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FDA Secondary Analyses of Submitted PRO Assessment Strategies & Data

Bellinda King-Kallimanis, PhD

Senior Staff Fellow – Oncology Center of Excellence

CDDF MULTI-STAKEHOLDER WORKSHOP on INVOLVING PATIENTS IN ONCOLOGY DRUG DEVELOPMENT

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Disclosures

- I have no financial relationships to disclose
- Examples of instruments are for discussion and not endorsement

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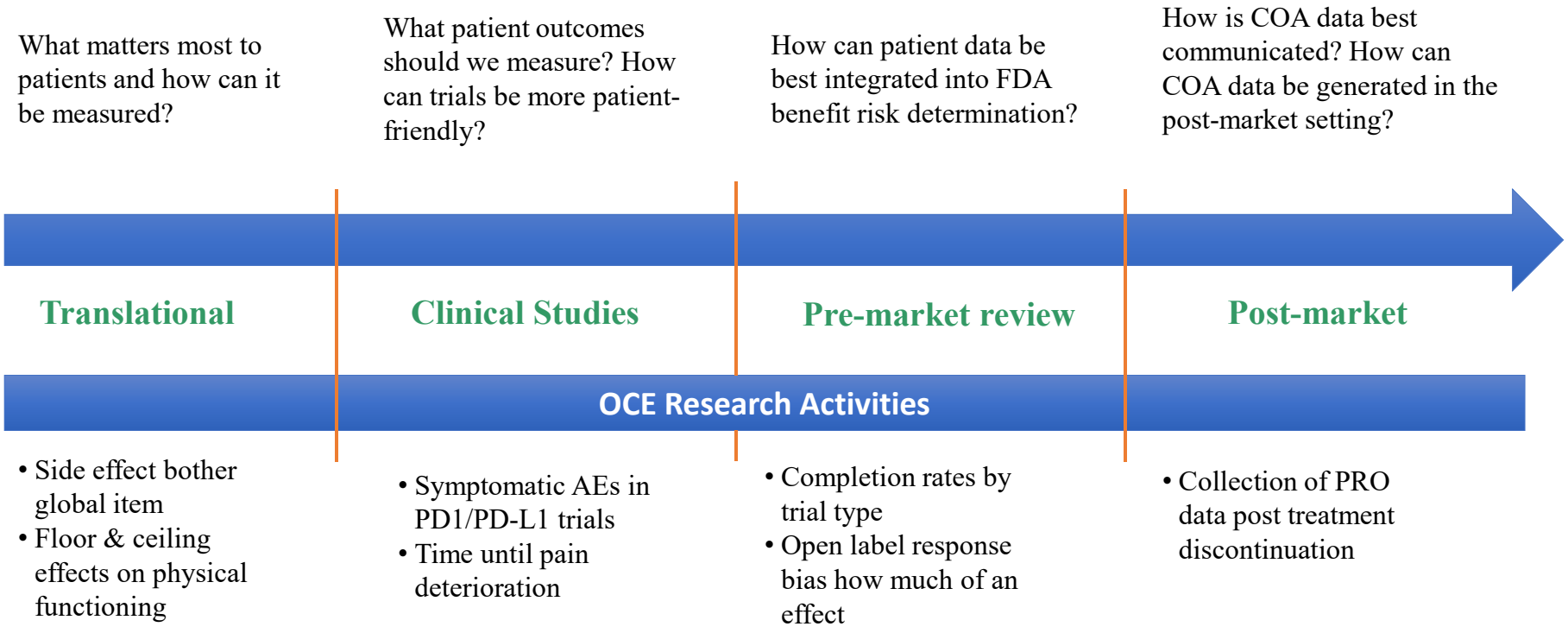
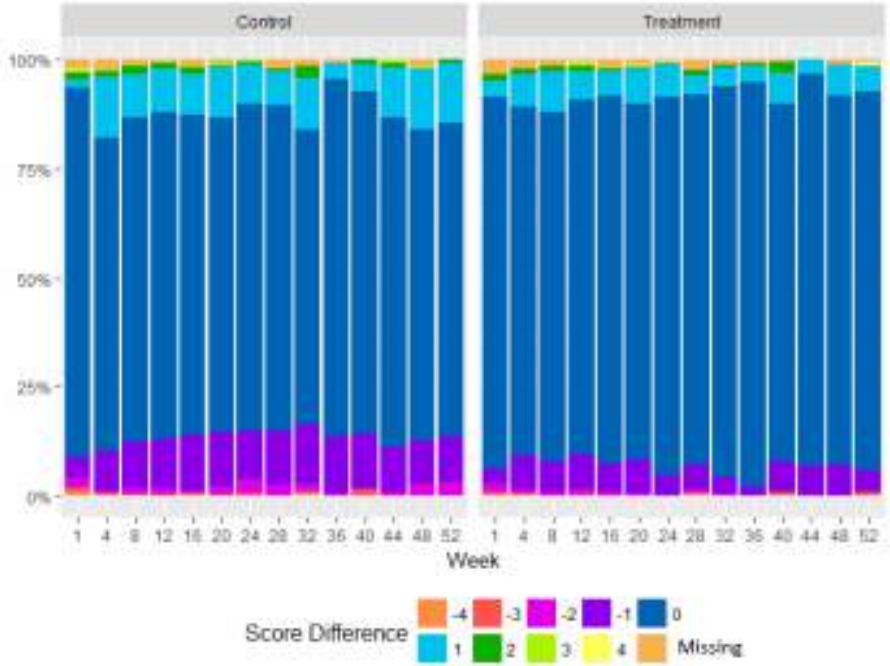
Patient-Focused Drug Development



