White Paper

Defining and Collecting Patient-Reported Treatment Tolerability to Inform Drug Development

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Background

The pharmaceutical industry is increasingly incorporating an assessment of patient-reported treatment tolerability in their clinical trials, mainly driven by the FDA requirements. Treatment tolerability is a multidimensional concept that has evolved significantly over the past 25 years.[1] Despite increasing recognition of its importance for patient experience, regulatory decisions, and clinical management, there is no universally accepted framework for defining or assessing tolerability, especially from the patient's perspective. This white paper aims to clarify the concept, review regulatory guidance and recent approvals, and recommend best practices for its measurement in clinical trials.

Defining treatment tolerability

Treatment tolerability has undergone significant evolution in its definition over the past decades. The International Conference on Harmonisation (ICH) E9 guidance (1998) originally defined tolerability as "the degree to which overt adverse effects can be tolerated by the subject," focusing primarily on observable adverse events. However, this definition has expanded in recent years to encompass a more patient-centered perspective. In 2018, Friends of Cancer Research proposed a broader definition.[2]

"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".

This definition underlines several key elements:

- Both symptomatic and non-symptomatic adverse events
- The direct patient-reported experience on how they feel and function during treatment
- The impact on adherence: Tolerability influences whether patients can or want to continue therapy
- The multidimensionality: Tolerability encompasses physical symptoms, psychological burden, functional impact, and overall treatment experience

By integrating all these elements, the field is moving toward a more holistic and meaningful understanding of treatment tolerability — one that supports regulatory decision-making, clinical management, and, most importantly, patient-centered care.[2,3]

Regulatory guidances and measurement tools

The FDA and EMA have emphasized the importance of incorporating tolerability considerations into drug development, as reflected in their recent guidance documents and regulatory reflections.

In its recent draft reflection paper on Patient Experience Data released in September 2025, the EMA acknowledges the value of patient-relevant disease and/or treatment outcomes, including symptomatic adverse events and their tolerability.[4] They emphasize the importance of early patient engagement and collection of the patient perspective to provide a more comprehensive view of the benefits/risks of a new treatment under investigation, by "enriching regulators' understanding of patients' symptoms, adverse effects and overall satisfaction". In addition, they underline that individual patient experience helps monitor the safety profile of a medicine in real world, especially on "issues that are difficult to identify via other sources, such as the persistence of an adverse reaction or its impact on quality of life".

The FDA also recognizes the value of "collecting robust patient input on symptoms and other aspects of their condition that matter most to patients" including Patient Reported Outcomes (PROs)/Clinical Outcome Assessments (COAs) in assessing the overall benefits and risks of treatments.[3]

In oncology, the FDA recommends symptomatic AEs and overall side effect impact be systematically collected and analyzed as core PROs in cancer clinical trials.[1] Their guidance highlights the use of two key measurement tools:

- **PRO-CTCAE (Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events):** Developed by the National Cancer Institute (NCI), the PRO-CTCAE library enables direct patient reporting of symptomatic AEs, capturing presence, frequency, severity, and interference with daily activities.[5] The FDA recommends selecting from this item library a concise set of the most important symptomatic AEs that are anticipated based on prior studies or the known mechanism of action of study agents. PRO-CTCAE is intended to complement, not replace, traditional safety data collected via CTCAE.

- **Single-Item Global Measures:** To assess overall side effect impact, the FDA supports the use of single global impression items. Examples include:

  - **FACT GP5:** "I am bothered by side-effects of treatment", from the Functional Assessment of Cancer Therapy (FACT) item library[6], and

  - **EORTC Q168:** "To what extent have you been troubled with side effects from your treatment?", from the European Organisation for Research and Treatment of Cancer (EORTC) item library.

  Including a single overall bother item helps capture the overall impact of treatment and serves as a valuable indicator of tolerability.[7]

These regulatory recommendations mark a shift from relying solely on clinician-reported safety data (e.g, CTCAE), in order to provide a fuller picture of treatment tolerability, and ultimately support benefit/risk evaluation, and inform shared decision-making with patients.

