# Assessing Tolerability of Anti-Cancer Agents Using Clinician- and Patient-Reported Outcomes: Methods for Analyzing and Interpreting CTCAE and PRO-CTCAE Data

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# Blue Ribbon Panel Recommendation

*"…identify approaches to monitor and manage patient reported symptoms.."*

*"…deploy these [patient reported outcome] PRO measurement technologies to provide a mechanism to report poorly controlled symptoms…"*

# Objectives

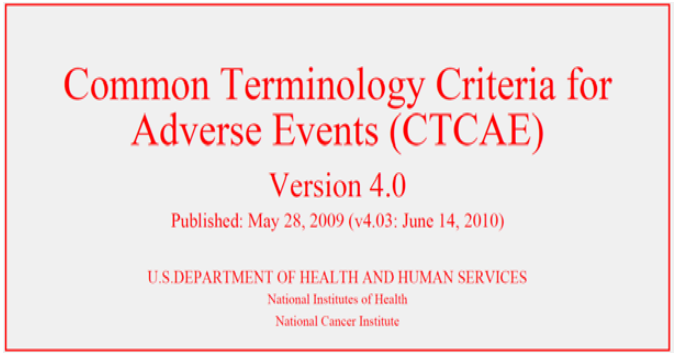
1. Review Common Terminology Criteria for Adverse Event (CTCAE) reporting system for assessing and reporting adverse events (AEs).
2. Discuss patient reported outcome version of CTCAE (PRO-CTCAE) measurement system.
3. Highlight need to identify tolerability.
4. Identify current gaps in analyzing adverse event data
5. Discuss how RFA will address these gaps

# CTCAE

- Library of > 800 adverse event (AE) Items
- Grading Criteria for AE items built into reporting
- Grading of AEs is used in protocol specific manner
  - Early Phase trial
    - Identifies the maximum tolerated dose
    - Provides safety assessment
    - Identifies recommended Phase 2 dose
- Late Phase
    - Evaluates risk/benefit in comparison to standard regimen

# Conventional Adverse Event Evaluation is Incomplete

- Does not account for the time profile of AEs
  - When do they arise?
  - How long will they last?
  - When will they be worse?




- Does not capture the impact of chronic, low grade toxicity on the ability to continue treatment, i.e.,
  - How best to capture tolerability?

- Does not incorporate patient reported outcomes (PRO)

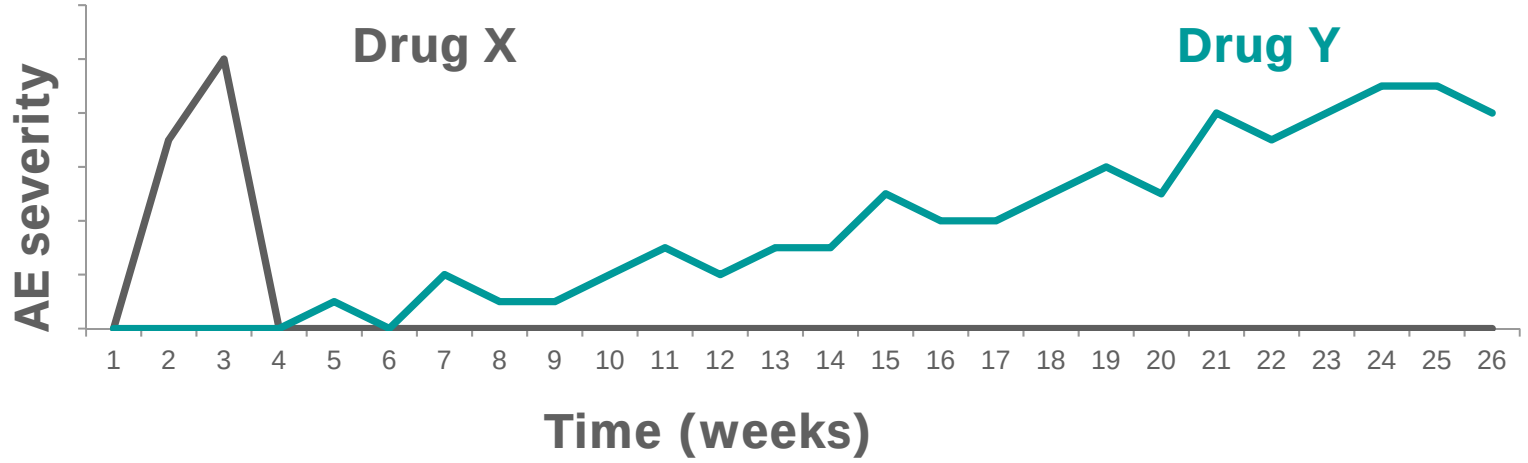
Basch E. N Engl J Med 2013; 369;5:397-400
Trotti A. J Clin Oncol 2007;25:5121-5127
Thanarajasingam **G** et al. J Natl Cancer Inst 2015. 107(10)
Carrabou M. Ann Oncol 2016; 27(8)1633-8.

