Confirmatory comparative tolerability endpoints in cancer clinical trials: Strategic opportunities and realisation challenges

Antoine Regnault, PhD

PSI Conference 2026 – Belfast | 15 June 2026

MODUS OUTCOMES
A THREAD Company

In 2024, FDA acknowledged the better tolerability of selpercatinib compared to cabozantinib or vandetanib in medullary thyroid cancer

US FDA label of RETEVMO (selpercatinib) in multikinase inhibitor-naïve RET-Mutant Medullary Thyroid Cancer

Patient-reported overall side effect impact was evaluated weekly in 222 patients (RETEVMO N = 145; cabozantinib or vandetanib N=77) who received at least one dose of treatment by at least 6 months prior to the data cutoff date and responded to the Functional Assessment of Cancer Therapy item GP5 (FACT GP5). Patient-reported overall side effect impact was derived as a proportion of time on treatment with high side effect bother (defined as response of 3 "Quite a bit" or 4 "Very much") per FACT GP5.

Patient-reported overall side effect impact results for LIBRETTO-531 are provided in Table 22.

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%)
% Patients with high side effect bother		
0% of time	61%	30%
≤25% of time	90%	66%

Patient-reported overall side effect impact results were supported by a lower incidence of treatment discontinuation due to adverse reactions for RETEVMO (4.7%) compared to cabozantinib or vandetanib (27%) in patients who received at least one dose of study treatment. The median time on treatment at the data cutoff was 14.5 months in the RETEVMO arm and 8.3 months in the cabozantinib or vandetanib arm in patients who received at least one dose of study treatment.

LIBRETTO-531 phase III (NCT02598661)

- PRO tolerability endpoint: **Proportion of time on treatment with high side-effect burden**
- **Secondary alpha-controlled confirmatory PRO endpoint**

Patients in the selpercatinib group reported significantly less proportion of time on treatment with high side-effect burden than in the control group (p<0.0001)

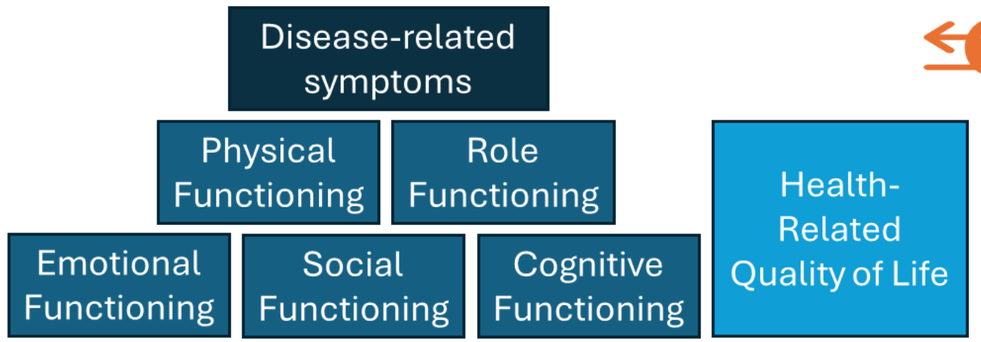
Sources: Wirth et et al. Future Oncology 2022 ; Elisei et al. Thyroid 2025

Evaluating tolerability in the demonstration of benefits of new cancer treatment

Concepts of interest for cancer clinical trials

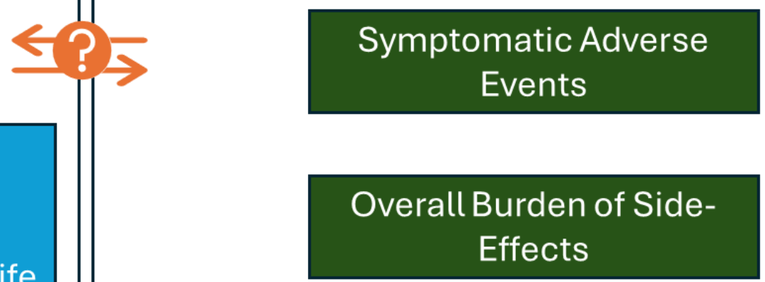
Clinical benefit

A positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives [Source: BEST Glossary]



