Glioma patient-reported outcome assessment in clinical care and research: a Response Assessment in Neuro-Oncology collaborative report

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Clinical trials of treatments for high-grade gliomas have traditionally relied on measures of response or time-dependent metrics; however, these endpoints have limitations because they do not characterise the functional or symptomatic effect of the condition on the person. Including clinical outcome assessments, such as patient- reported outcomes (PROs), to determine net clinical benefit of a treatment strategy is needed because of the substantial burden of symptoms and impaired functioning in this patient population. The US National Cancer Institute convened a meeting to review previous recommendations and existing PRO measures of symptoms and function that can be applied to current trials and clinical practice for high-grade gliomas. Measures were assessed for relevance, relationship to disease and therapy, sensitivity to change, psychometric properties, response format, patient acceptability, and use of self-report. The group also relied on patient input including the results of an online survey, a literature review on available clinical outcomes, expert opinion, and alignment with work done by other organisations. A core set of priority constructs was proposed that allows more comprehensive evaluation of therapies and comparison of outcomes among studies, and enhances efforts to improve the measurement of these core clinical outcomes. The proposed set of constructs was then presented to the Society for Neuro-Oncology Response Assessment in Neuro-Oncology Working Group and feedback was solicited.

Introduction

Traditionally, clinical trials of treatments for high-grade gliomas (defined as WHO grade II–IV diffuse gliomas of adulthood) have relied on measures of response such as reduction in tumour size, or time-dependent metrics including progression-free survival and the gold standard of overall survival. Although reduction in tumour size is an important objective endpoint to show antitumour activity, the goal of any therapy is to provide benefit to the patient. Evaluating treatment effects using these endpoints or other metrics can be complemented by assessment of clinical outcomes such as measurement of the functional or symptomatic effect of the condition on the person. Patients want to live longer, but they also want to continue to function as well as possible for as long as possible. Appropriate clinical outcome assessments (COAs) that directly measure how a patient feels or functions can better characterise the net benefit of a treatment strategy.

A clinical outcome is defined as "an outcome that describes or reflects how an individual feels, functions or survives".[1] COAs are an "assessment of a clinical outcome that can be made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment".[2] The four categories of COA measures are patient-reported outcomes (PROs) such as questionnaires on symptoms, functioning, or health-related quality of life (HRQOL); clinician-reported outcomes such as performance scales; observer-reported outcomes such as a questionnaire on observable events or behaviours (eg, vomiting, diarrhoea, and seizures) completed by someone other than the patient or health-care professional (eg, parent reporting for an infant); and performance outcomes—eg, neurocognitive testing or timed walk tests.[2]

PROs are distinct from other types of COAs in that they provide information on concepts only known to the patient, such as fatigue or nausea,[3] and can serve two functions: creating a dialogue between provider and patient to guide clinical care and capturing rigorous clinical outcome trial data. Emerging data from cancer studies show the potential value of incorporating PROs in clinical care, with one study reporting that overall survival was improved for people who monitored their symptoms using an online tool (Symptom Tracking and Reporting).[3] Patients in this study whose symptoms were routinely monitored with a PRO measure were less frequently admitted to an emergency room (34% *vs* 41%; p=0·02) or admitted to hospital (45% *vs* 49%; p=0·08), and remained on chemotherapy longer (mean 8·2 *vs* 6·3 months; p=0·002) compared with standard of care (no use of PROs).[3] These data suggest that monitoring of symptoms might lead to benefits for patients. A user friendly portal for patient–health-care provider engagement is likely to be crucial to successful implementation of a monitoring plan.

For regulatory approval, improvements in symptoms or function should be accompanied by objective evidence of tumour activity to support the benefit of an anticancer therapy. Products that improve symptoms or function in the absence of evidence of direct tumour effects or extended survival are likely to be considered supportive care medication (eg, antiemetics, anticonvulsants), which have a different tolerance for safety than anticancer therapies.

The utility of PRO data can be maximised with standardisation of methods to assess, analyse, interpret, and report results. Initiatives are underway to address

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standardisation of PROs in oncology trials including Recommendation for Interventional Trials in Patient-reported Outcomes (SPIRIT-PRO);[4] Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints (SISAQOL);[5,6] Consolidating Standards of Reporting Trials in Patient Reported Outcomes (CONSORT-PRO);[7,8] and Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN).[9] The work described herein extends the work in oncology described earlier to specifically focus on PROs in the population with malignant glioma, for both evaluation of clinical benefit in therapeutic trials and in clinical care.

