Fifth Annual

COA-CCT Workshop

FDA U.S. FOOD & DRUG ADMINISTRATION
ONCOLOGY CENTER OF EXCELLENCE

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SESSION 2

Considerations for assessment frequency and how it relates to the measurement of tolerability

MODERATOR
Bellinda King-Kallimanis, PhD

Joyce Cheng, PhD

Diane Fairclough, DrPH

Heidi Klepin, MD, MS

Wendy Sanhai, PhD, MBA

James Shaw, PhD, PharmD, MPH

Sundeep Agrawal, MD

#OCEOutcomes20

Why does timing matter?

- In cancer clinical trials, collection of PROs often occurs on day 1 of each cycle
- For IV infusions, Day 1 typically is the time point with the least potential for toxicity
- This has implications for:
  - Understanding the patient experience
  - Adequate comparison of different classes of drugs, e.g., IV infusion as compared to a daily oral

Example assessment frequency for first 12 months of an advanced cancer trial

	Standard 6 month treatment period												Follow-up		
	BL	w2	w3	w4	w5	w6	w7	w8	M3	M4	M5	M6	M9	M12	*
Symptomatic AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Single Item Side Effect Global	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Function	X		X		X		X		X	X	X	X	X	X	
Role Function	X		X		X		X		X	X	X	X	X	X	
Disease Symptoms	X				X				X			X		X	
Other HRQOL	X								X			X		X	

BL – baseline, w - week, M - month, * - context dependent long-term follow-up

In the upcoming presentation Drs Cheng & Agrawal will show how trial endpoints can be impacted by the selection of when to measure certain patient-reported outcomes

Considerations for Assessment Frequency

and How it Relates to the Measurement of Tolerability

Sundeep Agrawal, M.D.

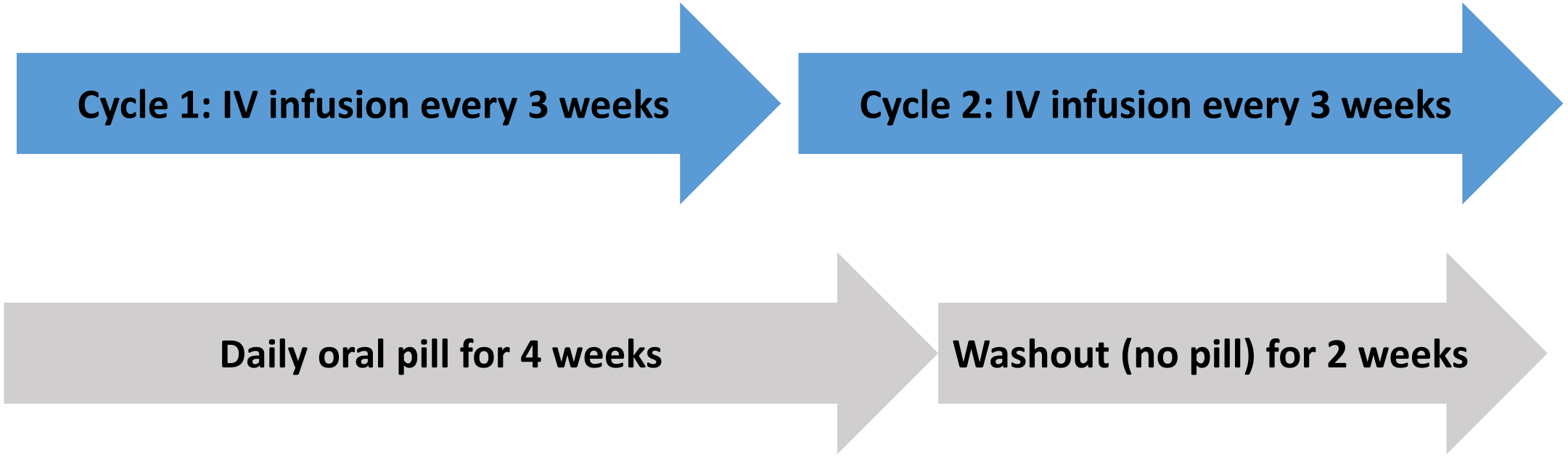
Joyce Cheng, Ph.D

The Evolving Treatment Landscape and PRO Assessments

- Traditional cytotoxic chemotherapy
  - Administered intravenously every several weeks
  - PRO assessments captured at clinic visits on Day 1 of cycle x
  - Assessment usually made just beyond the expected time of greatest toxicity

