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Emerging Patient-Centric Tolerability Endpoints

PSI 2024 Conference

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Acknowledgments

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Overview of the Presentation

Introduce emerging movement around defining treatment tolerability from the patient's perspective

Show the need for patient-reported tolerability endpoints

Review novel patient-reported outcome (PRO)-based estimands for comparative tolerability

Conclusions and next steps

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Defining and Assessing Tolerability: A Standard Definition

- Standard definition from the International Conference on Harmonization (ICH) "***the degree to which overt adverse effects can be tolerated by the subject***"
- An adverse event is a "disease, sign, or symptom" caused by the treatment (ICH)
- Primarily, tolerability is measured in terms of clinician-rated adverse events via the NCI's Common Terminology Criteria of Adverse Events (CTCAE) or clinical events like treatment discontinuation or hospitalization

ICH Harmonised Tripartite Guideline. *Statistical Principles for Clinical Trials.* February 5th 1998.

Tolerability: Shouldn't We Hear from the Patient?

- In many cases, tolerability is something that comes from the patient, especially when it concerns symptomatic adverse events
- Updated definition of tolerability from Friends of Cancer:

The tolerability of a medical product is 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.

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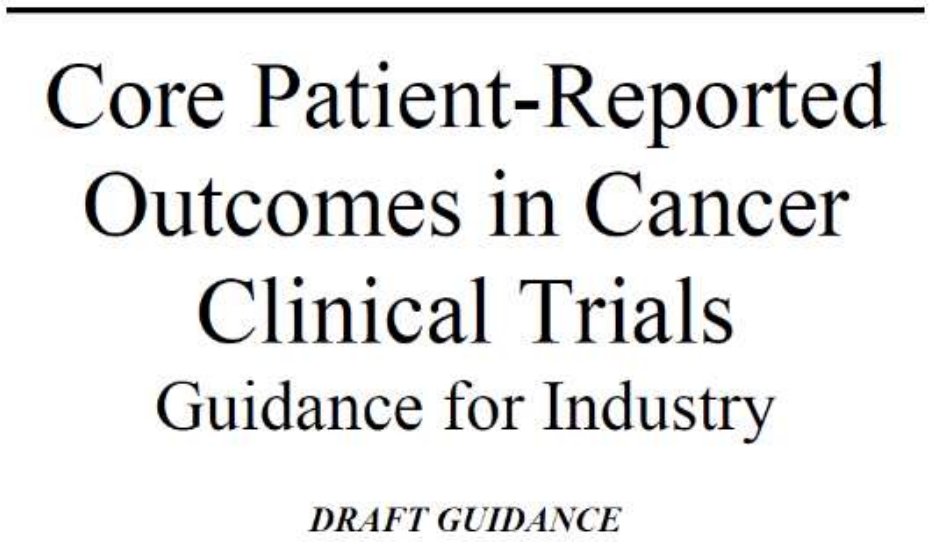
Basch E, Campbell A, Hudgens S, et al. *Broadening the Definition of Tolerability in Cancer Clinical Trials to Capture the Patient Experience.* Washington, DC: Friends of Cancer; 2020.

FRIENDS of CANCER RESEARCH

Cancer-Specific Guidance


Core Patient-Reported Outcomes in Cancer Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

Draft guidance issued in June 2021 to introduce a core set of PRO concepts to include in cancer clinical trials