Tolerability

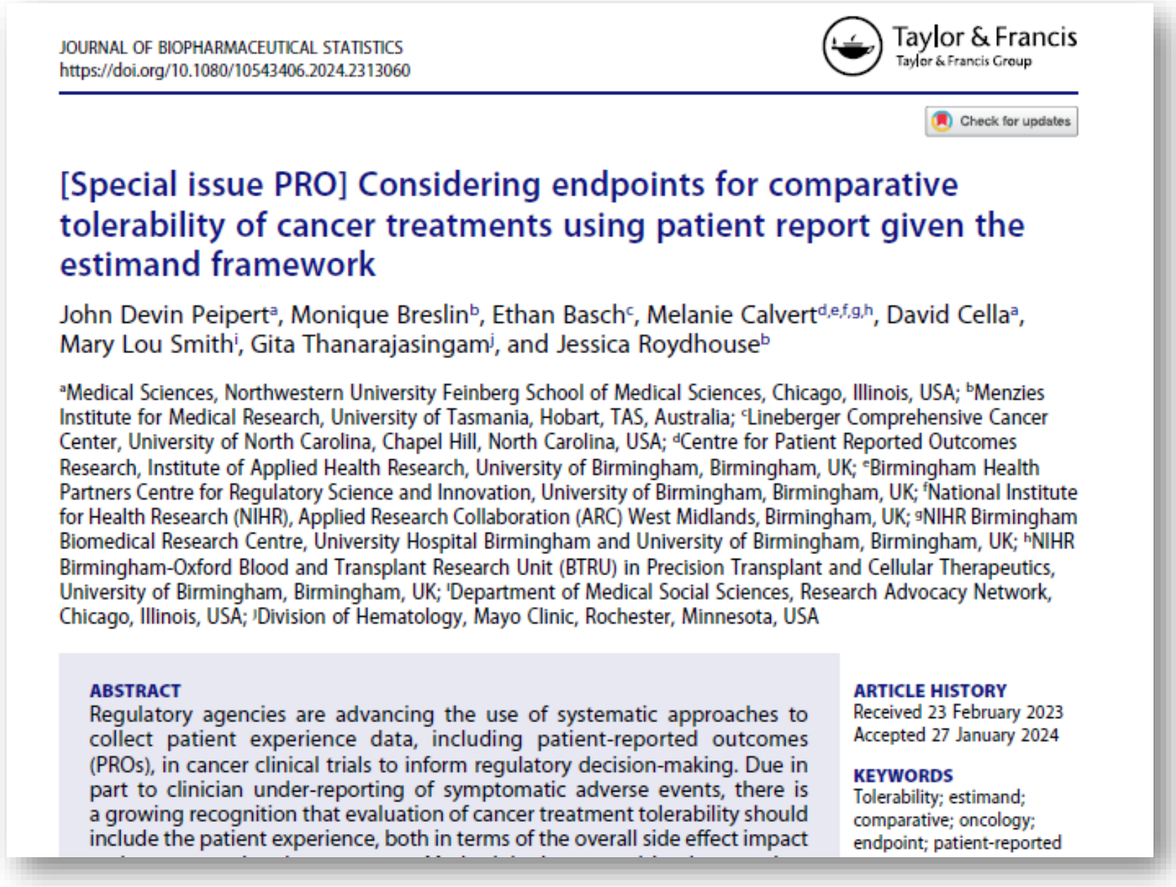
Degree to which symptomatic and non-symptomatic adverse events [...] affect the ability or desire of the patient to adhere to the dose or intensity of therapy [Source: Friends of Cancer Research White Paper]



Evaluation of tolerability through

- Description of patient-reported side effects and their associated burden
- Formal comparison of treatment arms – **Comparative tolerability endpoints**

