**Quality of Survival Assessment in European Childhood Brain Tumour Trials, for Children Aged 5 years and Over**

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**Abstract**

There is increasing recognition of the long-term sequelae of brain tumours treated in childhood. Five year survival rates now exceed 75% and assessing the quality of survival (QoS) in multiple domains is essential to any comparison of the benefits and harms of treatment regimens. This paper represents the consensus view of the QoS working group of the Brain Tumour group of the European Society of Paediatric Oncology regarding domains of QoS to prioritise for assessment in clinical trials. This consensus between clinicians and researchers across Europe has been arrived at by discussion and collaboration over the last eight years. Areas of assessment discussed include core medical (e.g. vision, hearing, mobility, endocrine), emotional, behavioural, adaptive behaviour and cognitive functioning. The aim of such a position statement is to rationalise assessments and facilitate collection of a common data set across Europe. Sufficient numbers of observations can then be made to enable reliable comparisons between outcomes following different tumour types and treatments. A ‘core plus’ approach is suggested in which core assessments (both direct and indirect tests) are recommended for all clinical trials. The core component is a relatively brief screening assessment that, in most countries, is a sub-component of routine clinical provision. The ‘plus’ components enable the addition of assessments which can be selected by individual countries and/or tumour-, age-, and location-specific groups. The implementation of a QoS protocol common to all European clinical studies of childhood brain tumours is also discussed.

**Highlights**

* We consider the range of functioning affected by childhood brain tumours
* We present domains of function with measures in use across much of Europe
* We present core areas of function that should be measured in all clinical trials
* We discuss additional areas of function that can be identified for specific trials

**Keywords:** assessment; quality of survival; brain tumour; children; late effects

**1. Background**

**a. Survivorship after childhood brain tumour.**

There is increasing recognition of the long-term neuro-cognitive, endocrine and other medical, behavioural, emotional and adaptive functional sequelae of brain tumours treated in childhood.**1-7** Collectively these outcomes refer to ‘Quality of Survival’ (QoS). This is a useful short-hand term for information about survivors that is intended to capture more than survival rates and is also broader than ‘Quality of Life’ (QoL) which refers specifically to the subjective view of the individual survivor about their life situation.

Although brain tumours account for 23% of all malignancies in children before the age of 15**8** the overall incidence of brain tumours in childhood is relatively low and specific tumour types can be extremely rare. Because 5-year survival rates are >75%, and most survivors live for several decades, prevalence rates increase with age with a current estimate of 1 in 4,000 adults being a survivor of a brain tumour in childhood. The small numbers of cases make it difficult to conduct clinical trials and research studies that have sufficient numbers of participants. This in turn limits the ability to make evidence-based decisions about treatment and supportive care for different tumour types and locations.

Given the high survival rates and the increased treatment intensity and hence, toxicity, it is our view that it is essential to collect robust data on both survival rates and QoS, to inform treatment decisions. This will then allow the development of better regimens for both treatment of the disease and rehabilitation tailored to the needs of the survivors of childhood brain tumours. This is true for patients diagnosed with any type of childhood brain tumour, and QoS evaluation is now a core part of clinical trials to improve the treatments available to them.

A clear distinction has to be made between data collected to inform clinical care provided to the individual patient participating in a trial (and also relevant to many patients receiving care for which no treatment trial is currently open) and data collected to address research questions posed as part of a clinical trial. It is possible, of course, that some data could serve both purposes but so far the QoS data collected in European trials have been used only to compare QoS outcomes between groups of patients; this is also the focus of the protocol outlined in this paper. However, it is acknowledged that clinicians in all countries are likely to want to identify every individual’s cognitive, behavioural, emotional, and neuroendocrine outcomes to better meet their individual clinical needs.

**b. Terminology and conceptual framework**

Discussion of measurement of QoS should embrace the conceptual framework used in the International Classification of Functioning, Disability and Health: Child and Youth Version (ICF-CY).**9**

In the context of health:

***Impairments*** are problems in *body function or structure* such as significant deviation or loss.

***Activity*** is the execution of a task or action by an individual. *Activity limitations* are difficulties an individual may have in executing activities.

***Participation*** is involvement in a life situation. *Participation restrictions* are problems an individual may experience in involvement in life situations.

***Environmental factors*** make up the physical, social, and attitudinal environment in which people live and conduct their lives.

