Working plan for the use of patient-reported outcome measures in adults with brain tumours: a Response Assessment in Neuro-Oncology (RANO) initiative

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The Response Assessment in Neuro-Oncology-Patient-Reported Outcome (RANO-PRO) working group is an international multidisciplinary collaboration that provides guidance on the use of patient-reported outcome (PRO) measures in clinical trials and practice for adult patients with brain tumours. Findings from both PROs and traditional outcome measures, such as survival, and clinical or radiological response, are essential to inform the research community, policy makers, physicians, and patients in the treatment decision-making process. Previous initiatives in oncology have focused on guidelines concerning the collection, analysis, interpretation, and reporting of PRO data. However, we recommend the application of appropriate PRO instruments, with respect to its content and measurement properties (ie, research question, content validity, and other measurement properties), in brain tumour research. PROs should be well defined and reliable to generate high-quality evidence, and our recommendations on the use of specific PRO measures could help to improve the quality of PRO evidence derived from neuro-oncological studies, and might add a new dimension in how the value of therapeutics is assessed in patients with brain tumours. In this Policy Review, we present the RANO-PRO working plan for the use of PROs in adults with brain tumours.

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Introduction

The goal of therapeutics is to improve people's lives who are suffering from a disease. The traditional metric that is used in oncology to determine this goal is prolonged survival or prolonged time to disease progression. However, patients and the regulatory community have also increasingly emphasised the need for therapies to show improvement in patient function and health-related quality of life. Patient-reported outcomes (PROs) are important measurements for quantifying symptoms, function, or health-related quality of life. The US Food and Drug Administration (FDA) and the European Medicines Agency have defined a PRO as a measurement directly reported by patients[1,2] that reflects the patients' perception of a disease and its treatment.[2] PROs can be measured either through a self-report or an interview (where the interviewer only reports the responses of the patient). PRO measures might cover symptoms, functioning, and health-related quality of life, and topics such as adherence to treatment or satisfaction with care. PROs are distinctive from other types of patient-centred outcome measures, such as neurological functioning, because they can capture concepts that are only known to the patient, such as nausea, fatigue, or pain severity, as well as mental health aspects, including distress and future uncertainty.[3] The FDA has defined four types of patient-centred outcome measures, which are collectively called clinical outcome assessments (COAs):[4] including PRO measures, clinician-reported outcome measures, observer-reported outcome measures, and performance outcome measures (panel). Unlike PRO measures, clinician-reported outcome measures are based on a report that comes from a health-care professional, whereas observer-reported outcome measures are based on reports from someone other than the patient or health-care professional (eg, a relative). In some patients, the same concept can be measured with different COAs—eg, cognitive symptoms.

COAs can provide additional information about the beneficial and adverse effects of a new treatment strategy, adding context to information on radiological response assessed on CT or MRI, clinical response based on a physical examination, and progression-free or overall survival.[5,6] In clinical trials, information from all sources can establish the net clinical benefit of a new treatment strategy, in which the effect of treatment on both patient-centred and tumour-centred outcome measures should be weighed. This information can inform regulatory agencies in their decision to approve an experimental drug for use beyond clinical trials.[7,8] In clinical practice, information from PROs can be applied to shared decision making in which patients, their primary caregiver, and their physician make a treatment decision based on the best available evidence.[9] Results of COAs assessed over time might also be applied in clinical practice for needs assessment, and to monitor a patient's symptoms or functioning during the disease trajectory.[10] With treatment effects monitored, opportunities for symptom management can be identified, so that patients can be referred to another health-care professional (eg, a patient with cognitive difficulties is referred to a neuropsychologist), or to identify potential warning signs that might lead to the intiation of palliative care. In one study, the integration of PROs into routine clinical care was even associated with improved survival.[11]

Determinants of quality of PRO evidence

Findings from PROs and other patient-centred outcomes, in conjunction with traditional outcome measures such as survival, and clinical and radiological response, are crucial

Panel: Definition of clinical outcome assessment and each outcome subtype

Clinical outcome assessment (COA)
A COA is any assessment potentially influenced by human choices, judgment, or motivation. It might support either direct or indirect evidence of treatment benefit. Unlike biomarkers that rely completely on an automated process or algorithm, COAs depend on implementation, interpretation, and reporting from a patient, clinician, or observer.

