# Treatment Tolerability and Quality of Life in Patients with Multiple Myeloma

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**3rd Oct 2025**
**GIMEMA International Meeting New Frontiers in Hematologic Research: Quality of Life and Artificial Intelligence**

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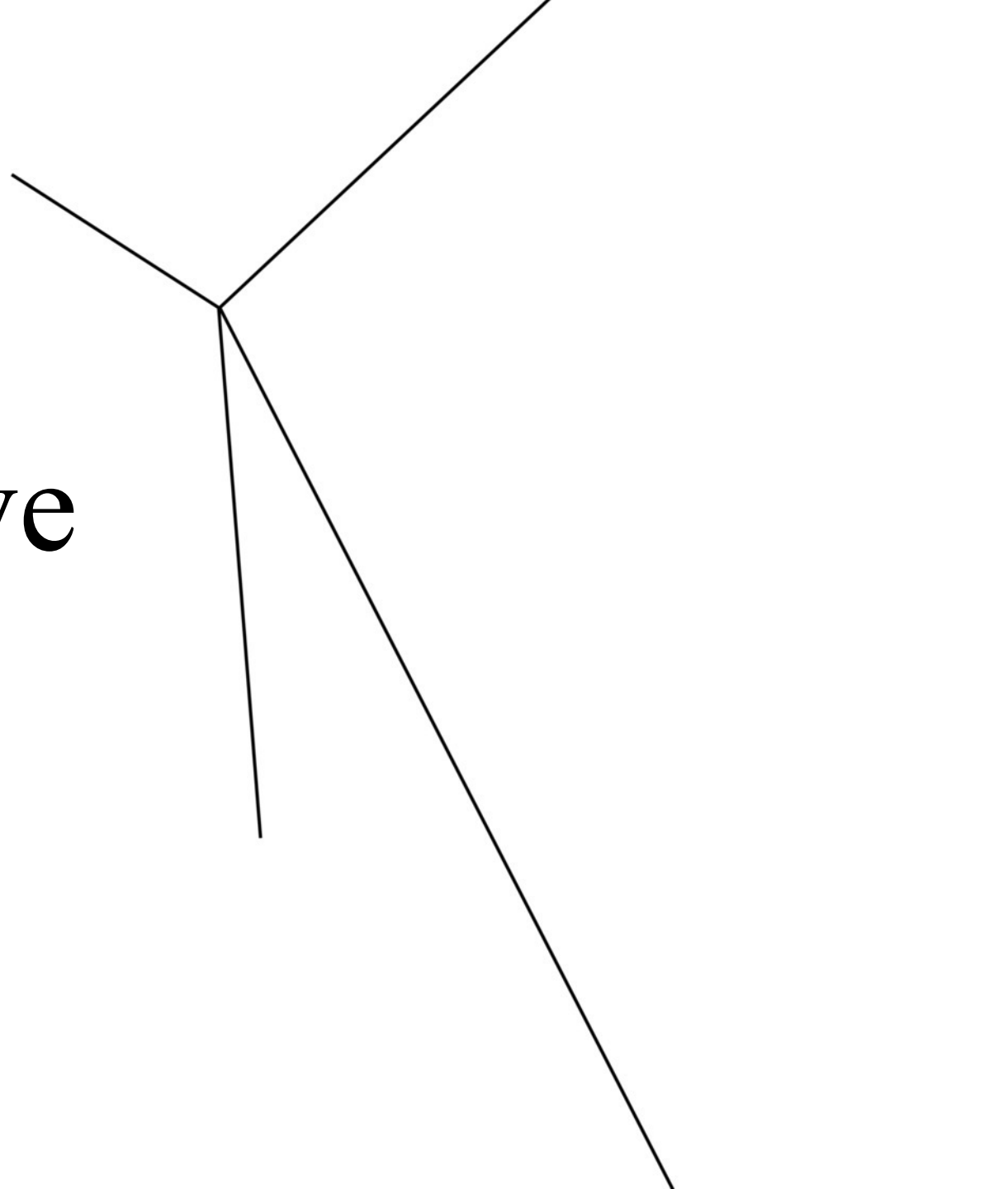
# Incorporating the Patient's Perspective into Treatment Tolerability Assessment



