**Quality of survival assessment in European childhood brain tumour trials, for children below the age of 5 years**

**Limond J1, Thomas S2,3, Bull KS4, Calaminus G5, Lemiere J6, Traunwieser T7, van Santen HM8, Weiler L9, Spoudeas HA10, Chevignard M11,12**

**Affiliations**

1Department of Psychology, University of Exeter, UK

2Department of Psychology and Neuropsychology, Nottingham University Hospitals NHS Trust, UK

3Children’s Brain Tumour Research Centre, University of Nottingham, UK

4Clinical and Experimental Sciences, University of Southampton, UK

5Pediatric Hematology and Oncology, University Childrens Hospital Bonn, Germany

6Pediatric Hemato-Oncology, UZLeuven, Leuven, Belgium

7 Swabian Children’s Cancer Center, University Children’s Hospital, Augsburg, Germany

8Department of Pediatric Endocrinology, Wilhelmina Children’s Hospital, UMCU, Utrecht, the Netherlands

9 Department of Pediatrics and Adolscent Medicine, General Hospital, Medical University of Vienna, Austria

10Department of Neuroendocrinology, London Centre for Paediatric and Adolescent Endocrinology at Great Ormond Street and University College Hospitals, London UK,

11Rehabilitation Department, and Outreach Team for children and adolescents with acquired brain injury, Saint-Maurice Hospitals, 14 rue du Val d'Osne, 94410 Saint-Maurice, France

12Sorbonne Université, Laboratoire d'Imagerie Biomédicale, LIB, 75006 Paris, France

**Corresponding Author:** Dr Jenny Limond, Department of Psychology, Washington Singer Building, University of Exeter, Perry Road, Exeter, EX4 4QG, U.K. <j.limond@exeter.ac.uk>

**Abstract**

The highest incidence rate of childhood brain tumours is in children below the age of five years, who are particularly vulnerable to the effects of treatments. The assessment of quality of survival (QoS) in multiple domains is essential to compare the outcomes for different tumour types and treatment regimens.

The aim of this position statement is to present the domains of health and functioning to be assessed in children from birth to five years, to advance the collection of a common QoS data set in European brain tumour trials.

The QoS group of the European Society of Paediatric Oncology (SIOP-E) Brain Tumour group conducted consensus discussions over a period of six years to establish domains of QoS that should be prioritised in clinical trials involving children under 5 years.

The domains of health and functioning that were agreed to affect QoS included: medical outcomes (e.g. vision, hearing, mobility, endocrine), emotion, behaviour, adaptive behaviour, and cognitive functioning.

As for children aged five years and older, a ‘core plus’ approach is suggested in which core assessments are recommended for all clinical trials. The core component for children from birth to three years includes indirect assessment which, in this age-group, requires proxy assessment by a parent, of cognitive, emotional and behaviour variables and both direct and indirect endocrine measures. For children from four years of age direct cognitive assessment is also recommended as ‘core’. The ‘plus’ components enable the addition of assessments which can be selected by individual countries and/or by, age-, treatment-, tumour type- and tumour location- specific trials.

**Keywords:** Assessment; Quality of Survival; Brain Tumor; Infants; Young children; Late effects.

1. **Introduction**
	1. **Survivorship after childhood brain tumor**

Incidence rates of brain tumours in children in Europe and the U.S. range from an overall rate of 2.99 to 5.26 per 100,000, with the highest incidence seen in children below the age of 5 years**1**. In Europe, survival rates in children diagnosed with CNS tumours before the age of 15 years have significantly improved since the late 1970s**2**, recently standing at 66.2% 5-year survival for all tumours combined**3**. This has been attributed to better histological and molecular diagnosis, the development of collaborative European randomised therapeutic trials of more intense multimodal therapies (chemotherapy, radiotherapy, and surgery) as well as improved imaging methods and supportive care. In particular, the increased use of intensive high dose and toxic treatments has contributed to higher survival rates, especially of younger children and those with higher grade or metastatic disease, but this may in turn reduce their quality of survival (QoS). This development has led to an increased recognition of the need to quantify the effects of different tumour locations and treatments on neurocognitive development and quality of life (QoL) for survivors. The cognitive and endocrine sequelae of the tumor and its treatments together constitute an under-recognised acquired brain injury, which can impact on the cognitive development of the growing child, including learning, reasoning, visual perception, working memory, attention, processing speed, executive function, and academic attainments, arguably worst in the youngest **4,5, 6, 7**. In addition, physical, neurological, sensory, endocrine, emotional, social, and behavioural difficulties can affect all areas of adaptive and day-to-day functioning and for children treated for a brain tumour these developmental trajectories may be altered**8**. It is therefore appropriate to consider measures of overall QoS which incorporate these multiple concepts over the long-term. By developing this evidence-base we can better inform clinical decision making and support the case for endocrine replacement and neurorehabilitation services to support these children by collecting QoS data in addition to event-free or overall survival.