Precedence in tolerability labeling claims granted by the FDA

Two FDA label claims including tolerability endpoints were recently granted by the FDA for selpercatinib (Retevmo) and inavolisib (Itovebi). These are the first labels including patient-reported comparative side effect impact and overall side effect bother. These cases demonstrate regulatory openness to descriptive patient-reported tolerability data as complementary information to safety and efficacy findings. Specifically, on September 27, 2024, the FDA granted a traditional approval to selpercatinib (Retevmo, Eli Lilly and Company) for adult and pediatric patients (2 years of age and older) with advanced or metastatic medullary thyroid cancer (MTC) with a RET mutation, as detected by an FDA-approved test, who require systemic therapy.[8]

The FACT GP5 single item ("I am bothered by side effects of treatment") was used to compare the two treatments for medullary thyroid cancer in an open-label design. The mean proportion of time with high side effect bother (participants reporting "quite a bit" or "very much" side effect bother) was evaluated to compare treatments, as well as the proportion of participants reporting "quite a bit" or "very much" side effect bother 0% and 25% of time (Figure 1). These findings were included in Section 14 of the United States Prescribing Information (USPI) under Clinical Studies, at the end of Efficacy results of one study, in the label.[8]

"The clinical benefit of selpercatinib was supported by a pre-specified analysis of patient-reported comparative side effect impact; patients in the selpercatinib arm reported less time with severe side effect bother than those receiving cabozantinib or vandetanib".[9]

Figure 1: Retevmo United States Prescribing Information (USPI) extract (Suppl 13, 09/27/2024)

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.

On October 10, 2024, the FDA approved inavolisib (Itovebi, Genentech, Inc.) with palbociclib and fulvestrant for adults with Hormone Receptor (HR)-positive, human epidermal growth-factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer. Patient-reported toxicities were assessed using PRO-CTCAE items in a double-blind, placebo-controlled phase 3 trial (INAVO120)[10]. The Itovebi's USPI specifically mentioned the percentage of participants that reported the PRO-CTCAE symptoms at baseline, any worsening on treatment, as well as worsening to a score of 3 or 4 [PRO-CTCAE items being evaluated on 0-4 point scales], with the exception of rash which was measured dichotomously as present or absent at baseline and post-baseline[11], as seen in Figure 2. Patient-reported overall side-effect impact was also assessed using the Modified Bother Item (MBI, "I am bothered by side effects of treatment").

The label noted "at baseline the proportion of patients with MBI responses of "not at all" were 70% in the ITOVEBI with palbociclib and fulvestrant arm and 76% in the placebo with palbociclib and fulvestrant arm. At Cycle 2 Day 15, the proportion of patients with MBI responses of "not at all" were 25% in the ITOVEBI with palbociclib and fulvestrant arm and 53% in the placebo with palbociclib and fulvestrant arm. Through 31 cycles of treatment, patients in the ITOVEBI with palbociclib and fulvestrant arm reported more side effect bother compared to the placebo with palbociclib and fulvestrant arm".[10]

These findings were Included in Section 6 (Adverse Reactions/Section 6.1. clinical trial experience) of the label complementing the CTCAE safety findings. This is aligned with the Xalkori example provided by the FDA in its final guidance on "Core PROs in Cancer clinical trials".[1]

Figure 2: Itovebi USPI extract (Original submission 10/10/2024)

Table 5: Patient-Reported Symptoms Assessed by PRO-CTCAE in INAVO120

Symptom (attribute)[a]	Any symptom before treatment (%)[b]		Any worsening on treatment (%)[e]		Worsening to score 3 or 4 (%)[d]	
	ITOVEBI + P+F (N=148)[e]	Placebo + P+F (N=152)[e]	ITOVEBI + P+F (N=148)[e]	Placebo + P+F (N=152)[e]	ITOVEBI + P+F (N=148)[e]	Placebo + P+F (N=152)[e]
Diarrhea (frequency), %	23	15	78	49	32	8
Nausea (frequency), %	21	21	59	50	20	11
Vomiting (frequency), %	9	6	35	26	6	3.3
Fatigue (severity), %	72	69	72	58	32	22
Mouth sores (severity), %	11	14	74	52	30	9
Decreased appetite (severity), %	38	28	78	55	26	12

