

**NCI's Patient-Reported Outcomes Version of the
Common Terminology Criteria for Adverse Events
(PRO-CTCAE):
Selecting Items and Assessment Frequency for Cancer
Trials**

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

April 27 - 28, 2016 ■ Silver Spring, MD



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Moderator

- *Sandra A. Mitchell, PhD, CRNP* – Research Scientist and Program Director, Outcomes Research Branch, National Cancer Institute (NCI)

Presenters

- *Paul G. Kluetz, MD* – Associate Director of Clinical Science, OHOP, OND, CDER, FDA
- *Lori Minasian, MD, FACP* – Deputy Director, Division of Cancer Prevention, NCI
- *Ethan Basch, MD, MSc* – Director, Cancer Outcomes Research Program, University of North Carolina
- *Katarina Halling, MSc* – Global Head Patient Reported Outcomes, AstraZeneca and Industry Co-Director, PRO Consortium

Panelists

- *Selena R. Daniels, PharmD, MS* – Reviewer and Acting Team Lead, COA Staff, OND, CDER, FDA

An Overview of the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events™

Sandra A. Mitchell, PhD, CRNP

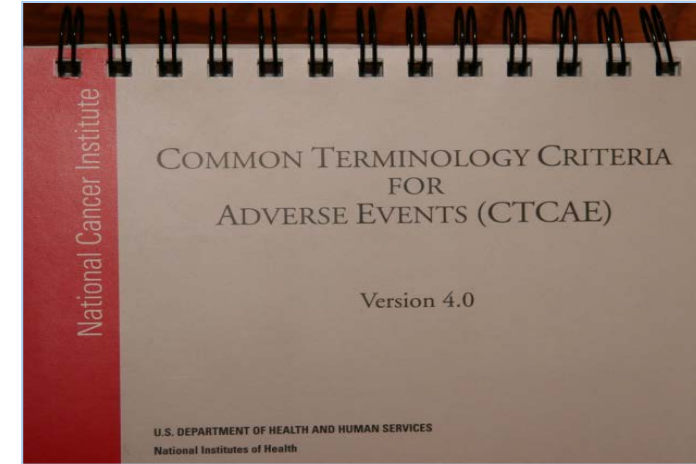
Research Scientist and Program Director
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Measuring Safety and Tolerability in Cancer Clinical Trials

- Fundamental to conclusions about the effectiveness of cancer therapies, including comparative effectiveness
 - Evaluated using **Common Terminology Criteria for Adverse Events (CTCAE)**
- 10% of the 800 adverse events listed in CTCAE are symptoms
 - Validity of symptoms reports is eroded when filtered through research staff and clinicians¹
 - Staff-based adverse event reporting occurs at clinic visits; adverse events that occur between visits may be missed
- Real-time ascertainment of symptom adverse events using patient-reported outcomes (PROs) could improve the precision and reproducibility of adverse event reporting
- **NCI's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)**
 - PRO measure of the frequency, severity and/or interference of symptoms experienced by patients participating in cancer clinical trials
 - Designed to be used as a companion to the CTCAE to capture the patient experience of symptomatic toxicities



¹Xiao et al. (2013). Comparison between patient-reported and clinician-observed symptoms in oncology. *Cancer Nurs.*,36(6):E1-E16

PRO-CTCAE™ Measurement System

1. Item Library

- 78 symptomatic adverse events drawn from CTCAE
- Items evaluate frequency, severity, interference, amount, presence of these symptoms

2. Software

- Creates customized surveys; manages survey administration
- Patient interface: paper, web or IVR
- Conditional branching (skip patterns)
- Write-ins with automatic mapping to standardized terminology
- Automated alerts

For more information about PRO-CTCAE visit: <http://healthcaredelivery.cancer.gov/pro-ctcae/>



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
Ring 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 menstrual periods	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



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

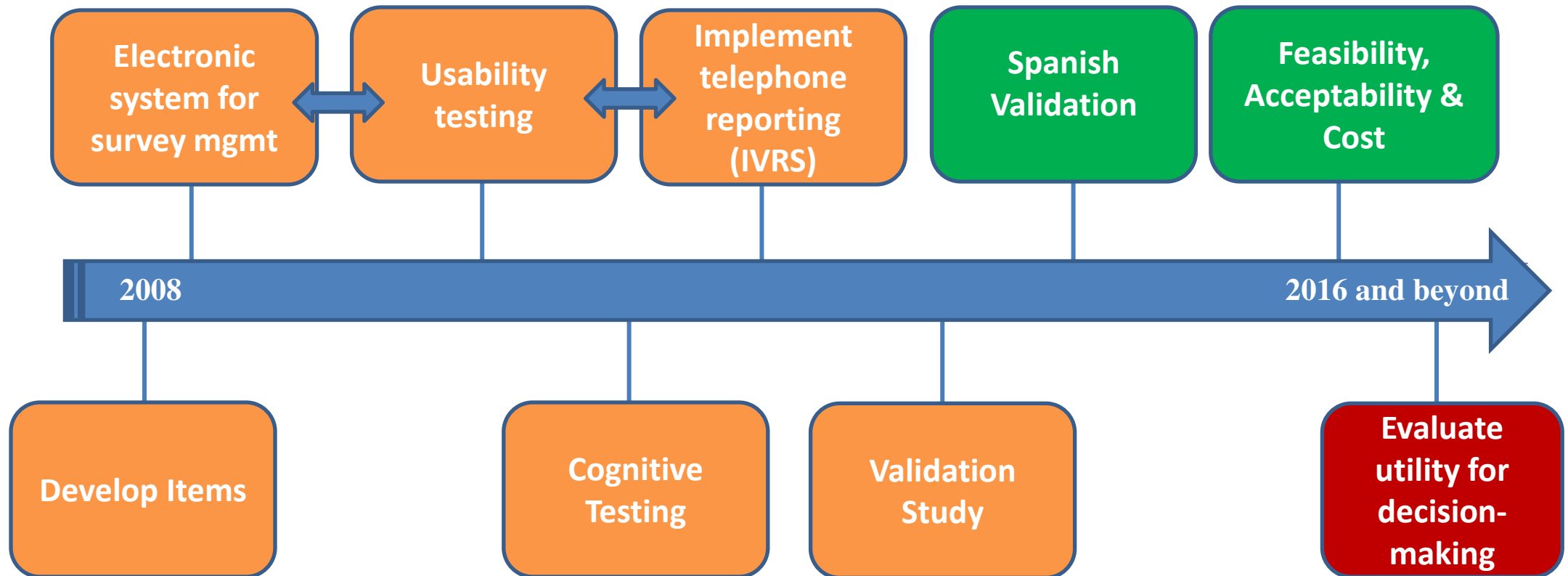
CTCAE vs. PRO-CTCAE™ Item Structures

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

- Psychometrically robust library of items
- Electronic system fits data collection smoothly into trials workflow and offers favorable user-experience
- Accommodate patients with limited English proficiency/digital literacy
- Supply meaningful data to improve understanding of symptomatic AEs



PRO-CTCAE Content Validity

- 78 symptomatic AEs identified from ~800 CTCAE terms for patient self-reporting
 - Plain-language AE terms identified
- Each symptomatic AE has 1 to 3 items¹
 - Frequency, severity, interference w/ activities
- Content validity established during three interview rounds with semi-structured interview using structured and open-ended probes (N=127)²
 - 63/80 symptom terms generated no cognitive difficulties; 17 modified and re-tested without further difficulties

¹Basch et al., (2014). Development of the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Journal of the National Cancer Institute*, 106(9). pii: dju244

²Hay et al. (2014). Cognitive interviewing of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to support content validity. *Quality of Life Research*, 23(1):257-269

PRO-CTCAE Validity and Reliability

- Results demonstrate favorable validity, reliability, and responsiveness of PRO-CTCAE in a large, heterogeneous sample of patients undergoing cancer treatment (n=940)¹
 - Most PRO-CTCAE items (119/124) reached a statistically significant ($p<0.05$) and meaningful effect size on one or more validity criteria
 - Majority of the items tested (n=27 items) exhibited acceptable test-retest reliability
 - All tested items (n=27 items) were sensitive to differences between groups

