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


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.

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 measures 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 that reflects the patients’ perception of a disease and its treatment. 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. The FDA has defined four types of patient-centred outcome measures, which are collectively called clinical outcome assessments (COAs): 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. 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. 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. 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. 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 initiation of palliative care. In one study, the integration of PROs into routine clinical care was even associated with improved survival.

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
to inform the research community, policy makers, physicians, and patients in treatment decision making. Therefore, PROs should be well defined and reliable measurements\(^2\) 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 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.\(^7\) 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.\(^6\)

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 Intervventional Trials in Patient Reported Outcomes initiative aims to provide guidance on what specific PRO protocol items should be included in trial protocols.\textsuperscript{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.\textsuperscript{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.\textsuperscript{21–28} 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\textsuperscript{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.\textsuperscript{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 measurement properties of health measurement instruments,\textsuperscript{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.\textsuperscript{26–28} 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.\textsuperscript{29–36} However, new treatment opportunities are being explored, and include targeted treatment and immunotherapy.\textsuperscript{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.\textsuperscript{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.\textsuperscript{42–46}

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\textsuperscript{48} or Hospital Anxiety and Depression Scale\textsuperscript{49} is

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\textsuperscript{1} PRO=patient-reported outcome.

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

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used to measure patient-reported symptoms, whereas cognitive complaints can be assessed with the MOS Cognitive Functioning Scale.\textsuperscript{39} Basic activities of daily living are often measured with the Barthel Index,\textsuperscript{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.\textsuperscript{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\textsuperscript{53} or the Functional Assessment of Cancer Treatment.\textsuperscript{54} These core questionnaires can be supplemented with tumour-specific questionnaires, which are specifically developed for patients with brain tumours.\textsuperscript{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.\textsuperscript{20} For example, the EORTC Quality of Life Questionnaire BN20 was developed in 1996 for patients with brain tumours,\textsuperscript{55} with a field validation in patients with glioma in 2010.\textsuperscript{56} With the introduction of new treatments, such as targeted treatment and immunotherapy, new toxicities have arisen (eg, eye and skin problems).\textsuperscript{20,56} 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 needs 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.\textsuperscript{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.\textsuperscript{57} Outcomes from this workshop included identification of priority signs and symptoms,\textsuperscript{57} review of COA properties,\textsuperscript{57} and consideration for trial design with COAs.\textsuperscript{57} 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.\textsuperscript{57} The position of the FDA on the use of COAs in clinical trials is outlined in the report published in 2016,\textsuperscript{57} 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. 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. 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 WHO International Classification of Functioning, Disability and Health (ICF). 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 practice.

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**Figure 2: Schematic representation of the Response Assessment in Neuro-Oncology-Patient-Reported Outcome working plan**

**Step 1**
Overview of existing recommendations concerning PRO measurement and provision of additional guidance

**Step 2**
Systematic scientific literature review to identify PRO measures used in patients with brain tumours (PRISMA)

**Step 3**
Assessment of the content validity of the identified PRO measures (WHO ICF)

**Step 4**
Assessment of the psychometric properties of the identified PRO measures (COSMIN)

Guidance on PRO use
trials on a global scale (as measured in the online survey of the Jumpstarting Brain Tumor Drug Development Coalition done in the USA). 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. 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. 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.

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JOB reports personal fees from AbbVie, and grants from GlaxoSmithKline, Sanofi, and Lilly, 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, Piser, 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. PJW 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.

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