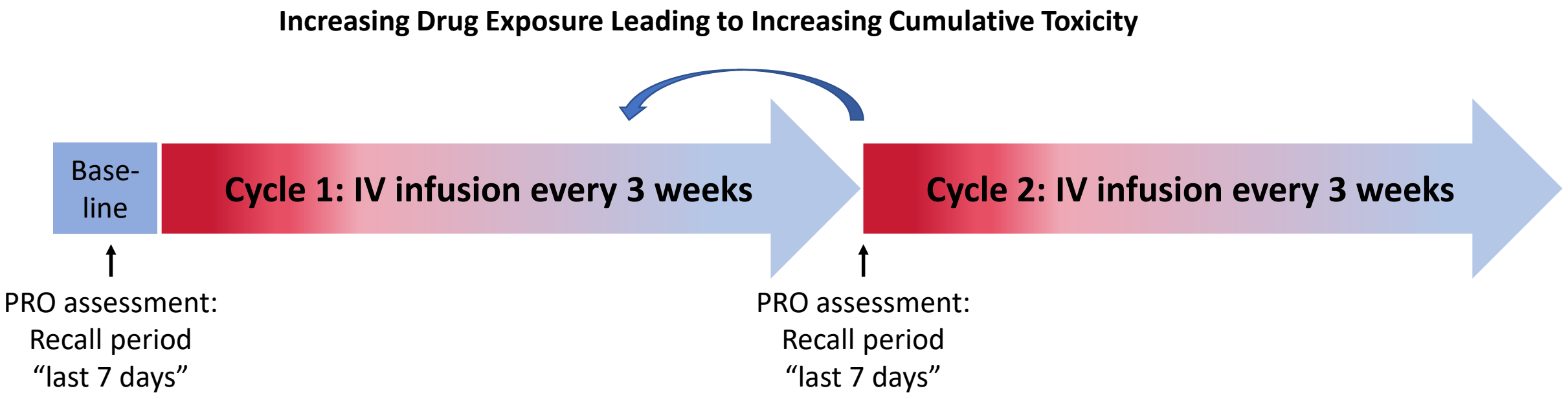
- Developing therapeutic landscape
  - Drug schedules can differ (e.g. continuously administered oral drugs)
  - Novel mechanisms of action → different expected onset of adverse events
  - The timing of PRO assessments should account for these factors

Considerations in Evaluating Different Schedules



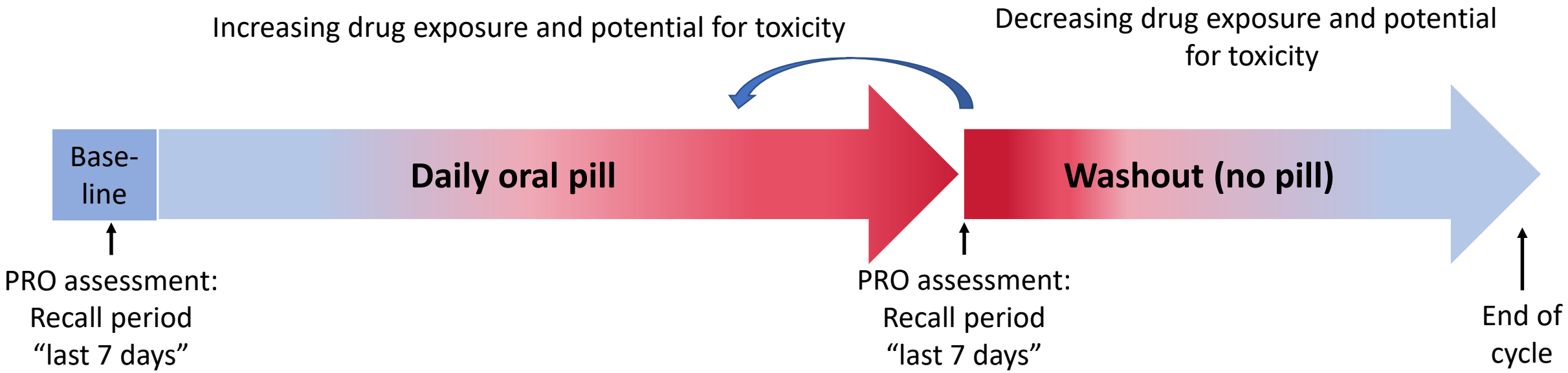
- Consider a trial with the following treatment schedule:
  - Arm 1: Cytotoxic chemotherapy administered every 3 weeks (3-week cycle)
  - Arm 2: Oral TKI drug administered 4 weeks on, 2 weeks off (6-week cycle)

Traditional Timing of PRO Assessments



- Intensity of toxicity will vary depending on timing of assessment
- Traditionally, PRO assessments linked to clinic visits due to convenience
- Trade-off between convenience of in-clinic visit vs. home PRO assessment

Assessment Timing With Washout Periods



- Intensity of toxicity will vary depending on timing of assessment
- Strategies for collecting PROs have varied for these dosing schedules
- If alternative arm has different dosing schedule, how will differences in peak toxicity be handled?

