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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Abstract: 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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Guidance on the use of patient-reported outcome measures in adult brain tumour patients: A Response Assessment in Neuro-Oncology (RANO) initiative

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Abstract

Response Assessment in Neuro-Oncology - Patient Reported Outcome (RANO-PRO) working group is an international multidisciplinary collaborative initiative with the aim to provide guidance on the use of PRO measures in clinical trials and practice for adult brain tumour patients. Findings of PROs and other patient-centred outcome measures are essential to inform the research community, policy makers, physicians and patients in treatment decision-making, in conjunction with traditional outcome measures such as survival and clinical/radiological response. However, to be of value, PROs should be well-defined and reliable in order to generate high-quality evidence. This requires not only proper collection, analysis, interpretation and reporting of PRO data, but also the application of appropriate PRO instruments, specifically with respect to the content and measurement properties. Previous initiatives in oncology have focused on guidelines concerning the collection, analysis, interpretation and reporting of PRO data. Our recommendations on the use of specific PRO measures (i.e. research question, content validity and other measurement properties) in brain tumour research may additionally help to improve the quality of PRO evidence derived from neuro-oncological studies, and may add a new dimension to how the value of therapeutics is assessed in brain tumour patients. Here we present the RANO-PRO working plan.

Role of patient-reported outcomes (PROs) in oncology

The goal of all therapeutics is to improve life for people suffering from disease. The traditional metric used in oncology to demonstrate this goal in therapeutic studies is prolonged survival or its surrogate, prolonged time to disease progression. However, the patient and regulatory community have increasingly emphasized the need to demonstrate that a therapy improves the patient function and health-related quality of life (HRQoL). Patient Reported Outcomes (PROs) are important tools for quantifying symptoms, function or HRQoL. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have defined a PRO as a measurement that is directly reported by patients[1,2], and reflects the patients' perception of a disease and its treatment.[2] A PRO can be measured either through self-report or interview, given that the interviewer only reports the responses of the patient. PRO measures may cover symptoms, functioning and health-related quality of life (HRQoL), but also topics such as adherence to treatment or satisfaction with care. PROs are distinctive from other types of patient-centred outcome measures, because they can capture concepts that are only known to the patient, such as nausea, fatigue or pain severity, but also mental health aspects including distress and future uncertainty.[3] The FDA has defined four types of patient-centred outcome measures, collectively called Clinical Outcome Assessments (COAs)[4], including PRO measures, clinician-reported outcome (ClinRO) measures, observer-reported outcome (ObsRO) measures and performance outcome (PerfO) measures (Table 1). Unlike PRO measures, ClinRO and ObsRO are measurements that are based on a report that comes from a health-care professional or someone other than the patient or the health-care professional (e.g. a relative), respectively. In some cases, the same concept, for example cognitive symptoms, can be measured with different COAs.

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 computed tomography (CT) / magnetic resonance imaging (MRI), clinical response based on a physical examination, and progression-free or overall survival.[6,7] In clinical trials, information from both

sources can be used to determine the net clinical benefit of a new treatment strategy, in which the impact of treatment on both outcomes should be weighed. This information can be used to inform regulatory agencies in their decision to approve an experimental drug for use beyond clinical trials.[8,9] In clinical practice, information from PROs can be used in shared decision-making, in which patients together with their primary caregiver and physician make a treatment decision using the best available evidence.[10] Results of COAs assessed over time may also be used in clinical practice for needs assessment, and to monitor an individual patient's symptoms or functioning during the disease trajectory.[11] By monitoring treatment effects, opportunities for symptom management may be identified, as well as timely referral to another health care professional (e.g., referral to a neuropsychologist in case of cognitive difficulties) or trigger points for initiation of palliative care. Integration of PROs into routine clinical care was even found to be associated with improved survival.[12]