The current position paper is the result of consensus discussions within the European Society of Paediatric Oncology (SIOP-E) Brain Tumour QoS working group, culminating in an agreed protocol for data collection in clinical trials for children under the age of five years. This was undertaken with direct reference to a similar paper focusing on children aged 5-18 years**9** to facilitate the collection of longitudinal data for children of all ages. As pointed out by Limond et al.**9**, it is vital to distinguish between data collected for clinical trials versus clinical assessment. The former, outlined in this paper, is intended to compare QoS outcomes between groups of patients with similar tumours and locations, receiving different treatment regimens. However, local clinicians may conduct more detailed assessments to meet each child’s individual clinical needs.

**1.2 Terminology and conceptual framework**

Discussions of measurement of QoS typically use the International Classification of Functioning, Disability and Health: Child and Youth Version**10** as a conceptual framework. The key areas of focus being separated into i) impairments, ii) activity, iii) participation, and iv) environmental factors. We have previously described in detail the application of this framework to brain tumour clinical trials for children from the age of 5 years**9**, an approach being adopted more widely in the field of paediatric neuro-oncology**11**.

In the current paper, the term QoS is used as an umbrella term relating to a range of medical, physical, cognitive, emotional, and behavioural domains that contribute to the overall outcomes (both objective and subjective) for individuals who have been treated for a brain tumour. Quality of life is the sub-domain of QoS that is essentially subjective and, therefore self-reported. In children aged less than five years, however, reliable self-report cannot be achieved and so proxy-report by parents has to be relied upon.

The terms ‘direct’ and ‘indirect’ assessment are used to highlight the different ways that data may be collected. Indirect measures are based on information reported by others whether self-report or proxy-report (e.g. parents), while direct measures are assessments undertaken by an examiner (e.g. completing cognitive tests, blood tests, or body measurements).

**1.3 Issues in assessment of young children**

While many of the concepts described in Limond et al.**9** also apply to the under-fives, there are additional issues regarding cognitive assessments to be considered in this younger age group, which were discussed during the development of this consensus.

Assessment of development in very young children may not be strongly predictive of long-term outcomes**12** and this may limit the reliability of comparisons between outcomes of different treatment approaches within trials in young children, unless based on long term outcome data. As described by Baron**13** it is increasingly recognised “that procedures, interpretive rules and algorithms applied to the evaluation of brain function in school-aged children do not translate optimally to pre-schoolers who have an even more immature brain” (p301). This creates a number of challenges in establishing a neurodevelopmental baseline in young children**14**. At all ages there are issues in optimal timing of baseline assessment, which can potentially be undertaken before diagnosis, surgery, or radiotherapy, or even after radiotherapy. Each choice involves different underlying assumptions and difficulties in obtaining both valid and reliable data for longitudinal research. Alternatively, proxy estimates (e.g. through parent education, occupation, and socioeconomic status) can provide estimates of baseline functioning at a broad level, whereas ‘premorbid measures’ or ‘hold tests’ used in older children or adults (often relating to vocabulary or word recognition) are not applicable to the under-fives**14**. Other proxy estimates can be generated through statistical modelling, actuarial formulas, and retrospective rating on questionnaires or interviews (e.g. Vineland Adaptive Behavior Scales) to evaluate functioning before diagnosis, but caution is recommended with all of these approaches. Ris et al.’s**14** review of methods used in establishing a baseline for children treated with radiation for brain tumours highlights the importance of collecting a range of data (e.g. demographics and direct measures) as well as using proxy measures to allow triangulation of data and thereby increase the level of confidence in the estimate of baseline functioning. In addition, careful consideration of how the baseline is estimated and reported is highlighted as a critical issue for clinical research.

