Second Annual Workshop on Clinical Outcome Assessments in Cancer clinical trials

April 25, 2017 ■ Bethesda, MD

Co-sponsored by

FDA U.S. FOOD & DRUG ADMINISTRATION

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Session 4
From Individual Symptoms to Overall Side Effect Burden

SECOND ANNUAL WORKSHOP ON

CLINICAL OUTCOME ASSESSMENTS IN CANCER CLINICAL TRIALS

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- The views and opinions expressed in the following slides are those of the individual presenters and should not be attributed to their respective organizations/companies, the U.S. Food and Drug Administration or the Critical Path Institute.

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Session 4: Objectives

- Introduce the potential use of a measure of overall side effect burden
- Explore possible options to measure overall side effect burden
- Discuss strengths and limitations of an overall measure of side effect burden

Session Participants

Chair

- *Paul G. Kluetz, MD* – Acting Associate Director of Patient Outcomes, OCE, FDA

Presenters

- *David Cella, PhD* – Professor & Chair, Department of Medical Social Sciences, Feinberg School of Medicine, Northwestern University
- *Charles S. Cleeland, PhD* – McCullough Professor of Cancer Research, University of Texas MD Anderson Cancer Center
- *Galina Velikova, BMBS(MD), PhD, FRCP* – Professor, University of Leeds

Panelists

- *Mary Lou Smith, MPA, MBA, JD* – Co-Founder, Research Advocacy Network
- *Daniel O'Connor, MB, ChB, PhD, MFPM* – Expert Medical Assessor, MHRA
- *Ethan Basch, MD, MSc* – Director, Cancer Outcomes Research Program, University of North Carolina
- *Michelle Campbell, PhD* – Reviewer and Scientific Coordinator, COA Qualification Program, COA Staff, OND, CDER, FDA

Tolerability: **PRO measurement opportunity**

- Symptomatic side effects are best assessed by patients
- Tolerability - important in all phases of development
- PRO measures can offer different but complementary data to current clinician reported safety data
- PRO measures can be systematically and longitudinally obtained <u>including a baseline measure</u>

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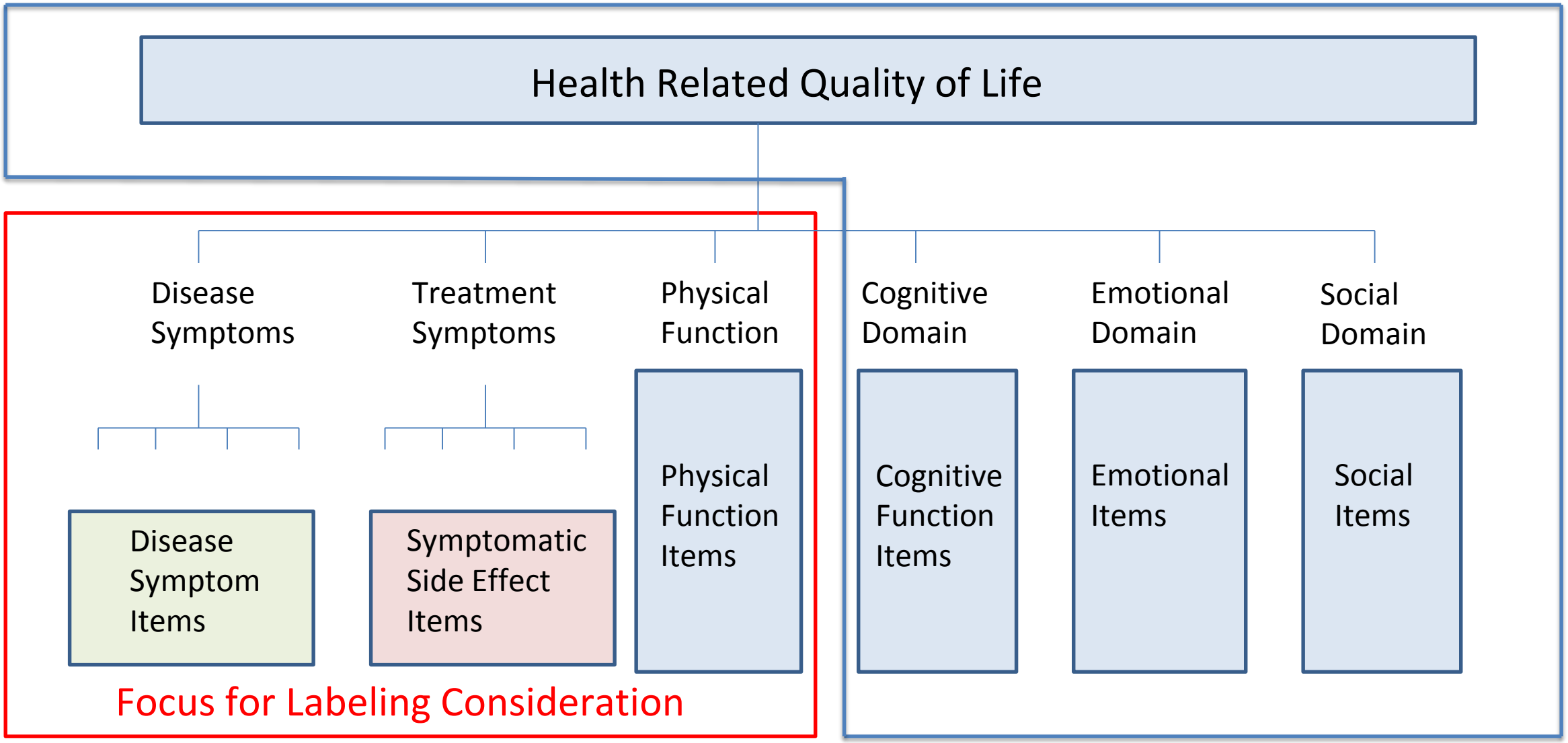
A combination of item libraries and generic short forms may provide needed flexibility to adapt to trial contexts



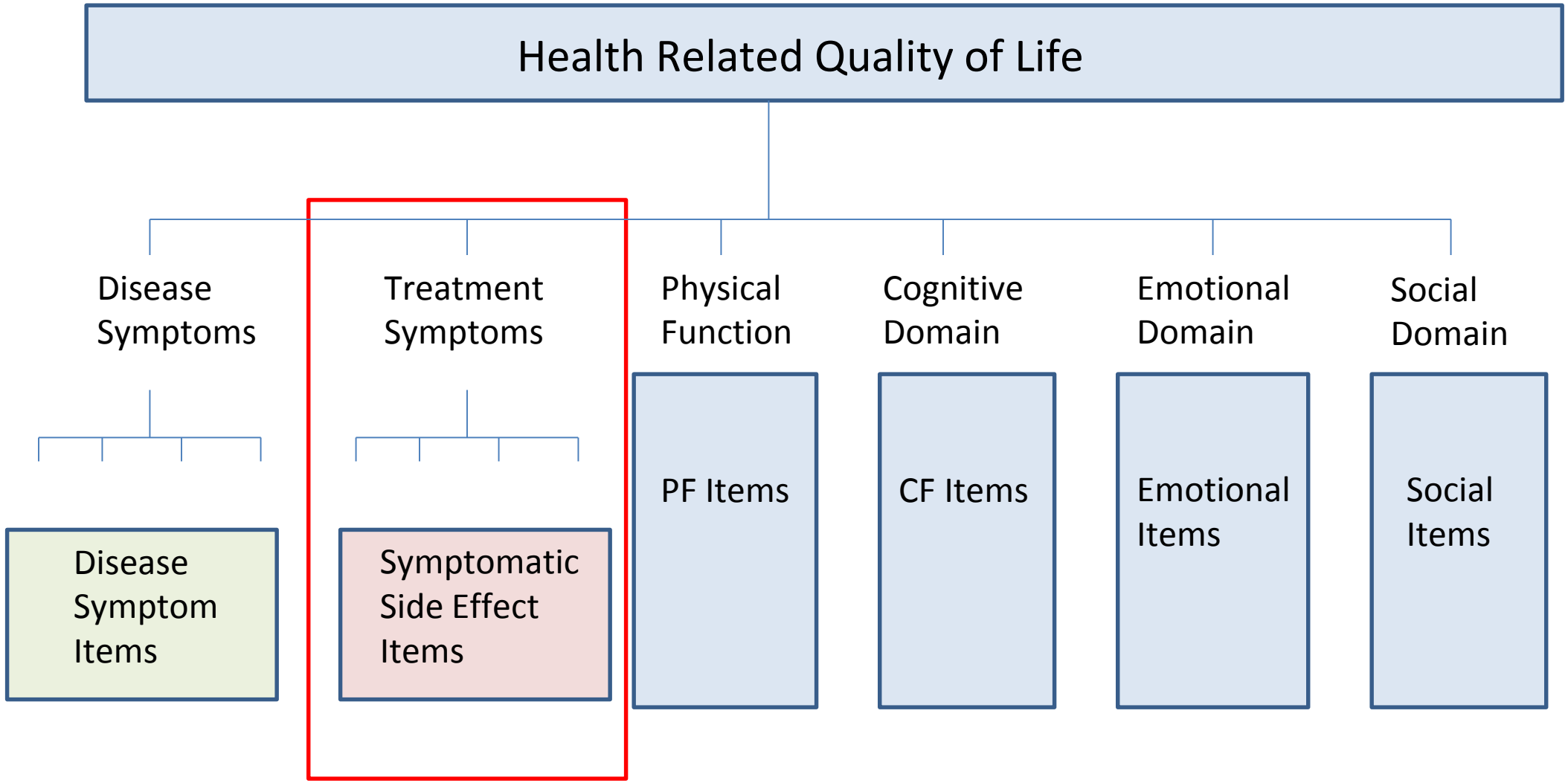
FDA is not suggesting trials *ONLY* measure patient-reported symptoms and physical function

- Symptoms and Physical Function are a focus for analysis to inform **FDA labeling**
- The FDA label is only **one limited method** to convey patient experience data to the public
- It does not mean these should be the ONLY concepts to measure in a clinical trial

The goal should be to achieve a comprehensive evaluation of the patient experience most affected by the therapy, while maximizing the relevance of individual questions and minimizing overall burden and duplication.[1]

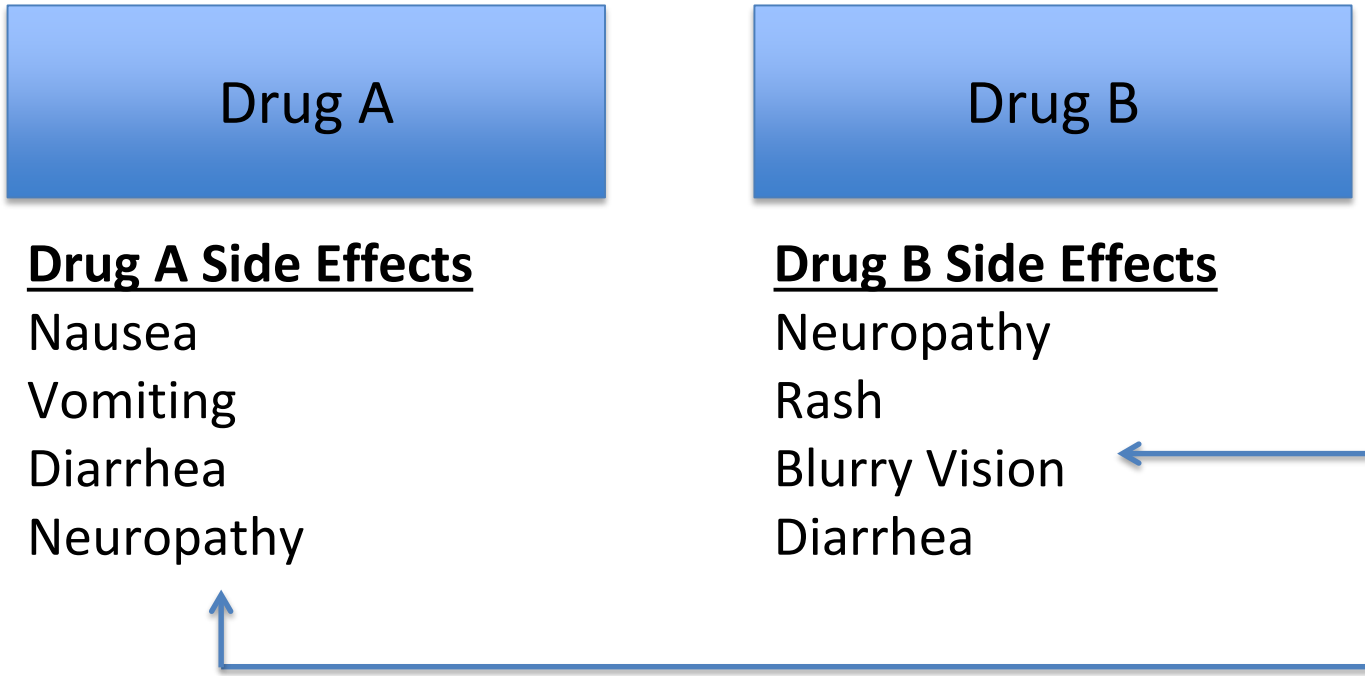
[1] Kluetz, Paul G., et al. "Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials—Response." *Clinical Cancer Research* 22.22 (2016): 5618-5618.

Today we have concentrated on symptomatic side effects to inform tolerability



Focusing on tolerability, Step 1 is to provide an unbiased selection of symptomatic side effects to measure

Fictitious Head-to-Head Randomized Trial



Symptomatic side effects informed by pre-clinical and clinical data with strong rationale for their selection

What is the overall burden of individual symptomatic side effects on the patient?

- How can we quantify the overall side effect burden?
- Do we just add them all up?
- How do we weight the importance of each symptom?
- Is nausea as impactful as vomiting?
- Won't that differ between patients?

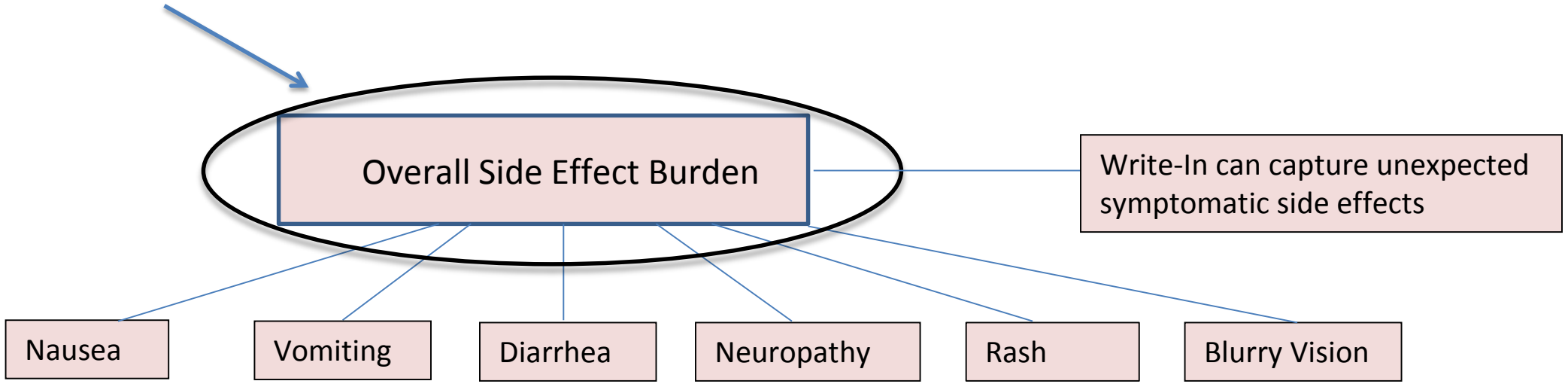
Write-In can capture unexpected symptomatic side effects

Nausea | Vomiting | Diarrhea | Neuropathy | Rash | Blurry Vision

Important symptomatic side effects from BOTH drugs will be asked of all patients on the trial

An item or domain assessing overall side effect burden could be useful

The focus of session 4



Important symptomatic side effects from BOTH drugs will be asked of all patients on the trial

How could a measure of overall side effect burden be useful?

- A generic “Treatment Tolerability Index” could be used across clinical trial settings and treatment contexts
- Provides an opportunity to build an endpoint
- May mitigate bias if symptomatic side effects are unevenly assessed
- Each patient will internally weight their individual side effects
- Can be interpreted by:
  - Important individual PRO symptoms selected from a PRO item library
  - Trial data such as dose modification and supportive care medication usage

What challenges exist in measuring overall side effect burden?

- Discriminating disease vs. treatment symptoms
- Baseline disease symptoms
- Residual toxicities from prior treatments
- Supportive care medication use

Thank you to all our Session 4 participants for joining us.

Our first speaker will be David Cella, PhD – Professor, Northwestern University

Concise Measurement of Cancer Treatment Side Effect Burden and its Relationship to Outcomes

David Cella, PhD
Ralph Seal Paffenbarger Professor and Chair
Department of Medical Social Sciences
Feinberg School of Medicine
Northwestern University

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Remembering a rock icon

Chuck Berry's style and riffs are still influential

IN LIFE

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Reports of drug side effects soar fivefold

FDA database could warn of dangerous products already on market

Matthew Wynn
MedPage Today
and John Fauber
Milwaukee Journal Sentinel

More than 1 million reports of drug side effects were filed with the U.S. Food and Drug Administration in 2015, a fivefold increase since 2004, according to an analysis by the *Milwaukee Journal Sentinel* and MedPage Today.

Numbers aren't final for 2016, but they are expected to match that all-time high.

Drugs to treat diseases such as rheumatoid arthritis, psoriasis, multiple sclerosis, a type of cancer and diabetes are among those with the greatest number of reports. Many of the drugs are for conditions that occur in 1% or less of the population, but several have seen increasing use.

For years, the FDA's adverse-events system has been derided because of its largely voluntary nature — only drug companies, not doctors or patients, are required to report problems. As a result, the system probably was capturing only a small percentage of cases.

In recent years, the number of reports has been multiplying, prompting more independent researchers and drug companies to use the data as a way to detect safety problems, the *Journal Sentinel* and MedPage Today found. But experts say the information still is largely untapped and — if used more — could become an important alarm that warns of dangerous drugs after they hit the market.

