

# Including the Patient Voice in Safety Reporting

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*No Conflicts of Interest*

# Reach into the Medicine Cabinet

## ADVERSE REACTIONS

### Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of NEXIUM was evaluated in over 15,000 patients (aged 18 to 84 years) in clinical trials worldwide including over 8,500 patients in the United States and over 6,500 patients in Europe and Canada. Over 2,900 patients were treated in long-term studies for up to 6-12 months. In general, NEXIUM was well tolerated in both short and long-term clinical trials.

The safety of NEXIUM was evaluated in 316 pediatric and adolescent patients aged 1 to 17 years in four clinical trials for the treatment of symptomatic GERD. [See **Clinical Studies** (14.2).] In 109 pediatric patients aged 1 to 11 years, the most frequently reported (at least 1%) treatment related adverse reactions in these patients were diarrhea (2.8%), headache (1.9%) and somnolence (1.9%). In 149 pediatric patients aged 12 to 17 years the most frequently reported (at least 2%) treatment related adverse reactions in these patients were headache (8.1%), abdominal pain (2.7%), diarrhea (2%) and nausea (2%). No new safety concerns were identified in pediatric patients.

The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1,240 patients on NEXIUM 20 mg, 2,434 patients on NEXIUM 40 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse reactions ( $\geq 1\%$ ) in all three groups were headache (5.5, 5.0, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking NEXIUM or omeprazole.

- How was this information collected?
- Who reported it?
- Can we improve quality and comprehensiveness?

# Adverse Event (AE) Data Collection

## 1. Clinical trials

### – Contexts:

- Preapproval (industry)
- Postapproval (industry and non-industry)

### – Benefits:

- Prospective, controlled
- Established data collection mechanisms

### – Limitations:

- Narrow selection criteria, limited follow-up
- Approach to adverse symptom collection

## 2. Postmarket surveillance

## 3. Voluntary reporting systems

# Sources of AE Data in Trials

<b>CATEGORY</b>	<b>EXAMPLE DOMAIN</b>	<b>DATA SOURCE</b>
Laboratory values	Hemoglobin	Lab report
Events	Hospitalization	Administrative data
Clinical measurements	Blood pressure	Clinical staff
Symptoms	Nausea	Clinical staff

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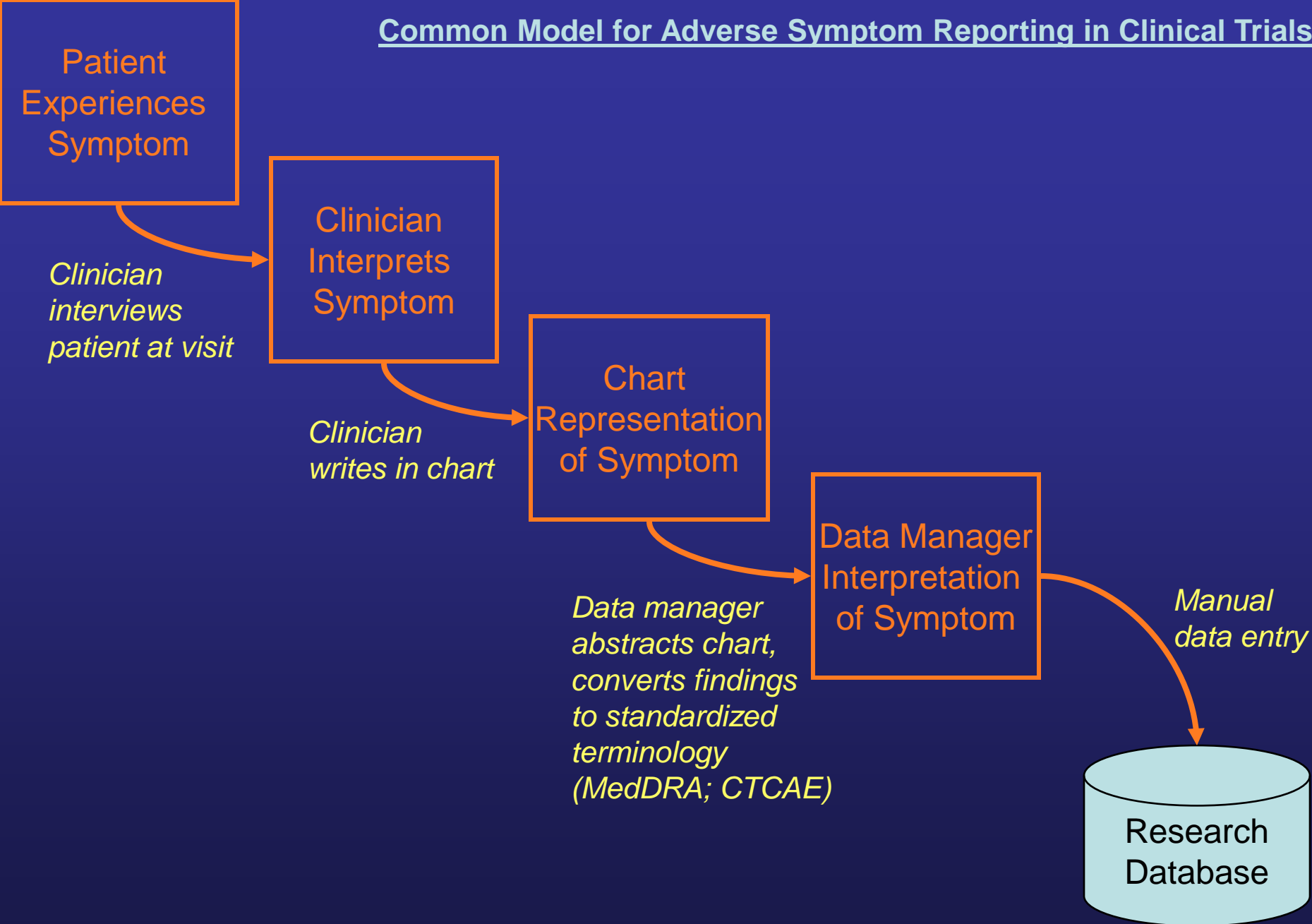
- Adverse symptoms differ from other categories in terms of their data source, process of data collection, and documentation procedures
- Merit special consideration for data collection