Determinants of quality of PRO evidence

Findings of PROs and other patient-centred outcomes are crucial to inform the research community, policy makers, and physicians and patients in treatment decision-making, in conjunction with traditional outcome measures such as survival and clinical and radiological response. Therefore, to be of value, PROs should be well-defined and reliable[13] in order to generate high-quality evidence. The generation of high-quality evidence requires consideration of several aspects (Figure 1). One aspect is that the selection of a PRO for a clinical study should coincide with the research question. PROs can be used as primary, secondary or exploratory outcome measures. For example, the primary objective of a study could be to improve symptoms or functioning of patients, for which a PRO can be used, while PROs can also be used as secondary endpoint to support the clinical benefit in a trial in which survival is the primary endpoint, or lastly, PRO data can be used as supportive data to better describe the patients' experience in clinical trials, including toxicity and tolerability assessments in dose finding studies. This requires the selection of an appropriate PRO measure,

reflecting the goal of the study. Moreover, it is important to measure the construct that is intended to be measured, for which different types of PROs can be used. For example, a specific symptom (e.g. fatigue, depression or anxiety) or multiple symptoms, functioning in daily life, or the perceived HRQoL. The design of the study is another important aspect, in particular with respect to the assessment schedule. If the objective of a study is to assess the immediate toxic effects of a treatment the timing of the measurements should be different from when the objective is to assess the impact of a treatment strategy on the longer term.[14,15] An important consideration here is the time frame addressed for the selected PRO, e.g., covering the last week or the last month. Certain toxicities may not be captured if the time is too short or too long. The statistical analysis of PRO data is also an important aspect in generating reliable results.[16] Different analytical approaches may lead to conflicting results. For example, results of a cross-sectional analysis may favour treatment B over A, while the longitudinal analysis may not favour one treatment over the other. Even when appropriate statistical methods have been applied, interpretation of the results is key in drawing conclusions. Looking at statistically significant differences only may result in a different conclusion when compared to looking at both statistically and clinically relevant differences. Another challenge in interpretation is when multiple outcomes are used that measure the same concept, but results are conflicting. A final important aspect that should be considered in the generation of high-quality PRO evidence is the level of reporting of the results. Key aspects of the used methodology, statistical approach, results (e.g., baseline scores, and a description of missing data) and interpretation (e.g. clinical significance and generalisability of results) should be reported adequately, to facilitate critical appraisal of study results[17].

To enhance the generation of high-quality PRO evidence, several efforts in the field of oncology have been established, some of which are currently ongoing (Table 2). For example, *Standard Protocol Items: Recommendation for Interventional Trials in Patient Reported Outcomes* (SPIRIT-PRO) aims to provide guidance on what specific PRO protocol items should be included in trial protocols.[18] The *Setting International Standards in Analyzing Patient-Reported Outcomes and*

Quality of Life Endpoints Data (SISAQOL) consortium aims to develop a guideline and best practices for standardising the analysis and interpretation of PRO outcomes in cancer clinical trials.[16] Recommendations for the standardisation of the level of PRO reporting were introduced by the *International Society for Quality of Life Research* (ISOQOL); *CONsolidated Standards of Reporting Trials in Patient Reported Outcomes* (CONSORT-PRO).[19,20] These efforts will result in international standards for the collection, analysis, interpretation and reporting of PRO data, contributing to an enhanced quality of PRO evidence. Also, the FDA published PRO Guidance for Industry, a framework describing optimal PRO development, trial design and analysis of PRO data, which can be specifically used to support oncology labelling claims.[8] Although the *COnsensus-based Standards for the selection of health Measurement INstruments* (COSMIN) initiative developed standards for the evaluation of the methodological quality of studies on the measurement properties of health measurement instruments[21], for many PRO measures this has not been investigated properly. However, if PRO findings should be of high quality, the tools should be appropriate as well, both in terms of content and measurement properties.

Use of PRO in brain tumour patients

Brain tumour patients are different from other cancer patients in that they have cancer that is directly impacting their neurological function, making their course of disease different. Although brain tumour patients also report general cancer-related symptoms such as fatigue, drowsiness and constipation, they also more frequently report disease-specific symptoms such as seizures, motor dysfunction, cognitive deficits, and symptoms caused by elevated intracranial pressure (e.g. headache).[22-29] This means that general cancer PRO instruments may not be appropriate or sufficient for brain tumour patients, as they may not cover all relevant issues.

Current standard treatment of brain tumours may comprise surgery, radiotherapy and/or chemotherapy, depending on the type and location of the tumour.[30-37] New treatment opportunities are currently being explored and include targeted treatment and immunotherapy.[38-42] Despite the

large variation in type and location of the tumour, treatments and prognosis, all brain tumour patients may suffer from impaired functioning.