The surge in reports could indicate a growing number of harmed patients or more vigilant reporting of adverse events, a goal of the FDA. Experts say both probably play a role.

Twelve years ago, 206,000 reports of side effects from medications were filed with the FDA — complaints as frivolous as flatulence and as serious as death.

By 2015, the most recent full year of data, the number had grown to 1.2 million.

The FDA has long discouraged use of the system for research

▶ STORY CONTINUES ON 2A

WHAT WE KNOW

Patients experience a wide range of treatment side effects, such as:

- Nausea and vomiting
- Fatigue
- Diarrhea or constipation
- Mood changes
- Taste and appetite changes

KNOWLEDGE GAP

Which side effects are more bothersome than others? Which are more likely to result in:

- Treatment non-compliance
- Treatment discontinuation
- Increased morbidity/mortality

Question

Can a single summary measure help assess the overall impact of adverse events?

Functional Assessment of Cancer Therapy Scale (FACT-G)

- Valid & reliable
- In wide use since 1993
- Developed with direct patient input
- Assesses physical, functional, social, and emotional well-being
- Responsive to:
  - Disease stage
  - Tumor response and progression
  - Performance Status
  - Hospitalization status
  - Change over time

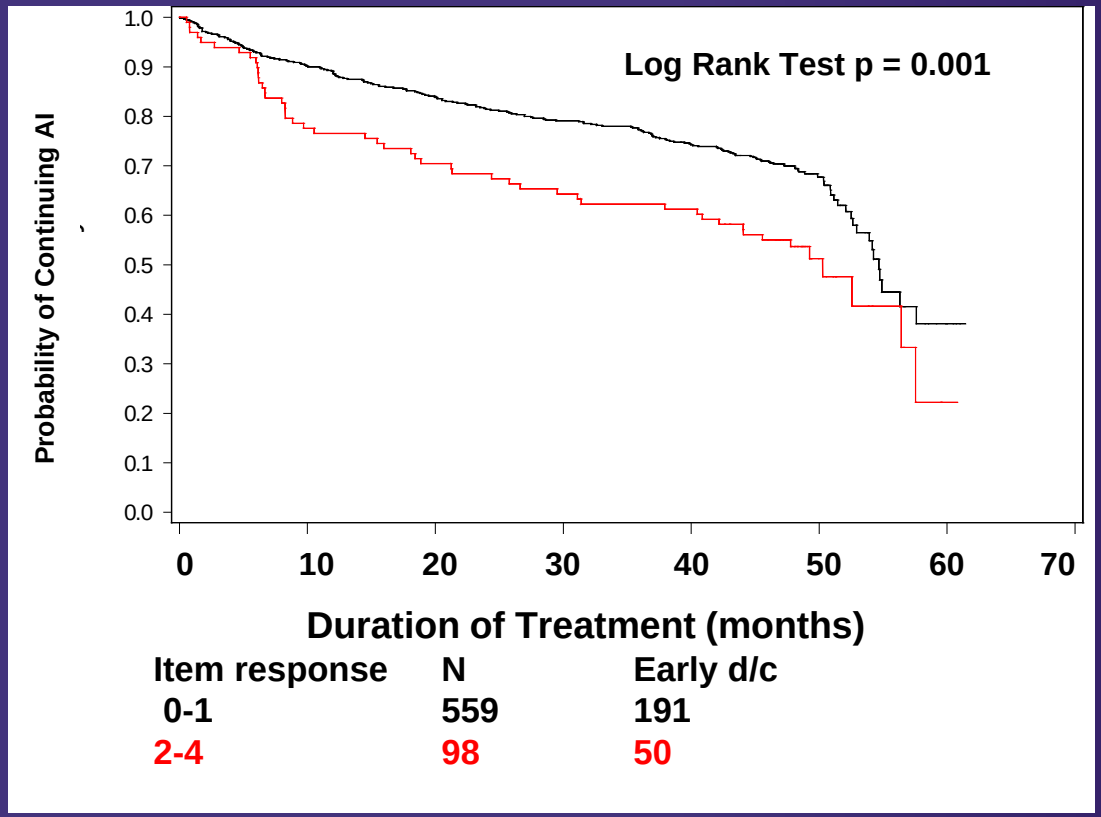
FACT-G: Physical Well-Being Subscale: Item GP5: "I am bothered by treatment side effects"

PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
I have a lack of energy	0	1	2	3	4
I have nausea	0	1	2	3	4
Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
I have pain	0	1	2	3	4
I am bothered by side effects of treatment	0	1	2	3	4
I feel ill	0	1	2	3	4
I am forced to spend time in bed	0	1	2	3	4

Adjuvant Breast Cancer: Predicting AI discontinuation

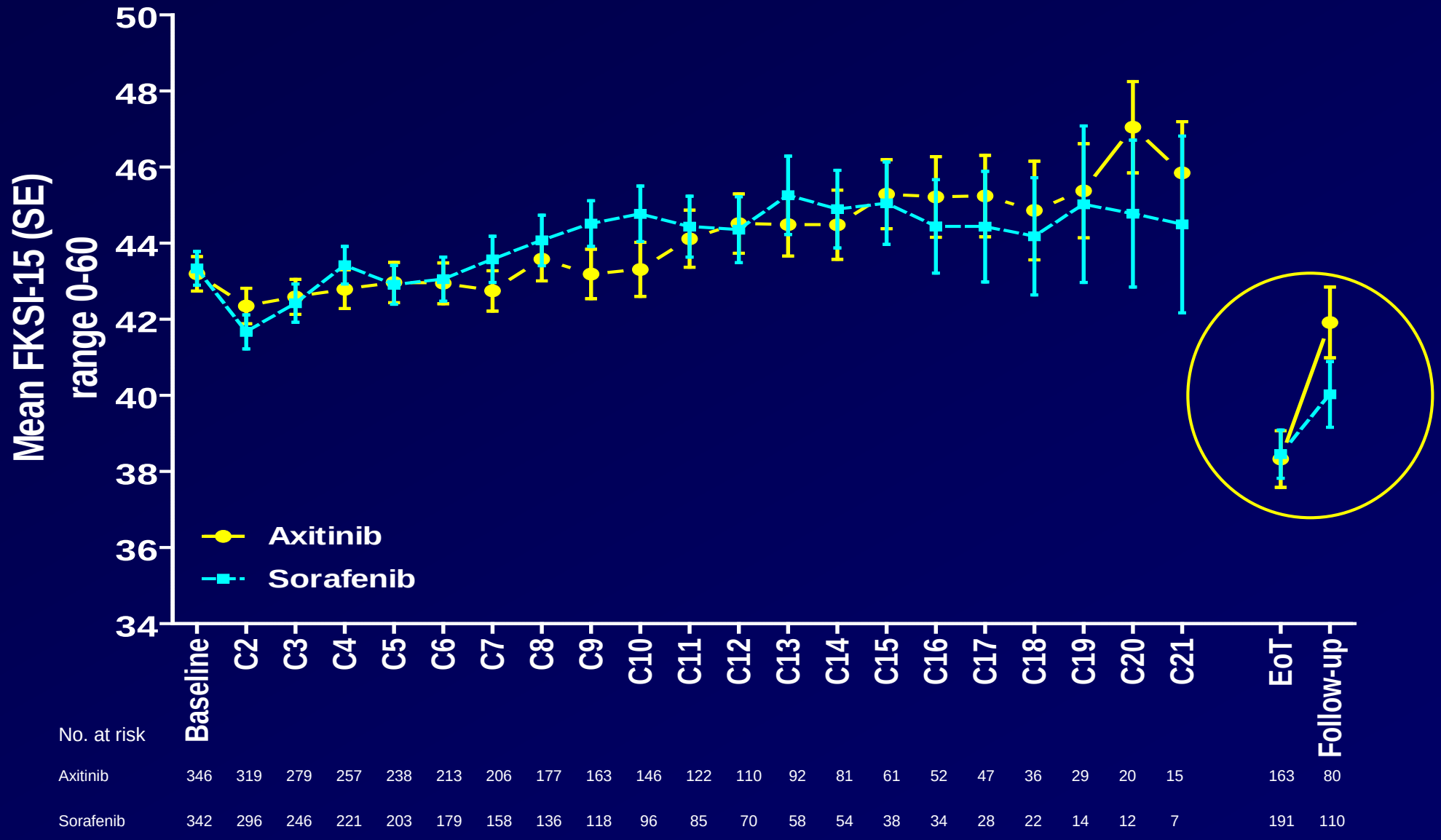
Response at Baseline:
"I am bothered by side effects of treatment"

0	1	2	3	4
Not at all	A little bit	Somewhat	Quite a bit	Very much



Wagner, Zhao, Chapman, Cella, Shepherd, Sledge, Goss. San Antonio Breast Cancer Symposium. Dec 6-10, 2011; San Antonio, TX

AXIS Trial: Observed FKSI-15 Scores on Treatment



Cella et al. British Journal of Cancer. 108 (8):1571–1578, 2013

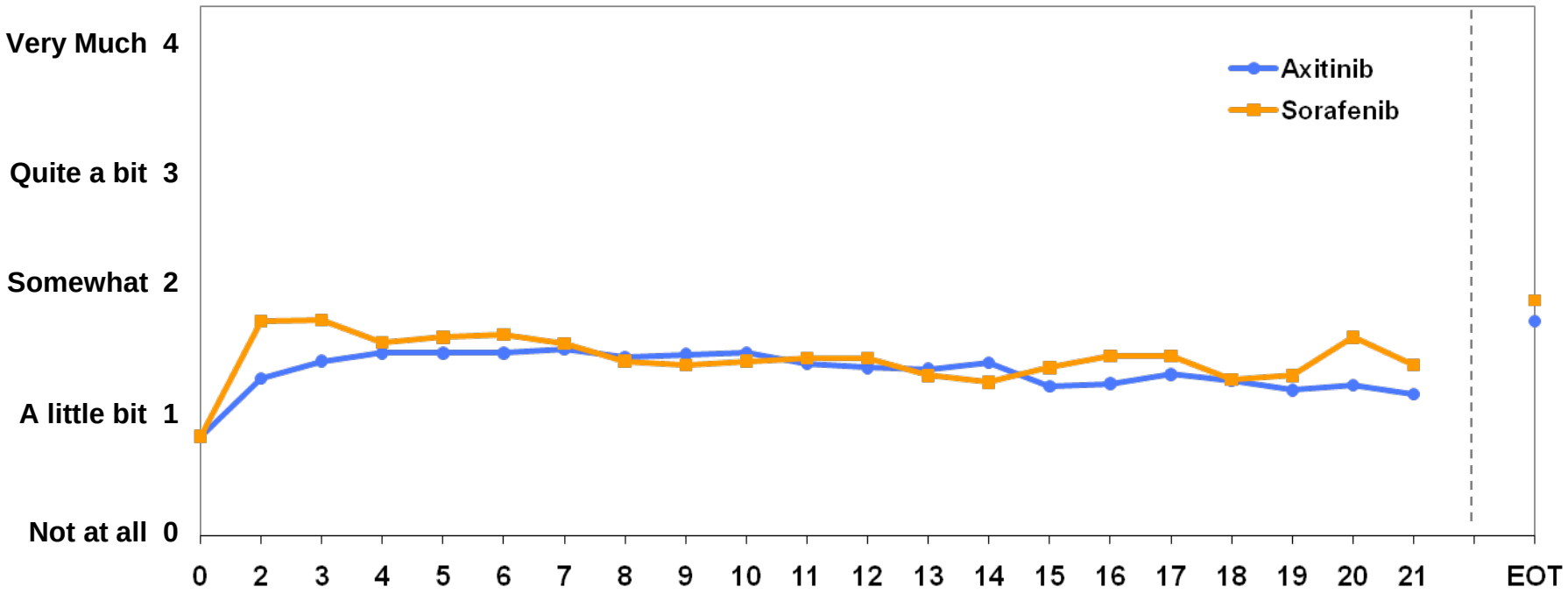
Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-15) – Item #2

Advanced Kidney Cancer Symptom Index – Long Form

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	Not at all	A little bit	Some-what	Quite a bit	Very much
I have a lack of energy	0	1	2	3	4
I am bothered by side effects of treatment	0	1	2	3	4
I have pain	0	1	2	3	4
I am losing weight	0	1	2	3	4
I have bone pain	0	1	2	3	4
I feel fatigued	0	1	2	3	4
I am able to enjoy life	0	1	2	3	4
I have been short of breath	0	1	2	3	4
I worry that my condition will get worse	0	1	2	3	4
I have a good appetite	0	1	2	3	4
I have been coughing	0	1	2	3	4
I am bothered by fevers	0	1	2	3	4
I am able to work (includes work from home)	0	1	2	3	4
I am bothered by blood in my urine	0	1	2	3	4
I am sleeping well	0	1	2	3	4

AXIS Trial: I Am Bothered by Side Effects of Treatment



Axitinib	327	327	285	260	246	219	212	179	166	148	127	112	93	82	63	54	48	37	30	21	15	164
Sorafenib	317	302	249	226	206	181	162	139	121	98	89	73	61	57	41	36	28	22	14	12	7	193

Cella et al, Br J Cancer (2013) 108, 1571–1578

Responses to the single FACT-G item (GP5), **"I am bothered by side effects of treatment"** compared with:

Clinician-reported adverse event (AE) severity for patients participating in 2 Novartis clinical trials	**Patient**-reported measures of overall QOL ("I am able to enjoy life") and EQ-5D health utility in 3 non-industry studies

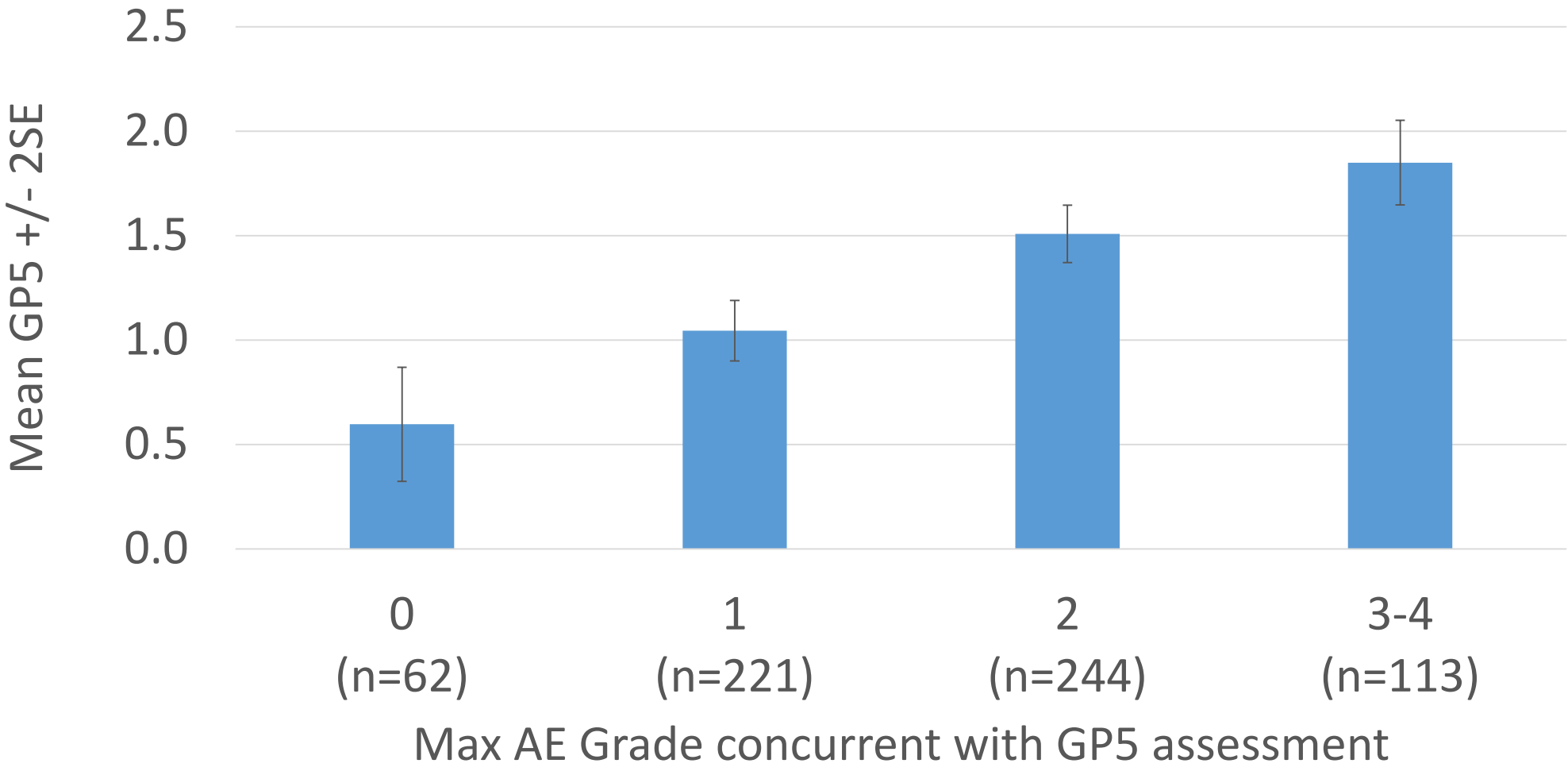
Clinician-level Analysis

Study	Cancer Type	Timeframe	No. of Patients
COMPARZ	Metastatic Renal Cell Carcinoma (mRCC)	2008-2011	1,110
ENESTnd	Newly diagnosed, Philadelphia chromosome-positive, chronic phase chronic myeloid	2007-2008	846

Methods

- All analyses on full sample (pooled treatment arms)
- Responses to FACT-G Item GP5 (“I am bothered by treatment side effects”) linked to simultaneous AEs
- Included AEs corresponding to the PRO-CTCAE item library
- For each GP5 assessment, we calculated the maximum AE grade linked to that assessment.
- Focused on visit with highest mean AE grade
- Chi-sqauare tests of significance

COMPARZ:
Mean GP5 Scores by Max AE Grade, Cycle 2, Day 28 (n=640)