Emerging standards for comparative tolerability endpoints



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

Taylor & Francis
Taylor & Francis Group

Check for updates

[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]

[a]Medical Sciences, Northwestern University Feinberg School of Medical Sciences, Chicago, Illinois, USA; [b]Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia; [c]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina, USA; [d]Centre for Patient Reported Outcomes Research, Institute of Applied Health Research, University of Birmingham, Birmingham, UK; [e]Birmingham Health Partners Centre for Regulatory Science and Innovation, University of Birmingham, Birmingham, UK; [f]National Institute for Health Research (NIHR), Applied Research Collaboration (ARC) West Midlands, Birmingham, UK; [g]NIHR Birmingham Biomedical Research Centre, University Hospital Birmingham and University of Birmingham, Birmingham, UK; [h]NIHR Birmingham-Oxford Blood and Transplant Research Unit (BTRU) in Precision Transplant and Cellular Therapeutics, University of Birmingham, Birmingham, UK; [i]Department of Medical Social Sciences, Research Advocacy Network, Chicago, Illinois, USA; [j]Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA

ABSTRACT
Regulatory agencies are advancing the use of systematic approaches to collect patient experience data, including patient-reported outcomes (PROs), in cancer clinical trials to inform regulatory decision-making. Due in part to clinician under-reporting of symptomatic adverse events, there is a growing recognition that evaluation of cancer treatment tolerability should include the patient experience, both in terms of the overall side effect impact

ARTICLE HISTORY
Received 23 February 2023
Accepted 27 January 2024

KEYWORDS
Tolerability; estimand; comparative; oncology; endpoint; patient-reported

Source: Peipert et al. Journal of Biopharmaceutical Statistics 2024

% Proportion of Patients with Severe Overall Side Effect Bother

Time with Severe Overall Side Effect Bother

Estimator for percentage of time with high side-effect bother

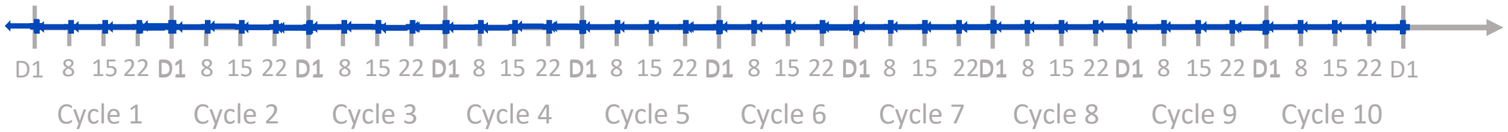
$$\%_{\text{time}} = \frac{\text{Cumulative amount of time during which the patients reports high side effect bother}}{\text{Total duration of drug exposure}}$$

Requirements

1) Unit of time (weeks/cycles) - similar for numerator and denominator !
2) Explicit definition of “high side-effect bother”
3) Explicit definition of starting and end of drug exposure period

High frequency data collection required for accurate estimation of tolerability

Tolerability refers to **ANY** unintended and unfavorable event occurring during the study follow-up



