White Paper

How to Successfully Use ClinROs in CNS Clinical Research

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Introduction

Clinician Reported Outcomes (ClinROs), the most frequent type of Clinical Outcome Assessments (COAs) used within the central nervous system (CNS) space, are challenged to meet current and forthcoming regulatory guidelines set by the FDA. As CNS disorders are on the rise and the healthcare landscape is becoming more patient-centric, legacy ClinROs face issues around endpoint reliability and sensitivity. In this Insight Brief, we illustrate how IQVIA can help address these challenges and strengthen the evidence needed to support the psychometric properties of ClinROs as fit-for-purpose throughout the study lifecycle.

How is the CNS study landscape changing?

COAs are tools that measure how a patient feels or functions, which can either be reported by the patient in the form of self-report (Patient Reported Outcomes – PROs); based on the patient's performance (Performance Outcomes – PerfOs); from observers (Observer Reported Outcomes – ObsROs); or, from experienced clinicians (ClinROs).

ClinROs are frequently used as clinical trial endpoints for neurological or psychiatric indications (summarized under the term "CNS space") as patients may lack reliability in self-reporting through PROs, have difficulty completing PROs, or show high inter- and intra-group variability in responses depending on their cognitive functioning and/or level of psychopathology.

The disability burden among CNS disorders is growing, with neurological disorders as the second largest cause of disability[1] and psychiatric disorders showing a sharp rise in prevalence[2]. Stakeholders in the healthcare

landscape are shifting to include a more patient-centric view when assessing the value of a treatment, designing a trial, or selecting clinical trial endpoints, as illustrated by growing FDA guidance on Patient-Focused Drug Development (PFDD)[3]. These trends will drive the use of COAs in CNS, and the selection and implementation of fit-for-purpose ClinROs specifically.

What are some of the current challenges in CNS ClinRO selection?

FDA Patient-Focused Drug Development (PFDD) guidance states that COAs need to meet certain qualitative requirements, including:

- Accurately reflect the patient experience in the target indication and patient population
- Cover the concept of interest and range of variation in responses with the items included
- Cover a period of time that the patient can recall
- Be administrated in a way and timeframe amenable to the patient

Additionally, the COAs must meet quantitative requirements towards the measured concept such as:

- Measure the concept of interest accurately and remain consistent over time
- Have high enough sensitivity to detect clinically meaningful change

ClinROs developed prior to current FDA PFDD guidance are challenged in a number of ways to meet today's fit for purpose requirements, which were not anticipated in their initial design.

As drug development continues to include rare CNS disorders or specific patient (sub-)populations, it is common practice to use an existing ClinRO outside of the context for which it was originally developed. Factors inherent to the rare CNS disease or (sub-)population may impact whether the legacy ClinRO accurately measures the concept of interest.

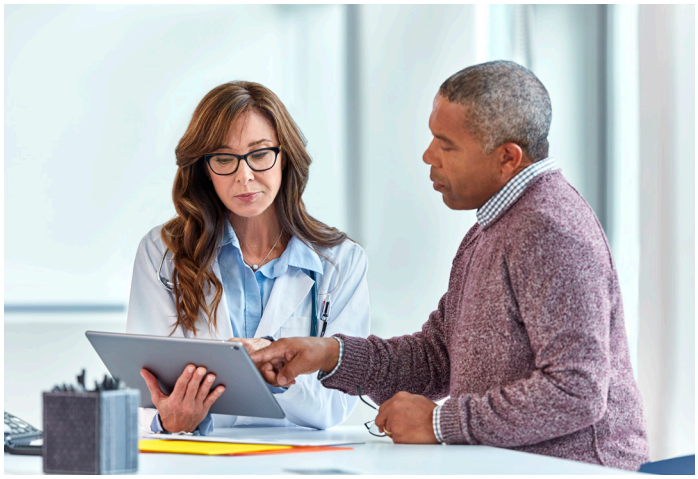
For example, existing measures in depression assess symptom severity including weight changes, but when used in post-partum depression, these existing measures do not appropriately consider normal changes in a mother's sleeping or eating habits with a new-born. As trials for Alzheimer's and dementia target patients earlier in the disease with less severe symptoms, existing COAs may not be sensitive enough to measure symptoms or detect change in these populations. It is therefore important to assess whether a legacy ClinRO is fit-for-purpose in the novel context as defined by FDA guidelines.