Evidence supports that symptoms can interfere with performance of daily life activities in patients with brain tumours, especially in those with high-grade gliomas. For example, patients report inability to work[10,11] and, for some, substantial time spent each day feeling ill and unable to do usual activities.[10,12] Baseline symptoms and the resulting interference with activities of daily life have also been reported to be associated with both progression-free and overall survival,[13] and severity of symptoms at follow-up with recurrence based on neuroimaging.[14] Tracking symptoms and function can inform clinicians and investigators about whether a treatment results in measurable benefits or adverse effects to patients. For example, in a randomised phase 3 study published in 2014 significant worsening in self-reported cognitive symptoms aligned with worsening in objective neurocognitive testing.[15] Studies in other CNS tumours, including ependymoma[16] and brain metastases,[17] have shown symptomatic benefit associated with therapeutic interventions, highlighting the potential use of PROs to measure meaningful outcomes with targeted therapeutic approaches, or when stability or regression of disease occurs.

Although many studies have underscored the importance of including PRO measures, lack of agreement on the optimal constructs and methods in brain tumour clinical trials remains a challenge and limits the implementation and interpretation of these data. The Response Assessment in Neuro-Oncology Patient Reported Outcomes (RANO-PRO) working group, an international, multidisciplinary collaboration, is developing a consistent approach for the use of PRO measures in neuro-oncology clinical trials and practice, and is dedicated to advancing the use of clinical outcome assessment in this patient population.[18] Dirven and colleagues[18] from the RANO-PRO group codified the recommendations for implementation in the neuro-oncology population and Sul and colleagues[19] addressed their use in US Food and Drug Administration (FDA) sponsored trials. These reports encouraged the investigation of existing COA tools used in neuro-oncology to identify elements that might be appropriate to measure specific priority symptoms.[19] In addition, the Jumpstarting Brain Tumor Drug Development (JSBTDD) Clinical Outcomes Workshop (2014) by the National Brain Tumor Society brought together researchers, industry representatives, the FDA, and advocacy organisations and determined key areas for clinical outcome assessment in clinical trials. At the conclusion, capturing concurrent medications, symptoms, and assessment of functioning[20] emerged as priorities, with the acknowledgment that further refinement of this work would be needed.

In response, the Fast Track COA Group, including representatives from RANO, the RANO-PRO working group, the JSBTDD workshop chairs, the FDA, and observers from the European Medicines Agency, was formed with the short-term goal to advance the work completed to date and to establish a core set of symptom and functional constructs as represented in existing PRO measures, for use in clinical care and trials for patients with high-grade gliomas.

Workflow and methods

The Fast Track COA Group built on the work of the JSBTDD workshop and RANO-PRO by evaluating recommended symptom and function constructs in commonly used PRO measures and then refining the identified symptom and function constructs to finalise a core set of constructs for use in high-grade glioma trials. These constructs should inform trial data on safety and efficacy and inform and guide discussions between patients and care providers (see the figure for the work output flow diagram). The JSBTDD workshop included a review of existing literature related to symptoms and function in patients with high-grade glioma,[12] and an online survey of patients and family members on what symptoms they deemed relevant and important, and resulted in consensus recommendations of key symptoms and functions to be considered in further work.[20] Building on these identified symptoms and functions from JSBTDD, the Fast Track COA Group first formed two subgroups around symptoms (Symptom Subgroup) and function (Function Subgroup), focusing on PRO outcomes for these efforts. The Symptom and Function Subgroups relied on patient input including the results of an online survey completed as part of the published JSBTDD guidelines, a literature review on available clinical outcomes, expert opinion, and alignment with work done by other organisations (including the FDA).

Symptom and function constructs were identified in existing PRO measures and were assessed for relevance, relationship to disease and therapy, sensitivity to change, psychometric properties, response format, patient acceptability, and use of self-report by two independent working group members with findings presented and discussed by the working group until consensus were reached. The proposed set of constructs was then presented at the Society for Neuro-Oncology RANO session in November, 2018, and feedback solicited. The final working group recommendations and feedback was incorporated in the discussion on relevant constructs by

working group members at the National Cancer Institute's (NCI's) Neuro-Oncology Branch in the Center for Cancer Research meeting on Nov 20, 2018, which included representatives from the FDA, RANO, the RANO-PRO working group, advocacy organisations, and the NCI. During the meeting, the Fast Track COA Group reviewed, condensed, organised, and finalised the identified constructs and existing measures that can be applied to trials and clinical practice.