Mode Equivalence

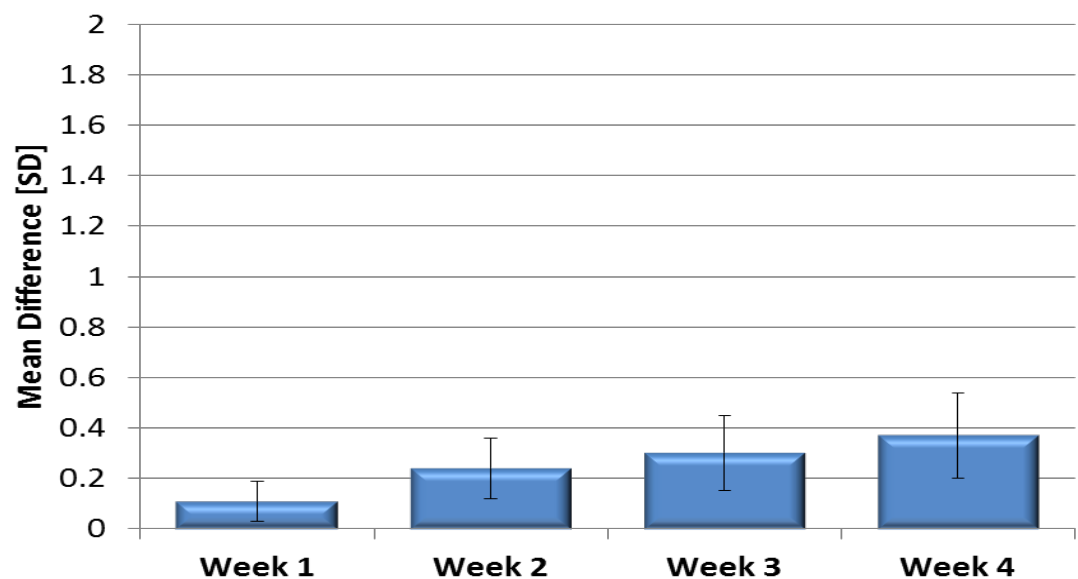
- N=112 patients completed 28 PRO-CTCAE items by each of the three modes of administration at a single clinic visit
- Average time to complete an item:
 - Web: 11.1 seconds (SD = ± 8.4)
 - Interactive Voice Response (IVRS): 16.3 seconds (SD = ± 6.3)
 - Paper: 10.3 seconds (SD = ± 5.8)

Between modes, item-level mean differences were very small, and the corresponding effect sizes were all less than 0.20

	Median ICC (Range)	Median (range) between-mode item-level mean difference
Web vs IVRS	0.78 (0.56 - 0.90)	-0.04 (-0.16 - 0.22)
Web vs paper	0.81 (0.61 - 0.96)	-0.02 (-0.11 - 0.14)
IVRS vs paper	0.78 (0.59 - 0.91)	0.02 (-0.07 - 0.19)

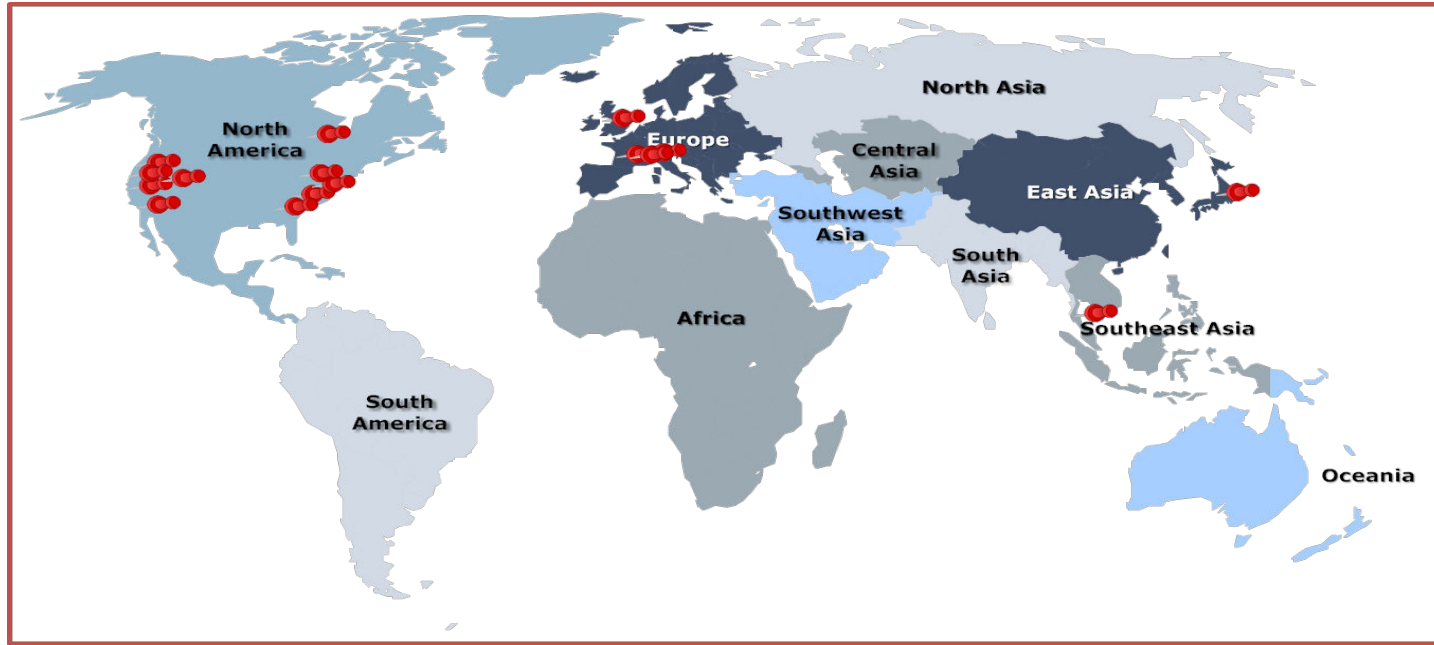
Comparison of Recall Periods

- N=110 patients completed 27 PRO-CTCAE items (14 symptomatic A/Es)
 - Comparison of 28 daily ratings to 1-, 2-, 3-, and 4-week recalled ratings
 - 1-week recall corresponds well to daily reporting. Differences between daily and longer recall periods widen with 2, 3, and 4 week recall



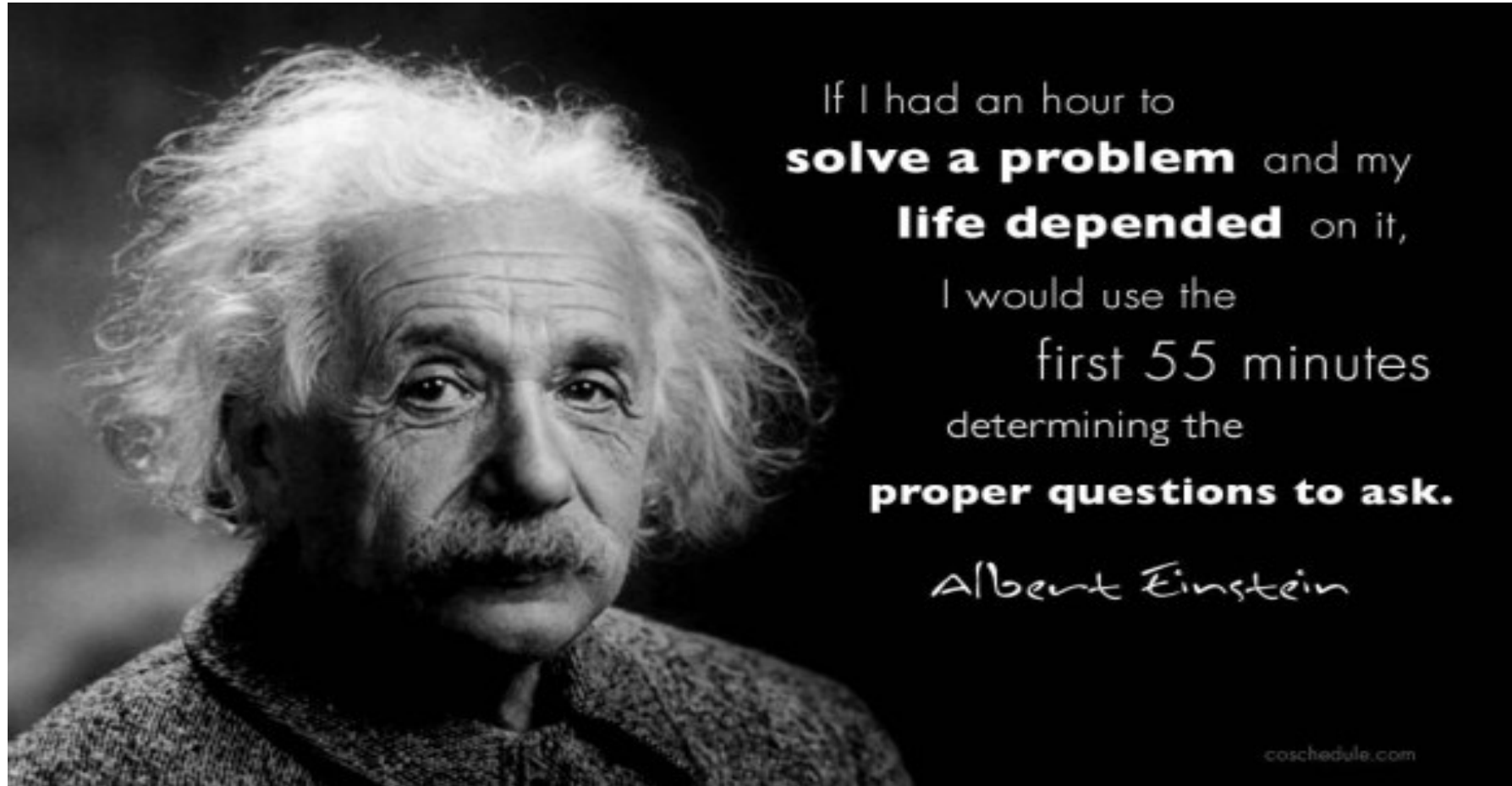
Recall Period	Effect Size of the Difference (compared to max. daily score within that period)
7 day	-0.2
14 day	-0.31
21 day	-0.39
Past month	-0.40