Summary of Timing of Assessments

- Timing of assessments should be linked to research questions
- Careful consideration of alternating dosing schedules is required
- Trade-off between convenience of clinic visit vs. home assessment

Common Scenario & Issues

- Consider a trial with the following treatment schedule:
  - Arm 1: Cytotoxic chemotherapy administered every 3 weeks (3-week cycle)
  - Arm 2: Oral TKI drug administered 4 weeks on, 2 weeks off (6-week cycle)

- Differential treatment schedules between arms → No clear approach for defining the PRO assessment schedule

- Different PRO assessment schedules may impact results of PRO analyses

Timing of PRO Assessments: Areas of Impact

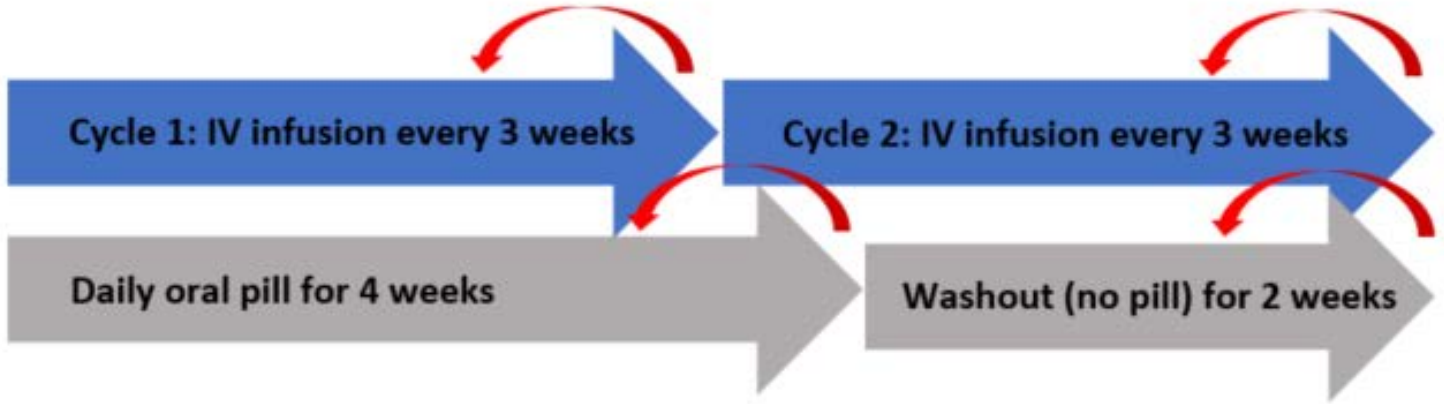
- Physical functioning/functioning (continuous endpoints)
- Disease symptoms (categorical single items)
- Drug side effects (categorical single items)
- Time-to-event endpoints