# Adverse Events in Current Labels

- Almost half are symptoms

<u>Indication</u>	<u># of U.S. Approved Drug Labels</u>	<u>Average # of AEs per Label</u>	<u>Total # of Unique AEs across Labels</u>	<u>Proportion of AEs which Are Symptoms</u>
Asthma	35	54	368	49% (180/368)
Breast Cancer	32	78	616	36% (223/616)
GERD	18	115	472	45% (213/472)
Hyperlipidemia	28	82	365	43% (158/365)
Osteoarthritis	39	94	684	41% (278/684)

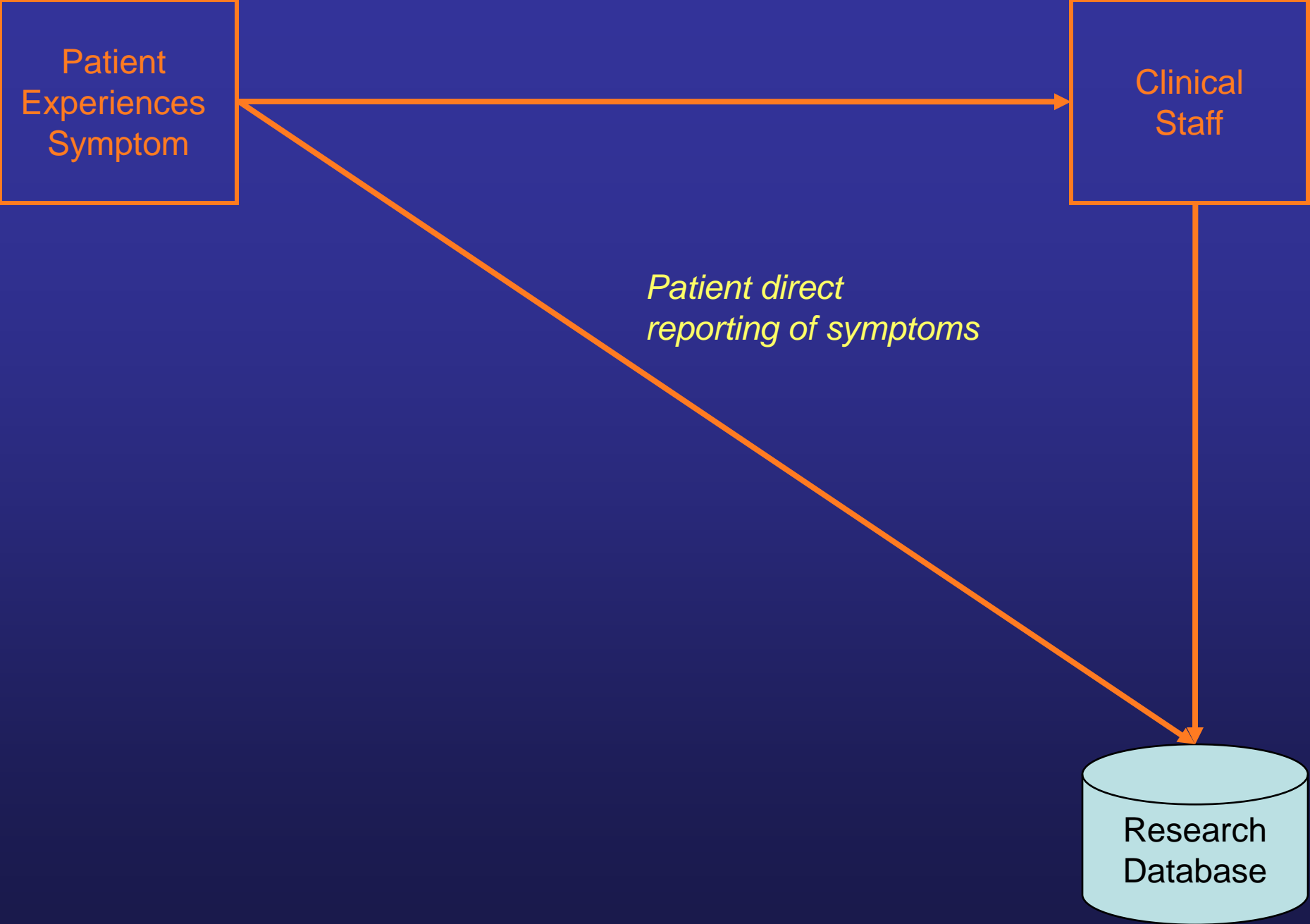
# Common Model for Adverse Symptom Reporting in Clinical Trials