Adapted slide by permission from Theresa Mullin, Office of Strategic Programs, FDA

Translational: Side Effect Bother

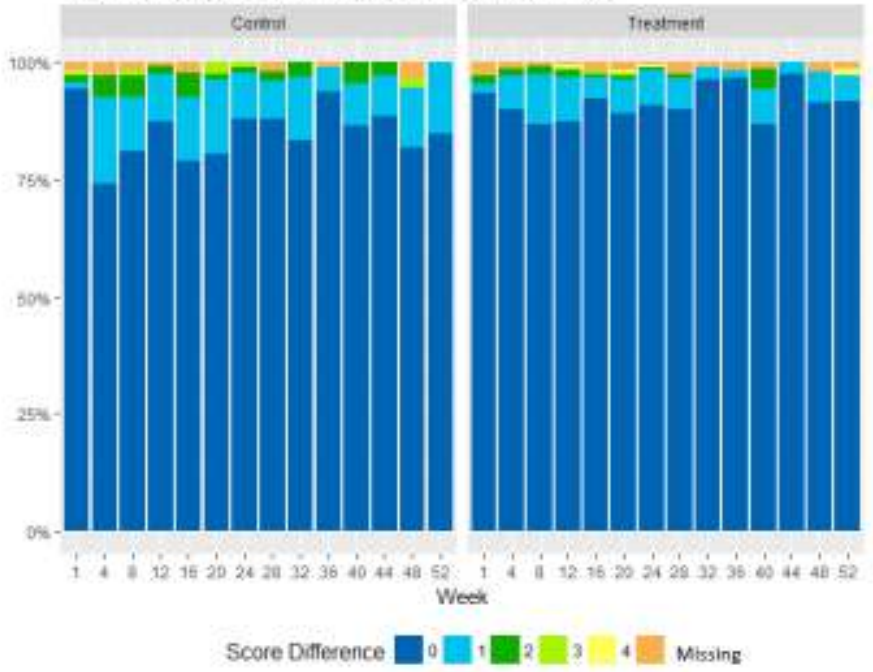
Figure 1: Difference in Fact-G and FKSI Scores



Note: 0 represents patients who responded to GP5 with the same response on both PRO instruments at the same week.

-1, for example, represent patients who, for example, reported "a little bit" on FKSI, but then reported "not at all" on FACT-G, whereas 1 represents patients who, for example, reported "not at all" on FKSI, but then reported "a little bit" on FACT-G.

Figure 2: Difference in Fact-G and FKSI Scores for Patients with a Zero at Each Assessment on FKSI



Note: 0 represents patients who responded to GP5 with "not at all" indicating no bother on both PRO instruments on the same week.

1, for example, represents patients who reported "not at all" on FKSI, but then reported "a little bit" on FACT-G

Fernandes, et al, 2019: ISPOR poster

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Side Effect Bother: Takeaways

- Inconsistencies were present for all comparisons and sub-group analyses
- Intra-patient discrepancy in response to GP5 occurred, differences were largely only 1 category apart
- Patients in the control arm reporting “Not at all” on the FKSI were slightly more variable in their response on GP5 on the FACT-G:
  - Diarrhea is a common adverse event in the control arm and a diarrhea item proceeds the GP5 item on the FKSI, however differences in the two the arms were not large
- Overall, no consistent direction for differences suggesting discrepancies not only driven by preceding items or ordering of items but also the response option categories

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Clinical Studies: Symptomatic AEs in PD-1/PD-L1 Trials

Table 1. Key adverse events and related PRO items used in PD-1/PD-L1 trials.

