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Clinical research tools in pediatric oncology: challenges and opportunities

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Abstract
Survival for childhood cancers has improved significantly over the last decades. However, patient outcomes have plateaued over the last decade for difficult-to-treat diseases. With high cure rates, decreasing long-term toxicities and sequelae remains crucial. Since many advances in childhood cancer research come from the adult oncology world, one of the key areas is improving the adaptation of tools that are essential for clinical trial conduct that were developed for adults into pediatrics. These include tools to evaluate toxicity, quality of life, radiological response, statistical methodology, or indicators of cancer care quality. In this review, we present ongoing international efforts to validate and adapt these tools for children and adolescents and discuss remaining challenges. These efforts will hopefully accelerate and improve the quality of pediatric oncology research in the upcoming years.

Keywords RECIST · CTCAE · Quality of life · Quality assurance · Childhood cancer · AYA oncology

1 Introduction

The survival of childhood cancer has improved significantly over the last decades, with recent reported overall survival (OS) rates in Europe of up to 79% in children (< 14 years) and 82% in adolescents (15–19 years), and in the USA of 83.8% (< 14 years) and 84% (15–19 years) [1–3]. This improvement has been achieved with international collaborative efforts in the frame of practice-changing clinical trials, by using intensive chemotherapy regimens (combined with surgery and/or radiotherapy in solid tumors and hematopoietic stem cell in some leukemias). However, patient survival has plateaued over the last 5 to 10 years for difficult-to-treat diseases, which calls for innovative treatments with new mechanisms of action [4]. Moreover, survivors of childhood cancer are at an increased risk of suffering long-term toxicities and sequelae, and have a high rate of illness owing to chronic health conditions [5, 6].

Globally, all stakeholders are working closely together to accelerate drug development for children and adolescents [7, 8]. Nonetheless, the race to improve childhood cancer care is impeded because of its high dependence on the advances

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made in the field of adult oncology [9–12]. One of the major challenges of new drug development for children is in evaluating the effect the drug has on the patient and the tumor. Current trials rely on tools such as Common Terminology Criteria for Adverse Events (CTCAE) used to grade and monitor toxicity [13], the quality of life questionnaires used to assess true patient-benefit endpoints [14], or the Response Evaluation Criteria in Solid Tumors (RECIST) employed to assess radiological tumor response [15, 16]. While these tools have been validated for adults, they have never been validated in children.

In this review, we will identify the unique challenges related to trial development for the pediatric population, identify potential limitations of current adult-validated assessment tools, and describe the ongoing efforts to validate and adapt these tools for children [17–19].

2 Ped-RECIST

RECIST were developed by adult oncology specialists for adults with cancer. The criteria derive from the World Health Organization (WHO) criteria proposed in 1979 to establish a common framework for the evaluation of surrogate endpoints of overall survival. Subsequent refinements led to the publication of RECIST v1.0 in 2000 [15] and RECIST v1.1 in 2009 [16]. Compared with other radiological criteria, RECIST offers a simple and reproducible method of tumor size measurement, which is broadly applicable across a wide range of tumor types. This pragmatic approach has led to the success of these criteria, which are implemented in early-phase trials as well as in confirmatory phase III trials [20]. Recent successful regulatory approvals given have also included RECIST-evaluated responses as a measure of success, facilitating early conditional or accelerated approvals [21].

However, the validity of these criteria for children and adolescents has been questioned since the release of the first version [22–24]. Even with these questions, RECIST v1.1 has become the most widely used tumor response criteria used in pediatric solid tumor trials [25, 26]. Some of the most important potential limitations of RECIST v.1.1 are related to the fundamental differences between adult and childhood cancers:

1) The landscape of tumor types and their incidence is vastly different. For example, in children, embryonal tumors predominate (neuroblastoma, nephroblastoma or Wilms' tumor, or medulloblastoma), as opposed to epithelial tumors (carcinoma) occurring more often in adults. Primary central nervous system (CNS) tumors account for approximately a third of all childhood cancers, whereas they are a minority in the adult population. Furthermore, some pediatric tumors, such as neuroblastoma or nephroblastoma, rarely occur in adults. The database used to support the development of RECIST included trials of patients with diagnoses such as gastrointestinal stromal tumor, breast, lung, and renal cell cancers [16], which are virtually non-existent in children and adolescents [1, 2, 27] and hence, childhood cancers were not adequately represented.
2) There are substantial differences in the molecular biology, clinical behavior, and natural history of pediatric tumors. For example, some subtypes of neuroblastoma may undergo spontaneous regression without treatment, even in some cases with metastatic disease, or evolve to biologically inactive ganglioneuromas [28]. Molecular and clinical differences are also present in tumors that occur in both children and adults, such as high-grade gliomas and hepatocellular carcinoma [29, 30].
3) There are also differences related to image interpretation, especially regarding the evaluation of disseminated and infiltrating disease. Furthermore, there is a potential underestimation of tumor bulk consequent to performing measurements that are solely in the usually preferred axial plane. This becomes inaccurate when applied to masses that are two or more times greater in length (longitudinal or z-axis) than width (x- or y-axis), as occurs in paraspinal neuroblastoma [22]. Also, for many pediatric cancers, response criteria include other imaging modalities (such as I123-mIBG scintigraphy for neuroblastoma) or tumor markers (alpha-fetoprotein in hepatoblastoma or urinary catecholamines in neuroblastoma).
4) There are differences related to image acquisition. First, RECIST v1.1 recommends the use of CT for tumor response assessment [16]. However, ultrasound and magnetic resonance imaging (MRI) are used more frequently in pediatric imaging. Second, RECIST v1.1 criteria do not allow for imaging to occur on multiple modalities over multiple time points. This becomes challenging in children where imaging may occur in multiple locations at different time points. Oftentimes children are first imaged (using CT) at a hospital that primarily cares for adults. After a diagnosis of a tumor is made, the patient may be transferred to a children's hospital where imaging follow-up utilizes MRI. Because of concerns related to cost, radiation protection, and the need for sedation/anesthesia in young patients, pediatric providers prefer not to repeat imaging using the initial modality primarily to evaluate future response assessment.
5) Appropriate size cutoffs have never been determined for pediatric tumors. The definition of measurable disease or pathologic lymph nodes may not be suitable for children and adolescents. For example, a 1.5-cm lymph node in a neonate is markedly abnormal and rarely occurs, even in the setting of confirmed metastatic disease. In sarcomas, tumors measuring > 5 cm as largest diameter are considered to have an adverse prognostic factor. The Milan

group showed that this size-based cutoff should be modified depending on the patient's age [31].

In spite of these limitations, the straightforward application, widespread acceptance, and large volume of evidence supporting the use of RECIST guidelines in adult cancer patients make these criteria the most fit-for-purpose tool to assess tumor response in children [26]. Consequently, there is a pressing need to assess the validity of RECIST in the pediatric population. Unfortunately, only a limited number of studies have assessed its applicability to children [22–26, 32–38]. The main studies are summarized in Table 1.

According to these studies, RECIST might be valid to evaluate pediatric patients with relapsed solid tumors in the context of phase I trials. However, RECIST criteria do not seem best suited for certain tumors (*e.g.*, Ewing sarcoma) and seem to achieve inferior results when compared with 3D evaluation methods in other tumors (*e.g.*, neuroblastoma) [39]. Interestingly, in the latter cases, RECIST is being more frequently implemented, as it is considered an easier method by radiologists. For instance, Bagatell *et al.* performed a retrospective, multicenter study to identify the preferred method of primary tumor response assessment for high-risk neuroblastoma [35]. They reviewed 229 patients comparing the International Neuroblastoma Response Criteria (INRC), which uses volumetric (3D) measurements, with RECIST v1.1. None of the methods was predictive of outcome in the multivariate analysis. Therefore, the final recommendation was to use RECIST to evaluate primary tumor response to facilitate response assessments in clinical trials. This was subsequently backed up by a consensus statement with revisions to the INRC [37]. Based on the findings of original study, it was agreed to use RECIST, instead of volumetric measurements, to assess response in primary and metastatic soft tissue sites.