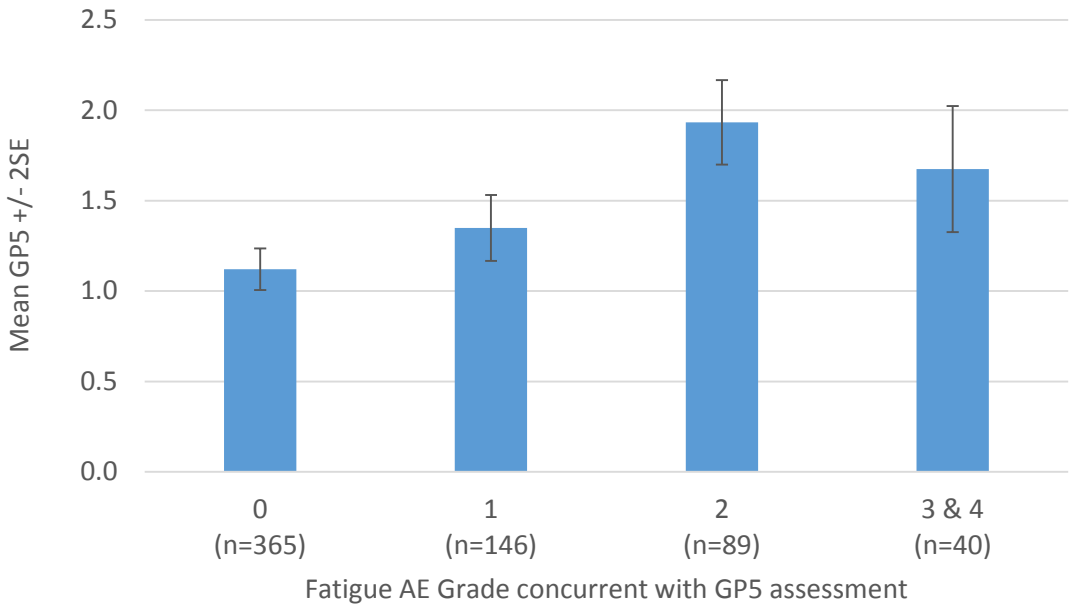


r=0.34; Effect sizes between adjacent groups range = 0.30 - 0.46

p<0.001

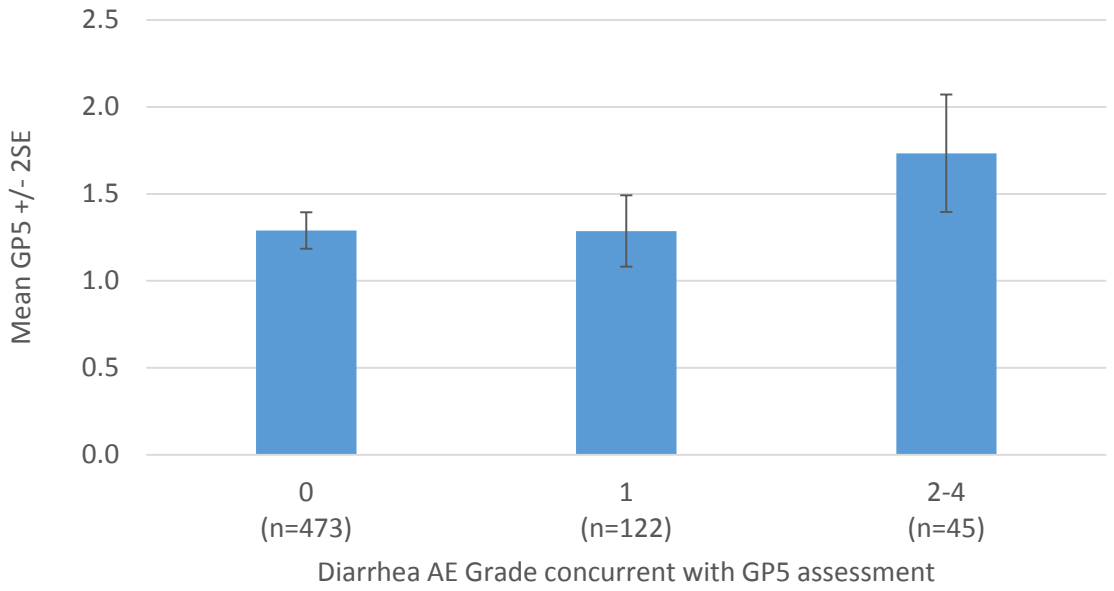
COMPARZ:
AE Grades Concurrent with GP5 Assessment

FATIGUE GRADE



p<0.001

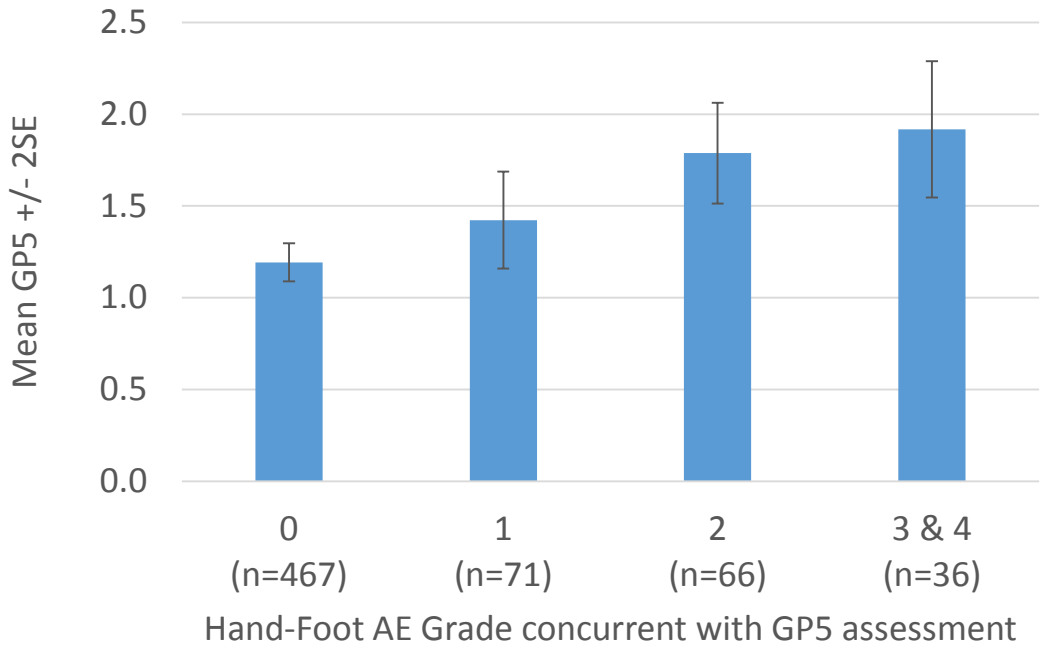
DIARRHEA GRADE



p=0.014

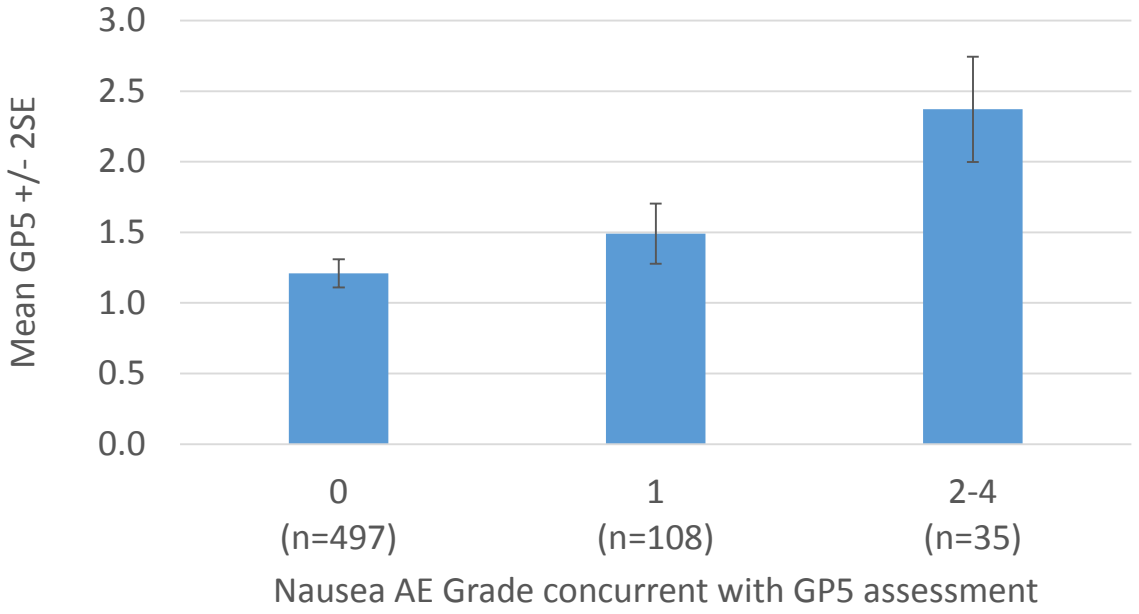
COMPARZ:
AE Grades Concurrent with GP5 Assessment

HAND-FOOT GRADE



p<0.001

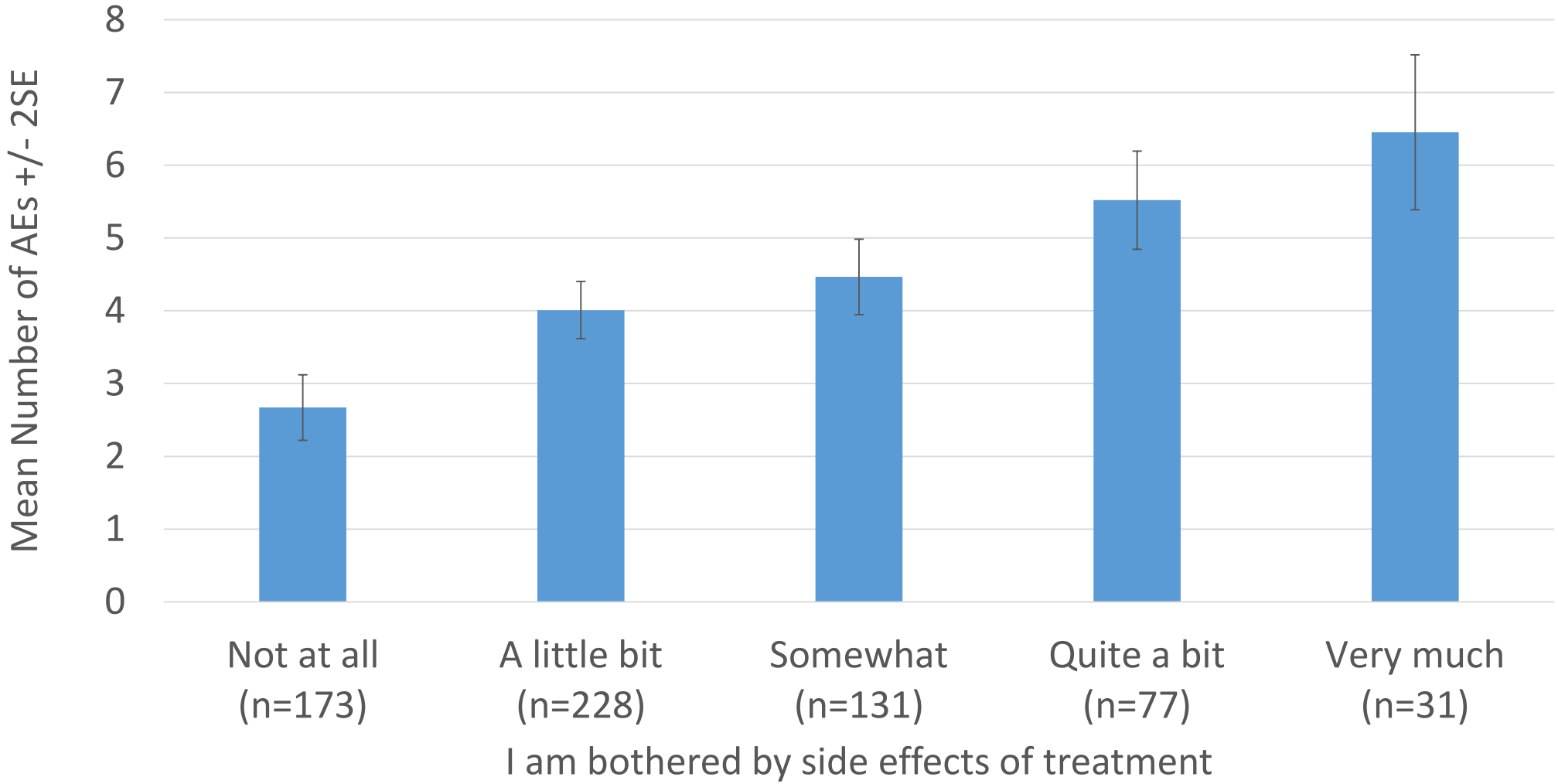
NAUSEA GRADE



p<0.001

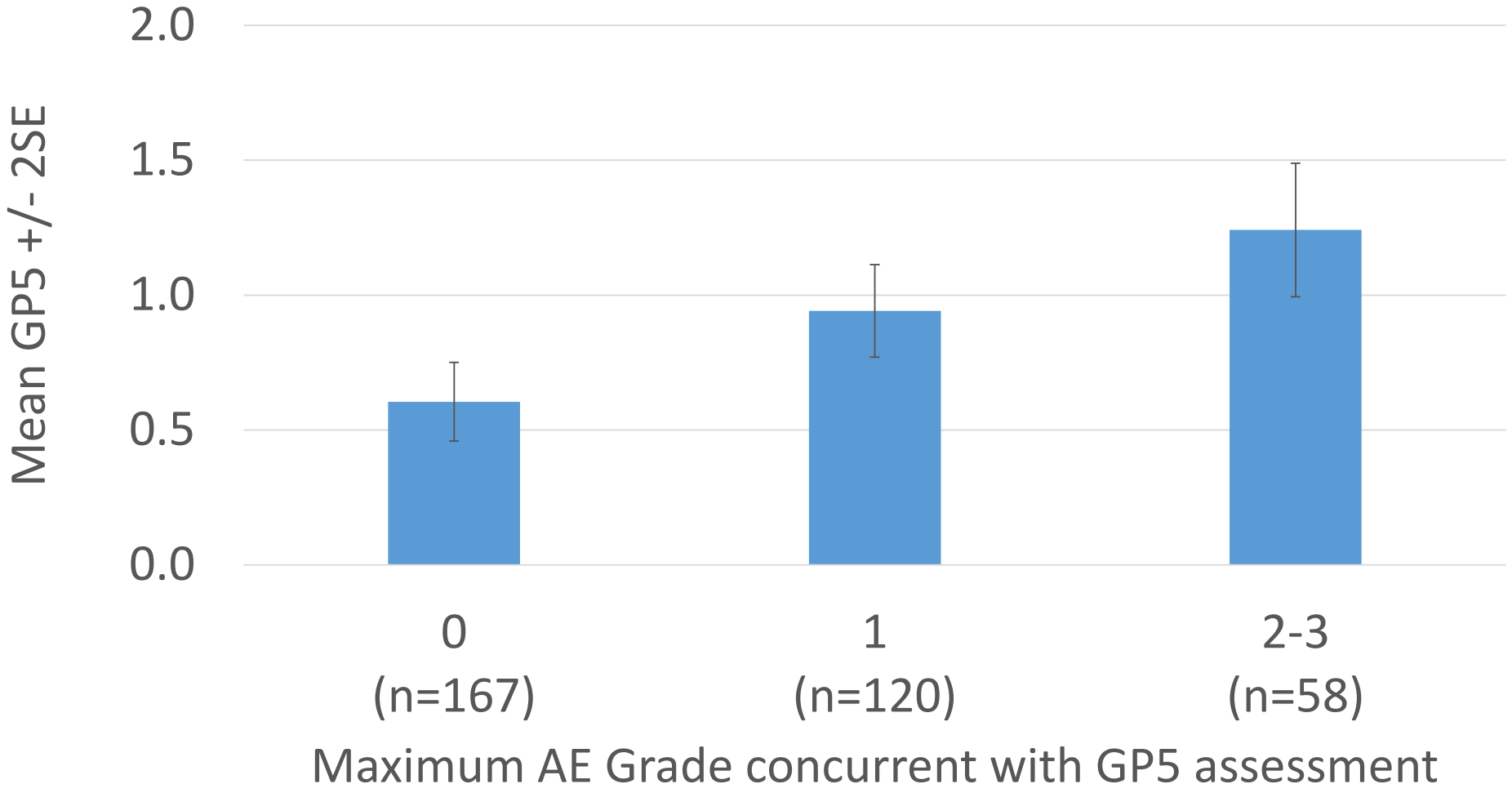
COMPARZ: Total # of PRO-relevant AEs at Cycle 2, Day 28

…by degree of side effect bother



p<0.001

ENESTnd: Mean GP5 Scores by Max AE Grade, Cycle 1, Day 28 (n=345)



r=0.28; Effect sizes between adjacent groups range = 0.30 - 0.36

p<0.001

Does Side Effect Bother Matter to Patients?

