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Clinical outcome assessments in neuro-oncology: a regulatory perspective

Joohee Sul, Paul G. Kluetz, Elektra J. Papadopoulos, and Patricia Keegan

Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland (J.S., P.G.K., P.K.); Clinical Outcome Assessments Staff, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland (E.J.P.)

Corresponding Author: Joohee Sul, MD, Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Avenue, White Oak 22, Room 2331, Silver Spring, MD, 20993-0002 (joohee.sul@fda.hhs.gov).

Overall survival, progression-free survival, and to a lesser extent objective response rate, have long been the most widely accepted endpoints used to evaluate clinical benefit in oncology trials. More recently, clinical outcome assessments (COAs) that measure the impact of disease and treatment on patients' symptoms and function have been recognized as having potential to be an integral component of the risk/benefit analysis of new therapies. Although COAs have been used to evaluate cognitive and physical functioning in neurological diseases, assessing patient-centered outcomes in individuals with malignant brain tumors presents unique challenges. The approach to developing appropriate instruments to measure COAs in neuro-oncology should include identifying areas requiring new tools, reviewing existing tools that may be suitable or adapted for use in clinical trials, and engaging early with regulatory agencies to standardize a set of well-defined and reliable instruments to quantify important patient-centered outcomes.

Keywords: clinical outcome assessment, patient-reported outcomes, regulatory guidance.

Regulatory Background

Historically, overall survival has been the favored endpoint in evaluating oncology therapies, as it is typically considered the most objective and reliable measure of clinical benefit. Clinical outcome assessments (COAs) that measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions[1] have generally been thought of as lesser priorities, often relegated to exploratory endpoints in therapeutic clinical trials. Recently, there has been a tremendous groundswell of interest in incorporating patient-centered outcomes assessments that evaluate the impact of disease and treatments on an individual's physical, cognitive, emotional, and social functioning in our analysis of drug efficacy and safety. Much of this effort has been spearheaded by patients and advocacy groups and although these patient-reported questionnaires and symptom inventories are becoming increasingly more commonplace in clinical protocols, it is not yet certain how the resulting data can be used by regulators, payers, and patients to better inform medical decision making. The measurement tools and data collection methods are heterogeneous and employ varying degrees of rigor; therefore, it is imperative that individual therapeutic areas standardize and optimize the COA effort to the extent possible, and maintain careful attention to thoughtful integration of COAs in clinical trials.

Regulatory agencies have been responsive to public demand for inclusion of the patient experience in evaluating and approving therapies. In 2005, the European Medicines Agency (EMA) presented a brief paper that provided general guidance on the context for evaluation of health-related quality of life (HRQoL), but did not address how to develop these instruments.[2] In 2006, the FDA presented a draft version of the *"Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims,"*[3] which addressed how the FDA reviews the development of patient-reported outcome (PRO) measures that may support regulatory approval or labeling claims. The Guidance defines a PRO as any measurement based on a report that comes directly from the patient that describes the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. Hence, PROs encompass very simple instruments from single-item pain intensity scales to more complex instruments such as HRQoL instruments with multiple questions and scores assessing the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life. The FDA final guidance was released in 2009,[4] expanding upon the discussion of how these instruments may be reviewed from a regulatory perspective to determine their suitability to support labeling claims. The fundamental tenets described are related to defining the clinical outcome endpoint of

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interest: what is being measured, how it is being measured, and the context in which it is measured. As we cannot assess every aspect of the patient experience in a clinical trial, we must be parsimonious by selecting the most important (and measurable) concepts for a particular patient population while remaining rigorous in how we measure them. The guidance cautions that inclusion of PROs in clinical trials should be founded on scientific rationale rather than indiscriminate addition of tests and questionnaires that result in data without a purpose, and that development of any metric must begin with input from patients to inform content validity, ie, the extent to which the instrument measures the concept of interest. All other measurement properties such as reliability and ability to detect change are considered important but only meaningful if content validity has been established. Drug developers are encouraged to assess whether an adequate PRO instrument exists for their particular goals. If it does not, a new PRO instrument may be constructed *de novo* or, in some situations, a new instrument can be developed by modifying an existing instrument.[4]

While the PRO Guidance represents an optimal approach to COA instrument development and validation, the FDA recognizes that regulatory flexibility is often needed to meet the practical demands of drug development while also ensuring that outcome assessments are well defined and reliable, and labeling is not misleading. Because of the inherent complexities that may be encountered when implementing PRO instruments and other COAs in clinical trials, advanced planning and communication with the FDA early in drug development is important. A voluntary, precompetitive process for development of publicly available COAs for unmet public health needs is also available under the Center for Drug Evaluation and Research Drug Development Tool Qualification program.[1]

