Received: 27 September 2021 | Revised: 23 November 2022 | Accepted: 24 November 2022

DOI: 10.1002/pbc.30171

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

SPECIAL REPORT

Transatlantic progress in measurement of cognitive outcomes in paediatric oncology trials

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Abstract

The importance of measuring quality of survival within paediatric oncology trials is increasingly recognised. However, capturing neuropsychological outcomes and other aspects of quality of survival in the context of large or multinational trials can be challenging. We provide examples of protocols designed to address this challenge recently employed in clinical trials in the USA and Europe. We discuss their respective strengths and challenges, obstacles encountered and future opportunities for transatlantic collaboration.

KEYWORDS
brain tumour, cancer, child, cognitive, late effects, paediatric, quality of survival

Abbreviations: BTG, Brain Tumour Group; CCLG, Children's Cancer and Leukaemia Group; COG, Children's Oncology Group; HRQoL, health-related quality of life; PROMs, Patient Reported Outcome Measures; QoS, quality of survival; SIOP-EEuropean, Society of Paediatric Oncology.

1 | INTRODUCTION

It is now widely accepted that although survival is the primary goal of treatments, it is no longer an appropriate single outcome measure within paediatric oncology trials. Consequently, more emphasis is being placed on measuring aspects of physical and psychosocial wellbeing that contribute to quality of survival (QoS). This includes a focus on cognitive outcomes, usually measured by neuropsychological testing, and other determinants of QoS including physical, emotional and social functioning. In paediatric patients, QoS is often measured by proxy-report questionnaires and, in the case of older children, self-report questionnaires, alongside direct measures of growth, sensory and endocrine function. Whilst both cognitive and QoS outcomes are of central importance, the primary focus of this article will be on trial protocols aiming to capture long-term cognitive outcomes and acute neurotoxicity, rather than cognitive assessment within routine clinical care. We provide examples of approaches recently employed in clinical trials in the USA and Europe which use both performance-based assessment and questionnaires as complementary methods of measurement within trials.

Historically, measures of cognitive outcome have either been absent from clinical trials or specific to individual studies, typically brain tumour treatment trials, with the aim of increasing survival and reducing tumour- and treatment-related morbidity. Batteries have tended to be lengthy and embedded within discrete therapeutic trials, often yielding small datasets. As no two protocols have been alike, it has been difficult to compare outcomes across different diagnoses, treatment regimens, cultural contexts and age cohorts. Additionally, with growing emphasis on stratification according to molecular biology or neuroimaging correlates, multinational trials are increasingly essential to obtain sufficient data in relatively rare childhood cancers. However, reaching consensus on QoS trial protocols can be challenging due to a lack of measures validated for use in multiple age ranges, cultural contexts and languages. An additional challenge involves disparities within and across countries with respect to the availability of staff to undertake cognitive assessments, administer questionnaires and coordinate return of data. Even when cognitive assessments are recommended clinically, in parts of both North America and Europe, neuropsychological evaluation is not universally provided as standard of care, even for children with brain tumours. Families in the USA without adequate insurance to cover cognitive assessments may incur additional expense at a time when financial resources are already stretched. In the UK, resources within publicly funded health care are constrained.[1] Even where service for families is adequate, providers may lack access to assessment tools in their patients' native languages.

There are further barriers to assessment for children undergoing cancer treatment. Children are often unwell and undergoing multiple medical procedures or treatments affecting their engagement. Parents are often distressed and sometimes reluctant to complete lengthy questionnaire batteries. Families may also be required to travel far from home for treatments or trials that are not available locally. Participation in pre-treatment assessment can also be limited by patients' psychological adjustment to their diagnosis, fatigue and/or sensorimotor impairments which also complicate data interpretation, especially comparison over time. Collectively, these issues raise concerns about patient burden and managing clinical versus research priorities.