Level 2 analysis of relation to life enjoyment

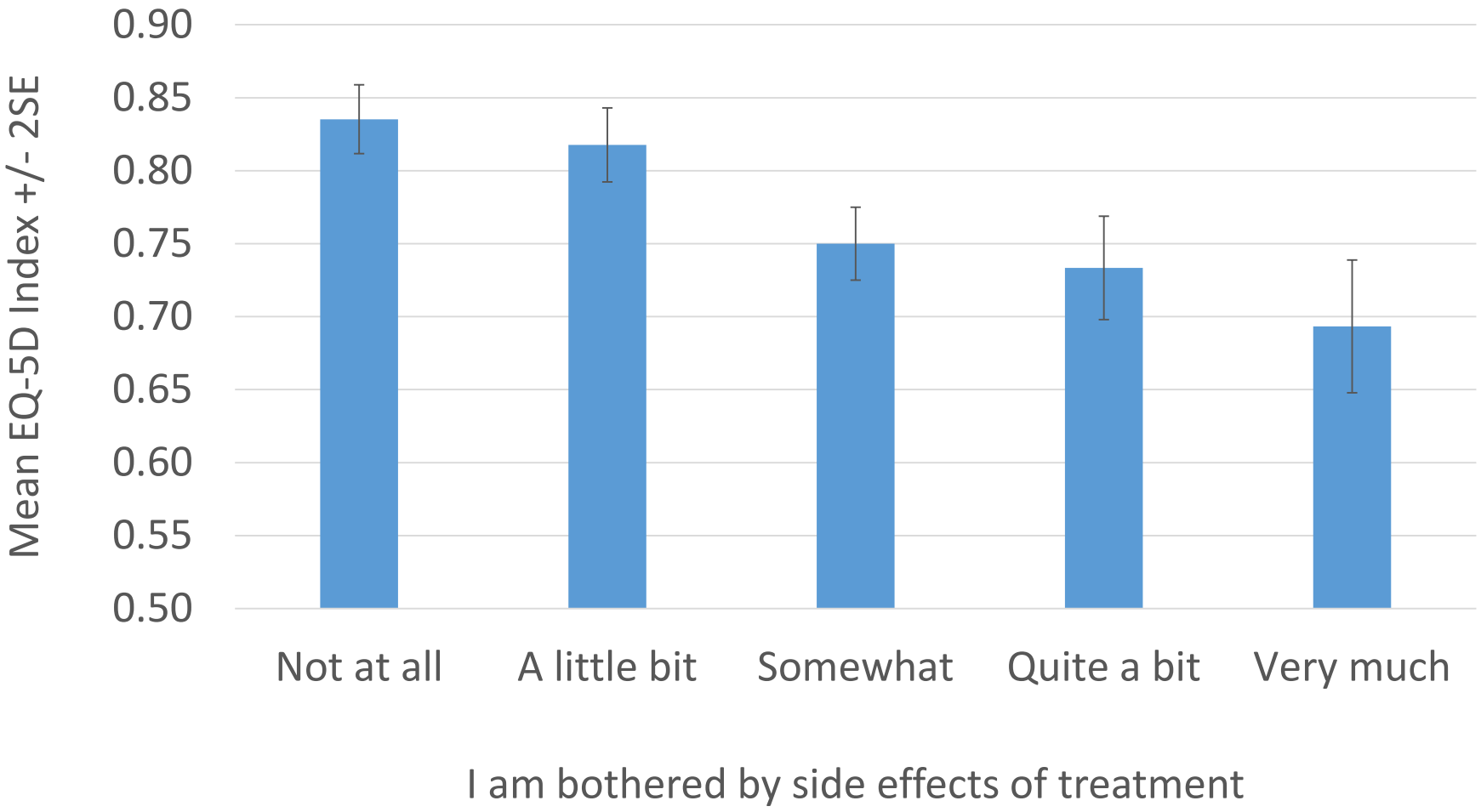
Study	Cancer Type	Timeframe	No. of Patients
NCCN Symptom Index Study	Bladder, brain, breast, colorectal, head & neck, hepatobiliary/pancreatic, kidney, lung, ovarian, and prostate cancers and lymphoma	2005-2006	533
BIOQOL	General (all cancers)	1994-1996	2,886
GOG 0249	High-risk, early stage endometrial carcinoma	2000-2014	474

Methods

Responses to GP5 ("I am bothered by side effects of treatment") correlated with indicators of QoL:

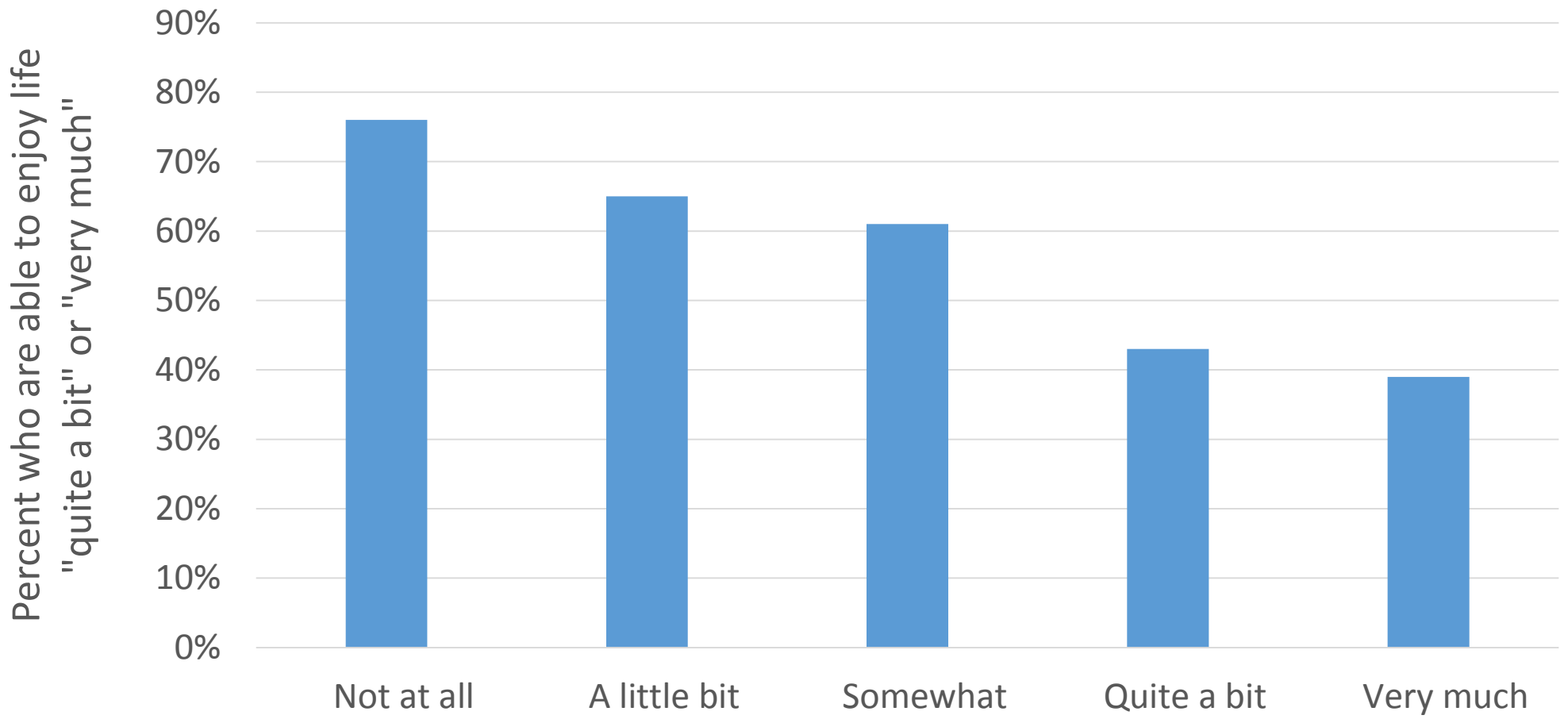
- FACT-G Item GF3 ("I am able to enjoy life") – % responding "quite a bit" or "very much" by GP5 response categories (ordinal chi-square)
- (NCCN study only) EQ-5D Health Utility score – means compared across GP5 response categories (analysis of variance)

NCCN Symptom Index Study (n=533)
EQ-5D utility by GP5 response



p<0.001

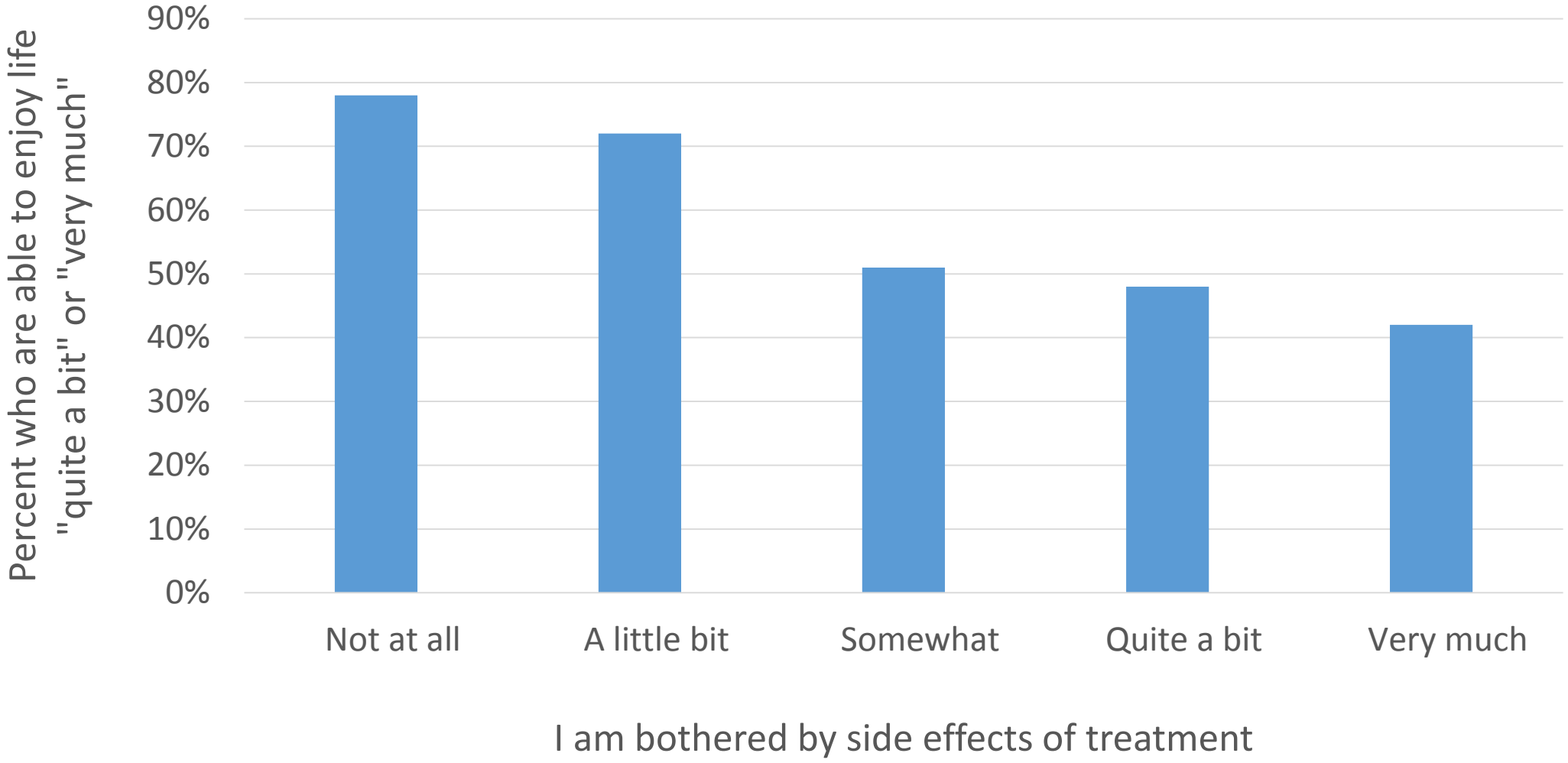
NCCN Symptom Index Study (n=533)
Percent of patients able to enjoy life by GP5 response



r=.028

ANOVA p<0.001

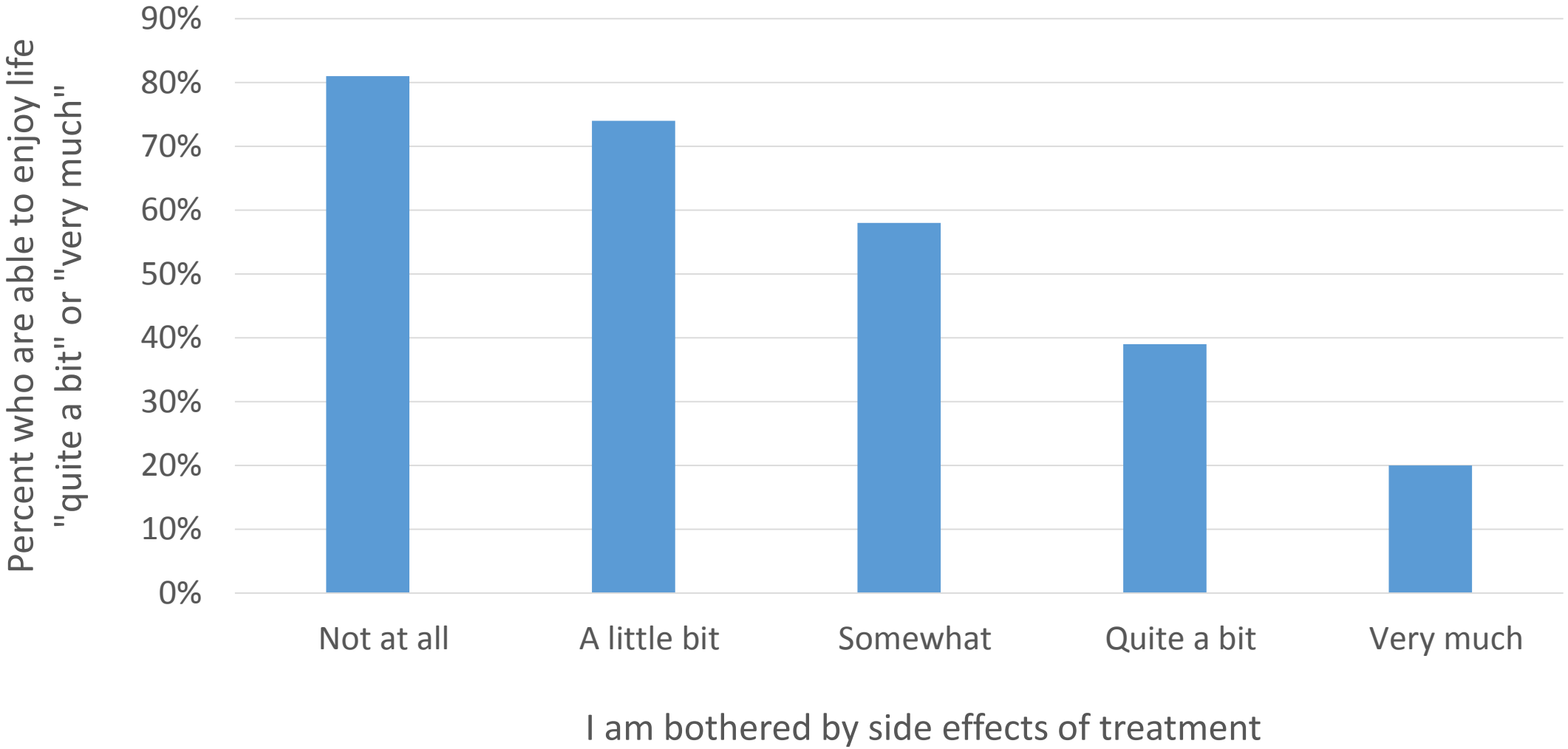
BIOQOL Study (n=2886)
Percent of patients able to enjoy life by GP5 response



ANOVA p<0.001

r=.028

GOG-0249 (n=474)
Percent of patients able to enjoy life by GP5 response



r=0.36

ANOVA p<0.001

“I thought cherry picking was illegal”… Steps to build custom assessments

- Educate
  - …oneself on the item library
- Evaluate
  - …fit of item content and language availability to research plan
- Create
  - …custom form
- Validate
  - …new questionnaire as to its responsiveness

Functional Assessment of Chronic Illness Therapy (FACIT) Item Library Overview

- 105 distinct questionnaires covering adults and children
  - Disease-specific (19 cancer; MS; HIV; Anemia)
  - Treatment-related (e.g., Neurotox; Taxanes; BRMs; Anti-angiogenesis, EGFR; BMT)
  - Symptoms
  - Function and well-being
- 716 Adult items
- 131 Pediatric items
- Covers all PRO-CTCAE major categories; maps to 55 of 80 symptom terms
- Translated into > 60 languages
- Select FACIT items and scales are part of PROMIS and NeuroQOL

Summary & Discussion

These analyses demonstrate validity of the single FACT-G item GP5, "**I am bothered by treatment side effects**," as linked to:

- Adverse event reporting
- Overall quality of life and utility

Future research can help:

- Identify the most bothersome side effects
- Identify the contribution of individual side effects in relation to one another and within the side effect profile
- Explore the validity and usefulness of custom assessments drawn from FACIT library

Symptoms and Functional Interference During Cancer Treatment

Charles S. Cleeland, PhD

McCullough Professor of Cancer Research

University of Texas MD Anderson Cancer Center

Overview

- Nearly one-third of cancer patients report at least three co-occurring moderate-to-severe symptoms during treatment
- “Treatment tolerability” is usually presented as percentage of all-grade and grade 3–4 adverse events
- Including the patient’s experience in judging tolerability is critical
- A simple scale (or item) that captures the patient’s perception of side effect burden would be useful
- The patient’s report of how much symptoms interfere with functioning during treatment might be a useful approximation of a tolerability measure

Tolerability from the Patient's Viewpoint: A Difficult Construct to Measure

- Tolerability is very context-dependent – risk/benefit will impact patient's judgment of tolerability
- Being context dependent, judgments of tolerability and expectations of treatment outcomes are likely to change over the course of treatment
- Very little qualitative work done on what "tolerability" means to patients
- Question for today: Could the Interference Scale of the MD Anderson Symptom Inventory (MDASI) contribute to understanding the construct of tolerability?

What is the MD Anderson Symptom Inventory Interference Scale (MDASI-INT)?