Because of the poor prognosis of patients with glioblastoma, primary central nervous system lymphoma (PCNSL) or brain metastases, 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 functioning during the entire disease trajectory. This resulted in an increased use of patient-centred outcomes in this field of research in the last decades. Although patients with low-grade glioma or meningioma may survive for many years, they may experience late effects (i.e. side effects that become apparent months or years after treatment has ended) caused by anti-tumour treatment (e.g. radiotherapy) and/or supportive treatment such as corticosteroids and anti-epileptic drugs. These late effects include for example fatigue, peripheral neuropathy, muscle weakness, cognitive dysfunction or radiation-induced secondary malignancies[43-47], and may also impact the patients' functioning in daily life. More recently there has been a shift towards focus on the evaluation of patient's functioning in these long-term survivors.[43,48]

Several PRO measures are available in neuro-oncology to measure the impact of the tumour and its treatment, both on the short- and long-term. These PRO measures may be one-dimensional (measuring one single aspect, e.g. symptoms of depression or anxiety) or multidimensional (measuring multiple aspects, e.g. HRQoL). Frequently used PRO measures to assess symptoms are the MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT)[49], or the Hospital Anxiety and Depression Scale[50], while cognitive complaints can be assessed with the MOS Cognitive Functioning Scale (MOS CFS)[51]. Basic activities of daily living are often measured with the Barthel Index[52], whereas instrumental activities of daily living (i.e. cognitively more complex activities such as food preparation) tend to be measured with the Lawton IADL Scale[53]. HRQoL is frequently assessed with the European Organisation of Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30)[54] or the Functional Assessment of Cancer Treatment (FACT)[55], both in conjunction with their tumour-specific questionnaire[56,57].

Although certain measures are often used in brain tumour research, not all are specifically developed for and/or validated in brain tumour patients (e.g. the Barthel Index was originally developed for patients undergoing rehabilitation after stroke, and the EORTC QLQ-BN20 was only validated in glioma patients, not in other types of brain tumour patients). In addition, it is unclear if currently used PROs have high content validity, i.e. if the instruments correspond with the construct that is intended to be measured, with respect to relevance and comprehensiveness.[21] For example, the EORTC QLQ-BN20 questionnaire was developed for brain tumour patients in 1996[14], with a field validation in glioma patients in 2010[56]. With the introduction of new treatments, such as targeted treatment and immunotherapy, also new toxicities have arisen (e.g. eye and skin problems).[40,41] The current QLQ-BN20 lacks sufficient coverage of domains that are affected by current and new treatment options, as well as issues like behavioural and personality changes, warranting a revision of this questionnaire. Moreover, most PROs are static questionnaires consisting of a fixed set of items. However, such questionnaires may not meet the current demands of academic researchers and industry. When assessing the impact of a new treatment, a fixed set of items may fail to detect important (new) adverse events. A more flexible approach, in which a standard set of items could be complemented with validated scales, might therefore be a solution.[58]

RANO-PRO initiative

The *Response Assessment in Neuro-Oncology - Patient Reported Outcome* (RANO-PRO) working group is an international multidisciplinary collaborative initiative aiming to provide guidance on the use of PRO measures in clinical trials and clinical practice for adult brain tumour patients. The multidisciplinary working group comprises key physicians and researchers in the field of neuro-oncology, including liaisons of other RANO working groups, which ensures implementation of appropriate PRO measures in future brain tumour research, in accordance with other RANO guidelines. Initiatives such as the SPIRIT-PRO, SISAQOL and CONSORT-PRO result in international standards for the collection, analysis, interpretation and reporting of PRO data, enhancing the

quality of PRO evidence, which are applicable to the whole field of oncology, including neuro-oncology. However, it is also important to ensure that the PRO instruments are of high quality, both in terms of relevance (content validity) for brain tumour patients and other measurement properties. In conjunction, these different initiatives may help to improve PRO evidence derived from neuro-oncological studies.