Early Adopters



- >100 early adopters in 12 countries are testing PRO-CTCAE in treatment trials and observational studies
- Collaborations with leading national and international organizations to promote implementation and testing in cancer clinical trials and observational studies
 - NCI National Clinical Trials Network (NCTN) and Early Therapeutics Clinical Trials Network (ETCTN)
 - US Food and Drug Administration
 - International: NHS in UK, Italian NCI, Japanese NCI, Danish Cancer Society, European Medicines Agency, Swedish Medical Products Agency

PRO-CTCAE in Cancer Clinical Research: Item Selection and Timing of Assessment



PRO-CTCAE in Cancer Clinical Research

- Item selection and timing of assessment are critical designs decisions to manage risk of bias and maximize interpretability and utility of results
 - Study aims and hypotheses
 - Apply what is known about side effects profile to select items and informative timepoints
 - Trial phase (early phase vs. randomized), study design (e.g. observational cohort, case-control)
 - Thoughtfully manage patient and investigator burden
- Decisions about item selection and timing must consider
 - Ascertainment bias
 - A systematic distortion in measuring the *true frequency* of a phenomenon due to the way in which the data are collected
 - What you ask about and when affect prevalence estimates
 - Sampling bias
 - Introduced when *some members of the intended population are less likely to be included* in the sample than others
 - Low literacy, language, missing data not at random from those patients with the greatest toxicity or who have early disease progression, small samples
 - Recall period: trade-off between longer recall and measurement error
 - Variable conditions of administration (in clinic, between visits)
 - Anticipated patterns of drop-out (e.g.. short duration of therapy anticipated with early phase trials)
 - Data analytic approach



PRO Assessment of Symptomatic Adverse Events

Paul G. Kluetz, M.D.

Office of Hematology and Oncology Products
US Food and Drug Administration

FDA's Use of PRO Data

- While all PRO data will be reviewed as supportive data, we focus on proximal concepts closest to the effect of the therapy on the disease (efficacy) and the patient (safety)
- For Labeling purposes, FDA requires well-defined and reliable assessments that can be accurately interpreted
 - Most PRO results in oncology labeling have been Symptom and Function measures

What Trial Objectives can PRO Measures Address?

- **Efficacy:** Does the drug provide superior improvement in disease related symptoms or functional deficits?
 - Pain, Total Symptom Score, Performance related outcomes
 - Supports a claim of treatment benefit
 - Substantial evidence from formal statistical analysis (statistical superiority)
- **Safety/Tolerability:** Describe the patient's experience while exposed to anti-cancer therapy?
 - Patient-reported symptomatic toxicities
 - If not claiming a treatment benefit of comparative safety, may use descriptive statistics as is done with CTCAE data

Challenges in Assessing **Efficacy** with PRO Measures in Cancer Clinical Trials

- Many patients enrolled on cancer trials are asymptomatic with good performance status
 - Time to deterioration endpoints typically utilized
 - Enriching for symptomatic patients to measure symptom improvement/palliation should also be considered
- Trials supporting regulatory approval more often single arm or open-label in contemporary drug development
 - Degree of open-label bias is not well understood
 - Research is needed to characterize the magnitude of potential overestimation of treatment benefit

Safety / Tolerability = **PRO Measurement Opportunity**

- Symptomatic adverse events are proximal to the therapy's effect on the patient
- Symptoms are best assessed by patients
- Safety and Tolerability- important in all phases of development
- PRO results may offer different but complementary data to current clinician reported safety data
- PRO measures can be systematically and longitudinally obtained including a baseline measure

Existing PRO Tools: Assessment of Symptomatic AEs

- Health-Related Quality of Life Instruments and Disease Specific Modules can assess some common symptomatic adverse events
 - Strengths: Translations, accumulated data, established measurement characteristics in some cases
- Key limitation is lack of flexibility
 - Same questions regardless of therapies under study
 - Can miss important toxicities or assess toxicities not expected to occur with a particular therapy
 - Often inadequate assessment frequency
 - Risk of a biased assessment if comparing drugs of different classes

Safety in a Changing Therapeutic Context

Prior Drug Development Era:

- Mechanism: Cytotoxic Chemotherapy
- Intermittent Intravenous Administration
- Shorter Duration of Treatment
- Adverse events typically Neuropathy, Mucositis, Bone Marrow Suppression, Fatigue, Nausea/vomiting, Diarrhea, Hair Loss, Taste Changes



Current Drug Development Era:

- Mechanism: Diverse, including Cytotoxic, Immune, Antibodies, Small Molecule targeting Various Pathways.
- Continuous Daily Oral Administration becoming more common
- More Prolonged Duration of Treatment
- **Adverse events can differ depending on mechanism and target.**

Can lead to cumulative low grade but bothersome symptomatic toxicities

There is a need for systematic PRO assessment of symptomatic adverse events with a standard yet flexible PRO instrument

Flexible Approach Would be Desirable

- An item library where questions and assessment frequency can be tailored to the toxicity of the agents under study is attractive for cancer drug development
- The National Cancer Institute Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a promising tool for this purpose
- Could provide well-defined descriptive PRO data to complement existing clinician reported safety data
- Significant work remains, but early adoption of PRO-CTCAE in commercial trials is underway

Summary

- Safety and tolerability: important trial objective across drug development
- Symptomatic adverse events can be bothersome and symptoms are best assessed by patients
- Existing PRO tools have some important limitations when assessing symptomatic adverse events
- PRO-CTCAE is a promising tool that can provide needed flexibility and involve patients in the assessment of safety and tolerability
- **An unbiased selection of the most important items to assess is critical**

PRO-CTCAE™:

STUDY DESIGN CONSIDERATIONS FOR PATIENT- REPORTED SYMPTOMATIC ADVERSE EVENTS

Lori Minasian, MD

Deputy Director, Division of Cancer Prevention, NCI

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

Health Related Quality of Life (HRQOL)

- Intended to capture overall effects of the cancer and its treatment upon the patient.
- Validated tools have specific questions
 - Questions do not vary over the course of the trial
 - All the questions to be answered at designated intervals
 - Questions may ask about work life, social impact or other topics not immediately related to the treatment itself.
- Results analyzed at the trial completion
- Comparison of HRQOL between 2 arms

HRQOL \neq Toxicity Reporting

- PRO-CTCAE is designed to bridge the gap
- PRO-CTCAE needs a different approach from HRQOL to item selection and assessment timing
- BUT, PRO-CTCAE is ONLY for descriptive reporting at this time
 - Not ready for clinical and protocol specific decision-making based upon individual PRO-CTCAE scores

How to Use PRO-CTCAE

- PRO-CTCAE intended to be complementary to CTCAE
 - Timeframes for reporting by patients & clinicians are comparable
- 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
 - Assessment times need to be balanced with data quality
- Translations
 - English and Spanish available now
 - *German, Japanese, Danish, coming soon*

PRO-CTCAE vs. CTCAE

- 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 \neq 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

