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PANEL TWO:
CAPTURING SYMPTOMATIC ADVERSE EVENTS FROM THE PATIENTS' PERSPECTIVE

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PATTY SPEARS

CANCER INFORMATION AND SUPPORT NETWORK

Patient Reported Outcomes

- "APROis any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."

Why is it important to hear directly from the patient?

Aid in Decision Making: **Benefits vs. Harms**

- Once a drug is approved, patients are faced with treatment decisions.
- Decision making on the part of the physician and patient is important and very complex.
- What is necessary to make that decision?

BENEFITS

What **benefits** are being measured and are they important to patient?

HARMS

What **harms** are being measured and are they important to patients?

Why PROs?

PROs Consider:

Not only **WHAT IS THE MATTER** with the patient

But also **WHAT MATTERS** to the patient

~~*Sandra Finestone*

Assessing harms and benefits is very subjective and needs to be done consistently and reliably to actually predict harms and benefits that ARE IMPORTANT to patients.

The Clinical Trial Landscape is Changing

- **Patients** are more involved in research, in clinical trials and in their own health care.
- **Patients** want to have a voice.
- **Patients** need the information from other patients on trials to make **Patient Informed Decisions** about their treatment.
- **The process to approve drugs is changing** – accelerated approval, breakthrough designations.
- **Precision Medicine Initiative** – it's changing the way we do trials.

What Changes are needed?

Now		Future
• Instrument validation	→	• Item (question) validation
• Combination of multiple instruments	→	• Combination of specific items
• Global HR-QOL	→	• Targeted measurements
• Used in phase 3 trials	→	• Use in early phase trials (1,2 and 3)
• Analyzed separate from efficacy and published at different times	→	• Analyzed along with efficacy and published together
• Information is not shared with patients	→	• Information is shared with public and patients

How do you effectively collect PRO data in trials?

- **Start Early** - collecting PRO data in early trials (Phase I and II) to better inform the collection of PROs in larger later trials (Phase III)
- **Develop targeted (precision) PROs for ALL trials**
  - Asks patients to report what matters to them
  - Make PROs acceptable to patients to complete
  - Make PROs an important part of the trial with well defined purpose and use
  - Make the PRO endpoints meaningful to patients
  - Make the PRO information available to patients

ASKING:
the right question - at the right time - in the right way

Why PRO-CTCAE?

- **Treatment drugs are changing**
  - Biologics have different side effects than cytotoxic agents
- **Treatment administration is changing**
  - No longer one injection every 1-3 weeks for 4-8 cycles, now oral and daily for a long period of time
- **Tolerability is not fully addressed by current assessments.**
  - Only high toxicity at predetermined times is reported and does not take into effect moderate toxicity over a long period of time (long treatments)
  - One time high toxicities may have complementary treatments, whereas long term and late toxicities may not
  - Clinic visits miss the interval between visits
  - Subjective measurements are usually reported lower by physicians than the patients themselves

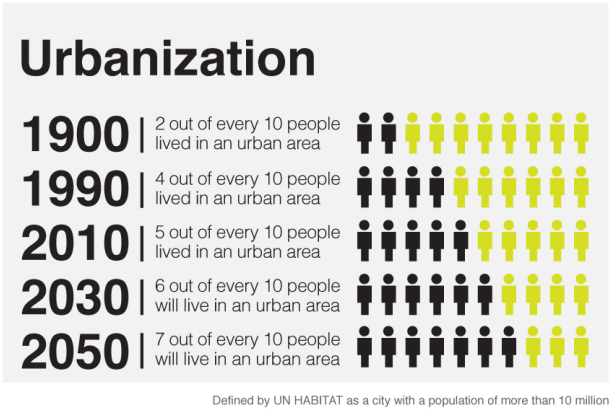
JNCI J Natl Cancer Inst (2015) 107(10):djv216

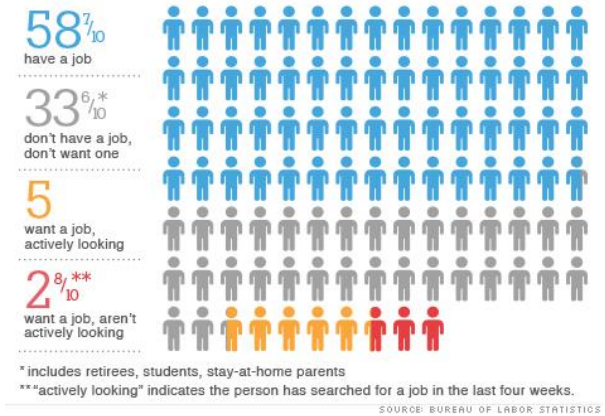
Solutions for
Safety and Tolerability Assessments

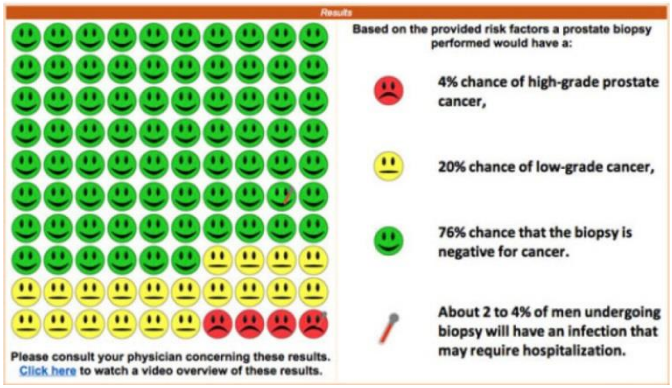
- **Use PRO-CTCAE** (or a subset specific to the agent being tested) to collect patient reported symptoms in all trials (even phase 1).
  - Consider the use of PROs during trial development focusing on outcome measures.
- **Develop standards** (Cella, 2015) to select the top 5 items (Qs) to ask that are relevant to what the patient will be experiencing.
- In phase 1 trials allow **a write in option** for unexpected toxicities. This information will inform future trials.
- **Make it short, simple, relevant and easy for patients.**
  - Electronic PRO
  - Symptoms as they happen
  - Ask 5-10 questions on regular intervals, not just at clinic visits
  - Collect data on frequent basis during treatments then less frequent during follow-up
- **By phase 2 and 3 there should be a well defined patient informed assessment that patients are able and willing to fill out.**

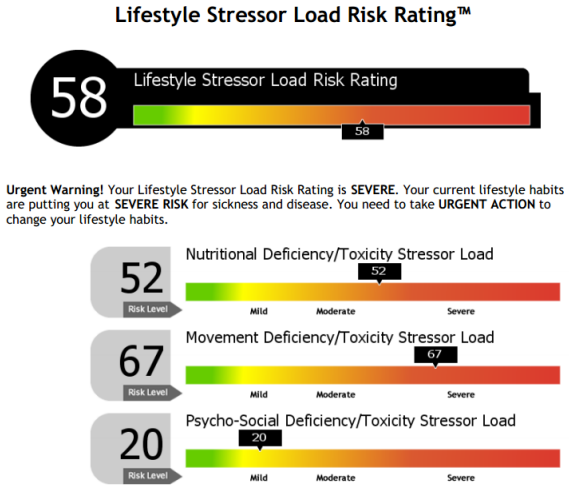
Things to keep in mind when developing PROs – from a patient/caregiver/advocate survey

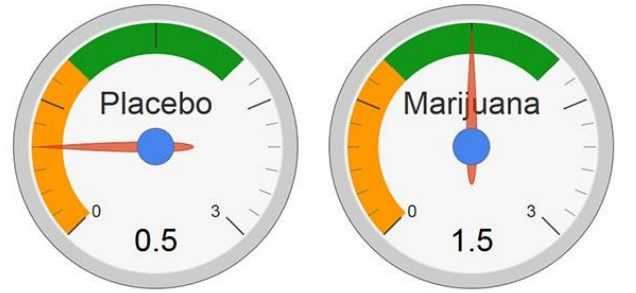
- Patients don't mind questionnaires
- The fewer questions asked, the more frequent you can ask them
- There is a limit to the number of questions or time it takes to answer questions
- Ask relevant/meaningful questions
- Don't ask the same question several times
- Let patients fill out the questionnaire at home (before or after visit)
- Use the information in a clinically meaningful way
- **Report results back to patients in an understandable way**



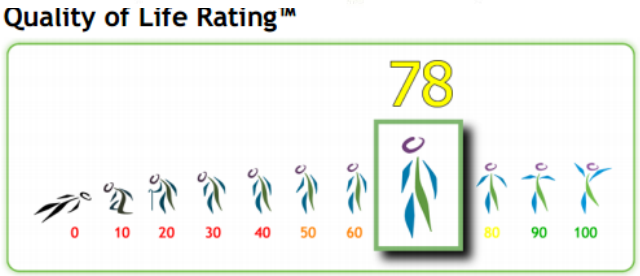


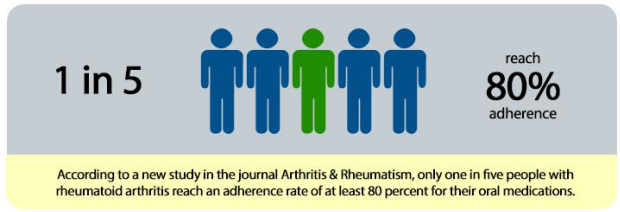


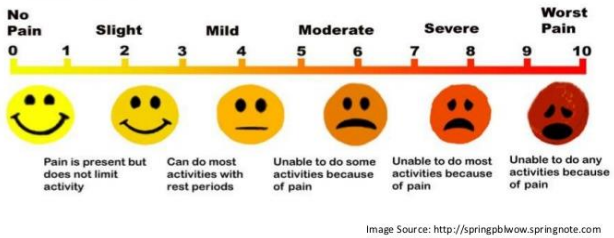




Guage graph depicting neuropathic pain relief with marijuana compared to placebo (data used from clinicaltrials.gov clinical trials)







