



ASCO[®]

FIFTH ANNUAL CLINICAL OUTCOME ASSESSMENTS IN CANCER CLINICAL TRIALS (COA-CCT) WORKSHOP

Lunch Session:

**Exploring a global question capturing side effect bother
to complement our understanding of tolerability**

#OCEOutcomes20



SESSION 3

An interactive panel discussion to explore how a global item capturing side effect bother complements the picture of tolerability



MODERATOR
Paul G. Kluetz, MD



Janet Freeman-Daily,
MS, ENG



David Cella, PhD



Laura Fernandes,
PhD



Sandra Spivey



Gita Thanarajasingam,
MD



Preeti Narayan, MD



Sandra Mitchell, PhD



#OCEOutcomes20



MODERATOR
Paul G. Kluetz, MD



What is “Tolerability”

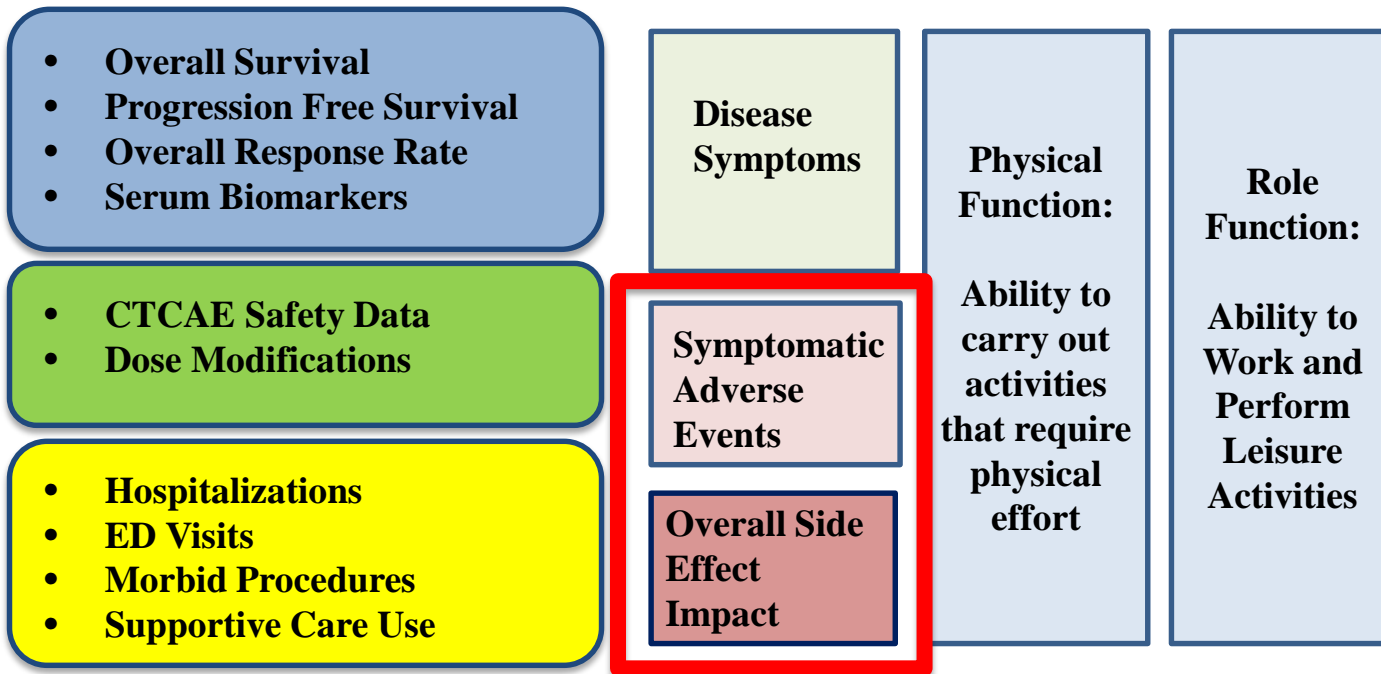
The degree to which overt adverse effects can be tolerated by the subject

International Conference on Harmonization (ICH) E9

What is “Tolerability”

The degree to which **symptomatic** and non-symptomatic adverse events associated with the product’s administration affect the ability **or desire** of the patient to adhere to the dose or intensity of therapy. A complete understanding of tolerability should include direct measurement from the patient on how they are feeling and functioning while on treatment.