This classification reflects a shift away from the ‘bio-medical model’ of disability that focuses on impairments towards the ‘social model’ of disability that takes an interdisciplinary approach. This includes the views of disabled people themselves, and reflects a view that the presence of impairments should not be the cause of individuals being excluded from participation in society. Measures of participation can be sensitive to change in the child’s participation resulting from change in their environment whereas measures of impairment cannot.

QoL measures vary greatly in the extent to which they map to ICF-CY domains**9** of impairment, activity limitation, and participation restriction, and there is considerable variation between QoL measures and their concept definition.

In the field of provision for intellectual impairment, reliance on IQ alone was replaced by the use of measures of adaptive behaviour that assess level of functioning in everyday life, that is determined partly by cognitive abilities and partly by other factors, including factors in the environment in which the individual is being assessed. By definition, adaptive behaviour is a reflection of the expectations that society makes of the individual being assessed and is rated by a third party. This makes it suitable for use in all individuals including infants, young children, and those with severe mental or physical disability.

A key component of QoS following treatment for a brain tumour in childhood relates to endocrine outcomes. Timely (and ideally pre-symptomatic) hormone replacement therapy may prevent health-related consequences of disturbed growth, thyroid, and gonadal function which affect virtually all children receiving therapy for brain tumours, regardless of their histology or position within the brain, and impact adversely on their QoL.**10,11** Other rarer more centrally placed suprasellar tumours may result in severe and life limiting hypothalamic-pituitary deficits which are as yet under researched and poorly understood, despite their propensity in a population with otherwise high and prolonged survival.**12-14**

Measures currently in favour in paediatric neuro-oncology are predominantly measurements of impairment (e.g. psychometric deficits, quantification of neurological deficit, height deficits, fertility impairment and endocrine replacement therapy) but also reflect activity limitations or participation restrictions (e.g. ability to plan and organise in everyday life, academic attainments at school, extent of engagement in sport). Quantification of impairment is more closely aligned with attempts to understand mechanisms but the principal clinical questions are related to the way in which a brain tumour, its location, and its treatment affect the probability of the child and adolescent reaching milestones such as the ability to live and work independently as a young adult, achieve sexual and reproductive maturity, form peer relationships, and achieve parenthood.

**2. Developing an Agreed Protocol**

While variations of national practice pose numerous challenges to the implementation of outcome assessments across Europe, we propose that it is a worthwhile and essential endeavour in the field of central nervous system (CNS) tumours in childhood. There is preliminary evidence from the United States to suggest that multi-site assessment of neurocognitive functioning comprised of a small number of indirect assessments (i.e. validated questionnaires) supplemented by a short battery of direct assessments (i.e. brief psychometric assessment) is feasible and potentially efficacious in North America.**15** Similarly, a short battery of direct assessments has been successfully applied across multiple sites in Germany.**16** Questionnaire-based indirect assessment of neurocognitive, QoL, and growth aspects of QoS has also proved feasible and informative across seven European countries and languages.**17,18**

It is with this in mind that the SIOP-E Brain Tumour QoS working group has conducted international meetings attended by those responsible for providing care to children across Europe after diagnosis of a brain tumour. In these meetings, a strong consensus view was expressed in favour of a ‘core plus' approach, in which core assessments (both indirect and direct tests) are recommended for all clinical trials. The core component is a relatively brief screening assessment that is compatible with routine clinical provision in most countries, and allows comparisons across countries within and between tumour types and tumour locations). The 'plus' component of this approach enables the addition of assessment which can be selected by individual countries and/or tumour-, age-, and location-specific groups. We have also met, in the USA, with members of relevant working groups of the North American Children’s Oncology Group (COG) and are grateful for their willingness to share their experience of the challenges of systematically assessing QoS and for their pioneering work in establishing an ongoing QoS study to which investigators undertaking studies of individual tumour types can add assessment of QoS by offering participants in their studies the opportunity to be included in the ongoing QoS study (see final paragraph of this paper).