Commonly used measures of tolerability have a one week recall period

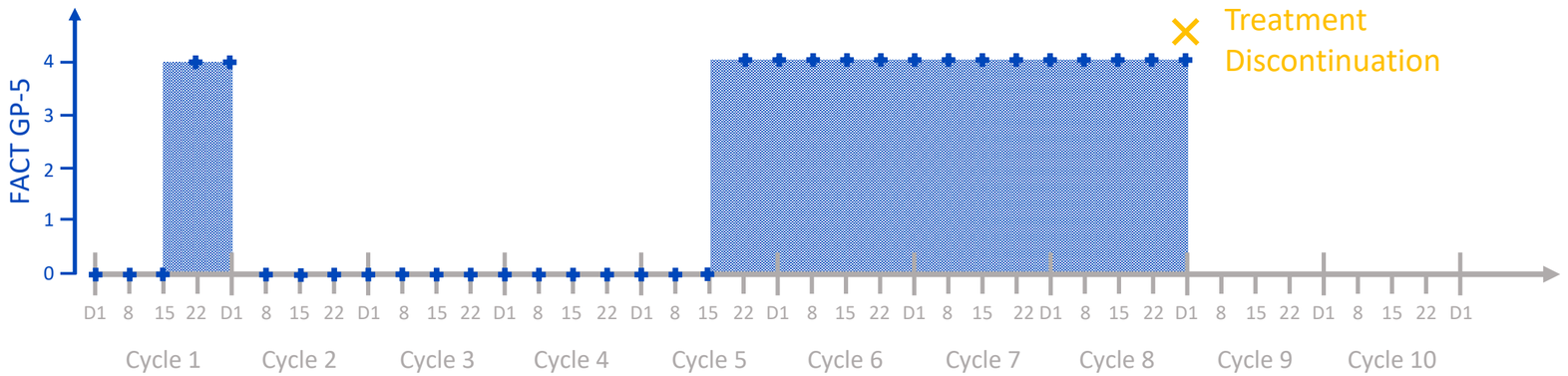
Collection once per cycle only informs on the experience of participants for a limited part of the study

Substantial uncertainty and possible bias in the estimation of the percentage of time with high side-effect bother

Weekly assessment of tolerability with single-item ratings allows full coverage of the period and is typically recommended

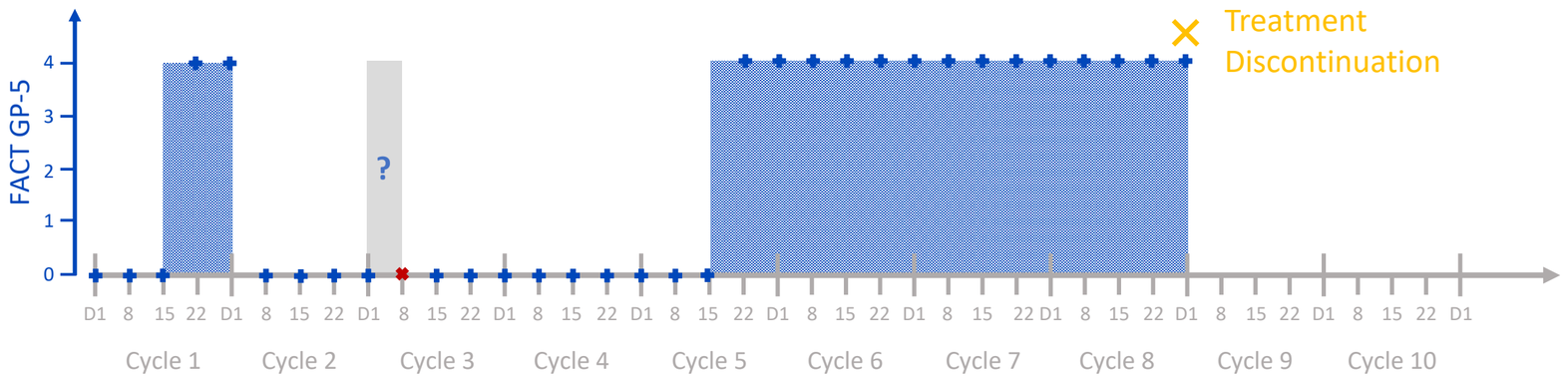
Handling missing data in the calculation of percentage of time with high side-effect bother

Example of patient response profile to FACT-GP5 item



Handling missing data in the calculation of percentage of time with high side-effect bother