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Overview of the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

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PRO-CTCAE Measurement System

1. Item Library	2. Software
• 78 symptomatic adverse events drawn from CTCAE • Items evaluate frequency, severity, interference, amount, presence of these symptoms	• Creates customized surveys; manages survey administration • Patient interface: choice of 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/





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

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 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

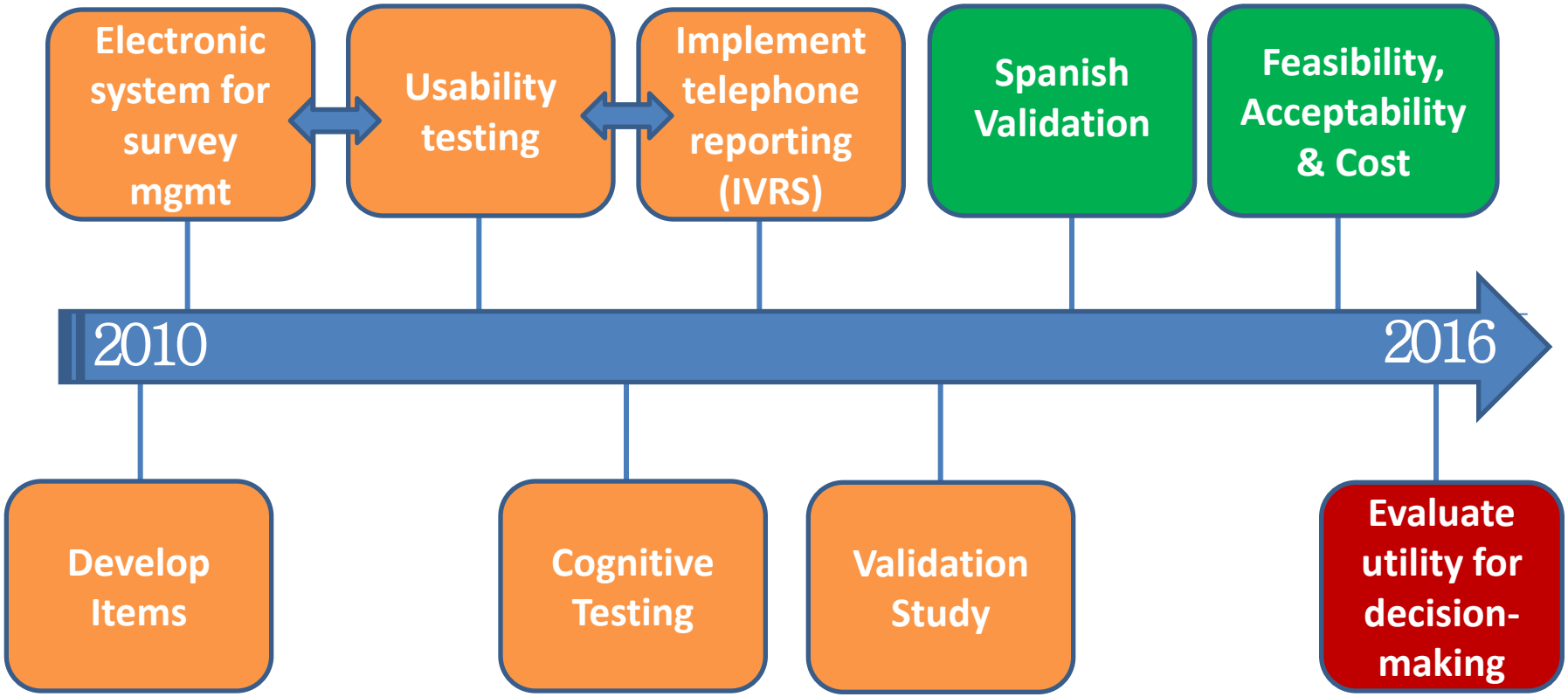
Sexual	
Achieve and maintain erection	S
Ejaculation	F
Decreased libido	S
Delayed orgasm	P
Unable to have orgasm	P
Pain w/sexual intercourse	S

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

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

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

- 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



Funded by NCI contracts HHSN261200800043C, HHSN261201000063C, and HHSN261200800001E

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 items[1]
  - Frequency, severity, interference w/ activities
- Three interview rounds with predetermined and open-ended probes (N=127)[2]
  - 63/80 symptom terms generated no cognitive difficulties; 17 modified and re-tested without further difficulties

[1]Basch 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

[2]Hay 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)
  - 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) exhibited responsiveness to change

Dueck AC, et al. (2015). Validity and reliability of the U.S. National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *JAMA Oncology*, Epub ahead of print.

Mode Equivalence

- N=112 patients completed 28 PRO-CTCAE items (14 symptomatic A/Es) 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

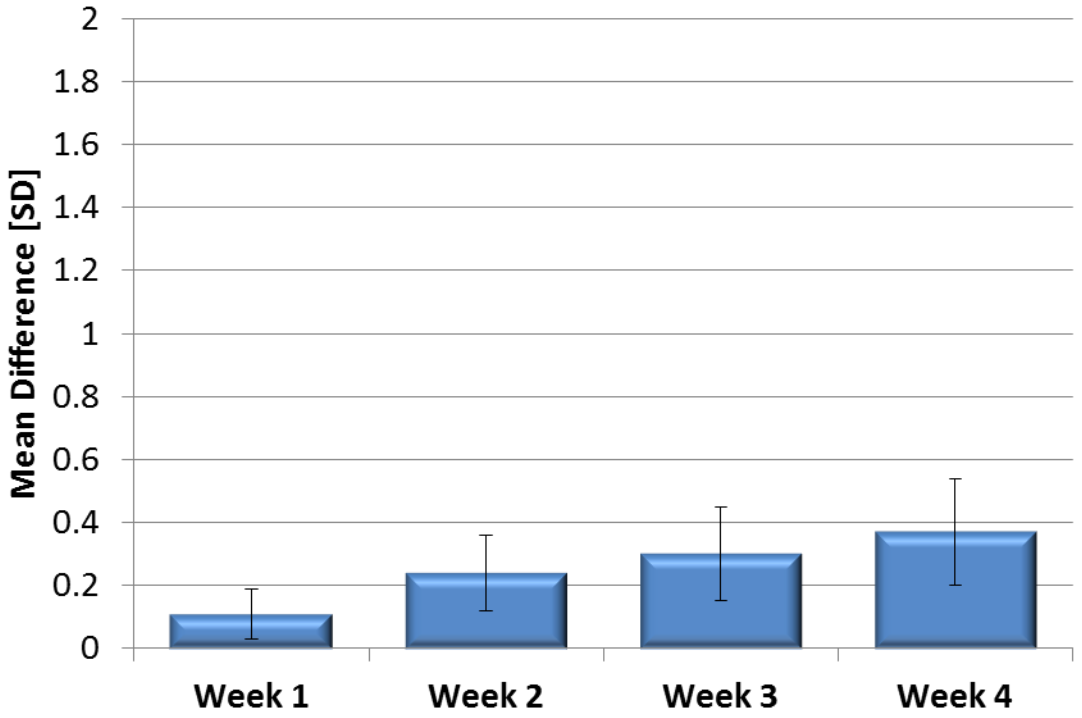
	Median ICC (Range)	Median (range) between-mode item-level mean difference
Web vs IVRS	0.78 (0.56 - 0.90)	-0.04 (-0.16 - 0.22)
Web vs paper	0.81 (0.61 - 0.96)	-0.02 (-0.11 - 0.14)
IVRS vs paper	0.78 (0.59 - 0.91)	0.02 (-0.07 - 0.19)

Bennett et al. Mode Equivalence and Acceptability of Tablet Computer-, Interactive Voice Response System-, and Paper-based Administration of the U.S. National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Under review *Health and Quality of Life Outcomes.*

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
  - Mean difference between the average daily score and recalled score

1-week recall corresponds well to daily reporting. Differences between daily and longer recall periods widen with 2, 3, and 4 week recall



Mendoza et al. Evaluation of different recall periods for the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). In preparation for *Clinical Trials*.

Future Directions

- Standard analytic validation for a patient-reported outcome measure completed
  - PRO-CTCAE demonstrates favorable validity and reliability
  - Recall period of past 7 days has lower measurement error compared to longer recall periods
  - Mode equivalence supported for paper, IVRS and tablet-based administration
- PRO-CTCAE item library can be used for descriptive purposes
  - English, Spanish[1], German[2] and Japanese language versions will be publicly available in first quarter of 2016

[1]Arnold et al. Linguistic validation of the Spanish translation of the US National Cancer Institute's Patient-Reported Outcomes version of the common Terminology Criteria for Adverse Events (PRO-CTCAE). Under review *Journal of Supportive Care in Cancer.*

[2]Kirsch et al. (2014). Linguistic and content validation of a German-language PRO-CTCAE-based patient-reported outcomes instrument to evaluate the symptom experience in survivors of allogeneic haematopoietic stem cell transplantation. *European Journal of Oncology Nursing*, 19(1):66-74.