@FDA Oncology Core Outcomes



Clinician Reported and Biomarker Data

Patient-Reported and other COA Data

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

Fictitious Head-to-Head Randomized Trial

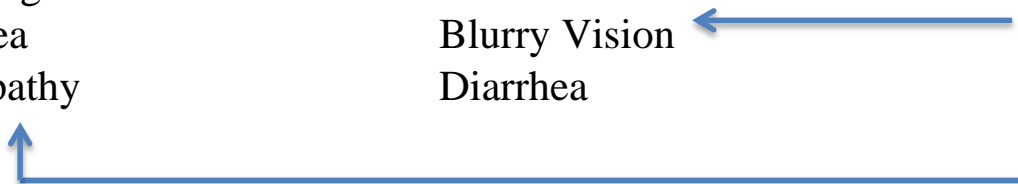


Drug A Side Effects

Nausea
Vomiting
Diarrhea
Neuropathy

Drug B Side Effects

Neuropathy
Rash
Blurry Vision
Diarrhea



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

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

Fictitious Head-to-Head Randomized Trial



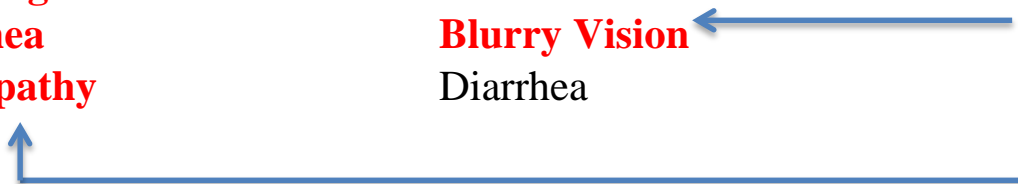
Drug A Side Effects

Nausea
Vomiting
Diarrhea
Neuropathy

Drug B Side Effects

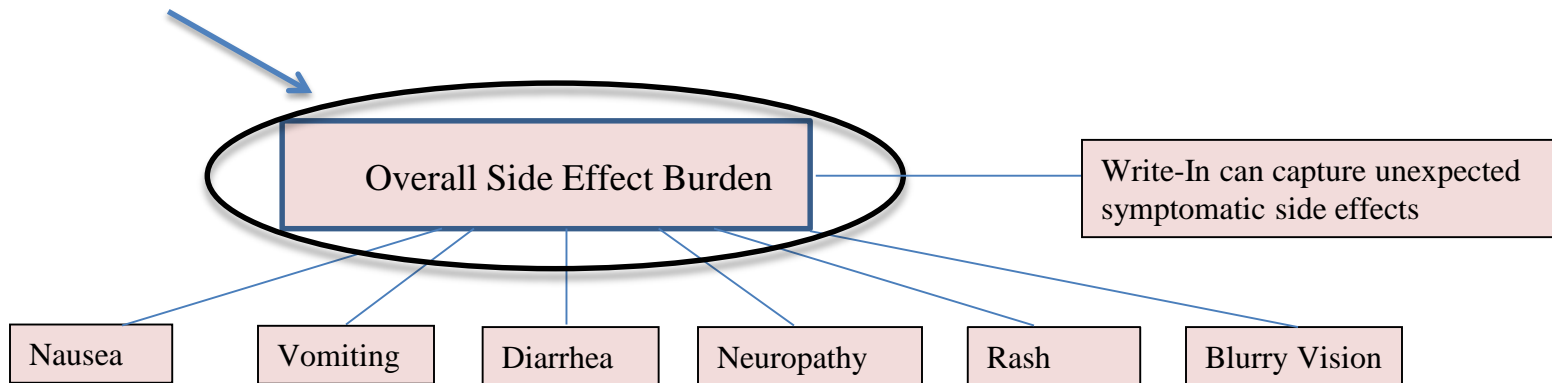
Neuropathy
Rash
Blurry Vision
Diarrhea

Select the side effects that are expected from both arms and ask all patients this set of questions



Overall side effect burden could be a consistent data element to compare treatments

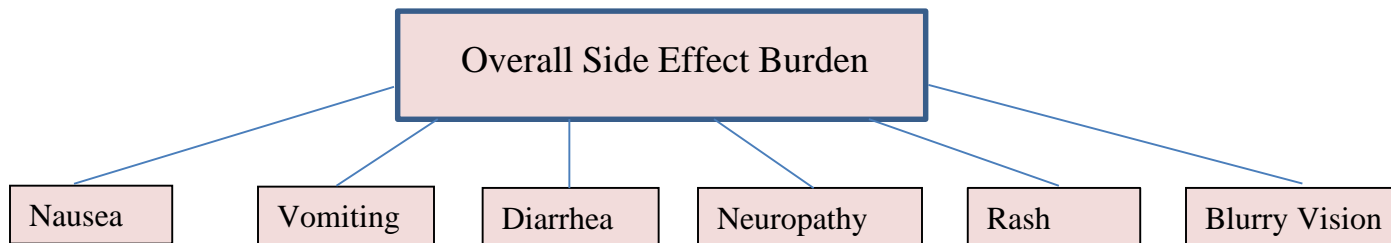
The focus of our lunch session



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

How can we quantify the overall side effect burden?

- Do we just add them all up?
- Do we weight the importance of each symptom?
- Won't that differ between patients?
- How would we identify “meaningful” change in an overall side effect score?



Issue: Even if the right symptomatic toxicities are assessed, we still do not know the overall side effect impact from the patient perspective.

1. Some advocate for “summing” the responses to all the questions
2. Some advocate for a single summary question

Discussion topic: What are the strengths and limitations of using a *single question* like FACIT GP5 below as a summary measure of overall side effect impact?