Currently, since no extensive review has been performed, it is not well-known what PRO measures have been used in brain tumour research to date, whether these measures exhibit good measurement properties, and whether they demonstrate relevance and comprehensiveness for brain tumour patients specifically. In addition, 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.[13] Outcomes from this workshop included identification of priority signs and symptoms[59], review of COA properties[60], and consideration for trial design using COAs[61]. This work could serve as a starting point for further guidelines for use in neuro-oncology. Moreover, from a regulatory perspective it is important to include high-quality PROs in neuro-oncological clinical trials as they can provide important information for evaluation of benefits and risks of a new treatment, and an approach to evaluate or develop appropriate tools is therefore promoted.[9] In this paper[9], the position of the FDA on the use of COAs in clinical trials is outlined, including the demonstration of improvement in how patients' function, feel or survive', as necessary for product approval. These recommendations encourage disease-related function and symptom measures, consideration of the impact of therapeutic toxicity, and use of COAs early in the drug development process.

The goal of the RANO-PRO initiative is to gain insight above mentioned problems, and to provide guidance on the use of PRO measures in neuro-oncology. In addition, this initiative will result in suggestions for the revision of existing PRO measures and/or development of new PRO measures, if 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 RANO-PRO working group, taking into account the recommendations that resulted from the Jumpstarting Brain Tumor Drug Development Coalition and FDA clinical trials clinical outcome assessment endpoints workshop. This may comprise recommendations on the selection and collection (including feasibility and patient acceptability) of PROs, particularly with respect to the research question and study design. Liaisons from other RANO working groups (e.g. RANO epilepsy, RANO NANO, RANO brain metastases and RANO corticosteroids) will be consulted in the process, to ensure that their specific needs with respect to the use of PRO will be incorporated.

A *second step* would therefore be to identify what PRO measures have been used in brain tumour studies so far. As mentioned, several PRO measures are already frequently used (e.g. MDASI-BT, FACT-Br, EORTC QLQ-C30 and QLQ-BN20, and the Barthel Index), but other instruments may exist that are relevant and of methodological high quality. Therefore, a systematic literature review will be performed to identify all PRO measures that are used in studies with brain tumour patients, following the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guideline (*step 2*).[62] The review will focus on all types of studies (i.e. randomised controlled trials, phase I and II trials, natural history studies, symptom management studies, and studies describing use of PRO in daily clinical practice) in which a PRO instrument is used to assess symptoms, functioning and/or HRQoL in patients with glioma, PCNSL, meningioma or brain metastases.

The *third step* would be to determine the content validity of these existing PRO measures; are all important aspects of functioning and health for brain tumour patients covered by these instruments? In other words, is a PRO available for each relevant aspect? Also, it would be important

to look at the coverage of each PRO instrument. Do the items in a specific PRO cover the domain(s) that it intends to measure, such as fatigue (single domain) or HRQoL (multidimensional). This information would facilitate the choice for a specific PRO instrument. For this we aim to use the framework of the *World Health Organisation International Classification of Functioning, Disability and Health* (WHO ICF) published in 2001.[63] This framework refers to functioning at three distinct levels. The most basic level is a patient's impairment, which are problems in body functions, with muscle weakness as an example. Assessment of these impairments can be done with PRO measures, for instance a symptom questionnaire, but also with ClinRO measures such as a neurological examination. Next, the consequences of this impairment in daily life can be observed on a higher level, the limitations in a patients' activity. This would mean that the patient with muscle weakness is not able to walk around or drive a car. PRO instruments assessing (instrumental) activities of daily living can be used to measure these activity limitations. The highest level of functioning, the so-called participation restrictions, reflects the way the dysfunction affects the patient's well-being and social interaction. In line with our example, this would mean that the patient with muscle weakness who is unable to walk or drive a car, may be less likely to visit friends or family. HRQoL measures usually include domains reflecting these participation restrictions. Nevertheless, since this ICF classification system is very extensive, it would be important to determine the aspects of functioning that are most relevant for (each type of) brain tumour patients. To detect these most important aspects, we aim to conduct an international survey amongst brain tumour patients, their informal caregivers, and experts in the field of neuro-oncology. This would allow to further refine the list of most relevant disease-related symptoms for assessment in clinical trials on a global level, as measured in the online survey of the Jumpstarting Brain Tumor Drug Development Coalition conducted in the United States.[13] Based on these results, we will be able to evaluate if current PRO instruments cover all aspects that are relevant to brain tumour patients. For relevant aspects not covered in existing PRO measures, we might consider revision of certain instruments or development of new PRO measures.