Patient-reported outcome (PRO) measures
A PRO is a measurement based on a report from the patient (ie, study participant) about the status of the patient's health condition, without amendment or interpretation of the patient's report by a clinician, or anyone else. It can be measured by self-report or interview, provided the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient (eg, pain severity or nausea) can only be measured by PRO measures. PROs assess the patient's perspective on functioning or activities that might also be observable by others.

Clinician-reported outcome (ClinRO) measures
A ClinRO is based on a report from a trained health-care professional after observation of a patient's health condition. These measures involve a clinical judgment or interpretation of observable signs, behaviours, or other physical manifestations thought to be related to a disease or condition. They cannot directly assess symptoms that are known only to the patient (eg, pain intensity).

Observer-reported outcome (ObsRO) measures
An ObsRO is a measurement based on an observation by someone other than the patient or health-care professional—eg, parent, spouse, or other non-clinical caregiver—who can regularly observe and report on a specific aspect of the patient's health. An ObsRO measure does not include medical judgment or interpretation. For patients unable to respond for themselves (eg, infants or cognitively impaired patients), we encourage observer reports that include only events or behaviours that can be observed—eg, observers cannot validly report an infant's pain intensity (a symptom), but can report infant behaviour thought to be caused by pain (eg, crying).

Performance outcome (PerfO) measures
A PerfO measurement is based on a task performed by a patient according to instructions administered by a health-care professional—eg, gait speed, memory recall, or other cognitive tests. It requires patient cooperation and motivation.

Definitions provided by the Clinical Outcome Assessment Program, US Food and Drug Administration.[4]

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to inform the research community, policy makers, physicians, and patients in treatment decision making. Therefore, PROs should be well defined and reliable measurements[12] to be of value and to generate high-quality evidence. For high-quality evidence to be generated, several aspects need to be considered (figure 1). One aspect is that the selection of a PRO for a clinical study should coincide with the research question. PROs can be primary, secondary, or exploratory outcome measures. For example, the primary objective of a study could be to improve symptoms or patient functioning, for which a PRO is suitable; a PRO can also be used as a secondary endpoint to support the clinical benefit of a trial in which survival is the primary endpoint; finally, PRO data can be supportive, to better describe the patients' experience in clinical trials including toxicity and tolerability assessments in dose-finding studies. Therefore, selection of an appropriate PRO measure that reflects the goal of

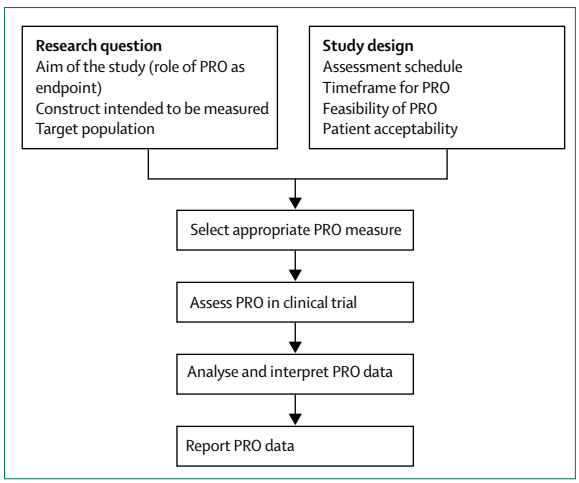

Figure 1: **Aspects relevant for the generation of high-quality PRO evidence**
PRO=patient-reported outcome.

the study is required. Moreover, measurement of the intended construct is important, for which different types of PROs are suitable—for example, a specific symptom (eg, fatigue, depression, or anxiety) or multiple symptoms, functioning in daily life, or the perceived health-related quality of life. The study design is another important aspect, with respect to the assessment schedule. If the objective of a study is to assess the immediate toxic effects of a treatment, timing of the measurements should be different from that of a study that assesses the impact of a treatment strategy long-term.[13,14] An important consideration then is the timeframe under consideration for the selected PRO—eg, covering the past week or the past month. Some toxicities might not be captured if the time period covered by the PRO measurement is too short or too long. Statistical analysis of PRO data is also a crucial step in generating reliable results.[15] Different analytical approaches could lead to conflicting results. For example, results of a cross-sectional analysis might favour treatment B over treatment A, whereas a longitudinal analysis might not favour either treatment option. Even when appropriate statistical methods have been applied, interpretation of the results is key to draw the correct conclusions. Looking at statistically significant differences only might result in a different conclusion compared with looking at both statistically and clinically relevant differences. Another challenge in data interpretation is when multiple tools are used that measure the same outcome, but the results of each tool are conflicting. A final important aspect is the quality of reporting of the results. Key aspects of the chosen method, statistical approach, results (eg, baseline scores, and description of missing data), and interpretation (eg, clinical significance and generalisability of results) should be reported adequately to facilitate the critical appraisal of study results.[16]

