# *Update on the Clinical Outcome Assessment Qualification Program*

*PRO Consortium Workshop April 29-30, 2014*

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Study Endpoints and Labeling Development (SEALD)
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)

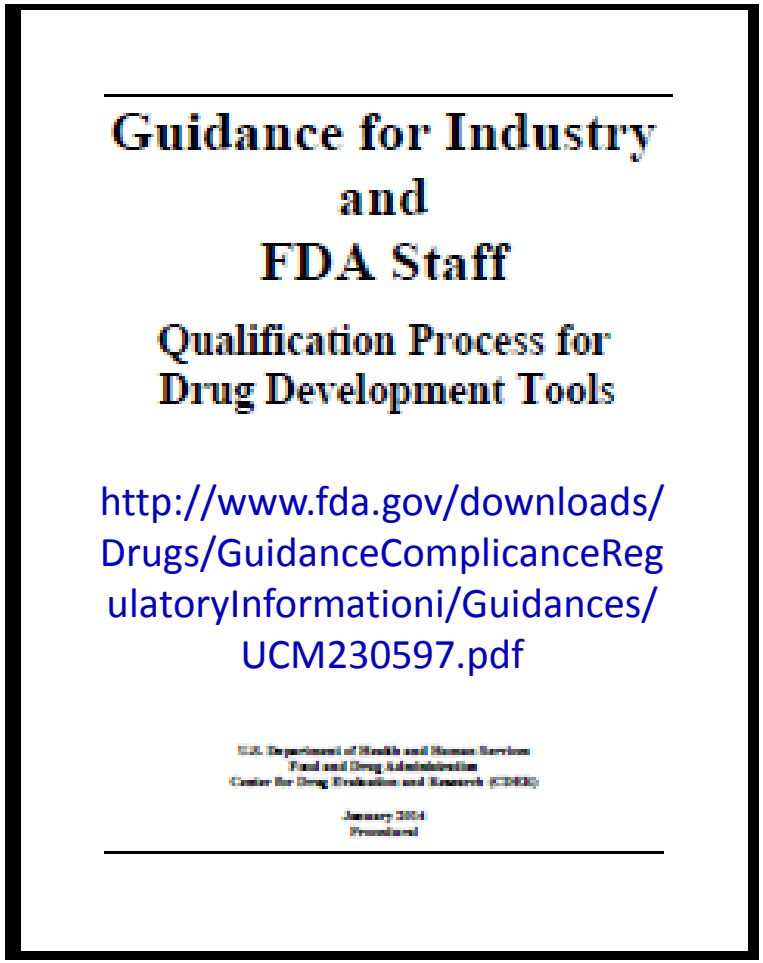
# Disclaimer

- The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position

# Overview

- Update on Qualification Activities
- New Communication Tools
- Modification in Qualification Timeline / Process

# DDT Guidance (Final January 2014)


Guidance for Industry
and
FDA Staff

Qualification Process for
Drug Development Tools

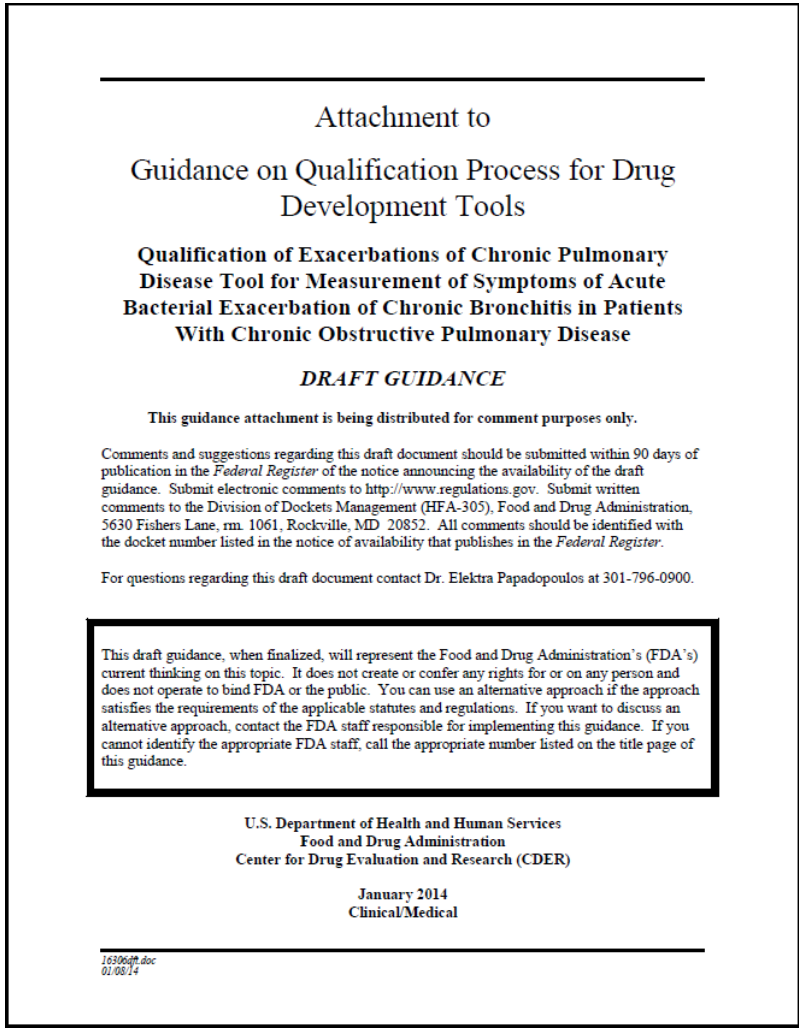
http://www.fda.gov/downloads/Drugs/GuidanceComplicanceRegulatoryInformationi/Guidances/UCM230597.pdf

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2014
Procedural

- Describe a process NOT evidentiary standards
- Qualification process described for Biomarkers, Animal Models, and Clinical Outcome Assessments (COA)

# First Clinical Outcome Assessment Qualified in January 2014



Attachment to

Guidance on Qualification Process for Drug Development Tools

**Qualification of Exacerbations of Chronic Pulmonary Disease Tool for Measurement of Symptoms of Acute Bacterial Exacerbation of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease**

***DRAFT GUIDANCE***

**This guidance attachment is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Dr. Elektra Papadopoulos at 301-796-0900.

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**January 2014**
**Clinical/Medical**

*16306dft.doc*
*01/08/14*

- EXACT
  - A PRO for the measurement of symptoms of acute bacterial exacerbation of chronic bronchitis in patients with chronic obstructive pulmonary disease

# COA Qualification Projects (4/1/14)

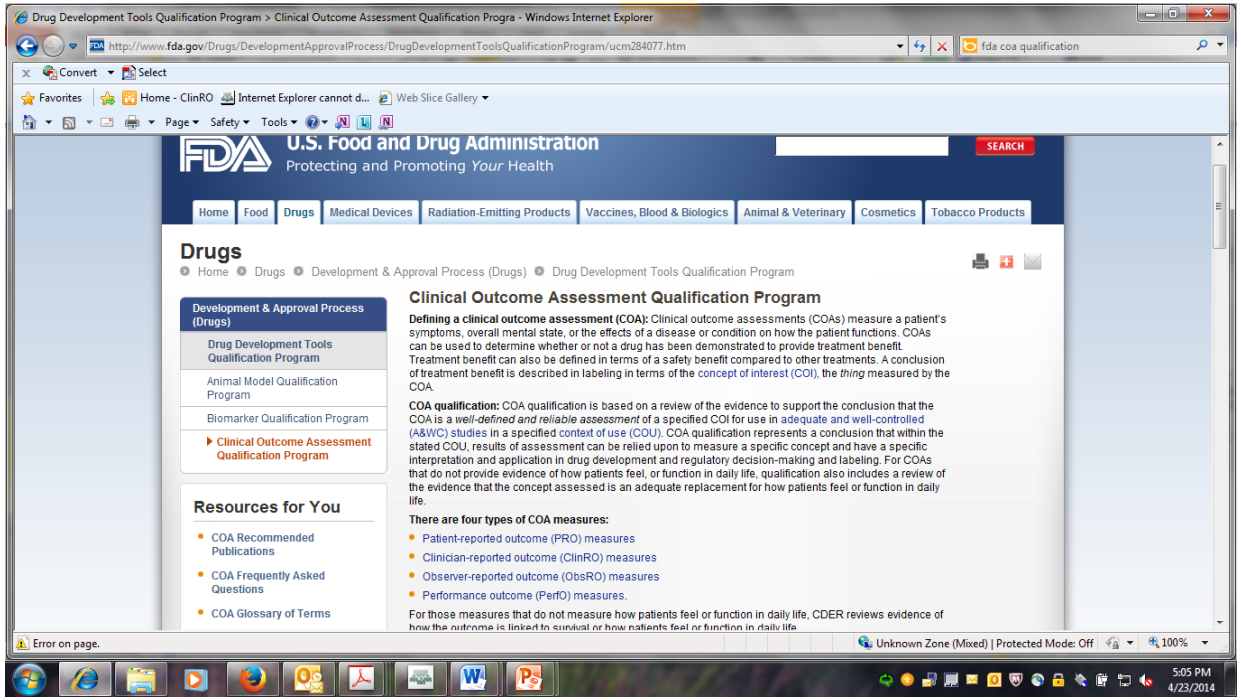
| COA DDT Stage | Number in Stage |
|---|---|
| **Initiation Stage** | **17** |
| Initiation – DDT # assigned | 10 |
| Initiation – Letter of Intent (LOI) received | 4 |
| Initiation – revised LOI requested | 3 |
| **Consultation and Advice Stage (C&A)** | **29** |
| C&A – Initial Briefing Package requested | 12 |
| C&A – Active | 17 |
| **Review Stage** | **2** |
| **Qualified for Use in Exploratory Studies** | **1** |
| **Qualified for Use as Primary or Secondary Endpoints** | **0** |