COAs in Oncology

There are four types of COAs that can be used depending upon the research question(s) of interest, patient population, and clinical trial context; these are patient-reported, clinician-reported, caregiver-reported, and performance outcome assessments. A performance outcome is a measurement based on specified, standardized task(s) performed by a patient, typically in a clinical setting. Examples include measures of gait speed or memory. It is important to keep in mind that multiple types of COAs are often used within clinical trials as they provide complementary information about treatment effect or lend strength to the totality of the evidence supporting treatment effect. For example, in patients with cognitive impairment, PROs are problematic due to uncertainty of the patient's ability to provide reliable self-report; therefore, caregiver or clinician reports may be more appropriate with performance outcomes and other types of COAs providing supplementary information. We must consider thoughtful integration of different COAs dependent upon the research aims and context (eg, patient population).[5]

Disease and treatment-related symptoms and functional impairment are commonly seen among patients with cancer; however, few oncology drugs have included COA data in labeling compared with treatments for other diseases.[6] Challenges including small patient populations, single-arm trials, inadvertent unblinding to study treatment, and logistical hurdles have all been cited as impediments to successful inclusion of COAs in oncology trials. Since the introduction of the FDA's PRO Guidance, two approved oncology drugs have included references to COAs in their label: ruxolitinib and abiraterone. Ruxolitinib was approved by the FDA in 2011 for the treatment of myelofibrosis. The regulatory basis for full approval of ruxolitinib included decrease in splenomegaly and an improvement in disease-related symptoms as measured by the modified Myelofibrosis Symptom Assessment Form version 2.0 diary. Development of a successful COA tool involved early and frequent discussions between the FDA and sponsor, and multiple refinements. An expanded indication for abiraterone was approved by the FDA in 2013 for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer, based on a large delay in the time to radiographic progression or death accompanied by other key secondary endpoints, including a significant delay in the time to opiate use. The FDA label describes a delay in patient-reported pain progression that was supportive of the time-to-opiate-use result. Patients in the pivotal trial had minimal baseline pain symptoms prior to beginning study treatment, necessitating a time to pain progression analysis.

COAs in Neuro-oncology

It is well-recognized that patients with malignant gliomas may experience progressive deterioration of neurological functioning that impacts physical, cognitive, emotional, and social domains. Given the overwhelmingly poor prognosis of these patients, the lack of effective therapies, and the challenges of evaluating disease response, one can argue that COAs in this population could be an especially vital component to inform the value of an investigational therapy. Although assessment of patient functioning, cognition, mood, and symptoms have long been an informal component of the patient-clinician encounter in conjunction with review of imaging, the use of more standardized COAs that are appropriate for clinical trials has proven to be challenging for multiple reasons.[7] Patients with brain tumors may have variable symptoms and impairments related to factors such as tumor type and location as well as history of prior therapies. Such heterogeneity among patients affected by brain tumors adds to the challenges associated with conducting clinical trials in relatively small patient populations, making careful attention to outcome measurement imperative.

Neuro-oncology is a unique field in that it necessitates the evaluation of traditional oncology outcomes such as radiographic tumor assessments and overall survival, but also relies heavily on the examination of neurological functioning to assess disease status. In contrast, endpoints used in clinical trials of nonmalignant neurology are generally oriented to clinical outcomes since many neurological diseases are defined by the clinical symptoms themselves rather than by histopathology or imaging findings, and because survival endpoints become less relevant in these chronic diseases. Therefore, examining the basis for approval of treatments for neurological disorders may provide insights on building a framework for developing COAs for neuro-oncology; however, this approach has limitations as instruments developed for one condition may not be valid, reliable, or sensitive to change when applied in another condition. In addition, other

well-developed and fit-for-purpose tools currently available may not be found in drug labeling.

Drug approvals for neurologic diseases over the past 4 years are listed below (Table 1). A description of the clinical outcomes used as a basis for approval, and included in drug labeling, are also listed. Nearly all drugs were reviewed by the Division of Neurology Products at the FDA, and treatments for pain disorders and diseases that are generally thought of as psychiatric were excluded (eg, depression, insomnia).