Symptom and functional constructs

The JSBTDD identified a broad set of symptom and functional constructs that might be important in patients with brain tumours on the basis of review of the literature, symptoms identified as part of instrument development, and data obtained directly from patients and caregivers related to what led to their diagnosis and what symptoms they would like to have improved. This work identified that as well as monitoring concurrent medications, additional clinical outcomes that could be important in brain tumour trials include seizures; symptoms of headache or pain, aphasia, weakness (paresis or plegia), perceived cognitive function, and mood (depression or anxiety); and key function constructs of physical function, basic activities of daily living, instrumental activities of daily living, cognition (memory, concentration, and executive function), role function, social function, emotional function, neurological function, and overall health status.[12,20] This list was used to inform the current work of the Fast Track COA Group on the basis of the aims and goals outlined earlier.

Several studies have supported the importance of many of these outcomes; one report included identification of core symptoms for inclusion in systemic cancer clinical trials,[21] other studies evaluated core symptoms in patients with brain tumours,[22,23] and a separate project identified key symptoms in patients participating in The North Central Cancer Treatment Group studies.[22] In addition to confirming important constructs and items, these studies supported the relevance of these constructs regardless of whether the patient is currently on active treatment, or their recurrence status or tumour grade.[23] Moreover, these published data show that patients with primary brain tumours report multiple co-occurring symptoms throughout the disease trajectory, even beyond disease progression,[23,24] emphasising the use of symptom reporting in all patients in all phases of disease.

In advance of the November, 2018, workshop, the Symptom and Function Working subgroups reviewed existing instruments for inclusion of the identified constructs. This review included validated scales or items of the most commonly used instruments in neuro-oncology identified by members of the two subgroups: the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire C30 and BN20 brain tumour module (QLQC30)/BN20), SF-36, MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT), Functional Assessment of Cancer Therapy-Brain Tumor (FACT-BR), Functional Assessment of Cancer Therapy Central Nervous System (FACT-CNS), and NCI Patient Reported Outcome of the Common Toxicity Criteria Adverse Events (NCI PRO-CTCAE) as well as symptom or function scales or items in item libraries (EORTC and MDASI) or Patient Reported Outcomes Measurement System (PROMIS) and quality of life in neurologic disorders. The considered symptoms and functions are shown in the appendix (pp 1–3). Coverage of the identified constructs by these measures, sensitivity to change, and proximity to disease were considered in formulating the final list of recommended key constructs for inclusion in clinical trials and practice.

See Online for appendix

To further narrow this broader set of outcomes to arrive at a core set, possible relevant symptoms were discussed by the Fast Track Symptom Subgroup. For example, pain was identified as adequate to address both pain and headache, whereas mood, although considered clinically important, was removed as a core trial outcome measure because of multiple confounding factors. Specifically, mood alteration might be related to the disease, but also can be a pre-existing condition or be affected by non-drug contributors making mood alteration less sensitive to disease progression or response. Subsequently, this group selected the following symptom constructs for further discussion during the Consensus Meeting in November, 2018: pain, weakness (loss of strength) and walking, or both, fatigue, difficulty speaking (aphasia), perceived cognition (memory and concentration), and seizures. Additionally, a recommendation was made for