48 COA qualification projects including: 38 PROs, 3 ClinROs, 4 PerfOs, 1 containing multiple elements including, PRO, ClinRO, ObsRO components, and 3 TBD (appropriate reporter will be based on additional research)

# New Communication Tools

- Website update
- Roadmap
- Revised Wheel and Spokes
- Others under consideration
  - If suggestions please raise during the Q&A

# Updated COA Qualification Website




http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm

# Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

## 1 Understanding the Disease or Condition

**A. Natural history of the disease or condition**
- Onset/Duration/Resolution
- Diagnosis
- Pathophysiology
- Range of manifestations

**B. Patient subpopulations**
- By severity
- By onset
- By comorbidities
- By phenotype

**C. Health care environment**
- Treatment alternatives
- Clinical care standards
- Health care system perspective

**D. Patient/caregiver perspectives**
- Definition of treatment benefit
- Benefit-risk tradeoffs
- Impact of disease

## 2 Conceptualizing Treatment Benefit

**A. Identify concept(s) of interest (COI) for meaningful treatment benefit, i.e., How a patient:**
- Survives
- Feels (e.g., symptoms)
- Functions

**B. Define context of use (COU) for clinical trial:**
- Disease/Condition entry criteria
- Clinical trial design
- Endpoint positioning

**C. Select clinical outcome assessment (COA) type:**
- Patient-Reported Outcome (PRO)
- Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- Performance Outcome (motor, sensory, cognition)

## 3 Selecting/Developing the Outcome Measure

**A. Search for existing COA measuring COI in COU:**
- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

**B. Begin COA development**
- Document content validity (qualitative or mixed methods research)
- Evaluate cross-sectional measurement properties (reliability and construct validity)
- Create user manual
- Consider submitting to FDA for COA qualification as exploratory endpoint

**C. Complete COA development:**
- Document longitudinal measurement properties (construct validity, ability to detect change)
- Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- Submit to FDA for COA qualification as effectiveness endpoint to support claims

# Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

## 1 Understanding the Disease or Condition

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**Patient/caregiver perspectives**
- Definition of treatment benefit
- Benefit-risk tradeoffs
- Impact of disease

## 2 Conceptualizing Treatment Benefit

**A. Identify the *meaningful health aspect* that is the intended benefit to patients in their daily lives**
- Survives (e.g., length of survival)
- Feels (e.g., symptom severity)
- Functions (e.g., walking ability)

**B. Identify the measureable *concept of interest* that represents the meaningful health aspect, which can be:**
- Equivalent to the meaningful health aspect (e.g., patients' self-reported ambulatory activities in daily life) OR
- Distinct from, but related to the meaningful health aspect (e.g., 6-minute walk test)

**C. Define context of use for clinical trials, e.g.:**
- Disease/Condition entry criteria
- Clinical trial design
- Endpoint positioning

**D. Consider appropriate clinical outcome assessment type(s):**
- Patient-Reported Outcome (PRO)
- Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- Performance Outcome (motor, sensory, cognition)

## 3 Selecting/Developing the Outcome Measure

**A. Search for existing clinical outcome assessment measuring the concept(s) of interest in the context of use :**
- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

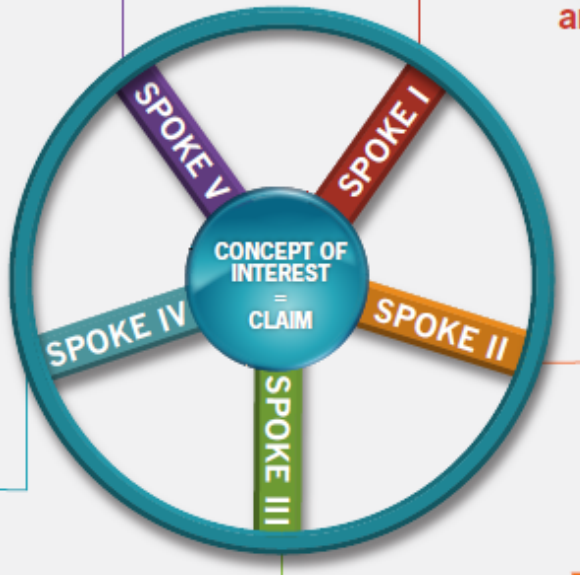
**B. Begin clinical outcome assessment development**
- Document content validity (qualitative or mixed methods research)
- Evaluate cross-sectional measurement properties (reliability and construct validity)
- Create user manual
- Consider submitting to FDA for qualification for use in exploratory studies

**C. Complete clinical outcome assessment development:**
- Document longitudinal measurement properties (construct validity, ability to detect change)
- Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- Submit to FDA for qualification as effectiveness endpoint to support claims

Updated on March 14, 2014

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
**http://www.fda.gov/Drugs**

# Qualification of **CLINICAL OUTCOME ASSESSMENTS** (COAs)




## I. Identify Context of Use (COU) and Concept of Interest (COI)

- Outline hypothesized concepts and potential claims
- Determine intended population
- Determine intended application/characteristics (type of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework
- Position COA within a preliminary endpoint model
- Document COU and COI

## II. Draft Instrument and Evaluate Content Validity

- Obtain patient or other reporter input
- Generate new items
- Select recall period, response options and format
- Select mode/method of administration/data collection
- Conduct cognitive interviewing
- Pilot test draft instrument
- Finalize instrument content, format and scoring rule
- Document content validity

## III. Cross-sectional Evaluation of Other Measurement Properties

- Assess score reliability (test-retest or inter-rater) and construct validity
- Establish administration procedures & training materials
- Document measure development
- Prepare user manual

***Consider submitting to FDA for COA qualification for use in exploratory studies prior to longitudinal evaluation.***

## IV. Longitudinal Evaluation of Measurement Properties/ Interpretation Methods

- Assess ability to detect change and construct validity
- Identify responder definition(s)
- Provide guidelines for interpretation of treatment benefit and relationship to claim
- Document all results
- Update user manual

***Submit to FDA for COA qualification as effectiveness endpoint to support claims.***

## V. Modify Instrument

- Identify a new COU
- Change wording of items, response options, recall period, or mode/method of administration/data collection
- Translate and culturally adapt
- Evaluate modifications using spokes I - IV
- Document all changes

***Consider submitting to FDA for qualification of new COA, as appropriate.***

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# COA Qualification Timeline/Process Modification

- Qualification for use in exploratory studies
- Qualification for use as primary or secondary endpoint

# Qualification for Use in Exploratory Studies

- CDER has reviewed the development and initial validation of the tool and we are confident that it is measuring what it sets out to measure
- The tool is made publicly available and may be used more widely in clinical trials providing the opportunity to gather more information on how sensitive the tool is in detecting change and to gain a better idea of how to interpret change

# Qualification for Use as a Primary or Secondary Endpoint

- When longitudinal data and guidelines for interpretation of change are available, the tool will be reviewed for qualification for use as a primary or secondary endpoint measure of effectiveness in phase 3 studies.

# Common Qualification Questions and Answers

- Is qualification required in order to use an instrument in a clinical trial
  - NO! A tool that is not formally qualified should be discussed with the review division within an IND.
- Are sponsors required to use only qualified instruments?
  - NO! While we believe there are benefits of using a qualified tool, sponsors are free to select whatever tool they believe will be best suited for their clinical trial(s), and discuss with the review division.

# Common Qualification Questions and Answers

- An instrument has been used to support claims in labeling. Does this mean that tool is qualified?
  - NO! Only tools that have been reviewed through the formal DDT qualification process, about which a positive qualification decision has been made (and published as an attachment to the qualification guidance), and are made publically available are considered “qualified”. Tools that have not been formally qualified may still be acceptable for use.

# Common Qualification Questions and Answers

- What does the Qualification Review Team (QRT) team look like?
  - SEALD, Division(s), Biostatistics, representatives from other centers when appropriate
- How do FDA and EMA work together on COA qualification?
  - Harmonization efforts on projects submitted concurrently to FDA and EMA
  - Regular and ad hoc TCs to discuss

# Common Qualification Questions and Answers

- What are some of the benefits of qualification?
  - For sponsors:
    - Improved Efficiency: Sponsors can be assured in advance / early that FDA agrees with use of the tool
    - Reduced Risk: tools are developed with input from multiple stakeholders and scientific minds to increase the likelihood that the instrument will be successful at detecting interpretable treatment benefits that exist
  - For FDA: Reduced review time
  - For patients (the reason we're all here):
    - Improved outcome assessments for better communication of meaningful treatment benefit
    - Effective (and safe) drugs coming to market more quickly

# Common Qualification Questions and Answers

- There haven't been many instruments qualified yet. Are there other (less visible) benefits of the qualification process?
  - Yes! Building partnerships, opening lines of communications internally and externally, sharing learnings, discussing problems/challenges

# SEALD is Recruiting!

If interested, please send your resume / CV to:

CDER SEALD Endpoints:
SEALD.ENDPOINTS@fda.hhs.gov

# The EXACT-PRO Journey: From Concept to Qualification

**Nancy Kline Leidy, PhD**
**Evidera**
**Bethesda, MD**

***FIFTH ANNUAL***
***PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP***

**April 29 - 30, 2014 ■ Silver Spring, MD**

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# Disclaimer

The views and opinions expressed in the following slides are those of the individual presenters and should not be attributed to their respective organizations/companies, the U.S. Food and Drug Administration, the Critical Path Institute, the PRO Consortium, or the ePRO Consortium.

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# Disclaimer

Nancy Kline Leidy is employed by Evidera, which provides consulting and other research services to pharmaceutical, device, government and non-government organizations. These services include consortia-based research and the development and validation of PRO instruments, including the EXACT and EXACT-PRO.

Dr. Leidy works with a variety of companies and organizations and, as an employee of  Evidera, is expressly prohibited from receiving payment or honoraria directly from these organizations for services rendered.

