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PERSPECTIVE

OPTIMAL COA MEASUREMENT STRATEGY IN MODERN ONCOLOGY TRIALS

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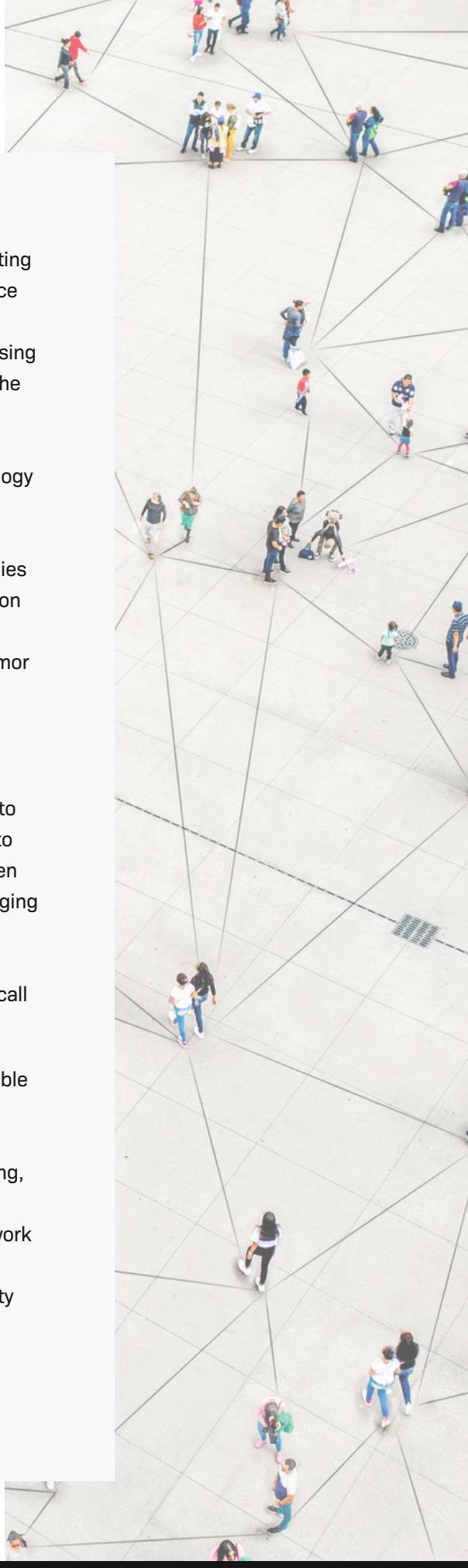

In our white paper[1], we summarized the recent FDA draft guidance relating to core patient-reported outcomes (PROs) in cancer trials[2]. This guidance lays out a framework for effective patient-reported outcome measure (PROM) selection and implementation, and may be important in addressing the current limited use of PRO data in oncology medication labeling in the US. As a case in point, only three drug approvals out of 85 medications submitted to the FDA between 2010 and 2016 included PROM-related labeling claims[3,4]. While low representation of PROM endpoints in oncology medication labeling may be partially due to study design – single-arm and open-label studies are often used in oncology trials – the new draft guidance illustrates some of the weaknesses in common PROM strategies used in oncology clinical trials. The inclusion of PROM data on medication labeling provides valuable additional information for the prescribing physician to inform risk/benefit discussions with the patient beyond tumor response and survival endpoints.

First, measures tend to be implemented at clinic visits during the start of each cycle when patients are feeling well enough to receive the next cycle of treatment. Most of the commonly used measures ask patients to recall their health status over the previous week, but this strategy fails to measure the impact of treatment in the earlier stages of each cycle when treatment-related side effects are likely to be most pronounced. Leveraging an instrument with a longer recall period could address this, but it may be prone to inaccuracy due to response shift – patients changing their perception of the severity of a symptom they experienced during the recall period because they feel improved at the time of the assessment.

Second, the guidance recommends researchers select PROMs that enable specific and focused measurement around five core domains: disease-related symptoms, symptomatic adverse events, an overall side effect impact measure (single item), physical function (aspects such as walking, lifting, and reaching that are considered important for independent functioning), and role function (impact of a treatment on the ability to work and carry out daily activities). This implies that current commonly used instruments may not always provide measures that deliver the specificity required to separately assess each of these core areas.

In this perspective article, we explore these two areas in more detail.