A number of measurement issues were highlighted during the consensus discussions. Assessments such as the Bayley Scales of Infant Development, one of the few measures available in multiple languages, typically overestimates ability**15**, but this is less problematic in randomised clinical trials of treatment arms where group differences are the focus of analysis. Also, measures are normed for very narrow age ranges, in some cases with normative data collected for different age ranges in different countries. This can result in the use of different measures evaluating the same construct both within tests, and between tests used across the lifespan. As a result, the reliability and validity of measures being pooled to evaluate the same construct will need to be carefully considered in the statistical analysis of the data and clearly reported.

The concept of participation is different for very young children compared to older children, and parental views on participation in very young children are likely to be heavily influenced by parental socioeconomic status. In addition, impairments in participation are potentially more likely to be identified when children are older. However, there are measures of participation for children from the age of 18 months, which demonstrate relatively good levels of reliability and validity (Child engagement in daily life**16**) and measures of school participation for older children (School participation scales**17**).

An area of particular importance when assessing young children is that of adaptive functioning. This is conceptually different to intelligence and also relates to participation, as it examines levels of functioning in everyday life, and includes communication skills, daily living skills, and socialisation. These areas are determined partly by cognitive abilities and partly by other factors, including the environment in which the individual’s behaviour is being described e.g. home or school, as well as family and cultural expectations. It is particularly important to recognise that, in very young children who may be unable to undertake a direct cognitive assessment, adaptive functioning and intellectual abilities are only modestly correlated**18** and these two concepts should not be considered as interchangeable. In young children, these adaptive functioning measures have pros and cons, as described above, but are one of the more reliable approaches to obtain an overview of functioning in this age group. Adaptive functioning assessments are typically based on parent reports and can therefore be used with even the most physically and cognitively impaired children, including those with challenging behaviour.

**1.4 Issues in Endocrine Assessment of Young Children**

 Endocrine morbidities fall into two broad categories:

1. Those related to primary defects of growth (skeleton), thyroid, and gonadal glands which result from direct neuraxial radiation or systemic chemotherapy. These issues affect virtually all children treated for brain tumours regardless of its position within the brain**19, 20, 21**

2. Those due to disturbed hypothalamo-pituitary function caused by disease and treatment related cumulative acquired brain injury to the diencephalon**22**. Excepting growth hormone deficiency,the latter are almost exclusively associated with tumours and/or surgery in the suprasellar midline position,occurring more quickly and completely the greater the burden of tumour and focal injury to the area**22, 23, 24** or very rarely after high dose >54Gy focal irradiation to the area**25, 26, 27**. Hypothalamic damage may occur in association with a diencephalic or suprasellar tumour, especially in infancy. It is less common than deficits of thyroid or gonadal function but infants are at higher risk than older children. It can cause a severe neuropsychiatric and behavioural syndrome ofdisrupted sleep-wake cycles, hunger, satiety, temperature, blood pressure, growth, puberty, fertility (gonadotrophic releasing hormones), life-threatening metabolic disturbances from diabetes insipidus (deficiency of arginine-vasopressin) and absent stress responses (adrenocorticotrophic hormone deficiency**24**).

A key component of QoS following treatment for a brain tumour in childhood hence relates to endocrine outcomes; evaluation of which poses specific challenges in infants. Lying height and crown-rump (sitting height) measurements are often inaccurate or are omitted in sick infants in neuro-oncology settings. Physiological slowing or acceleration of growth in the first two years of life may complicate interpretation of pre-treatment height centile trajectory. Infants with suprasellar gliomas can often present with diencephalic syndromes causing failure to thrive and emaciation with relative height preservation**28** but later followed by obesity**29**, whereas neurofibromatosis 1 or raised intracranial pressure syndromes may present with sexual precocity and increased growth rate with later gonadotropin deficiency**22**. For this reason, all infants with brain tumours require endocrine review at baseline so that Tanner pubertal staging and careful auxology, including parental heights, can be properly recorded and interpreted in relation to growth velocity, bone age, or pituitary chemistry, as required.