# The EXACT-PRO Journey: Overview

- Background
  - Concept & EXACT-PRO Consortium Approach
- Development Steps
  - Content Validity & Empirical Testing
- Further Validation
  - Clinical trial settings
- Timelines
  - Additional activities
- Qualification
  - Context and questions
- Observations
  - Key success factors
- Conclusions

# Method: The Big Picture

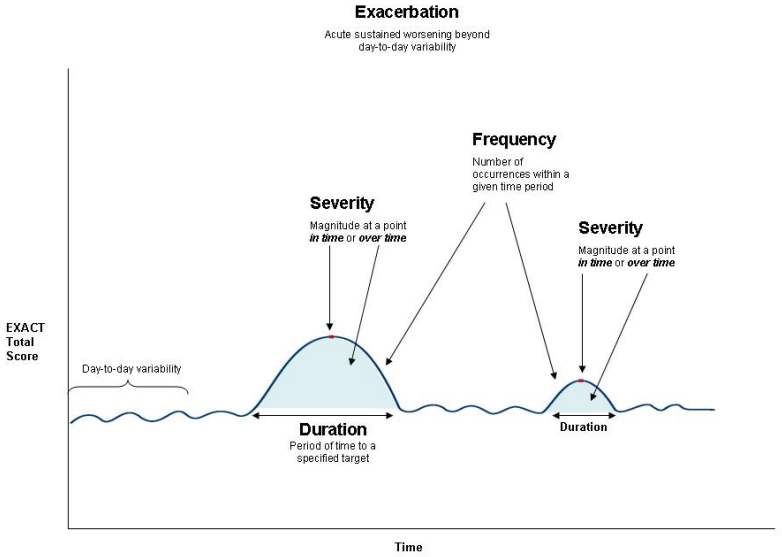
- Pictures & 1,000 words

# Background

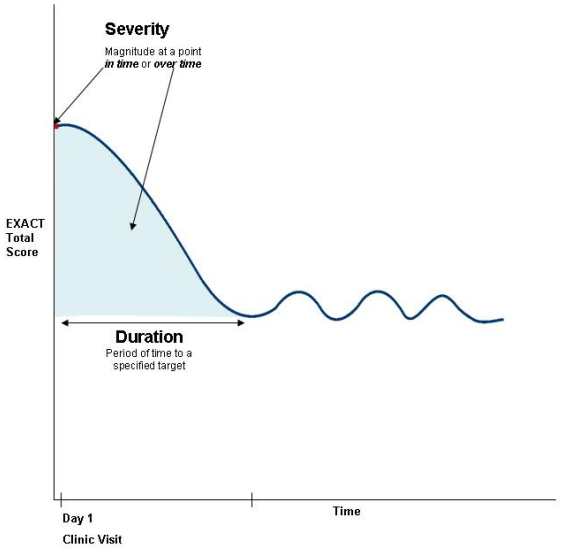
- Concept:  Exacerbations of COPD
- An event in the natural course of the disease characterized by a *change* in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying disease. (GOLD 2006; 2011)
  - Symptomatic worsening – dyspnea, cough, and/or sputum + "others"
  - No diagnostic test – clinical judgment
- Treatment:
  - Prevention:  Drug therapy
  - Acute:  Antibiotics and/or steroids, outpatient or hospitalization
  - Adjuvant therapies:  Drugs, education, activity, rehabilitation

# Exacerbation Treatment Outcomes

## Preventive Therapies




## Acute Treatment




An event in the natural course of the disease characterized by a *change* in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying disease.

Leidy et al. *Value Health*. 2010;13(8):965-975

# Outcome Measures: Historically

## Health Care Resource Utilization (HCRU)

- Presence (frequency)
  - # of clinic or emergency room visits, hospitalizations
- Severity
  - Clinic with antibiotic and/or steroids – moderate
  - Hospitalization – severe
- Duration
  - Length of treatment

# Problems with the HCRU-Based Outcomes

- Global, regional and individual differences
  - Health policy and medical practice
- Hospitalization = severe; Clinic = moderate
  - Comorbidity, risk, access, home care
- Treatment Duration = Duration
  - Symptoms and recovery
- HCRU=Frequency
  - Clinic visits and hospitalizations

# HCRU - The Tip of the Iceberg

- 50 to 70% of exacerbations are unreported

Seemungal et al. *Am J Respir Crit Care Med*. 1998;157:1418–1422.
Wilkinson et al. *Am J Respir Crit Care Med*. 2004;169:1298–1303.
Langsetmo et al. *Am J Respir Crit Care Med.* 2008; 177, 396-401.

# HCRU - Where is the Patient's Voice?

- No reference to or standardization of symptoms that defined "exacerbation".
  - An event in the natural course of the disease characterized by a *change* in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a *change in regular medication* in a patient with underlying disease. (GOLD 2006; 2011)
- Symptom diary cards
  - Highly variable
  - No content validity and validation

# Purpose

- To develop a PRO measure to provide a:
  - Direct assessment of patient-reported symptoms at the time of a medically-treated event (symptom severity and recovery)
  - Direct assessment of unreported events – frequency, severity, duration
- Standardized, rigorously developed & validated
- For use in drug development trials

# Target Claims

- Maintenance therapies (Pulmonary Division)
  - Reduces the frequency of exacerbations
  - Mitigates/attenuates/reduces the severity of exacerbations
  - Reduces/speeds time to recovery
- Acute therapies (Ant-infective and Special Pathogen Divisions)
  - Reduces/speeds time to recovery
  - Mitigates/attenuates/reduces the severity of exacerbations

# EXACT-PRO Initiative/Consortium

- Multiple pharmaceutical sponsors
- Discussion with the FDA
- Expert Panel
  - Clinical (COPD)
  - Measurement
  - Regulatory Issues
- Academic Advisors/Senior Consultants
  - Preventive therapies and measurement
  - Anti-infective therapies and clinical practice

# EXACT-PRO Expert Panelists

| *Senior Clinical Research Consultants:* | *Affiliation:* |
|---|---|
| • Paul Jones, M.D., Ph.D.* | St. George's, London |
| • Sanjay Sethi, M.D.* | University at Buffalo |

| *Expert Panelists:* | *Affiliation:* |
|---|---|
| • Carol Bosken, M.D. | FDA – Pulmonary Division |
| • Laurie Burke, M.P.H. | FDA - SEALD |
| • James Donohue, M.D.* | University of North Carolina, Chapel Hill |
| • Steven Gitterman, M.D., Ph.D. | FDA - Special Pathogens (Day 2) |
| • Fernando Martinez, M.D.* | University of Michigan |
| • Eileen Navarro, M.D. | FDA – Special Pathogens (Day 1) |
| • Donald Patrick, Ph.D.* | University of Washington |
| • John Powers, M.D.* | George Washington University (Day 2) |
| • Stephen Rennard, M.D.* | University of Nebraska |
| • Roberto Rodriguez-Roisin, M.D., Ph.D.* | University of Barcelona |
| • Holger Schünemann, M.D., Ph.D.* | University at Buffalo |
| • Wisia Wedzicha, M.D.* | Royal Free & U College Medical School |
| • Sulabha Ramachandran, Ph.D. | Industry |

* EXACT-PRO Study Group

# A Phased Approach

- Phase I
  - Literature review
  - Focus groups and interviews, Item pool development
  - Cognitive debriefing
  - Expert participation
- Phase II
  - Validation study design, execution, SAP development
  - Analyses, interpretation
  - Expert participation
- Phase III
  - User manual, dossier development, dissemination, user guidance
  - Regulatory review
- Phase IV
  - Qualification review and responses
  - Further validation, qualification submission, responses
  - Revised User Manual
  - Translation, user guidance, dissemination

# Critical Attributes

- Content Validity
  - Qualitative and quantitative
- Reliability
  - Internal consistency and reproducibility
- Validity
  - Construct, known-groups
- Responsiveness
  - Sensitive, interpretable

*In the target population and clinical trial settings*

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# EXACT-PRO Content Validity

- Methods
  - Focus groups, 2:1 and 1:1 interviews
  - Cognitive interviews
  - ePRO user testing
- Sample
  - N=83, mean age: 65 (+10)
  - Current/former smokers; FEV-1% predicted: 44.4 (+15.8)
- Results
  - Description and framework of exacerbation
  - Item pool (23 candidate items)
  - Draft conceptual framework
  - For quantitative evaluation and item reduction

Development of the EXAcerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT):A Patient-Reported Outcome (PRO) Measure

Leidy et al. *Value Health*. 2010;13(8):965-975

Rennard S, Leidy NK. In: *Exacerbations of chronic obstructive pulmonary disease (COPD)*. 2009.

# Item Reduction and Initial Validation

- Methods
  - Prospective validation study (N=410)
    - 222 Acute patients (clinic visit) – 28 days
    - 188 Stable patients – 7 days
- Sample – Target population
  - Inclusion/exclusion consistent with clinical trials
- Key Analyses
  - Item-level, dimensionality, Rasch
  - Reliability – internal consistency, reproducibility
  - Validity
    - Acute:  Sensitivity to change over time
    - Acute vs stable: Known-groups