- The first part of the MDASI asks patients to rate the severity a set of “core” symptoms, and possibly several disease-specific or treatment-specific symptoms, on 0–10 scales with either a 24-hour or 1-week recall
- MDASI-INT scale: After rating individual symptoms, patients rate how much their (collective) symptoms have interfered with six domains of function (work, general activity, walking, mood, relations with others, enjoyment of life, and mood) on 0–10 scales, with anchors of “not at all” to “completely” with either a 24-hour or 1-week recall
  - Physical functioning subscale: Work, general Activity, Walking (WAW)
  - Affective functioning subscale: Relations with others, Enjoyment of life, and Mood (REM)
- This presentation will explore how the MDASI-INT reflects overall treatment burden

MDASI-INT Scale

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***? Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
14. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
15. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
16. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
17. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
18. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
19. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

Impact of Disease: Treatment-naïve NSCLC Patients (n=561); MDASI at Admission to MD Anderson

Unpublished data

Symptom	Mean Severity	SD	Percentage of Patients Reporting	
			Moderate to Severe Symptoms	Severe Symptoms
Fatigue	3.66	3.77	39	20
Disturbed sleep	3.24	3.26	35	22
Distress	3.12	3.08	34	19
Shortness of breath	3.01	3.02	31	20
Pain	2.90	3.01	31	20
Sadness	2.63	2.61	27	16
Drowsiness	2.28	2.36	23	13
Lack of appetite	1.90	1.99	19	12
Dry mouth	1.81	1.83	17	11
Difficulty remembering	1.48	1.48	12	5
Numbness or tingling	1.11	1.08	10	5
Nausea and vomiting	0.91	.89	9	6

Differences in Interference by Disease Stage: Treatment-naïve NSCLC Patients (n=561)

Unpublished data

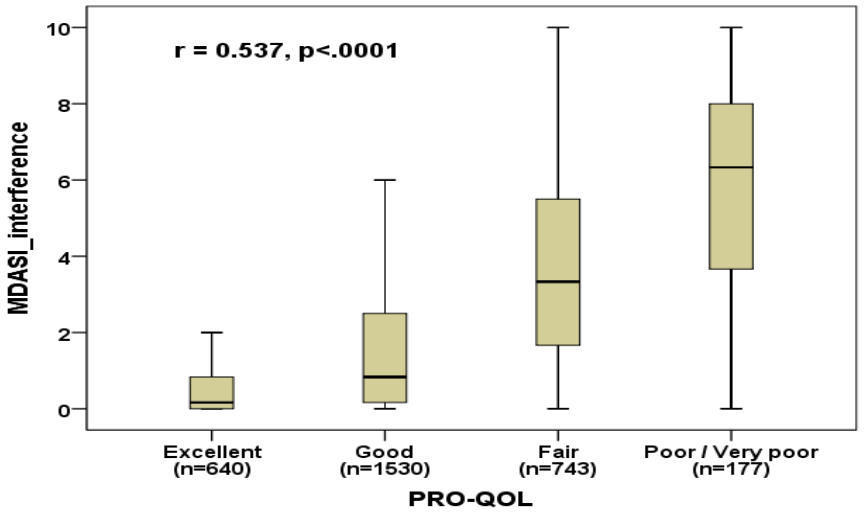
	Early (n=196)	Advanced (n=354)	Effect Size
WAW (physical interference subscale)			
Work	2.4 (3.1)	4.4 (3.6)	0.60
General activity	2.1 (2.8)	3.9 (3.4)	0.58
Walking	1.9 (2.9)	3.4 (3.5)	0.47
REM (affective interference subscale)			
Relations with others	1.3 (2.4)	2.2 (2.9)	0.34
Enjoyment of life	2.4 (3.0)	3.9 (3.5)	0.46
Mood	2.4 (2.8)	3.4 (3.1)	0.34
Total interference	2.1 (2.4)	3.5 (2.8)	0.54

Correlations of MDASI-INT Health Status: Glioma Patients (n=100)

Vera-Bolanos, Acquaye, Mendoza et al. *Neuro Oncology Practice*, in press

	EQ-5D Index Scores
Total interference	–0.64
WAW (physical interference)	–0.64
REM (affective interference)	–0.55

Correlations between MDASI-INT and a Single-Item Quality-of-Life Rating

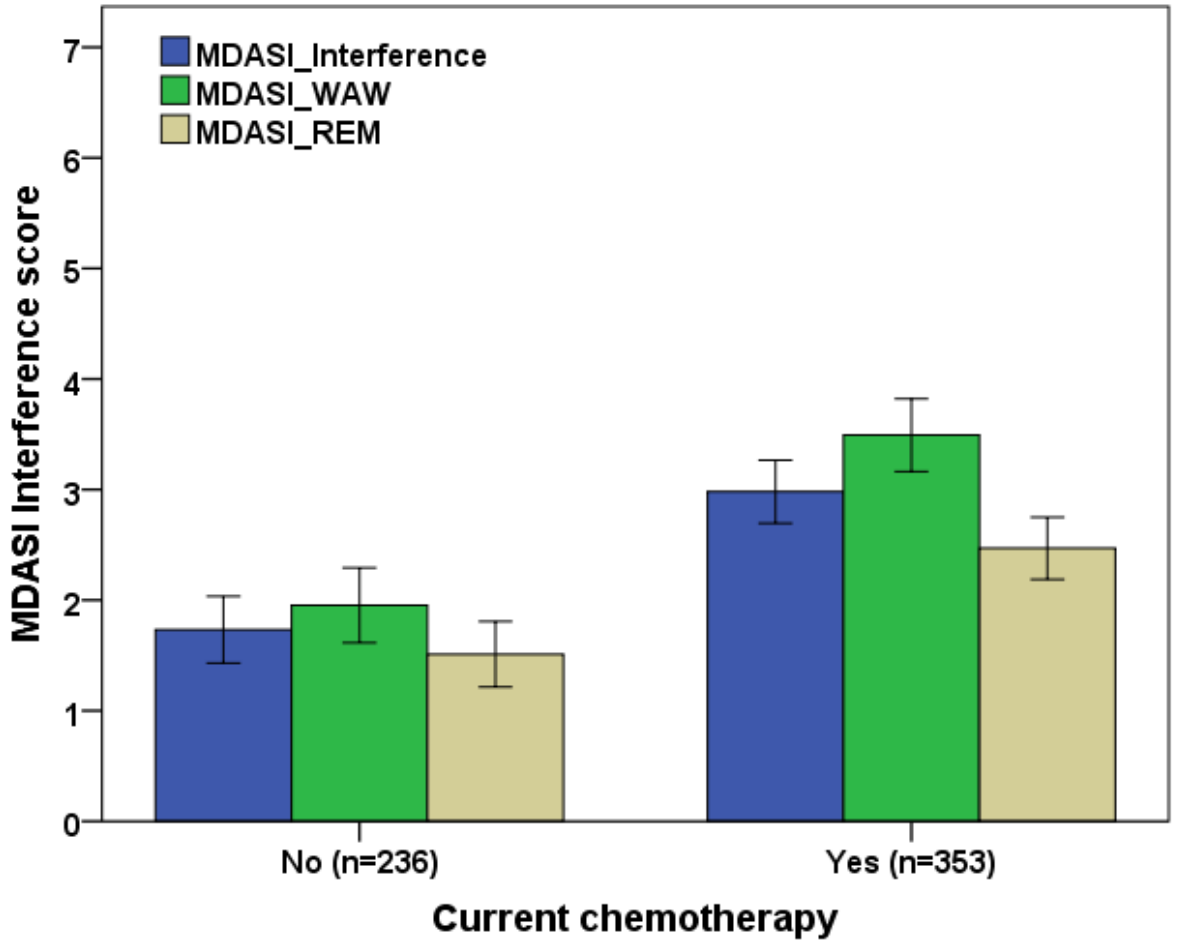


- ECOG SOAPP
- Cancer patients (n=3090)
- MDASI-Core & PRO-QoL
- Spearman correlation coefficient
  - Total interference 0.537
  - WAW 0.513
  - REM 0.514

Cohen's *d* effect size between adjacent QOL groups

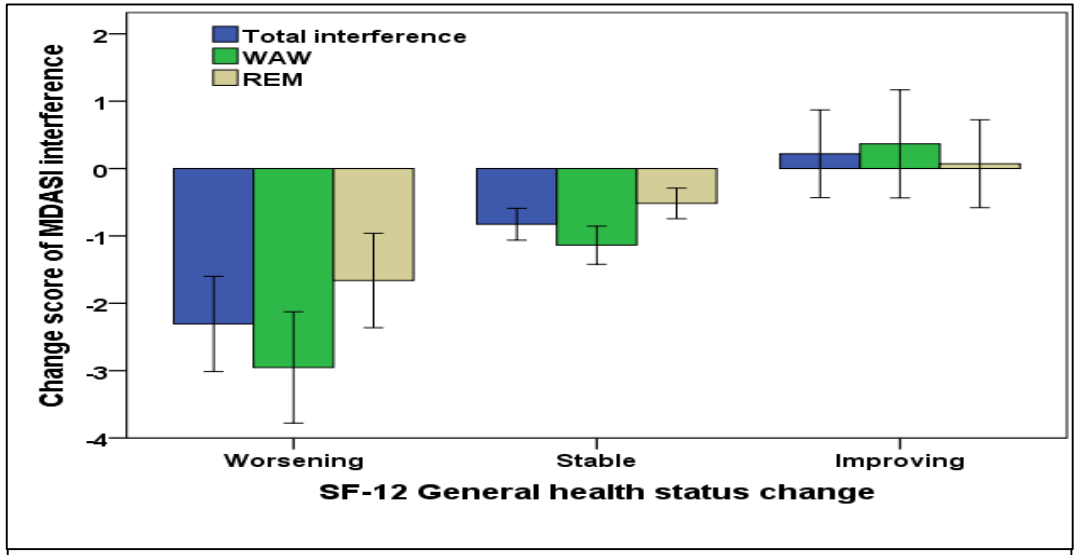
	Excellent vs. Good	Good vs. Fair	Fair vs. Poor/Very Poor
Total interference	0.54	1.08	0.88
WAW	0.51	0.89	0.76
REM	0.46	0.87	0.88

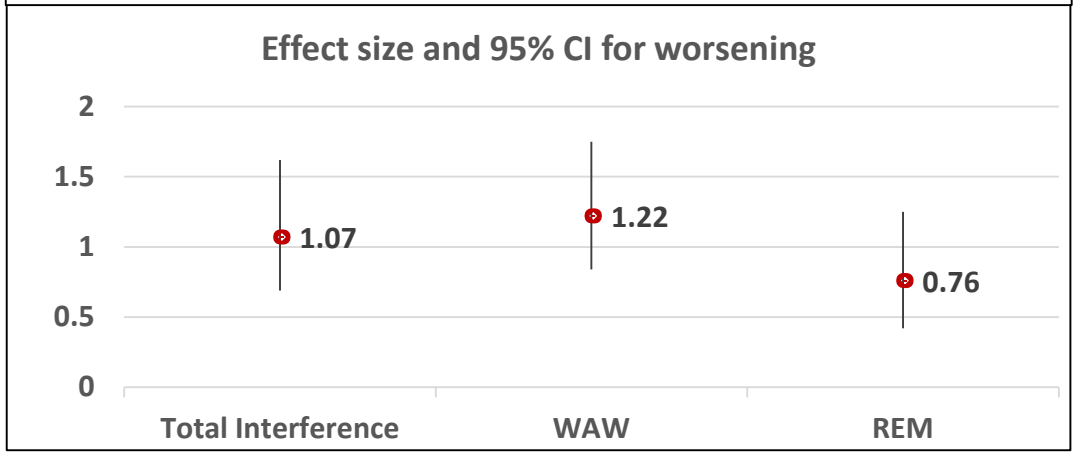
MDASI-INT in Patients with Local/Regional Cancer: Current Chemotherapy versus Not



MDASI-INT: Sensitive to General Health Worsening during Cancer Treatment

Shi et al. *Eur J Cancer* 2016





- Cancer patients
  - Surgery n=80
  - Chemoradiation n=110
  - Chemotherapy n=20
- MDASI and SF-12
  - Pre-treatment and 4–6-week follow-up
- SF-12 general health status as the anchor
  - 71 worsening, 138 stable, 9 improving
- Glass Delta effect size (ES = mean change score/standard deviation [baseline]) for general health worsening

Differences in Interference: Primary Brain Tumor, With Progression vs. Without (n=294)

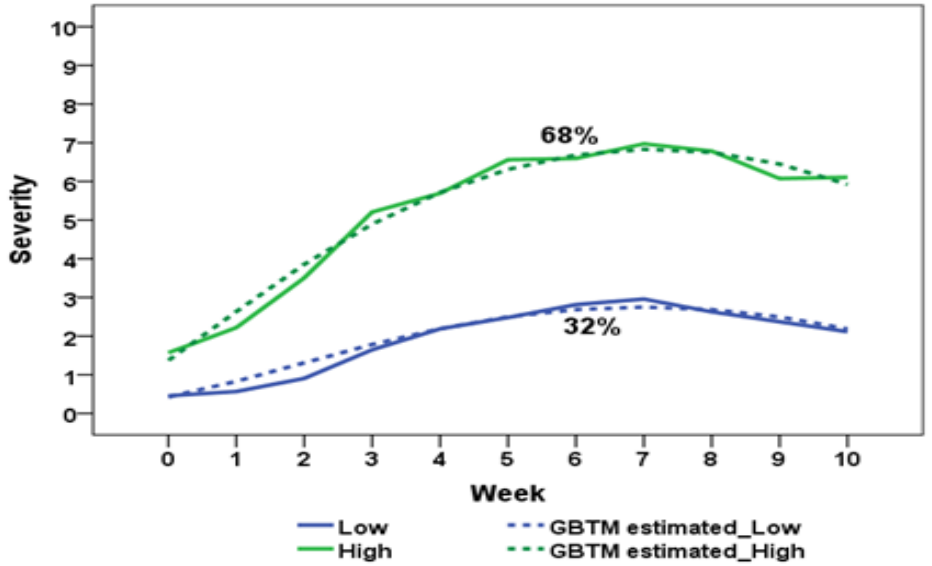
Armstrong, Vera-Bolanos, Gning et al. *Cancer* 2011

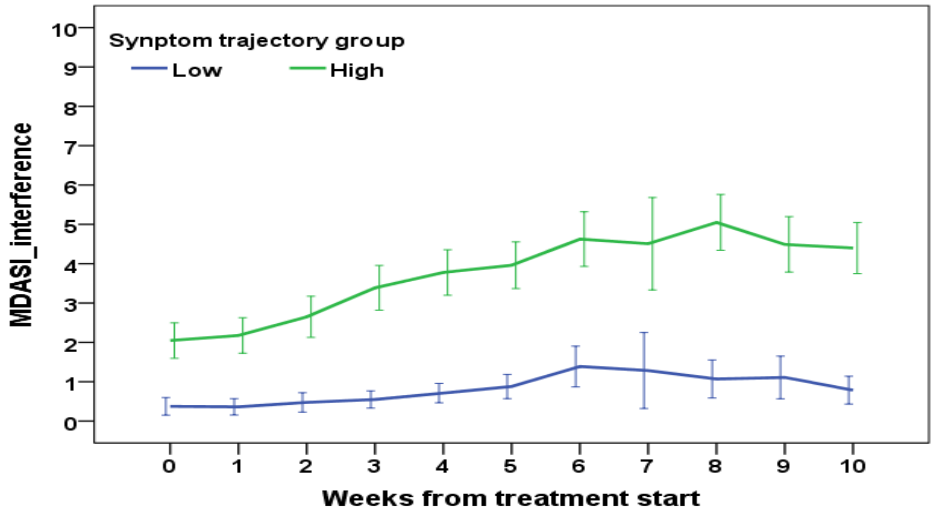
	With Progression (n=71)	Without Progression (n=223)
Total interference mean	3.93	2.00
REM mean	3.09	1.83
WAW mean	4.76	2.17
With WAW mean rating ≤4	36 (50%)	178 (80%)
With WAW mean rating ≥5	35 (50%)	45 (20%)

Greater MDASI-INT is Associated with Higher Symptom Severity

Shi, et al. *Qual Life Res* 2013

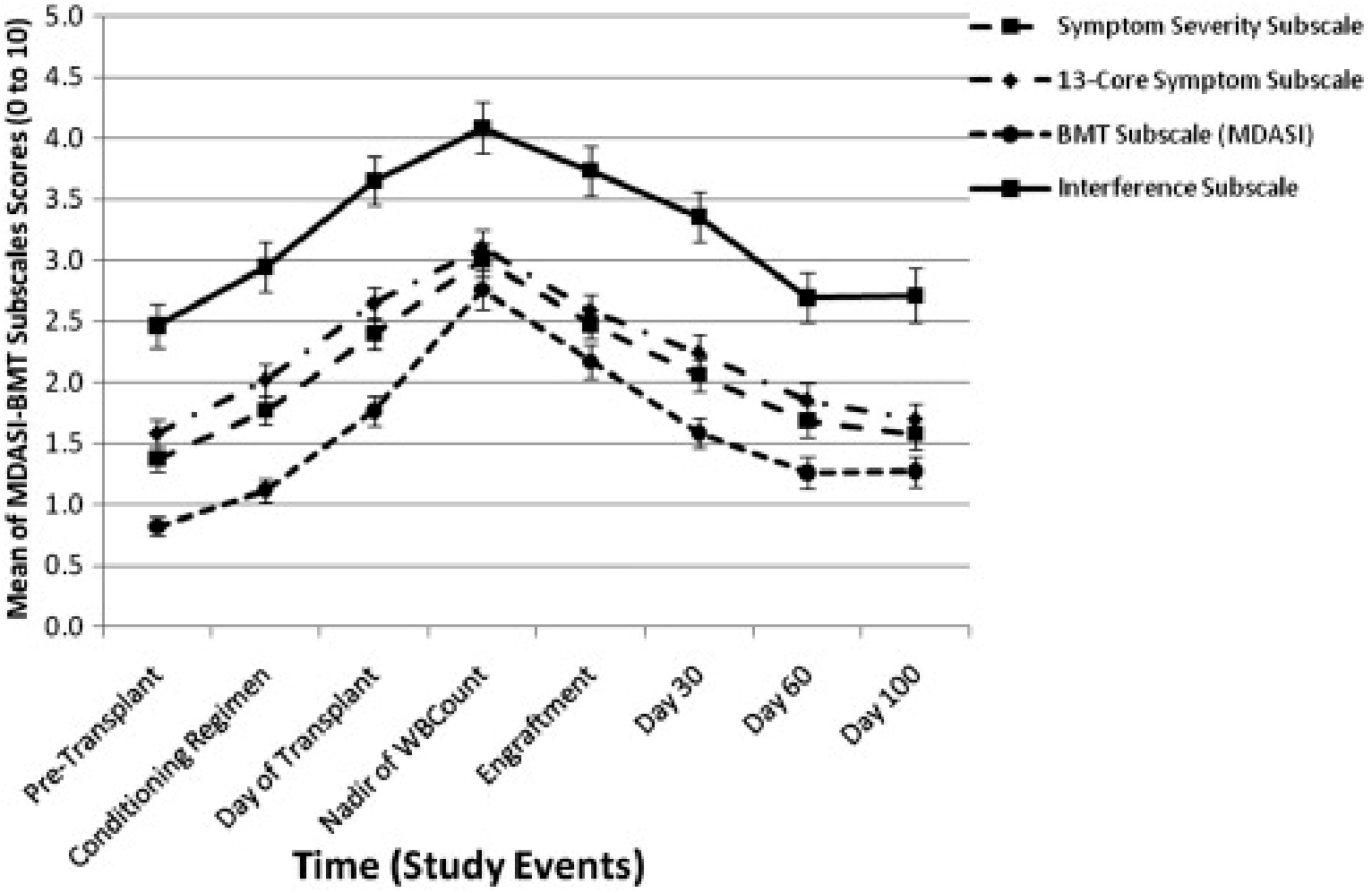
- Patients with head and neck cancer (n=131)
- Undergoing radiotherapy
- Top 5 most-severe symptoms: difficulty tasting food, difficulty chewing or swallowing, mucus, fatigue, and dry mouth
- Group-based trajectory modeling (GBTM)
- Two trajectories were identified
  - High 68% vs. low 32%
- MDASI total interference scores were higher in the high-symptom group than in the low-symptom group



