PRO-CTCAE™

PATIENT-REPORTED SYMPTOMATIC ADVERSE EVENTS

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Disclosures

- I work for the USA Federal Government
- I have no financial conflicts to disclose
- Presenting on behalf of the NCI PRO-CTCAE Scientific Leadership Team

Outline

- Introduce PRO-CTCAE™
- Identify key factors to include PRO-CTCAE™ items in clinical trials
- Discuss how to present PRO-CTCAE™ data
- Where to find the tool for use

Adverse Event Reporting

- Common Terminology Criteria for Adverse Event (CTCAE)
  - Standard terminology (~ 800 items) for NCI trials
  - All Items NOT required for use, but available for use
  - Items are selected to be monitored over the course of the trial including baseline.

  - Items are collected and reviewed for patient **SAFETY**
  - Any unexpected events are reported/reviewed in real time
  - All adverse events reviewed during the course of the trial
  - Serious unexpected reports are reported/reviewed in expedited manner
  - Clinical and protocol specific decisions made based upon AE events occurrence and outcomes

Why Include Patient Reporting in Adverse Event Reporting?

- Clinician and Patients Provide Complimentary Information
  - Clinicians Focus on Safety or Toxicities Requiring Action
  - Patients Focus on Day to Day Effects of Therapies

- Safety data typically presented as CTCAE reports of most severe event experienced over the course of the study.

- Patient reported data has typically been collected as HRQOL and presented as a longitudinal trajectory of specific domains.

What is PRO-CTCAE™?

- PRO-CTCAE is designed for patient reporting of symptomatic adverse events
- PRO-CTCAE is an item bank of questions
  - Derived from the CTCAE adverse event items
  - Complimentary to CTCAE (and to be used with)
- PRO-CTCAE is ONLY for descriptive reporting
  - Not ready for clinical and protocol specific decision-making based upon individual PRO-CTCAE scores

PATIENT-REPORTED OUTCOMES VERSION OF THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (PRO-CTCAE™) ITEM LIBRARY (Version 1.0)

Oral	
Dry mouth	S
Difficulty swallowing	S
Mouth/throat sores	SI
Cracking at the corners of the mouth (cheilosis/cheilitis)	S
Voice quality changes	P
Hoarseness	S

Gastrointestinal	
Taste changes	S
Decreased appetite	SI
Nausea	FS
Vomiting	FS
Heartburn	FS
Gas	P
Bloating	FS
Hiccups	FS
Constipation	S
Diarrhea	F
Abdominal pain	FSI
Fecal incontinence	FI

Respiratory	
Shortness of breath	SI
Cough	SI
Wheezing	S

Cardio/Circulatory	
Swelling	FSI
Heart palpitations	FS

Cutaneous	
Rash	P
Skin dryness	S
Acne	S
Hair loss	P
Itching	S
Hives	P
Hand-foot syndrome	S
Nail loss	P
Nail ridging	P
Nail discoloration	P
Sensitivity to sunlight	P
Bed/pressure sores	P
Radiation skin reaction	S
Skin darkening	P
Stretch marks	P

Neurological	
Numbness & tingling	SI
Dizziness	SI

Visual/Perceptual	
Blurred vision	SI
Flashing lights	P
Visual floaters	P
Watery eyes	SI
Ringing in ears	S

Attention/Memory	
Concentration	SI
Memory	SI

Pain	
General pain	FSI
Headache	FSI
Muscle pain	FSI
Joint pain	FSI

Sleep/Wake	
Insomnia	SI
Fatigue	SI

Mood	
Anxious	FSI
Discouraged	FSI
Sad	FSI

Gynecologic/Urinary	
Irregular periods/vaginal bleeding	P
Missed expected menstrual period	P
Vaginal discharge	P
Vaginal dryness	S
Painful urination	S
Urinary urgency	FI
Urinary frequency	PI
Change in usual urine color	P
Urinary incontinence	FI

Sexual	
Achieve and maintain erection	S
Ejaculation	F
Decreased libido	S
Delayed orgasm	P
Unable to have orgasm	P
Pain w/sexual intercourse	S