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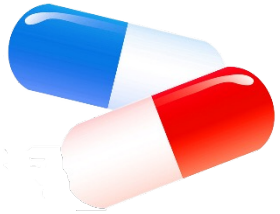
# Overview: Treatment Tolerability

- In addition to their efficacy, tolerability of treatments is a key consideration for regulatory approval and prescribing
- In clinical trials and in routine care, inability to tolerate treatment leads to non-adherence, discontinuation, delays, and dose reductions
- Tolerability and safety are primary concerns of early phase clinical trials, but remain very relevant in Phase III and after market settings



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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 or clinical events like treatment discontinuation or hospitalization

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

# Shouldn't We Hear from the Patient Too?

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 Research:

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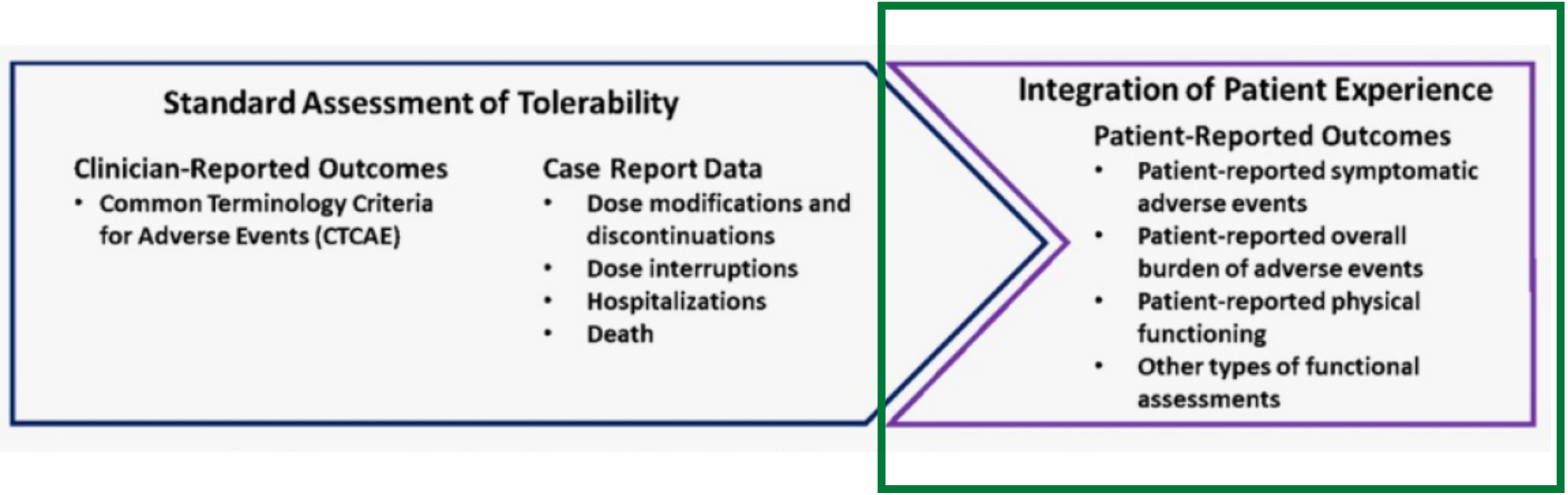
Basch E, Campbell A, Hudgens S, et al. *Broadening the Definition of Tolerability in Cancer Clinical Trials to Capture the Patient Experience.* Washington, DC: Friends of Cancer; 2020.

FRIENDS of CANCER RESEARCH

# Using Patient Reported to Capture Treatment Tolerability

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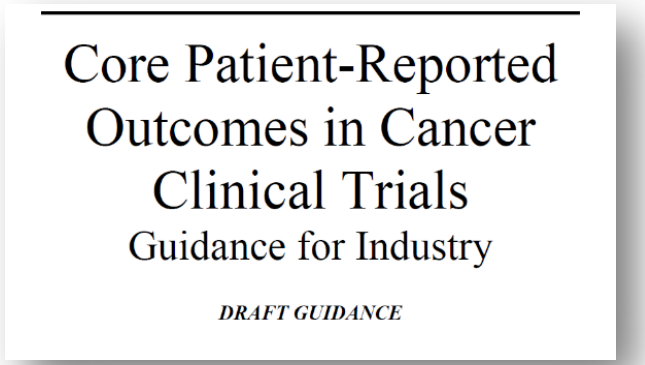
Basch E, Campbell A, Hudgens S, et al. *Broadening the Definition of Tolerability in Cancer Clinical Trials to Better Measure the Patient Experience. 2018.* https://friendsofcancerresearch.org/wp-content/uploads/Comparative-Tolerability-Whitepaper_FINAL.pdf