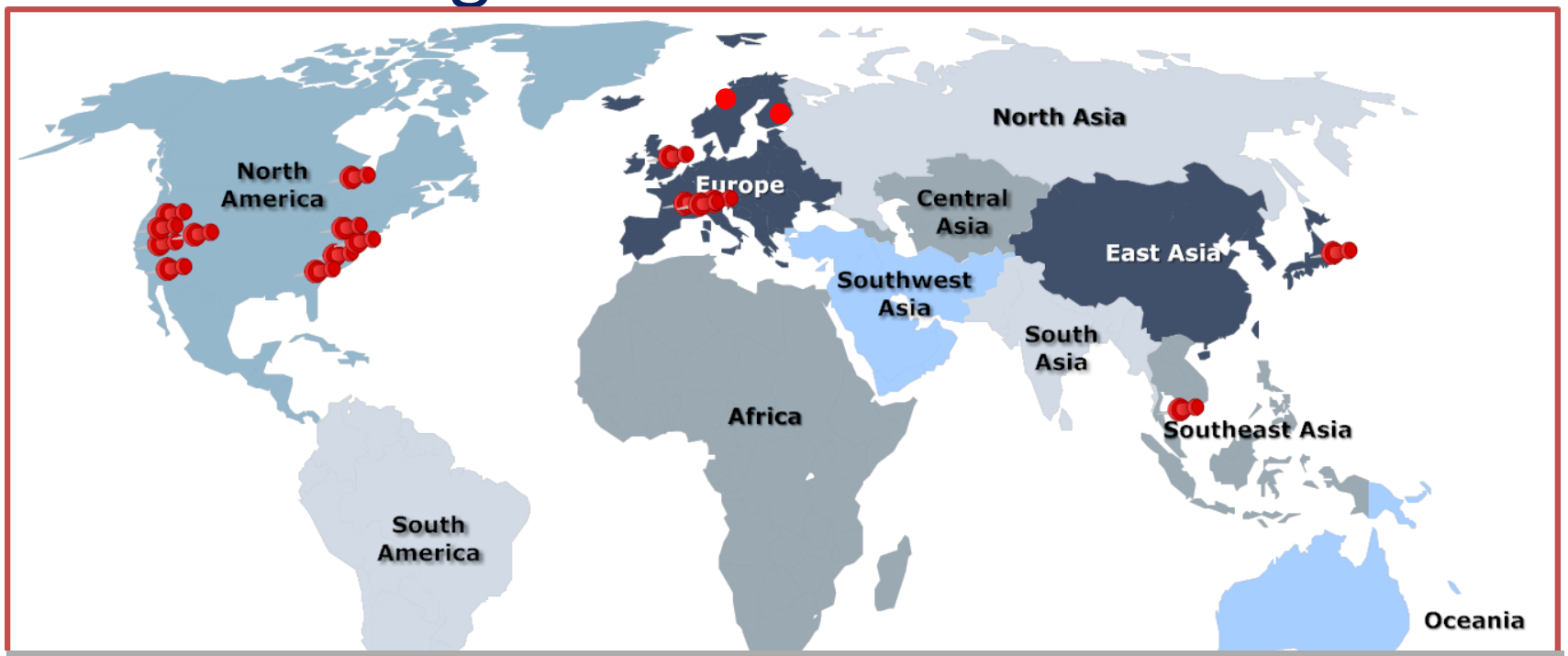
Future Directions

- Interpretation and clinical utility of PRO-CTCAE is still evolving
- Ongoing work
  - Responsiveness, minimal clinically important difference, cut-points, relationship among the attributes
  - Empirically-derived mapping PRO-CTCAE item scores into CTCAE grades
  - Evaluate different approaches to patient-investigator grade reconciliation and to analyzing and representing PRO-CTCAE data
  - Testing additional items to expand the library
  - Six languages in development/validation: Chinese, Korean, Italian, French, Swedish and Danish

Early Adopters

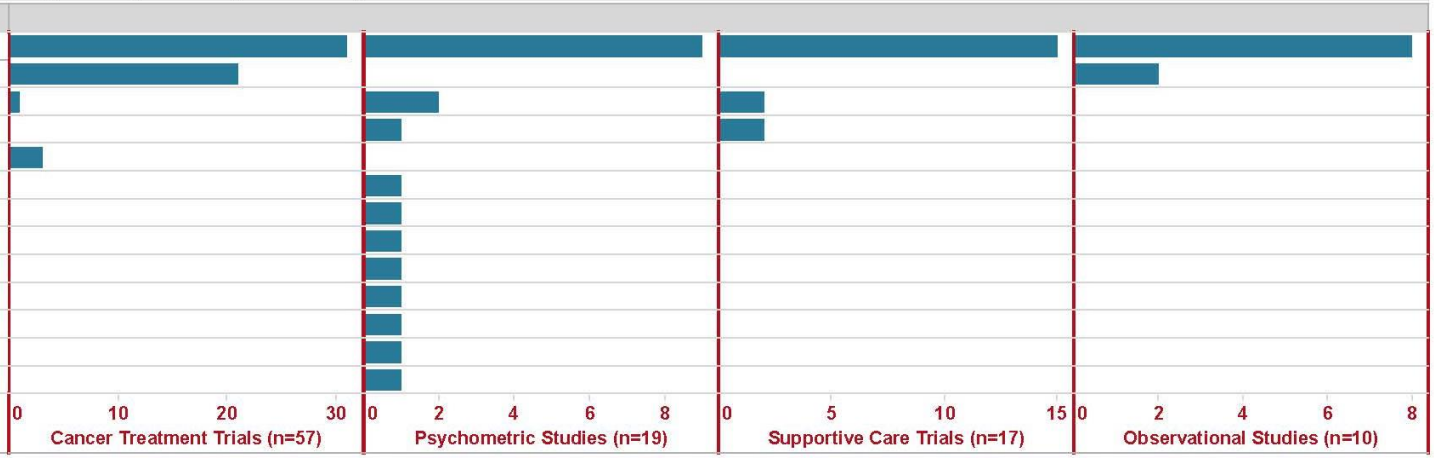
- >100 early adopters in academic settings and in industry-sponsored trials are testing PRO-CTCAE in treatment trials and observational studies
- Agreements established between NCI and investigators:
  - Ensure continuing integrity of the PRO-CTCAE tool while it is in active development
  - Stimulate efficient and coordinated testing of PRO-CTCAE
  - Allow for sharing of data and collaborative analysis
  - Generate evidence about best approaches for data interpretation and reporting in particular study contexts and specific patient populations
- 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

Collaboration Agreements Established with Investigators in 12 Countries



103 Early Adopters by Country, Setting and Study Aims/Design

Country	Setting
U.S.	Academia
	Industry
Germany	Academia
Canada	Academia
Japan	Academia
Singapore	Academia
Switzerland	Academia
United Kingdom	Academia
Denmark	Academia
France	Academia
Italy	Academia
Korea	Academia
Sweden	Academia



Study Design Considerations

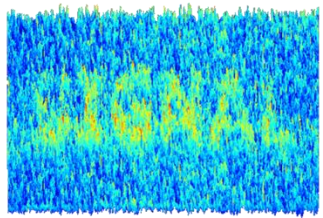
- Which toxicities to be measured?
  - Based on CTCAE derived from earlier phase studies of agent, knowledge of drug class, and anticipated on- and off-target effects; qualitative work in the population (if it exists); input from investigators
  - Thoughtful item selection to minimize patient burden
- At what timepoints of measurement?
  - Baseline, regular intervals during treatment, at treatment discontinuation
  - Toxicity surveillance using CTCAE and PRO-CTCAE elements should reflect comparable timeframes
- Planned analysis (descriptive, graphical, cumulative distributions, time-to-event analyses, mixed models…)?
- Inclusion of back-up data collection strategies and real-time monitoring of data quality to limit missing data
- Write-ins for unsolicited symptoms

When to Include PRO-CTCAE in a Trial?

- **Phase I:** Preliminary Profile of Symptomatic Side Effects
  - Develop measurement approaches (items, timing) for later phase studies
- **Phase II:** Describe Toxicity in Depth
  - Identify means to reduce symptomatic side effects
  - Profile chronic grade 2 toxicities
- **Phase III:** Assess Overall Benefit/Risk for Regimen
  - Evaluate tolerability
  - Assess strategies to reduce chronic grade 2 toxicities that may impair adherence
- **Phase IV:** Efficacy ⟶ Effectiveness
  - Optimizing tolerability
  - Tailoring regimens for those with co-morbidities, frailty

Scaling Towards Implementation

- PRO reporting of symptomatic adverse events yields data that is:
  - Actionable clinically in real time (trial eligibility, dose reductions etc)
  - Essential to determinations of benefit and harm at the study level
  - Crucial to regulators, sponsors, and the public
- PRO-CTCAE will ultimately be interpreted within a CTCAE reporting framework
  - Establish clinical validity across trial designs and populations so that integration is empirically-driven
- Ongoing efforts to embed PRO-CTCAE into trials
  - Understand how reporting could influence dose modifications
  - Efficiently incorporate into trial designs
  - Yield information that is interpretable and useful for decision-making (individual and trial-level)



NCI PRO-CTCAE Study Group

Supported through NCI contracts HHSN261200800043C and HHSN261201000063C

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Ram Chilukuri	Jessica Hess	Barbara Perez	Vish Viswanath
Steven Clauser	Lori Hudson	Richard Piekarz	Gordon Willis
Charles Cleeland	Norval Johnson	Liora Pollick	Jennifer Wind

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National Cancer Institute

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IMPLEMENTATION AND REPORTING OF PRO-CTCAE: A PRACTICAL EXAMPLE

ETHAN BASCH, MD
UNIVERSITY OF NORTH CAROLINA

“PROSPECT” Trial (Alliance N1048)

- Multicenter RCT in US and Canada
  - 127 sites, N=340 to date (ongoing)
- Patients with locally advanced rectal cancer assigned to receive chemoradiotherapy (current standard) vs. chemotherapy alone prior to surgical excision
  - Relative toxicities of high interest

PROSPECT Principal Investigator: Dr. Deborah Schrag (Dana-Farber Cancer Institute)

