Efforts to Advance Core Clinical Outcomes and Standard Analyses in Oncology

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Clinical Outcome Assessments in Cancer Clinical Trials

Disclaimer

- I have no financial relationships to disclose

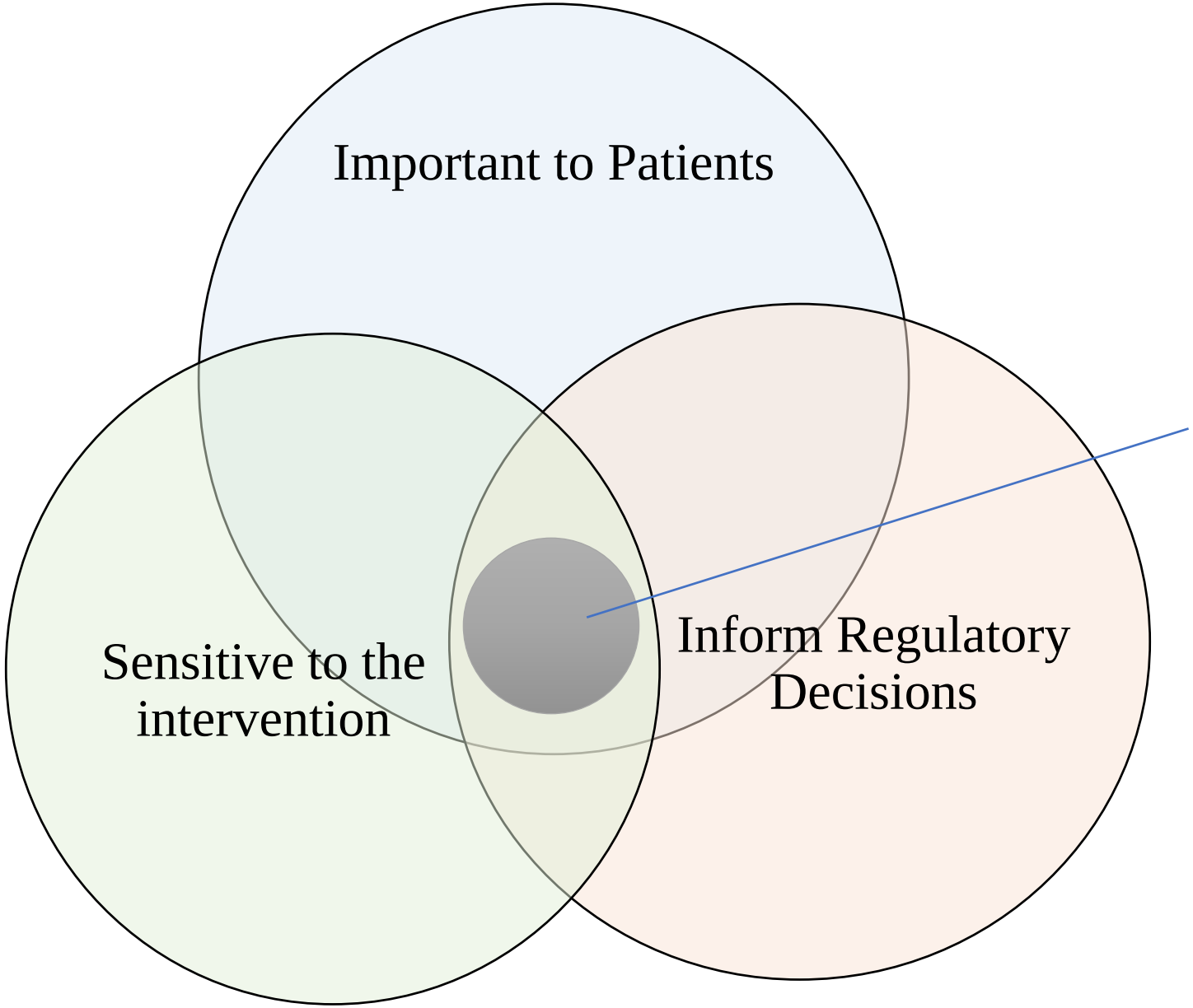
- Specific PRO instruments discussed in this talk are used as examples, not direct endorsements

FDA uses all available data to inform its review of safety and efficacy of new cancer treatments

- *Anti-cancer therapies* must demonstrate robust durable tumor response and/or control in the setting of acceptable safety (including no detriment in OS).
- We use Overall Survival endpoints when they are feasible and make sense for the clinical context
- We encourage standardization of symptom and functional measures that can complement standard safety and efficacy data.