Patient  
Experiences  
Symptom

*Patient direct  
reporting of symptoms*

Research  
Database



# FDA Draft Guidance

- Patient is in the best position to report on his or her symptoms, in the setting of making *claims*
- Is it scientifically merited and feasible to expand this approach to encompass *adverse event* reporting?

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

### *DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit 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*.

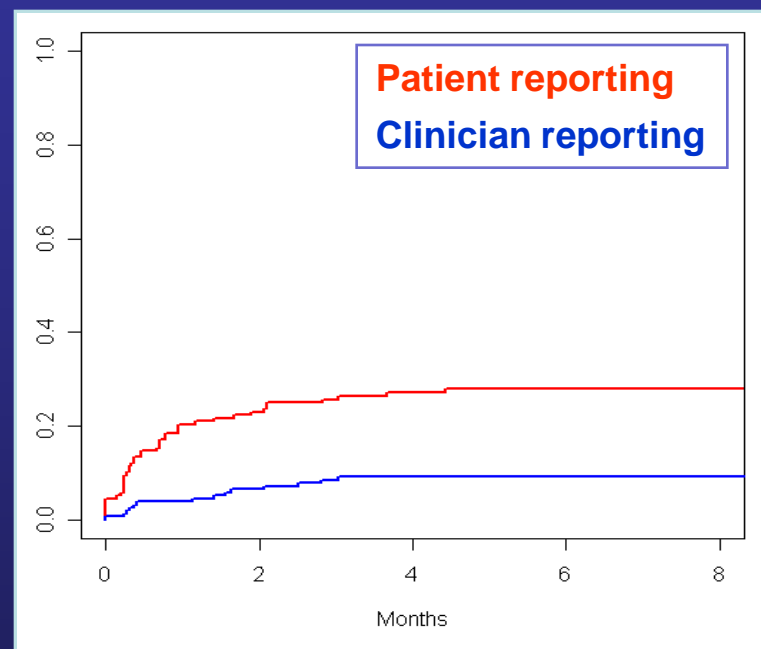
For questions regarding this draft document contact Laurie Burke (CDER) 301-796-0700, Toni Stifano (CBER) 301-827-6190, or Sahar Dawisha (CDRH) 301-594-3090.