PRO-CTCAE in PROSPECT

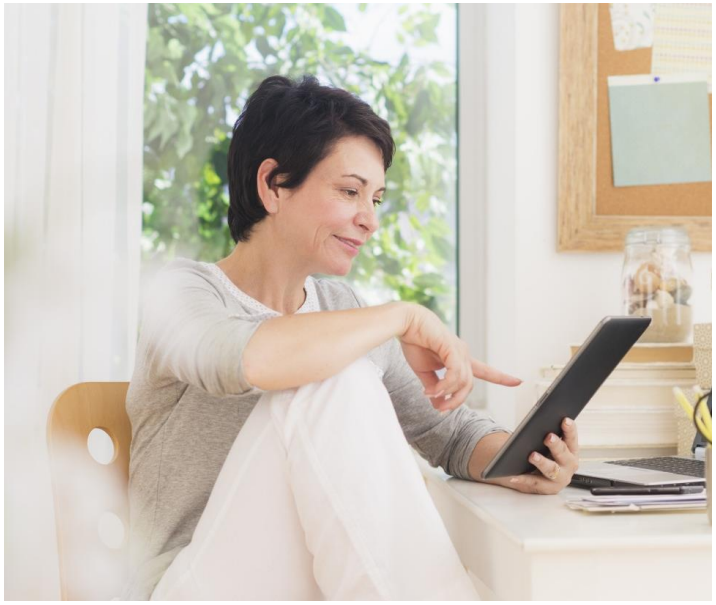
- 15 AEs (30 items)
  - Selected by investigators with patient input
  - Cross-cutting* + context specific
- Available in English or Spanish
- Patient choice of “IVR” or Web
- PRO-CTCAE weekly from home between visits during active treatment, then every 6 months x 3 years

PRO-CTCAE

*Reeve: J Natl Cancer Inst;2014;106(7)

Patient Reminders and Backup Data Collection

- On due day of each week, automated email or call
- Up to 2 reminders
- If no self-report after 72 hours, central coordinator calls patient



Overall Compliance with Self-Report

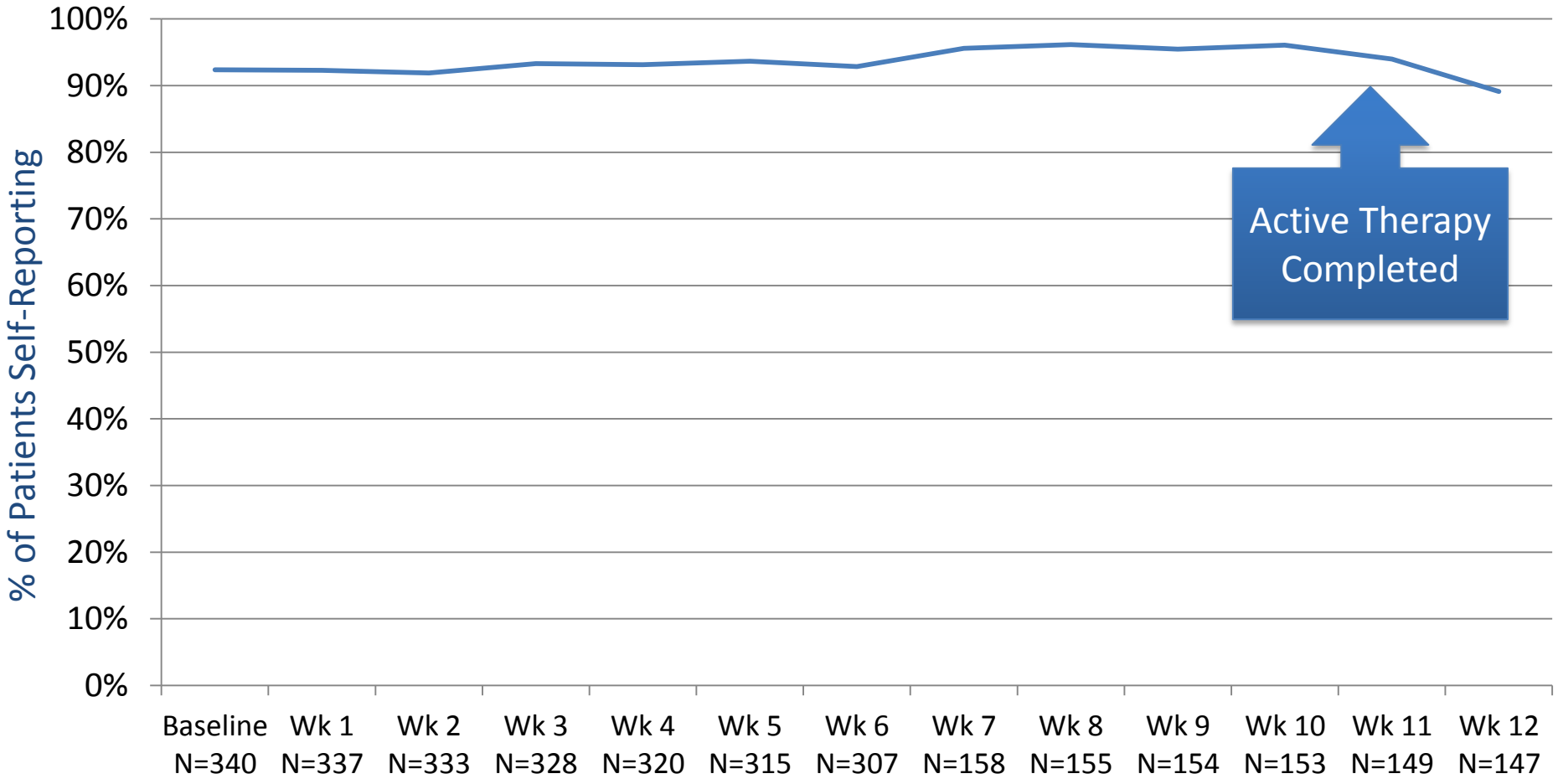
- PRO-CTCAE completed at **93%** of expected time points
  - Patient self-report: 78%
  - Backup calls recovered additional: 15%

- Compliance by mode:

Web: **95%**

IVRS (**91%**)

Compliance over Time

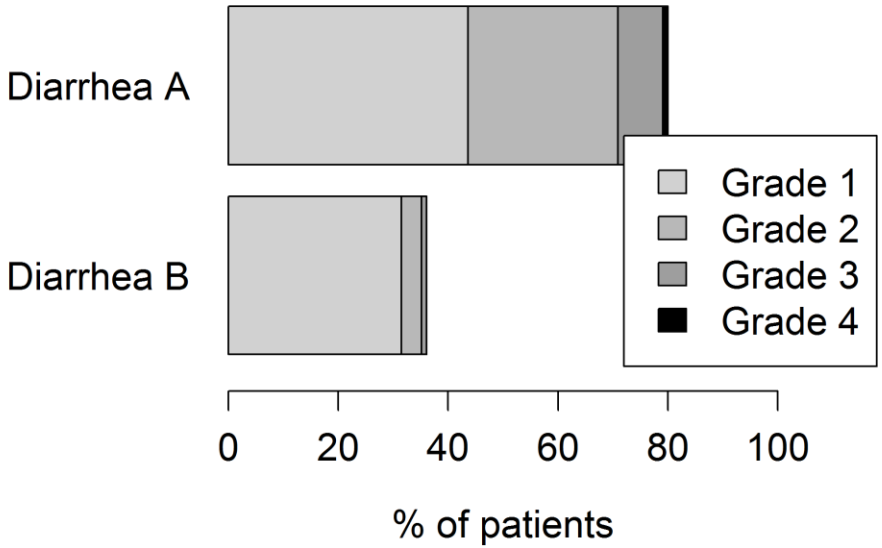


PRO-CTCAE Compliance Rates

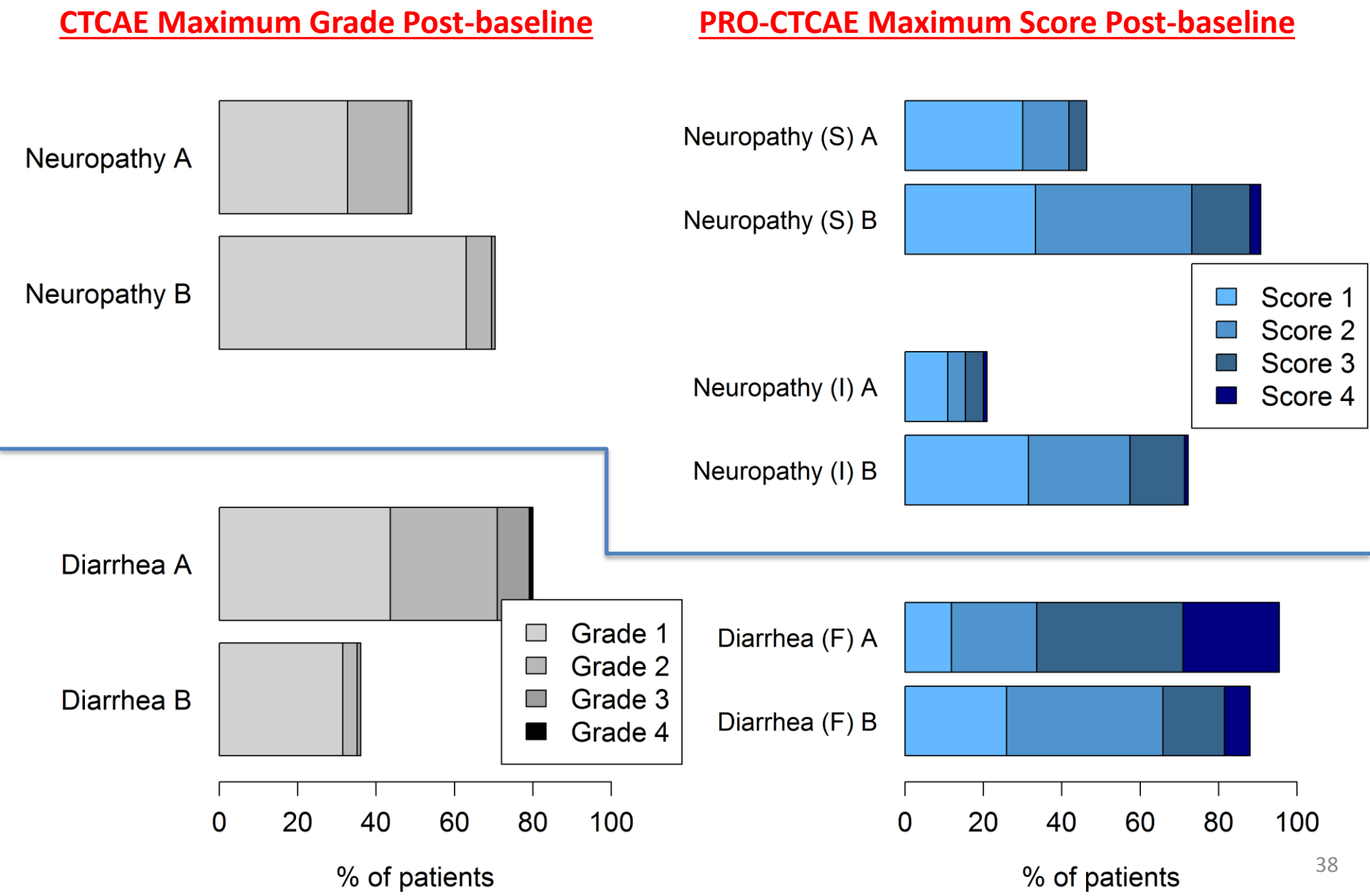
- Similar in 2 other ongoing trials using same PRO-CTCAE approach
- In a 4th trial, PRO-CTCAE collected via iPads at clinic visits without backup reminders
  - → 86% compliance during active treatment
  - → 71% at post-treatment follow up