A *fourth step* would be to determine the psychometric properties of these identified PRO measures. How valid and reliable are these instruments for the use in brain tumour patients? 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, i.e. reliability, validity, and responsiveness, each including one or more measurement properties.[21] Reliability refers to the degree to which the measurement is without measurement error, while validity refers to the degree to which an instrument truly measures the construct it intends to measure. Responsiveness refers to the ability of an instrument to detect (clinically relevant) changes over time.[21] PRO measures that do not meet the standard as set by the COSMIN might still be important and relevant. For example, a measure that has not yet been validated in brain tumour patients, and as such does not meet the requirements for satisfactory measurement properties, might be evaluated in a field validation study to meet these standards.

Conclusion

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

References

1. US Food and Drug Administration. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. U.S. Department of Health and Human Services Food and Drug Administration. 2009. https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf (accessed 01-05-2017).

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. 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/04/WC500205159.pdf (accessed 01-05-2017).

3. US Food and Drug Administration. Drug Development Tools Qualification Programs. 2015. https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/ucm370262.htm (accessed 01-05-2017).

4. US Food and Drug Administration. Clinical Outcome Assessment Qualification Program. 2016. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm (accessed 01-05-2017).

5. Pickard AS, Knight SJ. Proxy evaluation of health-related quality of life: a conceptual framework for understanding multiple proxy perspectives. *Medical care* 2005; **43**(5): 493-9.

6. Armstrong TS, Gilbert MR. Net clinical benefit: functional endpoints in brain tumor clinical trials. *Current oncology reports* 2007; **9**(1): 60-5.

7. Institute P-COR. Patient-Centered Outcomes Research Definition. 2012. http://www.pcori.org/assets/PCOR-Definition-Revised-Draft-and-Responses-to-Input.pdf (accessed 01-05-2017).

8. US Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health and quality of life outcomes* 2006; **4**: 79.

9. Sul J, Kluetz PG, Papadopoulos EJ, Keegan P. Clinical outcome assessments in neuro-oncology: a regulatory perspective. *Neuro Oncology Practice* 2016; **3**(1): 6.

10. 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 Review of Quality of Life in Cancer Care* 2016; **1**(1): 37-44.

11. 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. *Medical care* 2015; **53**(2): 153-9.

12. 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.

13. 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-oncology* 2016; 18 Suppl 2: ii26-ii36.

14. Osoba D. Rationale for the timing of health-related quality-of-life (HQL) assessments in oncological palliative therapy. *Cancer treatment reviews* 1996; 22 Suppl A: 69-73.

15. Osoba D. What has been learned from measuring health-related quality of life in clinical oncology. *European journal of cancer (Oxford, England : 1990)* 1999; **35**(11): 1565-70.

16. 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. *The Lancet Oncology* 2016; **17**(11): e510-e4.

17. Calvert M, Brundage M, Jacobsen PB, Schunemann HJ, Efficace F. The CONSORT Patient-Reported Outcome (PRO) extension: implications for clinical trials and practice. *Health and quality of life outcomes* 2013; **11**: 184.

18. 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**(10): e110229.

19. Brundage M, Blazeby J, Revicki D, et al. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2013; **22**(6): 1161-75.

20. 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**(8): 814-22.

21. 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. *Journal of clinical epidemiology* 2010; **63**(7): 737-45.

22. Armstrong TS, Cohen MZ, Eriksen LR, Hickey JV. Symptom clusters in oncology patients and implications for symptom research in people with primary brain tumors. *Journal of nursing scholarship : an official publication of Sigma Theta Tau International Honor Society of Nursing* 2004; **36**(3): 197-206.

23. Sizoo EM, Braam L, Postma TJ, et al. Symptoms and problems in the end-of-life phase of high-grade glioma patients. *Neuro-oncology* 2010; **12**(11): 1162-6.

24. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *The Lancet Neurology* 2004; **3**(3): 159-68.

25. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *The Lancet Neurology* 2007; **6**(5): 421-30.

26. Buckner JC, Brown PD, O'Neill BP, Meyer FB, Wetmore CJ, Uhm JH. Central nervous system tumors. *Mayo Clinic proceedings* 2007; **82**(10): 1271-86.