Table 1 Summary of studies assessing the application of RECIST in children and adolescents

Author, year [ref.]	Tumor type	Study type	*N*	Main conclusion(s)
Bagatell, 2016 [35]	Neuroblastoma	Retrospective, multicenter	229	- Neither INRC (3D) nor RECIST (1D) predictive of outcome. - RECIST preferred (easier method, 1D)
Park, 2017 [37]	Neuroblastoma	Position paper	NA	- INRC will use RECIST for primary and metastatic soft tissue sites
Guenther, 2017 [36]	Osteosarcoma	Retrospective, monocentric	74	- PD according to RECIST predicts poor outcome in localized disease. - No association between RECIST and % of tumor necrosis post-neoadjuvant chemotherapy
Aghighi, 2016 [38]	Ewing sarcoma	Retrospective, multicenter (3x)	74	- COG criteria (3D) correlate better with therapeutic response and clinical outcomes than RECIST (1D) or WHO criteria (2D).
Schoot, 2013 [34]	Rhabdomyosarcoma	Retrospective, multicenter (2×)	64	- EpSSG (3D) and RECIST are not interchangeable. - RECIST does not underestimate response compared to EpSSG.
Nguyen, 2018 [32]	Unresectable hepatoblastoma	Retrospective, monocentric	34	- Decrease in tumor volume was associated with improved OS. But not response according to RECIST.
O'Neill, 2017 [33]	Hepatoblastoma (lung metastases)	Retrospective, multicenter (clinical trial)	29	- Measurable disease as per RECIST or sum of nodule diameters did not correlate with EFS. - ≥ 10 nodules at presentation correlated with worse EFS.
Carceller, 2016 [26]	Solid tumors (phase I trials)	Retrospective, multicenter (2×)	61	- Tumor response by RECIST correlated with OS in phase I trials. - Reduction in sum of longest diameters at best response correlated with more prolonged responses. - In 1/3 of patients with measurable disease at baseline, tumor size was not optimal to determine progression.
Barnacle, 2006 [24]	Solid tumors	Retrospective, monocentric	10	- Several specific problems to apply RECIST in disseminated pediatric tumors. - Need for debate regarding RECIST in pediatric oncology
Therasse, 2006 [25]	Solid tumors	Literature review	*	- General concerns: disseminated disease with diffuse infiltration, minimum size of target lesions should be < 10 mm. - Imaging concerns: favoring ultrasonography in children, including bone lesions, considering all radiological plans to measure lesions, possibly using functional imaging.

1D, one dimension; *2D*, two dimensions; *3D*, three dimensions; *COG*, Children's Oncology Group; *EFS*, event-free survival; *EpSSG*, European pediatric Soft tissue sarcoma Study Group; *INRC*, International Neuroblastoma Response Criteria; *NA*, not applicable; *OS*, overall survival; *PD*, progressive disease; *WHO*, World Health Organization

*60 papers were included in the review, three of them specific to pediatric oncology

Despite the limitations of the aforementioned studies, such as their retrospective nature, limited sample size, few participant centers, heterogeneous methodology, and the focus on specific tumor types for some of them, the main conclusion that can be drawn out of this literature review is that RECIST v.1.1 may work for some pediatric solid tumors. However, there are a number of tumor types (including neuroblastoma, osteosarcoma, and Ewing sarcoma) that are not adequately addressed by these criteria.

The recently launched project Ped-RECIST [40] aims to assess whether the current RECIST guideline (v. 1.1) is valid for use in children and adolescents with solid tumors, excluding lymphomas. If it is not, the second aim is to adapt the RECIST criteria for use in this population. To that purpose, an international academic collaborative group has been built under the umbrella of the RECIST consortium, including experts from Europe, North America, and Japan. This work remains in the early planning stages.