Advancing a pragmatic approach to a more standard use of PRO data in cancer trials

- Identify subset of HRQL concepts -> Core Clinical Outcomes
- Identify well-defined and reliable measurement tools
- Create standard research objectives



FDA Oncology Core Clinical Outcomes

- Disease Symptoms
- Symptomatic Adverse Events
  - Global Side Effect Summary
- Physical Function and Ability to Perform Activities

Kluetz, P.G., et al., *Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms.* Clin Cancer Res, 2016. **22**(7): p. 1553-8.

Advancing a pragmatic approach to a more standard use of PRO data in cancer trials

- ~~Identify subset of HRQL concepts -> Core Clinical Outcomes~~
- Identify well-defined and reliable measurement tools
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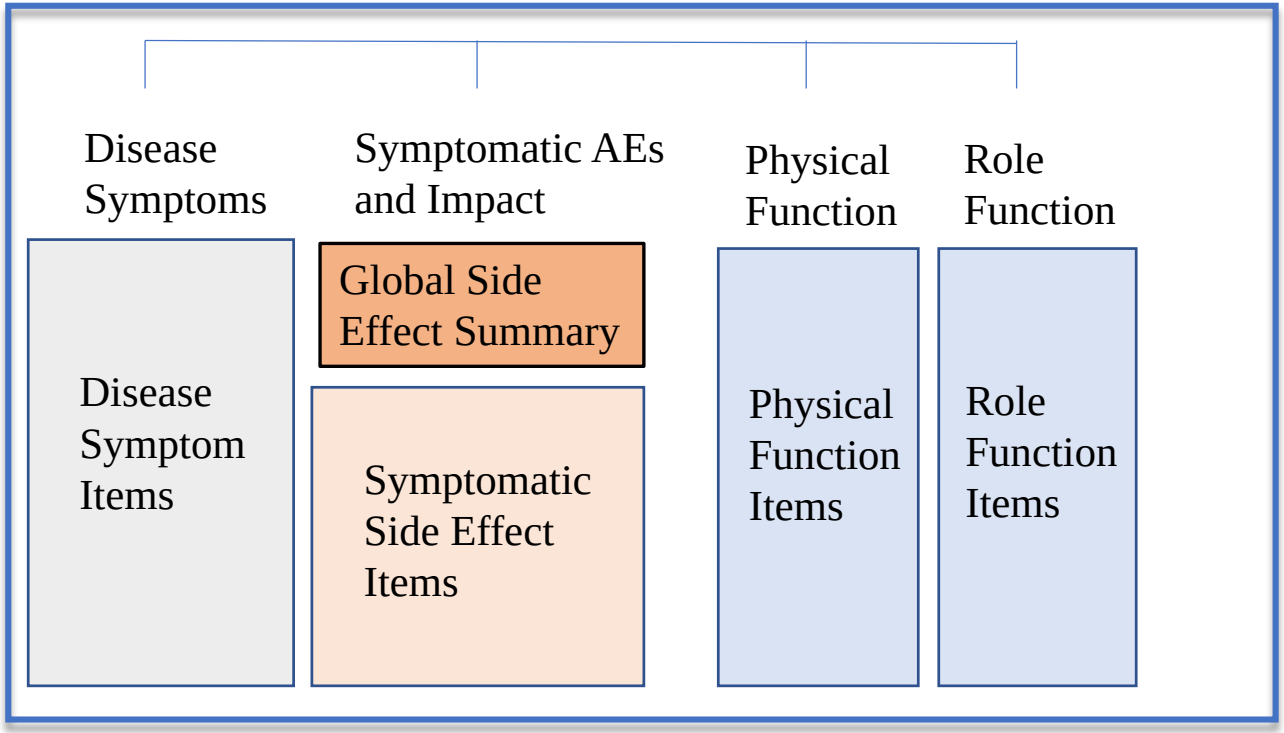
PRO assessment tools are available- none are “perfect”

* Example of use of existing PRO tools in a lung cancer trial

FDA Oncology Core Clinical Outcomes



NSCLC-SAQ- Non-small cell lung cancer symptom assessment questionnaire. **FACT**- Functional Assessment of Cancer Therapy. **PRO-CTCAE**- Patient-reported outcome Common terminology criteria for adverse events. **EORTC-QLQC30** European Organisation for the Research and Treatment of Cancer – Quality of Life Questionnaire

* These are examples and not endorsements. Seek advice from FDA regarding a PRO strategy for your specific trial context.