Symptom (attribute)	Baseline presence		Post-baseline presence	
	ITOVEBI + P +F (N=148)	ITOVEBI + P +F (N=152)	ITOVEBI + P +F (N=148)	ITOVEBI + P +F (N=152)
Rash (yes), %	5	5	50	38

ITOVEBI+P+F = ITOVEBI with palbociclib and fulvestrant arm; Placebo+P+F = placebo with palbociclib and fulvestrant arm.
[a]The symptom attribute scoring is defined by amount/frequency/severity with a score of 0= 'not at all'/'never'/'none'; 1 = 'a little bit'/'rarely'/'mild'; 2='somewhat'/'occasionally'/'moderate'; 3 = 'quite a bit'/'frequently'/'severe'; 4= 'very much'/'almost constantly'/'very severe'.
[b]The percentage of patients whose symptom score before treatment was 1-4.
[c]The percentage of patients whose symptom score increased during treatment, with respect to their score before treatment.
[d]The percentage of patients whose symptom score increased to 3 or 4 during treatment, with respect to their score before treatment.
[e]The number of patients who provided a score before treatment and at least one on-treatment score.

While sponsors may be wary of showing greater symptomatic AEs on a new treatment than on a comparative regimen, the ITOVEBI label claim shows that a product achieved approval despite having a higher side effect profile than standard of care. Sponsors thus should be encouraged to include PRO-CTCAE items, particularly for treatment-related side effects that are known and expected based on prior studies or the known mechanism of action of the study treatment agents. While providing a full picture of treatment tolerability, this level of transparency can support the FDA in benefit/risk evaluation, as well as inform clinical decision-making in the management of symptomatic AEs and ultimately facilitate shared decision-making with patients.

Further, Retevmo's approval also demonstrates the FDA's openness to consider a single overall tolerability item (e.g., GP5) as part of the efficacy package (section 14). Of note, these findings were descriptive and exploratory in nature with no p values to support the comparison.

These recent FDA-approved tolerability labeling claims signal a shift toward greater transparency and the expectation that descriptive patient-reported tolerability data will be included as complementary information to safety and efficacy data. It also demonstrates that products can achieve approval even when patient-reported data reveal a higher side effect profile than standard of care, provided the overall benefit-risk profile is favorable.

Key considerations for including tolerability endpoints in future studies

These two recent label examples are very exciting but may not be replicable in and relevant to all studies. When designing clinical trials and considering tolerability endpoints, sponsors must address several practical and strategic factors to ensure a meaningful and regulatory-compliant measurement. The assessment of tolerability is contingent upon the context in which the study is conducted and the goals the sponsor wants to achieve. The main aspects that should be considered for the inclusion of a tolerability endpoint to grant a labeling claim are described below.

Oncology vs. non-oncology settings

In oncology, high treatment-related toxicities are anticipated due to the aggressive nature of regimens, and tolerability assessments often serve to complement safety data. Sponsors should proactively consider which symptomatic AEs are likely to emerge, ideally informed by the treatment's mechanism of action, prior qualitative and quantitative data — including both clinician- and patient-reported outcomes — and findings from previous clinical studies involving the treatment(s) under investigation or similar agents. In non-oncology indications, however, tolerability may require a different lens: one that emphasizes patient dissatisfaction, preference and inability or unwillingness to continue treatment. These factors can be critical to understanding real-world adherence and treatment acceptability and may not be captured by oncology-derived endpoints.