Neuropathy & Diarrhea: CTCAE and PRO-CTCAE in PROSPECT

CTCAE Maximum Grade Post-baseline



Neuropathy & Diarrhea: CTCAE and PRO-CTCAE in PROSPECT



PROSPECT: Toxicity Table with CTCAE & PRO-CTCAE

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

PROSPECT: Toxicity Table with CTCAE & PRO-CTCAE

Adverse Event		Any Level (>0) Arm A	Any Level (>0) Arm B	High-Level* Arm A	High-Level* Arm B	$P^{\dagger}$
Anorexia	CTCAE	34%	35%	3%	--	0.89
	PRO-CTCAE: *Severity*	66%	84%	9%	17%	0.003
	Interference	43%	71%	9%	14%	<0.001
Anxiety	CTCAE	30%	36%	--	--	0.39
	PRO-CTCAE: *Frequency*	58%	71%	8%	12%	0.048
	Severity	56%	69%	5%	7%	0.07
						0.13
Cons						0.41
						<0.001
Depre						0.34
						0.005
						0.003
						0.003
Diarrh						<0.001
						0.05
Dysphagia	CTCAE	5%	17%	1%	--	0.004
	PRO-CTCAE: *Severity*	14%	64%	--	7%	<0.001
Dyspnea	CTCAE	15%	23%	1%	--	0.17
	PRO-CTCAE: *Severity*	35%	57%	1%	5%	0.001
	Interference	28%	49%	3%	9%	0.002

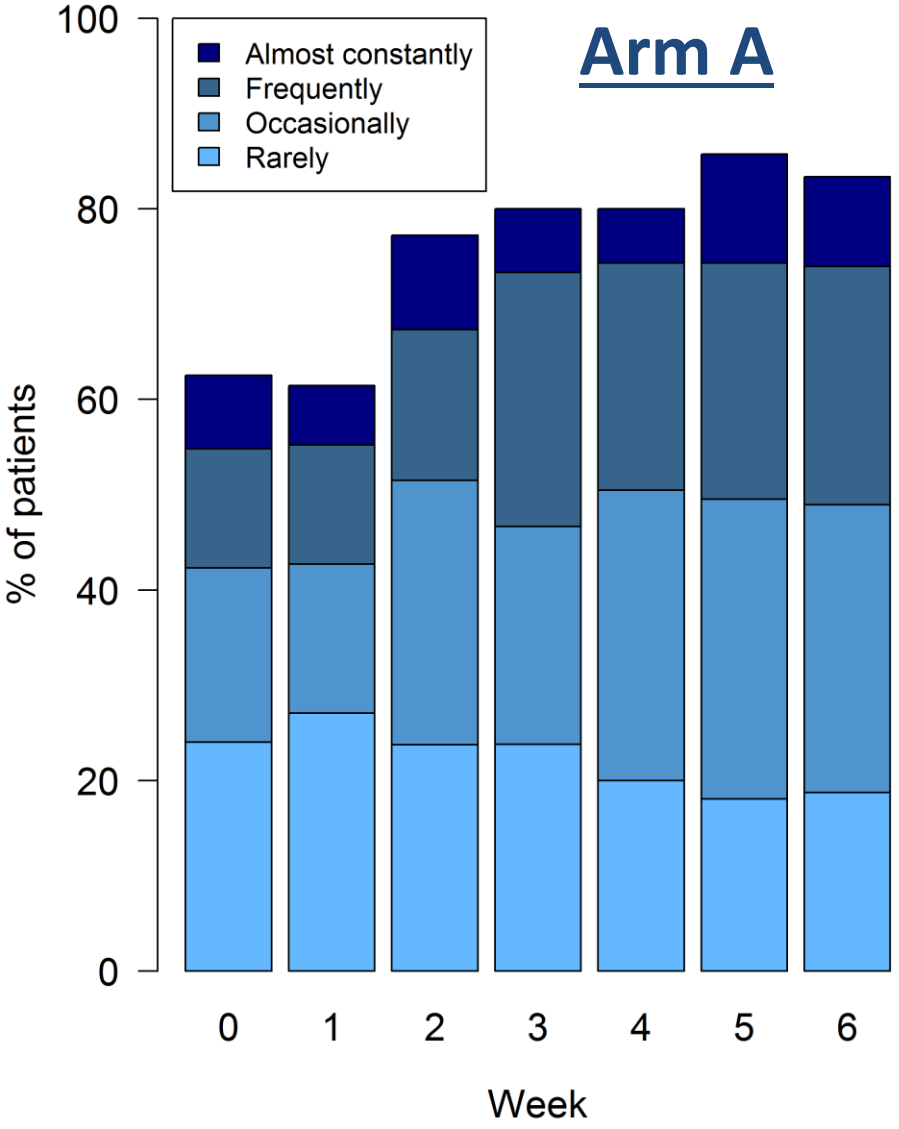
- **Number of AEs found to be statistically significantly different between study arms:**
  - **CTCAE: 4/15 (27%)**
  - **PRO-CTCAE: 11/15 (73%)**

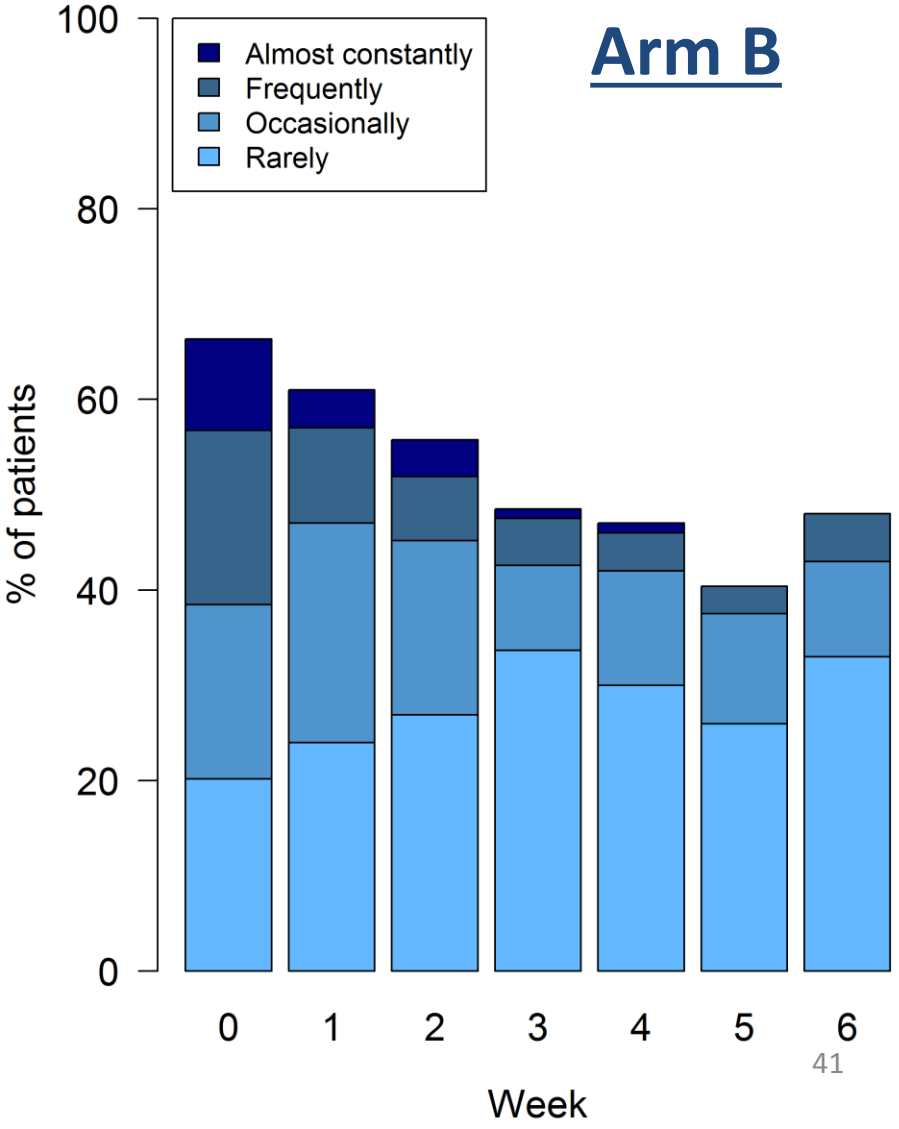
* High-level for CTCAE: ≥Gr3. High-level for PRO-CTCAE: score level 3 or 4 (*severe* or *very severe*; *frequently* or *almost constantly*; *quite a bit* or *very much*).