PRO-CTCAE Item Selection

- PRO-CTCAE items selected based upon earlier data for Adverse Events
 - As with CTCAE items, identify those items which need to be monitored for safety and tolerability based upon previous clinical or pre-clinical data.
 - AE items from early clinical data
 - Mechanism based or drug class effects
 - Choose limited number of symptomatic adverse events to prospectively monitor
 - 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

- Early (non-randomized) phase trials
 - Limited number of cycles given to patients with different diseases
 - Start with a provisional list of items
 - Incorporate additional items as study develops
 - Baseline assessment
 - Unexpected reports may due to toxicity, disease progression or previous treatment
 - Clinical information at off-study is essential for attribution of event

PRO-CTCAE Item Selection

- Randomized trials
 - Better defined cohort of patients
 - Identify agent/regimen specific symptomatic toxicities associated with each arm
 - Include same items in all arms irrespective of expectation in order 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

Summary

- PRO-CTCAE is ONLY for descriptive reporting
- CTCAE Grade \neq 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 and aims
 - Timeframes should be consistent with clinician grading

Practical Considerations for Implementation of PRO-CTCAE in Clinical Trials

Ethan Basch, MD and Amylou Dueck, PhD

April, 2016

- Item selection
 - What approaches can be used to pick PRO-CTCAE items from the broader PRO-CTCAE item library for use in a given trial?
- Frequency
 - How often should items be administered?
- How can PRO response rates be optimized?
 - Reminders and backup data collection
- How can PRO-CTCAE results be tabulated and reported?
- *Will use examples from multicenter cooperative group trials supported by NCI contract HHSN261201000063C*

78 Symptomatic Adverse Events in PRO-CTCAE Item Library
(Represented by 124 Items)

78 Symptomatic Adverse Events in PRO-CTCAE Item Library (Represented by 124 Items)

Cross-Cutting (“Core”)

- Anorexia (appetite loss)
- Constipation
- Dyspnea
- Diarrhea
- Fatigue
- Nausea
- Pain
- Sensory neuropathy
- Sleep disturbance
- Vomiting

- *Prevalent across advanced cancers, based on systematic review (Support Care Cancer, 2013: PMID 23314601)*
- *Recommended by NCI clinical trials planning meeting consensus (JNCI, 2014: PMID 25006191)*
- *These 10 AEs are represented by 17 PRO-CTCAE items*

78 Symptomatic Adverse Events in PRO-CTCAE Item Library (Represented by 124 Items)

Cross-Cutting (“Core”)

- Anorexia (appetite loss)
- Constipation
- Dyspnea
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- Fatigue
- Nausea
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- Sensory neuropathy
- Sleep disturbance
- Vomiting

Identified in Prior Clinical Studies

- XXX
- XXX
- XXX
- XXX

- *Reported/published AEs for products in all arms of planned trial (Clin Ther, 2016: PMID 27045992)*
- *Ideally based on interviews/surveys in study population prior to pivotal trial, and/or structured literature review*

78 Symptomatic Adverse Events in PRO-CTCAE Item Library (Represented by 124 Items)

<u>Cross-Cutting (“Core”)</u>			
<ul style="list-style-type: none">• Anorexia (appetite loss)• Constipation• Dyspnea• Diarrhea• Fatigue• Nausea• Pain• Sensory neuropathy• Sleep disturbance• Vomiting			
	<u>Identified in Prior Clinical Studies</u>		<i>• Based on safety profile of all study drugs and/or other in-class therapeutics</i>
	<ul style="list-style-type: none">• XXX• XXX• XXX• XXX		
	<u>Mechanism of Action/Preclinical</u>		
	<ul style="list-style-type: none">• XXX• XXX		

- Phase 3 trial comparing drug derived from natural product with anti-microtubule properties vs. standard of care (taxane) as first- or second-line therapy in a metastatic solid tumor type
- Clinical investigative team worked with PRO expert to select PRO-CTCAE items for the trial

Example from Ongoing Trial Using PRO-CTCAE



PRO-CTCAE Item Library

Cross-Cutting (“Core”)

- Anorexia (appetite loss)
- Constipation
- Dyspnea
- Diarrhea
- Fatigue
- Nausea
- Pain
- Sensory neuropathy
- Sleep disturbance
- Vomiting

• *Total: 12 AEs, represented by 20 PRO-CTCAE items*

Additional Based on Prior Studies

- Study Drug
- Hair loss

- Control Arm
Drug
- Mucositis

Mechanism of Action/Preclinical

- No additional

Healthcare Delivery Research Program

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Measurement of Outcomes

CanCORS

HealthMeasures: A Person-Centered
Assessment Resource (PCAR)

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

What Is PRO-CTCAE?

How Do I Use PRO-CTCAE?

Overview

Instrument

Permission to Use

Build a Custom Form

Development Team

PRO-CTCAE Scientific Leadership at NCI

Resources

Frequently Asked Questions



[Data Resources and Research Initiatives](#)

[Measurement of Outcomes](#)

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

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.

- [What Is PRO-CTCAE?](#)
- [How Do I Use PRO-CTCAE?](#)
- [Overview](#)
- [Instrument](#)
- [Permission to Use](#)
- [Build a Custom Form](#)
- [Development Team](#)
- [PRO-CTCAE Scientific Leadership at NCI](#)
- [Resources](#)
- [Frequently Asked Questions](#)

How Often Should PRO-CTCAE Be Collected?

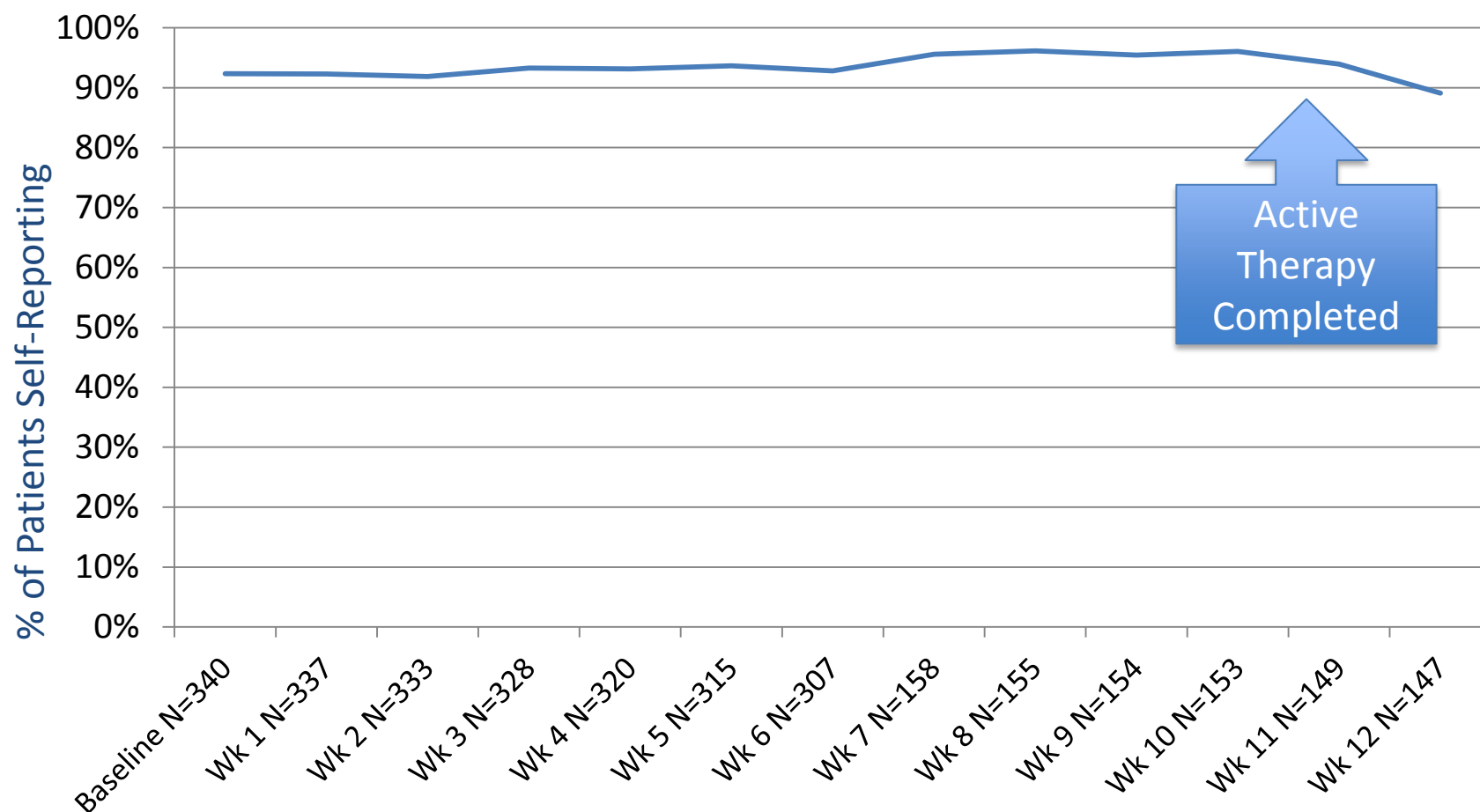


- During active treatment
 - Include baseline assessment
 - Ideally weekly, through electronic data collection remotely
- During post-treatment follow-up
 - Less frequent, e.g., every 3 or 6 months, depending on population/context
- Considerations:
 - If in-clinic data collection is unavoidable during active treatment, can space out to every 2-, 3-, or 4-week reporting to match study visit frequency
 - In such cases, the recall period of the PRO-CTCAE items should be adjusted to match the questionnaire administration frequency; it can be adjusted up to 4-weeks, but testing shows some loss of information
 - Frequency should be the same in all study arms