CHEST Original Research

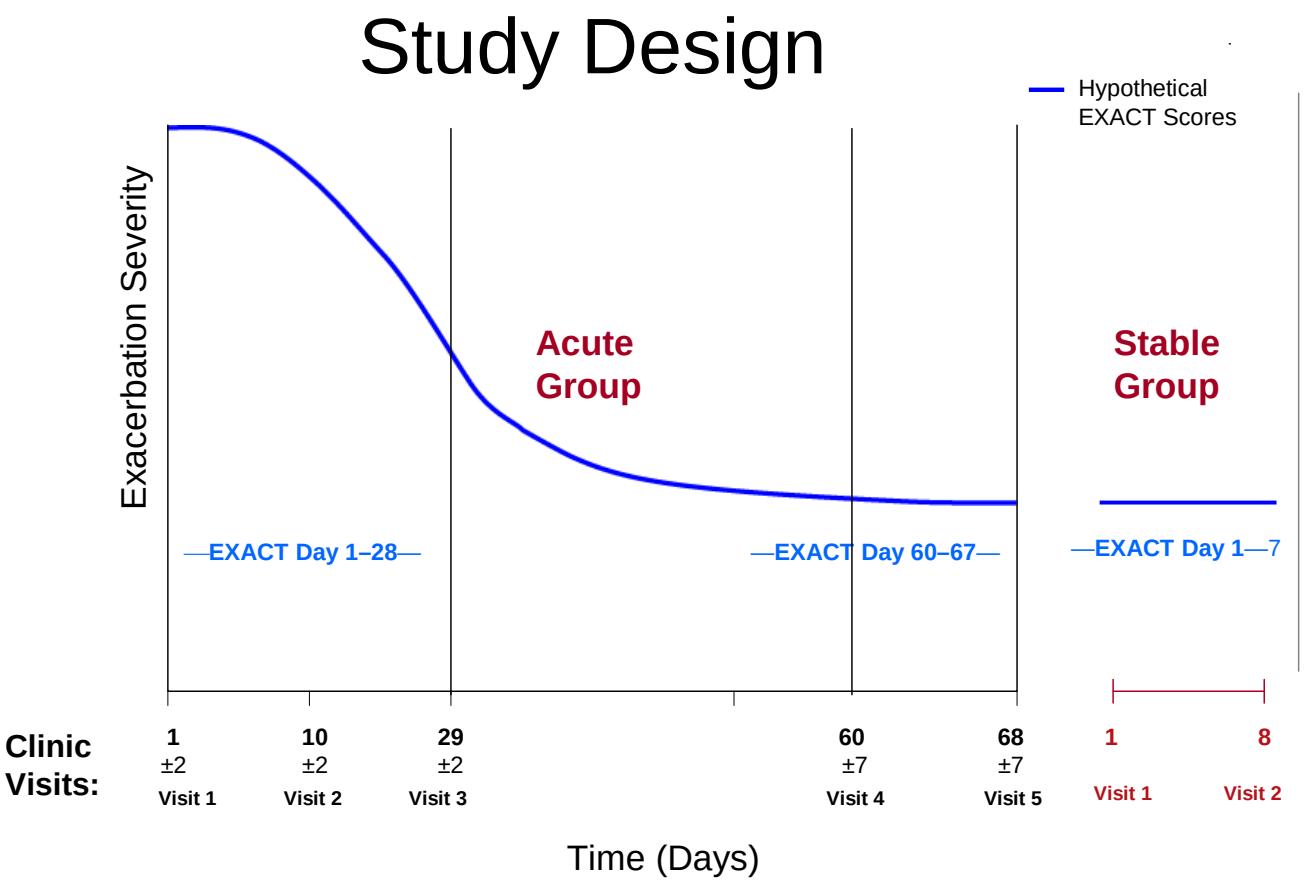
Characterizing and Quantifying the Symptomatic Features of COPD Exacerbations


Standardizing Measurement of Chronic Obstructive Pulmonary Disease Exacerbations

Reliability and Validity of a Patient-reported Diary

Jones et al. *Chest*. 2011;139(6):91388-1394.
Leidy et al. *Am J Respir Crit Care Med.* 2011;183(3):323-329.

# Item Reduction and Initial Validation

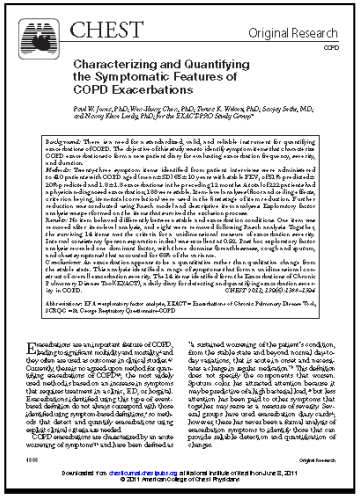




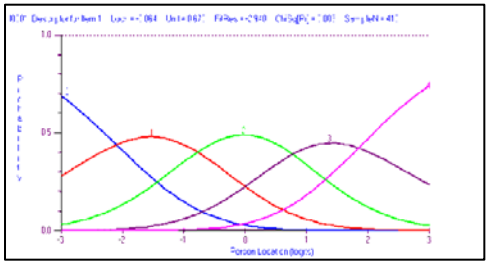
Jones et al. *Chest*. 2011;139(6):91388-1394.
Leidy et al. *Am J Respir Crit Care Med.* 2011;183(3):323-329.

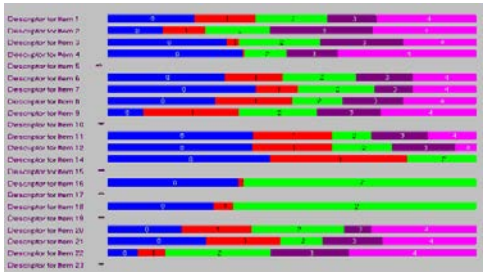
# Item Reduction – Rasch Analyses

- Item evaluation and factor analysis
- Classical test theory
  - Acute and stable patients
- Item response theory (IRT) with Rasch Model
  - Order of response options
  - Individual item model fit
  - Differential item functioning
  - Overall model fit
- Scoring


CHEST Original Research

Characterizing and Quantifying the Symptomatic Features of COPD Exacerbations





Jones et al. *Chest*. 2011;139(6):91388-1394.
Leidy et al. *Am J Respir Crit Care Med.* 2011;183(3):323-329.

# The EXACT

- 14-item eDiary completed each evening before bedtime
  - Recall: “Today”; < 3 minutes to complete
- Total score
  - 0 to 100 — higher scores = worse
- Content
  - Breathlessness (5 Items)
  - Cough and sputum (2 Items)
  - Chest symptoms (3 Items)
  - Difficulty with sputum
  - Tired or weak
  - Sleep disturbance
  - Worry or concern

**EXA**cerbations of **C**hronic Pulmonary Disease **T**ool (EXACT) – a **P**atient-**R**eported **O**utcome (PRO)

Leidy et al. *Value Health*. 2010;13(8):965-975.
Jones et al. *Chest*. 2011;139(6):91388-1394.
Leidy et al. *Am J Respir Crit Care Med.* 2011;183(3):323-329.

# Reliability and Validity

Reliability:

- Internal Consistency (N=410) $\alpha = 0.91$
- Test-retest (Day 1 to 7) (n=171; Stable Group)

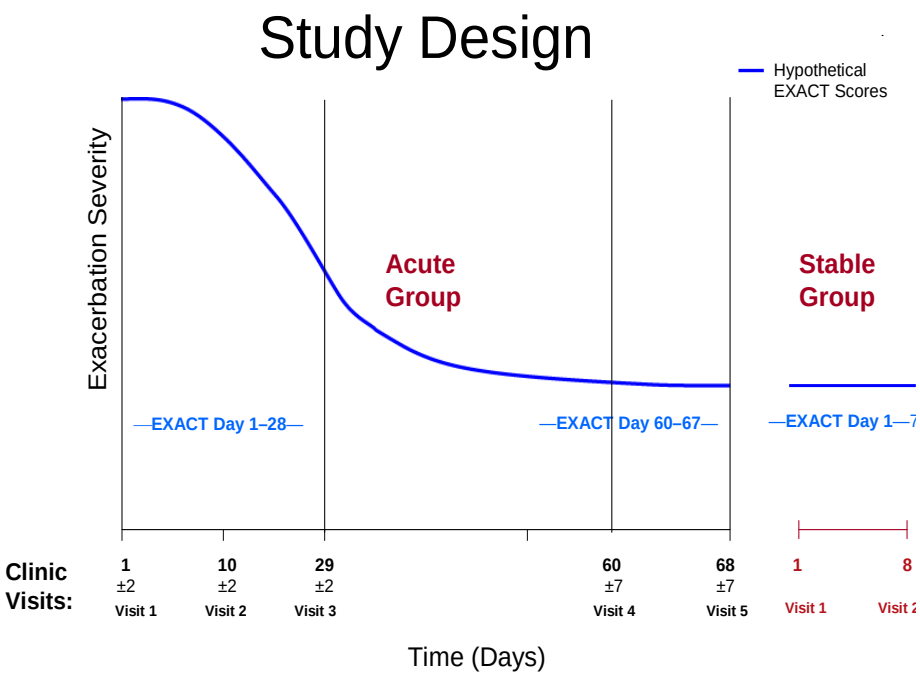
| | ICC | Mean Difference | ES |
|---|---|---|---|
| Total (14 items) | 0.77 | -0.35 | .03 |

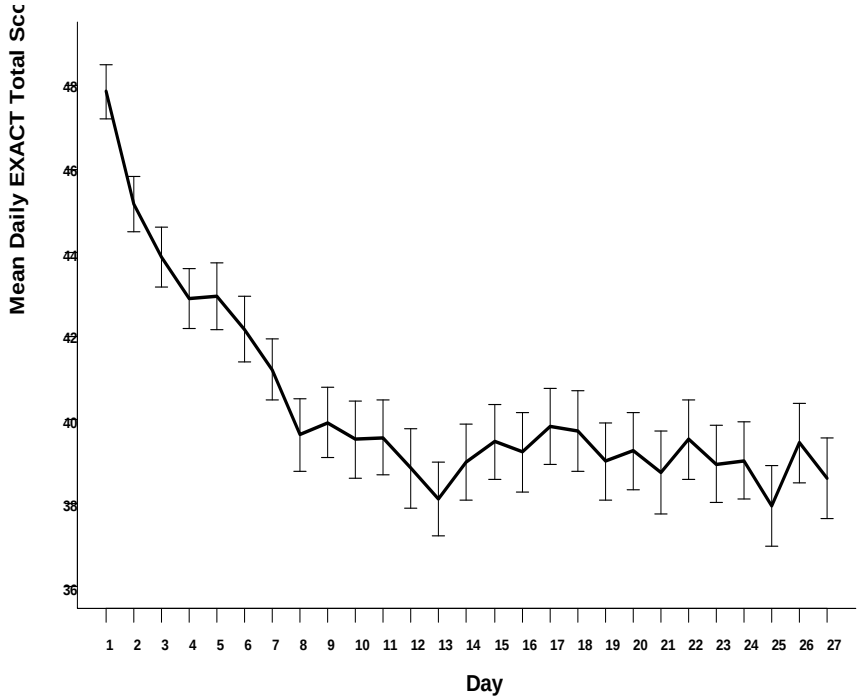
Validity:

- Correlated appropriately with SGRQ-C, FEV-1% predicted, MMRC, and rescue medication use
- Change over time in acute patients (Responsiveness = Validity)
- Differentiate acute and stable patients
- Differentiate acute patients by clinician-rated exacerbation severity

Leidy et al. *Am J Respir Crit Care Med.* 2011;183(3):323-329.