# US FDA: Core PRO Concepts

- Disease-related symptoms
- Symptomatic adverse events
- Overall side effect impact summary measure
- Physical function
- Role function

Directly Focused on Tolerability

Indirectly Focused on Tolerability

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United States Food and Drug Administration. *Core Patient-Reported Outcomes in Cancer Clinical Trials Guidance for Industry. 2024. October 24th.*

# Example Tolerability PRO: FACT Item GP5

"I am bothered by side effects of treatment"

| Not at all, A little bit, Somewhat | Quite a bit, Very much |
|---|---|
| Low bother | High bother |

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Core Patient-Reported Outcomes in Cancer Clinical Trials

Guidance for Industry

FDA

JAMA Network Open

Original Investigation | Oncology

# Patient-Reported Adverse Events and Early Treatment Discontinuation Among Patients With Multiple Myeloma

John Devin Peipert, PhD; Fengmin Zhao, PhD; Ju-Whei Lee, PhD; Shu-en Shen, MS; Edward Ip, PhD; Nathaniel O'Connell, PhD; Ruth C. Carlos, MD, MS; Noah Graham, MB; Mary Lou Smith, JD, MBA; Ilana F. Gareen, PhD, MPH; Pamela J. Raper, BSN, RN; Matthias Weiss, MD; Shaji K. Kumar, MD; S. Vincent Rajkumar, MD; David Cella, PhD; Robert Gray, PhD; Lynne I. Wagner, PhD

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## Figure 2. Sankey Bar Chart of GP5 Values

