



Meaningful Treatment Benefit from the Patient's Perspective

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Have you been told by the U.S. Food and Drug Administration (FDA) to include the patient's perspective about treatment benefit in your drug development program? The feedback could be a question such as *"what magnitude of change does the patient consider to be a meaningful treatment benefit?"* or a statement such as *"patient input on what amount of change they consider meaningful is recommended."* With the 21st Century Cures Act, there is an increased focus on the patient's perspective and now, more than ever, regulators are seeking feedback from patients throughout the drug development process.

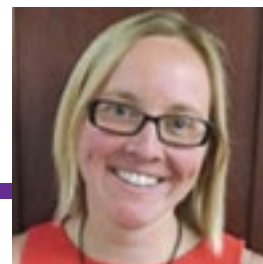
There are a few critical issues to be addressed during the drug development process. First, the concepts being evaluated from the patient's perspective should be meaningful and relevant to the patients. While this seems like an intuitive and unnecessary statement, evidence demonstrating the relevance of an outcome to the patient is critical.¹ The evidence can be obtained from qualitative patient interviews or focus group discussions. After confirming that the concept/outcome is relevant and meaningful to the patient, patients should be consulted

about the benefit of their treatment. This can occur pre-study as a hypothetical exercise or can occur during exit interviews during the clinical trial program. Finally, patients can work closely with their clinicians to monitor their treatment to fit their individualized treatment goals (this is beyond the scope of this article). This article will focus on the qualitative research that can be conducted to evaluate a meaningful treatment benefit both before and during clinical trial implementation.

Pre-trial interviews are one approach to gain patient insight as to meaningful treatment benefit. There are multiple goals that should be kept in mind when pre-trial interviews are designed, the first of which is to identify the concept(s) of interest. In other words, determine the primary symptom(s) or impact(s) that are drivers for that patient population of interest (for example, a key concept in many disease areas is pain). A second goal of pre-trial interviews is to assess the current severity/intensity/frequency of the experienced concept(s). A third goal may be to explore meaningful outcomes related to the concept(s) of interest that patients would like to see improved, e.g., a meaningful outcome related to the experience of pain may be to sleep better or to return to work. The final goal is to ascertain the amount of change on the assessment that is measuring the



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concept that would need to be experienced for the patient to perceive having experienced a meaningful treatment benefit.

In conjunction with each of these four goals, some example questions that can be tailored, and incorporated into pre-trial interview guides, are shown below in Table 1.

There are multiple challenges of pre-trial interviews to keep in mind. For one, there is no existing guidance within industry on how best to conduct pre-trial interviews. Secondly, conceptually, the idea of meaningful treatment benefit can be very difficult for patients to grasp. Add in the fact that the conversation about the expected/anticipated/desired benefit is hypothetical, and it is easy to see how experienced methodologists are needed for the design and execution of the interview guides. Another challenge is the COA itself, typically a patient-reported outcome (PRO). Some COAs, like the numeric rating scale (NRS) for pain, are a single item, a single concept, and are easily scored from 0-10. Meanwhile, others are multi-item, multi-scale instruments, sometimes with complex scoring algorithms. Discussing score changes on multi-item, multi-scale instruments with patients requires the input of skilled methodologists with creative approaches for establishing patient understanding and engagement.

Once meaningful concepts have been identified and a meaningful outcome included in the trial program (e.g., PROs), another opportunity to receive feedback directly from the patient (including assessment of meaningful treatment benefit) is during the clinical trial itself. These interviews are often referred to as “exit interviews” but do not necessarily need to be conducted at the end of the trial period. The study’s primary efficacy endpoint time may be a better fit to receive patient insight.

There is no formal regulatory guidance on how best to conduct exit interviews in terms of the proportion of trial subjects to be interviewed, timing of the interview, handling of qualitative data analyses against the quantitative data, etc. Often, the Sponsor’s impetus for exit interviews is in reaction to regulatory feedback but often the Sponsor does not receive direct reaction about the study design. This is likely a reflection of the increased focus on the patient’s perspective during drug development. Guidance for best practices should be developed. In terms of an adequate sample size, there is evidence that the FDA has received exit interview data from as few as three interviews, which was related to Amgen’s Aimovig™ (erenumab).²

Patients from all treatment arms should be included in the exit interviews; both treatment and placebo. Of course, the randomization assignment will be masked during data collection and the sample size should be large enough to accommodate a representative reflection of randomization arms. Even patients who withdraw early from the trial may hold deep insight as to why the treatment did not provide a treatment benefit. If the patient withdraws early it could be because of perceived lack of efficacy, adverse events, or simply personal barriers in the trial (e.g., travel, time at the clinic site, etc.).

