# Efforts to Advance Core Clinical Outcomes and Standard Analyses in Oncology

Paul G. Kluetz, MD
Deputy Director, Oncology Center of Excellence
U.S. Food and Drug Administration

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**Clinical Outcome Assessments in Cancer Clinical Trials**

# Disclaimer

- I have no financial relationships to disclose

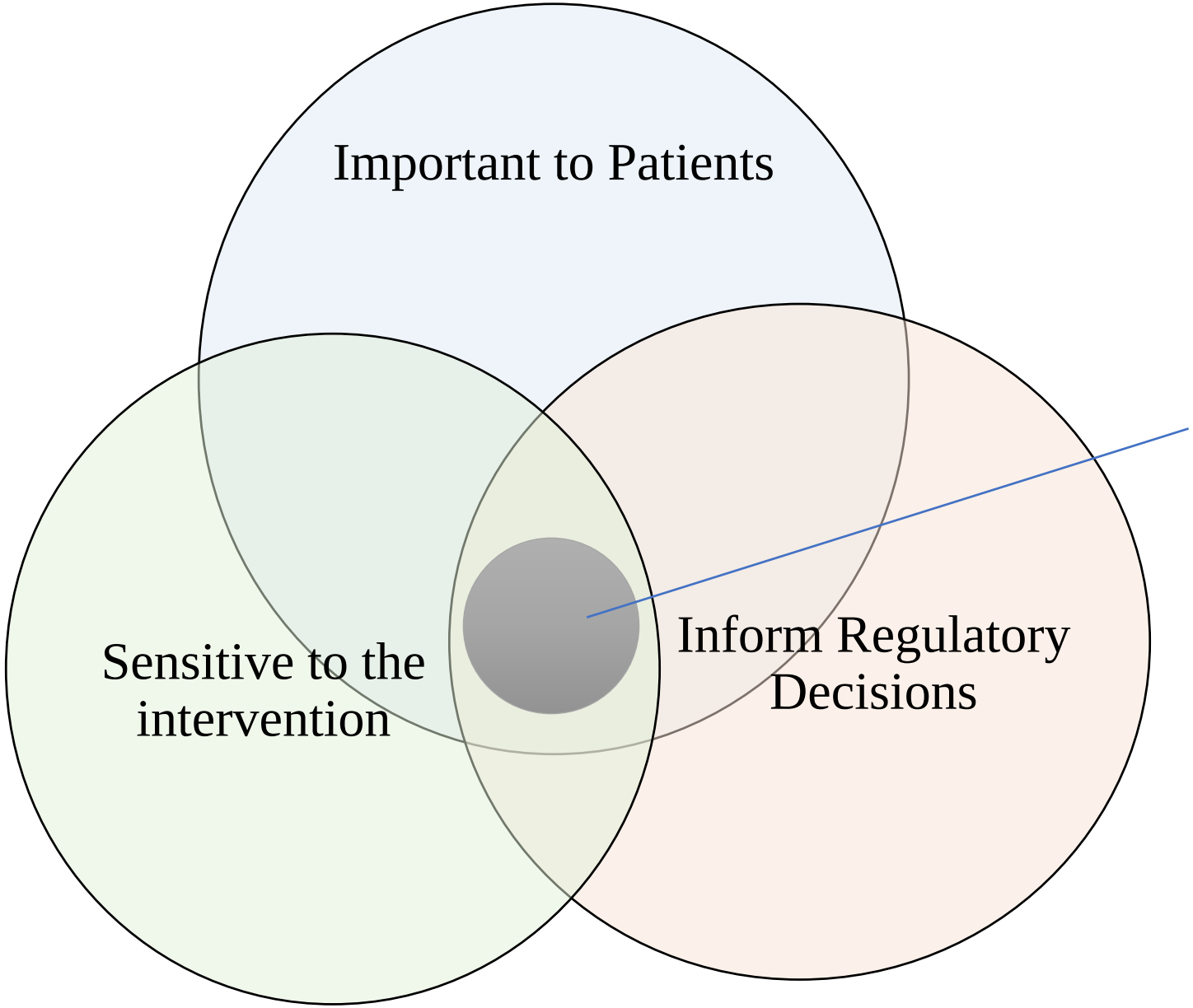
- Specific PRO instruments discussed in this talk are used as examples, not direct endorsements

# 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.

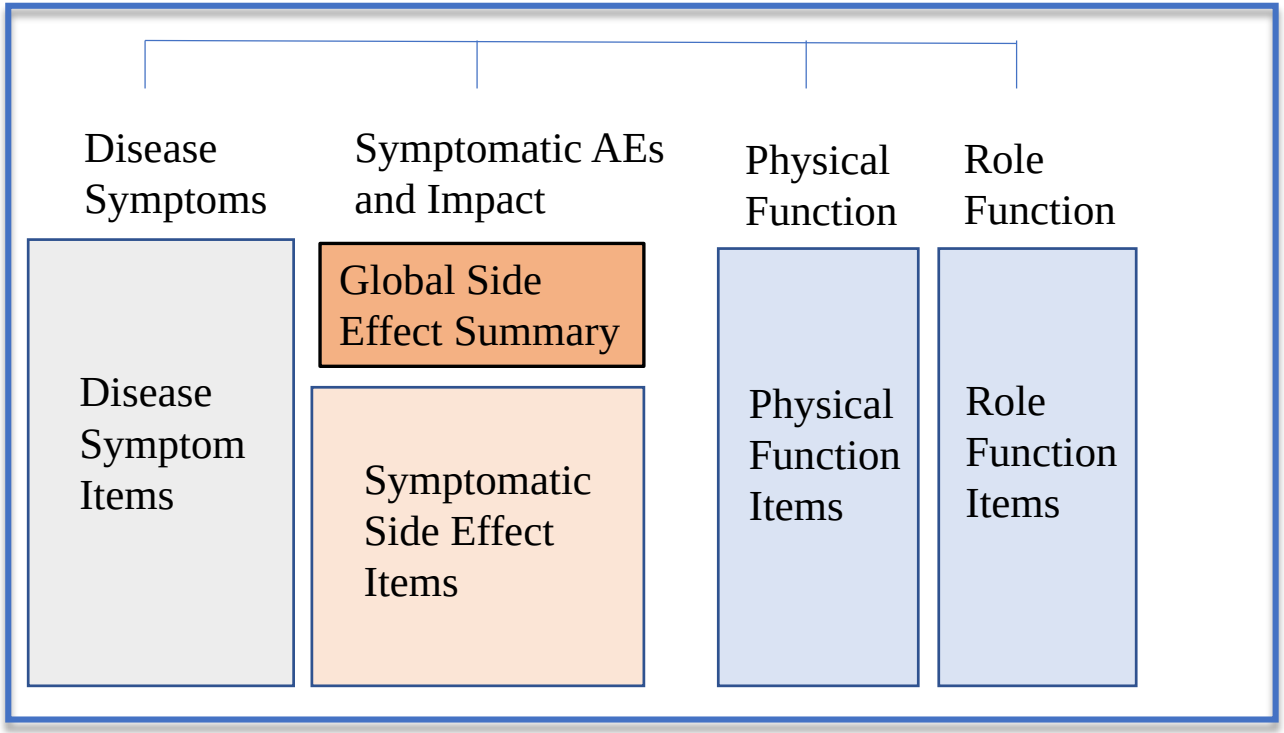
# Advancing a pragmatic approach to a more standard use of PRO data in cancer trials

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

# 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