MEASUREMENT FREQUENCY

The draft guidance recommends more frequent assessments in early cycles and fewer later in the treatment process (Figure 1). Specifically, certain core domains such as symptomatic adverse events (AEs), the overall impact of side effects, and physical function should be measured frequently at the start of treatment before moving to less frequent cadences later in the treatment period. This mitigates the limitation of common current measurement approaches in which assessments are implemented only at the start of new treatment cycles as described above.

	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

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

This increased frequency of assessments raises a number of practical questions:

- If these domains are measured by subscales of existing instruments, is it valid to use only the subscale items at these more frequent timepoints?
- To enable more frequent measurements, we would need to ask patients to complete PROMs at home. Is this practical for patients experiencing challenging treatment-related symptoms and side effects?
- Should measurement timings be adjusted if treatment is delayed due to side effects?

Subscale use

Using only the subscale items when needed is an attractive approach, but researchers should always discuss this with the instrument owner or license holder. Some instrument owners permit subscales of instruments to be used independently of the full measure. For example, the EORTC QLQ-C30 core measure is comprised of a number of subscales that provide discrete scores for specific concept areas, such as physical functioning and role functioning. The European Organization for Research and Treatment of Cancer (EORTC) makes it possible to use these as discrete "item lists." Referring to the schedule of assessments in Figure 1, it would be possible to take the five physical function items from the QLQ-C30 and apply these independently on a weekly basis to enable the more frequent assessment of this core domain, in line with the FDA thinking. When doing this, it will be important to include the complete set of physical function subscale items, represent them in the same order as within the full instrument, and apply the same scoring rules as defined for the subscale within the full instrument.

Patient acceptance

A more frequent assessment schedule necessitates at-home PROM collection. The draft guidance states that "methods to lessen patient burden should be explored, including use of electronic PRO capture that may allow for assessments outside of the clinic." However, burden is an important consideration. There is a reasonable perception that patients may be too ill at times to consider PROM completion. In our qualitative interview study of oncology patients, we identified that certain days within typical treatment cycles are the most difficult – for example, one patient stated, "Days 3 to 6 were my 'dark' days, and I did not leave my bed, speak to anyone, or even eat any food[5]." Despite the side effects of the treatment that could affect their interaction with technology, the study participants did not feel this would deter or inhibit them from completing PROM instruments on devices. For example, one patient stated, "You can be bad, but not so bad that you can't use nothing at all. . . I would make the effort[5]."

Given that as a backdrop, there are some key considerations for optimizing the use of ePRO in these circumstances:

1. Ensure instruments are as short as possible to measure the domains of interest. For example, the physical function scale of the QLQ-C30 is five items.
2. Implement multi-day completion windows, so that patients can elect to complete assessments on a subsequent day if they do not feel able to complete their PROM immediately.
3. If implementing more than one PROM, enable patients to come back later to complete the second instrument.
4. Consider a bring-your-own-device (BYOD) option. On days when the patient is feeling unwell, they may be interacting with their own mobile device but are less likely to have the study device on hand.
5. Collect reasons for missing assessments so that intercurrent events, such as feeling too unwell to complete the PROMs at a given time, can be taken into account in the analysis plan and in the interpretation of the results.
6. Implement the usual PROM completion compliance strategies, such as patient reminders as well as site notifications and reports, to monitor and proactively encourage completion behavior.

Treatment delays

In oncology studies, it is common for physicians to implement delays in treatment when a patient has not recovered sufficiently from the previous cycle of treatment. In these instances, it is common to adjust the timing of collection of site-based PROMs to the new cycle start date. With the change in focus to more frequent measurement, should a similar approach be applied? For example, should a patient be asked to complete a weekly PROM for 3 weeks after each cycle, or simply to complete the PROM weekly for a number of months independent of any cycle delays? While it is possible to implement either approach quite easily using an ePRO solution, it is our opinion that the study objectives would be met using the simpler and less complex approach of asking the patient to simply complete the PROMs weekly without tying the assessments to the timing of cycles.

MEASUREMENT SPECIFICITY

The FDA draft guidance states that PROMs should enable the separate and independent assessment of each of the five core domains (disease-related symptoms, symptomatic adverse events, overall side effect impact, physical function, role function). For each domain, measures should be well-defined and reliable, and questions representing each domain should all be related to the concept of interest. A core domain may be measured by a certain instrument or by a subscale of a broader instrument.

This provides a valuable framework for assessing how to select PROMs that meet the requirements of the FDA draft guidance. Let's examine this further by considering several PROMs that are commonly considered for use.