		Not at all	A little bit	Some- what	Quite a bit	Very much
GP5	I am bothered by side effects of treatment	0	1	2	3	4

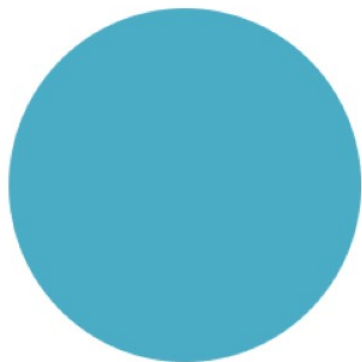
What is the patient perspective on importance of overall tolerability of a cancer treatment?



Sandra Spivey



**Janet Freeman-Daily,
MS, ENG**



A patient perspective on cancer treatment tolerability

Janet Freeman Daily, Lung
Cancer Research Advocate

Sandi Spivey, Breast Cancer
Patient Advocate

Per Institute of Medicine (now National Academies of Medicine)

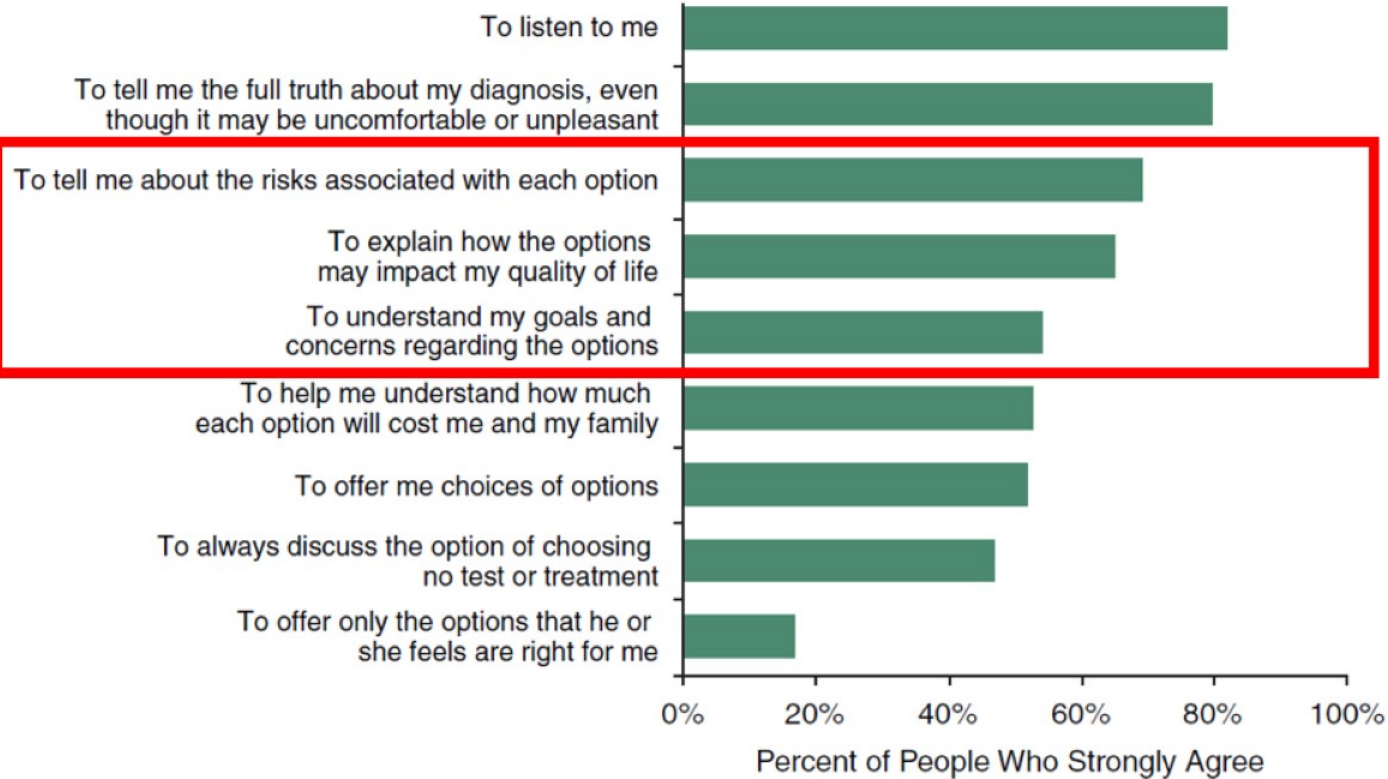
Definition of “Values”

a patient’s concerns, expectations, and choices regarding health care, based on a *full and accurate understanding of care options*

“The cancer care team should *collaborate with their patients* to develop a care plan that *reflects their patients’ needs, values, and preferences*”

