FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

BROADENING THE DEFINITION OF TOLERABILITY IN CANCER CLINICAL TRIALS TO BETTER MEASURE THE PATIENT EXPERIENCE

OBJECTIVE

Robust safety and tolerability data are essential in cancer therapeutic studies, and some trials are specifically designed with a key objective of demonstrating improved safety and tolerability. The development of a clinical trial framework and data elements to demonstrate comparative safety and tolerability requires a suite of endpoints and approaches to enable meaningful interpretation of results for regulatory and clinical decision-making. Identification of data elements suitable for a comparative tolerability trial design would be useful across cancer clinical trial settings where a comprehensive characterization of safety and tolerability is a critical component in the evaluation of individual and collective patient benefit.

A multi-stakeholder working group was convened, including drug sponsors, regulators from the US and Europe, researchers, and patients, to develop a contemporary definition of tolerability that better encompasses the patient experience receiving a given treatment; to identify a broader array of data elements and methodologies that more fully characterize tolerability; and to consider a trial design framework that includes patient-reported outcome (PRO) endpoints and other clinical outcomes to support patient treatment choice, regulatory and clinician decision-making, and direct patient communication in U.S. Food and Drug Administration (FDA) labeling. The concepts outlined in this whitepaper were conceived to foster patient focused drug development. In particular, this whitepaper presents opportunities to enhance the collection of the patient's perspective on symptomatic adverse events including their impacts on work and daily activities and overall side effect burden. Advancing the use of clinical outcome assessments, including PRO measurement, can complement our understanding of safety and tolerability, and the principles discussed in this whitepaper may extend into the broader cancer clinical trial setting.

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ABOUT FRIENDS OF CANCER RESEARCH

Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients.

INTRODUCTION

Focused efforts in clinical cancer research have led to treatment options with novel therapeutic modalities for a given cancer target. These drugs are often associated with unique safety profiles and are more frequently administered over prolonged periods of time. They can, for example, be associated with low-grade toxicities that in the short-term may be tolerable but can become burdensome over the course of treatment leading to dose reduction or treatment discontinuation despite promising treatment effects. Therefore, longitudinal assessment of patient-reported symptomatic adverse events can help better describe the tolerability of a drug and inform patient decision-making.

Tolerability is a complex concept defined by the International Conference on Harmonization (ICH) as "the degree to which overt adverse effects can be tolerated by the subject" (ICH E9).[i] Information currently used in oncology trials to assess tolerability includes clinician-reported safety data using the Common Terminology Criteria for Adverse Events (CTCAE), and other trial data including dose modifications, dose discontinuations, and hospitalizations (Figure 1). Many symptomatic adverse events are unobservable (e.g., nausea, fatigue), and how adverse events may interfere with a patient's life is best known and reported by the patient. It is known that these treatment-related symptoms impacting a patient's daily activities and quality of life frequently go undetected by investigators.[ii,iii] Therefore, integration of patient-reported data is critical to fully understand the tolerability of a therapy and provide complementary information to clinician-reported safety that identifies which symptomatic adverse events are most burdensome to patients.[iv] This is particularly important in diseases with multiple therapeutic choices, where there is a poor overall prognosis and where an optimal treatment algorithm has not yet been established. Data characterizing tolerability can also provide important additional information in a non-inferiority trial, so that better tolerated regimens with similar clinical efficacy can be more easily identified.

The current ICH definition of tolerability does not emphasize the patient experience* while on treatment and lacks focus on how adverse events associated with a treatment can be best evaluated from the patient's perspective.

* Patient experience data: Defined in Title III, section 3001 of the 21st Century Cures Act, as amended by section 605 of the FDA Reauthorization Act of 2017 (FDARA), and includes data that are collected by any persons and are intended to provide information about patients' experiences with a disease or condition. Patient experience data can be interpreted as information that captures patients' experiences, perspectives, needs, and priorities related to (but not limited to): 1) the symptoms of their condition and its natural history; 2) the impact of the conditions on their functioning and quality of life; 3) their experience with treatments; 4) input on which outcomes are important to them; 5) patient preferences for outcomes and treatments; and 6) the relative importance of any issue as defined by patients." https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm610317.htm

Thus, a new working definition is proposed that incorporates the patient experience by measuring treatment burden and patient-reported symptomatic toxicity and function.

> *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.*

This whitepaper will focus on data elements that can be used to assess tolerability based on the new definition above in cancer product development. It is expected that these elements could be used to generate evidence to evaluate treatment tolerability as part of a comparative tolerability trial design.