PRO Assessment Schedules

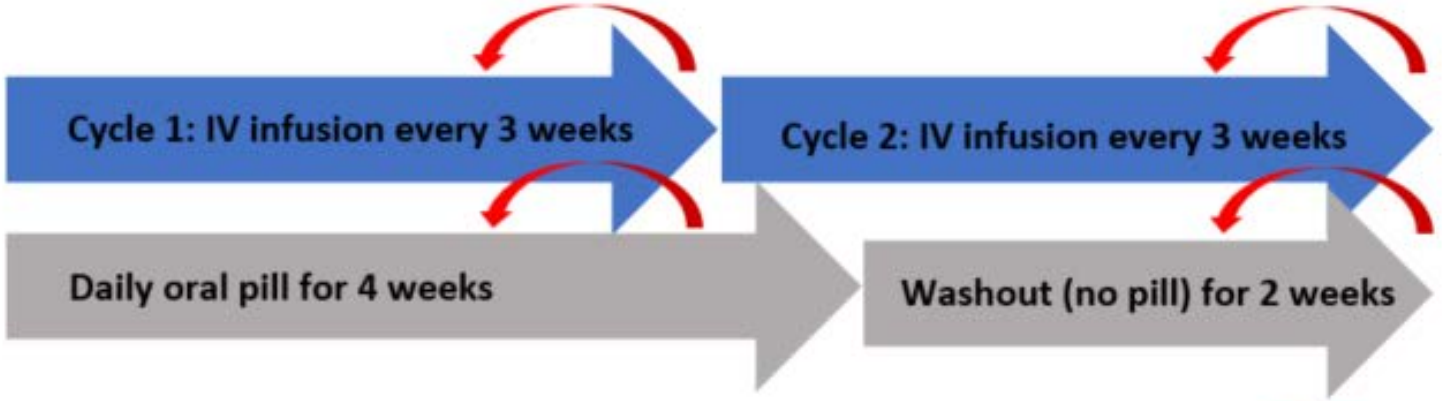
3 Trials

- Same treatment schedule
- 3 different PRO assessment schedules

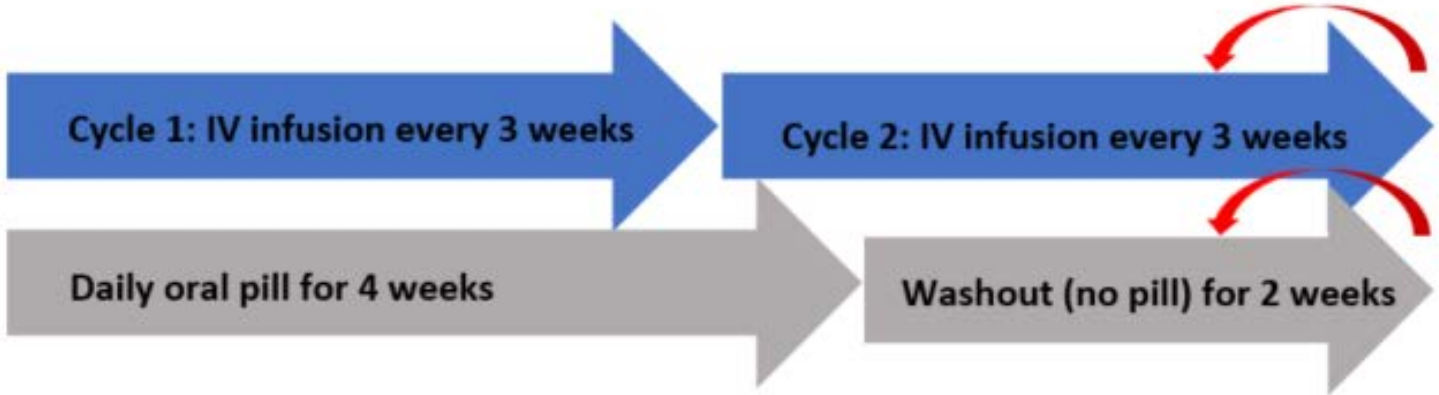
Trial 1



Trial 2

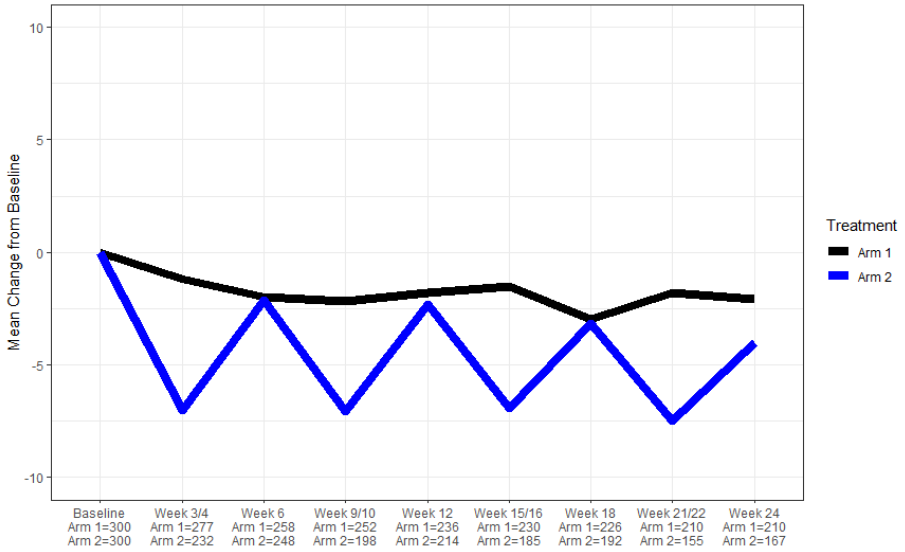


Trial 3

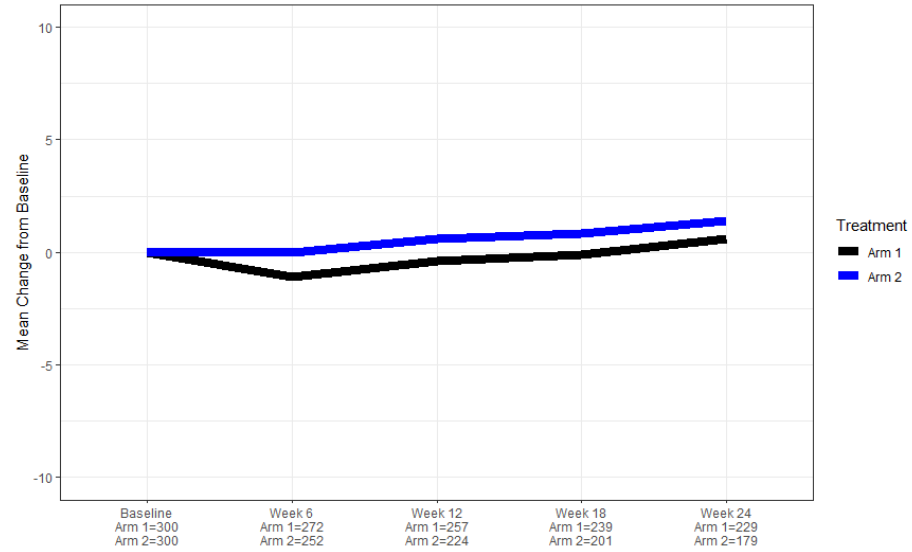