27. Portenoy RK, Thaler HT, Kornblith AB, et al. Symptom prevalence, characteristics and distress in a cancer population. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 1994; **3**(3): 183-9.

28. Reeve BB, Mitchell SA, Dueck AC, et al. Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. *Journal of the National Cancer Institute* 2014; 106(7).

29. 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-oncology* 2016; 18(1): 70-7.

30. 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. *The Lancet Oncology* 2016; **17**(11): 1521-32.

31. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. *The New England journal of medicine* 2016; **374**(14): 1344-55.

32. Goldbrunner R, Minniti G, Preusser M, et al. EANO guidelines for the diagnosis and treatment of meningiomas. *The Lancet Oncology* 2016; **17**(9): e383-91.

33. 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 treatment reviews* 2014; **40**(1): 48-59.

34. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *The New England journal of medicine* 2005; **352**(10): 987-96.

35. 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. *The Lancet Oncology* 2010; **11**(11): 1036-47.

36. 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; **31**(3): 344-50.

37. 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009; **27**(35): 5874-80.

38. 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. *Hematological oncology* 2016.

39. 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. *Annals of oncology : official journal of the European Society for Medical Oncology* 2017; **28**(3): 634-41.

40. 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-oncology* 2016.

41. 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-oncology* 2015; **17**(6): 854-61.

42. 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. *International journal of radiation oncology, biology, physics* 2013; **85**(5): 1312-8.

43. Boele FW, Douw L, Reijneveld JC, et al. Health-related quality of life in stable, long-term survivors of low-grade glioma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33**(9): 1023-9.

44. Cancer.Net. Long-Term Side Effects of Cancer Treatment 2017. http://www.cancer.net/survivorship/long-term-side-effects-cancer-treatment (accessed 01-05-2017).

45. 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. *International journal of psychiatry in medicine* 2010; **40**(2): 163-81.

46. 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. *Journal of cancer survivorship : research and practice* 2016; **10**(2): 302-11.

47. Stein KD, Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. *Cancer* 2008; **112**(11 Suppl): 2577-92.

48. Zamanipoor Najafabadi AH, Peeters MC, Dirven L, et al. Impaired health-related quality of life in meningioma patients-a systematic review. *Neuro-oncology* 2016.

49. Armstrong TS, Mendoza T, Gning I, et al. Validation of the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). *Journal of neuro-oncology* 2006; **80**(1): 27-35.

50. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica* 1983; **67**(6): 361-70.

51. Stewart AL, Ware Jr JE. Measuring Functioning and Well-Being: The Medical Outcomes Study Approach: Durham: Duke University Press; 1992.

52. Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. *Maryland state medical journal* 1965; **14**: 61-5.

53. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *The Gerontologist* 1969; **9**(3): 179-86.

54. 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. *Journal of the National Cancer Institute* 1993; **85**(5): 365-76.

55. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1993; **11**(3): 570-9.

56. 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. *European journal of cancer (Oxford, England : 1990)* 2010; **46**(6): 1033-40.

57. 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**(5): 1151-61.

58. Groenvold M, Aaronson NK, Darlington AE, et al. Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials-Letter. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2016; **22**(22): 5617.

59. 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-oncology* 2016; **18**(2): 252-60.

60. 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-oncology* 2016; **18 Suppl 2**: ii13-ii20.

61. Gilbert MR, Rubinstein L, Lesser G. Creating clinical trial designs that incorporate clinical outcome assessments. *Neuro-oncology* 2016; **18 Suppl 2**: ii21-ii5.

62. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of clinical epidemiology* 2009; **62**(10): 1006-12.

63. World Health Organisation. International Classification of Functioning, Disability and Health. 2001. http://www.who.int/classifications/icf/en/ (accessed 01-05-2017).