Traditional cognitive test batteries involve specialised tasks requiring administration by trained psychologists or neuropsychologists. These are clinically useful to identify needs and facilitate intervention though require on-site, often lengthy, evaluation procedures. Many such tests were not developed for frequent use and are inappropriate for short-term assessment of acute changes. Measures that are more psychometrically robust to repeated administration over short intervals are available but tend to be less familiar to clinicians and offer less value to patients and families seeking information to facilitate appropriate clinical support. Development of batteries that are cost effective, acceptable to clinicians and families and can be widely implemented to yield sufficiently detailed data can therefore be challenging. An optimal approach to evaluating cognitive and QoS outcomes requires a compromise between use of comprehensive batteries requiring substantial time, resources and patient burden and shorter research batteries that may have less utility for patient care. In this article, we describe recent approaches to resolving these difficulties in cooperative group trials in the USA and Europe.

2 | USA CHILDREN'S ONCOLOGY GROUP

Prior to the early 2000s, comprehensive assessment of cognition, behaviour and QoS in children and young people treated for brain tumours and acute leukemias on Children's Oncology Group (COG) clinical trials in North America relied heavily on direct psychometric testing, but typically achieved adherence rates below 30% with high risk of associated attrition bias.[2] To address the barriers identified, including many of the issues described above, two complementary strategies have since been developed to evaluate neuropsychological functioning: ALTE07C1 and Cogstate computerised battery. Each was developed to address unique assessment needs for children with cancer within the context of clinical trials.

2.1 | COG protocol ALTE07C1

ALTE07C1 is a free-standing companion protocol designed for COG therapeutic trials using traditional cognitive tests. Consensus was obtained from a panel of experts regarding the measures and timing of assessments at three discrete time points (9-, 30- and 60-months post-diagnosis ±3 months). Measurements selected have robust psychometric properties, broad age range utility, relatively brief administration time (i.e., 60–90 min), administration proficiency by most psychologists and established relevance to "real-world" functioning (e.g., school performance).[3] Domains assessed include global intellectual functioning, working memory, processing speed and visual and verbal long-term memory. Parents also complete questionnaires relating to HRQoL and psychosocial and adaptive functioning (Table 1).

The initial evaluation takes place when a child is beyond the window of acute illness, but before deficits typically emerge. The second

TABLE 1 ALTE07C1 standardised neuropsychological and behavioural battery

	Participant's Age (Years : Months)					
		2:0	5:0	6:0	17:0	
		↓	↓	↓	↓	
Test	< 2:0	4:11	5:11	16:11	17:11	≥ 18:0
Children						
Intelligence						
WPPSI-III† (Vocabulary, Block Design) *(15 min)*		X*	X			
WISC-IV† (Vocabulary, Block Design) *(15 min)*				X		
WAIS-III† (Vocabulary, Block Design) *(15 min)*					X	X
Attention/Processing Speed						
WPPSI-III† (Symbol Search, Coding) *(10 min)*		X (4:0 to < 6:0)				
WISC-IV† (Symbol Search, Coding) *(10 min)*				X		
WAIS-III† (Symbol Search, Coding) *(10 min)*					X	X
Memory						
CMS† (Story Memory, Faces, Dot Location) *(15 min)*			X	X		
CVLT-C† *(15 min)*			X	X		
WISC-IV† (Digit Span) *(5 min)*				X		
WAIS-III† (Digit Span) *(5 min)*					X	X
WMS-III†(Logical Memory, Faces, Spatial Span)*(15 min)*					X	X
CVLT-II† *(15 min)*					X	X
Parents						
COG Language Preference Questionnaire		X	X	X	X	
Attention and Behavior/Social/Emotional Function						
BASC-II† *(20 min)*		X	X	X	X	X**
Executive Function						
BRIEF-P† *(5 min)*		X	X			
BRIEF† *(5 min)*				X	X	
Adaptive Function						
ABAS-II† *(15 min)*	X	X	X	X	X	X**
Quality of Life						
PedsQL 4.0† (Generic Version, NOT Cancer Module)		X	X	X	X	X**

*For patients <4:0: administer Receptive Vocabulary; for patients ≥4:0: administer vocabulary.