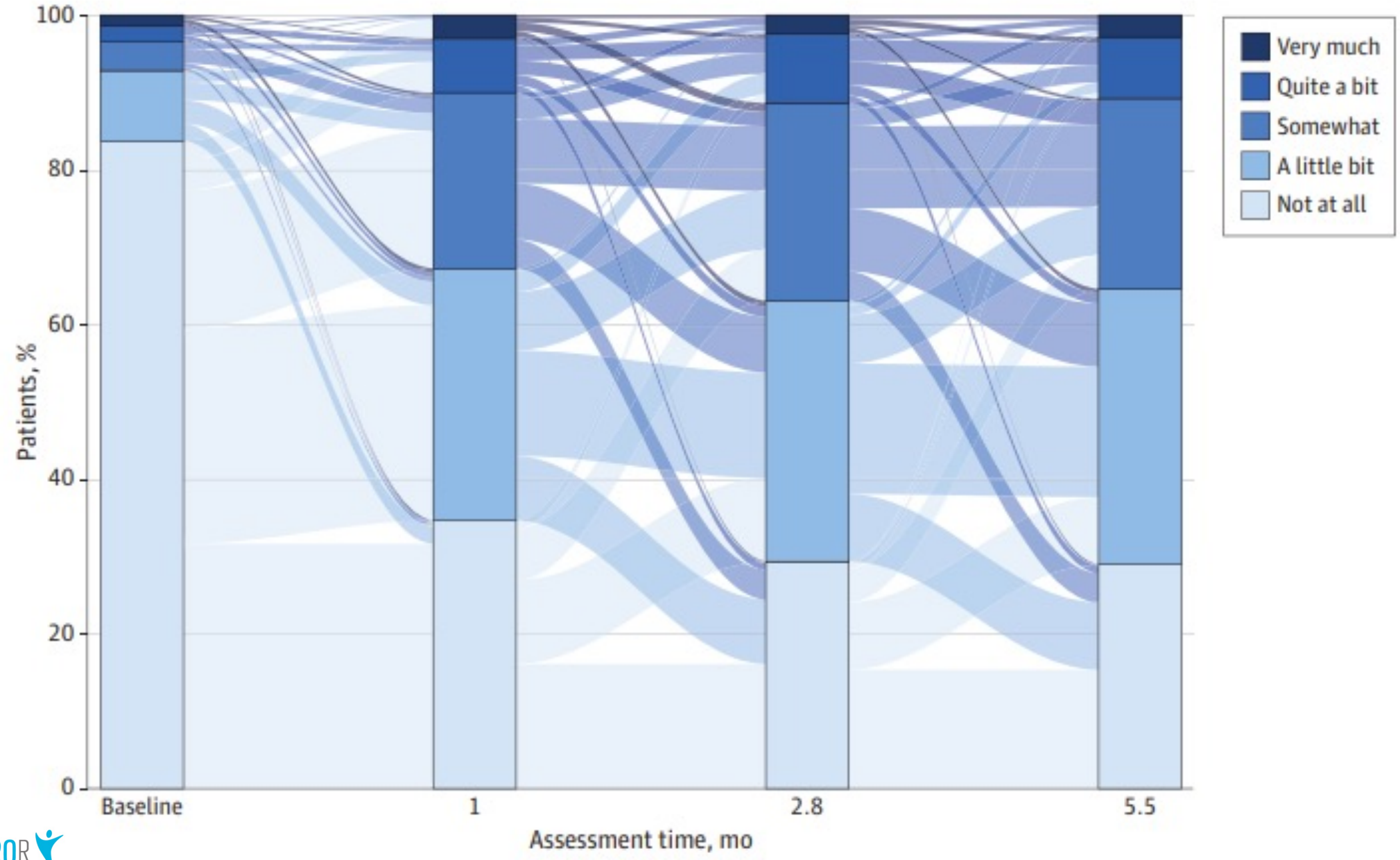

**Table 3. Logistic Regression Models of Early Treatment Discontinuation and GP5 While UndergoingTreatment or Change From Baseline in GP5[a]**

| Indicator | Odds ratio (95% CI) | |
|---|---|---|
| | Unadjusted | Adjusted[b] |
| GP5 while undergoing treatment | | |
| 1-mo GP5 (high vs low bother)[c] | 2.01 (1.17-3.45) | 2.20 (1.25-3.89) |
| 2.8-mo GP5 (high vs low bother)[c] | 3.93 (2.38-6.49) | 3.41 (2.01-5.80) |
| 5.5-mo GP5 (high vs low bother)[c] | 4.55 (1.75-11.84) | 4.66 (1.69-12.83) |
| Maximum GP5 while undergoing treatment (high vs low bother)[c] | 1.39 (0.94-2.05) | 1.32 (0.89-1.98) |
| Baseline-adjusted, maximum GP5 while undergoing treatment (high vs low bother)[c] | 1.61 (1.09-2.37) | 1.54 (1.04-2.30) |

Patients reporting **high side effect bother** had **2.2–4.6 higher odds of early treatment discontinuation**.

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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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Funded by a Broad Area Announcement from the United States Food and Drug Administration contract awarded to Drs. Peipert and Roydhouse [#75F40121C00162].

# Estimand: Objective, Variable, & Population

**Objective**

Time/cycles patients who benefit from treatment at cycle X spend in severe bother

**Variable of Interest**

Severe overall side effect bother on GP5

**Population**

On treatment at cycle X

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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.*

# Recent Tolerability-Based FDA Drug Label

Patient-reported overall side effect impact results were supported by a lower incidence of treatment discontinuation adverse reactions for RETEVMO (4.7%) compared to cabozantinib or vandetanib (27%) in patients who received at

**Table 22. Descriptive Summary of Patient-reported Overall Side Effect Impact While on Treatment in LIBRETTO-531**

| | RETEVMO (N=145) | Cabozantinib or Vandetanib (N=77) |
|---|---|---|
| **Mean proportion of time with high side effect bother (95% CI)** | 8% (4.8%, 10%) | 24% (17%, 31%) |

Revised September 2024

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213246s011s013lbl.pdf, Accessed 24/04.2025

# Real-World Tolerability Monitoring

## Approach

- The Carevive PROmpt® remote symptom capturing platform collected **FACT GP5** at least once weekly among MM patients with lengthy treatment course
- Merged with clinical data from electronic medical records
- Treatment tolerability: % of time with high bother (very much/quite a bit vs. somewhat/a little bit/none)
- Persistent high bother:  76-100% of time on treatment