Impact on Continuous Physical Functioning

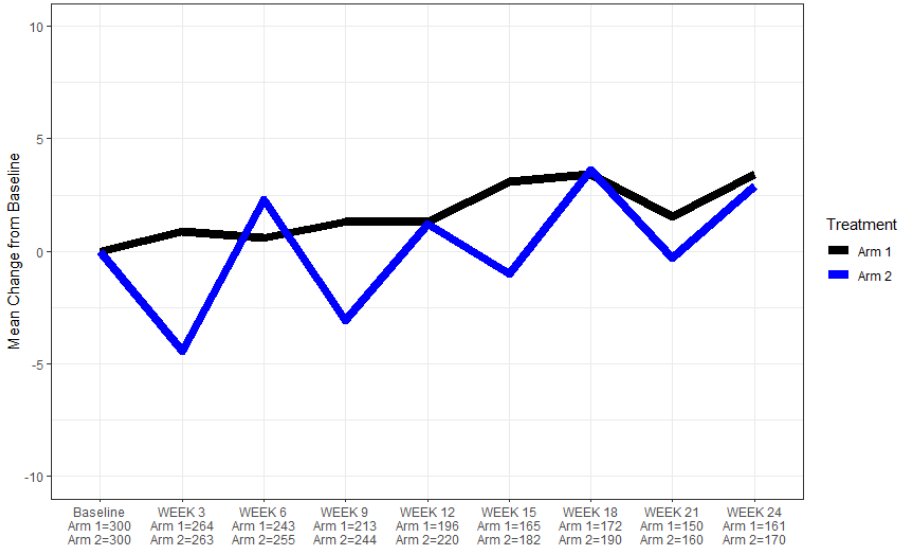
Trial 1



Trial 3



Trial 2

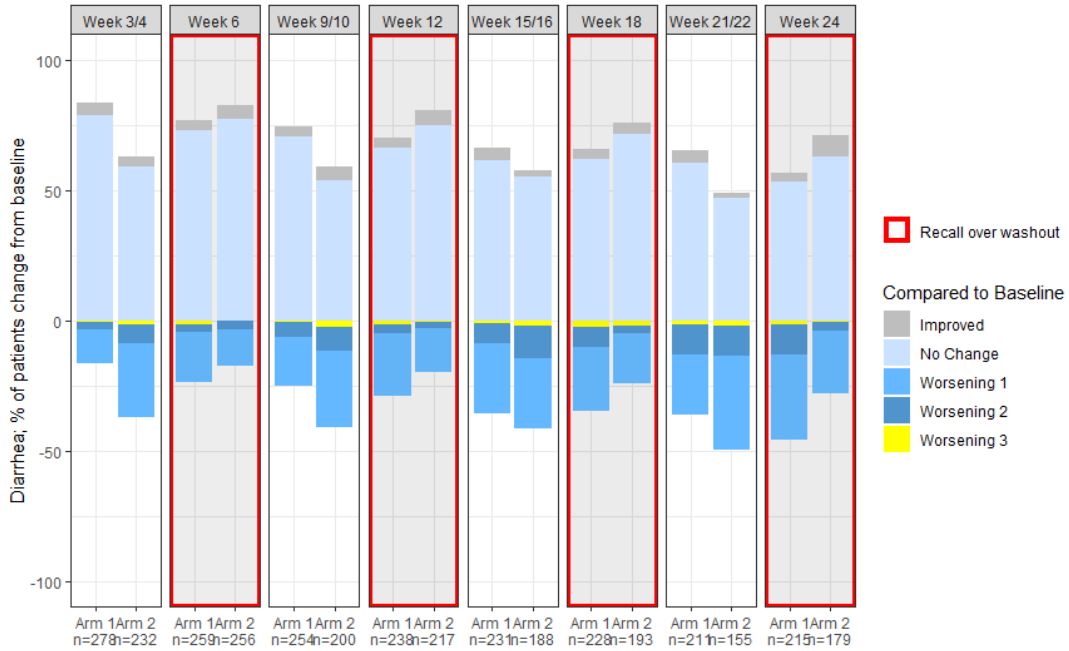


- Trials 1 and 2: PRO assessments before and after washout → "Sawtooth" pattern
- Trial 3: PRO assessments after washout → Results may be misleading