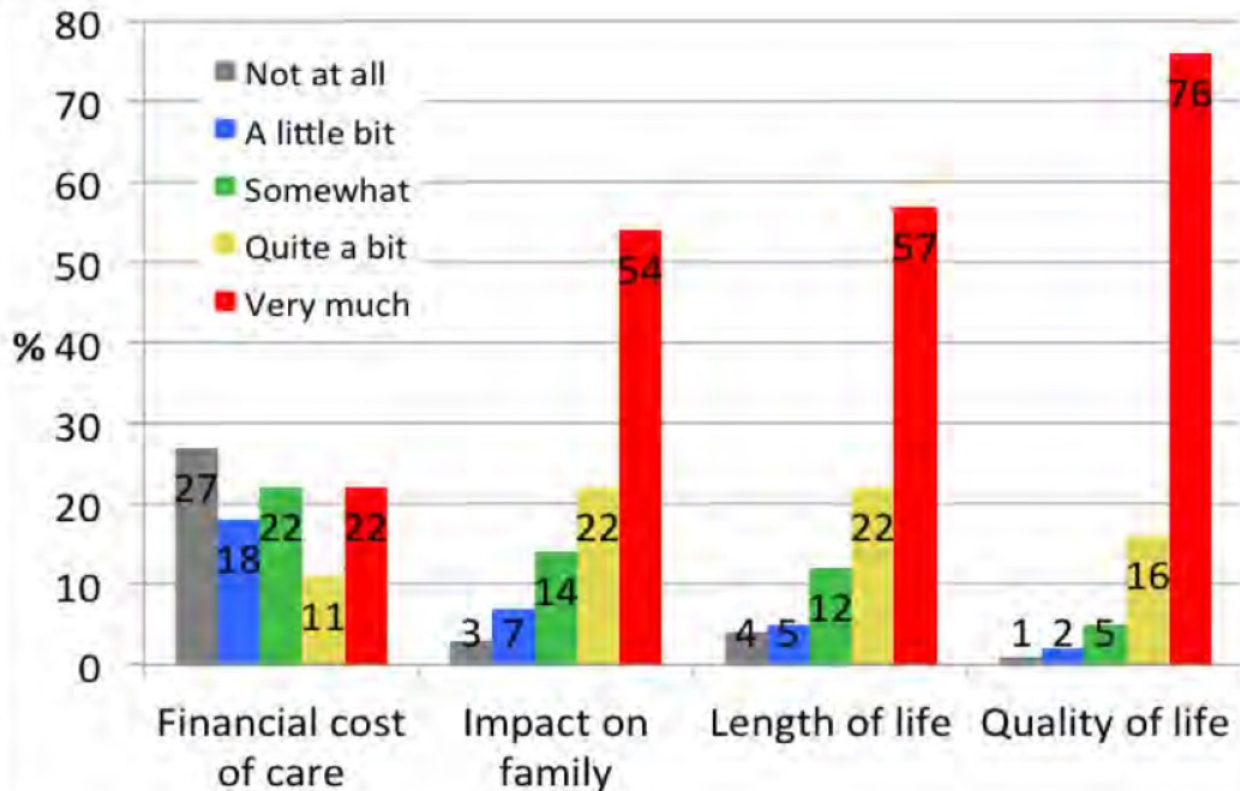
Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis. 2013

I want my health care clinician ...



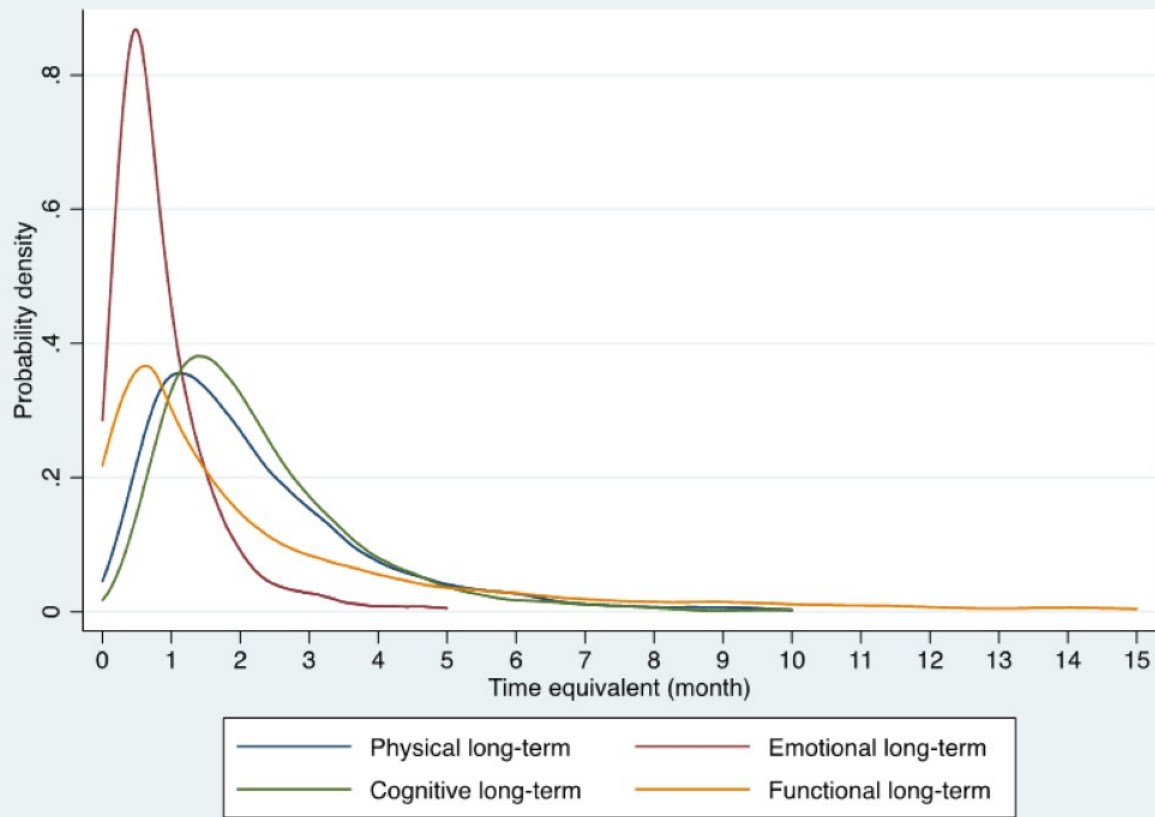
Cancer patients want their clinician to tell them about risks, quality of life, and options