3 CTCAE

The United States National Cancer Institute (NCI) has published standardized definitions for adverse events (AEs), commonly known as Criteria for Adverse Events (NCI-CTCAE), to grade and report organ toxicity in patients receiving anticancer therapy [41]. NCI-CTCAE is used for the management of anticancer therapies and, in clinical trials, to provide standardization and consistency in the definition of treatment-related toxicity.

However, pediatric oncologists have noticed recurring deficiencies in their daily practice when the CTCAE criteria are applied to children. The degree of severity for some CTCAE terms cannot be applied uniformly in children of all ages. For example, the normal values for hemoglobin reference are different in children aged 1 or 15 years, let alone infants or neonates. In addition, there are some conditions and disorders that exclusively affect children that are not considered. For example, when developmental delays occur as a result of cancer therapy, there is no way to code this adverse effect, which diminishes the accuracy of AE descriptions for children.

In prior work evaluating NCI-CTCAE (version 4.03, June 14, 2010) [17], it was already noticed that up to 26 items should be adjusted and 21 were missing (Table 2). These 47 items were divided into three groups: age-specific laboratory ranges, developing organ dysfunction, and child-exclusive defects/toxicities; the authors of the study advocated to include both missing and in need of adaptation pediatric items in future versions of the NCI-CTCAE, prioritizing by age-specific laboratory ranges, because they are systematically applied in daily practice. The NCI-CTCAE v.5.0 was published in November 2017 and became effective in April

Table 2 Examples of CTCAE terms that are misleading, not applicable, or in need of adaptation for children. Adapted from [17]

CTCAE terms	
Age-specific laboratory ranges	
Blood disorders	Anemia
	Decreased CD4 lymphocytes
	Lymphocyte count
	Neutrophil count
	Decreased platelet count
	Decreased white blood cell count
Endocrine disorders	Abnormal blood gonadotropin
	Abnormal blood prolactin
	Growth hormone
	High cholesterol
	Hypertriglyceridemia
	Glucose
Renal and urinary disorders	Decreased urine output
	Creatinine (acute kidney injury)*
	Creatinine clearance (chronic kidney disease)*
Other investigations	C-reactive protein*
	Procalcitonin*
Developing organ dysfunction	
Sense organs disorders*	Hearing impairment
	Visual accuracy
	Visual field (papilledema)
Musculoskeletal disorders	Green stick fractures*
	Growth plate closure*
	Bone age disorders*
Cardiac disorders	Hypertension
	Decreased ejection fraction
Neurocognitive development*	Activities of daily living (ADL assessment)
	Neurodevelopmental disorders*
	Pain
	Irritability
	Decrease in intelligence quotient*
	Language delay*
	Learning disability*
Child-exclusive defects/toxicities	
Neonates/premature infants*	Fetal incontinence
	Neonatal death
	Necrotizing enterocolitis*
	Bronchiolitis*
	Hyaline membrane disease*
	Infant respiratory distress syndrome*
Growth*	Weight gain/loss
	Deviations in growth percentile curves*
	Body mass index*
	Growth velocity disorders*
	Failure to thrive*
Psychiatric disorders	Attention deficit hyperactivity disorder*
	Oppositional defiant disorder*
	Encopresis*
	Selective mutism*

Categories may overlap. *CTCAE*, Common Terminology Criteria for Adverse Events

*Terms that are not included in the CTCAE

2018. Globally, differences between version 4.0 and 5.0 pertain to grading certain AEs (*e.g.*, cytokine release syndrome, hyperglycemia) and to terminology (*e.g.*, the adverse event "prehypertension" is not used anymore). Out of the 47 items mentioned above, only 3 have been modified in version 5 to include pediatric-adapted values: urine output has included infant and children strata for grade 3 and a pediatric stratum for grade 4; hearing impairment has been modified to include sensorineural hearing loss for grade 1 toxicity; and hypertension has included pediatric and adolescent strata for grades 1 to 3 and merged adult and pediatric for grade 4. Osteoporosis, an item that was not identified in the prior work, was modified to include a pediatric stratum for grades 1 to 3.