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Table 1. Definition of Clinical Outcome Assessment (COA), and each subtype

Table 2. Current efforts to standardise practice for use of patient-reported outcomes in oncology

Figure 1. Aspects relevant for the generation of high-quality PRO evidence

Figure 2. Schematic representation of the RANO-PRO working plan

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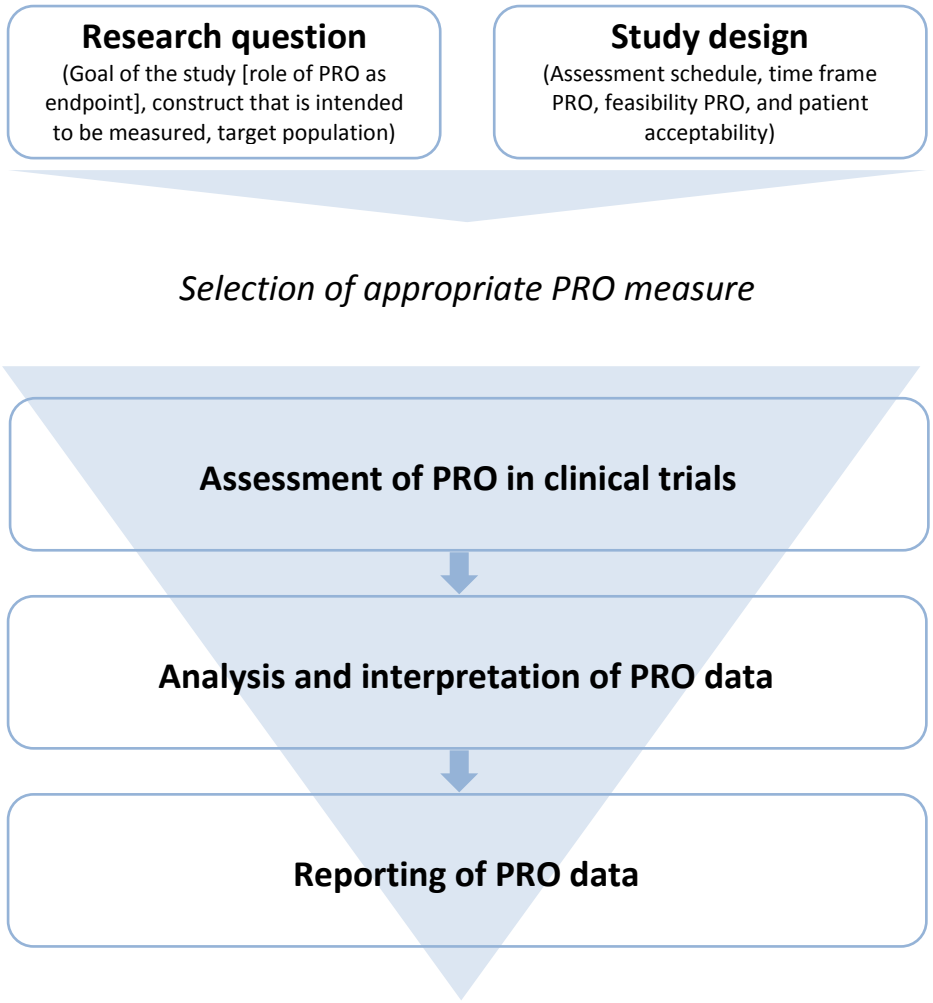

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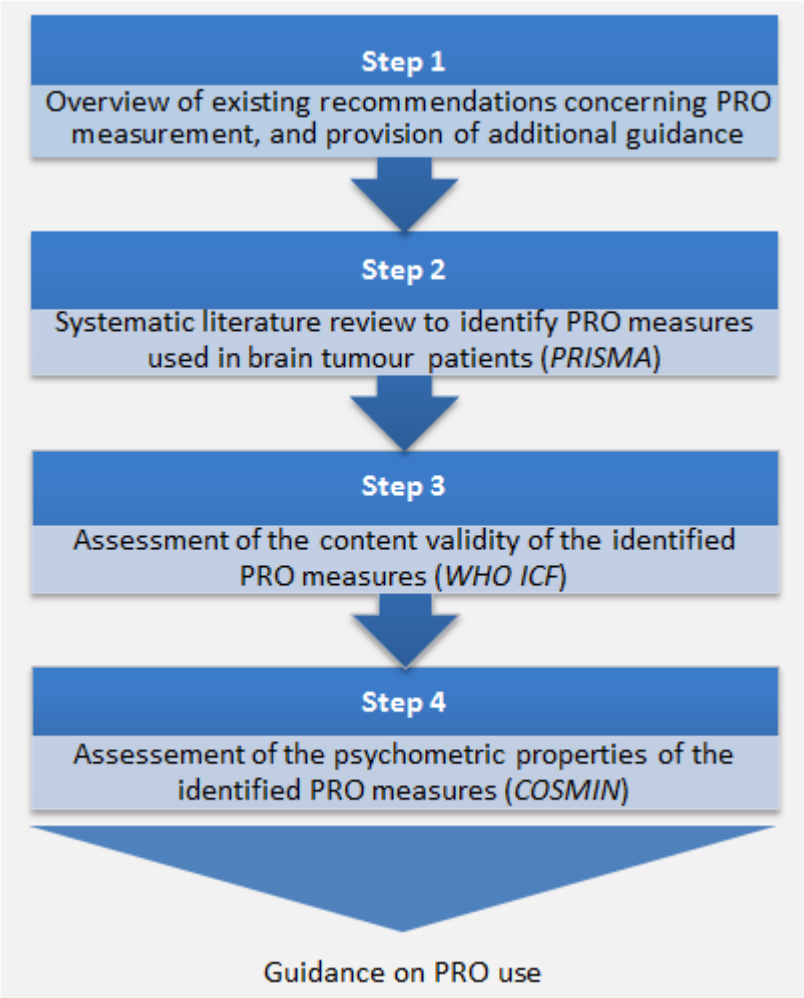