Figure 1. Components that Inform Tolerability. Clinician-reported outcomes and case report data are routinely collected to assess the safety and tolerability of a therapy. Although this information is important, it provides a limited understanding of the full scope of tolerability from a patient's perspective. Routine systematic collection of patient-reported outcomes and gaining the patient's view on treatment burden can provide important information regarding how patients experience treatment and which symptoms and adverse events might impact treatment decisions.

CONTRIBUTION OF PATIENT-REPORTED OUTCOMES TO UNDERSTANDING TOLERABILITY

PRO assessments provide important supportive data in oncology trials and are becoming more commonly used to assess both treatment benefits and adverse events (toxicities) to fully evaluate the impact of the treatment and disease on the patient. Regulatory recommendations exist: the FDA released guidance in 2009 for drug manufacturers seeking PRO claims of treatment benefit and the European Medicines Agency (EMA) released an Appendix 2 to the "Guideline on the Evaluation of Anticancer Medicinal Products in Man" on the use of PROs in 2016. The FDA is currently developing additional and updated guidance to further encourage the development and use of PROs in clinical trials.

Table 1 outlines a proposed list of key conceptual data elements that should be considered in a trial design to measure tolerability based on the expanded definition. Importantly, the incorporation of PRO measures allows for the characterization of tolerability based on direct patient experience. Several categories of PROs for tolerability assessment are identified:

- Patient-reported symptomatic adverse events
- Patient-reported overall burden of adverse events
- Patient-reported physical functioning
- Other types of functional assessments

We acknowledge there are other types of PRO measures such as patient preference and satisfaction that support optimal patient decision-making, but for the purposes of this whitepaper we intend to focus on symptomatic adverse events and functional concepts most proximal to the effects of the therapy in the clinical trial setting. We also encourage exploring other existing and emerging sources of data for physical function such as wearable devices and performance outcome measures that can be used to support and complement PRO measurement of physical function. The outcomes of such trials may support patient choice based on better overall understanding of the treatment experience for a particular therapy.

Patient-reported data must be obtained from PRO instruments that are well-defined and reliable and that are fit-for-purpose. The FDA defines fit-for-purpose as "a conclusion that the level of validation associated with a medical product development tool is sufficient to support its context of use."[v] There are available PRO measurement systems that can be used to generate this data including item libraries like the National Cancer Institute's PRO-CTCAE (Patient-Reported Outcomes version of the Common Toxicity Criteria for Adverse Events), which was developed specifically for the assessment of symptomatic adverse events and is mapped to the CTCAE and MedDRA. Other single item questions on symptom severity and well-defined functional scales could be selected from existing measurement systems, although the acceptability of various approaches should be discussed with regulatory agencies in scientific advice.

Table 1: Key Data Elements for an Oncology Clinical Trial Assessment of Tolerability Alongside Traditional Measures of Efficacy

Source	Clinical Outcome	Utility of Elements
Efficacy Data	Response rate (RR)	Need to demonstrate efficacy using well recognized endpoints
	Progression free survival (PFS)	
	Overall survival (OS)	
Clinician-Derived Safety/Tolerability	Common Terminology Criteria for Adverse Events (CTCAE)	Traditionally used signals of tolerability are reported by the clinician/healthcare professional and should continue to be routinely captured
	Dose interruption	
	Dose modification	
	Dose discontinuation not due to progressive disease or death	
Patient-Derived Adverse Event Data	Symptomatic adverse events	The importance of the patient experience of the treatment is emphasized in the new definition of tolerability Suitable PRO tools should be selected that capture patient derived data concerning the impact of the adverse events of the therapy and the overall treatment burden for the patient
	Global side effect impact/bother/burden	
Additional Supportive Patient-Derived Data	Physical function	Depending on the objectives of the study and the type and intensity of therapy (including known adverse events of special interest), other elements may contribute to defining the tolerability of a treatment regimen
	Role function (ability to work and carry out daily activities)	
	Other well-defined functional domains (e.g., emotional, social, cognitive)	
	Specific key symptoms (e.g., pain, fatigue, anorexia)	
	Disease symptom scale (if applicable)	
Healthcare Utilization	Hospitalization rates/duration	These items may provide a more holistic healthcare view of the tolerability of a treatment for a patient and may help determine the requirements for managing medical needs
	Emergency department visits	
	Supportive care medication use	

TRANSLATING DATA FROM MULTIPLE SOURCES TO COMMUNICATE TOLERABILITY

Through the new definition of tolerability, four key components for measuring tolerability have been identified. In addition to efficacy endpoints, each data element described in Table 1 brings a unique quality to characterizing tolerability, providing a more patient-centric view of a treatment regimen.