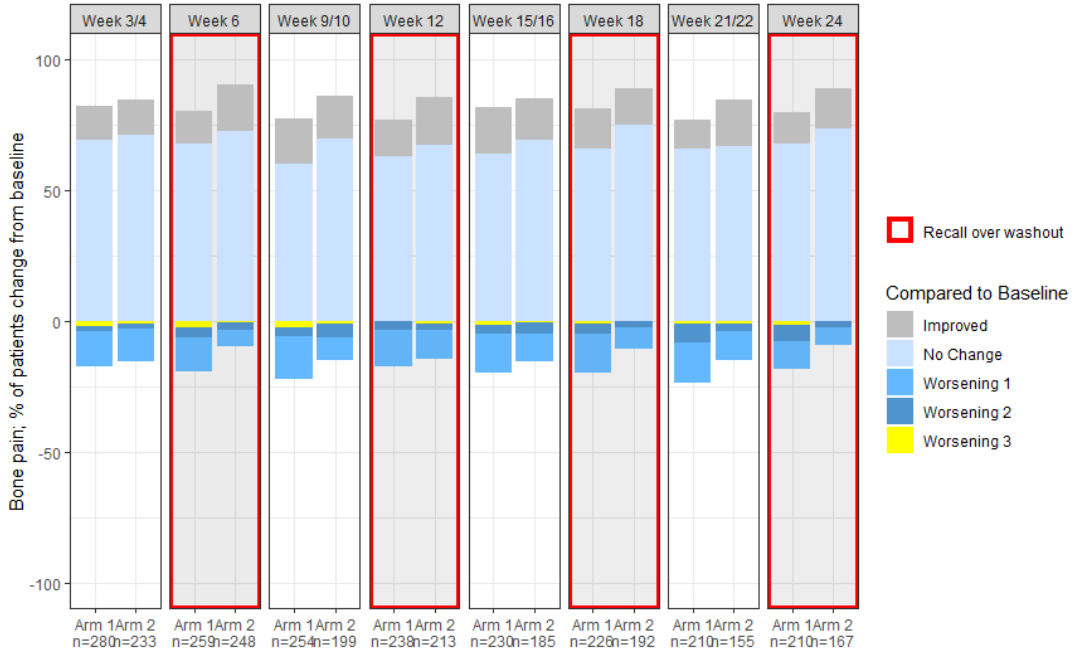
Impact on Single Item PRO Measures

- Categorical single-item measures assess individual symptoms, could be a drug side effect or a disease symptom, but often there is not a clear distinction
- Some symptom measures may be impacted more than others