- Without central monitoring and backup data collection, PRO-CTCAE self-report adherence is 80-85% at any given time point, whether in-clinic or between visits
- When central monitoring and backup human phone calls are added, adherence rises to 90-95%
- Adherence rates are durable over time during active treatment (i.e., little attrition)
- Rates are lower during post-treatment follow-up

Example from Actual Trial: Compliance over Time

Weekly reporting from home via Web or IVRS (patient choice), with central monitoring and backup human telephone calls



Approaches to Reporting Results

- Can report like AEs in general
 - Maximum grade post-baseline at the patient level, expressed as proportions

NCI-CTC Grade 3–4 Adverse Events in Study 1
(Occurring at Higher Incidence [$\geq 2\%$] Avastin vs. Control)

	Arm 1 IFL + Placebo (n = 396)	Arm 2 IFL + Avastin (n = 392)
NCI-CTC Grade 3-4 Events	74%	87%
<u>Body as a Whole</u>		
Asthenia	7%	10%
Abdominal Pain	5%	8%
Pain	5%	8%
<u>Cardiovascular</u>		
Hypertension	2%	12%
Deep Vein Thrombosis	5%	9%
Intra-Abdominal Thrombosis	1%	3%
Syncope	1%	3%
<u>Digestive</u>		
Diarrhea	25%	34%
Constipation	2%	4%
<u>Hemic/Lymphatic</u>		
Leukopenia	31%	37%
Neutropenia ^a	14%	21%

Example from Clinical Trial: CTCAE & PRO-CTCAE Together

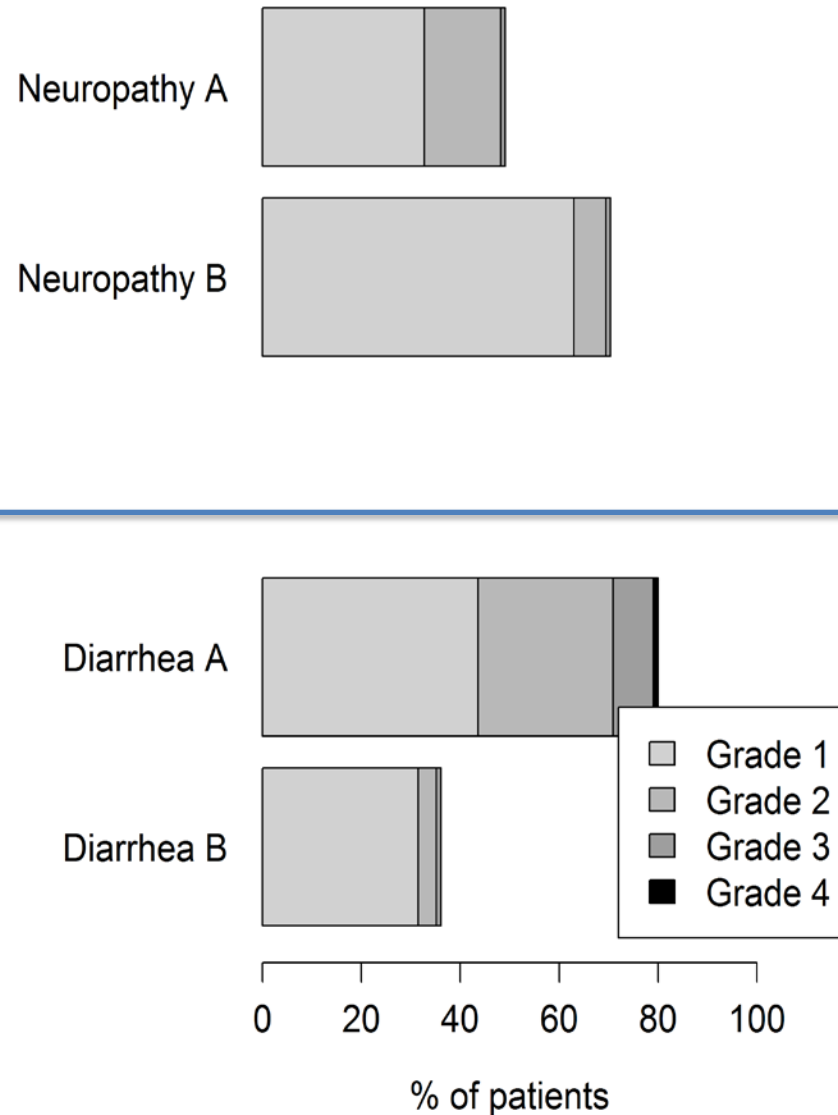
Adverse Event		<u>Any Level (>0)</u>		<u>High-Level*</u>		<i>p</i> [†]
		Arm A	Arm B	Arm A	Arm B	
Anorexia	CTCAE	34%	35%	3%	--	0.89
	PRO-CTCAE: <i>Severity</i>	66%	84%	9%	17%	0.003
	<i>Interference</i>	43%	71%	9%	14%	<0.001
Anxiety	CTCAE	30%	36%	--	--	0.39
	PRO-CTCAE: <i>Frequency</i>	58%	71%	8%	12%	0.048
	<i>Severity</i>	56%	69%	5%	7%	0.07
	<i>Interference</i>	39%	50%	5%	8%	0.13
Constipation	CTCAE	36%	43%	2%	--	0.41
	PRO-CTCAE: <i>Severity</i>	58%	83%	16%	21%	<0.001
Depression	CTCAE	17%	12%	1%	--	0.34
	PRO-CTCAE: <i>Frequency</i>	29%	48%	3%	8%	0.005
	<i>Severity</i>	26%	46%	2%	7%	0.003
	<i>Interference</i>	22%	41%	2%	10%	0.003
Diarrhea	CTCAE	80%	36%	9%	1%	<0.001
	PRO-CTCAE: <i>Frequency</i>	95%	88%	62%	22%	0.05
Dysphagia	CTCAE	5%	17%	1%	--	0.004
	PRO-CTCAE: <i>Severity</i>	14%	64%	--	7%	<0.001
Dyspnea	CTCAE	15%	23%	1%	--	0.17
	PRO-CTCAE: <i>Severity</i>	35%	57%	1%	5%	0.001
	<i>Interference</i>	28%	49%	3%	9%	0.002

* High-level for CTCAE: ≥Gr3. High-level for PRO-CTCAE: score level 3 or 4 (*severe or very severe; frequently or almost constantly; quite a bit or very much*).