Many of the instruments used in the evaluation of neurological disease are rating scales familiar to most neurologists. These scales are used to measure disability, which supposes the presence of impairments. In fact, a striking commonality among the trial designs that we assessed in our review is the requirement for patients to exhibit a baseline level of dysfunction or symptoms in order to assess the clinical outcome of interest. This differs from the common paradigm used thus far to examine clinical outcomes in neuro-oncology patients, where asymptomatic patients may be included in the population of interest thereby diluting any symptomatic or functional benefits of therapy. Arguably, patients with newly diagnosed GBM eligible for trials are likely to be at their best clinically before starting treatment, making it challenging to detect a meaningful improvement in disease-related symptoms or neurological functioning. It may be feasible to measure the time to the deterioration of a particular disability or symptom scale for asymptomatic or minimally symptomatic neuro-oncology patients, similar to the methodology used to measure time to pain worsening in patients treated with abiraterone. Another strategy would be to enrich for a population of patients with prespecified deficits and reversible symptoms or functional deficits, thereby allowing for a measure of improvement rather than time to deterioration (eg, change in seizure frequency in epilepsy trials). This may even be done within a larger study by prospectively identifying a subset of patients with clinically significant, well-defined, disease-related symptoms. In either case, study endpoints designed to analyze disease-related clinical outcomes are not as straightforward as measurements of time to death or centimeters of tumor growth, and concentrating the assessment on the core disease symptoms or functional impairments that are closely related to the disease and that can be improved with an effective therapy is critical. Care should also be taken to measure important patient-reported symptoms of the toxicity of treatment in order to provide a balanced assessment of the effect of the treatment on the patient and their disease. Finally, the complete COA strategy must take into account the total number of questions or functional evaluations performed, as duplicative or burdensome assessments may lead to missing data or impaired data quality.

Despite publication of guidance on development pathways for COAs, successful use of these measures in the oncology setting have been uncommon, and more must be done to advance the use of COA tools by multiple stakeholders, including the FDA, other regulatory agencies, measurement experts, clinical trialists, and pharmaceutical companies.[8] To that end, the FDA participated in a workshop sponsored by the Jumpstarting Brain Tumor Drug Development Coalition: "Brain Tumor Clinical Trial Endpoints Workshop 2 – Clinical Outcome Assessment". The primary goal of this workshop was to discuss issues related to use of PROs and other COAs assessing symptoms and functional endpoints in clinical trials for malignant gliomas. During the workshop, in addition to identifying content validity as a fundamental step towards the development of suitable COAs, the FDA encouraged investigation of existing COA tools used in neuro-oncology to identify elements that may be appropriate to measure specific priority symptoms. The FDA also supported the proposal to incorporate COAs earlier in the drug development process and standardization of data analysis.

One of the most valuable outcomes of the workshop was the presentation of results from a web-based patient and caregiver survey designed to capture symptoms and function that patients feel are important to consider in the evaluation of new therapies, and are the highest priority for inclusion in clinical trials.[9] This survey was developed and refined by the Jumpstarting Brain Tumor Drug Development Coalition, with feedback from neuro-oncologists and health professionals with expertise in the brain tumor patient care. After pilot testing of the web-based format and content, the survey was distributed to the community through social media and email notifications. There were 1824 participants who completed the survey, roughly half being patient caregivers. For patients with high-grade glioma ($n = 85$), the survey identified the top 3 priorities for patients (other than survival) to assess in clinical trials. Retaining brain function emerged as the most important, followed by maintaining ability to walk and perform basic physical tasks and improving memory and concentration.

"Retaining brain function" is a vague term, and deserves further careful dissection to isolate the principal themes and domains that are meaningful to patients. Nonetheless, the first 2 priorities appear to place emphasis on maintaining neurologic function, including physical and cognitive function, which is consistent with the predominant parameters evaluated in neurology therapeutic trials. Cognitive deficits and hemiparesis are also likely to be the most common impairments seen in acute rehabilitation settings, further signifying their prevalence and clinical importance.[10] Instruments to assess these deficits in neurologic diseases are already widely used and moreover, are generally intended to measure patient functional outcomes rather than more difficult-to-assess multidimensional domains such as quality of life. These more specific tools may prove to be valuable as existing COAs for use in neuro-oncology with appropriate modifications.