Incorporating QoS data in clinical trials across Europe is particularly difficult due to the number of different languages in which assessments are conducted. Questionnaires and psychometric assessments are developed and translated at different times, and the same assessments are not necessarily available in each country. We have attempted to address the issue of different test availability in different countries by using z-score comparisons. We are proposing that data from tests that measure the same domains and constructs can be pooled using analysis of z-scores. Endocrine and other medical data provided on Case Record Forms by clinicians can, however, usually be obtained across European countries using questions in the English language. Growth and pubertal data thus obtained may be age and sex-standardized against UK British growth reference values (1990 standards),**19** to allow inter- and intra-group comparisons at varying ages and time points for all European data sets.**18** From information on time to hormone therapy it is possible, by Kaplan Meier statistics, to determine Endocrinopathy Event-Free Survival (EEFS).**14**

This position statement is largely confined to core domains of function and to relatively brief assessments that might then indicate the need for additional assessment and intervention whereas more detailed assessments are beyond the scope of this paper. In relation to neurological function, for example, the measures within scope include patient and parent report, and in some cases physician report on Case Record Forms, of pain or impaired function relating to hearing, vision, facial weakness, swallowing, limb stiffness or weakness, ataxia or restricted activity in the domains of ambulation, dexterity, emotion, learning, and emotion but quantitative assessments of seizure burden, visual fields, audiograms, ataxia or mutism are out of scope. These quantitative assessments might be required in particular contexts (e.g. cerebral cortical tumours, optic pathway tumours, treatment with platinum-containing therapies and posterior fossa tumours for the respective assessments). Similarly, the measures of psychological function within scope include core measures of emotional symptoms, conduct problems, hyperactivity, peer problems, pro-social behaviour, fatigue, concern about appearance and self-report of health and wellbeing but do not include more specific domains of psychological function such as locus of control, or self-esteem.

***Consensus Methodology*:**

In keeping with the proceedings of the SIOP-E Brain Tumour working groups, formal consensus methodology was not used. However, elements of Delphi and RAND consensus methods**20, 21** were employed. At the time of the final consensus agreement of this position paper, the Quality of Survival Group had 23 registered members, representing 11 European countries.

Face to face discussions between members of the SIOP-E Brain Tumour Quality of Survival group, were held on 11 occasions at meetings across Europe between 2006 and 2013. At these meetings research papers and other information were shared, and followed up with e-mail discussions and telephone conferences. These discussions were minuted, and all the information was collated and distributed to all members of the QoS Group for comment. Each country described in this paper had at least one clinical neuropsychology representative or a clinical psychologist with expertise in neuropsychology. In addition, experts in neurology, endocrinology, oncology, and rehabilitation medicine were represented and all agreed upon the final proposed protocols. Consensus agreement of the protocol was specifically in relation to domains of functioning rather than assessment tools *per se* due to a lack of universal availability of specific tests. The final protocol includes only those elements on which there was complete consensus.

**3. Domains and Measures of Neurocognitive and Quality of Life Outcomes**

**a. Direct Assessment**

As part of the process of developing a core battery, current approaches in Europe and the USA were considered. These core batteries are broadly summarised in Table 1.

Following discussions of the different national approaches, domains and constructs of direct assessment have been developed, broadly based on the Cattell-Horn-Carroll integrated model of Cognitive abilities.**21** The proposed constructs for brain tumour trials have been decided by group consensus, discussion of current literature, and clinical experience relating to outcomes for survivors of childhood brain tumours. The domains identified for assessment are frequently reported to be impaired for these children. Domains for a core battery of assessments, supplementary domains, and examples of tests for abilities in those domains are provided in Table 2. The estimated time for administration of the core battery of direct assessments is 50-75 minutes, depending on the precise tests selected to assess those core domains. Priority has been given to using tests that are widely available internationally even in cases where the use of these tests sometimes also results in a loss of information relative to other tests that are only available in one or two countries.

The group concluded that the direct assessment of executive functions is a complex area with numerous tests available and few tests common to more than one country. Therefore, specific tests cannot be identified for use across Europe, but the test batteries from which they are commonly derived are provided in Table 2. Details of all languages in which tests are available are not provided due to the time-sensitive and changing nature of this information. Some measures are available in all European languages (e.g. versions of the Wechsler Intelligence Scales for Children), whereas others have very few translations (e.g. Test of Everyday Attention for Children) and the use of a family of tests that differ between countries but that measure the same domain will be the only option available. Similarly, if direct assessment of executive functioning in specific tumour types is required, specific tests would need to be agreed by individual countries.