In order to bring all the elements together in a way that can help inform tolerability, it is suggested that a descriptive analysis is provided in a table format where the key aspects of the data from each component can be considered, summarized, and their impact noted. Any uncertainties can also be recorded. It is therefore not envisaged that a binary statement of tolerability will be made (i.e., on treatment and tolerating versus discontinued due to AE and not tolerating), but rather a more complete picture of the patient experience obtained from the various data elements.

Quantitatively, a large component of tolerability is likely the overall impact of the side effects of treatment. It would be useful to quantify a range of overall side effect burden on the patient, and in this case the data element of overall side effect impact or burden could be used as a key endpoint. This side effect impact or treatment burden endpoint would be informed and interpreted by the other tolerability data elements including symptomatic AEs and the potential impact the side effect burden would have on other patient-reported functional domains (e.g., physical and role function). Some statistical methods that could be applied to the evaluation of this data could include but are not limited to:

- Proportion of patients experiencing the worst magnitude of each response level of each elicited symptomatic AE PRO item, by treatment, each time point of measurement, and for the total period of study participation
- Proportion of patients with each response level of an item eliciting overall perceived burden of adverse events
- Qualitative inquiry with patients on relevant PRO items contributing to tolerability (e.g., end of treatment questionnaire)
- Impact of frequent or high-grade symptomatic AEs on physical function
- Impact of frequent or high-grade AEs on other functional measures and HRQoL
- Comprehensive description of global side effect impact

BENEFITS OF IMPROVED TOLERABILITY INFORMATION

Including PRO measures and other tolerability data elements throughout drug development can have numerous benefits. Tolerability data can provide information for clinical dose selection early in development and allow more precise dose-finding by balancing the biologically optimal dose with the dose that has the most favorable tolerability profile. For example, when deciding between possible dose regimens of similar clinical activity, PRO measurement of symptomatic AEs and overall treatment burden can provide evidence beyond the traditional clinical AE reporting on the impact of cumulative symptomatic toxicity (e.g., the impact of fre-

quent and prolonged symptomatic Grade 1 AEs may be more burdensome to patients than less frequent and potentially asymptomatic Grade 3 adverse events). Identifying a more tolerable dose can maximize patient adherence to the selected late stage or approved dose, rather than ad hoc dose modification in the registration trial or post-marketing setting, which can lead to unnecessary patient burden and suboptimal dose intensity potentially affecting efficacy. In addition, exploration of tolerability in early dose-finding trials can identify candidates for later-phase comparative tolerability trial designs.

Tolerability data elements should be used in late stage settings to support clinical benefit by complementing standard safety data. Where the objective is comparative improvement in safety or tolerability, one trial design that could be considered is a superiority trial design against an active comparator considered standard-of-care. Such a trial would have an efficacy-based primary endpoint. The results of the primary endpoint could either be enhanced or diminished by an added 'comparative tolerability' endpoint. Another example of a trial design that would benefit from tolerability data elements is the non-inferiority trial design. Non-inferiority trials have an efficacy primary endpoint and typically do not prioritize tolerability assessment. In some cases, there may be a similarly effective drug amongst available therapies that appears to have improved safety and tolerability. In this setting, one or more elements of 'tolerability' could be a co-primary endpoint with efficacy data (unless comparative efficacy has been previously assessed in a head to head study). Regardless of whether data elements for tolerability are used as primary, secondary, or descriptive exploratory data, there is a benefit for improved characterization of tolerability through the inclusion of patient-reported symptomatic adverse events and function, across early and late stage drug development.

The advantages of collecting rigorous patient relevant evidence also creates new challenges. PRO assessments are commonly incorporated into registration trials, but best practices for incorporating PRO data with the objective of demonstrating improved safety and tolerability will require careful clinical trial design.[vi] While item libraries such as the PRO-CTCAE can provide the needed flexibility to adapt to different toxicity profiles, an objective method to select which symptomatic adverse events to assess will be important to ensure an unbiased selection is obtained. Identifying an appropriate PRO assessment frequency will be important as well as monitoring for completion rates to mitigate missing data. In addition, standard methods to analyze and present PRO data and other tolerability data have been initially developed and are being further advanced.[vii, viii] Several international efforts have been undertaken in these areas.[iv,v]