Miscellaneous	
Breast swelling and tenderness	S
Bruising	P
Chills	FS
Increased sweating	FS
Decreased sweating	P
Hot flashes	FS
Nosebleed	FS
Pain and swelling at injection site	P
Body odor	S

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Dimensions	
F: Frequency	I: Interference
S: Severity	P: Presence/Absence /Amount

CTCAE vs. PRO-CTCAE™ Item Structures

CTCAE					
Adverse Event	Grade				
	1	2	3	4	5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	-

PRO-CTCAE
Please think back over the past 7 days:
What was the severity of your MOUTH OR THROAT SORES at their WORST? None / Mild / Moderate / Severe / Very severe
How much did MOUTH OR THROAT SORES interfere with your usual or daily activities? Not at all / A little bit / Somewhat / Quite a bit / Very much

How to Use PRO-CTCAE

- PRO-CTCAE intended to be complimentary to CTCAE

- Principles for use
  - Item selection
  - Timeframe for assessments
  - Scoring versus Grading

- Data Presentation
  - Work in Progress

- Regulatory Interest (FDA & EMA)
- Translations: English, Spanish,
  - Others under development (Italian, Korean, French, Swedish, etc)

PRO-CTCAE Item Selection

- PRO-CTCAE items selected based upon expectation for symptomatic adverse events
  - Similar to CTCAE items selection: identify those items which need to be monitored for safety and tolerability based upon
    - Pre-clinical or animal data
    - AE items from early clinical data
    - Mechanism based or drug class effects
  - Choose limited number of symptomatic adverse events to mointo
    - Use all the dimensions available for a symptomatic toxicity
  - Need baseline and off-study assessments
  - Allow for unanticipated symptomatic adverse events to be reported through a write-in feature

PRO-CTCAE Item Selection

- Consider:

- Ascertainment Bias
  - *What* you ask and *when* you ask affect the prevalence estimates
  - Baseline assessment
  - Expectations for recovery of symptomatic adverse events
  - Post progression assessment of symptomatic adverse events

- Sampling Bias
  - Missing data is not at random, (patients on early phase trials experience toxicity, declining performance status, and progressive disease)

PRO-CTCAE Item Selection

- Early (non-randomized) phase trials
  - Patients with advanced stage
  - Phase 1 patients with different diseases

- Start with a provisional list of items and add new items as needed through the course of the study
  - Typical of AE reporting and early phase trials in general
  - Incorporate new information into study design as the study progresses
  - Frequently, new AE items are identified in early phase

PRO-CTCAE Item Selection

- Late Phase (Randomized) trials
  - Better defined cohort of patients
  - More known about agent/regimen specific symptomatic toxicities

- Include same items in all arms irrespective of expectation
  - To define and confirm relative symptomatic toxicity profiles of each arm
  - Arm A has 5 symptomatic AEs
  - Arm B has 4 symptomatic AEs, (one of which is in A)
  - Use 5 + 4 – 1 = 8 symptomatic AEs

Timeframe for Assessments

- Recall period is 7 days
  - Anticipate weekly reporting
  - Currently, data to demonstrate ~ 90% compliance for weekly reporting up to 20 weeks with reminders.
  - Baseline and off-study assessment are essential
- Need to balance data quality with the number of items & the frequency of assessment over the course of the study
- If asking questions with an interval of longer than one week, the recall period remains the last 7 days

PRO-CTCAE Score vs. CTCAE Grade

- PRO-CTCAE responses are scored from 0 to 4
  - Up to three questions per AE Item
    - Frequency, Severity, Interference

- Clinician CTCAE Grade
  - Bundles the constructs of severity, frequency and interference
  - Grading dependent upon clinician judgement of medical significance

- Clinician Grade ≠ PRO-CTCAE Score
  - One grade by clinician
  - Up to three patient reported scores per Item
  - CTCAE Grade 4 does not exist for most of the PRO-CTCAE items