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

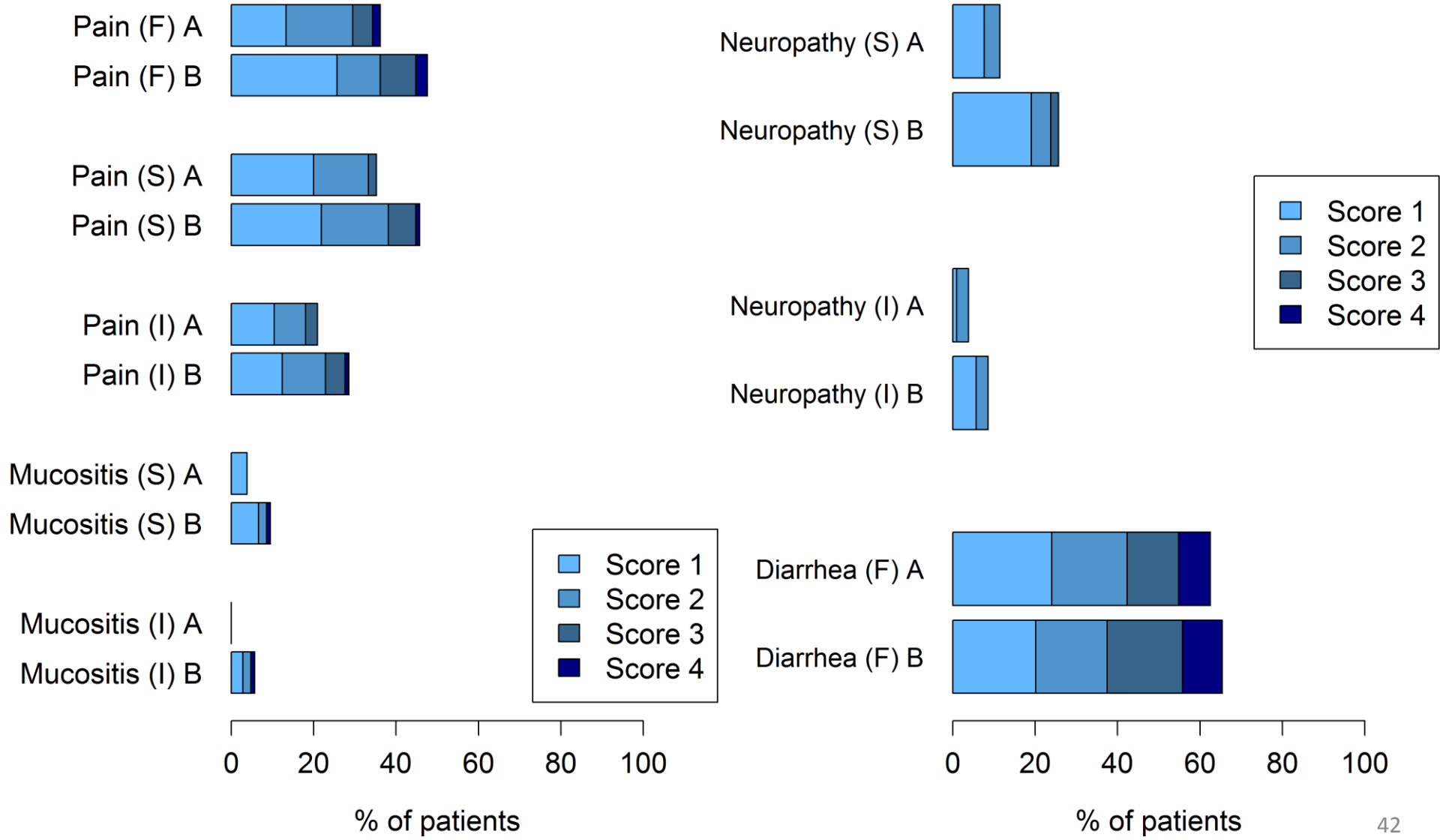
Longitudinal PRO-CTCAE Trajectories over Time

Diarrhea (F)



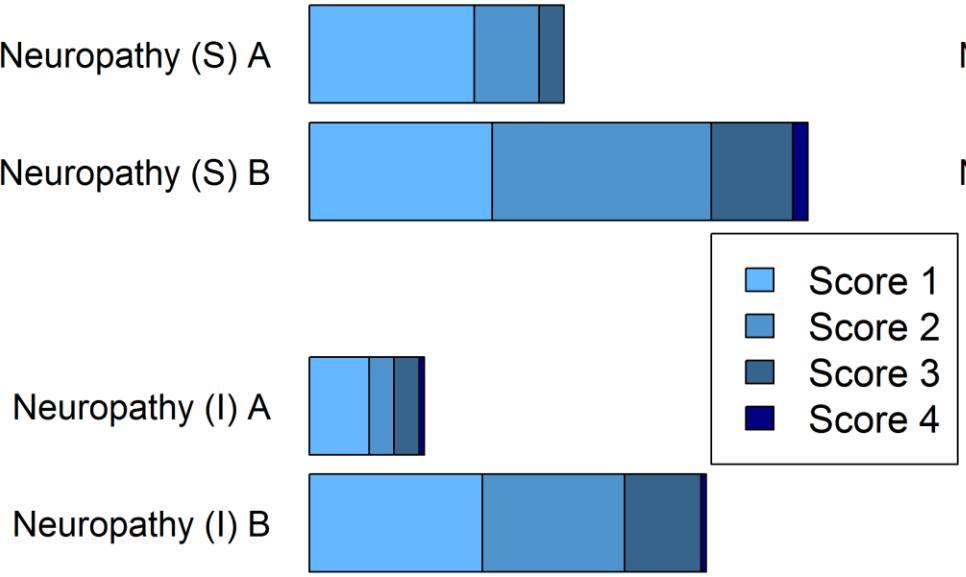


PRO-CTCAE Baseline Scores

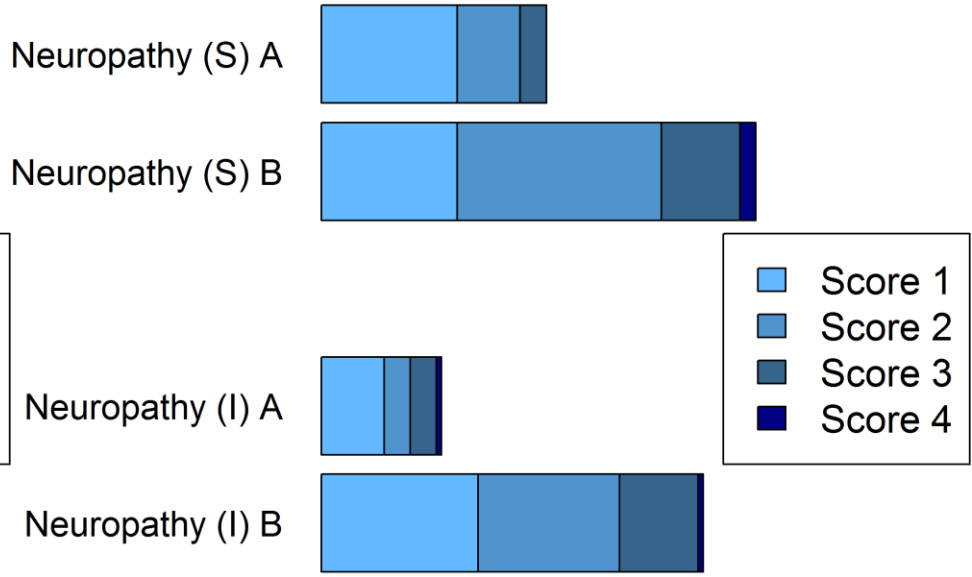


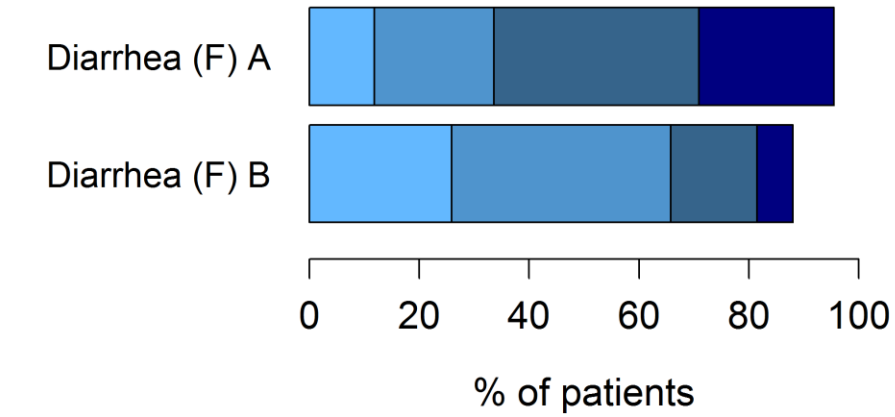
PRO-CTCAE with/without subtraction of baseline scores

