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

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

#OCEOutcomes20
What is “Tolerability”

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

Definition proposed by 2018 Friends of Cancer Research Working Group with Patient Input
@FDA Oncology Core Outcomes

- Overall Survival
- Progression Free Survival
- Overall Response Rate
- Serum Biomarkers

- CTCAE Safety Data
- Dose Modifications

- Hospitalizations
- ED Visits
- Morbid Procedures
- Supportive Care Use

Clinician Reported and Biomarker Data

Patient-Reported and other COA Data

- Disease Symptoms
- Physical Function:
  - Ability to carry out activities that require physical effort
- Role Function:
  - Ability to Work and Perform Leisure Activities

Symptomatic Adverse Events

Overall Side Effect Impact
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

- Nausea
- Vomiting
- Diarrhea
- Neuropathy

Drug B

- 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

Overall Side Effect Burden

- Nausea
- Vomiting
- Diarrhea
- Neuropathy
- Rash
- Blurry Vision

Write-In can capture unexpected symptomatic side effects

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 “summating” 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?

<table>
<thead>
<tr>
<th>GP5</th>
<th>I am bothered by side effects of treatment ....</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
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

Janet Freeman-Daily  @JFreemanDaily  Sandra Spivey  @SpiveySandra
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
Cancer patients want their clinician to tell them about risks, quality of life, and options.
Cancer patients value **quality of life** and **impact on family** as well as **length of life**


Janet Freeman-Daily  @JFreemanDaily
Sandra Spivey  @SpiveySandra
Individual patient preferences vary depending on type of side effect and expected survival.


Janet Freeman-Daily  @JFreemanDaily  Sandra Spivey  @SpiveySandra
Patient preferences vary with lines of therapy

N = 331

Healthy Months Equivalence

<table>
<thead>
<tr>
<th>Short-term Side Effects</th>
<th>Long-term Side Effects</th>
<th>10% Chance of Late-onset Side Effects</th>
<th>Pills daily anytime</th>
<th>Pills daily without food</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Compared to Infusion
* Significant at the 0.05 level

One or less
Two or more

HME - additional months of PFS a treatment would need to provide for participants to accept additional side effects

Janet Freeman-Daily @JFreemanDaily
Sandra Spivey @SpiveySandra
# SEs captured by clinicians in clinical trials differ from patient-reported SEs in real-world

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>FLAURA (N = 279)</th>
<th>Project PRIORITY (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>58</td>
<td>2.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>29</td>
<td>0.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>58</td>
<td>1.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21</td>
<td>1.4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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 I perform my daily functions at home?
- Can I continue to work?
- Can I do things that bring me joy?
- Do I have control over my time?
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

Janet Freeman-Daily @JFreemanDaily  Sandra Spivey @SpiveySandra
Exploring the patient perspective on overall tolerability of a cancer treatment

- Discussion
@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)
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
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

Discussion

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

<table>
<thead>
<tr>
<th>O5S</th>
<th>I am bothered by side effects of treatment....</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>O5S</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
@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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Disease</th>
<th>Prior Rx</th>
<th>Investigational Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line Metastatic Prostate Ca</td>
<td>Hormones, Surgery, Radiotherapy</td>
<td>Cytotoxic Chemotherapy</td>
</tr>
<tr>
<td>2</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line Metastatic Prostate Ca</td>
<td>Hormones, Surgery, Radiotherapy, Cytotoxic Chemotherapy</td>
<td>Cytotoxic Chemotherapy</td>
</tr>
<tr>
<td>3</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line Metastatic Prostate Ca</td>
<td>Hormones, Surgery, Radiotherapy</td>
<td>Hormonal Therapy</td>
</tr>
<tr>
<td>4</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line Metastatic Renal Cell Ca</td>
<td>Surgery, Radiotherapy</td>
<td>Kinase inhibitor, Immunotherapy</td>
</tr>
<tr>
<td>5</td>
<td>Localized HER2 +ve Breast Ca</td>
<td>Extended adjuvant therapy</td>
<td>Kinase inhibitor</td>
</tr>
</tbody>
</table>
# Exploration of baseline patient-reported side effect bother from cancer therapy

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

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

QOL: quality of life.

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

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

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

QOL: quality of life.

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

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

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

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

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

• 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?

<table>
<thead>
<tr>
<th>GP5</th>
<th>I am bothered by side effects of treatment ....</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
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 (@FDAAUCOncology Core Outcomes).
Closing Thoughts on a Single Item Summary Measure of Side Effect Bother

<table>
<thead>
<tr>
<th>GP5</th>
<th>I am bothered by side effects of treatment....</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Laura Fernandes, PhD

MODERATOR
Paul G. Kluetz, MD

Janet Freeman-Daily, MS, ENG

Sandra Spivey

Sandra Mitchell, PhD

David Cella, PhD

Gita Thanarajasingam, MD

Preeti Narayan, MD
Thank you!

Enjoy your break....
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!