Early phase trials and dose optimization

Early phase trials in oncology and non-oncology settings generally focus on safety and tolerability. As explained by Lai-Kwon et al., "there is an increased interest in the use of PROs in early phase studies, where Maximum Tolerated Dose (MTD) is used to define the dosing for subsequent efficacy trials".[11] Understanding how patients experience and tolerate different doses can inform dose selection and optimization. In its recent guidance for "Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases", the FDA thus recommends the inclusion of PROs "to enhance the assessment of tolerability in dose-finding trials, as well as subsequent trials".[12] Ultimately, it can provide complementary information for benefit/risk assessment. In 2021, FDA announced Project Optimus, which seeks to place a greater emphasis on dose optimization and dose selection in early phases of oncology drug development towards doses that maximize the efficacy, safety, and tolerability of a drug. The benefit of using both clinician and patient reports of toxicity has been shown to determine the maximum tolerated dose of a given investigational treatment.[13] Further, Trask et al. outlined considerations for PRO-CTCAE inclusion in phase 1 dose escalation studies.[14] In late phase randomized trials in oncology, inclusion of PROs that assess symptomatic AEs can provide insight into whether the inclusion of a new agent, while still associated with side-effects, is substantially different than a Standard of Care (SOC) treatment. For example, findings from KEYNOTE-533 noted that treatment-related SEs were associated with both treatment groups with no significant between-group differences.[15,16] This could also be applied to non-oncology settings, in which it will help to compare the tolerability profile of the new agent to other treatments.

Non-inferiority vs. superiority trials

Measuring tolerability is crucial in both non-inferiority and superiority trials to support comparisons between treatment arms. In non-inferiority trials, the objective is to demonstrate that a new treatment is not significantly worse than an existing treatment by a pre-specified margin.[17,18] Evaluation of tolerability using the PRO-CTCAE, helps ensure that the new treatment is at least as tolerable as the existing one from the patient's perspective. This is important because even if the efficacy is similar, a less tolerable treatment may not be acceptable to patients or clinicians.[19]

In superiority trials, the objective is to show that a new treatment is better than the control, whether it is a placebo or an existing treatment. Demonstrating superior tolerability can have a significant advantage, even if the difference in efficacy is modest. Superior tolerability can lead to better adherence and overall patient satisfaction.

While promising, including tolerability PRO instruments to support an endpoint in future clinical trials would also need several other considerations:

- The tolerability endpoint should be pre-specified.
- Time and frequency of PRO assessments should be sufficiently collected to reflect the drug effect and its evolution, but not too frequent to minimize patient burden.
- Management of missing data should be explained. This point being crucial in oncology.

Given the complexity of evaluating tolerability, sponsors need to be prepared to justify focused measurement of treatment tolerability in regulatory interactions. Table 1 lists a range of considerations and potential actions to finalize a strategic clinical study design that focuses on treatment tolerability.

Table 1. Further considerations to evaluate patient-perceived tolerability

Consideration	Potential actions
Will the study treatment demonstrate a different safety profile than the comparator (better or worse)?	In either case, it is important to measure key symptomatic AEs using validated tools such as EORTC scales and relevant PRO-CTCAE items. For transparency, emphasize symptoms expected to differ — whether anticipated to be worse or better — based on prior data or the mechanism of action. Additionally, include a single overall item to assess side effect burden or tolerability (e.g., FACT GP5, EORTC Q168). A global benefit/risk item or scale may also be a useful alternative. While specific symptomatic experiences may vary, capturing overall impressions can provide valuable context to help balance and interpret differences in safety profiles.
Will regulatory agencies expect sponsors to collect patient-reported tolerability data?	Yes, regulatory agencies like the FDA[1] and EMA[4, 20] do expect sponsors to collect patient-reported tolerability data in clinical trials. This data is crucial for understanding the patient's perspective on the treatment's side effects and overall impact on their quality of life and can ultimately inform clinical decision making. The FDA has issued guidance documents emphasizing the importance of Patient-Reported Outcomes (PROs) in oncology clinical trials, particularly for assessing symptomatic adverse events and overall tolerability.[1] Similarly, the EMA also values PROs for providing insights into the patient's experience with the treatment, which can be critical for benefit-risk assessments.[4] However, there are important caveats regulatory authorities will consider. As with any PROs, tools must be strategically selected and collected to ensure their scores are reliable, valid, and fit for purpose in their context of use, to ensure they capture relevant patient experience. Further, strategic consideration of endpoints and planned statistical analyses (including accounting for missing data, intercurrent events/estimands) are required to ensure meaningful interpretation of findings.[1] Although most FDA discussions on tolerability have centered on oncology, sponsors conducting non-oncology trials should align measurement strategies with FDA's broader patient-focused drug development principles and engage early with regulators to ensure tools and endpoints are fit-for-purpose.