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)

February 2006  
Clinical/Medical

# Scientific Evidence

- Clinicians report fewer symptoms than patients
- Clinicians report lower severity of symptoms than patients
  - Across disease types
  - Clinical trial and routine care settings



*Basch: Lancet Oncol, 2007*  
*Pakhomov: Am J Manag Care, 2008*  
*Sprangers, Acta Oncologica, 2000*  
*Stromgren: Acta Anesth, 2001*  
*Weingart: Arch Intern Med, 2005*

# Why Might They Differ?

- Limited time during visits
- Patients may downplay concerns
- Clinicians may downgrade
- *Patients and clinicians have different clinical orientations when they report*

# Complementary Perspectives

- Clinician adverse symptom reports are more highly associated with clinical endpoints (such as death or hospitalization)

while:

- Patient adverse symptom reports are more highly correlated with measures of day-to-day health status (such as HRQL or global health measures)

# Complementary Perspectives

- Clinician-reporting better reflects trajectory towards major clinical benchmarks
  - Clinicians are oriented towards these events
- Patient-reporting better reflects suffering from day-to-day
  - This represents additional information which is not currently collected in trials

# Feasibility

- Patients willing and able to self-report AEs
  - Over long periods of time
  - Even end-stage with high symptom burdens
  - Via wide variety of approaches (paper, computer, PDA, IVR)
  - From clinic and from home
  - Similar methods can be used as for efficacy-related PROs
- Clinicians and investigators consider this information valuable
  - Will change treatment based on PRO AE data
  - 88% feel AEs should be reported by patients in trials

# Advantages and Disadvantages of Direct Patient Safety Reporting

## Advantages

Eliminates data transcription errors

More direct account of experience

Patients can take time to report

Enables between-visit reporting

Capitalizes on existing PRO methods

Consistent with FDA draft Guidance

Informs future patients about their peers

## Disadvantages

May become unable to report (too ill)

May neglect to report (too busy)

Would require new infrastructure

- Patient questionnaires
- PRO administration techniques
- Infrastructure at sites
- Home reporting techniques

Would require new labeling approach

May increase incidence of reported AEs

## NCI Contract

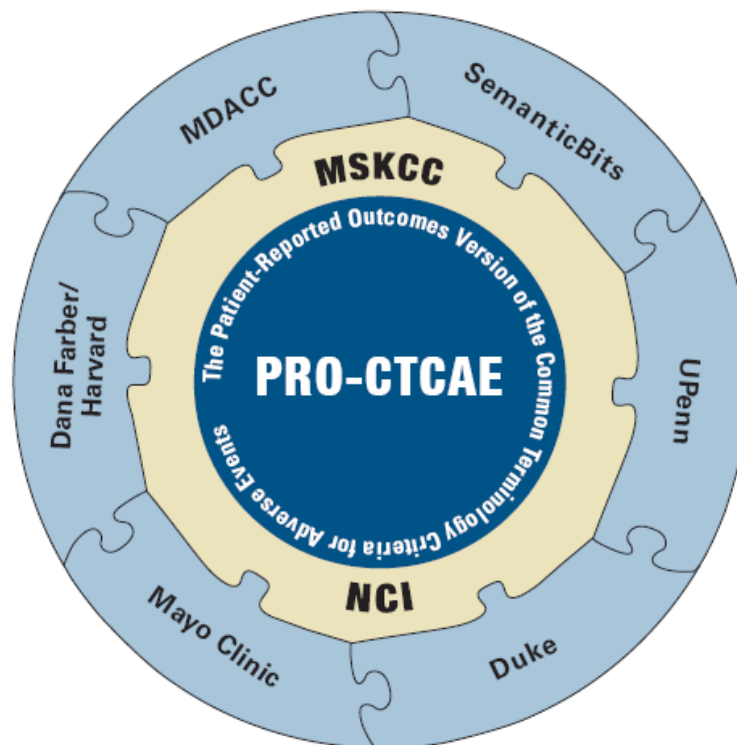
- Initiated 9/08

### Development of the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

NCI HHSN261200800043C

RFP: N02-PC-85002-29

DUNS Number: 064-931-884



# PRO-CTCAE Scope

COMPLETE

1. Determine methodological and logistical barriers to collecting PRO AEs in trials
2. Identify items in CTCAE (existing clinician-oriented AE item bank) amenable to PRO
3. Create PRO-CTCAE items
4. Build electronic platform for in-clinic reporting

ONGOING

5. Assess content validity of items
6. Evaluate usability of platform
7. Study measurement properties of items
8. Develop multicenter feasibility study

# Summary

- AE reporting is essential in clinical trials to ensure patient safety and provide data about drug effects
  - Adverse symptoms reported primarily by clinical staff
  - Patient self-reporting adds valuable information
- Patients are willing and able to self-report AEs
  - Clinicians value this information
- Practical models in development

# Future

- Determine optimal approach to representing patient-reported adverse symptoms in published trial results and labels
- Identify future role of clinician-reported adverse symptoms
  - Should both patient- and clinician-reporting continue?
  - Should clinician-reporting be discontinued?
  - Should shared evaluation models be considered?
- Determine strategies to integrate this approach into existing workflows for data collection and analysis