Central midline suprasellar tumours of the optic pathway or hypothalamic pituitary area (e.g. craniopharyngioma, astrocytoma) constitute a higher proportion of all brain tumours in infants than in older children and may present with endocrinopathies, visual impairment and diencephalic syndromes unrelated to treatment. Hypothalamo-pituitary hormone deficits evolve in a typical order with early/precocious puberty and growth hormone deficiency occurring first and adrenocorticotropin deficiency last**22, 23, 26**, whilst diabetes insipidus is seen only in the context of pituitary stalk disease or surgery to that area**22, 24**. In the post-operative setting, the perioperative triphasic salt/water imbalance can be life threatening and/or contribute to strokes, especially in infants**30.**

Children presenting with precocious puberty may eventually develop gonadotropin deficiency resulting in late or arrested puberty and hypogonadism**22**. Children with cortical and cerebellar tumours away from the suprasellar midline may experience central growth hormone deficiency and early puberty, additionally complicated by peripheral glandular impairment of gonadal or thyroidal hormone secretion by chemotherapy or spinal irradiation**19, 20, 21**. Unrecognised or untreated primary or compensated hypothyroidism may exacerbate the risk of thyroid nodules after radiation exposure**19** and may theoretically add to the recognised risk of thyroid cancer after spinal radiation**31**. Reduction in growth is only partially reversible by GH replacement32, 33 because of additional spinal shortening following radiotherapy with or without chemotherapy20. In all cases, growth and pubertal development should be monitored from diagnosis and after treatment. Growth hormone, thyroid hormones and sex steroids are all essential for normal growth, development, and well-being, and they also have an important respective role in brain maturation and cognition **34**. If endocrine deficits go unrecognized and are not substituted promptly, an adverse impact on participation in daily life, learning, and behaviour might be expected, resulting in diminished QoS.

Infants, more than older children, have low-grade suprasellar disease and hence are at risk of an evolving central and potentially life threatening panhypopituitarism and diabetes insipidus by virtue of the tumour’s proximity to the hypothalamo-pituitary axis. The assumption that neurocognitive and endocrine toxicities are predominantly late effects of cranial irradiation - now avoided in the youngest children – rather than evolving early effects from tumour-related harm at diagnosis aggravated by neurosurgical intervention and recurrence **22, 24, 27**, has paradoxically meant that these children may not undergo routine endocrine assessment at diagnosis. Infants with suprasellar disease are at risk of morbid hypothalamic obesity, hypodipsia, sleep, temperature, visual, and behaviour disorders. These may shorten life or severely affect its quality during survival which may be prolonged **22, 23, 24**. It is tumours in these anatomical locations that particularly require routine early endocrine referral and calculation of endocrine morbidity scores in the ‘plus’ component of specific trials**22**.

Growth and pubertal data obtained can be age- and sex-standardized against each country’s own growth reference values to allow inter- and intra-group comparisons at varying ages and time points for all European data sets**36**. A novel way to distinguish central pituitary from peripheral target gland dysfunction using time to hormone replacement therapy and basal biochemistry (TSH and FSH) has been described in Gan et al**22** using Endocrinopathy Event-Free Survival for each pituitary hormone deficit (EEFS), and Endocrine Morbidity Score (EMS**22**) that can be recorded on specifically designed Case Report Forms (CRFs).

1. **Developing an agreed protocol**

In Europe, differences in national practice, availability of different cognitive assessment tools, and the multiple native languages, adds a degree of complexity to developing a protocol that is comparable across countries. However, as identified in Limond et al.**9**, the SIOP-E Brain Tumour QoS working group has hosted international meetings where a consensus view has been developed, again recommending a ‘core plus’ approach, with core measures for both direct and indirect assessments, for all clinical trials. For cognition, the core component is relatively brief, and in children less than four years old, involves only indirect measures. As before, consensus agreement of the protocol in relation to cognitive function was related to domains of functioning rather than assessment tools per se due to a lack of universal availability of specific tests and the possibility of new measures being published in coming years. We suggest that the issue of different test availability in different countries be managed by z-score comparison and data from tests measuring the same domains and constructs is pooled using analysis of z-scores.

In addition, endocrine and other medical data (e.g. height, weight, Tanner stage, hydrocephalus, epilepsy, peri-operative complications including stroke and triphasic responses, auditory, and visual impairments) may require direct assessment and should also be documented on CRFs and via the self-reported Medical Educational Employment and Social questionnaire (MEES**35**) which provides a basic framework for the quantitative assessment of endocrine as well as neurological function, use of therapeutic and educational services, and re-integration into society and independence following treatment for a brain tumor. The MEES distinguished between treatment groups in terms of physical restriction and need for therapeutic and educational support in PNET3 survivors32 and identified treatment related decrement in height in PNET4 survivors33.