Consideration	Potential actions
Does the sponsor have a rationale/solid empirical basis for focused measurement?	Potential rationales/justifications/empirical basis for strategically focused tolerability measurement include: 1. An understanding of the mechanism of action of the study agent or agents with similar molecular make-up and/or mechanisms of action 2. Review of medical charts identifying trends in the symptomatic AEs associated with the study treatment or similar treatments 3. Targeted literature review identifying patient-reported concepts including symptoms, impacts, and symptomatic toxicity experiences and/or AEs associated with study treatment 4. Clinician interviews, Delphi panels of relevant stakeholders to provide rationale/justification of item selection and measurement strategy to ensure clinical relevance, measurement selection, effective implementation and study design 5. Patient interviews designed to elicit relevant treatment-related symptoms and impacts to support a conceptual model and comprehensive measurement strategy, including concepts of greatest importance to patients[11]
Will the data be used in the benefit-risk assessment?	The FDA Patient-focused Drug Development and Benefit/risk assessment guidances, and the EMA draft reflection paper on patient experience data emphasize the importance of incorporating Patient-Reported Outcomes (PROs) to support safety outcomes and benefit-risk assessments in clinical trials. While more emphasis has been placed on using tolerability data to complement traditional safety data, the recent example of Itovebi's label claim — supported by the GP5 item from the PRO-CTCAE — demonstrates that PROs can meaningfully contribute to the overall benefit-risk evaluation of a product. By capturing patient-reported tolerability, regulators gain insight into how adverse effects are experienced and managed by patients in real-world settings. This is particularly valuable when adverse events are subjective (e.g., fatigue, nausea, pain) and may not be fully captured through clinician-reported measures alone. When systematically collected and analyzed, PRO data can highlight differences in tolerability profiles between treatment arms, inform labeling, and support claims of improved patient experience. Moreover, the strategic integration of PROs into the statistical analysis plan — accounting for missing data, intercurrent events, and estimands — ensures that the data are robust and interpretable. This methodological rigor strengthens the credibility of PRO-derived tolerability data in regulatory decision-making and can ultimately influence product labeling, prescribing decisions, and patient access.
What additional data can provide greater understanding and context beyond the PRO-CTCAE and single item overall tolerability scores?	While the PRO-CTCAE items or overall side effect bother items (FACT GP-5, EORTC Q168 or others) will provide an understanding of side effect magnitude, additional qualitative interviews with trial participants may help to better understand if the side effects experienced are tolerable/bearable for them in regards to the benefits experienced with the treatment and their expectations. This will help to evaluate the overall balance patients are making between benefits and harms experienced with a new treatment. An alternative to in-trial interviews could be the use of the PQATv2 instrument[21–23] including open-ended questions on benefits and harms experienced, as well as an overall item of weighing benefits/harms. Patient preference studies could also be conducted to evaluate what a patient is willing to accept in hypothetical scenarios.

Beyond PRO-CTCAE: Complementary approaches and methodologies

Beyond the PRO-CTCAE items or overall side effect bother items highlighted by the FDA that provide insight into side effect magnitude, there are other ways to capture concepts that matter to patients with respect to tolerability. Methodologies such as patient preference studies or patient qualitative interviews, that could be embedded in clinical trials (i.e. in-trial interviews), can also support a better understanding of patient treatment experience including tolerability. Please see Table 2 below for further trial considerations and potential actions.

Table 2. Complementary approaches to understand tolerability beyond GP5 and PRO-CTCAE evaluations

Approach	Purpose	Value for tolerability assessment
In-trial qualitative interviews	Capture real-time patient narratives to understand the 'why' side effects are bearable or not, and the overall balance patients are making between benefits and harms of treatment experienced	Reveals nuanced individual experiences, coping strategies, and evolving perceptions
PQATv2 (Patient's Qualitative Assessment of Treatment version 2) instrument[21–23]	Capture real-time patient narratives (open-ended questions) and quantitative assessment of benefits and disadvantages of treatment and balance between them (alternative to in-trial qualitative interviews)	Measures individual real experiences of treatment benefits and disadvantages and the balance made by patients between them
"Was it worth it?" instrument[24]	Post-treatment reflection	Captures patient trade-offs and perceived value of treatment
Global impression scores: • Treatment tolerability • Benefit-risk • Change (e.g., in overall condition) • Severity (e.g., in overall severity of condition)	Single-item global ratings	Provides high-level, patient-centered summaries of experience and perceived change
Patient preference studies	Quantify trade-offs patients are willing to make in hypothetical scenarios	Informs benefit-risk assessments by identifying which side effects or outcomes matter most to patients
Clinical and demographic context	Baseline characteristics, comorbidities, prior therapies	Helps interpret tolerability in light of individual patient profiles