Diarrhea

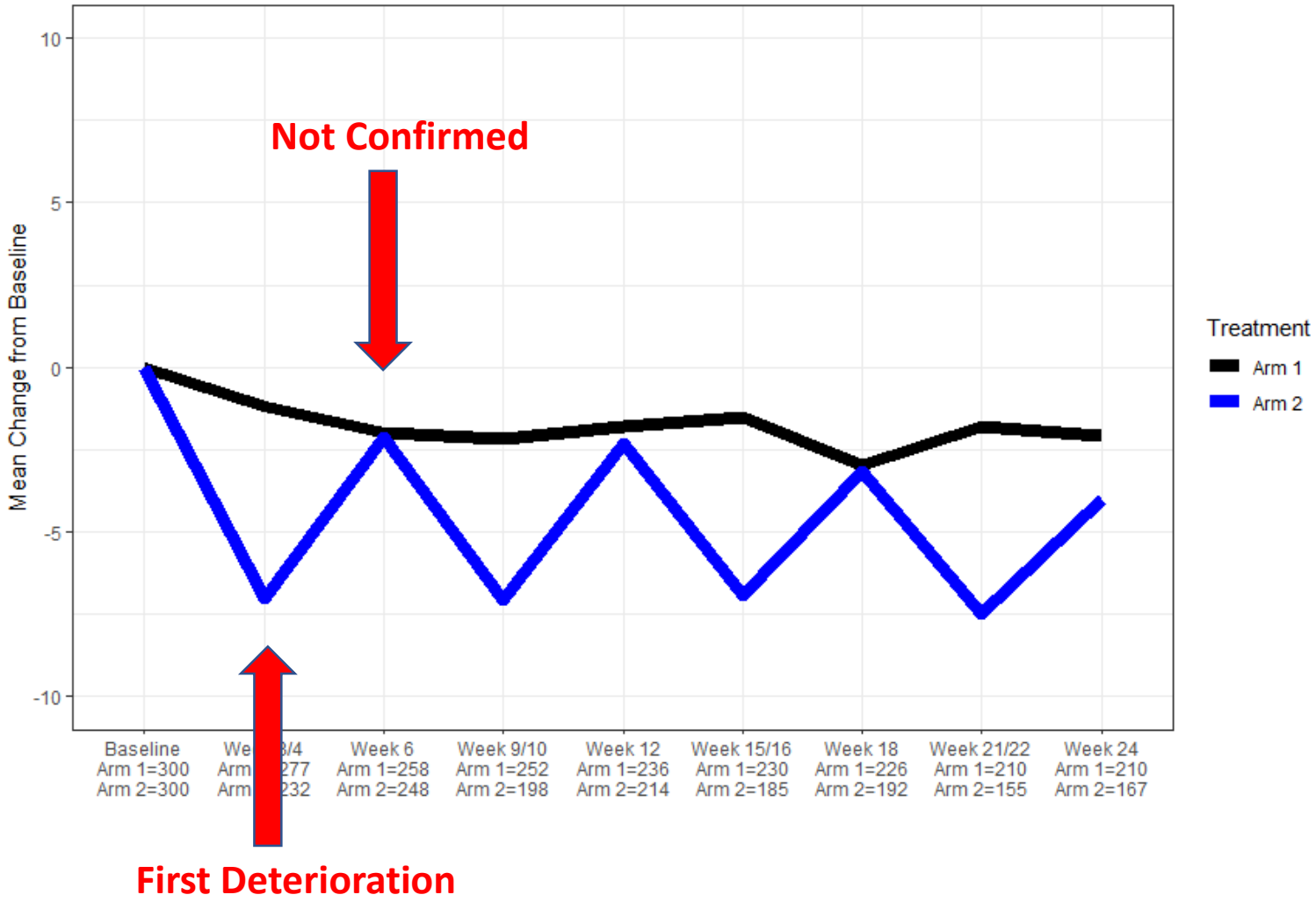


Bone Pain



Impact on Time-to-Event PRO Endpoints

- Time to deterioration defined as time to first deterioration with or without confirmation
- If there is a sawtooth pattern, often first deterioration cannot be confirmed at next assessment



Summary of Analysis Issues

- When drug administration schedules differ between arms, it is difficult to determine the optimal PRO assessment schedule
- Washout periods within a treatment schedule will impact item recall period for symptoms
- PRO assessment schedules should include assessments before and after washout, otherwise results may be misleading
- Best way to compare PROs across arms in this scenario is still unknown

The Clinical Perspective

- Must consider the specific question being asked:
  - What exactly is being measured?
  - When is the best time to measure it?
- Clinically relevant questions for patients:
  - When will toxicity begin?
  - What is the severity?
  - Does it resolve, and if so, when?
  - Will it occur every cycle?
- Different research questions require different assessment strategies

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James Shaw,
PhD, PharmD, MPH

- **What are some of the logistical barriers to collecting PRO data outside a scheduled clinic visit?**
- **In thinking of the case example presented, what are strategies to improve capture of tolerability?**

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Diane Fairclough, DrPH

- **What are some of the statistical challenges associated with analyzing PRO data collected on different schedules?**
- **How do you propose overcoming some of these challenges?**