To enhance the generation of high-quality PRO evidence, several efforts in the field of oncology have

been established, some of which are ongoing (table). For example, the Standard Protocol Items: Recommendation for Interventional Trials in Patient Reported Outcomes initiative aims to provide guidance on what specific PRO protocol items should be included in trial protocols.[17] The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data consortium aims to develop a guideline and best practices for standardising the analysis and interpretation of PRO endpoints in cancer clinical trials.[15] Recommendations for the standardisation of the level of PRO reporting were introduced by the International Society for Quality of Life Research, Consolidated Standards of Reporting Trials in Patient Reported Outcomes.[18,19] These efforts will result in international standards for the collection, analysis, interpretation, and reporting of PRO data, and will contribute to high-quality PRO evidence. The FDA has also published guidance[7] for industry that describes optimal PRO development, trial design, and analysis of PRO data, which can be specifically used to support oncology labelling claims.[7] Although the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) initiative developed standards for the assessment of the methodological quality of studies reporting on the measurment properties of health measurement instruments,[20] for many PRO tools this factor has not been investigated properly. However, high-quality PRO tools should be appropriate in terms of content and measurement properties.

Use of PROs in patients with brain tumours

Patients with brain tumours have a different course of disease than other cancer patients because their cancer directly affects their neurological function. Although patients with brain tumours report general cancer-related symptoms, such as fatigue, drowsiness, and constipation, they report disease-specific symptoms such as seizures, motor dysfunction, cognitive deficits, and symptoms caused by elevated intracranial pressure (eg, headaches) more frequently than do patients with cancer not of the CNS.[21–28] This difference in symptoms means that PRO instruments for those patients with non-CNS cancer might not be appropriate or sufficient for patients with brain tumours because they might not cover all relevant issues.

Standard treatment of brain tumours might comprise surgery, radiotherapy, or chemotherapy depending on the type and location of the tumour.[29–36] However, new treatment opportunities are being explored, and include targeted treatment and immunotherapy.[37–41] Despite large variation in the type and location of a tumour, treatments, and prognosis, all patients with brain tumours might suffer from impaired functioning.

Poor prognosis of patients with glioblastoma, primary CNS lymphoma, or brain metastases means that brain tumours are a good example of a disease in which not only prolonged (progression-free) survival is important, but also maintenance or improvement of patient function during the entire disease trajectory. Therefore, use of patient-centred outcomes has increased in the field of brain cancer research during the past decade. Although patients with low-grade glioma or meningioma might survive for many years, they might have late effects (ie, side-effects that become apparent months or years after treatment has ended) caused by antitumour treatment (eg, radiotherapy), or supportive treatment, such as corticosteroids and antiepileptic drugs. These late effects include fatigue, peripheral neuropathy, muscle weakness, cognitive dysfunction, and radiation-induced secondary malignancies.[42–46] These late effects might also affect the patient's functioning in daily life. During the past few years, the focus has shifted towards the assessment of functioning in patients who are long-term cancer survivors.[42,47]

Several PRO measures are available in neuro-oncology to measure the short-term and long-term effects of a tumour and its treatment. These PRO measures might be one dimensional (ie, they only measure one single aspect, such as symptoms of depression or anxiety) or multidimensional (ie, they measure multiple aspects, such as health-related quality of life). Frequently, the MD Anderson Symptom Inventory Brain Tumor Module[48] or Hospital Anxiety and Depression Scale[49] is

	Aim
Standard Protocol Items: Recommendation for Interventional Trials in Patient-Reported Outcomes (SPIRIT-PRO)[17]	To provide guidance on the specific PRO protocol items that should be included in trial protocols
Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints (SISAQOL)[15]	To develop a guideline of best practice for standardising the analysis and interpretation of PROs in cancer clinical trials
International Society for Quality of Life Research (ISOQOL); COnsolidated Standards of Reporting Trials in Patient Reported Outcomes (CONSORT-PRO)[18,19]	To standardise the level of PRO reporting
COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN)[20]	To develop standards for the assessment of method quality in studies about the measurement properties of health measurement instruments, including PRO measures
US Food and Drug Administration, Guidance for industry patient-reported outcome measures: use in medical product development to support labelling claims[7]	To provide guidance on the optimal PRO development, trial design, and analysis of PRO data, which can specifically support oncology labelling claims

PRO=patient-reported outcome.