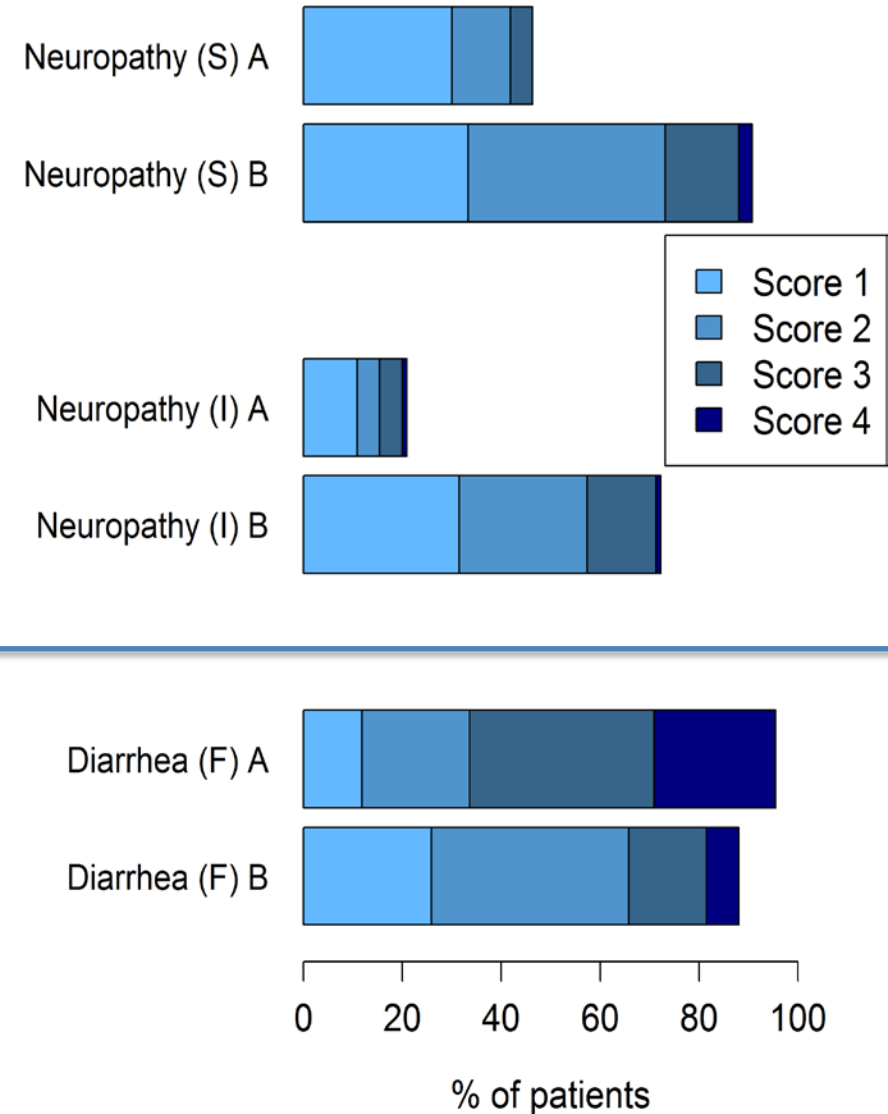
†Based on Fisher's exact test comparing rate of Grade or Score >0 between arms