One could argue that the exit interview feedback about meaningful treatment benefit is more insightful than pre-trial, abstract interviews as these patients can be directly interviewed about their study experience. Patients from both active and placebo arms can provide valuable feedback about their experience. Interviews can be targeted to include the patient’s experience with their condition before the study, their expectations for the study, the changes they experienced during the study, how those changes impacted their daily life, and about potential

Table 1. Example Pre-Trial Interview Questions

Goal	Example Questions
Identify Concept(s)	<ul style="list-style-type: none"> What symptoms do you experience as a result of your <i>condition</i>? Do some symptoms from your <i>condition</i> bother you more than others?
Assess Current Intensity/Severity/Frequency Level	<ul style="list-style-type: none"> How often do you experience <i>symptom</i>? How severe is the <i>symptom</i>? This questionnaire is about your current experience of <i>symptom</i>. How did you rate your <i>symptom</i>?
Explore Meaningful Outcome(s)	<ul style="list-style-type: none"> How does <i>symptom</i> impact your daily life/activities? Tell me how your life would be different if you didn’t experience <i>symptom</i>? Assuming there is no complete cure for <i>condition/symptom</i>, what improvements to your <i>condition/symptom</i> would make you say that a treatment is effective?
Ascertain Meaningful Change on Clinical Outcome Assessment (COA)	<ul style="list-style-type: none"> If you received a treatment for <i>condition/symptom(s)</i>, what is the smallest level of change on this scale that you would have to experience to know the treatment is working? If you received a treatment for <i>condition/symptom(s)</i>, what level of change on this scale would be meaningful to you? If you received a treatment for <i>condition/symptom(s)</i>, what amount of change in <i>relevant anchor</i> would be meaningful to you?

Table 2. Example Exit Interview Questions

Goal	Example Questions
Pre-Trial Experience with Condition	<ul style="list-style-type: none"> ● What were your <i>symptom(s)</i> from <i>condition</i> before the start of the study? ● Before the start of the study, how did your <i>symptom(s)</i> impact your daily life/activities?
Expectations of Treatment	<ul style="list-style-type: none"> ● What were your expectations in terms of a change in your <i>condition/symptom(s)/impact(s)</i> through participation in this study?
Experiences During the Trial	<ul style="list-style-type: none"> ● Tell me about how your <i>symptom(s)/impact(s)</i> changed from the beginning to the end of this study.
Impact the Changes had on Daily Life/Activities	<ul style="list-style-type: none"> ● How did the changes in <i>symptom(s)</i> affect what you were able to do in your daily life?
Were the Changes (Symptoms/Impacts) a Benefit that was Meaningful?	<ul style="list-style-type: none"> ● Did the changes that you noticed in <i>symptom(s)/impact(s)</i> matter to you? ● Did your <i>symptom(s)/impact(s)</i> improve enough that you would continue this treatment?
Other Questions Unique to the Intervention	<ul style="list-style-type: none"> ● Would you change the device in any way to make it easier to use?

treatment benefits. The rich detail patients provide about their experiences helps enrich the comprehension about the patient’s understanding of treatment efficacy. Finally, patients can also be asked about the intervention itself or other unique aspects specific to the intervention. Table 2 displays some example questions for these exit interviews.

One recent example of a mixed methods exit survey and interview study involving 242 quantitative exit surveys and 80 qualitative telephone interviews is arguably a gold standard for this type of exit study.^{3,4} The survey asked trial participants to assess specific experiences using the following responses:

- Overall, I did not benefit
- Overall, it was beneficial but was not meaningful to me
- Overall it was beneficial and was meaningful to me

Statistically significant group differences between treatment and placebo groups were demonstrated in terms of proportion of patients reporting meaningful benefits. Further, the research was able to illustrate the patient-centered findings using the richness of the qualitative data – the verbatim patient quotes.

Together, the pre-trial interviews and trial exit studies can help inform drug development programs of the patient’s perspective about meaningful treatment benefit. There are a number of methodological considerations for both approaches. For example, how easy or difficult the conceptual exercise of a pre-trial interview about meaningful benefit can be to the target population. Are the patients being realistic with their expectations? Strategic considerations for exit interviews should also be considered, such as the sample size, the operational aspects of planning such interviews (e.g., stand-alone protocol or included in the trial protocol; clinic site contracting; ethics approvals with the trial applications or stand-alone applications, etc.), handling of suspected adverse events, and timing of exit interviews. Without question, patients are at the center of any drug development program. Obtaining patient feedback about meaningful treatment benefits is an integral component of a patient-centric approach to drug development. ■

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