One limitation of the Jumpstarting Brain Tumor Drug Development Coalition survey was that patients with all types of primary brain tumors were petitioned, including those with low-grade gliomas or meningiomas, and patients with malignant gliomas were a small proportion of the 1824 participants. Important differences in priorities are likely to exist among patients with different tumor types, and also at different stages of disease (eg, newly diagnosed, recurrent). Despite the limitations of the survey, efforts such as these are recognized as integral to the development of a successful COA tool. Obtaining input from patients with brain tumors, and their caregivers, on priority symptoms and functional impairments is an essential step to defining content validity. As stated in the 2009 FDA PRO guidance:

> Documentation of patient input in item generation as well as evaluation of patient understanding through cognitive interviewing can contribute to evidence of content validity. Evidence of other types of validity (eg, construct validity) or reliability (eg, consistent scores) will not overcome problems

Table 1. FDA approval of neurology products in the Center for Drug Evaluation and Research[a,b]

	Drug	Indication[c]	Primary Clinical Outcome Measure[d]	Symptoms at Baseline Required for Study Entry[d]
2015	Duopa (carbidopa and levodopa)	Treatment of motor fluctuations in patients with advanced Parkinson's disease	Mean change from baseline to Week 12 in the total daily mean "off" time	≥3 hours of "off" time on current Parkinson's disease drug treatment
	Rytary (carbidopa and levodopa) extended-release	Treatment of Parkinson's disease, postencephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication	*Patients with early PD:* Mean change from baseline in the sum of the UPDRS Part II and III *Patients with advanced PD:* Percentage of "off" time during waking hours as assessed by patient's Parkinson's Disease Diary	*Patients with early PD:* Hoehn and Yahr Stages I–III with a median disease duration of 1 year *Patients with advanced PD:* Hoehn and Yahr Stages I-IV maintained on a stable regimen of at least 400 mg per day of levodopa prior to entry into the trial
2014	Lemtrada (alemtuzumab)	Treatment of patients with relapsing forms of MS	Annualized relapse rate over 2 years and time to confirmed disability progression defined by EDSS sustained for 6 months. MRI outcome measure was change in T2 lesion volume	≥2 relapses in the 2 years prior to trial entry and at least 1 relapse during the year prior to trial entry
	Namzaric (memantine hydrochloride extended-release + donepezil hydrochloride)	Treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on memantine hydrochloride and donepezil hydrochloride	*Memantine:* Mean difference in the SIB score at 24 weeks and the mean difference in CIBIC-Plus score *Donepezil:* Change from baseline in SIB score and ADCS-ADL-severe scores	*Memantine:* Moderate to severe Alzheimer's disease, diagnosed by DSM-IV criteria and NINCDS-ADRDA criteria with MMSE ≥3 and ≤14 at screening and baseline *Donepezil:* Probable or possible Alzheimer's disease, diagnosed by NINCDS-ADRDA and DSM-IV criteria
	Northera[e] (droxidopa)	Treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy	OHSA Item #1 score ("dizziness, lightheadedness, feeling faint, and feeling like you might black out") at week 1	Patients with decrease of ≥20 mm Hg or 10 mm Hg, respectively, in systolic or diastolic blood pressure, within 3 minutes after standing and symptoms associated with neurogenic orthostatic hypotension
	Plegridy (peginterferon beta-1a)	Treatment of patients with relapsing forms of MS	Annualized relapse rate over 1 year. Secondary outcomes: proportion of patients relapsing, number of new or newly enlarging T2 hyperintense lesions, and time to confirmed disability progression defined by EDSS	Patients with baseline EDSS score from 0 to 5, with ≥2 relapses within the previous 3 years, and at least 1 relapse in the previous year
2013	Aptiom (eslicarbazepine acetate)	Adjunctive treatment of POS	Standardized seizure frequency (based on data collected from patients or caregivers in seizure diaries)	Required to have an average of ≥4 POS per 28 days with no seizure-free period >21 days, during the 8 weeks baseline period

