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WHITEPAPER

THE IMPACT OF THE FDA'S DRAFT GUIDANCE FOR ONCOLOGY PATIENT-REPORTED OUTCOMES ON FUTURE TRIAL DESIGN

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In recent years, we have seen enhanced emphasis on the importance of patient-reported outcome measures (PROMs) collected in oncology clinical trials reflected by the FDA. Project Patient Voice[1], for example, was established to provide a mechanism to share patient-reported symptom data from cancer clinical trials with approved treatments to provide more information to patients and healthcare providers in treatment decision making.

Despite this, US labelling claims based on oncology PROM endpoints remain rare. Gnanasakthy et al.[2] reported the difference in attitudes between EMA and FDA in the use of PROM data in drug labelling in their review of 2012-2016 oncology drug approvals. While EMA granted labelling based on PROM endpoints to a third of submissions, the FDA did not approve labelling claims based on PROM data for any application during this time. An earlier review of FDA approvals identified three of 40 approved drugs achieved labelling claims based on PROM data in the earlier interval from 2010 – 2014, the three approvals granted in 2011[3]. Gnanasakthy et al. identified a number of reasons for this divergence of regulatory opinion, including: the FDA considering only randomized, controlled trials due to concerns over placebo effect influencing conclusions based on PROM data from open label studies; lack of specificity within health-related quality of life endpoints; commonly used disease-specific measures and sub-scores may be insufficiently precise and sensitive; missing PROM data affecting the reliability of conclusions; and assessment schedules may be suboptimal to capture the impact of treatment effectively.

These are very reasonable concerns. In terms of specificity of common measures, Gnanasakthy et al.[2] report that common generic and disease-specific scales used in oncology trials, such as those developed by EORTC and FACIT, may lack sensitivity and specificity in several ways. Some scale items may be irrelevant in certain circumstances, some may not be precise enough to capture the patient experience with specific therapies, and summary scores for total and sub-scales may be insufficiently sensitive due to equal weighting of items leading to dilution of the impact of the most meaningful symptoms. Further, common sub-scales developed within existing PROMs may not be specific enough to the measurement of single domains of interest, and therefore lead to less robust conclusions.

Typically, in oncology trials patients are asked to complete PROMs at clinic visits at the start of each cycle of treatment. This is the point at which patients have recovered sufficiently from the previous treatment to receive the next cycle. If patients are not well enough to commence treatment, then cycle starts and the associated PROM assessments are delayed. This assessment schedule is, therefore, less optimal for PROMs assessing the impact of treatment.

The FDA's recent draft guidance on core patient-reported outcomes (PROs) in cancer clinical trials[4] proposes an approach to addressing a number of these concerns and will enable robust and reliable PROM data for better regulatory consideration and potentially increased inclusion of this data on US oncology drug labelling.

We reviewed the draft guidance and its impact on the selection and implementation of PROMs in oncology clinical trials, to provide recommendations for future study planning.

KEY ELEMENTS OF THE DRAFT GUIDANCE

A MEASURES RECOMMENDED

Building from earlier published work[5], the FDA identified a core set of PROMs to separately measure the following concepts:

1. Disease-related symptoms
2. Symptomatic adverse events (AEs)
3. Overall side effect impact measure (single item)
4. Physical function
5. Role function

Standard instruments exist and are commonly used for some of these concepts.

DISEASE-RELATED SYMPTOMS

The draft guidance cites only one example of a disease-related symptom measure: the Critical Path Institute's NSCLC-SAQ for non-small cell lung cancer[6]. This may correspond to the commentary of Gnanasakthy et al.[2] in terms of their considerations of the possible limitations of common scales such as those provided by EORTC and FACIT. They conclude that these scales may contain some irrelevant items when used in certain patient groups, may not consistently assess the most important symptoms, and may provide sub-scores that are diluted by applying equal weight to less important symptoms.

It's important to note that the requirements of the FDA draft guidance are to be able to report measures of each of the five domains separately. Some existing instruments and their sub-scale scores may not be immediately suitable for this in their current form. For example, the FACT-B measure, commonly used in breast cancer, contains items within the "physical well-being" domain that contain both treatment-related symptoms (e.g., "I am bothered by side effects of treatment") and disease-related symptoms (e.g., "I have pain"). The causality in changes in the sub-scale measure, therefore, cannot be easily distinguished between treatment-related or disease-related symptoms. However, it is possible that new sub-scales could be developed from these existing instruments to meet the required specificity of the FDA requirements. This could also be achieved by selecting pertinent items from emerging item libraries, such as that developed by EORTC. In both cases, with scale author approval, additional content validity and other work may be required to support the new sub-scale measures.

SYMPTOMATIC AEs

The PRO-CTCAE is well accepted for the collection of symptomatic AEs and is cited in the draft guidance as an example instrument. This tool uses an item library from which specific AE items are selected for assessment, and sponsors should provide a careful rationale to support the selection of a concise set of the most important and/or high frequency AEs.

The draft guidance also suggests consideration of additional free text items to capture missing important symptom items. This does present a challenge for researchers as free text data is harder to manage and analyze than items with defined response options. While electronic solutions can collect free text data, key data management considerations include how to deal with ambiguous or misspelled entries and how to manage the different languages used.

It's important to note that while PRO-CTCAE data are reported and analyzed independently of clinician-reported AEs, these self-reports can provide a valuable input to inform and enhance clinician identification, documentation and reporting of adverse events[7]. The self-report data without clinician interpretation does not fall within the requirements of the formal safety reporting processes associated with clinician-reported AEs, but timely review of these data alongside clinician assessment may enhance the detection and interpretation of AEs by the investigator.