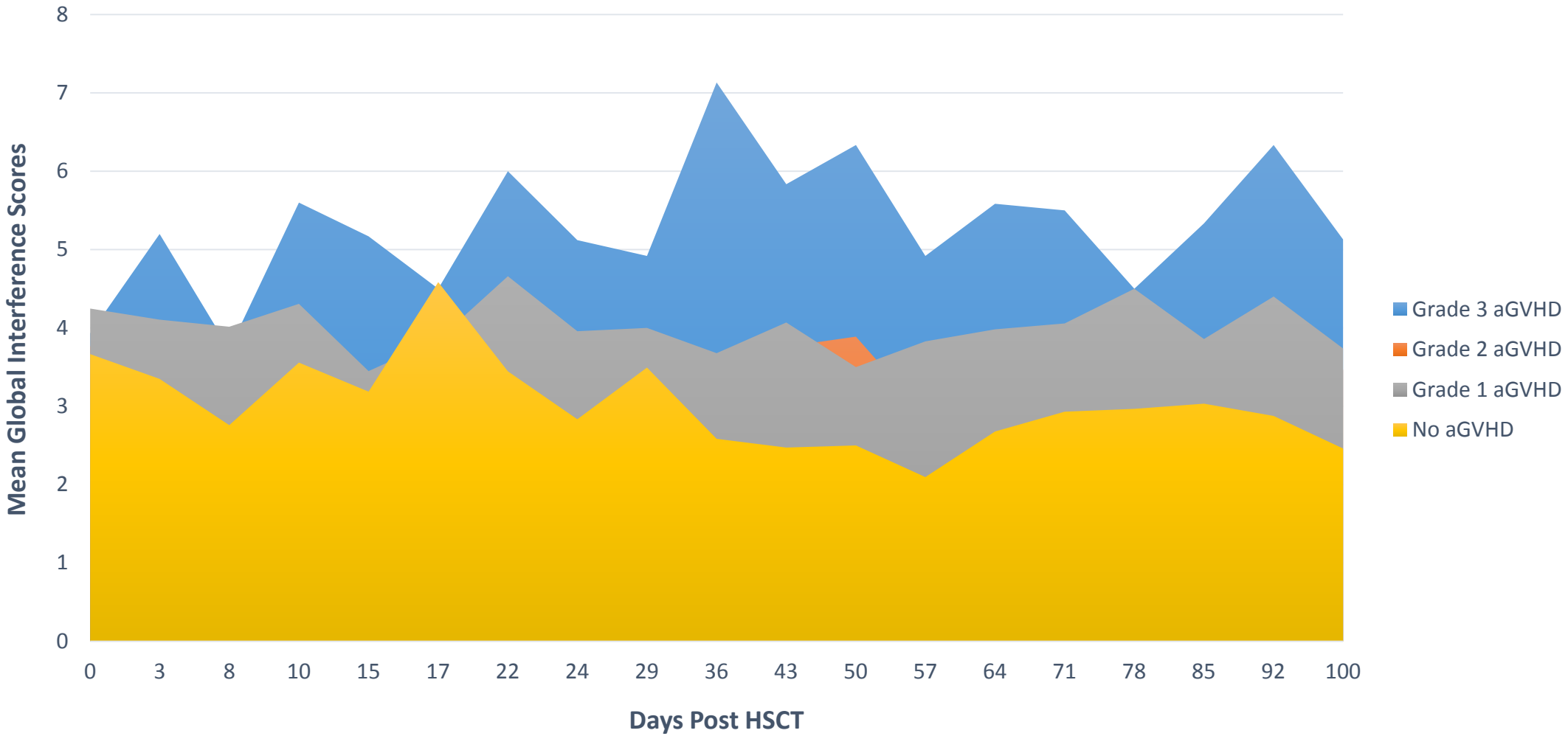


Longitudinal Symptom Severity and Interference: Hematopoietic Stem Cell Transplant (n=164)

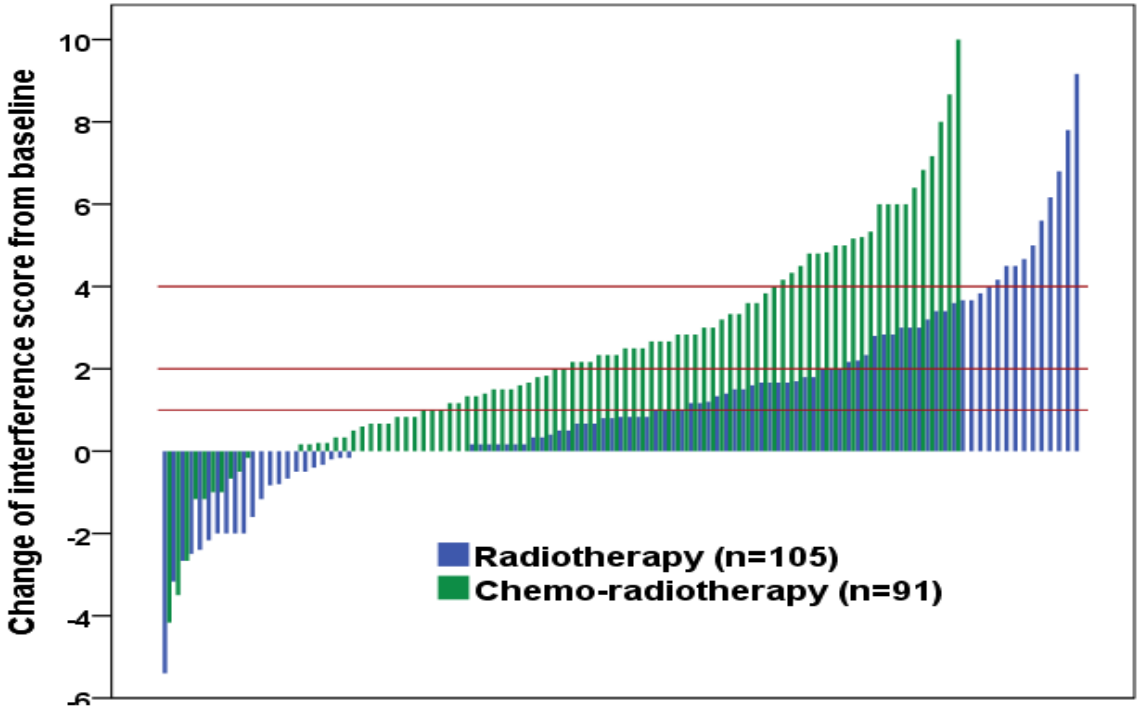
Cohen, Rozmus, Mendoza et al. *J Pain Symptom Manage* 2012



Reflection of Adverse Events: Longitudinal MDASI-INT Scores, First 100 Days after Allogeneic HSCT, by presence and grade of aGVHD



MDASI-INT: Change from Pre-treatment to End of Radiotherapy, by Treatment Modality

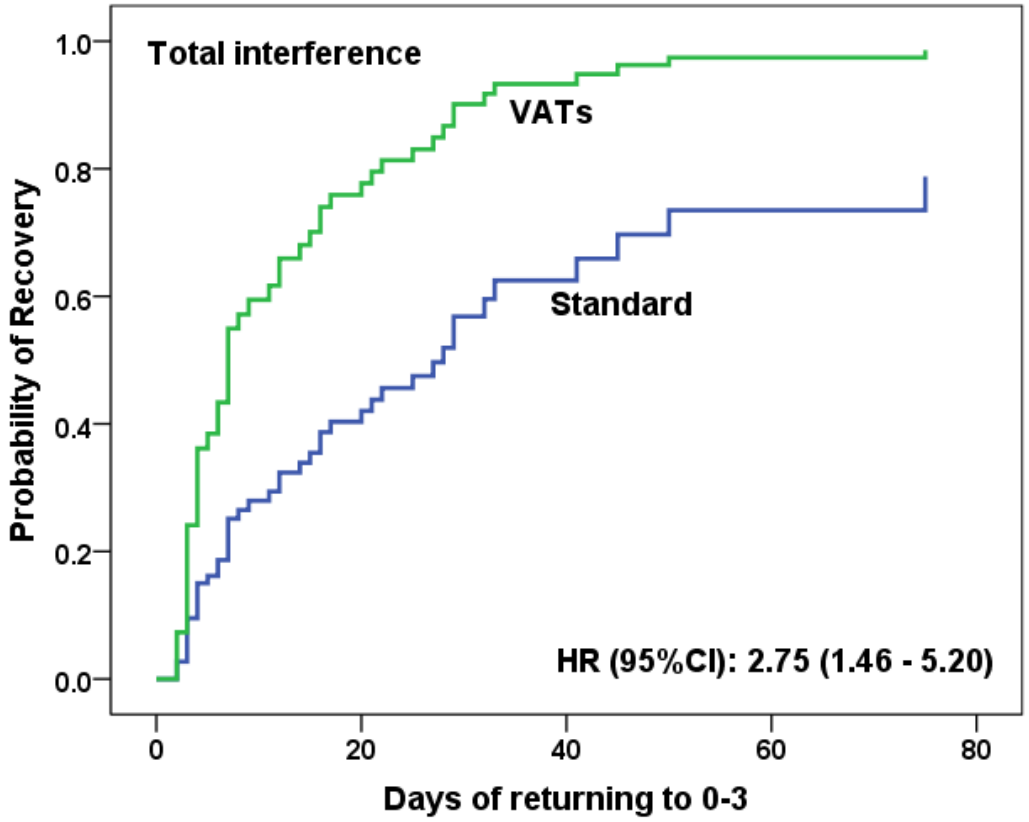


- Patients with head and neck cancer
- Treatment
  - Radiation only (RT) n=105
  - Concurrent chemoradiation (CXRT) n=91
- MDASI total interference change score from pre-treatment to end of treatment

Change Score	RT	CXRT	Fisher's Exact χ^2	P
1+	45.7%	67.0%	8.93	.004
2+	28.6%	51.6%	10.83	.001
4+	10.5%	24.2%	6.50	.013

MDASI-INT: Differentiating Functional Recovery to Preoperative Status, by Surgery Type

Shi et al. *J Pain Symptom Manage* 2016



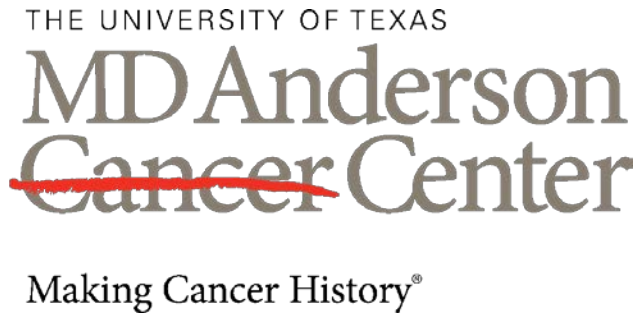
- Non-small cell lung cancer N=72
  - Open thoracotomy n=40
  - VATs (video-assisted thoracoscopic surgery) n=32
- Early stage cancer – stage I/II
- Treatment naïve
- MDASI-Core
  - pre-surgery
  - days 3 and 7
  - Months 1, 2, and 3

Summary

- The MDASI interference scale (MDASI-INT) is responsive in expected directions (improvement, deterioration) to changes in treatment status and meets expected psychometric properties
- The MDASI-INT takes 1–3 minutes to complete
- The 3 items of the MDASI-INT measuring interference with activity (WAW) perform as well as all 6 items (even shorter)
- But…ratings on this scale depend on status at time of assessment, including impact of disease – not a “pure” measure of treatment impact
- Change from baseline needs to be explored

Conclusions and Questions

- MDASI-INT scores vary with the dynamics of treatment and disease change; not a summary score reflecting total treatment; should treatment burden be treated as dynamic, or should it be a “global” summary impression at treatment end?
- How would a longitudinal summary of MDASI-INT (trajectory) reflect tolerability? AUC? Would another method be better?
- How would MDASI-INT perform without the preceding MDASI ratings of symptom severity?
- Requires frequent assessment, weekly or more often, rather than at baseline and end of cycle
- How responses to this scale, other scales, or single items reflect treatment tolerability needs to be explored with extensive qualitative interviews with patients


THE UNIVERSITY OF TEXAS
MD Anderson
Cancer Center
Making Cancer History®

Overall side effects burden Summary score?

Galina Velikova, MD
Professor/Consultant in Medical Oncology

Section of Patient-Centred Outcomes Research
Leeds Institute of Cancer and Pathology
University of Leeds
St James's Institute of Oncology
Leeds, UK

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The challenge

- Heterogeneity of new drugs
- How to compare drugs with different side effects profiles?
- How to address overall burden?
- New drugs with side effects not covered by existing instruments?
  - Need for rapid selection of PRO items
  - Create items lists that cover both drugs? Use of item libraries?
- What are the strengths and limitations of simply summating individual PRO measures of symptoms into an overall side effect score?

Outline

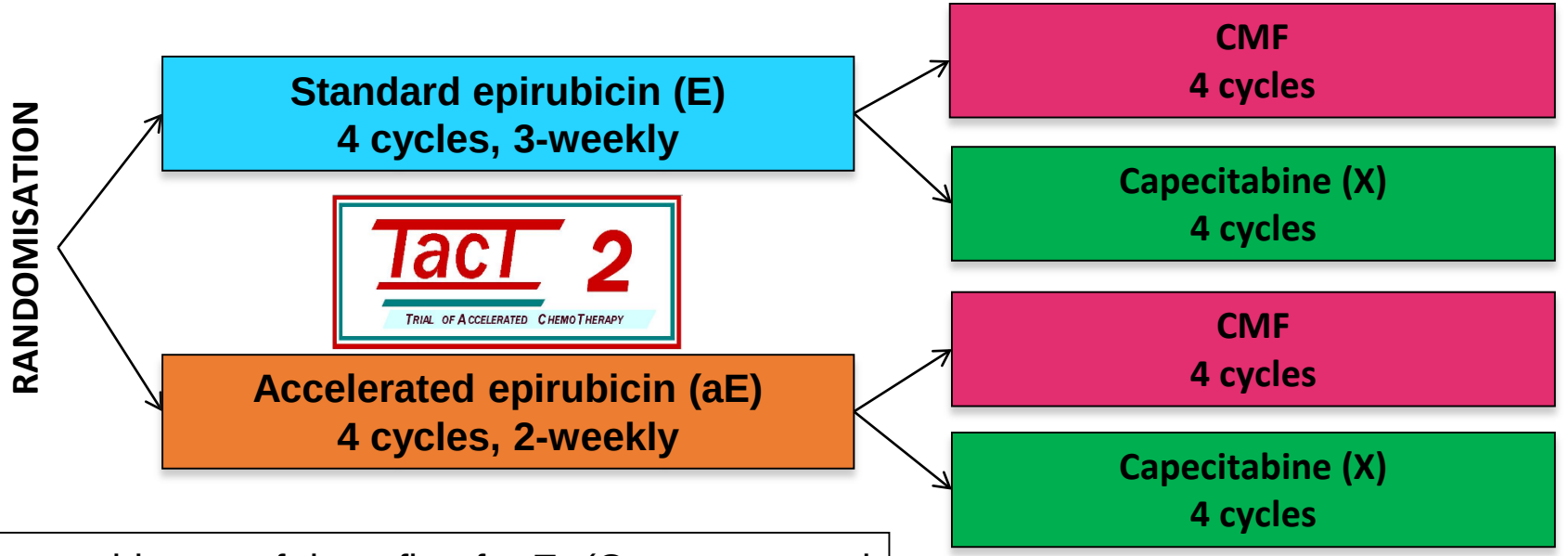
- Examples of clinical trials comparing drugs with different side effects profiles
- Existing PRO instruments with a summary score
- Potential approach to creating side effects lists for new drugs
- How to create a summary score
- Strengths and limitations

Example of drugs with different side effects profiles

TACT2, a phase III trial with 2 x 2 factorial design, E-CMF as control, tests two hypotheses:

A) Accelerating anthracycline chemotherapy (aE) offers greater efficacy

B) Oral capecitabine (X) gives similar efficacy but better toxicity profile to CMF