Continued

Table 1. *Continued*

	Drug	Indication[c]	Primary Clinical Outcome Measure[d]	Symptoms at Baseline Required for Study Entry[d]
	Trokendi XR (topiramate)	Initial monotherapy in patients ≥10 years of age with POS or PGTC seizures and adjunctive therapy in patients ≥6 years of age with POS or PGTC seizures adjunctive therapy in patients ≥6 years of age with seizures associated with LGS	Between-group comparison of time to first seizure	1 or 2 well-documented seizures during the 3-month retrospective baseline phase
2012	Eliquis (apixaban)	To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	Rate of stroke and systemic embolism	Patients had ≥1 of the following risk factors: prior stroke or TIA, prior systemic embolism, age ≥75, arterial HTN requiring treatment, diabetes mellitus, heart failure ≥NYHA Class 2, left ventricular ejection fraction ≤40%
	Fycompa (perampanel)	Adjunctive therapy for the treatment of POS with or without secondarily generalized seizures in patients with epilepsy aged ≥12 years	Percent change in seizure frequency per 28 days during the treatment period as compared to the baseline	Required to have >5 seizures during 6-week baseline period
	Horizant (gabapentin enacarbil)	Management of postherpetic neuralgia in adults	Improved the mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline at all doses tested	Minimum baseline 24-hour average pain intensity score of at least 4.0 on the 11-point numerical PI-NRS
	Lyrica[f] (pregabalin)	Neuropathic pain associated with spinal cord injury	Improvement in weekly mean pain score as recorded by daily pain rating and sleep scales upon awakening	Score of ≥40 mm on the visual analogue scale of the SF-MPQ and neuropathic pain associated with spinal cord injury that persisted continuously for ≥3 months or with relapses and remissions for ≥6 months
	Neupro (Rotigotine Transdermal System)	Treatment of moderate-to-severe primary RLS	Mean change in the IRLS sum score and CGI score from baseline to the end of treatment	Moderate-to-severe RLS
	Oxtellar XR (oxcarbazepine extended release)	Adjunctive therapy in the treatment of partial seizures in adults and children 6 to 17 years of age	Percent change from baseline in seizure frequency per 28 days during the treatment period relative to the baseline period	Required to have ≥3 seizures during 8-week baseline period

[a]Accessed July 2015 from Center Watch at https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/10/neurology.
[b]Excluding drugs for pain disorders and drugs reviewed by the psychiatry division.
[c]Modified from product labeling, accessed July 2015 from Drugs@fda: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
[d]Modified from product labeling and clinical reviews, accessed July 2015 from Drugs@fda: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
[e]Reviewed by the Division of Cardiovascular and Renal Drug Products (DCaRP).
[f]Reviewed by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).
ADCS-ADL, Alzheimer's Disease Co-operative Study - Activities of Daily Living Inventory; ALS, Amyotrophic Lateral Sclerosis; CIBIC-Plus CIBIC-Plus, Clinician's Interview-Based Impression of Change Plus Caregiver Input; CGI, Clinical Global Impressions; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; EDSS, Expanded Disability Status Scale; HTN, Hypertension; IRLS, International Restless Legs Scale; LGS, Lennox-Gastaut Syndrome; MMSE, Mini Mental State Examination; MS, Multiple Sclerosis; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NYHA, New York Heart Association; OHSA, Orthostatic Hypotension Symptom Assessment; PI-NRS, Pain Intensity Numerical Rating Scale; POS, Partial Onset Seizure; PGTC, Primary Generalized Tonic-Clonic; RLS, Restless Leg Syndrome; SF-MPQ, Short-Form-McGill Pain Questionnaire; SIB, Severe Impairment Battery; TIA, Transient Ischemic Attack; UPDRS, Unified Parkinson's Disease Rating Scale.

with content validity because we evaluate instrument adequacy to measure the concept represented by the labeling claim. It is important to establish content validity before other measurement properties are evaluated.[4]

Additional efforts of this kind to solicit the patients' experience are strongly encouraged and will certainly inform the development of valid and reliable COA tools that are suitable for clinical trial use.

Conclusion

High-quality COAs can provide important information for evaluation of benefits and risks of a new cancer therapy, and FDA continues to encourage exploration of methods to integrate patient-centered outcomes into drug development. Ultimately, a combination of endpoints and outcomes assessments including survival, response rates, and clinician-reported and patient-centered data should lead to a more complete picture of a therapy's impact on neuro-oncology patients. Approval of oncology therapies in the US requires demonstration of direct clinical benefit measured by improvement in how patients "function, feel or survive"[11] or an established surrogate, and the rigorous inclusion of well-developed COAs in neuro-oncology clinical trials is representative of the effort to capture this. While this manuscript concentrates on disease-related function and symptom measures, of equal importance is the patient perspective on the toxicities of oncology therapies. Although further discussion is outside the scope of this manuscript, tools such as the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) are being developed to assess symptomatic adverse events and could be considered for use in future oncology trials with registration intent. In addition to development of COAs *de novo*, the FDA is open to efforts to modify existing instruments used in neuro-oncology or neurology to ensure they are appropriate for use in neuro-oncology clinical trials to demonstrate treatment benefit. Subscales of existing instruments might also be considered, if appropriate for the specific context of use and if prespecified in the clinical trial protocol. We have seen COAs incorporated into oncology trials with increasing frequency to better describe benefits and risks of treatments as they relate to patient-centered outcomes. Our responsibility as regulators, health care providers, and drug developers is to promote efforts to cultivate effective development and thoughtful use of COAs in clinical trials as an important adjunct to standard tumor and survival measures.

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