COMMUNICATING TOLERABILITY INFORMATION

Tolerability data elements including PRO assessments and healthcare utilization data can further inform a product's clinical benefit and form part of the totality of the evidence evaluated by the FDA and other regulatory agencies when determining benefit:risk. Regardless of whether tolerability data are included in product labeling, all PRO and other tolerability results can be reviewed as part of the totality of data to support a benefit:risk determination. Tolerability as currently communicated in product labels and other data sources (e.g., dose modifications) can be further characterized by PRO data assessing symptom severity/occurrence and impact on function in addition to overall treatment burden as previously described. This data could be descriptively analyzed and presented in product labeling, provided the assessments are well-defined and

fit-for-purpose, there is an acceptable level of PRO completion in the trial, and the data add information that informs safety and tolerability (as is done with CTCAE data in section 6 of FDA labeling).

Importantly, communicating tolerability data must be balanced by describing both the positive and negative effects of the therapy. While descriptive data can be labeled to inform safety and tolerability, where a marketing claim of treatment benefit is the objective, a hypothesis must be stated, and this requires an endpoint to be constructed and statistically tested, including adjustment for multiple testing (i.e., multiplicity). This is no different than an efficacy marketing claim of improved progression-free survival. A claim of improved safety or tolerability such as "drug A causes less overall side effect burden than drug B" or "drug A causes less diarrhea than drug B" will need to be supported by substantial evidence in a well-controlled trial using well-defined a priori described methodology and reliable assessments. Space limitations and layout of product labels will necessitate concise, accurate, and non-misleading presentation of the data that will be interpretable and meaningful to providers.

Multiple other forms of communication such as guidelines and clinical pathways should also be explored and have potential as additional communication vehicles. Standard analytic and presentation methods will also be useful for other communication avenues such as published literature. Initial analytics are likely to be directed to scientific and policy audiences, however it is acknowledged that technical presentations may not be intuitive for patients. For example, common scientific descriptions of data that include p-values, means, and hazard ratios can be challenging to understand and translate into meaningful decision making for patients. Patients may find bar charts, arrays, and graphs easier to interpret, whereas forest plots that display relative risks may be more intuitive for physicians. More work will need to be carried out with both clinical and patient groups to test various data displays and layouts, identifying the most interpretable visualization for the target audience. The ability to include valid, understandable, and reliable data in communication materials beyond the product label, such as patient and clinician facing educational materials, can provide another opportunity for better and more informed decision-making in a more flexible format.

CONCLUSION

We have proposed a new working definition for tolerability that incorporates the patient experience by including patient-reported data elements that measure symptomatic adverse events, overall impact of adverse events, and function as well as elements of healthcare utilization. These tolerability elements can impact the ability and desire of the patient to adhere to the dose or intensity of therapy. Incorporating patient-reported symptomatic adverse events and impacts into early and late stage drug development holds promise to improve dose selection, provide additional information on the side effect profile of a therapy, and support informed therapeutic decision-making for patients. Sponsors should engage regulators early in the drug development program to discuss concepts and trial designs. Measurement tools such as the PRO-CTCAE and measures of patient-reported impacts are available, and efforts to identify best practices for using PRO assessment to meet the objective of safety and tolerability are underway. Standard analytic and visualization methods will need to be tested with various stakeholders who will use this information for policy decisions as well as patient and clinical decision making. Communicating tolerability data via multiple venues is important to provide valid

and reliable information to guide treatment decisions. In conclusion, as cancer treatment evolves and two, three, and four drug regimens become more common in oncology, more systematic and rigorous assessment of tolerability is key for patients, providers, regulators, and payers when assessing the impact of new treatments.

NEXT STEPS

The authors encourage comments and reactions to the perspectives presented in this whitepaper. To further develop the conclusions and concepts presented in this whitepaper, we propose these next steps:

1. Encourage the integration of patient-reported symptomatic adverse events, overall side effect impact, and functional endpoints into oncology clinical trials to provide improved understanding of tolerability.
2. Explore methodology and analytical methods to quantify tolerability data elements (Table 1) to ensure each aspect can be considered and summarized, and their impact understood.
3. Develop a case study to demonstrate how to operationalize the concepts in this whitepaper.
4. Understand how tolerability data can be better disseminated and communicated in a variety of formats, with an initial focus on patient-centric healthcare professional material.
5. Engage payers and international regulators to discuss and identify how tolerability endpoints and improved patient experience data will impact decision-making.

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