Table 1. Definition of Clinical Outcome Assessment (COA), and each subtype

Clinical Outcome Assessment (COA)	*Any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. Unlike biomarkers that rely completely on an automated process or algorithm, COAs depend on the implementation, interpretation, and reporting from a patient, a clinician, or an observer.*
Patient-reported outcome (PRO)	*A measurement based on a report that comes from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's report by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient (e.g., pain severity or nausea) can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others.*
Clinician-reported outcome (ClinRO)	*Is based on a report that comes from a trained health-care professional after observation of a patient's health condition. A ClinRO measure involves a clinical judgment or interpretation of the observable signs, behaviours, or other physical manifestations thought to be related to a disease or condition. ClinRO measures cannot directly assess symptoms that are known only to the patient (e.g., pain intensity).*
Observer-reported outcome (ObsRO)	*A measurement based on an observation by someone other than the patient or a health professional. This may be a parent, spouse, or other non-clinical caregiver who is in a position to regularly observe and report on a specific aspect of the patient's health. An ObsRO measure does not include medical judgment or interpretation. Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life. For patients who cannot respond for themselves (e.g., infants or cognitively impaired), we encourage observer reports that include only those events or behaviours that can be observed. As an example, observers cannot validly report an infant's pain intensity (a symptom) but can report infant behaviour thought to be caused by pain (e.g., crying). For example, in the assessment of a child's functioning in the classroom, the teacher is the most appropriate observer. Examples of ObsROs include a parent report of a child's vomiting episodes or a report of wincing thought to be the result of pain in patients who are unable to report for themselves.*
Performance outcome (PerfO)	*A measurement based on a task(s) performed by a patient according to instructions that is administered by a health care professional. Performance outcomes require patient cooperation and motivation. These include measures of gait speed (e.g., timed 25 foot walk test), memory recall, or other cognitive testing (e.g., digit symbol substitution test).*

** Source: Food and Drug Administration (FDA), Clinical Outcome Assessment Qualification Program*

Table 2. Current efforts to standardise practice for use of patient-reported outcomes in oncology

Initiative	Aim
Recommendation for Interventional Trials in Patient-Reported Outcomes *(SPIRIT-PRO)*	To provide guidance on what specific PRO protocol items should be included in trial protocols
Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints *(SISAQOL)*	To develop a guideline and best practices fore standardising the analysis and interpretation of PRO outcomes in cancer clinical trials
International Society for Quality of Life Research (ISOQOL); CONsolidated Standards of Reporting Trials in Patient Reported Outcomes *(CONSORT-PRO)*	To standardise the level of PRO reporting
COnsensus-based Standards for the selection of health Measurement Instruments *(COSMIN)*	To develop standards for the evaluation of the methodological quality of studies on the measurement properties of health measurement instruments, including PRO measures
Food and Drug Administration Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims	To provide guidance on the optimal PRO development, trial design and analysis of PRO data, which can be specifically used to support oncology labelling claims