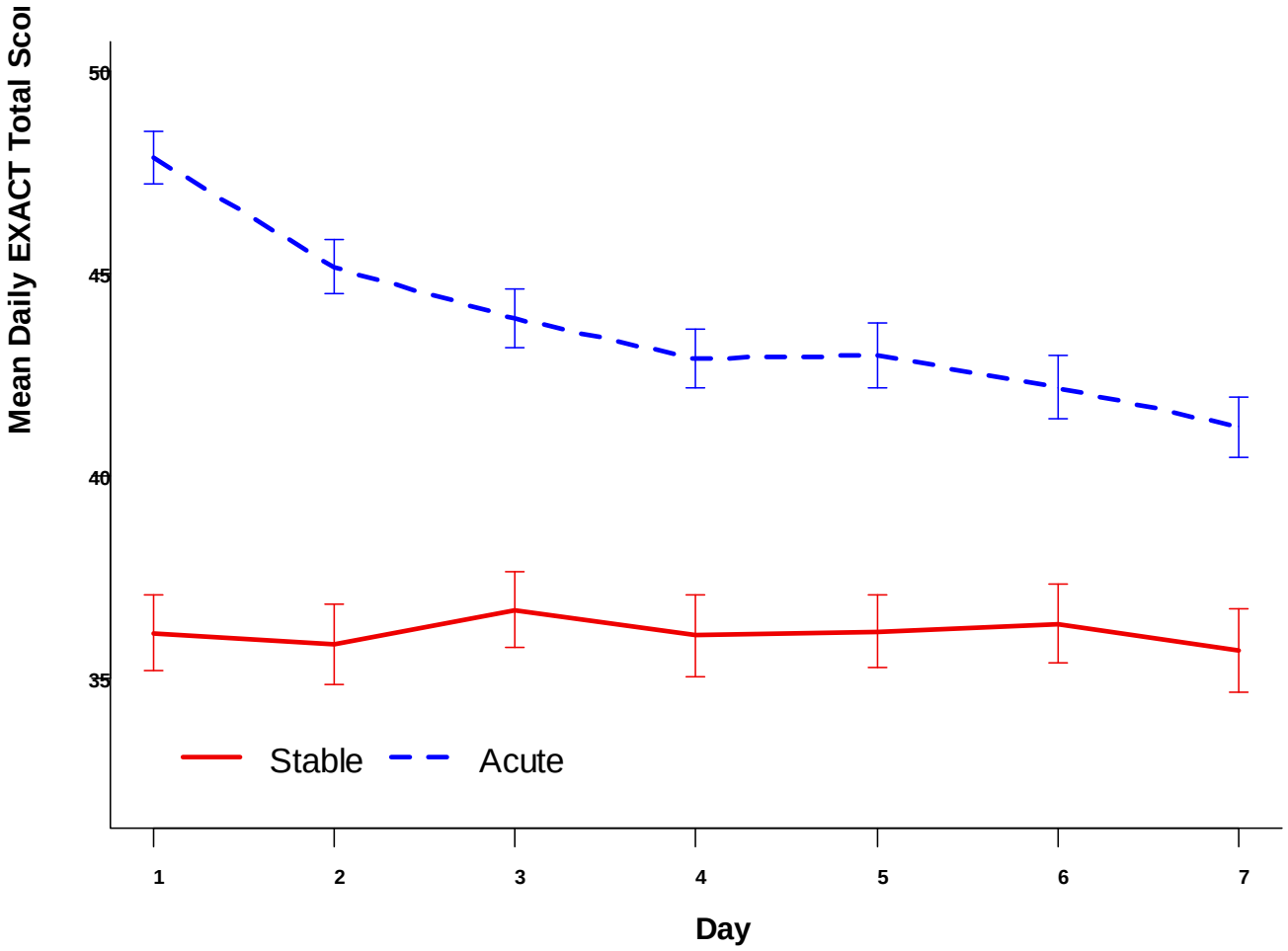
# Acute: Sensitivity to Change



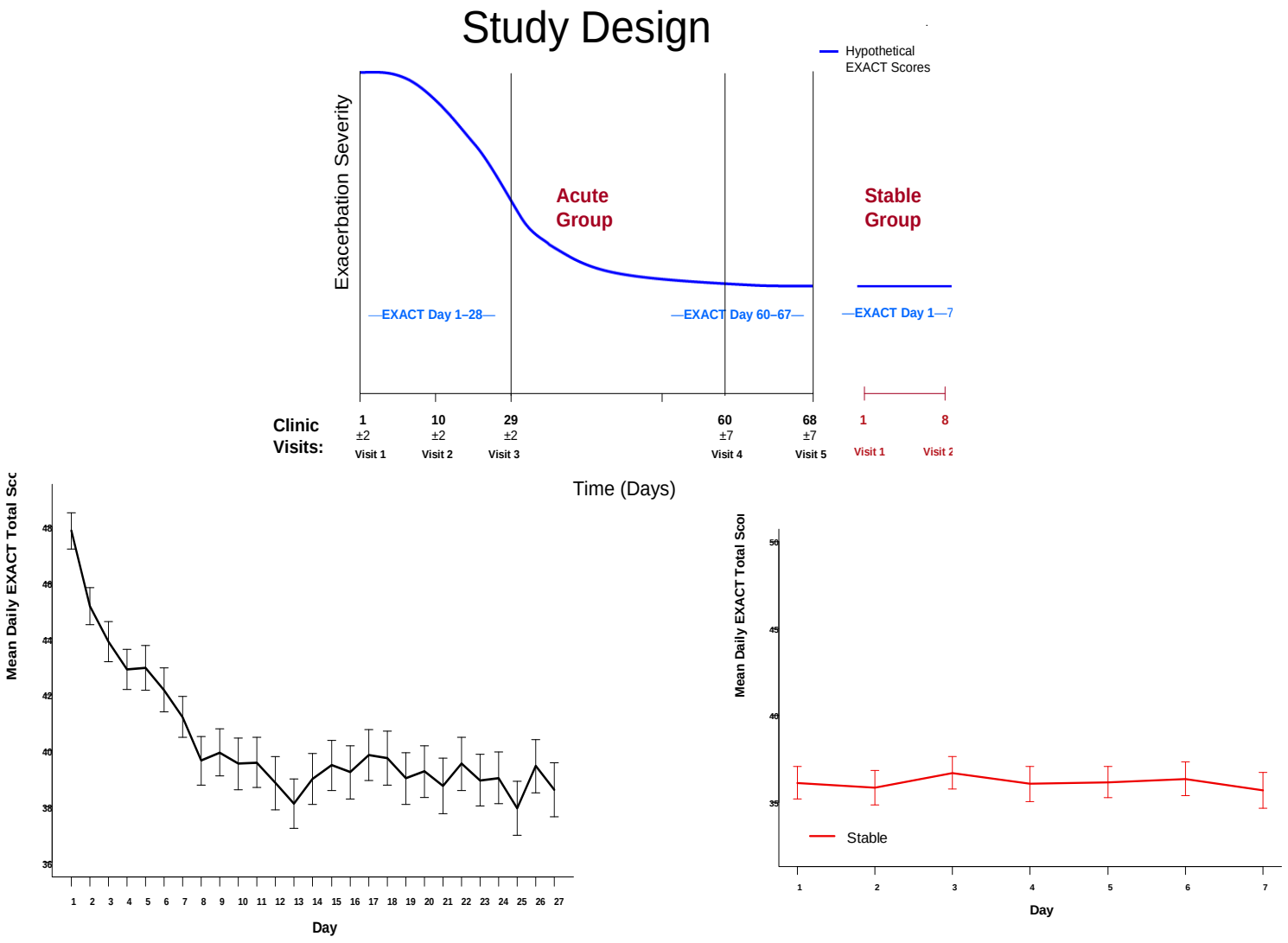

Leidy et al. *Am J Respir Crit Care Med.* 2011;183(3):323-329.

# Acute versus Stable: Known-Groups




Leidy et al. *Am J Respir Crit Care Med.* 2011;183(3):323-329.

# The Complete Picture




Leidy et al. *Am J Respir Crit Care Med.* 2011;183(3):323-329.