**b. Indirect Assessment**

Four well validated indirect generic QoS assessments available in eight or more European languages, supplemented by a fifth questionnaire that provides demographic, service use, and categorical outcome data**23** have been used in SIOP-E trials.**17,18** Two of the four generic assessments (the BRIEF and the PedsQL) also form part of the battery of indirect plus direct assessments used by COG.**15** Funded in part by EU grants, these questionnaires have been uploaded in eight languages into HealthTracker©, a web-based database which has a ‘patient portal’ at which each age group (young children, children, adolescents, and adults) is presented with age-appropriate information and access to interactive questionnaires to which they can directly provide their responses from any computer connected to the internet. Feedback from paediatric neuro-oncology patients using this system has been positive across Europe and the effectiveness of this means of patient- and parent- reported data collection will be tested in PNET5, the SIOP-E Brain Tumour Group study of treatments for standard risk of medulloblastoma commencing in 2014. The questionnaires will be supplemented by brief medical, endocrine, audiological, and neurological data provided by clinicians.

The questionnaires currently in use with families enrolled in SIOP-E trials are:

* Health Status (all ages):
	+ - The Health Utilities Index (HUI)**24**
* Quality of Life:
* Children <18 years:
	+ The Pediatric Quality of Life Inventory (PedsQL) – Core scales (version 4.0) and Multidimensional Fatigue modules.**25**
	+ Adults >18 years:
* The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)**26** and the Multidimensional Fatigue Inventory.**27**
* Behavioural Difficulties(children <18 years):
* The Strengths and Difficulties Questionnaire (SDQ).**28**
* Executive Function(all ages):
* The Behavior Rating Inventory of Executive Function (BRIEF).**29**
* Demographic, Endocrine and other Medical Information (all ages):
* Medical, Educational, Employment and Social Questionnaire (MEES)**23** (adapted).

Endocrine and other medical information provided by clinicians is provided as part of the data returned on the Case Record Forms.

Currently absent from the above list of indirect assessments is any measure of adaptive behaviour which may indicate an individual’s chances in the long-term, of living independently, gaining employment, sustaining a long-term personal relationship, or parenting. By definition this assessment is obtained from a third party’s ratings. These data could be obtained at all ages. The COG battery includes the Vineland Adaptive Behavior Scales (VABS)**30** questionnaire. This is applicable at all ages and can be completed from responses to telephone interview or to a parent or caregiver rating form.**31** This assessment has the following domains of adaptive behaviour: Communication (expressive and receptive), Daily Living Skills (personal, domestic, and community), Socialization (interpersonal relationships, play and leisure, coping skills), Motor Skills (gross and fine, with a ceiling of abilities at 5 years), and Problem Behaviours. There are alternative similar adaptive behaviour measures such as the Adaptive Behavior Assessment System (ABAS)**32** but these are not available in multiple languages.

Also currently missing from assessments in both Europe and North America are measures of participation which have been used across Europe in children with cerebral palsy. In that context, a study of 1,174 children aged 8 to 12 years in 6 European countries recently reported that more than half of the variance in the participation in home life, assessed with the Assessment of Life Habits (Life-H) questionnaire,**33** was determined by environmental factors. The authors suggested that, since environmental factors were more amenable to change than the child’s impairments, a trial of an intervention to modify the child’s environment was more likely to be cost effective than traditional approaches focused on modifying the child’s impairment.**34**

We therefore propose the following supplementary indirect measures:

* Adaptive Functioning: e.g. Vineland Adaptive Behavior Scale,**30** Adaptive Behavior Assessment System.**32**
* Participation: e.g. Life-H questionnaire.**33**

**c. Measurement of Endocrine Outcomes**

The different hypothalamic – pituitary (H-P) – target gland axes are dynamic, hormonal feedback signaling loops in which growth hormone (GH) secretion is always the most vulnerable and adrenocorticotropin (ACTH) the most robust in the event of any brain injury.**34‑36** The developmental transcriptional pathways are switched on and off in a similar hierarchy at vital developmental stages in the foetus and may be disrupted in children with brain tumours at several levels simultaneously, by tumour mass and multimodal focal and systemic therapy. Hence evolving deficits can only be characterised by careful longitudinal study; for example precocious puberty due to premature activation of hypothalamic gonadotropin releasing (GnRH) hormones, is a recognised presentation of suprasellar tumours regardless of histology. With time and increasing age, gonadotrophin deficiency (arresting pubertal development) is also possible, even in the same patients and especially after surgery and high dose irradiation.**10,12,14,36,37** Milder early puberty may occur after treatment for more laterally- or inferiorly-placed tumours despite the exposure to co-existent and additive gonadotoxic chemotherapy or spinal irradiation**10,11** which may only later manifest as premature ovarian failure or azoospermia.