This position statement is largely confined to core domains of function and to relatively brief assessments for the purpose of clinical trial data collection. More detailed assessments for clinical purposes are beyond the scope of this paper.

**2.1. Consensus methodology**

In keeping with the proceedings of the SIOP-E Brain Tumour working groups and the previous position paper**9**, formal consensus methodology was not applied, although elements of Delphi and RAND consensus methods**37, 38** were used where possible. At the time of the final consensus agreement of this position paper relating to children under the age of 5 years, the QoS Group had 58 registered members, representing 16 European countries and multiple specialities. Face-to-face discussions between members of the SIOP-E Brain Tumour QoS group, were held on six occasions at meetings across the world between 2012 and 2018. 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 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. In all areas, including cognitive, emotional, behavioural and medical, the final protocol includes only those elements on which there was complete consensus.

1. **Quality of Survival Outcomes**

**3.1. Indirect assessment**

***3.1.1 Indirect ‘core’ measures***

These measures relate to multiple aspects of functioning including cognitive, emotional, behavioural, endocrine and other medical (e.g. vision, hearing and physical morbidity). An agreement was reached that direct cognitive assessment of children below the age of four years is particularly difficult and not always reliable or valid. The following parent-report core measures are recommended for all under-fives in all trials but for children before their fourth birthday these will be the primary outcome measures in the absence of direct cognitive assessments:

* Demographic, Endocrine, and other Medical information (all ages):
	+ Medical, Educational, Employment, and Social Questionnaire (MEES, adapted**35**)
* Adaptive functioning (0-90 years):
	+ Vineland III parent/caregiver rating form**39**
* QoL (1 month-18 years)
	+ PedsQL – Generic Core and Multidimensional Fatigue Scales**40**
* Mental Health, Social Interactions, and Behavioral difficulties (from 2 years):
	+ The Strengths and Difficulties Questionnaire (SDQ**41**)
* Executive Functioning (from 2 years)
	+ The Behaviour Rating Inventory of Executive Function - Preschool**42**

There was considerable debate within the group with regard to establishing a developmental level in this young population, particularly whether a direct measure such as the Bayley Scales of Infant Development (3rd edition) should be used. It was also acknowledged that the indirect measure of adaptive functioning, the Vineland Adaptive Behavior Scales (3rd edition) provides an indication of developmental level. When two tests consistently differ in terms of their standardised scores within individuals it is recognised that they may be assessing different constructs. For example, the Vineland-II communication and motor scores consistently reported as significantly higher than corresponding scores for communication and motor skills from the Bayley-III direct assessment43.. However, it is also reported that Vineland-II and Bayley-III domain and subdomain scores are highly correlated**43, 44**. It was agreed that the Vineland-III parent/caregiver rating form would be the recommended measure for adaptive functioning and developmental level, and if both measures are used within a trial, or for comparison between trials, the data should be examined carefully before being considered as measuring the same construct. The most likely issue being that the Vineland could indicate higher levels of functioning, perhaps due to collecting reports of what is typically done by the child as measured by the Vineland, rather than how they perform within a single direct assessment as measured by the Bayley’s.

***3.1.2 Indirect ‘plus’ measures***

Measuring developmental level (rather than adaptive functioning) using an indirect measure is recommended as a ‘plus’ measure for trials and/or countries where measures are available. For example, the Ages and Stages Questionnaire**45** and the Child Development Inventory (CDI, translated into French; IDE**46**) can be utilised. Such scales are available in some languages and are being validated in others. Those developing clinical trials protocols should consider the potential use of these measures as they become available.

Measuring participation, as discussed above, is a field of enquiry that is developing rapidly and an appropriate questionnaire would be recommended as a ‘plus’ measure where available. Current potential measures include the Child Engagement in Daily Life questionnaire**16**, the Child and Adolescent Scale of Participation**47**, and the Life Habits Questionnaire**48**. It is also important to note that while participation measures were not indicated in the position paper for children aged five years and over**9** this would now be recommended as a ‘plus’ measure as described here for infants.