Institute of Medicine. (2013). Delivering high-quality cancer care: Charting a new course for a system in crisis. National Academy of Sciences.



Cancer patients value quality of life and impact on family as well as length of life

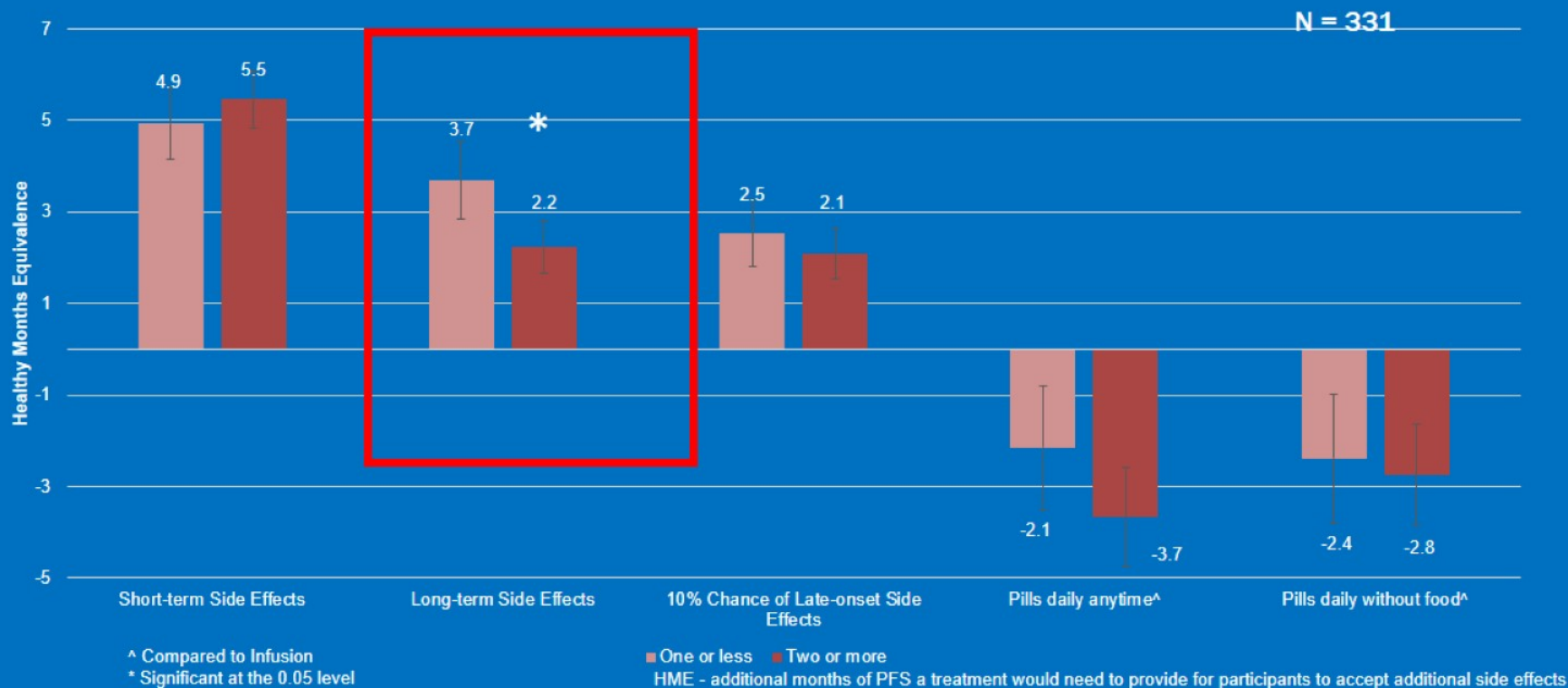
Buzaglo JS, Miller MF, Longacre ML. (2016) Cancer Patients' Priorities When Considering a Treatment Decision. Poster presentation at 8th Biennial Cancer Survivorship Research Conference.



Individual patient preferences vary depending on type of side effect and expected survival

Bridges JFP, Janssen EM. Project Transform: Incorporating the patient experience into lung cancer treatment, research, and policy, Presentation at LUNGevity National HOPE Summit 2017.