Endocrine morbidities fall into two broad categories:

1. Those related to primary defects of growth (skeleton), thyroid, and gonadal glands –

which result from direct radiation and systemic chemotherapy and affect virtually all children treated for brain tumours regardless of its position within the brain.

1. Those due to disturbed hypothalamic-pituitary (H-P) function caused by brain injury.**11**

Excepting central GH deficiency,**38** the latter are almost exclusively associated with rare tumours in the suprasellar midline position,**12‑14** are independent of their histology and, by implication, the chemotherapy imposed. Together with the visual, neurological and cognitive disturbances experienced, such endocrine deficits have a significant impact on subsequent health-related quality of survival. Pituitary GH deficits are thus almost universal consequences of cumulative brain injury resulting from the tumour itself, surgery and its complications and, in a dose-dependent way, of chemotherapy and radiotherapy. Potentially treatable GH deficiency occurs more quickly and completely where tumour, disease, and treatment burden are greater, and in the youngest children. These are also the patients in whom time to sexual maturity and skeletal fusion, and hence the potential deficit in growth, is greatest. Additional skeletal damage results from spinal irradiation and adjuvant chemotherapy**11** which is only partially reversible by GH replacement; as with thyroid and gonadal dysfunction, the major deficit is at the level of the target gland (skeleton). Unrecognised or untreated compensated hypothyroidism may exacerbate the risk of secondary tumours of the thyroid.**39,40**

By contrast, hypothalamo-pituitary damage is less common and only seen in midline, suprasellar tumours.**13,14,38,41** This may be manifest as disruption of sleep-wake cycles, hunger, satiety, temperature, blood pressure, puberty and fertility (gonadotrophic releasing hormones), and life-threatening disturbances of thirst (arginine-vasopressin) and stress response (adrenocorticotrophic hormone).

Thus "core" endocrine assessments should include birth demographics, together with longitudinal growth and puberty, and thyroid function assessments and the interval to any hormone replacement therapy, for all children with CNS tumours.

Core measures required for inclusion in European clinical trials must therefore include:

1. Birth weight (kg)
2. Gestation (weeks)
3. Parental heights (cm) from which mid-parental target height can be calculated
4. Standing height (cm)
5. Sitting height (cm) from which to calculate relative body proportions and spinal deficit
6. Weight (kg) for body mass index calculation
7. Tanner Pubertal Staging (and age at menarche in girls)
8. Follicle stimulating hormone (FSH), and thyroid stimulating hormone (TSH)
9. Start and end dates of any hormone replacement therapy

These core measures should be collected at baseline via the Case Record Form. Items 1 and 3 are also gathered using the MEES (see indirect measures above). Items 4-9 should be repeated at annual intervals and/or pre-specified cross-sectional assessment intervals thereafter.

Additional "core plus" assessments of detailed H-P hormone function are likely to be specific to central, suprasellar tumours irrespective of their histology and may include dynamic hormonal data collection to H-P provocation or hormonal profiling performed longitudinally from baseline and at pre-specified intervals thereafter.

**4. Individuals with Sensory Impairments**

Many children who have received treatment for a brain tumour experience motor, visual, and auditory impairments that may affect their ability to undergo direct assessment, or for caregivers to fully complete indirect assessments of their functioning. In such cases adaptations to standardised measures may be appropriate (e.g. using enlarged copies of visual stimuli). The clinicians therefore need to judge whether standardised administration of the task has been achieved in affected patients. Data collection sheets for the ‘core plus’ battery will include the option to state when adaptations have been made to compensate for sensory impairments.