**Table 1 - Core and Supplementary Indirect Measures and Order of Administration**

|  |  |  |
| --- | --- | --- |
| **Domain**  | **Measure** | **Starting age** |
| **Core Measures** |  |  |
| Demographic, Endocrine, and other Medical information | Medical, Educational, Employment, and Social Questionnaire (MEES, adapted**35**) | Birth |
| Adaptive Function | Vineland III parent/caregiver rating form | Birth  |
| Quality of Life | PedsQL – Generic Core and Multidimensional Fatigue Scales**40** | 1 month  |
| Mental Health, Social Interactions, and Behavioural difficulties  | The Strengths and Difficulties Questionnaire (SDQ**41)** | 2 years |
| Executive Function  | The Behaviour Rating Inventory of Executive Function - Preschool**42** | 2 years |
| **Plus Measures** |  |  |
| Developmental Level | E.g. Ages and Stages Questionnaire**45** or Child Development Inventory (CDI, translated into French; IDE**46**) or local equivalent. | Ages & Stages -1 monthCDI -15 months |
| Participation | E.g. Child Engagement in Daily Life questionnaire**16** or Child and Adolescent Scale of Participation**47** or Life Habits Questionnaire**48** | As per specific measure |

**3.2. Direct cognitive assessment**

Following discussions of current national approaches across Europe a small core battery of direct cognitive assessments is recommended for children between their fourth and fifth birthdays. Domains and constructs of direct cognitive assessment were again considered as for older children, using the Cattell-Horn-Carroll integrated model of Cognitive abilities**49** and the cross-battery approach**50** which uses information from multiple assessment batteries. The proposed constructs for brain tumour trials**9** were considered appropriate for this younger age group. The domains identified for cognitive assessment are frequently reported to be impaired in children treated for a brain tumour at any age and facilitate comparison between domains measured in the under-fives. Domains for a core battery of assessments, supplementary ‘plus’ domains, and examples of tests for abilities in those domains are provided in Table 2. For children before their fourth birthday, direct assessment of developmental level is included as a ‘plus’ measure.

The consensus discussions relating to children under the age of 5 years highlighted the risk of incomplete data collection as a consequence of young age and limited participation. As a result, a test administration order was agreed to ensure the same tests are completed in the same sequence to maximise data sets for cross-centre and cross-country comparison. It is recommended that the CRF for all protocols requests information regarding the reason why some or all tests could not be administered, including sensory impairments, fatigue, challenging behaviour, and anxiety. This is intended to facilitate data interpretation and inform future trial design.

Given the importance of environmental factors on overall activity and participation, and the major role played by socio-economic (SES) and environmental factors in predicting or at least moderating outcomes following early brain injury in general, and childhood brain tumours in particular**4**, proxies for measuring these factors should be collected, such as parental education level, as recorded in the MEES. In addition, the CRF should record the child and family’s first language (to inform interpretation and analysis).

**Table 2 - Core and Supplementary (‘Plus’) Cognitive Domains for Direct Assessment, and Order of Administration**

|  |
| --- |
| Domain |
| **Core Measures**  | **Supplementary/ ‘Plus’ Measures** | **Examples of specific measures available in Europe** |
| **Order** |  | **Order** |  |  |
| Developmental Level for children before 4th birthday  |
| Developmental quotient | Bayley-III; Griffiths, Brunet-Lezine R’ |
| Direct Assessment for children between their 4th and 5th birthdays  |
| Language  |
| 1. | Receptive  | Wechsler Receptive Vocabulary |
| 2. | Expressive | Wechsler Picture Naming |
| Perceptual/Fluid Reasoning  |
| 3. | Matrices | Wechsler Matrix Reasoning *or* Raven’s CPM |
|  | 9. | Visual motor reasoning | Wechsler Block Design |
| Processing Speed |
| 4. | Processing Speed | Wechsler – Bug Search or Symbol Search |
| 6. | Processing Speed | Wechsler - Animal Coding or Coding |
| Short Term / Working Memory |
| 5. | Number Recall | K-ABC – Digit Span Forwards |
|  | 10. | Locations recall | Wechsler – Picture memory |
| Fine Motor Skills |
|  | 7. | Pegboard | Purdue Pegboard; WRAVMA Pegboard |
| Visual Motor Skills |
|  | 8. | Visual motor integration | Beery VMI *or* WRAVMA Drawing Test *or* NEPSY Design Copy |
| Semantic Memory/Knowledge |
|  | 11. | Verbal semantic memory | Wechsler - InformationKaufman ABC - RiddlesWechsler - Vocabulary  |
| Long-term Memory |
|  | 12. | Verbal episodic memory | NEPSY-II Narrative Memory Kaufmann ABC - Atlantis  |

 *NOTE: Wechsler tests are based on the WPPSI-IV which may not be available in all countries and therefore details may need to be adapted accordingly*

**3.3. Direct Endocrine Assessment**

Core endocrine assessments for all children with CNS tumours should include birth demographics and parental heights, together with accurate longitudinal **annual** growth, puberty data, thyroid, and gonadal function assessments from baseline, as well as the interval to and time on any hormone replacement therapy.