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials

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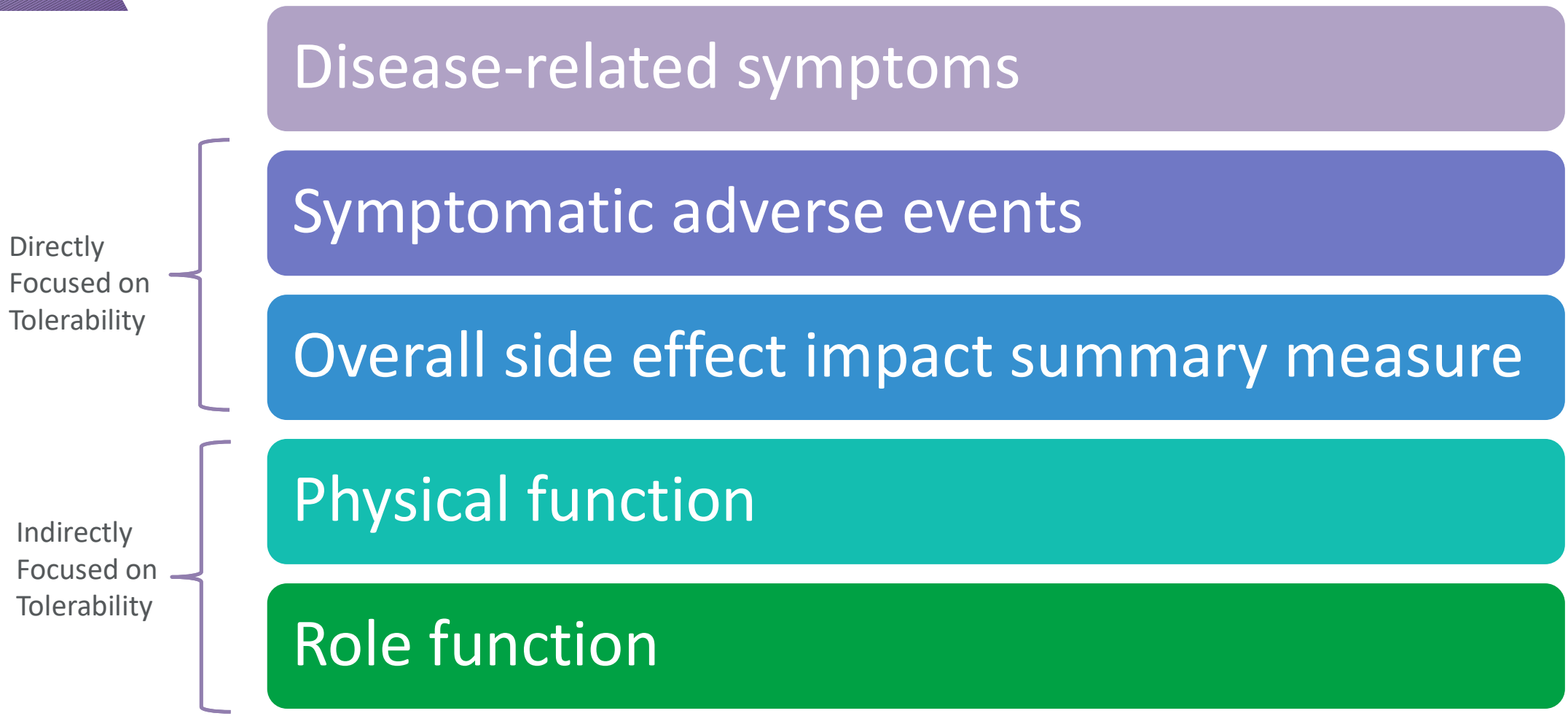
United States Food and Drug Administration. *Core Patient-Reported Outcomes in Cancer Clinical Trials Guidance for Industry. 2021. June 9th.*

US FDA: Core PRO Concepts



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United States Food and Drug Administration. *Core Patient-Reported Outcomes in Cancer Clinical Trials Guidance for Industry. 2021. June 9th.*

Is safety the same as tolerability?

US Regulatory Perspective

- **SAFETY:** The *medical risk* to the subject, usually assessed in a clinical trial by laboratory tests (including clinical chemistry and hematology), vital signs, clinical adverse events (diagnoses, signs and symptoms), and other specific diagnostic tests or evaluations (e.g. ECGs, visual field testing).
- **TOLERABILITY:** The degree to which *overt adverse effects* can be tolerated by the subject.

Kluetz PG, Kanapuru B, Lemery S, et al. Informing the Tolerability of Cancer Treatments Using Patient-Reported Outcome Measures: Summary of an FDA and Critical Path Institute Workshop. *Value in Health. 2018;21(6):742-747.*

But, from an endpoint and statistical perspective, there are similarities…

Statistical Challenges with Tolerability Endpoints

- Tolerability concepts poorly defined compared to efficacy
- Involve collection of information that cannot be predefined (e.g., AE duration, severity, recurrence)
- Trials typically powered for efficacy endpoints
- Large numbers of emerging events may lead to multiplicity

Approaches to summarise the patient's experience and enable hypothesis testing may help address these issues.