# Critical Attributes

- ✓ Content Validity
  - Qualitative and quantitative
- ✓ Reliability
  - Internal consistency and reproducibility
- ✓ Validity
  - Construct, known-groups
- ✓ Responsiveness
  - Sensitive, interpretable
    - ✓ *In the target population and clinical trial setting*

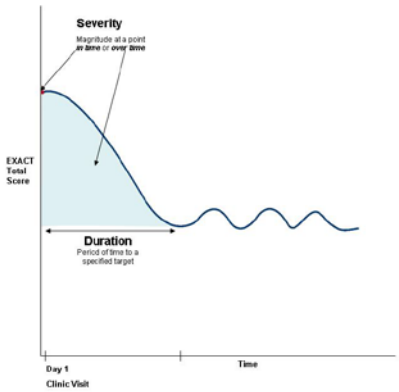
# A Phased Approach

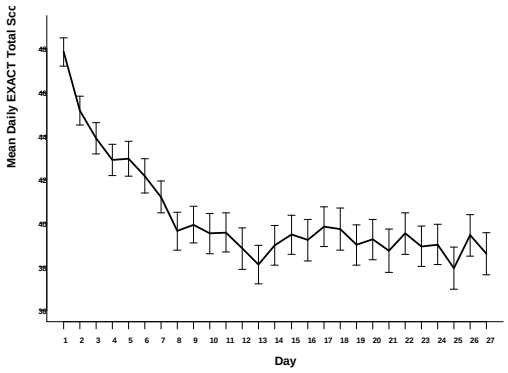
- Phase I
  - Literature review
  - Focus groups and interviews, Item pool development
  - Cognitive debriefing
  - Expert participation
- Phase II
  - Validation study design, execution, SAP development
  - Analyses, interpretation
  - Expert participation
- Phase III
  - User manual, dossier development, dissemination, user guidance
  - Regulatory review
- Phase IV
  - Qualification review and responses
  - Further validation, qualification submission, responses
  - Revised User Manual
  - Translation, user guidance, dissemination

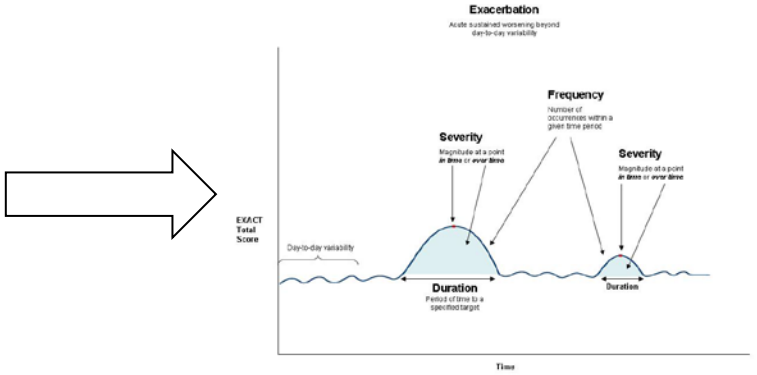
Trial Use

# Further Validation Required

- Prospective clinical trial setting

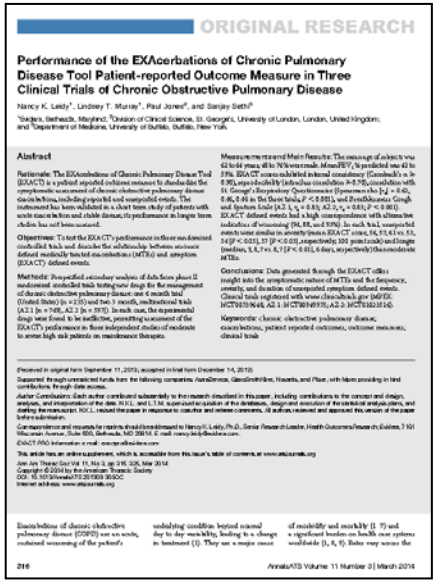


# Further Validation

- 3 Phase 2 RCTs
  - 1: 6 Month (n=235)
  - 2: 3 Month (n=749; n=597)
- Target population
  - COPD, exacerbation history
- Analyses
  - Replication – each trial separately



ORIGINAL RESEARCH

**Performance of the EXAcerbations of Chronic Pulmonary Disease Tool Patient-reported Outcome Measure in Three Clinical Trials of Chronic Obstructive Pulmonary Disease**

Nancy K. Leidy[1], Lindsey T. Murray[1], Paul Jones[2], and Sanjay Sethi[3]

[1]Bedjet, Bethesda, Maryland; [2]Division of Clinical Science, St. George's, University of London, London, United Kingdom; and [3]Department of Medicine, University of Buffalo, Buffalo, New York

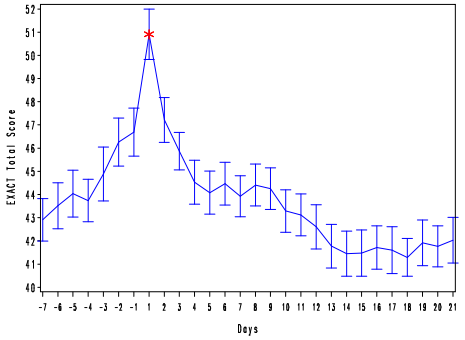
Abstract

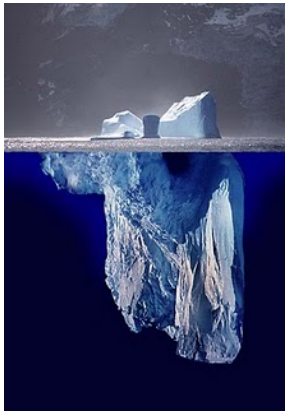
- Does the EXACT provide a
  - Direct assessment of patient-reported symptoms at the time of a medically-treated event (symptom severity and recovery)?
  - Direct assessment of unreported events – frequency, severity, duration?

Leidy et al. *Ann Am Thorac Soc*. 2014;11(3):316-325.

# Results

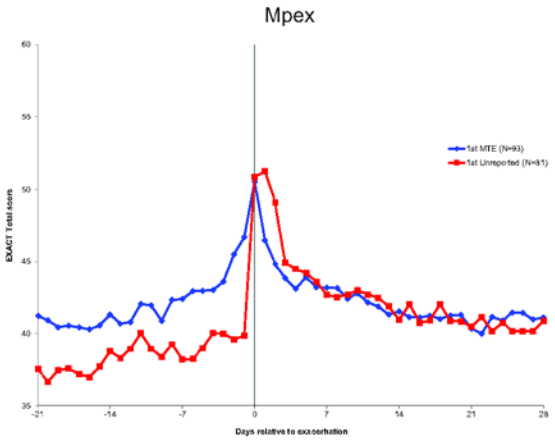
- Reliability and validity
- Parameter estimates
  - Medically Treated Events
    - Symptom severity and duration
  - Unreported events
    - Frequency, severity, duration
- Unreported events:
  - Unreported events
  - As severe as HCRU Events
  - As long or longer than HCRU Events

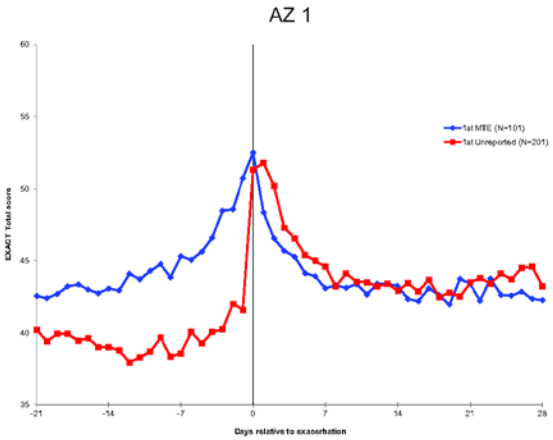


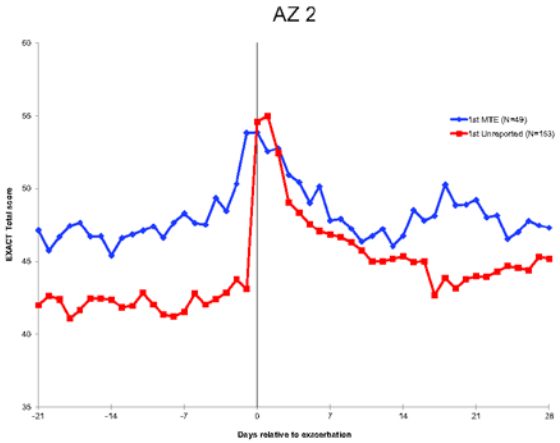



Leidy et al. *Ann Am Thorac Soc*. 2014;11(3):316-325.

# Results: First Reported & Unreported Event



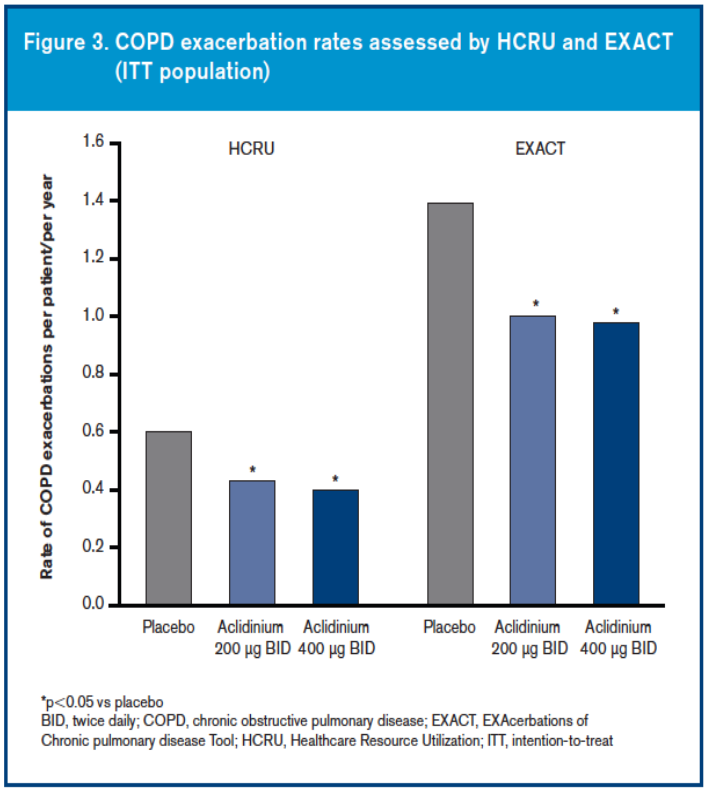




Leidy et al. *Ann Am Thorac Soc*. 2014;11(3):316-325.

# Independent Results: Sensitivity to Treatment Effects

4th Trial (N=819) – 3rd Company (Almirall)
Anticholinergic: M3 muscarinic antagonist.