Neuropathy & Diarrhea: CTCAE and PRO-CTCAE

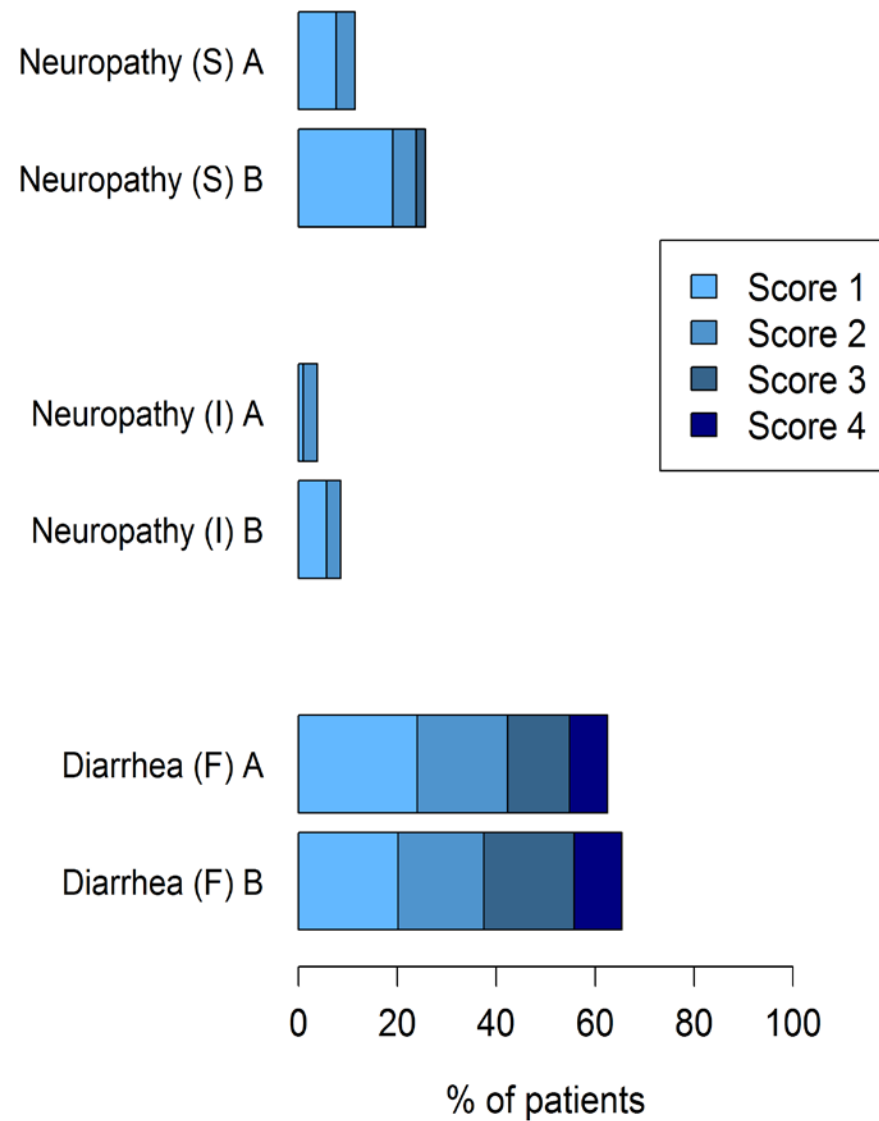
CTCAE Maximum Grade Post-baseline



PRO-CTCAE Maximum Score Post-baseline



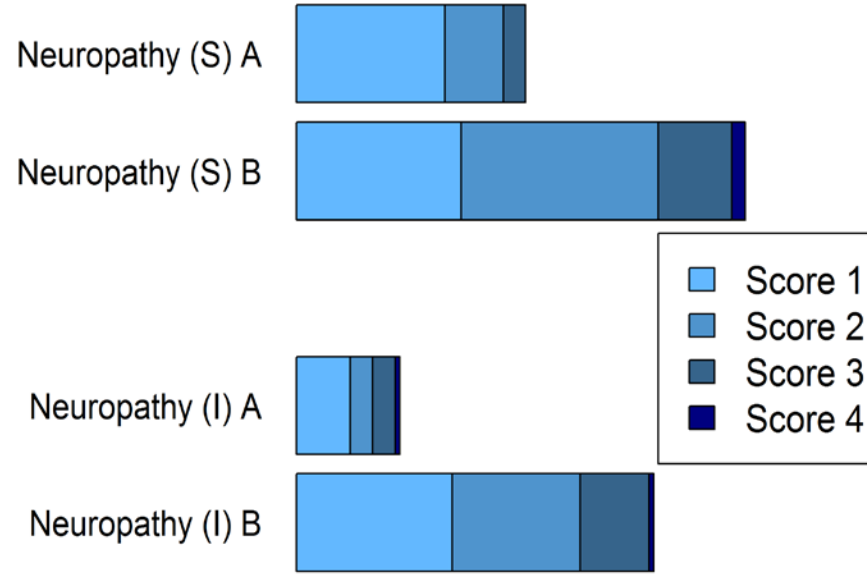
PRO-CTCAE Baseline Scores



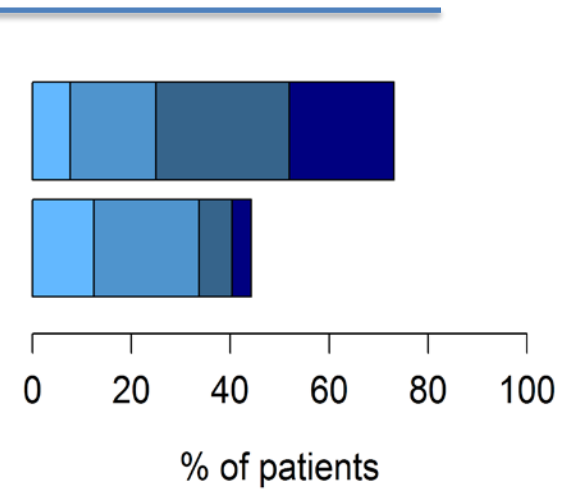
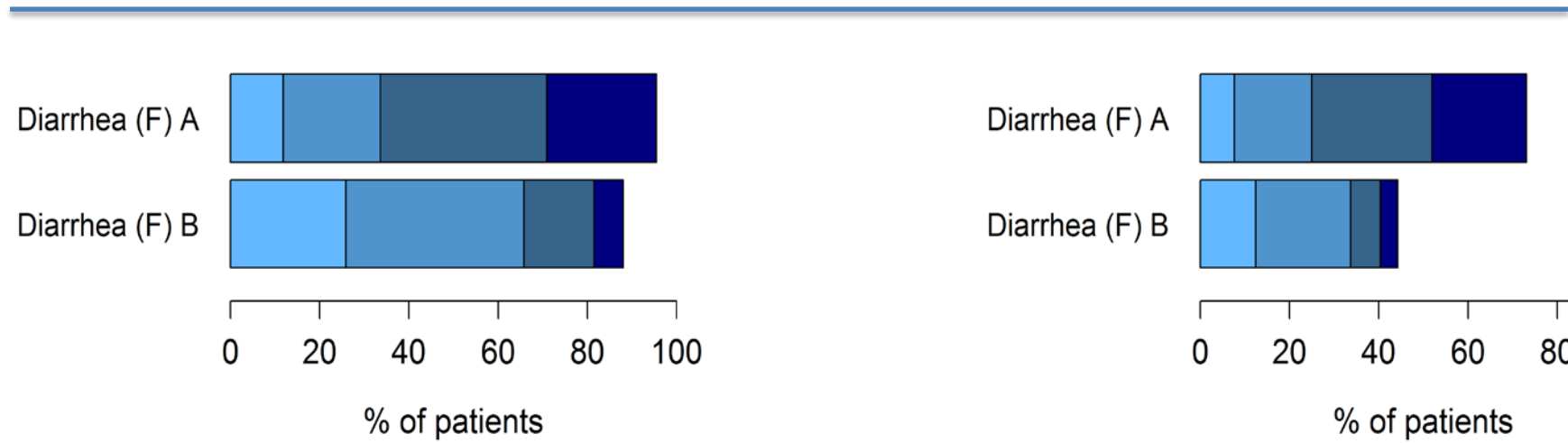
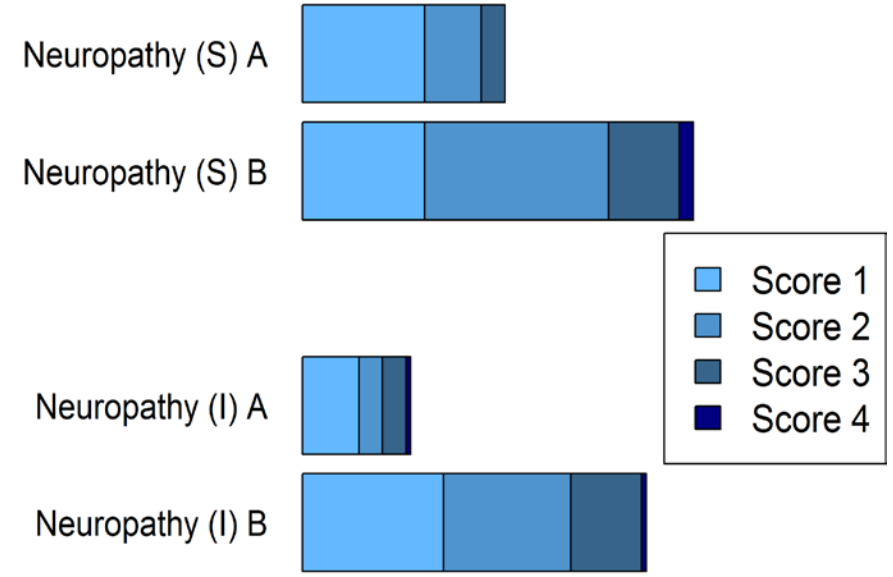
PRO-CTCAE with/without Subtraction of Baseline Scores

Treatment Arm A vs B

PRO-CTCAE Maximum Score Post-baseline



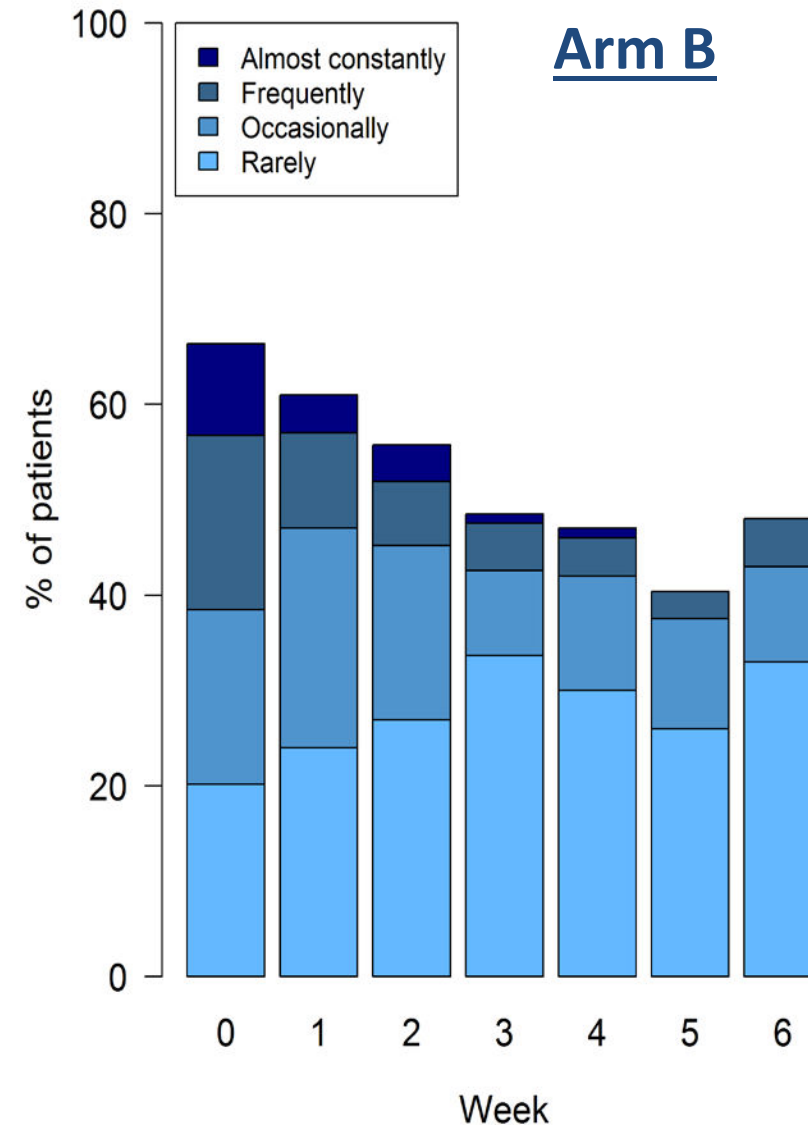
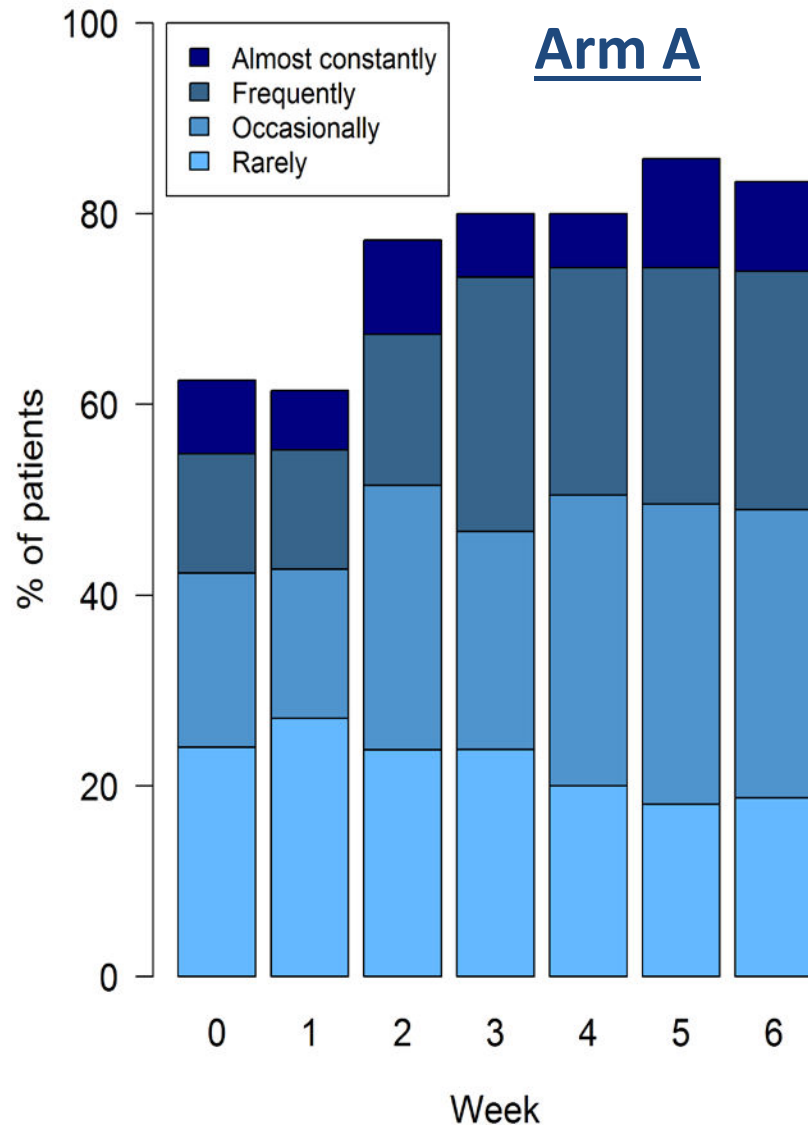
Same Using Baseline "Subtraction"