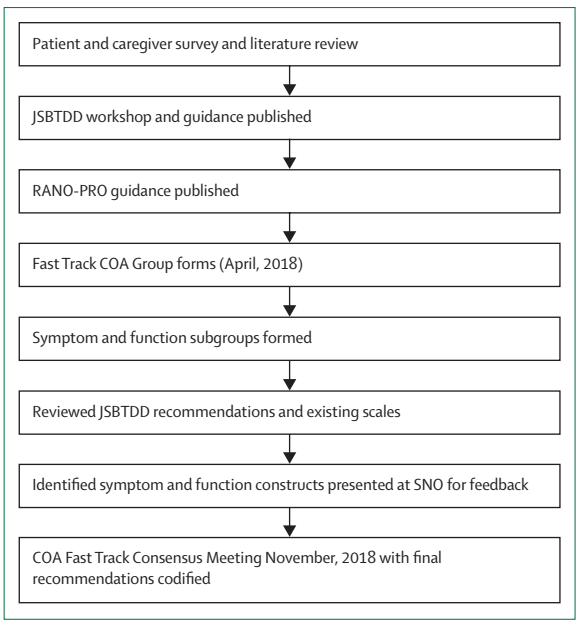

Figure: **COA Fast Track output flow diagram**
COA=Clinical Outcome Assessments. JSBTDD= Jumpstarting Brain Tumor Drug Development. RANO-PRO=Response Assessment in Neuro-oncology Patient Reported Outcomes. SNO=Society of Neuro-Oncology.

***Panel*: Patient-reported core symptoms and functions for inclusion in high-grade glioma trials and care**

Symptoms

Pain
An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage

Difficulty communicating
Subjective report of difficulty with the ability to express oneself in speech or writing, or understand speech

Perceived cognition
Subjective alteration in cognitive processes including executive function, memory, or concentration

Seizures
A physical convulsion, minor physical signs, thought disturbances, or a combination of symptoms that is brief and often self-limited resulting from abnormal electrical activity in the brain

Symptomatic adverse events
Symptomatic side-effects measured by self-report that are expected on the basis of known clinical and mechanistic understanding of the therapy

Functions

Physical functioning (including weakness or walking)
The ability to do basic daily activities that require physical effort and should include walking or apparent weakness

Role functioning
The ability to work and do or participate in leisure or social activities

assessment of a selection of the most relevant treatment-related symptomatic adverse events that would be expected to occur on the basis of existing clinical safety data from the agent of interest.

Concurrently with the Symptom Subgroup, the Function Subgroup discussed possibly relevant functions that could be further narrowed for inclusion in the core set of outcomes. The Subgroup identified the following function constructs for further consideration: physical functioning to include walking, role functioning including work at home, and social functioning including activities and communication. Other criteria include core interference in daily activities, such as general activity, ability to work, mood, memory or ability to concentrate, relationships with others, and enjoyment of life. These constructs were the basis of the workshop discussion in November, 2018.

Consensus meeting and final recommendations

During the November meeting, symptom and function constructs for COAs were further narrowed on the basis of consideration of symptom prevalence and frequency, effects of symptoms on functional status, disease stage at occurrence, differences between average and exceptional responders, how well a symptom can be captured with PRO measures, potential for confounding by non-drug or non-disease effects, and properties of the considered instruments. Logistically, the discussion focused on how to account for differences in the ways treatment is administered among institutions; the disadvantages of only collecting a snapshot of a patient's experience rather than measurement over time; the challenges of gathering data on patient-reported effects of symptoms on function versus actual measures of function; feasibility of data collection, including burden on patients, tools for measurement, and duration; and appropriate scales for measures.

Symptoms

The Fast Track COA Group proposed including the following symptoms as core symptom constructs for this population: pain, difficulty communicating, perceived cognition, and seizure occurrence (see the panel for a definition of each of these symptom constructs). The Group also followed the recommendation to include relevant treatment-related symptomatic adverse events related to the prescribed treatment or investigational drug. Patient burden can be reduced by focusing on the subset of the highest frequency or most bothersome symptoms and avoiding overlapping terms. We summarise the discussion of these and other symptoms under consideration.

Pain

Pain has many dimensions and is an important symptom to track. Follow-up questioning can focus on the location of pain (eg, headache or bodily pain). The working group agreed to include pain as a construct and noted that there are existing pain scales or items that can be used.

Weakness

Patients are not likely to describe themselves as experiencing weakness; rather, they are likely to describe specific dysfunction that could be classified as weakness, such as inability to lift an item. The working group considered including weakness as a component of physical functioning rather than as a separate symptom construct for COA purposes.

Fatigue

Fatigue is a challenging symptom to assess because it is multidimensional and can be related to treatment, as well as the disease itself. Although fatigue can be a large component of disease symptoms for haematological disorders or widely metastatic solid tumour malignancies, it might be less disease-related in the more localised brain tumour context. Thus, for purposes of drug development and regulatory approval in the brain tumour context, the working group concluded that considering fatigue as a treatment-specific toxicity rather

than as a core symptom construct might be best for COA purposes.