## Results

- 34% (n=61) had at least one instance of high bother
  - 82% had high bother 25% of the time
  - 7% had high bother 26-50% of the time
  - 4% had high bother 51-75% of the time
  - 7% had persistent high bother (>75% of the time)

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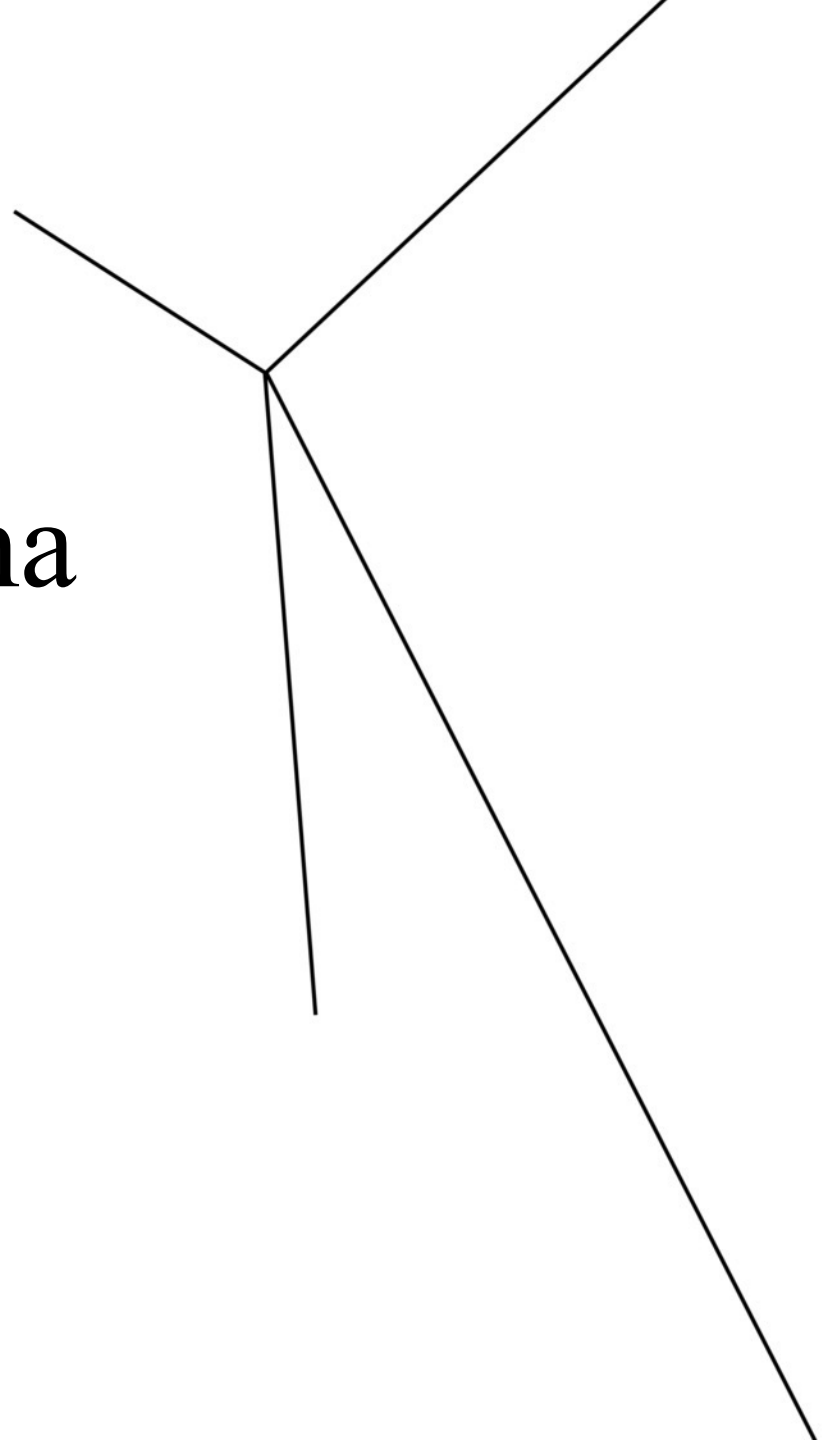
Rusli E, Galaznik A, Wujcik D. A Pragmatic Approach for Quantifying Treatment Tolerability in Multiple Myeloma Clinical Practice Using Patient-Reported Outcomes (PROs). *Blood. 2024/11/05/ 2024;144:3766. doi:https://doi.org/10.1182/blood-2024-208694*