Table: **Initiatives that aim to standardise practice for PROs in oncology**

used to measure patient-reported symptoms, whereas cognitive complaints can be assessed with the MOS Cognitive Functioning Scale.[50] Basic activities of daily living are often measured with the Barthel Index,[51] whereas instrumental activities of daily living (ie, cognitively more complex activities such as food preparation) tend to be measured with the Lawton Instrumental Activities of Daily Living Scale.[52] Patients with brain tumours often have cognitive deficits, which makes it more difficult for them to perform instrumental activities of daily living (which are cognitively more complex activities) when compared with basic activities (eg, getting dressed). Health-related quality of life is frequently assessed using the European Organization of Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30[53] or the Functional Assessment of Cancer Treatment.[54] These core questionnaires can be supplemented with tumour-specific questionnaires, which are specifically developed for patients with brain tumours.[55,56]

Although particular measures are often used in brain tumour research, not all are specifically developed for or validated in patients with brain tumours (eg, the Barthel Index was originally developed for patients undergoing rehabilitation after a stroke, and the EORTC Quality of Life Questionnaire BN20 was only validated for patients with glioma, not for other types of brain tumour). Additionally, whether or not current PROs have high content validity is unclear—ie, it is uncertain whether the instruments correspond with the construct intended to be measured with respect to relevance and comprehensiveness.[20] For example, the EORTC Quality of Life Questionnaire BN20 was developed in 1996 for patients with brain tumours,[13] with a field validation in patients with glioma in 2010.[55] With the introduction of new treatments, such as targeted treatment and immunotherapy, new toxicities have arisen (eg, eye and skin problems).[39,40] The Quality of Life Questionnaire BN20 insufficiently covers domains that are affected by current and new treatment options, as well as issues such as behavioural and personality changes, warranting a revision of this questionnaire. Moreover, most PRO tools are questionnaires consisting of a fixed set of items. However, such questionnaires might not meet the demands of academic researchers and industry because they might fail to detect important and new adverse events that are associated with new treatments. Therefore, a more flexible approach, in which a standard set of items could be complemented with validated scales, might be a solution to this problem.[57]

Response Assessment in Neuro-Oncology-PRO initiative

The Response Assessment in Neuro-Oncology (RANO)-PRO working group is a multidisciplinary collaboration that aims to provide international guidance on the use of PRO measures in clinical trials and clinical practice for adult patients with brain tumours. The group comprises key physicians and researchers in the field of neuro-oncology, and liaises with other RANO working groups to ensure implementation of appropriate PRO measures that are in accordance with other RANO guidelines in future brain tumour research. Initiatives such as the Standard Protocol Items: Recommendation for Interventional Trials in Patient-Reported Outcomes (SPIRIT-PRO), Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints (SISAQOL), and CONsolidated Standards of Reporting Trials in Patient Reported Outcomes (CONSORT-PRO; table) result in international standards for the collection, analysis, interpretation, and reporting of PRO data, enhancing the quality of PRO evidence, which is applicable to the whole field of oncology, including neuro-oncology. However, PRO instruments should be of high quality both in terms of relevance (content validity) for patients with brain tumours, and other measurement properties. In conjunction, these different initiatives might help to improve PRO evidence derived from neuro-oncological studies.

Since no extensive review has been done in this setting before, the PRO measures that have been used in brain tumour research until now are not well known, and it is unknown whether these measures exhibit good measurement properties, or whether they show relevance and comprehensiveness that are specific for patients with brain tumours. Additionally, more guidance is needed on the selection and collection of PROs for each specific study design. Recommendations to enhance several of these problems within the field of neuro-oncology have been previously propagated by the Jumpstarting Brain Tumor Drug Development Coalition and FDA clinical trials clinical outcome assessment endpoints workshop.[12] Outcomes from this workshop included identification of priority signs and symptoms,[58] review of COA properties,[59] and consideration for trial design with COAs.[60] This work could serve as a starting point for further guidelines in neuro-oncology. Moreover, from a regulatory perspective, high-quality PROs in neuro-oncological clinical trials can provide important information for the assessment of benefits and risks of a new treatment, and regulators therefore promote an approach to assess or develop appropriate tools.[8] The position of the FDA on the use of COAs in clinical trials is outlined in the report published in 2016,[8] including the improvement in how patients function, feel, or survive, which are necessary factors for a product's approval. The recommendations of the FDA encourage disease-related function and symptom measures, consideration of the impact of therapeutic toxicity, and the use of COAs early on in the drug development process.