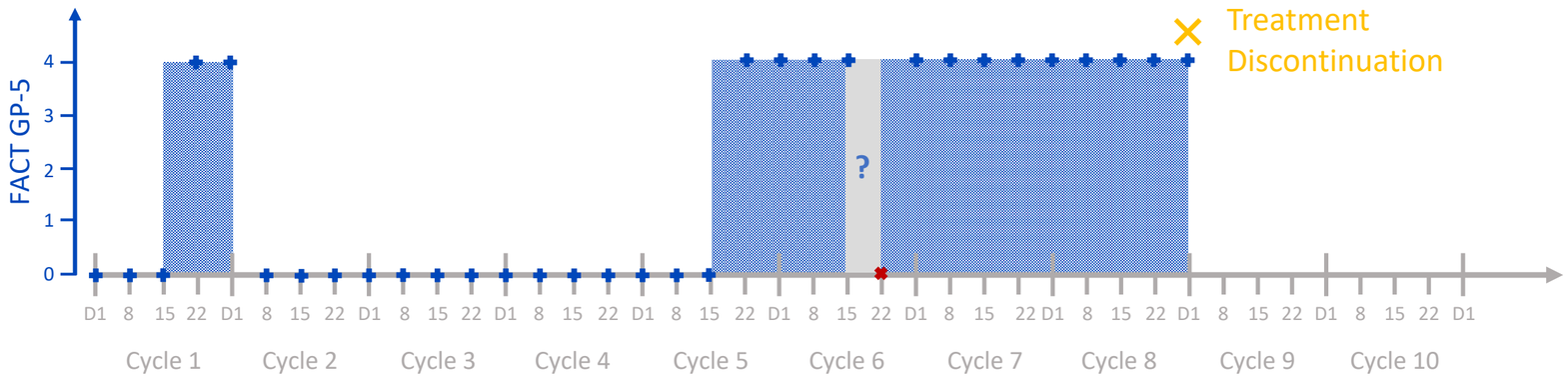
Example of patient response profile to FACT-GP5 item



How should we handle this missing assessment?

Handling missing data in the calculation of percentage of time with high side-effect bother

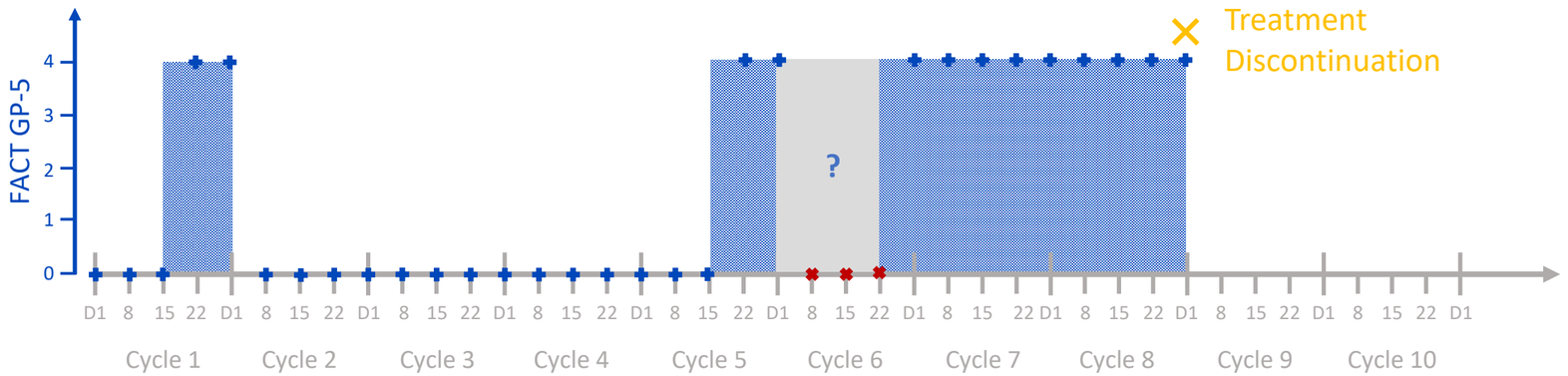
Example of patient response profile to FACT-GP5 item



How should we handle this missing assessment?