Perceived cognition

Testing of cognitive functioning can be lengthy and burdensome for patients. Yet changes in cognition are important symptoms for patients. Changes in perceived cognition (memory and concentration) have been shown to occur throughout the disease trajectory and to be sensitive to survival and between-arm treatment differences. Therefore, the group recommended retaining perceived cognition as a construct, recognising that the effect might overlap with several aspects of functioning.

Seizures

Although not strictly a symptom or functional measure, seizures are a very important clinical event for patients with brain tumours, underscoring the need to collect data on seizure frequency and severity. However, data collection can be complicated as seizures can be variable, including marked differences between focal and generalised seizures. Even within this classification, the frequency, intensity, and duration of the seizure might be very different between episodes and between patients, making classification and subsequent determination of the interference on patient functioning and HRQOL challenging. Yet tumour treatment has a correlation with seizures; therefore, gathering data about the frequency and severity of seizures is important. Severity has the greatest effect on patients and is the most important variable to assess. Frequency is not as informative, but the occurrence of a seizure should be captured as an event. To date, there is no validated tool that would be useful for capturing seizure data in patients with glioma, but one tool is in development.[25] Although the working group elected to retain the event of seizure and seizure severity as a construct, there might be some trials in which collecting additional data on timing or frequency would be important.

Aphasia

Patients report concerns related to language function, but it is a noisy variable (a measurement that can be influenced by other factors) and is very specific to the location of the tumour. The working group recommended that language function should be included as a factor in difficulty communicating, in both understanding and speaking. Including language function under the broader category of communication difficulties is more likely to yield meaningful data, as patients are more likely to report difficulty reading, concentrating, or understanding television than aphasia. The need to distinguish aphasia from dysarthria was discussed and concerns were expressed about the consequences of too broad a construct. The working group recommended searching existing validated tools (eg, EORTC, MDASI, and FACT) to determine whether any questions can be adopted for use in glioma trials. However, picking one question from a set can be misleading if the entire set is intended to assess a symptom or function.

Relevant symptomatic adverse events

In clinical trials, a subset of symptomatic side-effects to assess is selected on the basis of expected toxicities from both investigational and control groups, which differ according to the treatment approach used. Expected adverse events should be selected on the basis of preclinical data or the drug's mechanism of action and available clinical data while acknowledging the possibility of some overlap with symptoms related to disease. The most common or bothersome symptoms should be prioritised, and a free-text question should be included to ensure important symptoms are not missed in the item selection process.[25] The NCI's PRO-CTCAE item library was designed specifically for the purpose of assessing symptomatic adverse events; however, other item libraries from the EORTC and Functional Assessment of Chronic Illness Therapy systems might be considered.

Functioning

The working group proposed including physical functioning and role functioning as core functional constructs (panel). We summarise the discussion of these constructs.

Physical functioning to include walking

The working group concluded that physical functioning should be defined as the ability to do daily activities that require physical effort. Further, distinguishing the duration of time with physical functioning deficits in later stages of disease progression would be useful. Finally, the group concluded that walking or apparent weakness (eg, carrying a suitcase or dressing oneself) should be included as examples of the physical functioning construct. The Barthel scale, or Barthel index of activities of daily living, is an ordinal scale used to measure performance in activities of daily living, but is a clinician-reported physical functioning measure. In addition, the EORTC QLQC30 and MDASI-BT questionnaire and item library includes a physical functioning scale, as does the PROMIS item library. All instruments can be considered for assessing aspects of physical functioning. For regulatory purposes, physical function should be measured using a well defined scale in which all questions are measuring differing levels of physical function—eg, EORTC and PROMIS.

Patients in early stages of disease might not have substantial deficits in physical functioning and activities of daily living, and older patients might have higher baseline deficits at disease onset. Further, sensitivity to maintenance of function or changes in high-level functioning is needed because existing tools do not measure physical function at its highest levels. Patients with high-grade gliomas in the early stages of disease

Search strategy and selection criteria

No formal literature search was done; the Symptom Subgroup and Function Subgroup of the Fast Track Clinical Outcome Assessments Group reviewed specific symptoms and functions identified from the previous recommendations by Helfer and colleagues, 2016, and published literature review by Armstrong and colleagues, 2016. Additional literature and proposed clinical outcomes for high-grade gliomas published from 2016 to 2018 was reviewed by searching PubMed using the terms "clinical outcomes" and "high grade glioma".

might not have substantial deficits in physical functioning or activities of daily living and might in fact have a high level of functioning. This functioning might vary with age at diagnosis and underlying comorbid conditions. Because existing instruments do not measure the highest levels of physical functioning, the opportunity to capture stable function or changes in higher level functioning might be missed. Wearable devices provide an opportunity for collecting data related to physical functioning. The working group suggested that questions from existing scales can be extracted to assess physical functioning, noting that too few or too many questions can alter the sensitivity. Using a time-to-deterioration endpoint can be used when baseline function is high and unlikely to be improved.