The goal of the RANO-PRO initiative is to provide guidance on the use of patient-reported outcomes that are specific to neuro-oncology. This initiative will also result in suggestions for the revision of existing PRO

measures in neuro-oncology and the development of new PRO measures where appropriate.

RANO-PRO working plan

To achieve the aim proposed by the RANO-PRO working group, a working plan has been set up (figure 2). The first step would be to provide an overview of the guidelines of previous initiatives on the collection, analysis, interpretation, and reporting of PRO data, which are also applicable to the field of neuro-oncology. Gaps should be identified and completed with expert opinion from members of the working group, taking into account the recommendations that resulted from the Jumpstarting Brain Tumor Drug Development Coalition and the FDA clinical trials clinical outcome assessment endpoints workshop.[12] Recommendations might include information about the selection and collection (including feasibility and patient acceptability) of PROs, with respect to the research question and study design. Other RANO working groups (eg, RANO epilepsy, RANO Neurologic Assessment in Neuro-Oncology, RANO brain metastases, and RANO corticosteroids) will be consulted in the process to ensure that their specific needs are met with respect to the incorporation of PROs.

The second step would be to identify what PRO measures have been applied in brain tumour studies so far. As mentioned, several PRO measures are already used frequently (eg, MD Anderson Symptom Inventory Brain Tumor Module, Functional Assessment of Cancer Treatment-Br, EORTC Quality of Life Questionnaire C30 and BN20, and the Barthel Index), but other instruments that are both relevant and of high methodological quality might exist and should be included. Therefore, a systematic literature review following PRISMA guidelines will be done to identify all PRO measures used in studies of patients with brain tumours.[61] The review completed during the second step will focus on all types of studies (ie, randomised controlled trials, phase 1 and 2 trials, natural history studies, symptom management studies, and studies describing PROs in daily clinical practice) in which a PRO instrument assesses symptoms, patient function, or health-related quality of life in patients with glioma, primary CNS lymphoma, meningioma, or brain metastases.

The third step would be to establish the content validity of the existing PRO measures identified in the second step. Are all important aspects of functioning and health for patients with brain tumours covered by these instruments? In other words, is a PRO available for each relevant aspect? The assessment of the coverage of each PRO instrument is also important to consider. Do the items in a specific PRO cover the domains that it is intended to measure, such as fatigue (one-dimensional) or health-related quality of life (multidimensional)? This information would facilitate the choice for a specific PRO instrument. To establish the content validity of the existing PRO measures, we will use the framework of the

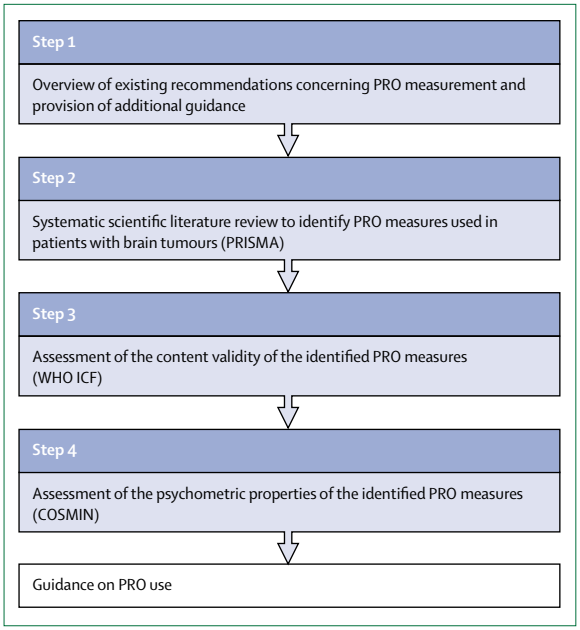

Figure 2: **Schematic representation of the Response Assessment in Neuro-Oncology-Patient-Reported Outcome working plan**
PRO=patient-reported outcome. PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses. WHO ICF=WHO International Classification of Functioning, Disability and Health. COSMIN=COnsensus-based Standards for the Selection of Health Measurement Instruments.