Handling missing data in the calculation of percentage of time with high side-effect bother

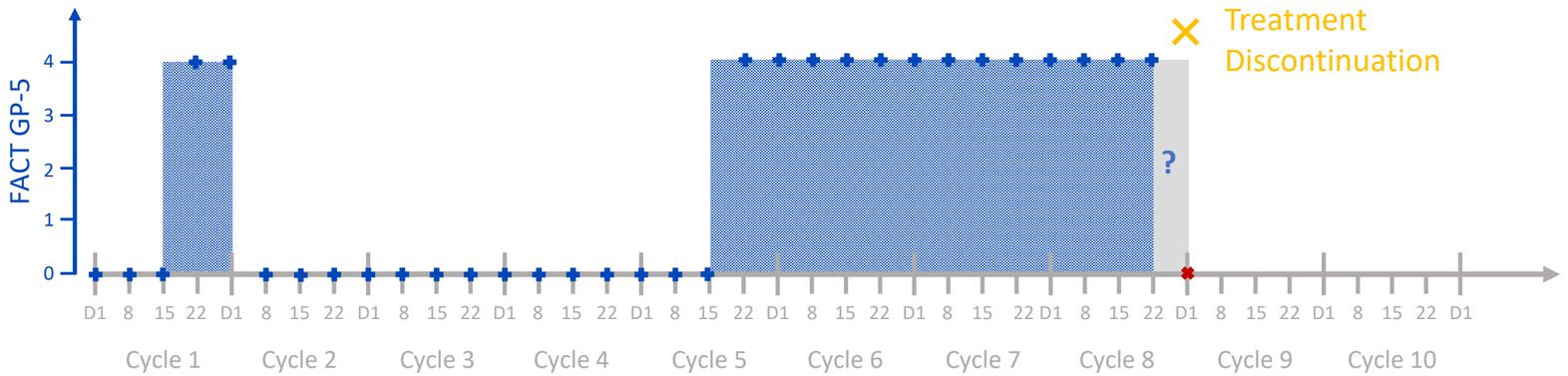
Example of patient response profile to FACT-GP5 item



How should we handle this missing assessment?

Handling missing data in the calculation of percentage of time with high side-effect bother

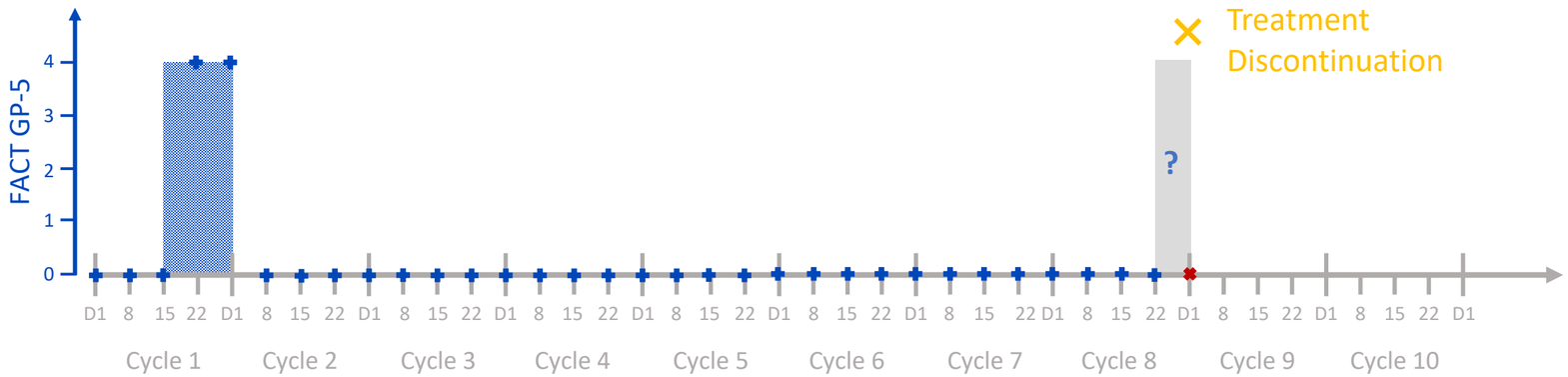
Example of patient response profile to FACT-GP5 item



How should we handle this missing assessment?