AEs	Items	Number of trials
Shortness of breath	5 tools include at least 1 item (e.g. "I have been short of breath")	21 trials
Fatigue	4 tools include at least 1 item (e.g. "I have a lack of energy")	21 trials
Cough	4 tools include at least 1 item (e.g. "How much coughing do you have?")[a]	7 trials
Musculoskeletal pain	3 tools include at least 1 item (e.g. I have aches and pains in my bones")[a]	6 trials
Fever	2 tools include at least 1 item (e.g. "I am bothered by fevers)[a]	2 trials
Diarrhea	1 tool includes at least 1 item (e.g. "Have you had diarrhea?")	17 trials
Rash	0 tools include any items	0 trials
Pruritus	0 tools include any items	0 trials

[a]Indicates items were only from disease-specific modules

King-Kallimanis et al, 2019 Clinical Trials

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Symptomatic AEs in PD-1/PD-L1 Trials: Takeaways

- PRO tools were variable and did not consistently assess important symptomatic AEs
- No trial assessed all key symptomatic AEs selected based on reported PD-1/PD-LI therapy AE profiles
- PRO tools should be supplemented by a tailored selection of items from symptom libraries to assess expected toxicities
- A PRO strategy that includes these things may allow for a more complete, unbiased understanding of the patient experience while receiving anti-PD-1/PD-L1

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Pre-market Review: Completion Rates

Trials with large gaps in completion rates at six months*

	Open-label trials	Double-blind trials
Completion rate	**(n = 25)**	**(n = 26)**
Trials with large (≥10%) completion rate differences, no. (%)		
Favoring control arm	0 (0.0)	4 (15.4)
Favoring experimental arm	4 (16.0)	3 (11.5)
Overall size of difference in completion rate between arms, median (range)	28.5 (10.0–69.0)	11.5 (10.0–21.0)
Size of difference in completion rate, median (range)		
Favoring control arm	NA	11 (10.0–17.0)
Favoring experimental arm	28.5 (10.0–69.0)	11.5 (10.0–21.0)

Roydhouse et al 2018 JNCI

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Completion Rates: Takeaways

- Most between-arm completion differences were small, but large gaps were seen
- When gaps existed, tended to be larger and favor the investigational arm compared to the control arm in open-label trials
- Maximizing completion rates is important:
  - Provides the data quality necessary to inform regulatory and other health policy decision making
  - Supports potential inclusion of PRO results in FDA product labels
  - Aides in meeting the assumptions of statistical methods used for data analysis
- We recommend that studies collect and report PRO completion rates per arm per visit, and document the reasons for missingness

Post-market Review: PRO Assessment Post-Treatment Discontinuation

Table 2 Summary of PRO Assessments Post Treatment Discontinuation for Breast Cancer

	Number of Trials (n =20)	Time Frame				Number follow-up of assessments	
		30 day	3-11 months	12 months	Post-12 months	Only 1	Multiple
Trials with PRO follow-up	13 (65%)	13 (100%)	7 (54%)	7 (54%)	6 (46%)	6 (46%)	7 (54%)
Double-Blind	9	9	6	6	6	3	6
Open-label	2	2	1	1	0	1	1
Single Arm, Open Label	2	2	0	0	0	2	0

Table 3 *Completion Rate of Earliest Post Treatment Discontinuation Follow-up for Breast Cancer*

	N	Mean (range)
Treatment Arm	9/13	71.2% (47.2% ; 90.9%)
Control Arm	8/11	71.6% (50.0% ; 100%)

**Note denominator in the control group is different due to single arm studies.*

King-Kallimanis et al – final drafting

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PRO Assessment Post-Treatment Discontinuation: Takeaways

- ~50% of trials reported collected PRO data after treatment discontinuation
  - For breast and prostate cancer, only ~50% trials reported completion rates for follow-up assessments; for liver and pancreatic cancer, no completion rates were reported
- Definitions of eligibility for post-treatment discontinuation follow-up were heterogeneous
- Quality of data is questionable; to be interpretable and useful for understanding the patient experience post-treatment discontinuation more robust data is needed

PFDD Program

- The PFDD Program is working to identify rigorous methods to assess the patient experience that will complement existing survival and tumor information to provide additional evidence about the effects of cancer therapies for patients
- We have a deep pipeline of projects that are aimed to further our understanding of how we can best incorporate PRO data into our reviews

https://www.fda.gov/about-fda/oncology-center-excellence/patient-focused-drug-development