WHO International Classification of Functioning, Disability and Health (ICF).[62] This framework refers to a patient's functioning at three distinct levels. The most basic level is a patient's impairment in body function, such as muscle weakness. Assessment of these impairments can be done with PRO measures, such as a symptom questionnaire, but also with clinician-reported outcome measures such as a neurological examination. The second level of functioning refers to the consequences of the patient's impairment in their daily activities. For example, a patient with muscle weakness is not able to walk around or drive a car. PRO instruments assessing (instrumental) activities of daily living can measure these activity limitations. The highest level of functioning, so-called participation restrictions, reflects the way the dysfunction affects the patient's wellbeing and social interaction. For example, a patient with muscle weakness who is unable to walk or drive a car might be less likely to visit friends or family. Health-related quality of life measures usually include domains reflecting these participation restrictions. Nevertheless, since the ICF classification system is extensive, the aspects of functioning most relevant for patients with brain tumours (of different types) would need to be determined. To detect these most important aspects, we aim to do an international survey in patients with brain tumours, their informal caregivers, and experts in the field of neuro-oncology to further refine the list of most relevant disease-related symptoms for assessment in clinical

Search strategy and selection criteria

We did not do a formal literature search for this Policy Review, and as such no specific language and date parameters were used. Papers were included at our discretion and through a manual search of the authors' own files.

trials on a global scale (as measured in the online survey of the Jumpstarting Brain Tumor Drug Development Coalition done in the USA).[12] On the basis of these results, we will be able to investigate whether or not current PRO instruments cover all aspects that are relevant to patients with brain tumours. For relevant aspects not covered in existing PRO measures, we might consider the revision of particular instruments or the development of new PRO measures.

The fourth step is to identify the psychometric properties of the identified PRO measures. How valid and reliable are these instruments for patients with brain tumours? To judge the methodological quality of studies on the measurement properties of PRO instruments, the COSMIN criteria will be applied. The COSMIN taxonomy distinguishes three quality domains: reliability, validity, and responsiveness, each of which include one or more measurement properties.[20] Reliability refers to the degree in which the measurement is without measurement error, whereas validity refers to the degree in which an instrument truly measures the construct intended to measure. Responsiveness refers to the ability of an instrument to detect (clinically relevant) changes over time.[20] However, PRO measures that do not meet the standard as set by the COSMIN criteria might still be important and relevant. For example, a measure that has not yet been validated in patients with brain tumours and does not meet the requirements for satisfactory measurement properties, might be assessed in a field validation study to meet these standards instead.

Conclusion

The objective of the RANO-PRO initiative is to provide guidance on the use of PRO measures in clinical studies and clinical practice for adult patients with brain tumours. In conjunction with guidelines on the collection, analysis, interpretation, and reporting of PRO data, this guidance might help to improve the PRO evidence derived from neuro-oncological studies, which might subsequently inform the research community, policy makers, physicians, and patients in the treatment decision-making process.

Contributors

All authors contributed to the design and concept of this Policy Review. LD and MJBT prepared a first draft. All authors revised the report for intellectual content. All authors approved the final submitted version.

Declaration of interests

JOB reports personal fees from Abbvie, and grants from GlaxoSmithKline, Sanofi, and Lily, outside the submitted work. TM reports personal fees from Amgen and Incyte outside the submitted work. LN reports personal fees from Bristol-Myers Squibb outside the submitted work. JCR reports non-financial support from Roche Netherlands BV outside the submitted work. ELR reports grants and personal fees from Mundipharma, grants from Amgen, and personal fees from Novartis, outside the submitted work. TW reports personal fees from NovoCure and AbbVie outside the submitted work. MW reports grants from Roche, OGD Pharma, Piqur, Acceleron, Actelion, and Bayer, grants and personal fees from MSD (Merck & Co), EMD (Merck Darmstadt), Abbvie, and Novocure, and personal fees from Mundipharma, Bristol-Myers Squibb, Celldex, and Tocagen, outside the submitted work. PYW reports grants, personal fees, and non-financial support from Agios and Novartis, grants and non-financial support from Merck, personal fees and non-financial support from AstraZeneca, Genentech–Roche, Vascular Biogenics, and Novogen, personal fees from Cavion, Insys, Monteris, Kadmon, Tocagen, Aurora Biopharma, and Ziopharm, and non-financial support from Angiochem, GlaxoSmithKline, Immunocellular Therapeutics, Karyopharm, Oncoceutics, Sanofi-Aventis, and VBI Vaccines outside the submitted work. MJBT reports personal fees from Hoffmann–La Roche outside the submitted work. All other authors declare no competing interests.