Patient preferences vary with lines of therapy



SEs captured by clinicians in clinical trials differ from patient-reported SEs in real-world

Adverse Reaction	FLAURA (N = 279) ¹		Project PRIORITY (N=115) ²	
	All Grades %	Grades 3	All Grades %	Grades 3
Diarrhea	58	2.2	77	9
Constipation	15	0	33	2
Vomiting	11	0	13	0
Stomatitis	29	0.7	53	3
Nausea	14	0	37	3
Rash	58	1.1	72	2.7
Fatigue	21	1.4	78	6
Dyspnea	13	0.4	30	3

¹ FLAURA trial (Soria et al, N Engl J Med. 2018 Jan 11;378(2):113-125. doi: 10.1056/NEJMoa1713137. Epub 2017 Nov 18.

² Feldman J, Basu Roy U, Elkins I, et al. Impact of an EGFR-lung cancer diagnosis on quality of life of patients: learnings from project PRIORITY. Presented at IASLC 2019 NAJLC. October 10-12, 2019: Chicago, Illinois. Abstract OA03.06

Patient preferences change with stage of their cancer

Early Stage/curable

- Can I withstand side effects for duration of therapy?
- Can I return to my life as it was before cancer?
- Will the therapy get rid of cancer? Will the cancer come back?

Metastatic/incurable

- Does the expected quantity of life gained outweigh the risk of quality of life limiting SEs?
- What is the severity of permanent SEs? Are they cumulative? How long will they last?
- Will SEs from this therapy reduce eligibility for future therapies?

**Tolerability
considerations
include
functional
impact**



Can the potential side effects be managed?

Temporary? Permanent? Cumulative?

Might I be hospitalized?

Can SEs be managed through dose reduction?

Do drugs to manage SEs have their own SEs?

Might it make coexisting conditions worse?

Is survival benefit worth the risk of side effects? Each patient has their own preferences

Type & Severity

- **Physical**
- **Emotional**
- **Cognitive**
- **Functional**

Functional impact

- **On daily tasks**
- **On work**
- **On joy-filled activities**
- **On control over my time**
- **On family relationships**



Persistence

- **Short term**
- **Long term**
- **Cumulative w/previous SEs**
- **Might remove tx or trial options**

Management

- **Is dose reduction possible?**
- **Can palliative care help?**
- **Will co-existing conditions interfere?**
- **Will I need assistance?**

***Patients currently get this information in online disease communities...
they'd like to get it from their clinicians***

Exploring the patient perspective on overall tolerability of a cancer treatment

- Discussion



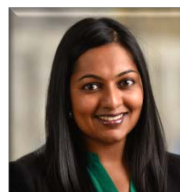
MODERATOR
Paul G. Kluetz, MD



Preeti Narayan, MD



Sandra Spivey



Gita Thanarajasingam,
MD



Janet Freeman-Daily,
MS, ENG



@FDAOncology has looked at cancer trials using GP5 single question

1. Measurement characteristics- test/retest, ordering effects
2. Issues with measurement at baseline (before treatment)

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP5	I am bothered by side effects of treatment	0	1	2	3	4

Test-Retest and Ordering Effects

- Randomized open-label trial comparing 2 active renal cell carcinoma treatments with differential toxicities
- General QOL assessed - FACT-G
- RCC specific PRO also assessed – FKSI-19

FACT-G: 5th question

PHYSICAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
Q01	I have a lack of energy.....	0	1	2	3	4
Q02	I have nausea.....	0	1	2	3	4
Q03	Because of my physical condition, I have trouble meeting the needs of my family.....	0	1	2	3	4
Q04	I have pain.....	0	1	2	3	4
Q05	I am bothered by side effects of treatment.....	0	1	2	3	4
Q06	I feel ill.....	0	1	2	3	4
Q07	I am forced to spend time in bed.....	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
Q08	I feel close to my friends.....	0	1	2	3	4
Q09	I get emotional support from my family.....	0	1	2	3	4
Q10	I get support from my friends.....	0	1	2	3	4
Q11	My family has accepted my illness.....	0	1	2	3	4
Q12	I am satisfied with family communication about my illness.....	0	1	2	3	4
Q13	I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
Q14	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.					
Q15	I am satisfied with my sex life.....	0	1	2	3	4

EMOTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
Q16	I feel sad.....	0	1	2	3	4
Q17	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
Q18	I am losing hope in the fight against my illness.....	0	1	2	3	4
Q19	I feel nervous.....	0	1	2	3	4
Q20	I worry about dying.....	0	1	2	3	4
Q21	I worry that my condition will get worse.....	0	1	2	3	4

FUNCTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
Q22	I am able to work (include work at home).....	0	1	2	3	4
Q23	My work (include work at home) is fulfilling.....	0	1	2	3	4
Q24	I am able to enjoy life.....	0	1	2	3	4
Q25	I have accepted my illness.....	0	1	2	3	4
Q26	I am sleeping well.....	0	1	2	3	4
Q27	I am enjoying the things I usually do for fun.....	0	1	2	3	4
Q28	I am content with the quality of my life right now.....	0	1	2	3	4