# FACT Multiple Myeloma (FACT-MM)

## Updates to a disease-specific PRO for multiple myeloma trials and clinical practice



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# FACT-MM Overview

- FACT-G

  28 items scored as four subscales (physical, social, emotional, functional wellbeing) and total score

- Additional Concerns scale (MMS):

  14 items covering several symptoms of multiple myeloma

  Sum items responses after reverse coding negatively worded items

  Scores range from 0-56, higher scores indicate better HRQOL

FACIT group

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# FACT-MM Additional Concern Scale

| Item Name | Item Stem |
|---|---|
| P2 | I have certain parts of my body where I experience pain |
| HI12 | I feel weak all over |
| BMT6 | I get tired easily |
| HI8 | I have trouble concentrating |
| N3 | I worry about getting infections |
| LEU3 | I feel discouraged about my illness |
| LEU4 | Because of my illness, I have difficulty planning for the future |
| LEU6 | I worry that I might get new symptoms of my illness |
| BRM9 | I have emotional ups and downs |
| BP1 | I have bone pain |
| An14 | I need help doing my usual activities |
| MM1 | I have trouble walking because of pain |
| HI7 | I feel fatigued |
| ES10 | I have gained weight |

# Confirmatory Factor Analysis – Additional Concerns Scale

| Item Name | Item Stem | Loading |
|---|---|---|
| P2 | I have certain parts of my body where I experience pain | 0.781 |
| HI12 | I feel weak all over | 0.832 |
| BMT6 | I get tired easily | 0.902 |
| HI8 | I have trouble concentrating | 0.693 |
| N3 | I worry about getting infections | 0.583 |
| LEU3 | I feel discouraged about my illness | 0.737 |
| LEU4 | Because of my illness, I have difficulty planning for the future | 0.750 |
| LEU6 | I worry that I might get new symptoms of my illness | 0.742 |
| BRM9 | I have emotional ups and downs | 0.716 |
| BP1 | I have bone pain | 0.770 |
| An14 | I need help doing my usual activities | 0.776 |
| MM1 | I have trouble walking because of pain | 0.785 |
| HI7 | I feel fatigued | 0.908 |
| ES10 | I have gained weight | 0.148 |

CFA = 0.960, TLI = 0.952, RMSEA = 0.191

# FACT-MM Additional Concerns Modification

- Factor analyses suggested that the item ES10 (“I have gained weight”) does not fit well with the other items.
- In addition, this item was deemed to be less relevant clinically than the other items
- Therefore, we modified the scale by omitting ES10
- New Additional Concerns scale (MMS v2):
  - 13 items
  - Sum items responses after reverse coding negatively worded items
  - Scores range from 0-52, higher scores indicate better HRQOL

# Addition of Pain Scale to FACT-MM

- Pain is a highly relevant symptom for multiple myeloma
- Using items already included in the FACT-MM instrument, we sought to create a new scale that would focus only on pain