References

1 US Food and Drug Administration. Patient-reported outcome measures: use in medical product development to support labeling claims. Silver Spring, MD: US Department of Health and Human Services Food and Drug Administration, 2009. https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf (accessed May 1, 2017).

2 European Medicines Agency. Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man: the use of patient-reported outcome (PRO) measures in oncology studies. London: European Medicines Agency, 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/04/WC500205159.pdf (accessed May 1, 2017).

3 US Food and Drug Administration. Drug development tools qualification programs. https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttools qualificationprogram/ucm370262.htm (accessed May 1, 2017).

4 US Food and Drug Administration. Clinical outcome assessment qualification program. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm (accessed May 1, 2017).

5 Armstrong TS, Gilbert MR. Net clinical benefit: functional endpoints in brain tumor clinical trials. *Curr Oncol Rep* 2007; **9:** 60–65.

6 Patient-Centered Outcomes Research Institute. Patient-centered outcomes research definition. Response to public input. Consensus definition as of Feb 15, 2012. Washington DC: Patient-Centered Outcomes Research Institute, 2012. http://www.pcori.org/assets/PCOR-Definition-Revised-Draft-and-Responses-to-Input.pdf (accessed May 1, 2017).

7 US FDA Center for Drug Evaluation and Research, US FDA Center for Biologics Evaluation and Research, US FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes* 2006; **4:** 79.

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

9 Dirven L, Koekkoek JAF, Reijneveld JC, Taphoorn MJB. Health-related quality of life in brain tumor patients: as an endpoint in clinical trials and its value in clinical care. *Expert Rev Qual Life Cancer Care* 2016; **1:** 37–44.

10 Jensen RE, Rothrock NE, DeWitt EM, et al. The role of technical advances in the adoption and integration of patient-reported outcomes in clinical care. *Med Care* 2015; **53:** 153–59.

11 Basch E, Deal AM, Dueck AC, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA* 2017; **18:** 197–98.

12 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 (Oct 15, 2014, Bethesda MD). *Neuro Oncol* 2016; **18** (suppl 2)**:** ii26–36.

13 Osoba D. Rationale for the timing of health-related quality-of-life (HQL) assessments in oncological palliative therapy. *Cancer Treat Rev* 1996; **22** (suppl A)**:** 69–73.

14 Osoba D. What has been learned from measuring health-related quality of life in clinical oncology. *Eur J Cancer* 1999; **35:** 1565–70.

15 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.

16 Calvert M, Brundage M, Jacobsen PB, Schunemann HJ, Efficace F. The CONSORT Patient-Reported Outcome (PRO) extension: implications for clinical trials and practice. *Health Qual Life Outcomes* 2013; **11:** 184.

17 Kyte D, Duffy H, Fletcher B, et al. Systematic evaluation of the patient-reported outcome (PRO) content of clinical trial protocols. *PloS One* 2014; **9:** e110229.

18 Brundage M, Blazeby J, Revicki D, et al. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. *Qual Life Res* 2013; **22:** 1161–75.

19 Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013; **309:** 814–22.

20 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.

21 Armstrong TS, Cohen MZ, Eriksen LR, Hickey JV. Symptom clusters in oncology patients and implications for symptom research in people with primary brain tumors. *J Nurs Scholarsh* 2004; **36:** 197–206.

22 Sizoo EM, Braam L, Postma TJ, et al. Symptoms and problems in the end-of-life phase of high-grade glioma patients. *Neuro Oncol* 2010; **12:** 1162–66.

23 Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol* 2004; **3:** 159–68.

24 van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *Lancet Neurol* 2007; **6**: 421–30.

25 Buckner JC, Brown PD, O'Neill BP, Meyer FB, Wetmore CJ, Uhm JH. Central nervous system tumors. *Mayo Clin Proc* 2007; **82:** 1271–86.

26 Portenoy RK, Thaler HT, Kornblith AB, et al. Symptom prevalence, characteristics and distress in a cancer population. *Qual Life Res* 1994; **3:** 183–89.

27 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.

28 Rouse C, Gittleman H, Ostrom QT, Kruchko C, Barnholtz-Sloan JS. Years of potential life lost for brain and CNS tumors relative to other cancers in adults in the United States, 2010. *Neuro Oncol* 2016; **18:** 70–77.

29 Baumert BG, Hegi ME, van den Bent MJ, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol* 2016; **17:** 1521–32.

30 Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med* 2016; **374:** 1344–55.

31 Goldbrunner R, Minniti G, Preusser M, et al. EANO guidelines for the diagnosis and treatment of meningiomas. *Lancet Oncol* 2016; **17:** e383–91.