Preceded by 3 symptom questions

FKSI-19: 16th question

		Not at all	A little bit	Some-what	Quite a bit	Very much
Q01	I have a lack of energy.....	0	1	2	3	4
Q02	I have pain.....	0	1	2	3	4
Q03	I am losing weight.....	0	1	2	3	4
Q04	I feel fatigued.....	0	1	2	3	4
Q05	I have been short of breath.....	0	1	2	3	4
Q06	I am bothered by fevers (episodes of high body temperature).....	0	1	2	3	4
Q07	I have bone pain.....	0	1	2	3	4
Q08	I have been coughing.....	0	1	2	3	4
Q09	I feel weak all over.....	0	1	2	3	4
Q10	I have had blood in my urine.....	0	1	2	3	4
Q11	I have a good appetite.....	0	1	2	3	4
Q12	I am sleeping well.....	0	1	2	3	4
Q13	I worry that my condition will get worse.....	0	1	2	3	4
Q14	I have nausea.....	0	1	2	3	4
Q15	I have diarrhea (diarrhoea).....	0	1	2	3	4
Q16	I am bothered by side effects of treatment.....	0	1	2	3	4
Q17	I am able to work (include work at home).....	0	1	2	3	4
Q18	I am able to enjoy life.....	0	1	2	3	4
Q19	I am content with the quality of my life right now.....	0	1	2	3	4

Preceded by 14 symptom questions

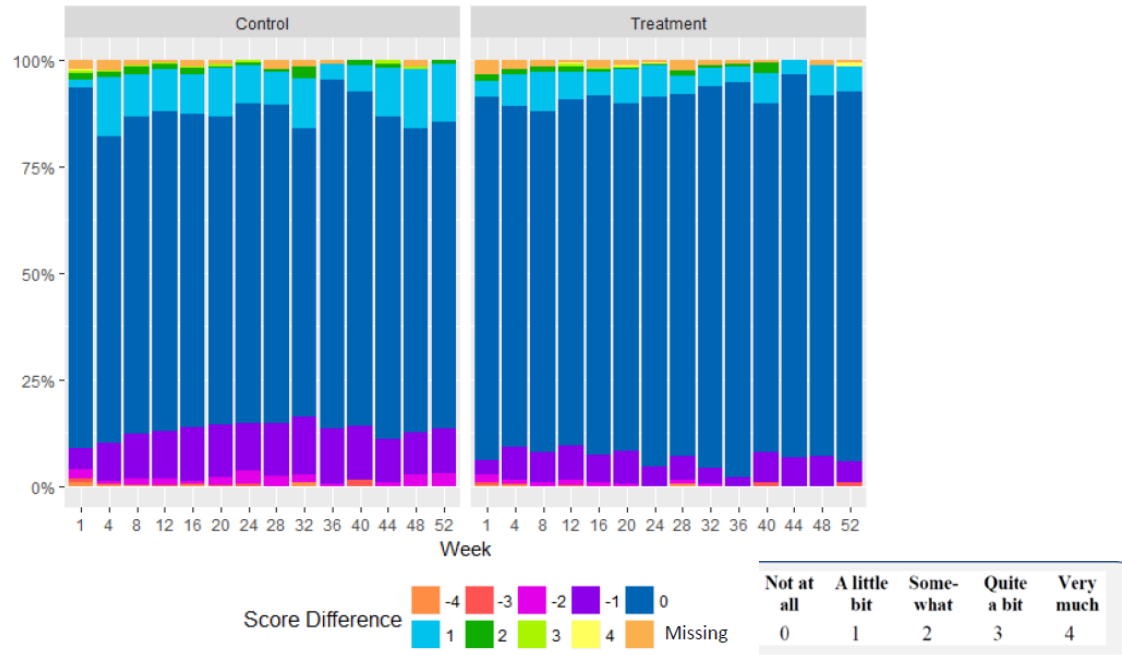
Question: What is test- retest agreement for this question?

Question: Does “priming” with multiple side effects (including the most common AE) lead to higher bother on the FKSI-19 compared to FACT-G?



Reasonable item agreement and no clear ordering effects were noted

Figure 1: Difference in Fact-G and FKSI Scores





MODERATOR
Paul G. Kluetz, MD



Discussion

- What are the issues around measurement characteristics for a single item global measure?



Laura Fernandes, PhD



David Cella, PhD



Sandra Mitchell, PhD

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP5	I am bothered by side effects of treatment ...	0	1	2	3	4



MODERATOR
Paul G. Kluetz, MD



@FDAOncology has looked at cancer trials using GP5 single question

1. Measurement characteristics- test/retest, ordering effects
2. Issues with measurement at baseline (before treatment)

Baseline Assessment of Side Effect Bother

- 5 Randomized Trials submitted to FDA for Review

Trial	Disease	Prior Rx	Investigational Rx
1	1 st line Metastatic Prostate Ca	Hormones, Surgery, Radiotherapy	Cytotoxic Chemotherapy
2	2 nd line Metastatic Prostate Ca	Hormones, Surgery, Radiotherapy, Cytotoxic Chemotherapy	Cytotoxic Chemotherapy
3	1 st line Metastatic Prostate Ca	Hormones, Surgery, Radiotherapy	Hormonal Therapy
4	1 st line Metastatic Renal Cell Ca	Surgery, Radiotherapy	Kinase inhibitor, Immunotherapy
5	Localized HER2 +ve Breast Ca	Extended adjuvant therapy	Kinase inhibitor

Exploration of baseline patient-reported side effect bother from cancer therapy

Table 2. Completion rates: baseline and follow-up.