**Patients ≥18 years of age will complete a self-report form.

†Abbreviations: WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence—3rd Edition[15]; WISC-IV, Wechsler Intelligence Scales for Children—4th Edition[16]; WAIS-III, Wechsler Adult Intelligence Scales—3rd Edition[17]; CMS, Children's Memory Scale[18]; CVLT-C, California Verbal Learning Test—Children's Version[11]; CVLT-II, California Verbal Learning Test—2nd Edition[19]; WMS-III, Wechsler Memory Scale—3rd Edition[20]; BASC-2, Behaviour Assessment System for Children—2nd Edition[21]; BRIEF-P, Behaviour Rating Inventory of Executive Function—Preschool Version[22]; BRIEF, Behaviour Rating Inventory of Executive Function[23]; ABAS-II, Adaptive Behaviour Assessment System—2nd Edition[25]; PedsQL 4.0, Paediatric Quality of Life Inventory Version 4.0 (Generic Version).[25]

is timed to coincide with the anticipated emergence of cognitive impairments. The final assessment corresponds with the transition to long-term survivorship. After initial activation of the ALTE07C1 protocol in 2008, the study was opened at 75% of all COG institutions (169 sites) and more than 900 patients were enrolled. Data have been captured for more than 90% of participants enrolled in this companion protocol at the first two assessment points, and nearly 80% at the final assessment, approximately 5 years post-diagnosis.

This evaluation strategy has been both feasible and successful within COG. However, in order to maintain consistency with guidelines and standard practices across cooperative groups, ALTE07C1 is no longer maintained as a free-standing protocol but has transitioned to a standardised battery that is embedded within newly developed therapeutic trials. Thus, specific, relevant research aims, hypotheses and analytic plans are contained within each treatment study, and the intact assessment battery is included as an appendix.

2.2 | Cogstate computerised assessment battery

There is often a need to evaluate the onset and trajectory of cognitive deficits over the course of therapy and into survivorship, including acute neurotoxicity and other early disease- or treatment-related changes. Computerised forms of cognitive testing, such as Cogstate, have been developed as an alternative and/or complement to traditional batteries and have the potential to reduce testing time and burden for patients and staff. Although computerised batteries can rarely evaluate all relevant aspects of cognitive functioning, they typically measure important domains vulnerable to decline and often have negligible practice effects, making them well-suited for use in longitudinal studies with assessment intervals shorter than 1 year.

Cogstate has been employed in eight COG clinical trials since 2011, with an additional two trials in development. Cogstate offers a range of tasks measuring some of the cognitive skills vulnerable to change following treatment with chemotherapy or radiation (e.g. attention, working memory, processing speed). For example, it is being used to identify the timing and trajectory of neurocognitive decline in children with high-risk leukaemia (AALL1131), to determine associations between poverty and cognitive change in children with ALL (AALL1731), to track cognitive changes in children with neurofibromatosis type 1 and low-grade glioma treated with a MeK inhibitor (ACNS1831) and to determine whether there is acute cognitive toxicity associated with arsenic trioxide treatment for Acute Promyelocytic Leukaemia (APML; AAML1331).

Cogstate has also been used as the primary outcome in two intervention trials for children with brain tumours, evaluating the efficacy of Modafinil in survivors with cognitive deficits (ACCL0922) and the feasibility of computerised cognitive training for children treated with cranial radiation (ACCL10P1). This approach appears feasible and acceptable across studies. For example, in AALL1131, 486 participants (70% of eligible patients) aged 6–11 years at diagnosis were enrolled. Over 900 individuals have been trained to administer the battery at almost 190 COG member institutions. Technical problems with the programme have occurred in less than 2% of cases and fewer than 2% of patients have been too unwell to complete testing.

3 | EUROPEAN SOCIETY OF PAEDIATRIC ONCOLOGY

The European branch of the International Society of Paediatric Oncology (SIOP-E) is an organisation representing professionals working in childhood cancer across 34 countries. In 2015, the SIOP-E Brain Tumour Group (BTG) published a position statement describing a common set of QoS assessments to be used in European trials in multiple languages for children over the age of 5 years.[4] A 'Core Plus' approach was introduced which recommended relatively brief 'Core' measures of cognition and QoS for all trials alongside more extensive 'Plus' measures where feasible. The initial SIOP-E position statement was subsequently modified to include children 5 years and under.[5]