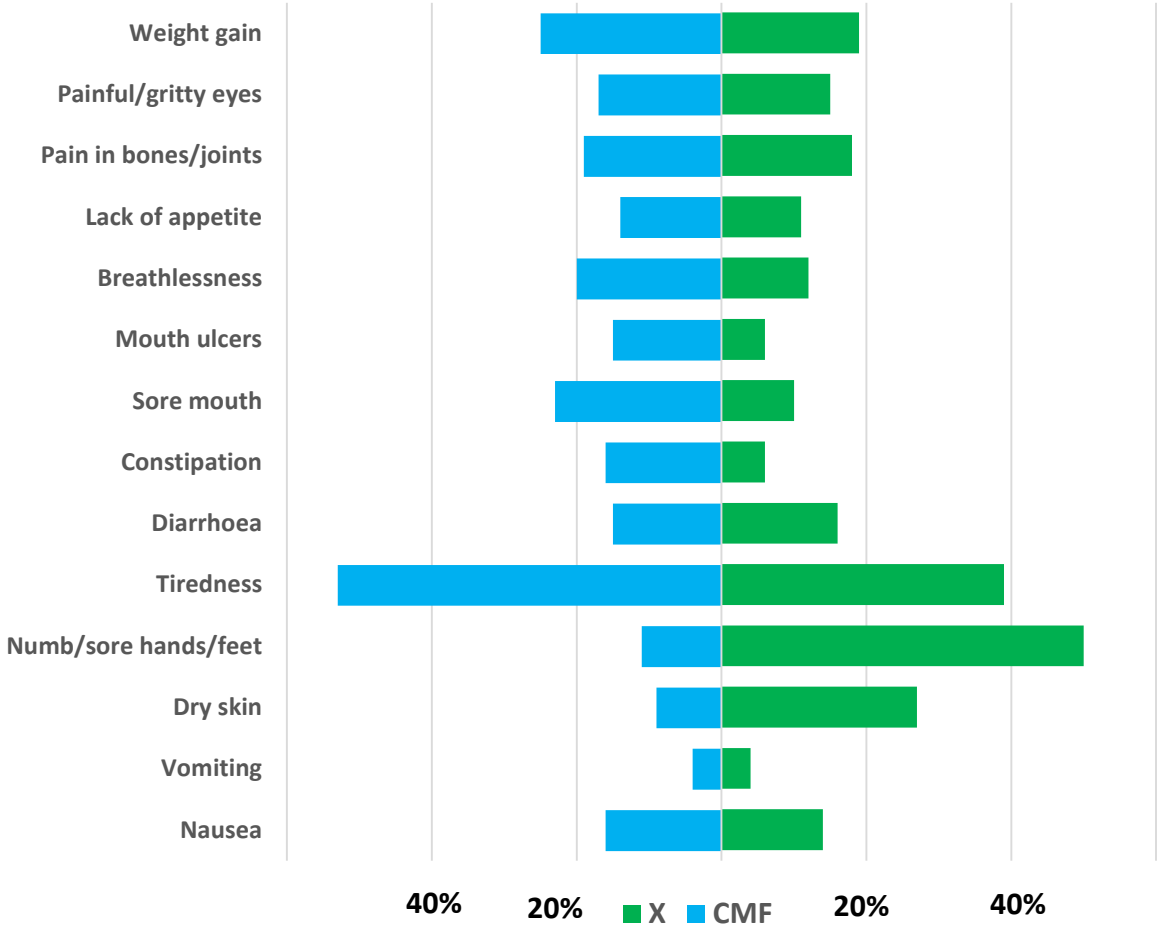


- Efficacy - no evidence of benefit of aE (Cameron et al SABCS 2012), & non-inferiority of X over CMF in time to tumour recurrence (Canney et al, EBCC 2014)
- Clinician-reported toxicity and patient-reported quality of life (QL) during treatment favoured E over aE and X over CMF (Cameron et al & Bliss et al, SABCS 2010)

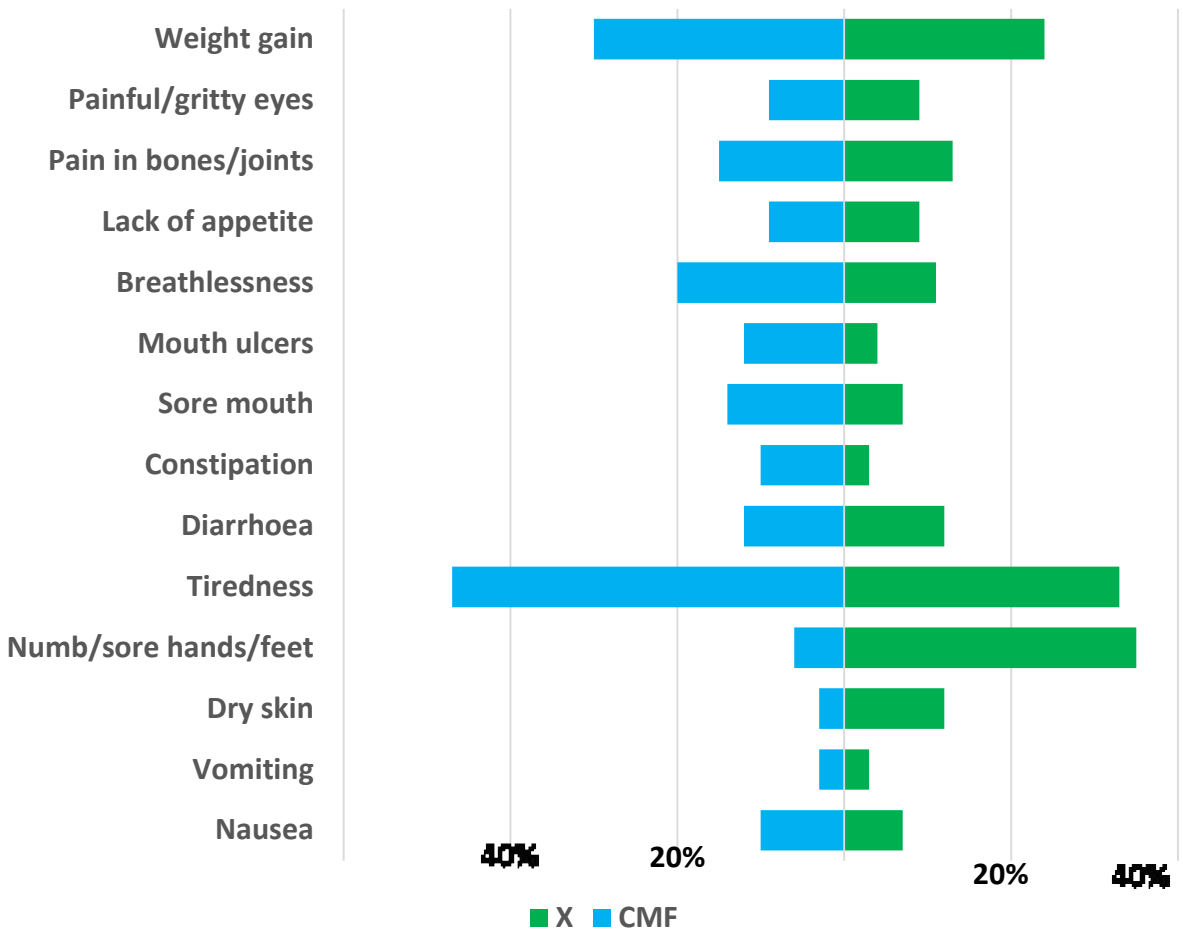
- **Patient-reported toxicity - Distress caused by toxicity and Daily Interference**
- **HRQOL- EORTC QLQ-C30 and BR23**

Distress and Daily interference caused by toxicity (N=888) (% patients Quite a bit + Very much)

Distress



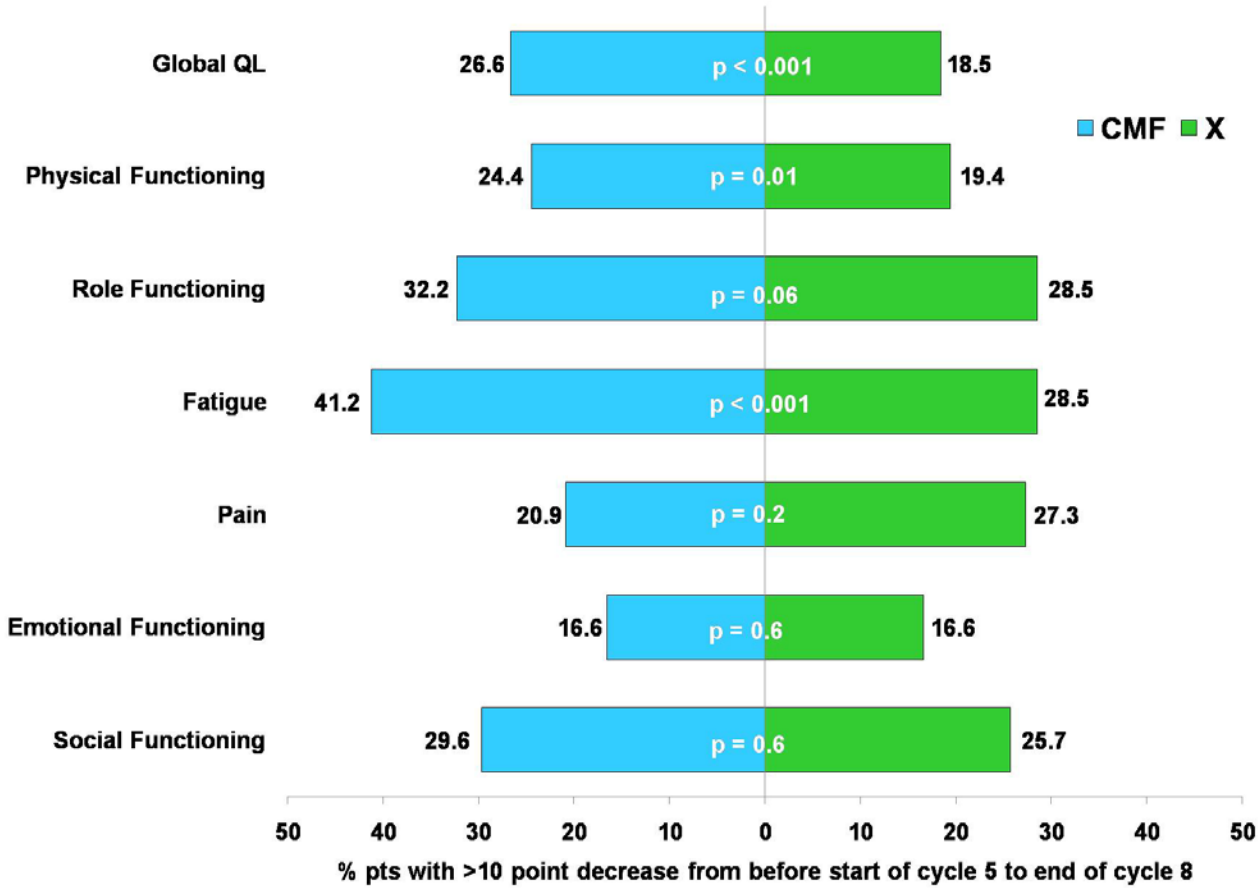
Daily Interference



Overall side effects burden – comparison of means of average distress scores per patient (range 0-4)

	N with data	Mean	SD	T-test p-value
Distress				
CMF	465	1.35	0.61	P=0.0018
X	492	1.22	0.62	
Daily interference				
CMF	465	1.18	0.58	P=0.0043
X	493	1.07	0.59	

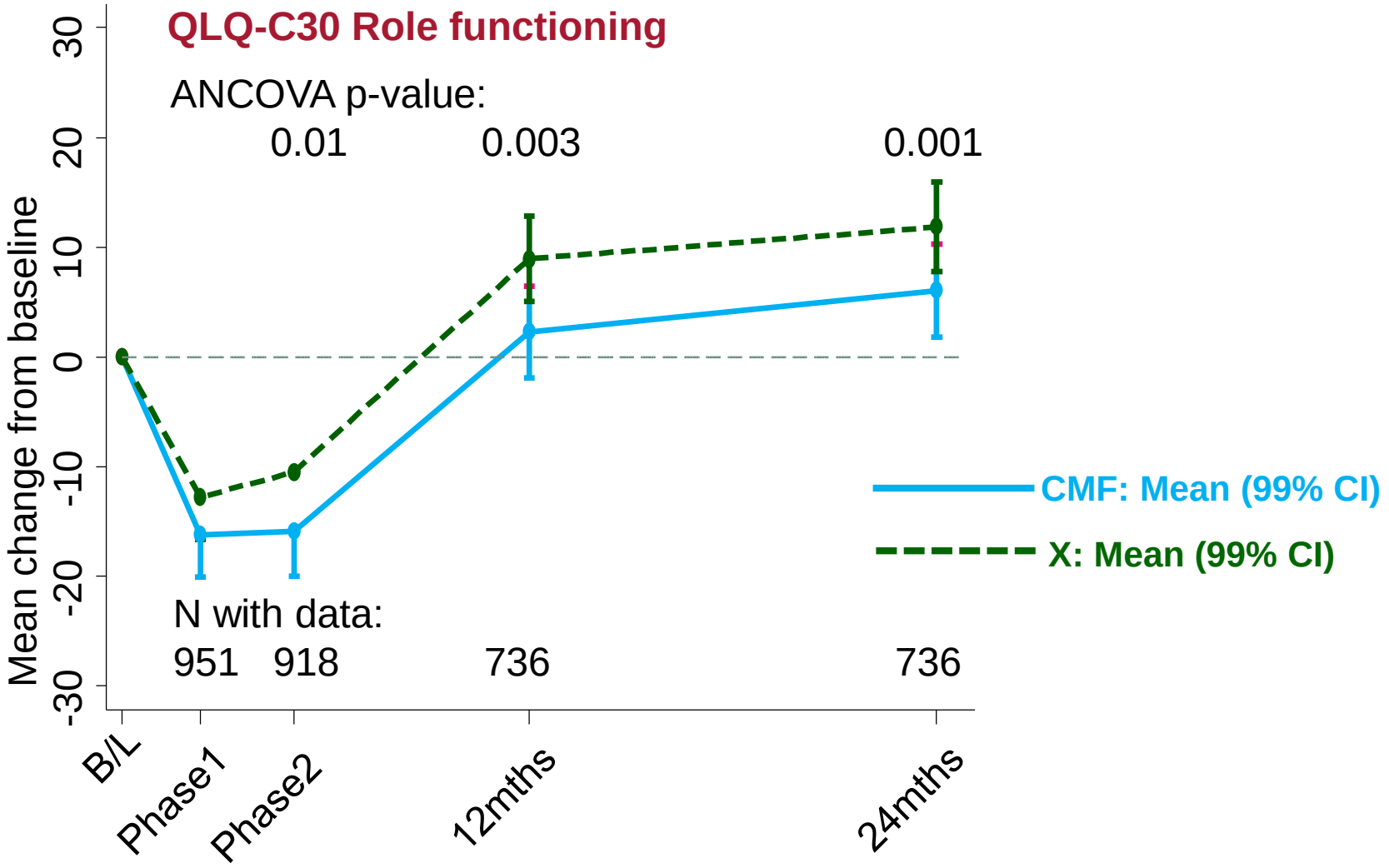
Impact on Quality of Life and functions (N=888)



The percentage of patients with >10 point decrease from before start of cycle 5 to end of CMF or X treatment (worse QL) are reported.

Global QOL, physical functioning & fatigue were worse with CMF than X

Impact on Role function over time



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Example of instrum... scores- FACIT

- FACT-BRM (Biological Response Modifiers) and
- Summary score – Trial Outcome Index TOI
- Physical, Functional and Additional concerns
- Score range 0-108

ADDITIONAL CONCERNS - Physical	Not at all	A little bit	Some-what	Quite a bit	Very much
I get tired easily	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I have a good appetite	0	1	2	3	4
I have pain in my joints	0	1	2	3	4
I am bothered by the chills	0	1	2	3	4
I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
I am bothered by sweating	0	1	2	3	4
ADDITIONAL CONCERNS - Mental					
I have trouble concentrating	0	1	2	3	4
I have trouble remembering things	0	1	2	3	4
I get depressed easily	0	1	2	3	4
I get annoyed easily	0	1	2	3	4
I have emotional ups and downs	0	1	2	3	4
I feel motivated to do things	0	1	2	3	4

Existing instruments with summary scores
FACT-BRM and TOI

Quality of Life in Patients With Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia on Imatinib Versus Interferon Alfa Plus Low-Dose Cytarabine:

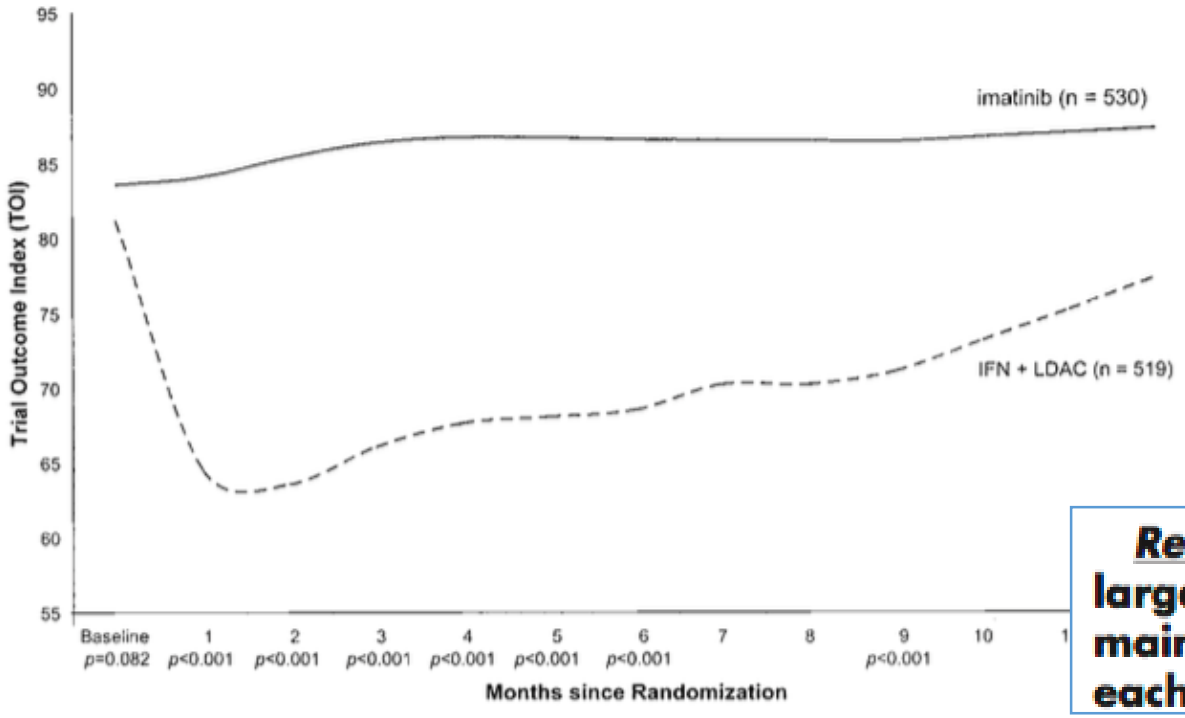


Fig 1. Estimated mean Trial Outcome Index scores by treatment arm, adjusted for missing data (intent-to-treat approach). *P* values are for difference in treatment arm means at each scheduled administration of the Functional Assessment of Cancer Therapy-Biologic Response Modifiers. IFN+LDAC, interferon alfa plus subcutaneous low-dose cytarabine.