# Relevance of Adverse Event Time Profile

**Two grade 3+ AEs with similar incidence (conventional maximum grade reporting)**

| Grade 3 or higher | Drug X + standard regimen (n=463) | Drug Y + standard regimen (n=456) |
|---|---|---|
| Dyspnea | **25 (5%)** | 10 (2%) |
| Peripheral neuropathy | 6 (1%) | **24 (5%)** |

**Patient experience of AE: which is more tolerable?**



# Why Include Patient Reporting of Adverse Events?

- Clinicians and patients provide complementary Information
  - Clinicians focus on safety or toxicities requiring action
  - Patients focus on day to day effects of therapies (tolerability)
- Safety data typically presented as CTCAE reports of most severe event experienced over the course of the study.
- Tolerability typically determined by the identification of AEs during the first cycle of therapy in phase I studies.
  - Does not typically include patient's assessment of tolerability or effect of the drug(s) over time

# PRO-CTCAE™*

- Designed to systematically and prospectively capture symptomatic adverse events from patients and complement clinician rated CTCAE
- Item Library of 78 AE items
  - Derived from CTCAE symptomatic AEs
  - Up to 3 independent questions per item (presence/absence, severity, frequency, and interference)
  - Has established measurement properties
  - Provides descriptive data complementing CTCAE
  - Publicly available in 7 languages since April 2016
  - ***Patient reported scores cannot currently be used for protocol adjustments***

*https://healthcaredelivery.cancer.gov/pro-ctcae

# CTCAE vs. PRO-CTCAE: *Similar Data, Different Purposes*

## CTCAE

- Clinician reported
- Safety signal
- Most ***symptomatic*** AEs are graded 1 - 3
- Grade prompts dosing decisions
- Grades 3-5 reported descriptively, do not account for trajectory of toxicity

## PRO-CTCAE

- Patient reported
- Tolerability signal
- Each symptomatic AE: 3 separate scores are available: frequency, severity, interference
- Scores do not prompt dosing decisions
- *Standard approach to analyzing scores not established*

# Goals of RFA

- Stimulate development of methods for analyzing PRO-CTCAE data in the context of cancer clinical trials by:
  - Using PRO-CTCAE and other clinically relevant data to determine tolerability
  - Evaluating both clinician reported and patient reported AE data
  - Using different approaches to missing PRO-CTCAE data, e.g., characterizing missingness, gauging bias
- Create a consortium of funded investigators to share analytic approaches
  - Include biostatisticians, investigators with patient reported outcome (PRO) measurement expertise, and cancer clinical trialists

# Portfolio Analysis: 2010 - 2016

- Funded R01s
  - Validation in pediatric population
  - Compare psychometric properties of PRO-CTCAE with other standard PRO measures
  - Palliative care in Phase I setting
- NCTN & NCORP trials
  - 14 phase II & III trials opened between 2010 and 2016
    - 6 have met accrual goals
- Industry
  - 200 Material Transfer Agreements

# Funding Mechanism & Proposed Budget

- U01 to allow creation of a consortium (funded investigators, NCI staff, regulatory representatives, patient advocates) to set framework for analyzing and drawing interpretations about patient-reported tolerability in the context of cancer clinical trials
- Estimate 4-6 funded teams of statisticians, clinical trialists, and PRO investigators
- Maximum $450K (DC) for $3.25M (TC) each year for 5 years ($16.25M)

# Evaluation Criteria

1. How do PRO-CTCAE data improve our understanding of treatment tolerability?

2. What discoveries have been made concerning the best ways to combine PRO-CTCAE, CTCAE, and clinical and pharmacokinetic data to determine tolerability and inform dose and schedule optimization?

3. Have these discoveries led to the development of new approaches to analyze, interpret or represent PRO-CTCAE data in the context of other data elements that reflect safety and tolerability, including CTCAE?

4. What new insights were produced through these analyses that inform future study design considerations for incorporating PRO-CTCAE in future early and late phase trials (including unbiased item selection, timepoints of measurement, and preventing and handling missing data)?

# Key Collaborators

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- Members of BRP Symptom Management Implementation Team

# *Questions?*