**5. Implementing an agreed protocol in European trials**

Implementing an agreed protocol for systematic longitudinal QoS assessments across different studies and many countries is extremely challenging. Each tumour-specific and any location-specific study has separately to comply with a lengthy list of research governance requirements and now has a lead time of several years before data collection can commence. The duration of funding of the QoS aspect of the trial will need to include a substantial period of follow-up, far in excess of the usual funding model predicated by the 5-year survival outcomes reported in oncology studies. Each national principal investigator of a study has specialised expertise in the treatment of brain tumours but this is unlikely to extend to the conduct of the QoS aspects to be addressed. There exists a wide spectrum of views, liaison with, delegation to, and locus of control for QoS aspects of ‘their’ study, overlaid by differing inter-country regulations on data protection, anonymisation, and centralisation, and the absence of agreed arrangements for national groups to share costs of international QoS data collection. Thus long-term QoS assessments have proved highly inefficient and will be virtually impossible to sustain across a larger number of studies.

Many of these difficulties would be surmounted by an ongoing QoS outcome study of the type currently in place in the USA Children’s Oncology Group group (Study ALTE07C1).**15** Individual tumour-specific treatment trials would seek to enrol patients into an ongoing QoS study adopting its existing procedures. The leads of individual SIOP-E Brain Tumour working groups have unanimously agreed to include QoS assessments, at least as secondary outcomes, in all future trials and have also accepted in principle, the goal of a single ongoing European QoS Outcome Study. The means of funding such a QoS study across Europe and implementing it in a truly collaborative (European) way is an important and, as yet, unresolved issue. Initiation of such a study would also require agreement on a schedule for QoS data collection that was applicable across several types of tumour and treatment and this is yet to be finalised. The pilot schedule for the collection of QoS information in ALTE07C1 study is at 9 months, 30 months and 60 months from diagnosis.**15** In PNET5, a SIOP-E European study, it is being collected between neurosurgery and radiation therapy; 24 and 60 months from diagnosis and at age 18 years. Both studies are evaluating QoS in children with medulloblastoma. The agreement, reported here, on the content of a common set of QoS assessments is, however, an important initial step towards a common QoS study for future European brain tumour trials in childhood.

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**Table 1 Tests and Subtests Commonly Used in Clinical Oncology Protocols in Europe and the United States of America**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **DOMAIN** | **USA** | **GERMANY** | **FRANCE** | **UK** | **BELGIUM**  | **ITALY**  | **NETHERLANDS** | **NORWAY** |
| Perceptual / Fluid Reasoning | Block Design (WISC-IV) | RPM  | Block Design Matrix Reasoning (WISC-IV) | Block Design Matrix Reasoning (WISC-IV) | Block Design (WISC-III) | Block Design (WISC-III) | Block Design (WISC-III) | Block DesignMatrix Reasoning (WASI) |
| Short-term memory |  | Number recall (K-ABC) | Digit Span\* (WISC IV or CMS) | Digit Span\* (WISC IV or CMS) | Digit Span\* (WISC III or CMS) | Digit Span\* (WISC III), | Digit Span\* (WISC III) | Digit Span (WISC-IV) |
| Visual-motor skills |  | Visual Motor Integration (Beery VMI) | Visual motor integration (VMI) | Design Copy(WRAVMA)  | Visual motor integration (VMI) | Visual motor integration (VMI) | Visual motor integration (VMI) |  |
| Motor Skills |  | Purdue Pegboard | Purdue Pegboard | Pegboard(WRAVMA) | Finger tapping  | Purdue Pegboard |  |  |
| Semantic Memory | Vocabulary (WISC-IV) | Vocabulary (WISC-IV) | Vocabulary (WISC-IV) | Vocabulary (WISC-IV) | Vocabulary (WISC-III) | Vocabulary (WISC-III) | Vocabulary (WISC-III) | Vocabulary (WASI) |
| Attention – vigilance and reaction times |  | Continuous Performance Test (CPT – short) | TEA-Ch / TEA / Mesulam | TEA-Ch / TEA | Amsterdam Neuropsychology Test Battery | Continuous Performance Test (CPT) | TEA-Ch/TEA | Continuous Performance Test (CPT-II), Knox, SDMT |
| Processing Speed | Coding and Symbol Search (WISC-IV) |  | Coding and Symbol Search (WISC-IV) | Coding and Symbol Search (WISC-IV) | Coding and Symbol Search (WISC-III) | Coding and Symbol Search (WISC-III) | Coding and Symbol Search (WISC-III) |  |
| Long-term Memory | Stories, Dot locations, Faces (CMS) List learning (CVLT) |  | Stories, Dot locations, Faces (CMS) List learning (CMS)Rivermead Behavioural Memory Test | Stories, Dot locations, Faces (CMS) List learning (CMS or CVLT), Word Pairs (CMS) | Dot locations, Family pictures, Word Pairs (CMS) | List Learning (BVN), TEMA | RAVLT, RCFT | CAVLT-II, Visual Reproduction(WMS) |
| Reading |  |  | Local reading measure | Basic Reading (WIAT-II) |  | Local reading measure |  |  |