3.1 | Use of Patient Reported Outcome Measures in SIOP-E

In the 1990s, proxy-reports were favoured by epidemiologists in the UK to assess QoS in multicentre treatment trials of infants with neurological disorders. This approach was later adapted in successful pilot studies in UK regional paediatric brain tumour treatment centres.[6,7] Subsequently, a battery of Patient Reported Outcome Measures (PROMs) was proposed for use by the UK Children's Cancer and Leukaemia Group (CCLG) to assess and monitor outcomes following brain tumour treatment trials. The battery used standardised PROMs to capture behavioural and emotional functioning, health status and HRQoL, and a novel Medical, Educational, Employment, and Social questionnaire[7] was developed. The battery was first applied in a study of UK survivors of the SIOP PNET3 medulloblastoma trial at a mean interval of 7.2 years after enrolment. QoS outcomes were obtained in 107 out of 143 (73%) survivors.[8] Following the successful implementation of the schema in the above study, the SIOP-E BTG QoS subgroup was formed and these indirect assessments were successfully applied across Europe in 62% of eligible survivors in the PNET4 trial.[9]

The SIOP-PNET5-MB medulloblastoma trial, which opened in 2014, provided an opportunity to capture PROM data via an on-line platform, rather than using paper questionnaires, thereby simplifying the process for patients and staff. At the time of writing the trial was still in progress and ascertainment of QoS at post-surgical baseline was 184 out of 255 (72%) of eligible participants, and 74 and 79% at 2 and 5 years follow-up, respectively. More recently, this online method was adopted in the SIOP-HRMB high-risk medulloblastoma trial using the KLIK-EU PROM portal (https://hrmb.klik-eu.org/).

3.2 | SIOP-E cognitive test battery

The first prospective application of the 'Core Plus' cognitive test battery[10] took place within the SIOP-Europe Ependymoma II trial which remains in progress.[11] The protocol mandates assessments at post-surgical baseline, 2 and 5 years from diagnosis and at age 18 years. The Core Plus two-tier approach to assessment addresses resource discrepancies by prioritising a minimum 'Core' battery of cognitive tests in centres where resources are limited, augmented by more comprehensive assessment using the additional 'Plus' battery (e.g. measures of attainment, attention and executive function) where feasible in a participating centre or country (Figure 1).

Ascertainment for baseline and 2-year assessment was consistently at 70% of eligible participants enrolled on the wider trial prior to COVID-19 constraints in 2020, decreased to around 60% across Europe as centres paused face-to-face testing, and is increasing back to pre-COVID levels now outpatient appointments have recommenced.