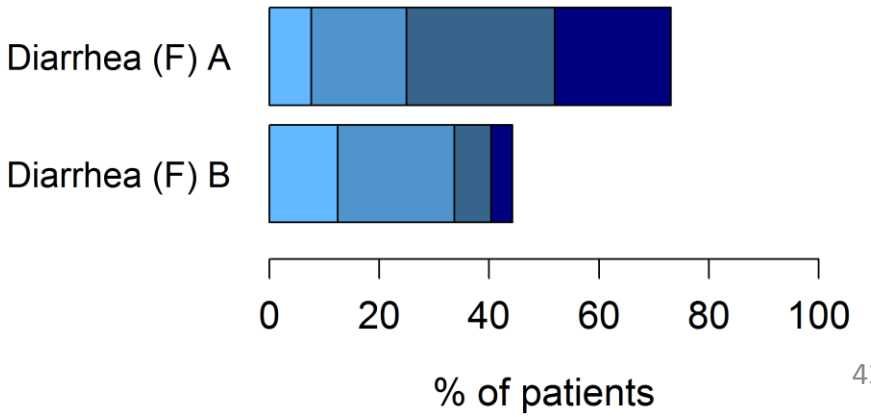
PRO-CTCAE Maximum Score Post-baseline



PRO-CTCAE Baseline Subtraction







Conclusions

- Collection of PRO-CTCAE is feasible in trials
- PRO-CTCAE detects significant differences between study arms for more AEs than CTCAE
- PRO-CTCAE detects baseline AEs that can be "discounted" in AE analyses
- PRO-CTCAE should be considered for use in any trial using CTCAE
  - Should be made freely available without permissions process, which is a barrier to use
  - Multiple language translations urgently needed

FRIENDS of CANCER RESEARCH

Center for Health Policy at BROOKINGS

FRIENDS / BROOKINGS ANNUAL MEETING

ALICYN CAMPBELL

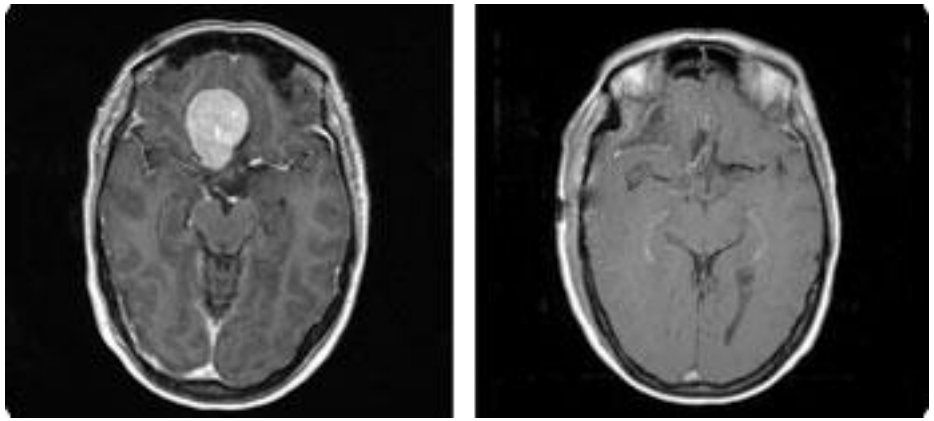
GLOBAL HEAD, PATIENT-CENTERED OUTCOMES RESEARCH FOR ONCOLOGY

GENENTECH, A MEMBER OF THE ROCHE GROUP

Disclosures

- I am currently an employee of Genentech, a Member of the Roche Group
- The opinions and thoughts expressed in this presentation are my own and do not reflect nor represent those of F. Hoffmann-La Roche AG, nor of Genentech, a Member of the Roche Group

How is the Benefit of a New Treatment Assessed in Clinical Trials?



What does this tell us about how this **patient feels** or **functions**?

…symptom burden?

Source: http://www.uchospitals.edu/specialties/neurosurgery/patient-stories/diane.html

Current Situation

- We collect vast amounts of patient-reported data in our ongoing trials, however, these data are rarely included in the US label and cannot be directly communicated to patients

- Patients are increasingly engaged and requesting relevant data to support their decision-making process

Future: Transform the Assessment of the Patient Experience in Oncology

- Develop and disseminate a set of tools assessing 3 core concepts:
  - Alleviation of tumor burden
  - Functional status
  - Treatment burden
    - We need to provide patients and providers with easy to interpret data to assess benefit:risk for treatment determinations
- Standardization: one level of evidence for all stakeholders
  - e.g. patients, providers, regulators, payers

Global Sponsors = Global Stakeholders

Health Care Providers

Publications

Treatment Guidelines

Regulatory Agencies

Assess risk/benefit

Label claims

HTA/ Payers

Value differentiation

Patients

Expected benefit:
function
symptoms

Global Sponsors = Global Stakeholders

- Evidence plan must suit needs of multiple global stakeholders, when determining the *tool(s*) to include when defining *endpoints* to assess the *outcomes* of interest

- There is still value assessing treatment burden with current tools
  - e.g. EORTC [core & disease modules], BFI, BPI, MDASI

Tactical Barriers to Industry Adoption

- Simplified license process
  - Current Material Transfer Agreement process is too lengthy for inclusion in global trials
- Availability of global translations
  - Current lack of global translations and inability to use standard vendors (e.g. Mapi)
  - Propose pre-competitive industry collaboration where multiple sponsors share in the upfront cost of translations and pay no future usage fees. Non-sponsors pay usage fees to supplement future languages.
- Data-driven rationale for item selection as part of trial assessment strategy
  - Minimize responder burden, multiplicity

Tactical Barriers to Industry Adoption

- Data collection standards
  - NCI platform vs. sponsor developed platforms
  - Enabling, coding & analyzing patient write-in responses
- Data analysis standards
  - Consensus on data scoring: descriptive vs. total score
  - Consensus on data analysis and presentation for submissions, manuscripts, labeling
  - Consensus on cross trial comparison methods when differing item sets included

Summary

- Treatment burden is one of the 3 core concepts to measure when assessing the patient experience of cancer
- We need to create a macro-level regulatory path *and* address tactical barriers to implementation for PROCTCAE to be broadly used in clinical trials
- We need to partner as a sponsor and academic community to provide patients with rigorous and understandable benefit:risk data to make informed treatment decisions when faced with a diagnosis of cancer

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PRO-CTCAE: TOWARD A SYSTEMATIC LONGITUDINAL ASSESSMENT OF SYMPTOMATIC ADVERSE EVENTS

PAUL G. KLUETZ
OFFICE OF HEMATOLOGY AND ONCOLOGY PRODUCTS
FOOD AND DRUG ADMINISTRATION

What questions can PRO answer?

- **Efficacy:** Does the drug improve disease related symptoms or functional deficits? Is it reducing the burden of cancer?
  - Pain, Total Symptom Score, Performance related outcomes
  - More conducive to formal statistical analysis and claims of treatment benefit

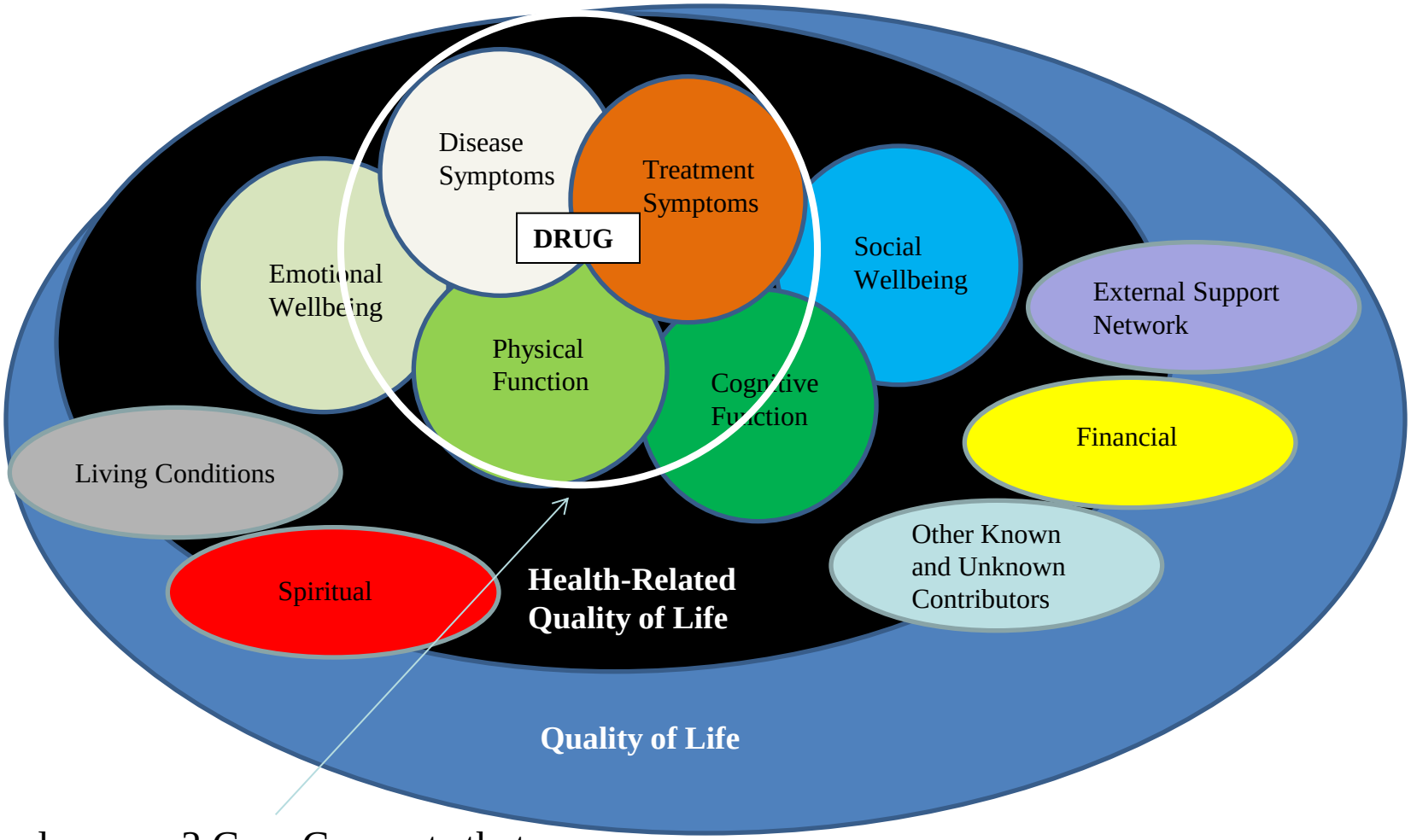
- **Safety/Tolerance::**How do patients feel while on therapy?
  - Tolerance/ Symptoms / "Quality of Life"
  - Like AE data, more descriptive in nature
  - Much harder to quantify and statistically test

What has been the default PRO strategy?