Building a patient-centered framework for tolerability assessment

While current approaches, particularly in oncology, offer a strong foundation for assessing tolerability through structured patient-reported endpoints, there is an opportunity to build on the Friends of Cancer Research definition[2] and regulatory guidance by broadening the lens through which tolerability is evaluated. This expansion supports the development of a more patient-centered framework — one that reflects the lived experiences and priorities of patients across disease contexts.

A truly patient-centered approach to tolerability recognizes that tolerability is a multidimensional construct shaped by more than just symptomatic AEs. Foundational insights from targeted literature reviews and a cancer patient survey confirmed that tolerability is influenced by treatment goals, treatment burden, treatment impact on overall quality of life, benefit-risk considerations, and the broader context of the patient's life and expectations.[25,26] Integrating these dimensions into clinical trial design would ensure that tolerability assessments are both comprehensive and meaningful to patients, enhancing the relevance of trial outcomes and supporting informed decision-making, symptom monitoring, and clinical management of treatment-related AEs.[15]

For a better understanding of what truly matters to patients when evaluating treatment tolerability, a Targeted Literature Review (TLR) in oncology was conducted in September 2023 to:

1. Explore how patients conceptualize tolerability
2. Identify existing Patient-Reported Outcome Measures (PROMs) used to assess tolerability, and
3. Examine the concepts captured within these PROMs.[25]

Findings confirmed that drug tolerability in oncology is a multidimensional construct. Beyond side effect experiences, it encompasses treatment expectations,

effectiveness, burden and satisfaction, impact on quality of life, adherence, self-efficacy, benefit-risk assessment, financial burden, and interactions with healthcare professionals. Notably, no existing PROMs identified in the literature comprehensively evaluate all these dimensions. Due to the limited availability of qualitative studies, further research was needed to gain a deeper understanding of how diverse cancer patients define tolerability and what factors influence their perceptions.

To address this gap, a set of tolerability-focused questions, including a combination of scaled-response and open-ended items, was added to the Cancer Experience Registry in November of 2023 — the Cancer Support Community's online platform designed to capture cancer survivor and caregiver experiences.[26-28] The survey revealed that cancer survivors heavily weigh their side effect experiences when assessing treatment tolerability, but also consider other critical factors such as treatment effectiveness, daily functioning, quality of life impact, personal treatment goals, and overall treatment burden.

These findings underscore the importance of incorporating a comprehensive patient perspective into tolerability assessments in clinical trials. Future strategies should move beyond collecting symptomatic AEs only to include broader aspects of the treatment experience and patient-defined goals.

Practical recommendations and future directions

Building on this multidimensional framework and regulatory expectations, the following actionable recommendations could be considered by sponsors, trial designers, and/or stakeholders seeking to integrate tolerability endpoints into clinical trials.

Best practices for sponsors and trial designers

- **Pre-specify tolerability endpoints:** Clearly define tolerability measures in the study protocol, including which PRO-CTCAE items and global impression scores will be used
- **Select appropriate measurement tools:** Use recommended instruments such as the PRO-CTCAE library, FACT GP5, EORTC Q168, and complementary qualitative methods to capture both symptomatic AEs and broader patient experiences
- **Balance assessment frequency and patient burden:** Schedule PRO assessments to capture meaningful changes without overburdening participants
- **Plan for missing data:** Develop strategies for managing and analyzing missing PRO data, especially in oncology trials where attrition may be high
- **Engage with regulatory agencies early:** Seek advice from agencies like the FDA and EMA to ensure study design aligns with current expectations and guidance
- **Justify measurement strategy:** Provide a clear rationale for selected endpoints, supported by mechanism of action, prior data, literature review, and stakeholder input