- HCRU rate reduction
  - 200 µg: 28% (rate ratio 0.72, 95% CI[0.52, 0.99], P<0.05)
  - 400 µg: 33% (rate ratio 0.67, 95% CI [0.48, 0.94]. P<0.05)
- Symptom-defined events (EXACT) rate reduction
  - 200 µg: 28% (rate ratio 0.72, 95% CI [0.55, 0.94], P<0.05)
  - 400 µg: 29% (rate ratio 0.71, 95% CI [0.54, 0.93], P<0.05)

# Critical Attributes

- ✓ Content Validity
  - Qualitative and quantitative
- ✓ Reliability
  - Internal consistency and reproducibility
- ✓ Validity
  - Construct, known-groups
- ✓ Responsiveness
  - Sensitive, interpretable
    - ✓ *In the target population*
    - ✓ *In clinical trial setting (3 trials)*

o Treatment effects were not part of the submission package

# The EXACT-PRO Journey: Overview

- Background
  - Concept & EXACT-PRO Consortium Approach
- Development Steps
  - Content Validity & Empirical Testing
- Further Validation
  - Clinical trial settings
- Timelines
  - Additional activities
- Qualification
  - Context and questions
- Observations
  - Key success factors
- Conclusions

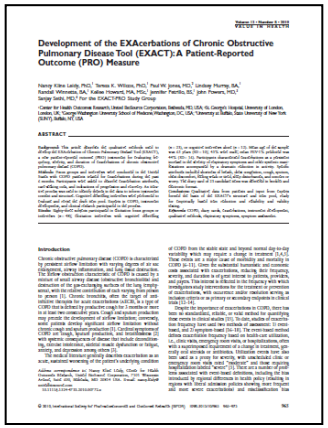
# Beyond Validation: Additional Activities

- Derivative Instrument – EXACT-RS
  - Development, validation, dossier submission
- EMA Submission and Review
  - EXACT and E-RS (2012; Meeting:  January 2013)
- Dissemination – Presentations & publications
- Translations - 40 to date
- ePRO Facilitation - New devices
- Communication - Website
- User Support
  - Pharma, academic
- Discussion of new contexts
  - IPF, CF

# Dissemination – Key Papers

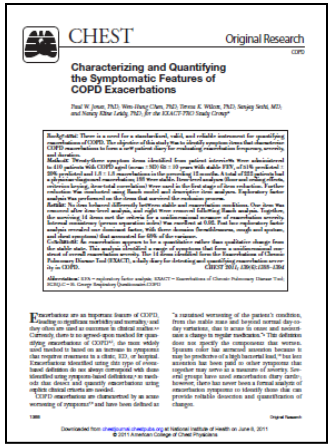
PRO CONSORTIUM
CRITICAL PATH INSTITUTE

## Qualitative Methods Elicitation and Cognitive


Development of the EXAcerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT):A Patient-Reported Outcome (PRO) Measure

*Value in Health (2010)*

## Quantitative Methods Item Analysis and Rasch


CHEST Original Research
Characterizing and Quantifying the Symptomatic Features of COPD Exacerbations

*Chest (2011)*

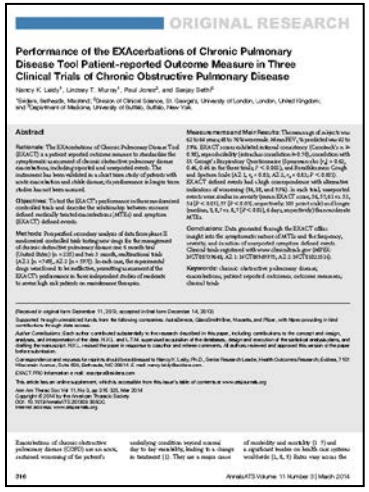
## Reliability, Validity, Sensitivity


Standardizing Measurement of Chronic Obstructive Pulmonary Disease Exacerbations
Reliability and Validity of a Patient-reported Diary

*AJRCCM (Blue) (2011)*

Key Paper of 2011 Clinical Year in Review, ATS 2012

## Validation in 3 Trials


ORIGINAL RESEARCH
Performance of the EXAcerbations of Chronic Pulmonary Disease Tool Patient-reported Outcome Measure in Three Clinical Trials of Chronic Obstructive Pulmonary Disease

*Annals of ATS (2014)*

# Timelines

- Phase I - **7 months**
  - Literature review
  - Focus groups and interviews, Item pool development
  - Cognitive debriefing
  - Expert participation
- Phase II - **17 months**
  - Validation study design, execution, SAP development
  - Analyses, interpretation
  - Expert participation
- Phase III - **12 months**
  - User manual, dossier development, dissemination, user guidance
  - Regulatory review
- Phase IV - **12+ months**
  - Qualification review and responses
  - Further validation, qualification submission, responses
  - Revised User Manual
  - Translation, user guidance, dissemination

2+ Years

Trial Use

# Chronology: 2006-2013

- Phase I - **7 months** (2006)
  - Literature review
  - Focus groups and interviews, Item pool development
  - Cognitive debriefing
  - Expert participation
- Phase II - **17 months**
  - Validation study design, execution, SAP development
  - Analyses, interpretation
  - Expert participation
- Phase III - **12 months**
  - User manual, dossier development, dissemination, user guidance
  - Regulatory review
- Phase IV - **12+ months**
  - Qualification review and responses
  - Further validation, qualification submission, responses
  - Revised User Manual
  - Translation, user guidance, dissemination

2008 - Trial Use

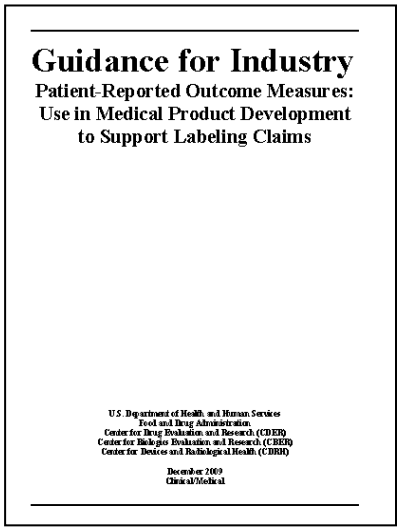
2006-2009

2010-2013

# FDA Guidances: 2006 - 2013

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

PRO Guidance

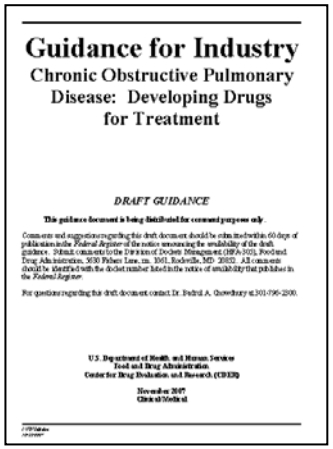

Guidance for Industry
Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

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

2006 – Draft
2009 – Final

COPD Draft Guidance


Guidance for Industry
Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment

DRAFT GUIDANCE

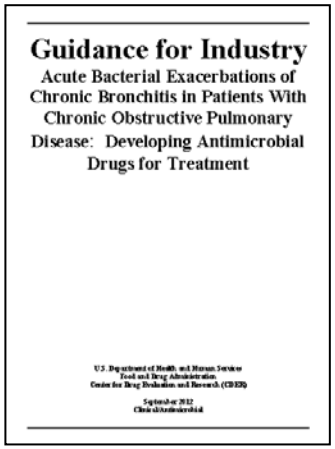
This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2007
Clinical/Medical

2007 – Draft

ABECB-COPD Guidance

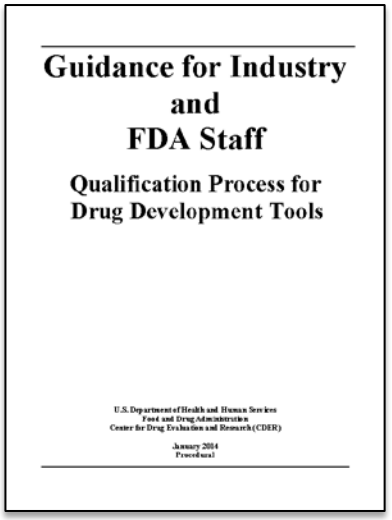

Guidance for Industry
Acute Bacterial Exacerbations of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2012
Clinical/Antimicrobial

2008 – Draft
2012 – Final

DDT Qualification Guidance


Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

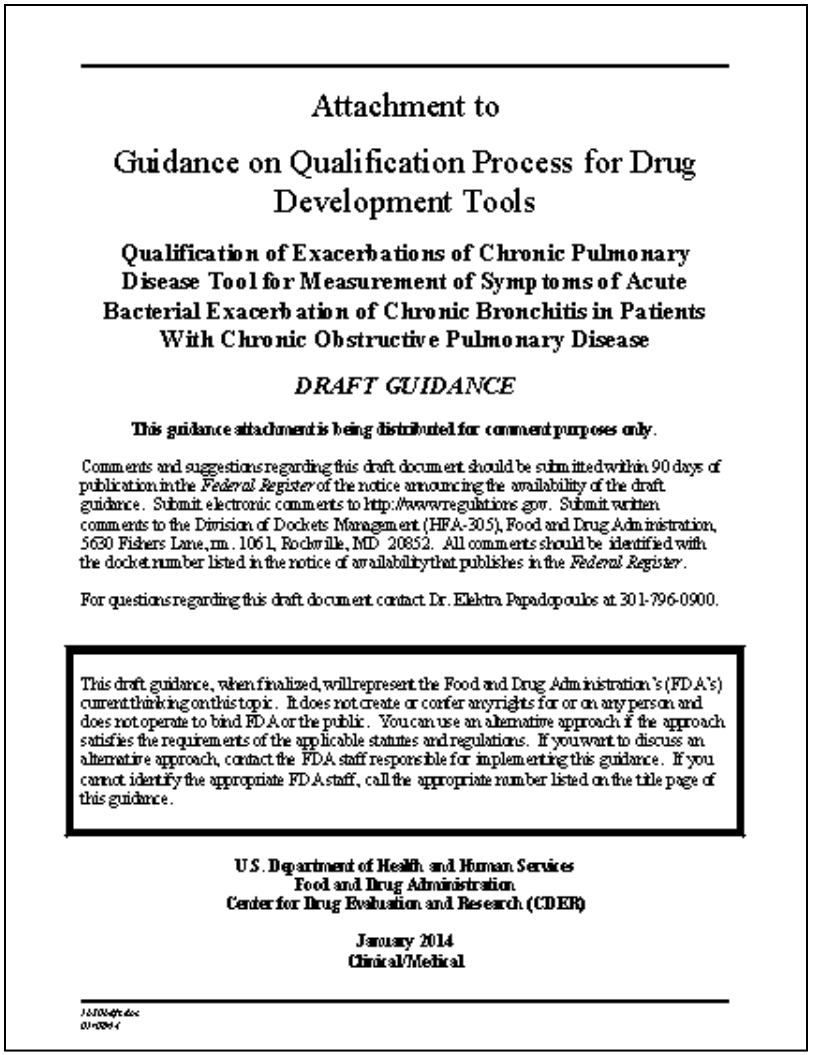
January 2014
Procedural

2010 – Draft
2014 – Final

# The EXACT-PRO Journey: Overview

- Background
  - Concept and context
- Concept Clarification
  - Content validity
- Empirical Testing
  - Prospective Validation
  - Further validation – clinical trial settings
- Qualification
  - Context and questions
- Observations
  - Key success factors
- Conclusions