Role and social functioning

Most individuals with high-grade gliomas have symptoms or deficits that prevent their return to work. Further, patients might spend a substantial portion of their lives feeling ill, unable to do usual activities, or meet occupational, social, financial, and family obligations. These deficits in role functioning, including social function, are important to track. The working group discussed role functioning as an overarching concept that refers to the ability to work or participate in leisure or social activities (ie, social functioning).

General recommendations

Going forward, to improve feasibility of data collection the optimum number of questions to be asked and input guidelines should be determined. Although experts in the field have their preferred instruments, the consensus was that decisions regarding the recommended scale to be used should be based on the instrument that is most fit for purpose in the context of the clinical trial or in clinical practice. The working group recommends several available measures that can be used, recognising that different institutions are likely to use different tools, but that measurement properties of the tools should be carefully considered. Investigators should consult with the FDA or other regulatory authorities to ensure that the measurement tools selected are appropriate to support the stated objectives of clinical trials.

Next steps: application of COAs in high-grade glioma trials

The goal of this Fast Track COA project is to develop a codified list of core symptoms and functional endpoints that could be used across high-grade glioma trials to characterise the clinical effects of the disease and its treatment. Several instruments can be used for this purpose. We have discussed several available tools including PRO-CTCAE and PROMIS, and have provided examples from two commonly used scales in neuro-oncology (MDASI-BT and EORTC QLQC30/BN20) and their recently developed item banks. The next steps are to establish how to align these constructs with the primary outcomes of trials (eg, time to deterioration, survival, and recurrence). Optimal frequency of assessment must also be established. For each construct, the wording of the questions and analytical methods must be decided on and standardised, if not already done so. Strategies for introducing these constructs to clinical trial cooperative groups and sponsors will be necessary. Finally, identification of key constructs for assessment in the paediatric population is warranted to provide an integrated and consistent approach across populations.

Conclusions

Including rigorous COAs, such as PROs, in neuro-oncology clinical care and clinical trials to characterise the net clinical benefit of a treatment strategy is especially important because of the substantial burden of symptoms and impaired functioning in this patient population. Although these signs and symptoms often lead to the initial diagnosis, they might persist or fluctuate through the course of the disease and its treatment, and can be associated with functional limitations. Importantly, although later development of signs and symptoms might precede or predict tumour recurrence, the treatment itself can also generate signs and symptoms, complicating assessment and negatively affecting functioning and life quality. These core concepts, including symptoms of pain, difficulty communicating, perceived cognition, seizures, and symptomatic adverse events related to the specific therapy, physical functioning (including weakness or walking), and role functioning, represent the priority constructs for patient care and treatment evaluation in this patient population throughout the disease trajectory and particularly beyond progression if the study endpoint is overall survival. The intent of the working group is to move toward the development of standardised COAs for the priority symptoms, signs, and functions so that ultimately drug and other treatment product development can better pursue a survival endpoint goal, as well as the patient-centred endpoints that patients with brain tumours want. By standardising the priority constructs for this population, efforts to track the effect of innovative care strategies and evaluate the clinical effect of therapies can occur, allowing for comparison among studies and enhancing efforts directed to improve these core constructs.

Contributors

All authors contributed to the analysis and interpretation of reviewed data, contributed to the writing of the manuscript, and reviewed and approved the final version.

Declaration of interests

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References

1 Basch E, Geoghegan C, Coons SJ, et al. Patient-reported outcomes in cancer drug development and US regulatory review: perspectives from industry, the Food and Drug Administration, and the patient. *JAMA Oncol* 2015; **1:** 375–79.

2 BEST. (Biomarkers, EndpointS, and other Tools) Resource. Silver Spring, MD: US Food and Drug Administration, National Institutes of Health, 2016.