Strategic integration

- **Incorporate patient-centered frameworks:** Move beyond symptomatic AEs to include treatment goals, burden, benefit-risk, and other dimensions that matter to patients
- **Leverage complementary data sources:** Use qualitative interviews, patient preference studies, and clinical context to enrich quantitative findings and support regulatory submissions
- **Support benefit-risk assessment:** Ensure tolerability data are robust, interpretable, and integrated into the overall benefit-risk evaluation for regulatory decision-making and product labeling incorporating effective data visualization strategies

Future directions

- **Advance thought leadership:** Continue research and collaboration to refine tolerability measurement and ensure it reflects evolving patient and regulatory priorities. Further research can help test the relevance of the "bothered by side effects" from GP-5 and "troubled with side effects" from EORTC Q168 items with cancer patients, as well as test other items that may reflect a more holistic experience of tolerability
- **Promote transparency and shared decision-making:** Use comprehensive tolerability data to inform clinical management, enhance patient-provider communication, and support informed treatment choices

By following these recommendations, sponsors and researchers can ensure that tolerability assessments are comprehensive, meaningful, and aligned with both regulatory requirements and patient needs — ultimately improving the relevance and impact of clinical trial outcomes.

To learn more about tolerability endpoints, please see chapter 7 of Defining and Analyzing Patient-centric Endpoints Based on COAs and Digital Technologies.[29]

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Dr. Buzaglo has over 20 years of professional experience in academia, patient advocacy and healthcare industry. As a clinical psychologist and behavioral researcher, her experience has focused on patient-reported outcomes, oncology, digital health and patient-centered care. She currently is a scientist in outcomes research with expertise in the development and validation of clinical outcome assessments, using mixed methodology, including direct patient and clinician engagement. She has a special interest in patient-reported tolerability and leads the PCS tolerability working group.

Prior to joining IQVIA, Joanne was the Executive Director of PRO Solutions at ConcertAI and the Senior Vice President of Research & Training at the Cancer Support Community where she led the establishment of the Cancer Experience Registry, an online platform designed to elevate the patient voice in research and advocacy. Earlier in her career, she was the Deputy Director of Fox Chase Cancer Center's Behavioral Research Core Facility. She earned her PhD in clinical psychology from Temple University and completed a postdoctoral fellowship in health services research at the VA Medical Center, Philadelphia, PA and at the University of Pennsylvania.

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Dr. Roborel de Climens has 20 years of experience in qualitative research and patient-centered outcomes. Before joining IQVIA, Aude worked at Sanofi for five years as COA Lead, contributing to development programs in diabetes, rare blood disorders, OTC products, and vaccines. In this position, she supported teams in considering the patient's perspective in drug development by offering guidance on identifying what matters to patients, selecting suitable COA tools to produce meaningful and interpretable outcomes, and converting these outcomes into endpoints to illustrate treatment effects. She developed a patient experience tool (the Patient Qualitative Assessment of Treatment, PQAT) that combines qualitative and quantitative data to assess patients' perspective on treatments' benefits and disadvantages, and the balance they make between them. She also led the Clinical Outcome Generation team.

Prior to Sanofi, Aude worked at Mapi for ten years in the Patient-Centered Outcome team, where she interviewed patients, caregivers, and clinical experts, designed questionnaires, and assisted pharmaceutical companies in establishing PRO endpoint strategies, with attention to FDA and EMA expectations. She directed international projects covering various acute and chronic diseases. Earlier in her career, Aude worked in several research organizations focused on oncology and obtained her PhD in Molecular and Cellular Biology from the Ecole Normale Supérieure of Lyon, in France.

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Before joining IQVIA, Matt held patient-centered research and care roles in pharmaceutical companies, universities, consultancies and hospitals. He has a PhD and MSc in Health Psychology and a BSc in Psychology and has been awarded Fellowships at both the Royal Society of Medicine and the Royal Society of Public Health, and an Associate Fellowship at the British Psychological Society. He has authored or co-authored more than 100 articles in peer-reviewed scientific journals, presented more than 125 congress presentations, authored/edited three prior books, and hosted a podcast on COA.

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