Trial number	GP4: Pain	GP5: Side effect bother	GP6: Feel ill	GF3: Enjoy life	GF7: Content with QOL
<i>Baseline</i>					
1	95.1%	83.8%	94.2%	94.6%	94.7%
2	94.8%	87.7%	94.7%	93.3%	94.1%
3	95.7%	95.7%	95.7%	95.7%	95.7%
4	95.3%	89.5%	95.5%	95.7%	96.0%
5	91.9%	91.9%	91.9%	91.9%	91.9%
<i>Follow-up</i>					
1	94.4%	93.9%	94.3%	94.7%	94.5%
2	92.9%	92.9%	93.1%	92.8%	93.1%
3	97.8%	97.8%	97.8%	97.8%	97.8%
4	92.7%	92.7%	92.8%	92.3%	92.4%
5	92.8%	92.8%	92.8%	92.8%	92.8%

ePRO “Forced”
Completion?

QOL: quality of life.

Exploration of baseline patient-reported side effect bother from cancer therapy

6-10% less patients did not complete GP5 at baseline compared to other items

Table 2. Completion rates: baseline and follow-up.

Trial number	GP4: Pain	GP5: Side effect bother	GP6: Feel ill	GF3: Enjoy life	GF7: Content with QOL
<i>Baseline</i>					
1	95.1%	83.8%	94.2%	94.6%	94.7%
2	94.8%	87.7%	94.7%	93.3%	94.1%
4	95.3%	89.5%	95.5%	95.7%	96.0%
<i>Follow-up</i>					
1	94.4%	93.9%	94.3%	94.7%	94.5%
2	92.9%	92.9%	93.1%	92.8%	93.1%
4	92.7%	92.7%	92.8%	92.3%	92.4%

QOL: quality of life.

Exploration of baseline patient-reported side effect bother from cancer therapy

Table 3. Degree of bother over time: baseline and follow-up.

Trial number	Quite a bit of bother (score = 3)	Very much bother (score = 4)	Total high levels of bother
<i>Baseline</i>			
1	3.3%	0.8%	4.0%
2	6.4%	3.0%	9.4%
3	1.8%	0.7%	2.4%
4	2.4%	1.4%	3.9%
5	1.8%	0.3%	2.1%
<i>Follow-up</i>			
1	3.6%	1.4%	5.0%
2	6.4%	1.9%	8.3%
3	1.0%	0.2%	1.1%
4	6.9%	2.5%	9.4%
5	4.2%	1.2%	5.4%

Across the 5 trials up to 9.4% of patients reported high levels of side effect bother AT BASELINE



MODERATOR
Paul G. Kluetz, MD



Sandra Spivey



David Cella, PhD



Sandra Mitchell, PhD



Gita Thanarajasingam,
MD



- What are issues to consider with respect to baseline measurement of overall side effect bother?
- Are there improvements that could be made to existing single item questions?

		Not at all	A little bit	Some- what	Quite a bit	Very much
GP5	I am bothered by side effects of treatment	0	1	2	3	4



MODERATOR
Paul G. Kluetz, MD

My Perspective on This Issue:



A single question has the obvious benefit of simplicity and low burden. The two most common arguments I've heard against using a single item global question for an overall summary measure of side effects:

1. It's not sensitive enough

Response: For comparative tolerability, we should be aiming for “meaningful” differences. We would *not use this for noninferiority or equivalence questions.*

2. It is insufficient to interpret overall tolerability with a single question

Response: I agree it should not be used alone as a single question, but as part of a PRO assessment strategy that includes most common expected symptomatic toxicities, ideally with a free text question as well as physical and role function (@FDAOncology Core Outcomes).

Closing Thoughts on a Single Item Summary Measure of Side Effect Bother

	Not at all	A little bit	Some-what	Quite a bit	Very much
GPS I am bothered by side effects of treatment ...	0	1	2	3	4



MODERATOR
Paul G. Kluetz, MD



Laura Fernandes,
PhD



Preeti Narayan, MD



Janet Freeman-Daily,
MS, ENG



Sandra Spivey



Sandra Mitchell, PhD



David Cella, PhD



Gita Thanarajasingam,
MD

Thank you!

Enjoy your break....



ASCO[®]

FIFTH ANNUAL CLINICAL OUTCOME ASSESSMENTS IN CANCER CLINICAL TRIALS (COA-CCT) WORKSHOP

BREAK – 1:00pm - 2:00pm

Please log back on at 1:55pm for session 4!



#OCEOutcomes20