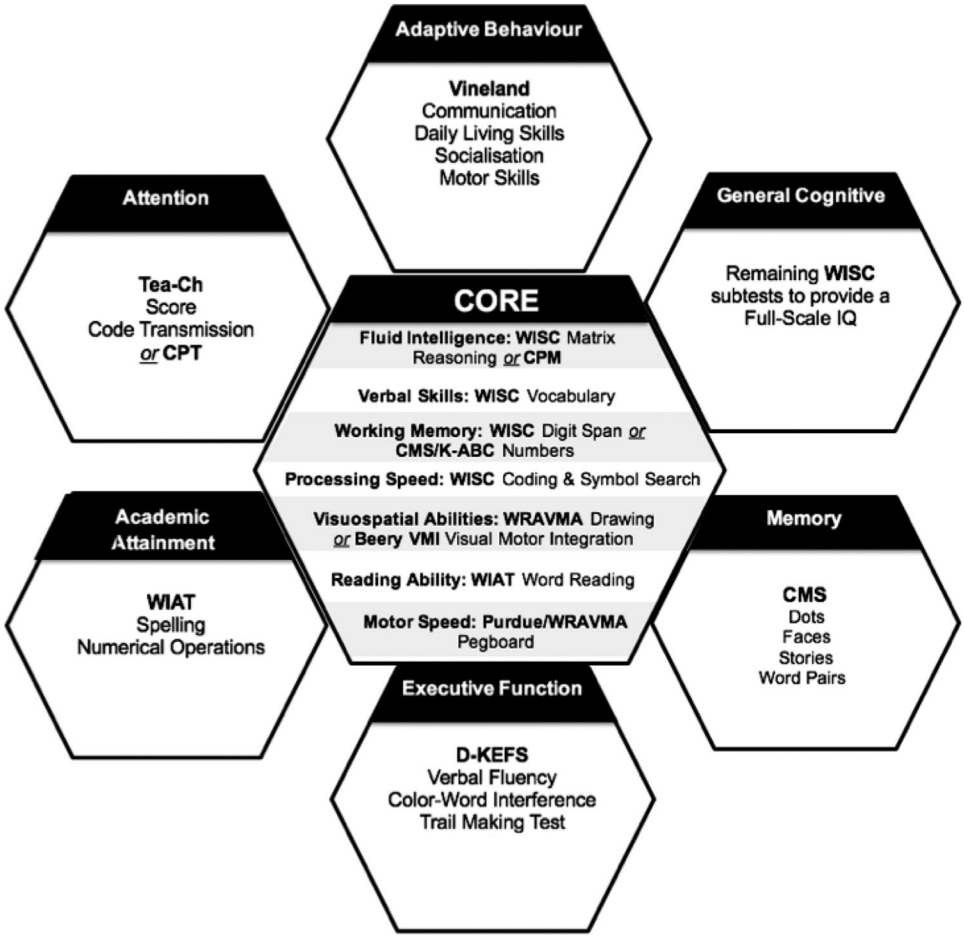

FIGURE 1 WPPSI-III[15] or IV[26]: The Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition or 4th Edition; WISC-IV[16] or V[27]: Wechsler Intelligence Scale Children's 4th Edition or 5th Edition; CMS[18]: Children's Memory Scale; WIAT-II[28] or III[29]: Wechsler Individual Achievement Test 2nd Edition or 3rd Edition; WRAVMA[30]: Wide Range Assessment of Visual Motor Abilities; Beery VMI[31]: Beery-Buktenica Development Test of Visual-Motor Integration; D-KEFS[32]: Delis-Kaplan Executive Function System; CPT[33]: Conners' Continuous Performance Test; TEA-Ch[34]: Test of Everyday Attention for Children; CPM[35]: Raven's Coloured Progressive Matrices (CPM); Vineland II[36]: Vineland Adaptive Behaviour Scales, 2nd Edition; Purdue Pegboard: Purdue Pegboard Test[37]

Direct testing was replaced by a developmental questionnaire for those under 3 years old in line with the SIOP-E recommendations.[4] The cognitive battery is also complemented by PROMs described in Section 3.1 above. A further development to encourage a consistent minimum dataset was the implementation of a consensus for a hierarchy of test administration where those tests considered most crucial were to be administered first. The Core Plus test battery has more recently been developed to take into account updated test versions for the SIOP-E High Risk Medulloblastoma trial which opened in 2021.

4 | DISCUSSION: LESSONS LEARNED

The above COG and SIOP-E approaches present a range of strengths, challenges and learning opportunities. Both ALTE07C1 and the Core Plus models include organised delivery of traditional well-validated cognitive tests, familiar to and used for clinical care by local psychologists, complemented by PROMs. The SIOP-E tests and PROMs are implementable in multiple European languages, and several of the measures overlap with those in the ALTE07C1 battery. The more recent modular approach of embedding the ALTE07C1 battery increases flexibility, eliminates need for a separate consent process and facilitates targeted assessment according to trial hypotheses. Cogstate provides an alternative pragmatic solution. It is deliverable by a range of clinic staff with minimal training and whilst some local psychologists seemed initially less comfortable with this unfamiliar measure the benefits are becoming increasingly understood and accepted within the clinical community. It can be repeated frequently to measure acute changes and may be implemented in multinational studies given its ease of application in many languages. As the functional significance of Cogstate is not yet fully clear, in the future, it will be imperative to utilise the data being gathered in research trials to characterise the relationship between Cogstate and traditional cognitive batteries within the paediatric oncology population. In the meantime computerised batteries such as Cogstate may be combined with approaches using traditional measures, such as ALTE07C1 and the Core Plus model, and have

potential as a screening mechanism to facilitate clinical referral for comprehensive assessment as described in the tiered model of Hardy et al.[12] Indeed, using both strategies may provide the ability to detect early signs of cognitive problems and describe acute neurotoxicities, whilst also determining the clinical and functional significance of those changes long after cancer treatment has ended.