J. Druker, Francois Guilhot,
on behalf of the IRIS Investigators

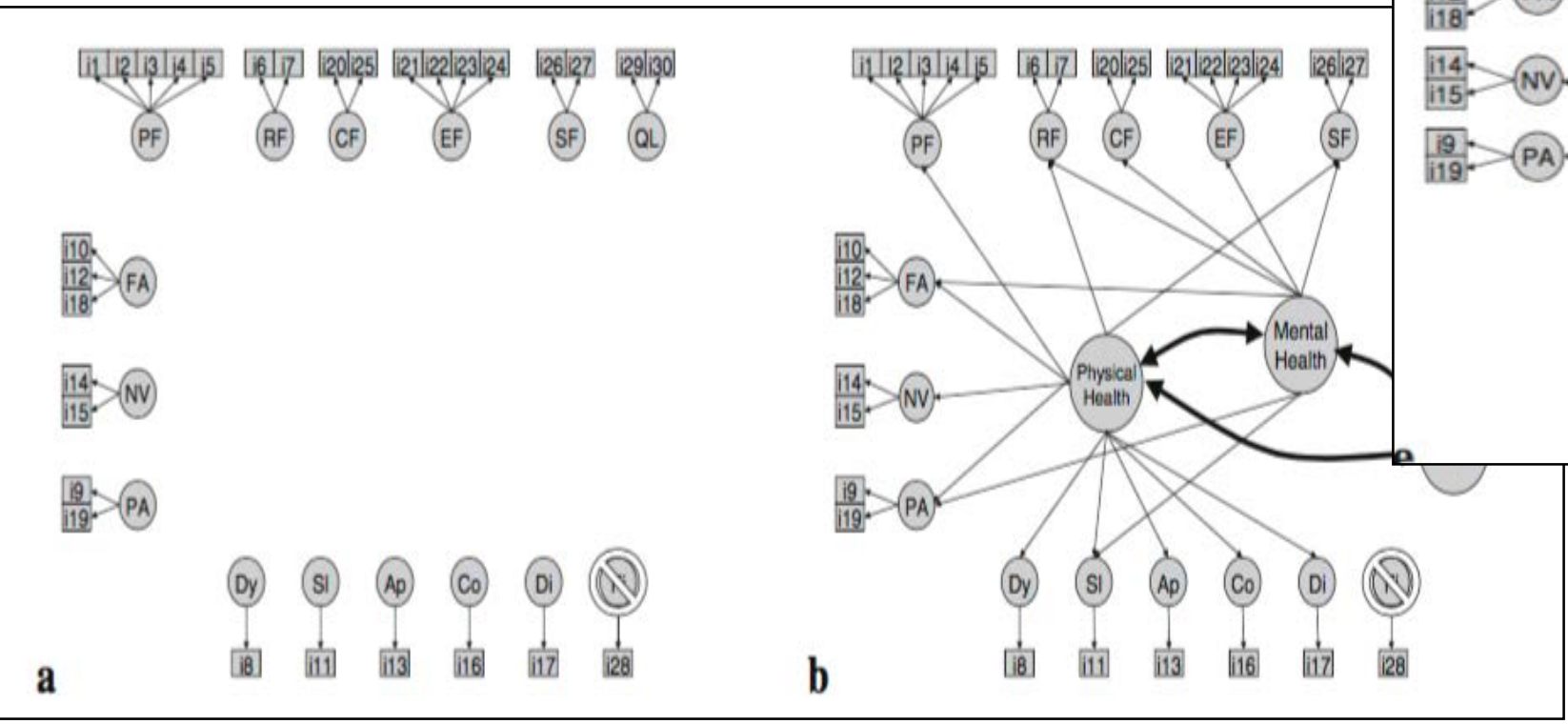
Results: **Patients receiving IFN+LDAC experienced a large decline in the TOI, whereas those receiving imatinib maintained their baseline level. Treatment differences at each visit were significant ($P < .001$) and clinically relevant**

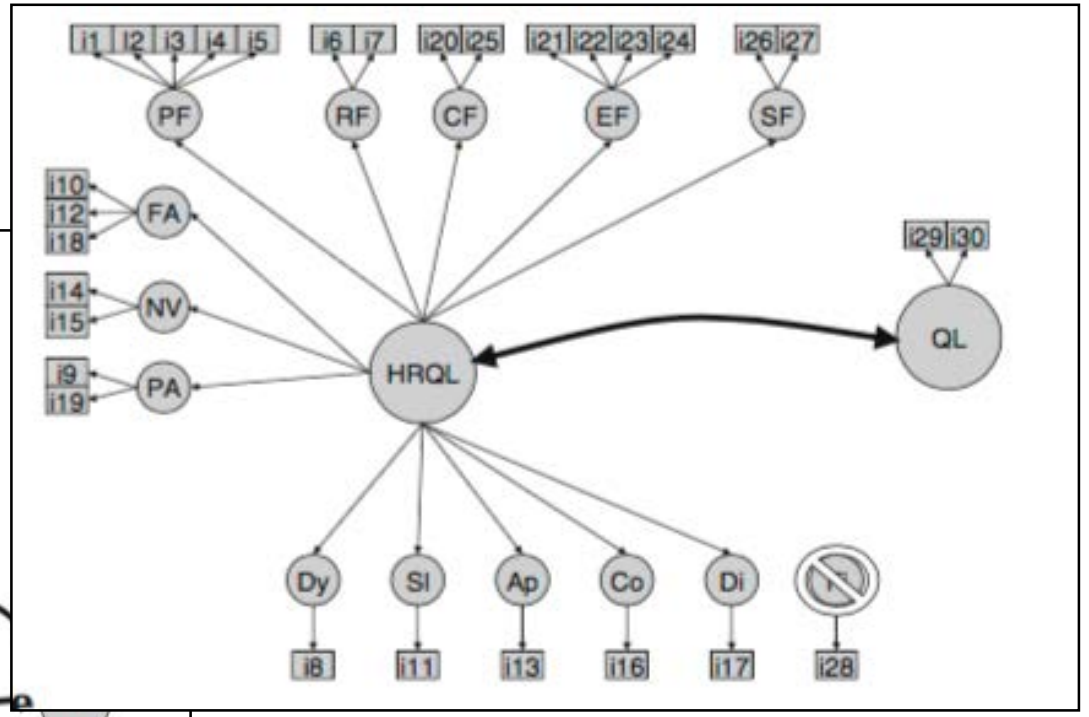
Evidence for a summary score?
EORTC QLQ-C30 confirmatory factor analysis

Qual Life Res (2012) 21:1607–1617
DOI 10.1007/s11136-011-0082-6

Comparing higher order models for the EORTC QLQ-C30

Chad M. Gundy · Peter M. Fayers · Mogens Groenvold · Morten Aa. Petersen · Neil W. Scott · Mirjam A. G. Sprangers · Galina Velikova · Neil K. Aaronson





Evidence for a single summary score?

ELSEVIER

CrossMark

Journal of Clinical Epidemiology 69 (2016) 79–88

Journal of Clinical Epidemiology

Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust

Johannes M. Giesinger[a,1], Jacobien M. Kieffer[a,1], Peter M. Fayers[b,c], Mogens Groenvold[d,e], Morten Aa. Petersen[d], Neil W. Scott[b], Mirjam A.G. Sprangers[f], Galina Velikova[g], Neil K. Aaronson[a,*], on behalf of the EORTC Quality of Life Group

[a]*Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands*
[b]*Institute of Applied Health Sciences, University of Aberdeen, Foresterhill Road, AB25 2ZD Aberdeen, UK*
[c]*Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Postboke 8905, N-7491 Trondheim, Norway*

- "The validity and responsiveness of this QLQ-C30 summary score was equal to, and in many cases superior to the original, underlying QLQ-C30 scale scores"

Table 5. Effect sizes and relative validities for the scales and summary score of the EORTC QLQ-C30 using the known-group comparison for performance status

	Karnofsky, 0–80, N = 693		Karnofsky, 90–100, N = 1,059			
Scale	Mean	SD	Mean	SD	ES	RV
Summary score	62.0	18.1	83.7	14.8	1.34	1.00[a]
PF	60.5	25.6	87.0	16.4	1.29	0.93
SF	57.4	33.1	84.1	23.4	0.97	0.52
RF	39.7	36.4	80.8	27.2	1.32	0.97
EF	67.5	25.8	75.2	23.4	0.32	0.06
CF	72.5	26.4	87.2	18.8	0.66	0.25
QL	43.8	23.1	68.5	22.1	1.10	0.67
FA	56.5	28.5	25.3	25.1	−1.18	0.77
NV	20.2	26.8	6.2	15.0	−0.68	0.26
PA	50.6	34.5	19.3	25.4	−1.07	0.63
DY	33.1	32.5	15.0	24.4	−0.65	0.24
SL	35.5	34.9	25.0	30.4	−0.33	0.06
AP	43.5	38.7	12.7	24.7	−0.99	0.55
CO	35.6	35.9	13.7	25.7	−0.73	0.29
DI	15.6	27.8	8.5	19.8	−0.30	0.05

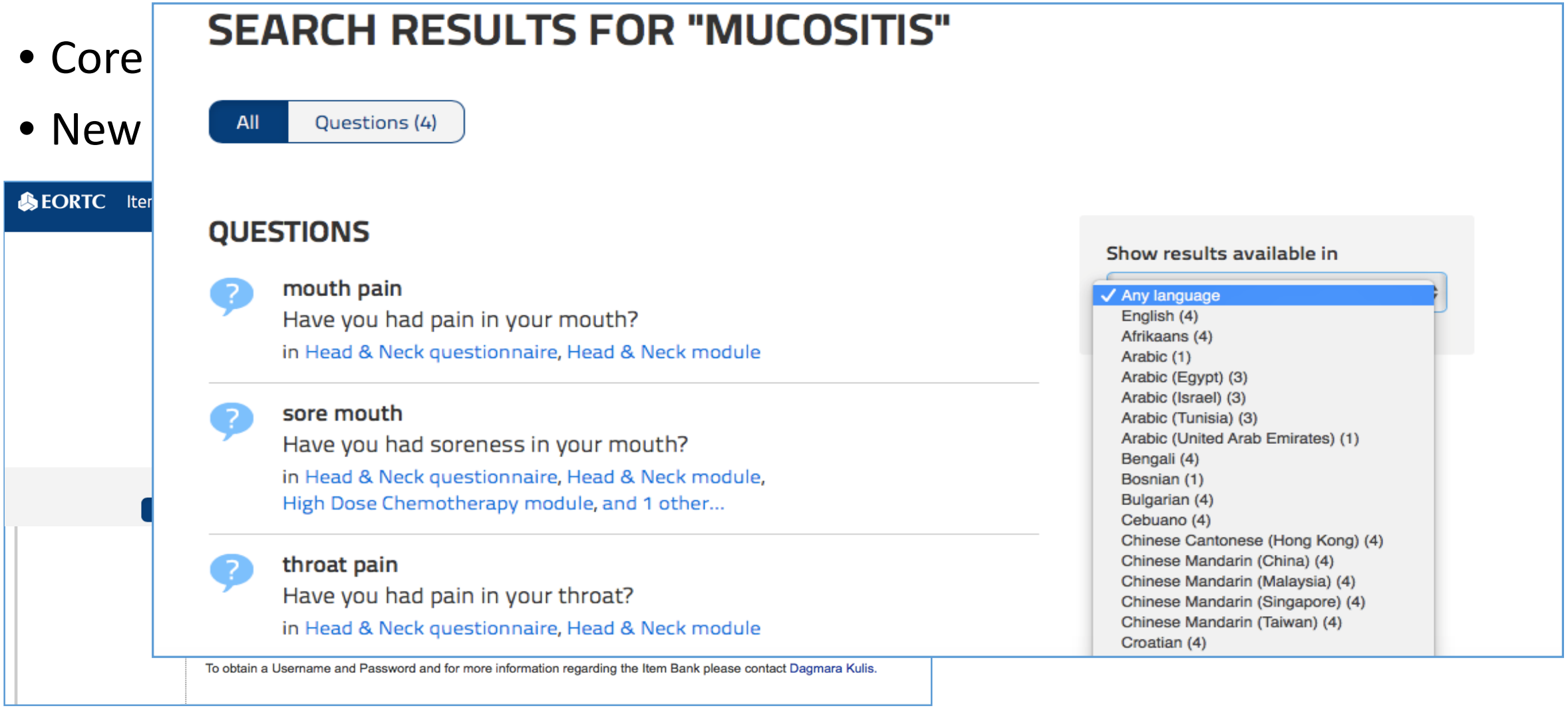
Abbreviations: AP, appetite loss; CF, cognitive function; CO, con-

Outline

- Examples of clinical trials comparing drugs with different side effects profiles
- Existing PRO instruments with a summary score
- Potential approach to creating side effects lists for new drugs
- How to create a summary score
- Strengths and limitations

EORTC measurement Strategy- Item library

- Core
- New



Suggested approach to Item list generation

- Follow in brief the stages of Module development guidelines
- Generate a list of side effects for each drug
  - Review Phase 1 and 2 trials for reported CTCAE
  - Interview clinicians and patients
- Finalize the list to cover both treatments, balance the number of expected side effects
- Search the item library and select the items
- Decide on scoring procedures

NCI PRO-CTCAE instrument and form builder

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

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

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

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

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

FACIT Item library- covered by Dave Cella

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How to create a summary score?

- Mean score or Total score
- Compare number of side effects
- Compare proportions of high severity? (akin to CTCAE reporting)
- Time effects
  - Mixed effects modelling
  - AUC approaches
  - Q-TWIST

Strengths and limitations

- Single score is attractive -HOWEVER
- Clinicians and patients still need to know which side effects contribute to the summary score - **add a profile**
- When creating new items lists - essential to **balance the side effects for each treatment. Need for guidelines?**
- Is it the number of side effects or the severity that matters? Weighting of side effects is difficult?
- In addition to a summary score - use **impact on function or interference questions**
- We need more **empirical testing** of summary score approaches using existing datasets

Listening to the Patient Voice

Mary Lou Smith, MPA, MBA, JD
Co-Founder, Research Advocacy Network

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What I heard from you

- Our task is to find a PRO to better describe the tolerability of cancer therapies
- Tolerability is not the same as QoL or patient experience - tolerable is "*I got through the treatment alive.*"
- Is tolerability the right measure or patient outcome?
- Could we use bothersomeness, MDASI Interference scale or overall side effect burden to provide a single measurement?

Why is this important to patients?

- Patients could use this information to:
  - Make treatment decisions
  - Set expectations for themselves and their caregivers
  - Make plans, e.g., leave work, go part time, arrange for help at home

- Research Advocacy Network listened to what patients had to say
  - Benefit matters more than toxicity
  - Side effects matter
  - Severity and duration of side effects affect treatment decision-making
  - Patient preferences differ
  - Some patients will take treatment no matter what
  - If a patient had experienced a side effect previously, they had a stronger preference either for or against a treatment based on that experience

What are patients willing to do?

- Patients And Caregivers Experience (PACE) study
  - Newly diagnosed with breast cancer requiring chemotherapy
  - Participated in online discussion board
  - Synchronous conversations between participant and moderator
  - New conversations each week
  - Study lasted 16 weeks
  - 100% of patients stayed engaged, 67% of caregivers
  - Study participants valued “someone was listening”, “it made me self-reflect”, “helped me deal with what I was going through”

What are patients willing to do?

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What are patients willing to do?

Patients are willing to fill out forms or participate in online chats as long as they are getting something out of it – it could be an intervention, an opportunity to be heard or a sense of altruism that they are helping others.

Caveats

- Patients may not be able to distinguish
  - Between a side effect of treatment and disease
  - Which drug in a multiple drug regimen is causing a side effect
- They need
  - Information about why it is important to them and their treatment?
    - What is the benefit to them?
    - Does it make a difference in their treatment?
- Quality of life may be influenced by life events other than cancer diagnosis and treatment
- Since patients in clinical trials are usually in better health than patients in the general cancer population does the experience of a clinical trial population equate to the experience of the general population with that cancer, drug and side effects?
  - What about post-marketing trials?
  - Why don't we do more of them?

Caveats

Could we ask patients to rate how side effects affected their lives using a question related to patient experience?

Panel Discussion and Q & A

Chair

- *Paul G. Kluetz, MD* – Acting Associate Director of Patient Outcomes, OCE, FDA

Presenters

- *David Cella, PhD* – Professor & Chair, Department of Medical Social Sciences, Feinberg School of Medicine, Northwestern University
- *Charles S. Cleeland, PhD* – McCullough Professor of Cancer Research, University of Texas MD Anderson Cancer Center
- *Galina Velikova, BMBS(MD), PhD, FRCP* – Professor, University of Leeds

Panelists

- *Mary Lou Smith, MPA, MBA, JD* – Co-Founder, Research Advocacy Network
- *Daniel O'Connor, MB, ChB, PhD, MFPM* – Expert Medical Assessor, MHRA
- *Ethan Basch, MD, MSc* – Director, Cancer Outcomes Research Program, University of North Carolina
- *Michelle Campbell, PhD* – Reviewer and Scientific Coordinator, COA Qualification Program, COA Staff, OND, CDER, FDA