Example 1. NSCLC-SAQ

The NSCLC-SAQ is a symptom assessment questionnaire for non-small cell lung cancer[6]. It is a 7-item questionnaire developed specifically to assess disease-related symptoms across 5 concept areas (Figure 2).

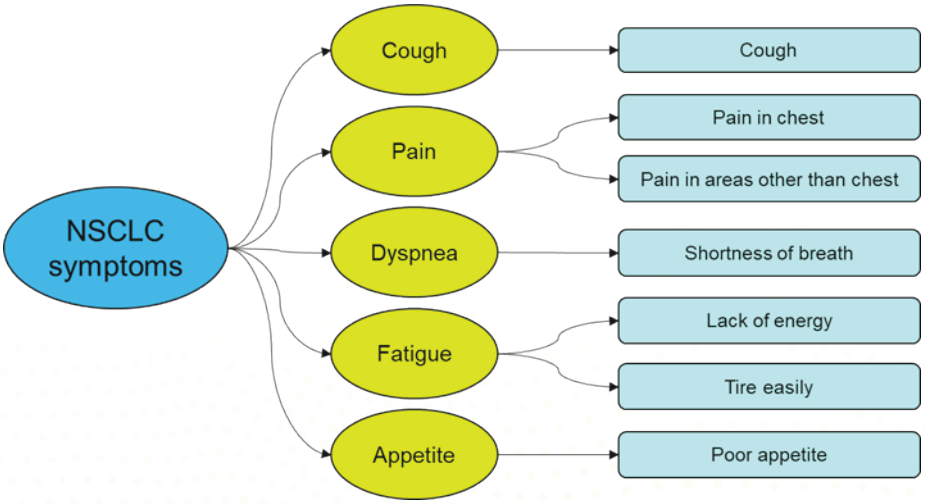

Figure 2. Conceptual framework for the NSCLC-SAQ, adapted from Bushnell et al[7]

The published concept elicitation and item development work[6] provide strong evidence of the measure's relevance in assessing the disease-related symptoms that are most important and meaningful to patients with this disease. For this reason, it is not surprising that this instrument was cited as an example of a suitable instrument to measure disease-related symptoms in the FDA draft guidance[2].

Example 2. EORTC QLQ-C30 Physical Function scale

The EORTC QLQ-C30 is a widely used instrument in oncology trials. It has been translated into over 100 languages and used in over 3000 studies worldwide[8]. The instrument provides subscales for five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning) and several symptom scales/items.

The physical functioning subscale comprises five items that assess difficulty with strenuous activity, difficulty taking long walks, difficulty taking short walks, the need to stay in bed or remain seated during the day, and the ability to complete self-care activities such as washing and eating. In terms of simple face validity, these five items certainly appear to all be measuring different aspects of physical functioning. The completeness of this set of items can be explored further by inspecting the published validation work. The FDA's draft guidance cites this physical function subscale as an example of a suitable instrument, along with the PROMIS physical function short form.

Example 3. FACT-B, Breast Cancer

The Functional Assessment of Cancer Therapy - Breast (FACT-B) is a 37-item questionnaire that is used to measure five domains of health-related quality of life in breast cancer patients: physical well-being, social/family well-being, emotional well-being, functional well-being, and a breast cancer subscale[9]. These domains are not named the same way as the FDA core domains, and if we examine them in more detail, we can see that they represent slightly different concepts than expressed by the five domains recommended by the FDA.

For example, the first three items of the FACT-B functional well-being subscale measure one's ability to work, whether that work is fulfilling, and one's ability to enjoy life. Mapping to the FDA domains, there appears to be some degree of core domain overlap. For example, there are aspects of role function expressed in the first item (ability to work), but other aspects of well-being expressed in the second item and so forth. To measure the FDA core domains using the FACT-B, some considerations beyond the standard author-defined subscales may be important, and greater domain specificity may be required. This takes us to considerations around instrument adaptation.

Adapting instruments

As described above, to meet the FDA draft guidance around specificity to measure the five core domain areas, it is important to select PROMs carefully. In some cases, it may not be as simple as implementing an instrument in its off-the-shelf format. Instead, it may require some degree of adaptation. We discuss two examples below.

Remapping existing items

Continuing the example of the FACT-B, while the subscale construction of the FACT-B does not appear to map directly to the FDA's core domains, the instrument and its items are well-validated. To address this, we might consider working with the scale author to validate an alternative subscale based on existing items within the instrument. Hypothetically, for example, we might consider grouping items from the physical well-being subdomain such as lack of energy, pain, and nausea along with other items from other subdomains such as shortness of breath and swelling/tenderness of the arms to provide a more specific measure of disease-related symptoms. This would require working with the scale author and evaluating the psychometrics of the new subscale.