OVERALL SIDE EFFECT IMPACT MEASURE

We rarely see the inclusion of an independent single item to summarize the overall impact of side effects in today's oncology protocols. A global measure of side effect impact is a valuable enhancement as it includes the impact of any side effects the patient may experience that were not measured using the PRO-CTCAE implementation, and the additional insight enables patients to attach greater importance to certain side effects when determining the collective impact of all side effects experienced[8].

Tools already exist for the measurement of overall side effect impact including the use of a patient global impression of severity scale (e.g., "Please select the response that best describes the severity of your overall side effects from treatment over the past 7 days (where 0 represents none and 3 represents severe)"); the GP5 question from the FACIT item library (a 5-point ordinal scale measuring the degree a patient is bothered by symptoms from "not at all" to "very much"); and the Q168 question from the EORTC item library (a 4-point ordinal scale rated from "not at all" to "very much"). These three approaches are cited within the draft guidance as examples of measures for overall side effect impact.

PHYSICAL FUNCTION

Physical function includes aspects such as walking, lifting, and reaching that are considered important for independent functioning. The draft guidance provides examples of measures of physical function, including the PROMIS physical function item library and EORTC QLQ-C30 physical function sub-scale. Some authors consider the PROMIS scale to have benefits over the EORTC sub-scale as it may be more versatile and support a wide range of severities and ages of patients[9]. An advantage of the EORTC instrument, however, is that it is used to measure other constructs in addition to physical function.

ROLE FUNCTION

In this context, role function should measure the impact of a treatment on the ability to work and carry out daily activities. The draft guidance cites the EORTC QLQ-C30 role function sub-scale as an example measure.

B FREQUENCY OF ADMINISTRATION

The draft guidance recommends more frequent assessment in early cycles and fewer later in the treatment process – this means at-home measurements in addition to (or instead of) on-site visits. We acknowledge the importance of this approach to capture the full impact of the disease and its treatment. It is common current practice in oncology trials to measure PROs at clinic visits at the start of each cycle of treatment. This is the point at which patients have recovered sufficiently from the previous treatment to receive the next cycle. If patients are not well enough to commence treatment, then the next cycle and associated PROM assessments are delayed. There is an aspect of convenience in this as these PROMs can be measured during clinic attendance and do not require at-home completion solutions. There is also a perception that patients may be unwilling or unable to complete PROMs during the earlier stages of each cycle due to the debilitating effects of treatment. However, if we want to truly measure treatment-related symptoms then it will be important to consider the optimal timing of these assessments to obtain a full and accurate picture. Our qualitative research on oncology patients confirms that the early stages of a cycle are debilitating, but despite this, patients are willing to provide data[10].

In their example schedule of assessment (Figure 1), the FDA illustrate the more frequent measurement recommended during the earlier part of the trial. The example suggests weekly measurement of symptomatic AEs, the overall impact of side effects item, and physical function for the first eight weeks before moving to a monthly cadence and then quarterly as patients progress through the 12-month treatment period. This is a change from the current pre-cycle measurement approaches we commonly see, requiring patients to complete instruments at-home during the early cycles of treatment, and optimizing measurements in the trial period when most patients are enrolled[11].

C CONSIDERATIONS AND RECOMMENDATIONS FOR FUTURE TRIAL DESIGNS

HOME-BASED ePRO

Implement a solution for the collection of PROMs in the at-home setting. This should be used to enable the higher frequency of assessments for certain measures earlier in the treatment period and should contain features to help drive timely entries and complete datasets. Less frequently measured PROMs could be collected at home or on site depending on the visit schedule, and could enable flexibility in administration setting. Site-based collection may be associated with higher completion rates when measurements are less frequent.

PROM DEVELOPMENT/ADAPTATION

In some cases, existing instruments or item libraries may require additional work to identify the correct set of items to measure each domain specifically and comprehensively for the disease studied. This may require discussion with scale authors to apply adaptations to sub-scores, or to develop pertinent item sets from libraries, and conduct any associated content validity and psychometric evaluation.

MEASUREMENT SELECTION

To meet the FDA draft guidance, PROMs should enable the discrete measurement of symptomatic AEs, overall side effect impact, physical function, role function, and disease-related symptoms. It will be important to select PROMs that contain appropriate means of measuring and reporting these domains independently and specifically.

MITIGATE MISSING DATA

Ensuring the measurement strategy is in line with FDA requirements is important, but attention must also be given to the FDA concern that missing data may limit the ability to draw robust conclusions. Attention to site and patient training, and ensuring that the solution to collect PROM data includes methods to remind and proactively monitor PROM completion, is an important consideration to limit missing data and lead to reliable conclusions which may lead to consideration for labelling claims. Electronic solutions are well suited to these requirements. Solutions should also capture reasons for missing assessments and enable PROMs to be collected at the point of withdrawal, where appropriate.

Figure 1. Example PROM assessment schedule for first 12 months of advanced cancer trial, as presented in the FDA draft guidance

	Standard 6-month treatment period												Follow up	
	BL	W2	W3	W4	W5	W6	W7	W8	M3	M4	M5	M6	M9	M12
Symptomatic AEs	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Overall side effect impact measure	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical function	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Role function	x		x		x		x		x	x	x	x	x	x
Disease-related symptoms	x				x			x	x			x		x
Health-related quality of life	x								x			x		x

BL - baseline; W - week; M -month.

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