Phillips R, Sauzet O, Cornelius V. Statistical methods for the analysis of adverse event data in randomised controlled trials: a scoping review and taxonomy. *BMC Medical Research Methodology. 2020/11/30 2020;20(1):288. doi:10.1186/s12874-020-01167-9*

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Comparative Tolerability Endpoints

JOURNAL OF BIOPHARMACEUTICAL STATISTICS
https://doi.org/10.1080/10543406.2024.2313060

[Special issue PRO] Considering endpoints for comparative tolerability of cancer treatments using patient report given the estimand framework

John Devin Peipert[a], Monique Breslin[b], Ethan Basch[c], Melanie Calvert[d,e,f,g,h], David Cella[a], Mary Lou Smith[i], Gita Thanarajasingam[j], and Jessica Roydhouse[b]

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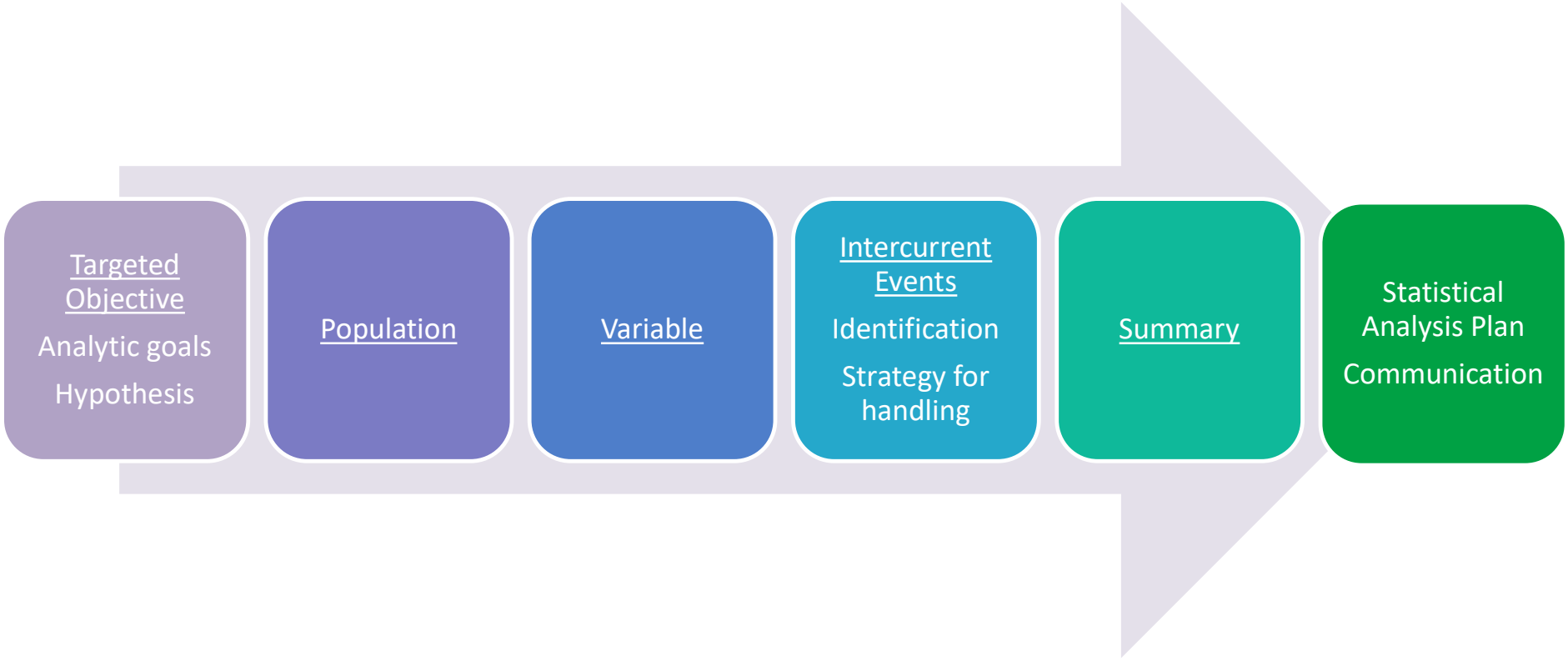
Estimand Framework



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Peipert JD, et al. Considering endpoints for comparative tolerability of cancer treatments using patient report given the estimand framework. *Journal of Biopharmaceutical Statistics. 2024:1-19.*

What kinds of questions would comparative tolerability estimands help answer?