Why is PRO standardization so poor?

Outcomes	Measure	Standardization
Overall Survival	OS	High
Tumor Progression	TTP, PFS, DFS	High (RECIST)
Tumor Shrinkage	ORR	High (RECIST)
Adverse Events	Clin-RO	High (CTCAE)
Symptomatic Adverse Events	PRO	Low*
Global Side Effect Summary	PRO	Low*
Physical Function	PRO / ?Wearables	Low*
Disease Symptoms	PRO	Low*

TTP- Time to Progression, PFS- Progression-free survival, DFS- Disease-free survival, ORR- Objective response rate, Clin-RO- Clinician-reported outcome, PRO- Patient-reported outcome, HRQL- Health-related quality of life

* Standardization with respect to measurement tool, endpoint definition and analysis methods

PRO frequently lack clear standard research objectives

- ~~Identify subset of HRQL concepts -> Core Clinical Outcomes~~
- ~~Identify a narrow set of measurement tools~~
- **Create standard research objectives**

Session 3 Examined Two Broad Research Objectives

- Support a claim of superior physical function on one arm compared to another
  - Which treatment arm reported better physical function over 28 weeks?

- Describe on-treatment physical function
  - What percentage of patient at least maintained their baseline physical function while taking the treatment?

Many potential endpoints- All have strengths and limitations

- Describing population means
  - Mean change from baseline type endpoints
- Describing individual patient “events”
  - Time to deterioration in physical function
  - % of ITT maintaining baseline function through time t
- Hybrid endpoints describing function while in response/tumor control
  - 12 month functional PFS rate (PFS with maintenance of function)
  - 6 month functional ORR rate (ORR with maintenance of function)
- Many others

*** Can the cancer community identify a few standard endpoints that are most informative and could serve as consistent metrics for physical function data in advanced/metastatic cancer trials?**

To Create a Level Playing Field, We Can Start by Identifying a Standard Assessment Frequency

- The sensitivity of many of these endpoints can be affected by the frequency of assessment

- Concentrate assessments in first 6 months, then reduce based on context
  - In most advanced metastatic trials, the first 6 months of treatment provides the most reliable PRO information

- At least one longer term follow up assessment **regardless of whether patient still on treatment**
  - Could be considered to reduce censoring for superiority/efficacy analyses
  - Comparison of change from baseline in physical function at some later timepoint such as 18mo or 24mo

For regulatory-grade data, *standard assessment frequency* in the first 6-12 months in advanced/metastatic cancer trials is needed

	BL	W2	W3	W4	W5	W6	W7	W8	Week 12	Week 16	Week 20	Week 24	9mo	12mo	Additional Context Dependent Follow up
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	
Disease Symptoms	X								X			X		X	
Other HRQL	X											X		X	

Standard 6- month "acute/subacute" period

Context Dependent Follow-up

Generalizing Todays Workshop- Estimand Framework

Thoughtful Endpoint Design is Broadly Applicable

- Different contexts
  - ✓Controlled clinical trials
  - ✓Registries/Observational studies
  - ✓Learning Healthcare Systems – “Real-World Data”
- Different outcomes
  - ✓Physical function, overall side effect global, disease symptoms, etc.
  - ✓E.g. % of patients with minimal or no side effect bother through 6 months of treatment
- Different technologies
  - ✓Physical function data from wearable devices will also require clear research objectives and endpoint development

Conclusion

For *anti-cancer* indications, symptom or function data are **complementary** to demonstration of overall survival or accepted tumor-based endpoints

✓We have identified ***Core Clinical Outcomes*** for FDA Oncology

- Symptomatic adverse events, global side effect summary, disease symptoms and physical function/ability to conduct daily activities

✓We have identified characteristics for ***acceptable measurement tools with examples***

❑ TO DO- identify **common research objectives** and **standardize an assessment frequency**

Apply a **systematic approach to develop endpoints** such as the estimand framework