Adding to existing instruments using item banks

Item banks are databases of individual PROM items. Items are gathered from existing, validated measures or are newly developed for the purpose of generating a comprehensive set of items to include within the item bank. Item banks are put through rigorous qualitative and quantitative evaluations to support their content and usage. It is possible to leverage pre-validated items within an item bank to enable researchers to accelerate the assembly and development of tailored PROMs for specific populations and measurement domains.

There are good examples of the use and development of items banks in the literature, and the ones most applicable to oncology research are the PROMIS and EORTC item banks. One published example uses the EORTC item bank to supplement items in the QLQ-C30 to ensure coverage of all important items to measure treatment benefit in a set of rare hematological stem cell disorders[10]. The EORTC item bank contains around 1,000 items, with many translated in up to 100 languages[11].

In this example, the instrument developers used a process to identify the additional items in the item bank that should be used alongside the QLQ-C30 (Figure 3). They accomplished this by identifying the symptom and impact concepts associated with the diseases by reviewing published qualitative research studies in these patients, interviewing physicians experienced in treating patients with these rare diseases, and performing a qualitative concept elicitation study. This enabled the team to perform a gap analysis to identify which symptoms and impacts were already measured by the items in the QLQ-C30. For the gap areas, they identified 13 items specific to these cancers that were not covered by the core instrument but were included in the wider EORTC item library. They conducted further testing in patients to confirm the suitability and content validity of these additional selected items.

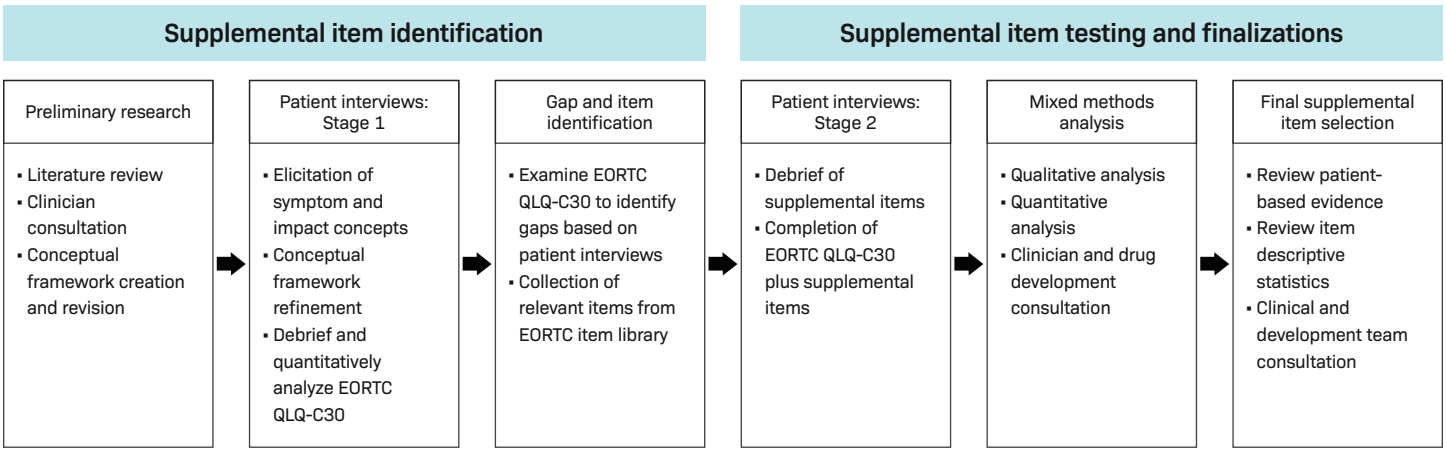

Figure 3. Item identification and selection process[10]

Taken from Bell JA et al.[10], under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/). No changes made.

This is an important example of an approach that we may see more often as we carefully and strategically consider PROM selection for future oncology clinical trials in the light of the FDA draft guidance.

TRIAL DESIGN CONSIDERATIONS & RECOMMENDATIONS

These recommendations for future oncology trial design, published in our earlier whitepaper, also address the measurement frequency, specificity concepts, and guidance explored above.

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.

Measurement selection / adaptation

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.

PROM development/adaptation

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

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 while ensuring that the solution used to collect PROM data includes methods that remind and proactively monitor PROM completion is an important consideration to limit missing data and draw reliable conclusions which may lead to consideration for labeling 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.

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