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Heidi Klepin, MD, MS

- **When talking to patients in the clinic about PRO data what are patients most interested in learning about?**
- **As part of a clinical trial, how does frequent assessment of PRO impact older adults with cancer?**

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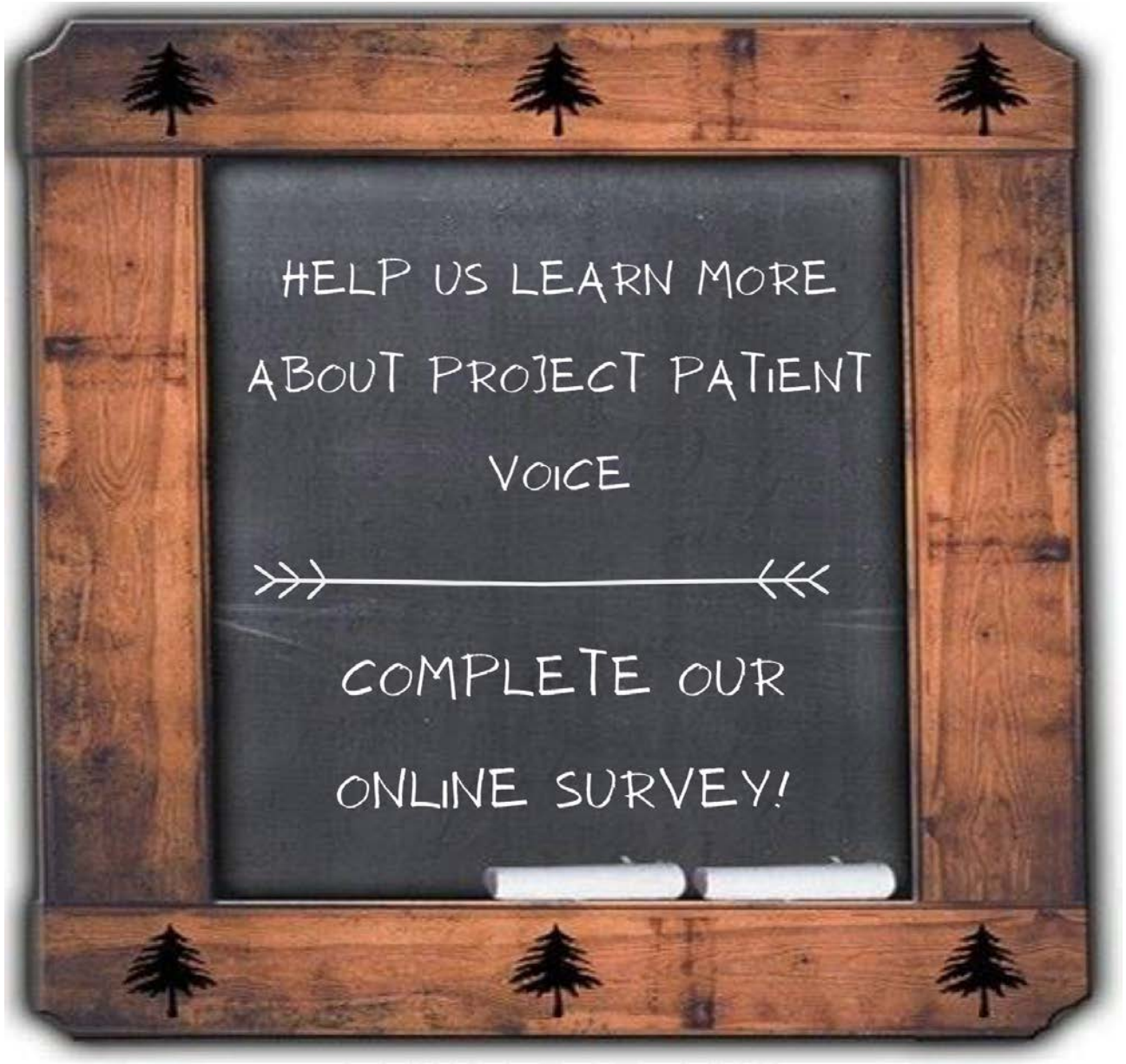
Wendy Sanhai, PhD, MBA

- **What are your thoughts about filling in PRO questionnaires at your clinic visit versus completing PRO questionnaires at home?**
- **From your perspective, how can trialists better strike a balance between convenience, relevance in timing and burden?**



Workshop Links

- PPV Survey (open from 9am-12pm)
- FDA OCE
- Project Patient Voice