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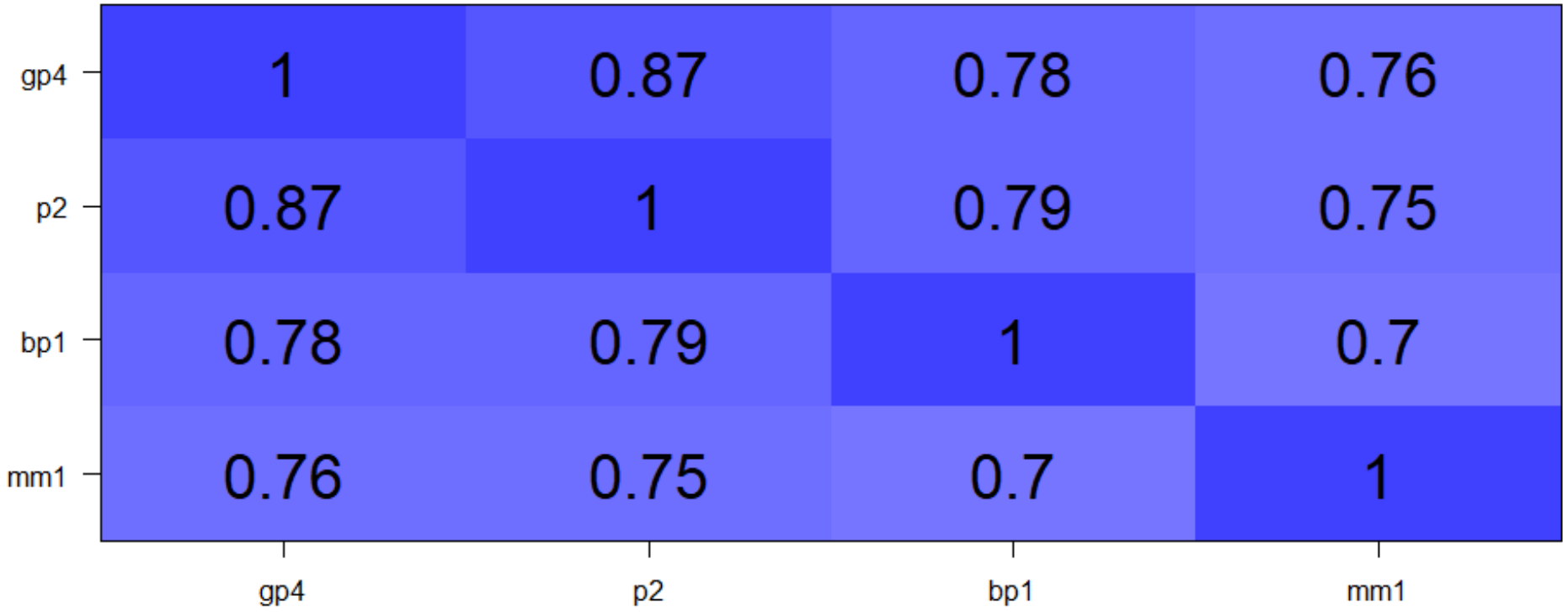
# Candidate Pain Items

| Item Name | Item Stem |
|---|---|
| GP4 | I have pain |
| P2 | I have certain parts of my body where I experience pain |
| BP1 | I have bone pain |
| MM1 | I have trouble walking because of pain |

# Pain Inter-Item Correlations

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# Confirmatory Factor Analysis – Pain Scale

| Item Name | Item Stem | Loading |
|---|---|---|
| GP4 | I have pain | 0.929 |
| P2 | I have certain parts of my body where I experience pain | 0.940 |
| BP1 | I have bone pain | 0.846 |
| MM1 | I have trouble walking because of pain | 0.812 |

CFA = 0.999, TLI = 0.999, RMSEA = 0.043

# Conclusions

- Patient-reported outcomes capture multiple-myeloma patients side effects and disease symptoms
- PRO measures like FACT GP5 and FACT-MM are fit for purpose to use as endpoints in multiple myeloma trials and could be considered for monitoring patients in routine care
- Including the patient's voice in treatment evaluation is critical in benefit/risk assessment