Core measures from baseline 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) or lying heights (if less than 2-3 years)
5. Sitting height (cm) from which to calculate relative body proportions and spinal deficit or crown rump measurements, taken lying (if less than 3 years)
6. Weight (kg) for body mass index calculation
7. Tanner Pubertal Staging (and age at menarche in girls), history on menstrual cycle
8. Concentration of FT4 and thyroid stimulating hormone (TSH)
9. FSH in girls and boys[[1]](#footnote-1)
10. Start and end dates of any hormone replacement therapy

These core measures should be collected at baseline (diagnosis) via the CRF. Items 1 and 3 are also gathered using the MEES (see indirect measures above). Items 4-9 should be repeated at annual intervals or at pre-specified cross-sectional assessment intervals thereafter, dependent on the trial.

Additional " plus" assessments of a) triphasic salt and water imbalance perioperatively (plasma sodium <130 or >150 mmol/l) and b) detailed assessment of hypothalamo-pituitary hormone function to inform EEFS and EMS are likely to be specific to central, suprasellar tumours irrespective of their histology and may include dynamic pituitary provocation testing or hormonal profiling performed longitudinally from baseline and at pre-specified intervals thereafter.

1. **Individuals with Sensory Impairments**

As discussed in Limond et al.**9** children receiving treatment for a brain tumour may experience motor, visual, and auditory impairments that may limit the use of direct assessment and affect interpretation of both direct and indirect assessment results. The presence of sensory impairments should be recorded on the eCRF so this can be taken into account at interpretation and analysis. Adaptations to standardised measures may be required (e.g. using enlarged copies of visual stimuli). In these cases, clinicians may choose to take a non-standardised approach to facilitate clinical care and should report this. For the purposes of the clinical trial, researchers will need to make a judgement as to whether standardised administration of the task has been achieved in these patients. Data collection sheets for the ‘core plus’ battery will need to include the option to state when adaptations have been made to compensate for sensory impairments, or whether impairments were of such severity that assessment could not be conducted (as discussed in 3.2).

1. ***Assessment Timepoints***

The group have agreed that ideally, despite the practical difficulties, baseline assessment data, and certainly auxology, should be collected at or very soon after (within 6 weeks of) diagnosis, during the acute stages of treatment. For direct cognitive assessment it may not be possible to collect all or any of the baseline data, and the consideration of assessment as prioritized above is recommended. Given the potential variability in timing of baseline data collection it is essential that this is reported accurately and is considered carefully by the clinical trials team when analyzing and reporting the data. The following subsequent time points advocated and agreed in other SIOP-E brain tumour trials of children over the age of 5 years should be more achievable during follow-up when the child is medically stable or feeling well enough to complete assessment: 2 years post-diagnosis, 5 years post-diagnosis, and at the age of 18 years as an end time point.

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

There continue to be challenges in implementing and funding an agreed protocol for longitudinal QoS studies across Europe. Suggestions to address this issue are discussed in Limond et al.**9**. When considering children under the age of 5 years it is important to maximize the use of a protocol which is consistent with the recommended protocol for children aged 5 -18 years. This will further allow the development of a more robust evidence-base with regard to different treatment and tumour-type outcomes over the course of childhood and early adulthood. First steps to implement the consensus reported here have been made and will be applied in the first randomised trial of treatments in atypical teratoid rhabdoid tumor trial protocol (SIOPe ATRT01).

**Declaration of interest**

None

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1. Since Limond et al**1** it has been agreed that FSH should be collected at all ages to help clarify the difference between suprasellar disease causing precocious puberty (under 8 years) or pituitary gonadotrophin deficiency for EEFS calculation**22** and gonadotoxicity from chemotherapy [↑](#footnote-ref-1)