Handling missing data in the calculation of percentage of time with high side-effect bother

Example of patient response profile to FACT-GP5 item



How should we handle this missing assessment?

Handling missing data in the calculation of percentage of time with high side-effect bother

$$\% = \frac{\text{Cumulative amount of time during which the patients reports high side effect burden}}{\text{Total duration of drug exposure}}$$

Algorithm for Missing Tolerability Assessments

Conditions

Side-effect bother status observed before and after the missing assessment

Duration of the missing period (1 assessment vs. Multiple consecutive assessments)

Timing (first cycles, before discontinuation)

Documented reason for missing assessment

Operations

Impute side effect status in the calculation of cumulative amount of time during which the patient reports high side-effect bother (numerator)

Discard the uncovered periods from the calculation (i.e. from both numerator and denominator)

+ Sensitivity analyses to assess the impact of the assumptions in the missing data handling algorithm

What does a patient report when asked about tolerability at baseline?

Overall burden of side effect (FACT-GP5)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Somewhat	Quite a bit	Very much
GP5	I am bothered by side effects of treatment.....	0	1	2	3	4

Patient responses at baseline may reflect

- Tolerability of previous treatment (when not first-line setting)
- Side-effects of other treatments
- Disease-related symptoms

Handling baseline ratings in tolerability analyses

Consequences of ambiguity of baseline tolerability

- Challenging interpretation
- Increased baseline variability
- Missing data

Current solutions for managing baseline tolerability values

Using statistics independent from baseline value

- Proportion of participants with high side-effect bother or with the targeted symptomatic AE
- Proportion of time on treatment with high side-effect bother

Baseline-adjusted symptomatic adverse events ratings (Basch et al.Clin Ther 2016)

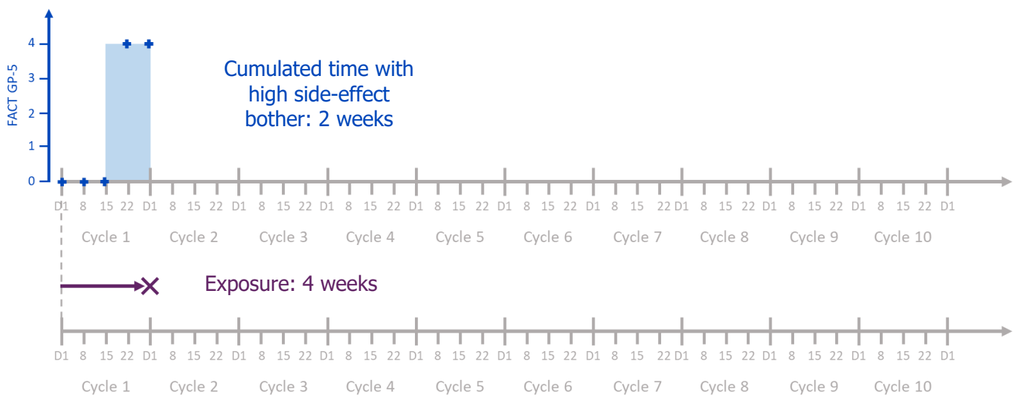
- Observed value at the visit if higher than the baseline value, and 0 otherwise

The value and methods for accounting for baseline levels in tolerability analyses is still debated (Roydhouse et al. Patients 2026)

Should evaluation of tolerability account for duration of exposure?