Data Presentation

- No best approach to present PRO-CTCAE data

- CTCAE data presented in table
  - Single point in time worst severity
  - No longitudinal data
  - No baseline comparison

- PRO-CTCAE data need not look the same as CTCAE data
- *No Summation Score for PRO-CTCAE*

Example of CTCAE Table

Table 2. Grade 2 or Higher Toxic Effects.*

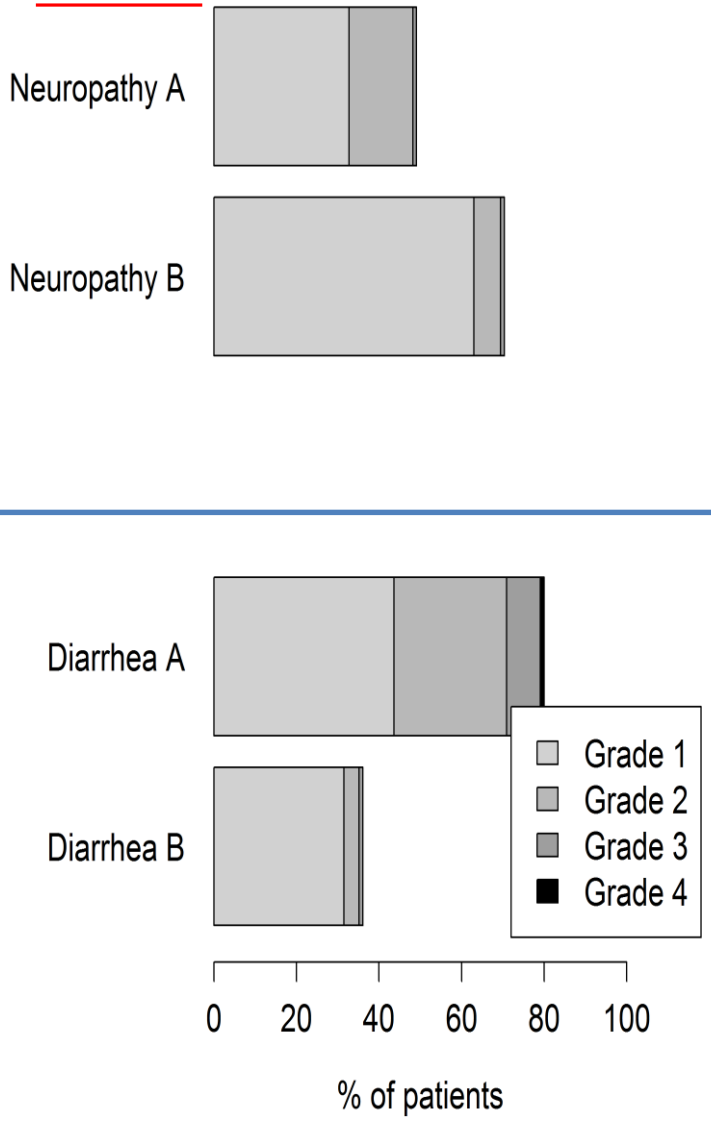
Adverse Event	Chemotherapy Alone (N=111)			Chemotherapy plus Goserelin (N=103)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Diarrhea	2	0	0	0	0	0
Fatigue	1	0	0	2	0	0
Hot flashes	14	3	0	29	4	0
Irregular menses	2	0	0	5	2	0
Decrease in libido	6	0	0	9	0	0
Agitation	4	1	0	6	0	0
Anxiety	4	0	0	9	0	0
Depression	3	0	0	8	1	0
Joint pain	1	1	0	0	0	0
Muscle pain	2	0	0	1	0	0
Headache	1	1	0	12	0	0
Sweating	7	0	0	10	0	0
Thromboembolism	0	0	0	0	0	1
Vaginal dryness	9	0	0	12	0	0

* Included are grade 2 or higher toxic effects that were reported in more than 1% of the patients in either study group. Patients may have had more than one toxic event for a given grade.