Activities of daily living (ADL) and self-ADL continue to be referred to in CTCAE as "age-appropriate ADL," without explicit mention to child specific. A recent initiative to integrate children and proxy assessments of symptomatic AEs, the so-called Pediatric Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE), has proven to be a useful tool to improve symptomatic AE reporting in clinical trials, which will eventually lead to enhancing the quality of care that children receive [42]. More broadly, the Pediatric Terminology Harmonization Initiative created a working definition of AEs and reviewed concepts from 16 pediatric clinical domains [43]. This unique project in terminology harmonization enhances communication between researchers and practitioners in the field of pediatrics and ensures that data meets the established standards in daily practice.

4 Health-related quality of life

Although treatment regimens are optimized to reduce unpleasant side effects, many pediatric cancer patients still experience significantly decreased physical, mental, emotional, and social health due to their disease and its treatment [44, 45]. Apart from acute side effects, survivors of childhood cancer are at an increased risk to develop treatment-related late effects (including cardiological and cognitive problems, impaired sexual development, and decreased fertility) over the course of their lives [5, 46, 47]. In fact, a high proportion of survivors develops early and severe chronic health conditions [6]. Thus, the assessment of health-related quality of life (HRQOL) is a critical outcome measure for pediatric cancer trials, so that the balance between benefits and risks of new therapeutic interventions can be better understood and therapies allowing better QOL in the short and long term can be preferentially used [48, 49].

Over the last two decades, patient-reported outcomes (PROs) have been identified as an essential tool to assess a patient's health status, symptom burden, and HRQOL [48, 50]. Key domains of HRQOL in pediatric oncology include the child's physical (*e.g.*, physical functioning, symptoms), psychological (*e.g.*, body image, self-esteem, distress, behavioral problems, cognitive functioning), and social health (interpersonal relationships, social functioning, and general health perceptions) [51]. In general, children with cancer report lower HRQOL-scores than children from the general population [52].

In addition to the recommendation to use PRO measures in pediatric oncology [48], it is common to use proxy assessment alongside PROs, especially in younger children due to their inability to directly communicate. Since research has indicated a certain degree of discrepancy between parent proxy report and child self-report, especially for less observable aspects (*e.g.*, emotional distress, pain, fatigue), the combined use of both information sources has been recommended for clinical research and practice [53–56].

An interdisciplinary taskforce associated with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has highlighted the importance of considering the developmental stage of the children when assessing PROs [49]. This group considers three age groups: < 5 years, 5–7 years, and 8–11 years. For children younger than 5 years of age, the use of self-report scales is discouraged. Instead, the child's health status may be assessed using proxy reports or observational reports [57, 58]. For children between 5 and 7 years of age, age-appropriate self-report assessment tools (simplified response scales and content) can be used for several aspects of the HRQOL. Finally, for children older than 8 years of age, age-specific health questionnaires designed for adolescents and young adults (AYAs) may be used [59, 60].

In order for PRO questionnaires to be considered applicable for clinical research and practice, the reliability, validity, and responsiveness of the tools should be assessed for children of different age groups [49, 61]. A recent study [50] has identified several applicable questionnaires, of which the *PedsQL* and the *Fatigue Scale* were most commonly used measures in pediatric clinical trials. While some promising questionnaires exist [50, 62], current research has also suggested that existing self-report instruments may not exhaustively reflect the HRQOL problems of pediatric oncology patients [63]. Thus, further work to improve and/or develop specific, age-appropriate questionnaires for children with cancer is warranted.

Historically, AYAs with cancer have been identified as a vulnerable group. The vulnerability relates to the observation that the improved survival trends seen in pediatric and adult oncology have not translated into adolescence and early adulthood [64, 65]. Reasons for these disparities include the difference in epidemiology of cancer types in AYAs [66] and the presentation of cancer at a more advanced stage often due to a protected route to diagnosis given an initial low suspicion and awareness of cancer [67]. In addition, compared with older and younger cohorts, AYAs are less likely to enroll into

clinical trials [67]. There is also a notable lack of healthcare providers specializing in AYAs or even AYA oncology units. The logistics of treating AYAs is often described as challenging because the patients cross both the pediatric and adult settings [67].