- Static- health related quality of life (HRQOL) instruments developed in a different therapeutic era
  - Often 30 or more questions
  - Static adverse event assessment: little ability to adjust to ever-changing therapeutic side effect profiles
  - Measures concepts that are considered far removed from the effect of the drug on the patient (social, financial wellbeing, etc.)
  - May measure concepts that are fixed deficits (sexual function in metastatic prostate cancer patients on androgen deprivation for life)
  - Often infrequently assessed with high levels of missing data

- Newer instruments under development are more flexible and can measure key contributors to HRQOL separately

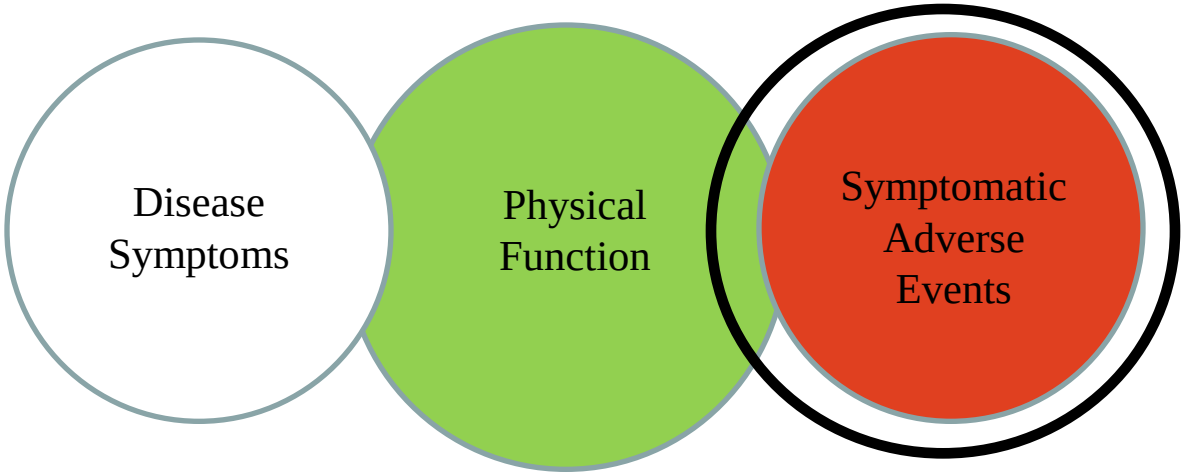
Common PRO Strategy: Single Static Instrument Measuring Health Related Quality of Life (HRQOL)-



Focus Analyses on 3 Core Concepts that are important Contributors to HRQOL

PRO Assessments of Core Concepts Focuses on Symptoms Closest to the Therapy's Effect on the Patient and Their Disease

- More narrow concepts, more well defined assessments
- Separate measures can allow for use of new instruments/item banks
    - We must acknowledge there will be some overlap between disease and treatment related symptoms
- Measures of these concepts may be more responsive to the positive or negative effects of a therapy on the patient and their disease



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 widely differ depending on mechanism and target.

- Commonly used PRO Instruments are Static:
  - They measure same Symptoms Regardless of Therapeutic Context

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

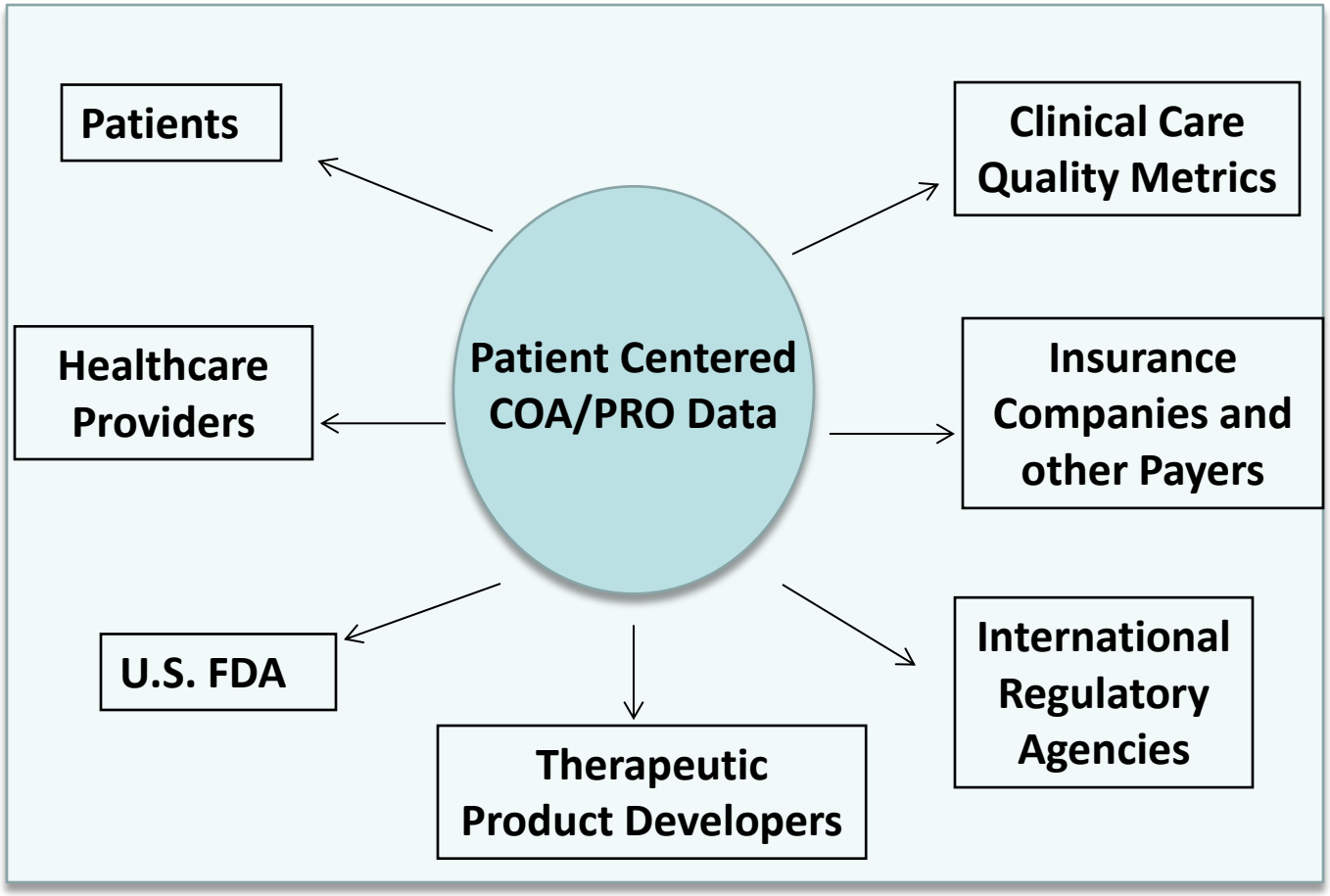
Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

- Strengths
  - Patient reported- (Symptoms are best reported by the patient)
  - Systematically and rigorously developed
  - Standard: provides a standard item bank and platform
  - Flexible: allows choice of relevant toxicities AND opportunity to update the item bank as novel mechanistic toxicities emerge
  - Familiar: Complimentary to existing safety evaluation (CTCAE)
- Work to be Done
  - Language Translations
  - Scoring
  - Unbiased Item Selection
  - How to use PRO-CTCAE Real-time for clinical management
  - Most informative least misleading way to analyze and present data
  - Comparative tolerability designs

Implementation Challenge: Burden and Duplication

- Some symptomatic adverse events are assessed in existing health related quality of life (HRQOL) instruments
  - Integrating PRO-CTCAE with unmodified existing HRQOL instruments and their disease modules would result in duplication and increased burden
- Can we take advantage of the strengths of existing AND newly developed instruments to provide a comprehensive PRO strategy?
- Can we modify existing HRQOL instruments to remove what is duplicative and measure isolated domains as exploratory data?
  - Single item global impression of health?
  - Emotional and Cognitive domains?

Many Stakeholders Rely on PRO Data: International Collaboration will be Necessary



Conclusion:

- Systematic longitudinal assessment of patient-reported symptomatic adverse events could compliment existing safety assessments
- PRO-CTCAE provides a standard yet flexible instrument to generate descriptive PRO symptomatic adverse event data
- Carefully assessed PRO-CTCAE data could be included in the FDA label descriptively
- Additional work must be done to integrate PRO-CTCAE into a comprehensive PRO strategy for cancer clinical trials:
  - Goal: Increase question relevance and decrease duplication and burden