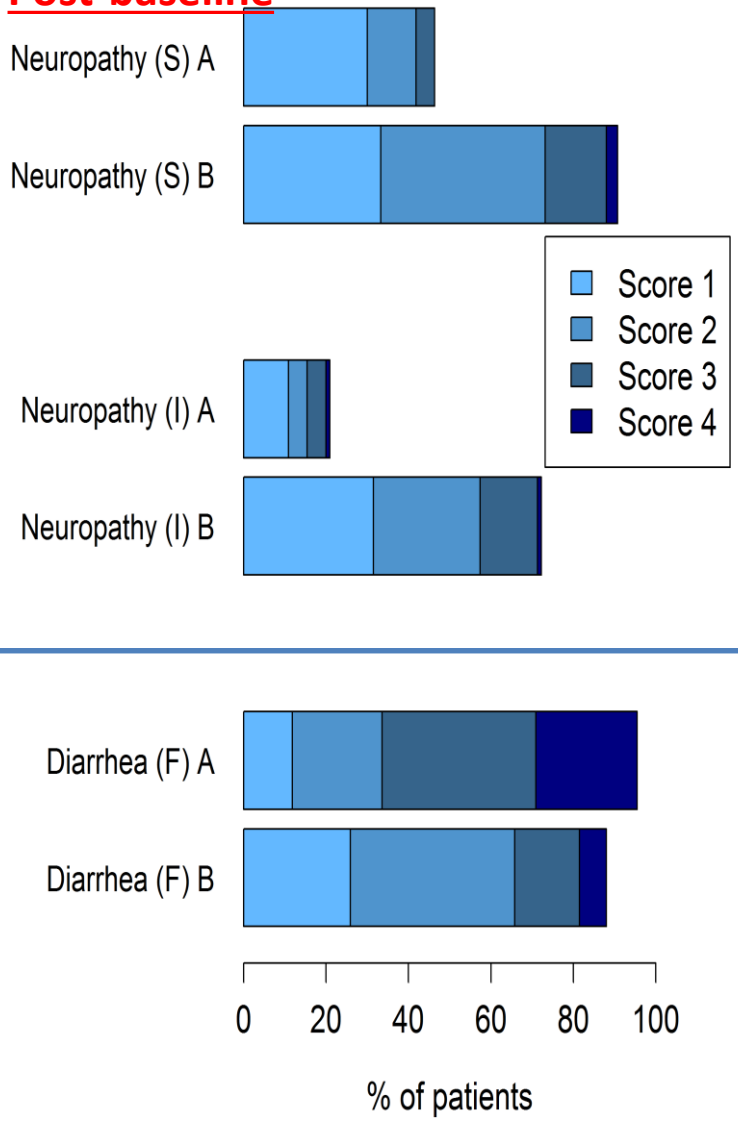
The NEW ENGLAND JOURNAL of MEDICINE

Neuropathy & Diarrhea: CTCAE and PRO-CTCAE

CTCAE Maximum Grade Post-baseline

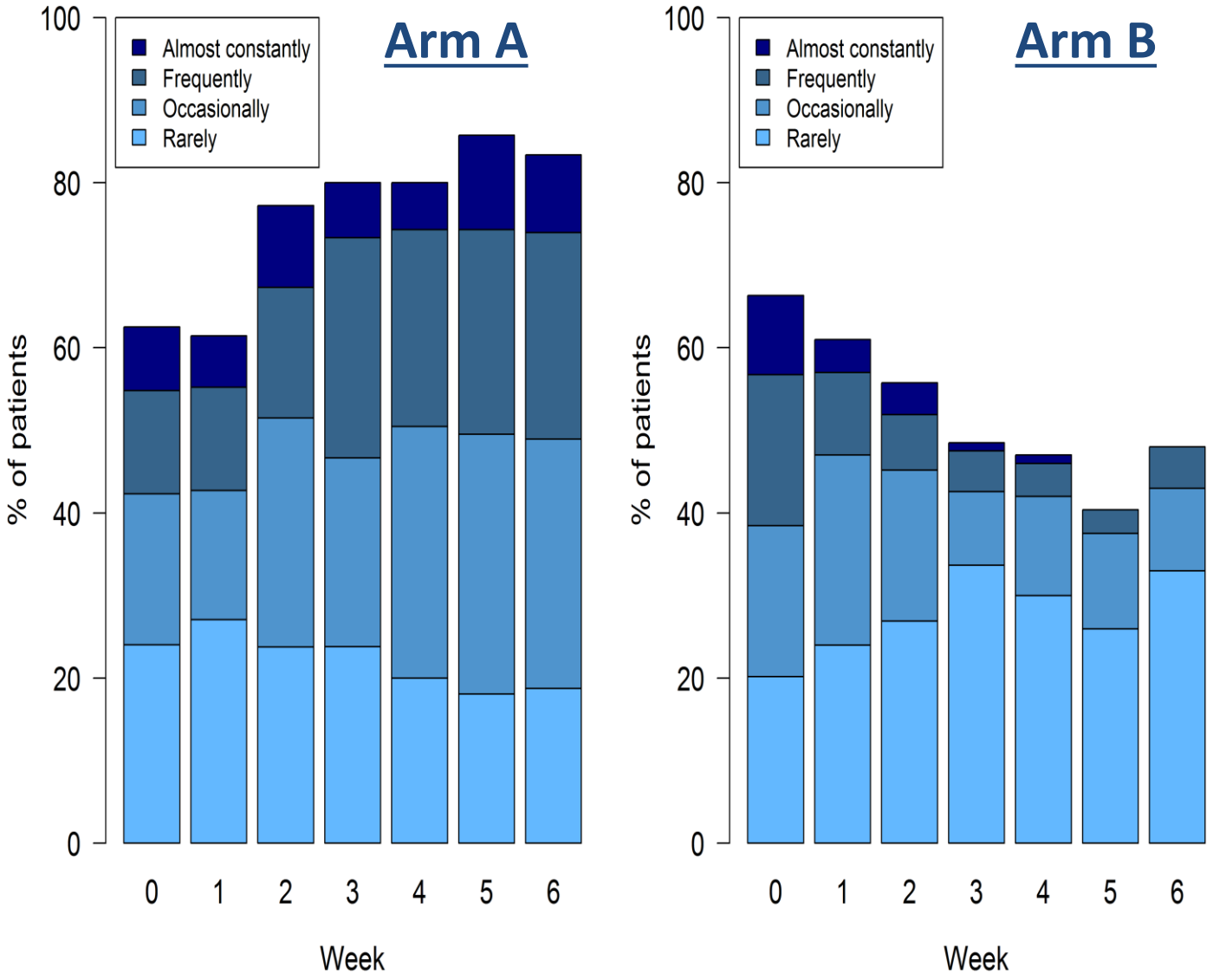


PRO-CTCAE Maximum Score Post-baseline



PRO-CTCAE Distributions at Successive Time Points

Example: Diarrhea between Arms



Summary

- PRO-CTCAE™ is ONLY for descriptive reporting
- CTCAE grade ≠ PRO-CTCAE score

- Item Selection
  - Anticipated symptomatic toxicities from agents/regimens

- Time-points of assessment
  - Baseline and off-study is required
  - Frequency of assessments depends on the study design
  - Timeframes should be consistent with clinician grading

Where do I Find PRO-CTCAE?

- Symptom Library publically released on April 1, 2016
  - Available in English and Spanish for all to use
    - http://healthcaredelivery.cancer.gov/pro-ctcae/
  - Simple registration
  - No cost to use
  - Form builder function at website to maintain instrument fidelity

- Pharmaceutical companies will likely create their own ePRO modules for use

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

This site was designed to provide you with information about the PRO-CTCAE, a patient-reported outcome measurement system developed by the National Cancer Institute to capture symptomatic adverse events in patients on cancer clinical trials.

The site includes an overview of the methods used to develop this measurement system, and resources and references for further information.

Psychometric Development

- Symptom Benefit Committee Presentation

- Content Validity
- Validity and Reliability
- Mode Equivalence
- Recall Period

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Questions?