- Can report distributions of PRO-CTCAE scores at successive time points for a more granular understanding
 - Assists in understanding dynamics of AEs over time
 - Assists understanding baseline symptoms not attributable to study drug

PRO-CTCAE Distributions at Successive Time Points

Example: Diarrhea between Arms



- Use of the PRO-CTCAE in clinical trials calls on approaches both from standard adverse event assessment, and from PRO questionnaire administration
- Consensus around best practices is quickly emerging
- Optimal approaches will increasingly be refined as the PRO-CTCAE comes into more common use, as with any measure

Experiences of PRO-CTCAE in oncology clinical trials - A Sponsor early perspective and first impressions

Katarina Halling, MSc

PRO Global Head AstraZeneca and Industry
Co-Director, PRO Consortium

Oncology PRO Directors:

- Arnold Degboe
- Anna Rydén
- Katja Rüdell

- Benefit – risk assessment from patients' perspective is critical in oncology
- Evolving regulatory oncology landscape
 - symptoms
 - tolerability
 - different aspects of HRQL, e.g. physical function
- The existing PRO instruments in oncology include side effects
 - not always the most relevant ones
 - often analysed in clusters with symptoms and impact
 - lack information on impact and bothersomeness
- No existing PRO instrument fit for purpose to assess tolerability
- AstraZeneca entered collaboration with NCI in 2014

Scope of this presentation

- To share the initial learnings and how these are shaping how we plan and execute oncology clinical trials moving forward

Number of studies where we included the PRO-CTCAE



Cancer type	Phase (1,2,3)	Approx. number of patients	Status (planned, ongoing, completed)
Non-Small Cell Lung Cancer	2, 3	950*	ongoing
Non-Small Cell Lung Cancer	3	675*	ongoing
Small Cell Lung Cancer	3	795*	planned
Bladder	3	525*	ongoing
Pancreas	2	375*	planned
Head and Neck Cancer	3	720*	ongoing
Head and Neck Cancer	3	628*	ongoing

- The opportunity of this data to feed into treatment decisions recognised
- Help set the expectations for patients
- Useful in management of toxicity symptoms
- Understanding low-grade toxicities and the impact to patients
- Few projects have been resistant
- In general, easier to implement than we expected

Principles applied for including the PRO-CTCAE in clinical trials



- Agreement with NCI
- **Selection of items**
- **Assessment schedule**
- Endpoint hierarchy
- Communication of available translations
- Mode of administration
- Analytical approach

- Agreement per study
- Overview of study design
- Discuss and agree on items selected
- Discuss translations needed
- NCI provides only items selected for specific study

- Gather AE information for each treatment in the trial – active & comparator (from safety reports, publications etc)
- Summarize AE information to guide discussions and decision-making
- Ensure capture of toxicities appearing early and later during treatment
- Input from key stakeholders: medical science director, study physician, medical scientist, safety physician etc
- In general, avoid overlap of items in other PROs
- Be focused in the selection of items, less is more

- Wish to keep the number of symptoms low – “pick a hand-full”
- In phase 1, we know little about the side effect profile
- In oncology phases overlap – phase 3 often start before read-out of phase 1
- Beneficial if we could lock down the toxicity symptoms to focus analyses on when phase 3 SAP is finalised in discussions with FDA

- The PRO-CTCAE items are included as exploratory endpoint
- The CTCAE is still the formal reporting for AEs

Assessment schedule

device)				
EORTC QLQ LC13 (by electronic device)		X^g	← weekly relative to first dose →	← every 3 weeks relative to first dose →
PRO-CTCAE (by electronic device) ^p		X^g	← weekly for first 18 weeks of treatment →	X^q

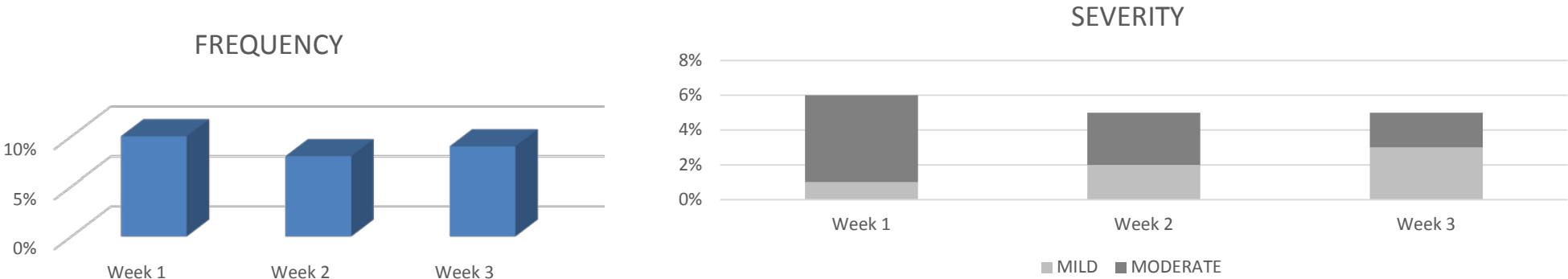
- Given the expected tolerability profile, weekly assessments during peak and then less frequent
- Consider the treatment cycles and when AEs might be expected

- ePRO – on the same device as the other PRO assessments
- Paper not recommended – no time stamp, difficult with skip patterns

Analytical approach

Side effect		Patient - BASELINE	TREATMENT
Nausea	Frequency	n (%)	
	Severity	MILD n (%) MODERATE n (%)	

- There is no established analytical approach at the moment, ongoing collaboration with NCI
- We have started with descriptive statistics and using graphs to facilitate interpretation
- There is ongoing work to establish analytics



Some initial reflections on results

- It may not be as bad as predicted
- Some side toxicity symptoms better tolerated IF the treatment has effect
- The pattern of different toxicity symptoms can clearly be described
- The information will help patients and physicians to make decisions and manage expectations

- Mixed reactions in study teams – overall positive with some initial skepticism
 - Some confusion about the aim and overlap with CTCAE
 - Payer/ HE and medical concerns
- Cross-functional collaboration
- The item selection approach has been helpful
- Assessment schedules (consider Early versus Late AEs)
- Limited availability of languages, demographic pre-selection
- Modes of administration (all ePRO or mixed)
- Scalability

Putting early results into context



- If indications in early development of unbearable toxicities to patients, it is better to know
- Development of drugs exceeding certain toxicity grades have historically been recommended by KOLs to be stopped

Moderator

- *Sandra A. Mitchell, PhD, CRNP* – Research Scientist and Program Director, Outcomes Research Branch, National Cancer Institute (NCI)

Presenters

- *Paul G. Kluetz, MD* – Associate Director of Clinical Science, OHOP, OND, CDER, FDA
- *Lori Minasian, MD, FACP* – Deputy Director, Division of Cancer Prevention, NCI
- *Ethan Basch, MD, MSc* – Director, Cancer Outcomes Research Program, University of North Carolina
- *Katarina Halling, MSc* – Global Head Patient Reported Outcomes, AstraZeneca and Industry Co-Director, PRO Consortium

Panelists

- *Selena R. Daniels, PharmD, MS* – Reviewer and Acting Team Lead, COA Staff, OND, CDER, FDA

Questions?