PROMs can include assessment of varied domains such as endocrine function, fatigue and behaviour. Questionnaires may have good ecological validity but do not necessarily correlate with performance-based measures[13] and are therefore best combined with direct assessments of cognition, as proposed in the ALTE7C1 modular battery and the SIOP-E position statements. Online data collection avoids the problem of missing/partial data that precludes scoring. It can be centrally co-ordinated and combined with support to facilitate patient engagement. We will eventually have the opportunity to compare PROMs data across multiple studies within and between disease groups and to further define their relationship with findings from cognitive testing.

From an implementation perspective we have learned that a clearly defined infrastructure has been critical to successful test protocol adherence. For both ALTE07C1 and Core Plus battery implementation a comprehensive tracking system was developed for all eligible participants which provided a mechanism for enhancing recognition of open time windows for assessments, whilst tracking relevant patient information and institutional contacts. Within ALTE07C1 a group of approximately 20 psychologists volunteered to serve as site monitors for specific COG institutions and made monthly contact with assigned sites to monitor test administration and ensure timely data submission. Similarly, on the SIOPE Ependymoma II trial, co-ordinators for each country were established, with evident improvement in adherence within those countries where charitable funding was obtained for a dedicated co-ordinator. In the UK, ascertainment in this trial was increased from 54% in the first year to 87% in the second year once a dedicated co-ordinator was employed to liaise with and support national centres.[10] Feedback from local clinical psychologists has indicated the guidance provided is helpful and valued.

There continue to be resource discrepancies between individual centres and 25% of COG sites were not able to open the ALTE7C1 study, many of which have limited psychological care. There are similar challenges in Europe. However, as centres disclose resource limitations prohibiting assessment of children on trials this is also highlighting gaps in clinical service provision and bringing this to the forefront for discussion. In some centres, funding for trial assessments is allowing children who would not have been assessed for clinical purposes to undergo assessment which is also of clinical utility and would not otherwise have been undertaken. This highlights the dual benefit of traditional batteries which can be of both research and clinical benefit versus targeted computerised batteries such as Cogstate. Indeed informal feedback indicates that local psychologists are most comfortable using the traditional measures which fit with their existing clinical practice. However, in contrast, Cogstate facilitates data collection in centres where resource constraints mean this would otherwise not have been possible as a qualified psychologist is not required for administration. This has potential to identify those most in need of referral for a clinical assessment and intervention, in order to facilitate optimal outcomes for individual patients. In the near future, it will be important to consider the scientific success of these respective batteries in identifying impairment and the extent to which they consistently identify impairments and predict long term functioning.

The challenges of COVID-19 have accelerated development and validation of remote administration of traditional cognitive tests. Centralised questionnaire data gathering via telephone and online platforms also promise decreased disruption and increased convenience for families and local centres. Thus, we may be cautiously open to new possibilities for clinical trials that have the potential to maximise the collection of quality data whilst minimising patient and staff burden. This may be timely, as we move towards further stratification utilising biological subtypes and imaging correlates requiring inter-continental collaborations, augmented by longer-term follow-up to establish true downstream effects upon cognition and QoS. This has the potential to not only inform treatment decisions but will facilitate further identification of risk factors to inform recommended cognitive monitoring and intervention for childhood cancer patients.[12,375]

5 | CONCLUSION

Establishing trial protocols to measure cognition and other aspects of QoS requires patience, persistence and often compromise, but recent approaches have been successful in large cooperative trials. Monitoring of the benefits and challenges of these approaches will enable us to develop and refine our protocols. Increasingly, it will be important to widen international collaboration. The pursuit of transatlantic protocol homogeneity, including new possibilities for centralised, remote data collection, presents exciting future opportunities.

CONFLICT OF INTEREST

No conflict of interest has been declared by the author(s).

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How to cite this article: Thomas S, Embry L, Walsh K, et al. Transatlantic progress in measurement of cognitive outcomes in paediatric oncology trials. *Pediatr Blood Cancer*. 2023;70:e30171. https://doi.org/10.1002/pbc.30171