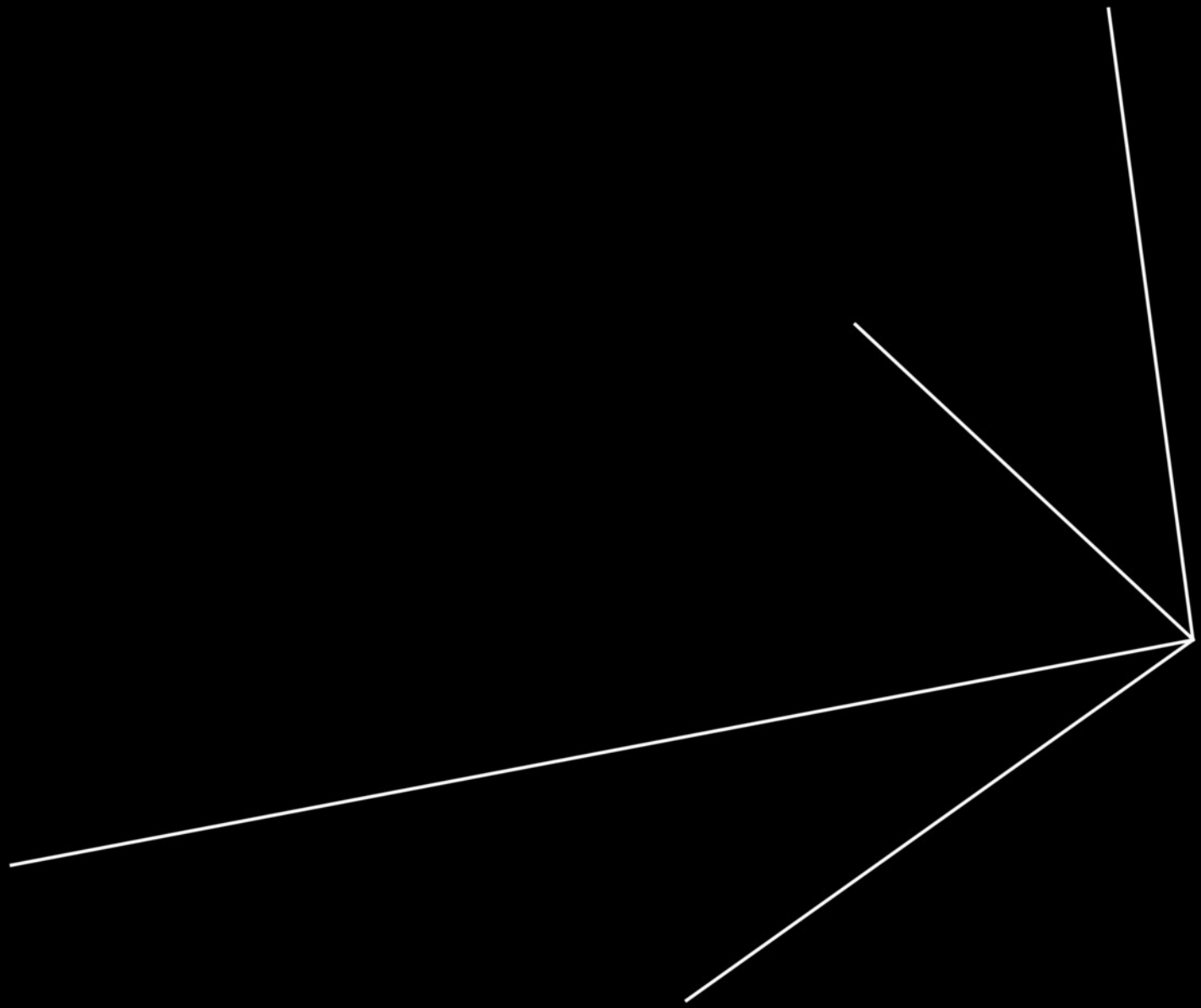
VIRTUAL | VIRTUAL

# FDA WORKSHOP: 10th Annual Clinical Outcome Assessment in Cancer Clinical Trials Workshop OCTOBER 8, 2025

**OCTOBER 8, 2025**

*Reflecting on a Decade of Progress*

# Thank you!
# Questions?



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# Modified Scale – Known Groups Validity

| Anchor | N | Mean | Difference | p-value | Cohen's d [a] |
|---|---|---|---|---|---|
| ECOG PSR | | | | | |
| 0 | 432 | 42.5 | - | - | - |
| 1 | 500 | 35.8 | 6.7 | <0.001 | 0.57 |
| 2/3 | 102 | 30.6 | 5.2 | <0.001 | 0.44 |
| ISS Stage | | | | | |
| 1 | 383 | 40.2 | - | - | - |
| 2 | 382 | 37.9 | 2.3 | 0.007 | 0.19 |
| 3 | 265 | 35.0 | 2.9 | 0.002 | 0.25 |

# Pain Scale – Known Groups Validity

| Anchor | N | Mean | Difference | p-value | Cohen's d [a] |
|---|---|---|---|---|---|
| ECOG PSR | | | | | |
| 0 | 431 | 11.3 | - | - | - |
| 1 | 500 | 8.2 | 3.1 | <0.001 | 0.63 |
| 2/3 | 105 | 6.2 | 2.0 | <0.001 | 0.41 |
| ISS Stage | | | | | |
| 1 | 382 | 10.1 | - | - | - |
| 2 | 382 | 9.3 | 0.8 | 0.04 | 0.16 |
| 3 | 265 | 8.1 | 1.2 | 0.001 | 0.24 |