Footnotes: see next page

Footnotes to Table 1

BVN (Italy): *BVN 5-11 - Batteria per la Valutazione Neuropsicologica per l'età evolutiva*.(A battery of neuropsychological tests developed for children aged from 5 to 11 years old)

(Tressoldi PE, Vio C, Gugliotta M, Bisiacchi PS, Cendron M: BVN 5-11 - Batteria per la Valutazione Neuropsicologica per l'età evolutiva. Trento, Erickson; 2005. OpenURL)

TOMAL/TEMA: Test of Memory and Learning (name recall)

CAVLT-II Child Auditory Verbal Learning Test

CMS Children Memory Scale

CPT Continuous Performance Test

CVLT California Verbal Learning Test

K-ABC Kaufman Assessment Battery for Children

RAVLT Rey Auditory Verbal Learning Test

RCFT Rey Complex Figure Test and Recognition Trial

TEA Test of Everyday Attention

TEA-Ch Test of Everyday Attention for Children

VMI Visual Motor Integration

WASI Wechsler Abbreviated Scale of Intelligence

WISC-III Wechsler Intelligence Scale for Children

WISC-IV Wechsler Intelligence Scale for Children

WMS Wechsler Memory Scales

WRAVMA Wide Raye Assessment of Visual Motor Abilities

WIAT-II Wechsler Individual Achievement Test

NB: Several countries use additional tests in their national protocols

**Table 2 Core and Supplementary (‘Plus’) Domains for Direct Assessment of participants in European childhood brain tumour studies**

|  |  |  |  |
| --- | --- | --- | --- |
| Domain | Core Measures  | Supplementary/ ‘Plus’ Measures | Examples of specific measures available in Europe |
| Perceptual/Fluid Reasoning |
|  | Matrices |  | Raven’s Progressive Matrices *or* Wechsler - Matrix Reasoning  |
|  |  | Visual motor reasoning | Wechsler - Block Design |
| Short-Term Memory |
|  | Number Recall |  | Kaufman ABC - Number Recall *or* Wechsler - Digit Span forwards |
| Working Memory |
|  | Number Recall backwards |  | Wechsler - Digit Span Backwards  |
| Visual Motor Skills |
|  | Visual motor integration |  | Beery Visual Motor Integration *or* Wide Range Assessment of Visual Motor Ability\*- Drawing Test *or* NEPSY Design Copy |
| Motor Skills |
|  | Pegboard |  | Purdue Pegboard, Wide Range Assessment of Visual Motor Ability - Pegboard |
| Semantic Memory/Knowledge |
|  | Verbal semantic memory |  | Wechsler - Vocabulary  |
| Attention |
|  | Sustained attention  |  | Conners’ Continuous Performance Test *or* Test of Attentional Performance (children’s version) – sustained attention *or* Test of Everyday Attention for Children\* - Score!  |
|  |  | Selective and Dual Attention | Test of Everyday Attention for Children - Sky Search, Sky Search DT and Score DT *or* Test of Attentional Performance (children’s version) – divided attention |
| Processing Speed |
|  | Processing speed |  | Wechsler - Coding and Symbol Search |
| Long-term Memory |
|  |  | Visual and verbal episodic memory | Wechsler Memory Scales - Stories, Word Lists, Dot Locations and Faces  |
| Executive Functioning |
|  |  | Fluency, Inhibition, Switching, Planning, Problem-solving | Behavioural Assessment of the Dysexecutive Syndrome for Children *or* Delis-Kaplan Executive Function System *or* Wisconsin Card Sorting Test *or* Amsterdam Neuropsychological Test Battery *or* Fonctions Exécutives de l’Enfant |
| Reading |
|  |  | Local reading measure |  Wechsler Individual Achievement Test - Basic Reading and Spelling |

\*In circumstances where an adolescent/young adult is beyond the age range of the test, adult versions should be substituted to measure the same construct