3 Basch E, Deal AM, Kris MG, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. *J Clin Oncol* 2016; **34:** 557–65.

4 Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO extension. *JAMA* 2018; **319:** 483–94.

5 Coens C, Madeline Pe M, Dueck AC, et al. International standards for the analysis of quality of life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. *Lancet Oncol* 2020; **21:** e83–96

6 Bottomley A, Pe M, Sloan J, et al. Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. *Lancet Oncol* 2016; **17:** e510–14.

7 Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013; **309:** 814–22.

8 Mercieca-Bebber R, Rouette J, Calvert M, et al. Preliminary evidence on the uptake, use and benefits of the CONSORT-PRO extension. *Qual Life Res* 2017; **26:** 1427–37.

9 Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol* 2010; **63:** 737–45.

10 Bradley S, Sherwood PR, Donovan HS, et al. I could lose everything: understanding the cost of a brain tumor. *J Neurooncol* 2007; **85:** 329–38.

11 Sherwood PR, Donovan HS, Given CW, et al. Predictors of employment and lost hours from work in cancer caregivers. *Psychooncology* 2008; **17:** 598–605.

12 Armstrong TS, Bishof AM, Brown PD, Klein M, Taphoorn MJ, Theodore-Oklota C. Determining priority signs and symptoms for use as clinical outcomes assessments in trials including patients with malignant gliomas: Panel 1 Report. *Neuro-oncol* 2016; **18** (suppl 2)**:** ii1–12.

13 Armstrong TS, Wefel JS, Wang M, et al. Net clinical benefit analysis of radiation therapy oncology group 0525: a phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma. *J Clin Oncol* 2013; **31:** 4076–84.

14 Armstrong TS, Vera-Bolanos E, Gning I, et al. The impact of symptom interference using the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) on prediction of recurrence in primary brain tumor patients. *Cancer* 2011; **117:** 3222–28.

15 Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 2014; **370:** 699–708.

16 Armstrong T, Yuan Y, Wu J, et al. RARE-24. objective response and clinical benefit in recurrent ependymoma in adults: final report of CERN 08-02: a phase 2 study of dose-dense temozolomide and lapatinib. *Neuro Oncol* 2018; **20:** vi241.

17 Gondi V, Pugh S, Brown PD, et al. NCOG-01: Preservation of neurocognitive function (NCF) with hippocampal avoidance during whole-brain radiotherapy (WBRT) for brain metastases: preliminary results of phase III trial NRG oncology CC001. *Neuro Oncol* 2018; **20** (suppl 6)**:** vi172.

18 Dirven L, Armstrong TS, Blakeley JO, et al. Working plan for the use of patient-reported outcome measures in adults with brain tumours: a Response Assessment in Neuro-Oncology (RANO) initiative. *Lancet Oncol* 2018; **19:** e173–80.

19 Sul J, Kluetz PG, Papadopoulos EJ, Keegan P. Clinical outcome assessments in neuro-oncology: a regulatory perspective. *Neurooncol Pract* 2016; **3:** 4–9.

20 Helfer JL, Wen PY, Blakeley J, Gilbert MR, Armstrong TS. Report of the Jumpstarting Brain Tumor Drug Development Coalition and FDA clinical trials clinical outcome assessment endpoints workshop (October 15, 2014, Bethesda MD). *Neuro Oncol* 2016; **18** (suppl 2)**:** ii26–36.

21 Reeve BB, Mitchell SA, Dueck AC, et al. Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. *J Natl Cancer Inst* 2014; **106:** dju129.

22 Lai JS, Jensen SE, Beaumont JL, et al. Development of a symptom index for patients with primary brain tumors. *Value Health* 2014; **17:** 62–69.

23 Armstrong TS, Vera-Bolanos E, Acquaye AA, Gilbert MR, Ladha H, Mendoza T. The symptom burden of primary brain tumors: evidence for a core set of tumor- and treatment-related symptoms. *Neuro Oncol* 2016; **18:** 252–60.

24 Armstrong TS. Survivorship in neuro-oncology. *Neuro Oncol* 2018; **20** (suppl 7)**:** vii4–vii5.

25 Chung AE, Shoenbill K, Mitchell SA, et al. Patient free text reporting of symptomatic adverse events in cancer clinical research using the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Am Med Inform Assoc* 2019; **26:** 276–85.