in the support of efficacy claims.

Assessment of stiffness should not be limited to "morning stiffness”

The Agency will **not participate in development of a "productivity" measure.**

RA-related fatigue is important to RA patients, and thus, the **Agency would consider a "fatigue" claim in the clinical studies section of labeling**, provided that "fatigue" is clearly defined and well-measured.
Status (February-mid March 2011)

- Sharing of previous work undertaken by member firms in RA (Eli Lilly, UCB)

- Discussions on the scope of the RA WG measurement concept(s)

- Development of a draft disease model

- Consultations with external experts
Next Steps

• Finalize the RA disease model

• Explore potential collaboration with external groups working in RA

• Define the hypothesized measurement concept(s)

• Clarify the role of the PRO instrument in the endpoint hierarchy

• Develop the *Scoping Stage Summary Document* for submission to the FDA