# EXACT Draft Qualification – January 2014



Attachment to

Guidance on Qualification Process for Drug Development Tools

**Qualification of Exacerbations of Chronic Pulmonary Disease Tool for Measurement of Symptoms of Acute Bacterial Exacerbation of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease**

*DRAFT GUIDANCE*

**This guidance attachment is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Dr. Elektra Papadopoulos at 301-796-0900.

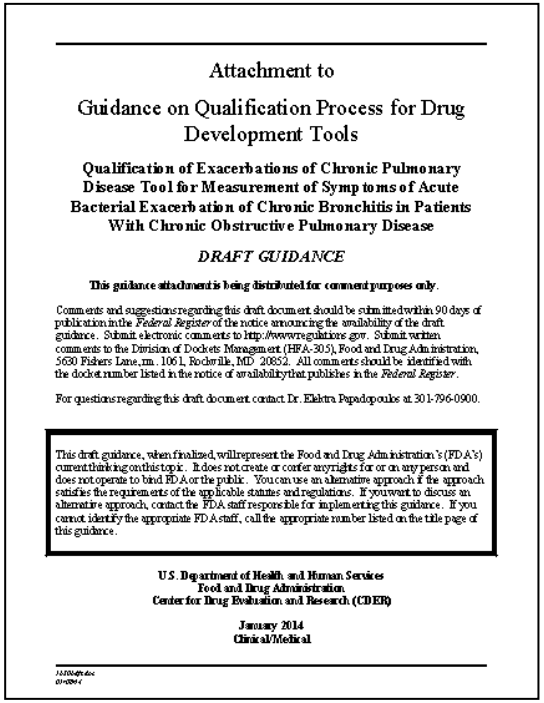
This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**January 2014**
**Clinical/Medical**

# Qualification – Key points

- The EXACT is qualified as a
  - Well-defined & reliable measure
  - of symptoms of acute bacterial exacerbation of chronic bronchitis
  - For use in phase 2 studies
- Additional development work
  - Measurement properties over the course of exacerbation in response to an acute intervention
    - Ability to detect meaningful response
    - Responder definition
- Encourage exploratory analyses
  - Interpretation of effectiveness



Attachment to

Guidance on Qualification Process for Drug Development Tools

**Qualification of Exacerbations of Chronic Pulmonary Disease Tool for Measurement of Symptoms of Acute Bacterial Exacerbation of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease**

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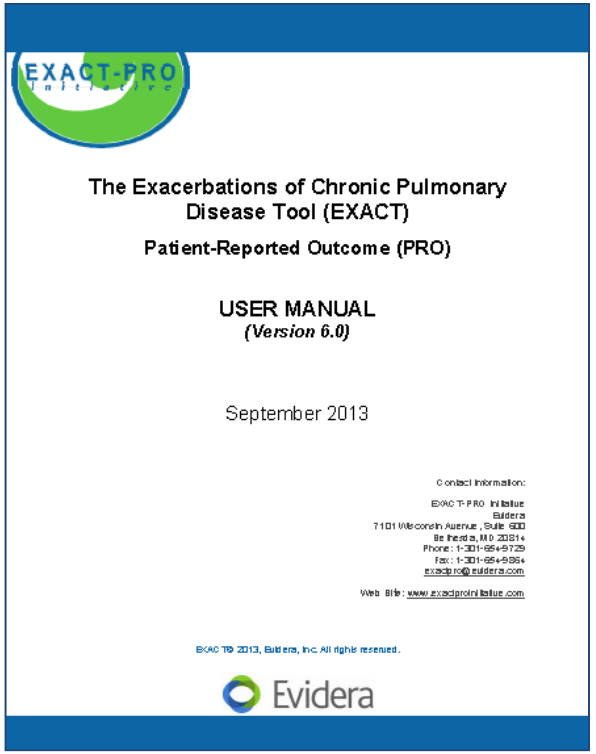
**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**January 2014**
**Clinical/Medical**

# User Manual

- Introduction
- Context of Use
- Development & Validation Overview
- Instrument Description
- Translations
- Methods of Administration
- Study Site & Patient Training
- Copyright & Licensing
- References
- Appendices
  - Example endpoint models & the conceptual framework
  - Scoring Instructions
  - Translation & E-Diary Information



# Communication - Website

- Instrument
  - Description, Development
  - Translations, e-PRO
- Publication List
- Licensing Options
- Resources – Links to Guidances etc.
- FAQs
- User Login
  - Instrument
  - User Manual
  - Test Data & Programs

www.exactproinitiative.com

# The EXACT-PRO Journey: Overview

- Background
  - Concept and context
- Concept Clarification
  - Content validity
- Empirical Testing
  - Prospective Validation
  - Further validation – clinical trial settings
- Qualification
  - Context and questions
- Observations
  - Key success factors
- Conclusions

# Key Success Factors

- Priority need for industry, academia, government
- Clinical and scientific readiness
- Support and commitment of multiple sponsors
- Involvement of interdisciplinary experts
- Strong research team
- Regular, open communication
- Commitment to excellence
- Persistence

# EXACT-PRO Sponsors

- Adams Respiratory
- Almirall
- Altana (Nycomed)
- AstraZeneca
- Bayer
- Boehringer Ingelheim
- DEY
- Forest Laboratories
- GlaxoSmithKline
- Mpex (Aptalis)
- Merck
- Novartis
- Ortho McNeil
- Pfizer
- Sepracor
- Schering-Plough

# EXACT-PRO People

- 20+ sponsor representatives
  - Commitment & expertise
- 15 experts
  - Clinical, research, measurement, regulatory
- 35+ UBC research staff
  - PI, project manager, programmers, assistants
- 70 clinical sites
  - Subject recruitment
- 490+ patients during development
  - Experience and commitment
- 1500 + patients in trials and validation
  - Sponsors who contributed the data

# The EXACT-PRO Journey: Overview

- Background
  - Concept and context
- Concept Clarification
  - Content validity
- Empirical Testing
  - Prospective Validation
  - Further validation – clinical trial settings
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  - Key success factors
- Conclusions

# Conclusions – The Big Picture

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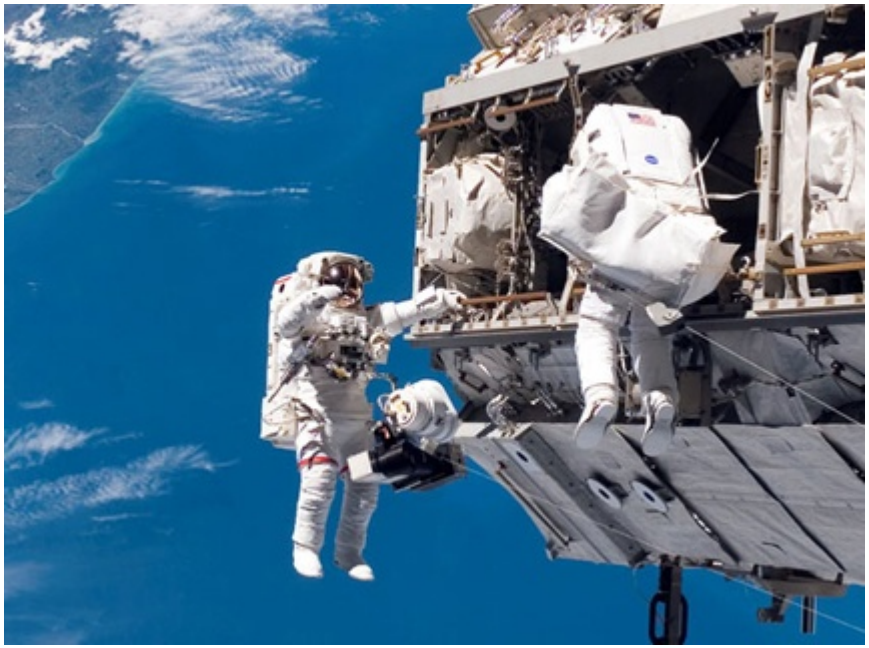

# Conclusions – The Big Picture

# Conclusions – The Big Picture

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CRITICAL PATH INSTITUTE

Take time to celebrate!!

# Conclusions

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

**Thank you!!!**

# References


- Leidy, NK, Wilcox T, Jones PW, Murray L, Winnette, R, Howard K, Petrillo J, Powers J, Sethi S and the EXACT-PRO Study Group (2010). Development of the EXAcerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT): A Patient-Reported Outcome Measure. *Value in Health.* 13(8):965-975.
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- Leidy NK, Murray LT. (2013). The COPD Biomarkers Pipeline: Patient-reported outcome (PRO) measures for clinical trials of COPD: the EXACT and E-RS. *COPD: Journal of COPD*. 10(3):393-8.
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- www.exactproinitiative.com

# Additional References


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