Additionally, changes in available treatments and how they affect patients mean existing scales may not measure the most important symptoms or assess change within a meaningful timeframe. For example, various scales measuring depression in patients assume slow changes due to treatment and therefore ask patients to assess sleep, appetite, and weight changes over the course of a week. However, with more rapid-acting treatments, patients' perceived changes over days or even within 24 hours may be of interest. Furthermore, as new products come to market with novel modes of action, existing COAs may also not cover anticipated or novel side-effects.

Further considerations towards ClinROs "fit-for-purpose" assessment need to include how existing COAs were developed and designed. Items in many existing COAs do not necessarily measure symptoms or impacts of importance to patients themselves. Since patients and/or caregivers of patients were not directly involved in the development of the COA, any change measured here may not be meaningful to them. Also, many ClinROs

measure the severity and frequency of a symptom together. This makes it difficult to assess whether the treatment had an effect on frequency, severity, or both, which is an important part of meeting FDAs PFDD quantitative requirements.

In summary, numerous aspects of ClinROs when applied in a clinical trial need to be assessed before selection and implementation. The above examples including novel context, novel treatments, or other methodological considerations and are only a selection of what needs to be taken into consideration.



How can ClinROs be implemented to increase signal detection?

Following appropriate ClinRO selection, correct implementation is also needed to ensure the success of a trial. When used as clinical trial endpoints, many CNS ClinROs are characterized by a high degree of variability because they were not developed to detect treatment benefit within the context of a multi-site, multi-rater, multi-national trial.

Noise can be introduced into the data when raters are unfamiliar with the ClinRO or don't have experience with the specific target population, different raters with varying experience levels are included, different methods of administration and scoring are used, or the measurement is inconsistently applied over the course of the study. These potential sources of low inter- and intra-rater reliability affect the signal detection of the COA within the trial, i.e., its ability to measure change accurately.

In addition, the interview guides used or EDC design may limit the rater within the trial to follow-up or clarify with the patient, leading to subjective ratings without sufficient supporting data. Rater drift and the source thereof (such as rater error, divergent reporting from patient versus informant, and/or an atypical patient presentation) cannot be assessed, affecting reliability and interpretability of the data.

Beyond fit-for purpose rater training, IQVIA recommends continued monitoring of ClinRO ratings throughout the life of a trial. Rater training must include selecting and certifying appropriate raters, training the raters to ensure correct measurement administration, as well as supporting less experienced raters or rater re-training where appropriate. In cases of rare disease studies, additional targeted, expert-driven training specific to the different concept of interest may be appropriate also.

While rater training is necessary, it is not sufficient. Continued monitoring of instrument administration and scoring by trained raters ensures consistency of ratings over time, enhancing signal detection. The IQVIA eCOA platform offers tailored EDC design to support not only ClinRO application using telehealth, but also the documentation of information supporting the rater's assessment via audio and/or video capture. This allows data capture not only of raters' score, but also why they arrived at the score of each item and scale for independent quality review. Electronic decision support systems for data monitoring, such as machine learning, can trigger direct contact with the rater to explore their scoring rationale in cases of inconsistency. This helps assess the degree and root cause of rater drift over time.

Further information

IQVIA's recent acquisition of Cronos brings together the expertise, technology, and services that is needed to help clinical trial sponsors identify the most appropriate COAs for their trials and provide state-of-the art COA implementation over the life of a study.

To find out more on the current CNS and ClinRO landscape, as well as FDA PFDD guidance on COA selection, implementation, and maintenance, please view the on-demand webinar, CNS COA Challenges: How to Succeed in an Evolving Landscape.

To learn more about IQVIA's CNS and Rater Services, please contact stella.karantzoulis@iqvia.com and shira.hoschander@iqvia.com.

References

1. Feigin, V. and G.E. Collaborators, Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology, 2019. **18**(4): p. 357-375.

2. Ferrari, A., et al., Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Psychiatry, 2022. **9**(2): p. 137-150.

3. FDA. Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-forPurpose Clinical Outcome Assessments - DRAFT GUIDANCE. 2022.

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