32 Lippitz B, Lindquist C, Paddick I, Peterson D, O'Neill K, Beaney R. Stereotactic radiosurgery in the treatment of brain metastases: the current evidence. *Cancer Treat Rev* 2014; **40:** 48–59.

33 Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; **352:** 987–96.

34 Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. *Lancet Oncol* 2010; **11:** 1036–47.

35 van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol* 2013; **31:** 344–50.

36 Wick W, Hartmann C, Engel C, et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. *J Clin Oncol* 2009; **27:** 5874–80.

37 Doorduijn JK, van Imhoff GW, van der Holt B, et al. Treatment of secondary central nervous system lymphoma with intrathecal rituximab, high-dose methotrexate, and R-DHAP followed by autologous stem cell transplantation: results of the HOVON 80 phase 2 study. *Hematol Oncol* 2016; published online Aug 17. DOI:10.1002/hon.2342.

38 McArthur GA, Maio M, Arance A, et al. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study. *Ann Oncol* 2017; **28:** 634–41.

39 Reardon DA, Lassman AB, van den Bent M, et al. Efficacy and safety results of ABT-414 in combination with radiation and temozolomide in newly diagnosed glioblastoma. *Neuro Oncol* 2017; **19:** 965–75.

40 Schuster J, Lai RK, Recht LD, et al. A phase II, multicenter trial of rindopepimut (CDX-110) in newly diagnosed glioblastoma: the ACT III study. *Neuro Oncol* 2015; **17:** 854–61.

41 Sperduto PW, Wang M, Robins HI, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *Int J Radiat Oncol Biol Phys* 2013; **85:** 1312–18.

42 Boele FW, Douw L, Reijneveld JC, et al. Health-related quality of life in stable, long-term survivors of low-grade glioma. *J Clin Oncol* 2015; **33:** 1023–29.

43 Cancer.Net. Long-term side effects of cancer treatment, 2016. http://www.cancer.net/survivorship/long-term-side-effects-cancer-treatment (accessed May 1, 2017).

44 Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's not over when it's over: long-term symptoms in cancer survivors—a systematic review. *Int J Psychiatry Med* 2010; **40:** 163–81.

45 Schmidt JE, Beckjord E, Bovbjerg DH, et al. Prevalence of perceived cognitive dysfunction in survivors of a wide range of cancers: results from the 2010 LIVESTRONG survey. *J Cancer Surviv* 2016; **10:** 302–11.

46 Stein KD, Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. *Cancer* 2008; **112:** 2577–92.

47 Zamanipoor Najafabadi AH, Peeters MC, Dirven L, et al. Impaired health-related quality of life in meningioma patients-a systematic review. *Neuro Oncol* 2017; **19:** 897–90

48 Armstrong TS, Mendoza T, Gning I, et al. Validation of the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). *J Neuro Oncol* 2006; **80:** 27–35.

49 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67:** 361–70.

50 Stewart AL, Ware Jr JE. Measuring functioning and well-being: the medical outcomes study approach. Durham, NC: Duke University Press, 1992.

51 Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J* 1965; **14:** 61–65.

52 Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969; **9:** 179–86.

53 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

54 Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993; **11:** 570–79.

55 Taphoorn MJ, Claassens L, Aaronson NK, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. *Eur J Cancer* 2010; **46:** 1033–40.

56 Weitzner MA, Meyers CA, Gelke CK, Byrne KS, Cella DF, Levin VA. The Functional Assessment of Cancer Therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. *Cancer* 1995; **75:** 1151–61.

57 Groenvold M, Aaronson NK, Darlington AE, et al. Focusing on core patient-reported outcomes in cancer clinical trials-letter. *Clin Cancer Res* 2016; **22:** 5617.

58 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.

59 Blakeley JO, Coons SJ, Corboy JR, Kline Leidy N, Mendoza TR, Wefel JS. Clinical outcome assessment in malignant glioma trials: measuring signs, symptoms, and functional limitations. *Neuro Oncol* 2016; **18** (suppl 2)**:** ii13–20.

60 Gilbert MR, Rubinstein L, Lesser G. Creating clinical trial designs that incorporate clinical outcome assessments. *Neuro Oncol* 2016; **18** (suppl 2)**:** ii21–25.

61 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62:** 1006–12.

62 WHO. International classification of functioning, disability and health. http://www.who.int/classifications/icf/en/ (accessed May 1, 2017).