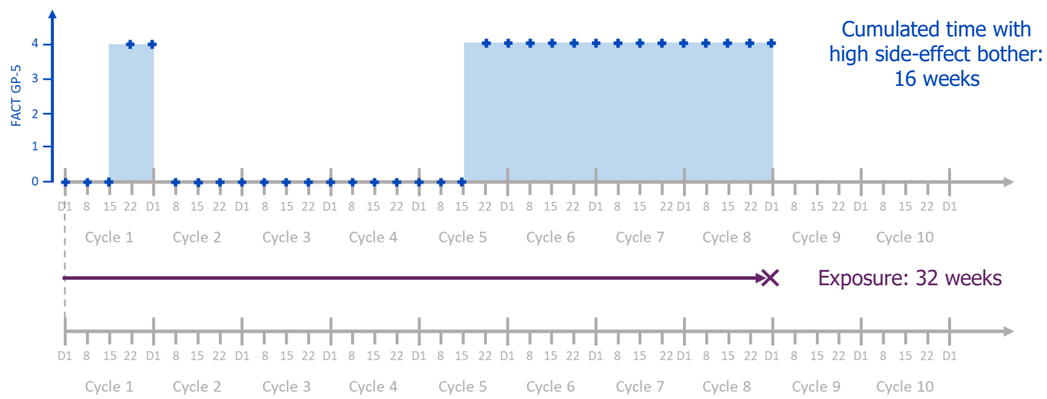
Examples of response profiles to FACT-GP5 item for two patients

Patient A



➡ Proportion of time with high side-effect bother: 50% (2/4)

Patient B



➡ Proportion of time with high side-effect bother: 50% (16/32)

Is the side-effect bother (tolerability) of patients A and B comparable?

Comparative tolerability in cancer trials: an evolving science for a critical endpoint

From patients to regulators, tolerability has become an important endpoint when evaluating cancer treatment options

First instances of successful evaluation of comparative tolerability in cancer clinical trials have been achieved through bespoke creative solutions

Several aspects of the demonstration on tolerability require consolidations to allow stronger conclusions on comparative tolerability of cancer treatments

References

Wirth LJ, Brose MS, Elisei R, Capdevila J, Hoff AO, Hu MI, Tahara M, Robinson B, Gao M, Xia M, Maeda P, Sherman E. LIBRETTO-531: a phase III study of selpercatinib in multikinase inhibitor-naïve *RET*-mutant medullary thyroid cancer. Future Oncol. 2022 Sep;18(28):3143-3150. doi: 10.2217/fon-2022-0657. Epub 2022 Aug 15. PMID: 35969032; PMCID: PMC10652291.

Elisei R, Wirth LJ, Capdevila J, Hoff AO, Tahara M, Sherman EJ, Hu MI, Ge MH, Wadsley J, Vaisman F, Kopeckova K, Krajewska J, Olvera D, Churchill C, Maeda P, Gilligan AM, Lin Y, Payakachat N, Robinson B, Hadoux J, Brose MS. Patient-Reported Tolerability of Selpercatinib Compared to Cabozantinib/Vandetanib: A Secondary Analysis of the LIBRETTO-531 Randomized-Controlled Trial in *RET*-Mutant Medullary Thyroid Cancer. Thyroid. 2025 Oct;35(10):1162-1172. doi: 10.1177/10507256251367352. Epub 2025 Aug 18. PMID: 40828665.

Peipert JD, Breslin M, Basch E, Calvert M, Cella D, Smith ML, Thanarajasingam G, Roydhouse J. [Special issue PRO] Considering endpoints for comparative tolerability of cancer treatments using patient report given the estimand framework. Journal of Biopharmaceutical Statistics. 2024 Feb 15:1-9.

Basch E, Rogak LJ, Dueck AC. Methods for implementing and reporting patient-reported outcome (PRO) measures of symptomatic adverse events in cancer clinical trials. Clin Ther. 2016;38(4):821-830.

Roydhouse J, Breslin M, Zola A, Basch E, Calvert M, Cella D, Smith ML, Thanarajasingam G, Peipert JD. Patient-Reported Side Effect Bother: Understanding the Value of the Baseline Report. Patient. 2026 Jan;19(1):93-101. doi: 10.1007/s40271-025-00766-2. Epub 2025 Aug 28. PMID: 40866741; PMCID: PMC12789233.