Akacha, et al. framework…

Understanding non-adherence or discontinuation due to inability to tolerate therapy

Understanding non-adherence or discontinuation due to lack of efficacy

→ Understanding efficacy and safety (or tolerability) among patients who adhered to therapy

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Akacha M, Bretz F, Ruberg S. Estimands in clinical trials – broadening the perspective. *Statistics in Medicine. 2017;36(1):5-19.*

Considerations for Developing Comparative Tolerability Endpoints

	Analysis Population	Estimand Strategies	Variable Measurement	Event Definition	Communication
Issues to consider	• Safety or modified safety population	• Accounting for unmeasured confounding • Varying duration of therapy • Appropriate handling of ICE of patient discontinuation due to toxicity	• Pre-treatment data collection and how it may inform analyses • Assessment frequency required for event detection • Assessment frequency and participant burden	• Identification of suitable thresholds for deterioration and improvement • Choice of reference score	• Adaptation or use of existing consensus-based strategies for PRO efficacy data or safety data

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Peipert JD, et al. Considering endpoints for comparative tolerability of cancer treatments using patient report given the estimand framework. *Journal of Biopharmaceutical Statistics. 2024:1-19.*

Example Tolerability PRO: FACT Item GP5

Overall Side Effect Impact Summary

"I am bothered by side effects of treatment"

Not at all, A little bit, Somewhat, Quite a bit, Very much

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Core Patient-Reported Outcomes in Cancer Clinical Trials
Guidance for Industry

FDA

Estimand 1: Proportion of Patients with Severe Side Effect Impact

Estimand Attribute	
Objective	Proportion of patients with severe overall side effect bother on treatment A vs B at cycle X
Variable of Interest	Severe side effect bother
Population	Safety population
Intercurrent Events	
Death	While on treatment
Disease progression	While on treatment
Discontinuation due to AE	While on treatment *or* Composite
Dose modification	Treatment policy
Summary Measure	Difference in % of patients

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Peipert JD, et al. Considering endpoints for comparative tolerability of cancer treatments using patient report given the estimand framework. *Journal of Biopharmaceutical Statistics. 2024:1-19.*

Estimand 2: Time with Severe Overall Side Effect Impact

Estimand Attribute	
Objective	Time/cycles patients who benefit from treatment at cycle X spend in severe bother
Variable of Interest	Severe side effect bother
Population	On treatment at cycle X
Intercurrent Events	
Death	While on treatment
Disease progression	While on treatment
Discontinuation due to AE	While on treatment *or* Composite
Dose modification	Treatment policy
Summary Measure	Difference in % of time/cycles

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Discontinuation Due to AE: Best ICE Strategy?

GP5 is strongly associated with subsequent discontinuation due to AE[1]

While on treatment

- Ignores discontinuation due to AE

Composite

- High bother + discontinuation due to AE

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Peipert JD, Zhao F, Lee J-W, et al. Patient-Reported Adverse Events and Early Treatment Discontinuation Among Patients With Multiple Myeloma. *JAMA Network Open. 2024;7(3):e243854-e243854.*

Additional nuances of the estimands still under consideration

- Uses safety population, loses randomisation
- Definition of “high bother” not yet evidence based
- Selection of endpoint cycle clinically driven
- Best estimators to be determined

Conclusions and Next Steps

- New estimands will help support comparative tolerability analyses
  - Useful for FDA Project Optimus?
- Currently testing in real trial datasets
- Will examine for use with other PROs (e.g., PRO-CTCAE)

Thank you!

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