Irrespective of a diagnosis of cancer, AYAs find themselves in a period of transition from childhood to adulthood characterized by significant physical and cognitive changes as well as critical psychosocial challenges. This developmental phase encompasses decisions regarding career choices, and challenges relating to peer relationships, as well as establishing autonomy from family members [68]. The development of intimate relationships and questions relating to sexuality are also integral features of adolescence and early adulthood. A diagnosis of cancer during this crucial developmental stage further complicates the negotiation of these challenges [69, 70]. Thus, not surprisingly, the impact on HRQOL is reported as more profound and broader in scope for AYAs compared with younger and older patients [71–73]. In a recent study, AYAs with cancer described numerous concerns, some of which overlap those identified above for children and include symptoms; restrictions to activities (attending school/college, pursuing leisure activities); disrupted life plans (career and life goals); body image; self-appraisals; outlook on life, lifestyle, treatment related concerns, and fertility; and the social, emotional, and financial impact on life [74]. In comparison between AYAs (14–25 years) and older adults (26–60 years), several HRQOL issues were recognized as more relevant or important to AYAs including interrupted education, greater motivation to achieve academic goals, increased maturity, boredom, fertility, and change in living situation (*e.g.*, moving back to the family home) [72].

HRQOL assessment in AYAs with cancer is imperative to better understand and address the specific needs of this patient group. Many of the HRQOL measures used to evaluate HRQOL in AYAs with cancer represent adaptations of pediatric measures, such as the PedsQL [75] or measures developed with and designed for older adults, thus raising concerns over their validity [72]. In an outline of research priorities for AYAs with cancer, the AYA Oncology Progress Review Group acknowledged that the research infrastructure for assessing AYA cancer-related issues is inadequate and needs to be supported by the development or modification of existing AYA assessment tools [71].

5 Statistical considerations

Randomized controlled clinical trials (RCTs) represent the gold standard for evidence-based medicine and play a key role in evaluation strategies for new treatments [76, 77]. However, the conduct of conventional RCTs in children faces numerous challenges [78, 79].

Cancer is uncommon in children and meets the definition of "rare disease" [1]. As a rare disease, one of the major concerns in conducting pediatric clinical trials is the small available patient population. With the limited number of patients available, RCT may not have sufficient power to detect clinically meaningful differences (treatment effect) [80–82]. Pediatric trials are thus often underpowered or difficult to complete within a reasonable timeframe. Multi-centric international studies or intergroup trials can sometimes overcome the issue of small sample sizes. While improving the generalizability of the results, such trials introduce challenges in the data management and in meeting the regulatory requirements in different countries.

Moreover, in conventional RCTs, key study elements such as primary outcome, response variability, and treatment effect must be pre-specified [83, 84]. The success of traditional RCTs depends thus on the accuracy of the key assumptions made prior the recruitment of the patients. In pediatric trials, there is often only limited data available upon which to base the design characteristics. While it may be possible to estimate efficacy results in adults to children if the disease process and outcome of therapy are comparable, it is known that treatment responses differ between adults and children. For example, drug responses are more heterogeneous in children as compared with adults [85]. Thus, relying solely on evidence obtained from adult populations can lead to misspecification of the design parameters leading to serious consequences for the actual power and the false positive error of the trial [86].

Similar considerations exist in designing clinical trials for small populations in adult conditions. This challenge has been addressed through innovative trial designs (*e.g.*, adaptive designs, Bayesian approach) which allow researchers to obtain substantial evidence with a limited number of patients [87–90]. Adaptive designs are very attractive due to their flexibility, whereas the Bayesian approach provides a formal framework for borrowing information. Although potentially desirable compared with traditional RCTs, innovative and yet complex trials designs may introduce operational bias and consequently increase the risk of making errors. Whatever the trial design chosen, the quality, validity, and integrity of the trial must be maintained. The need for alternative approaches has been reported in the European Medicines Agency (EMA) guideline ICH Topic E11 guideline [91], reference document for planning and conducting clinical trials in pediatrics, and is also discussed in detail in the EMA guideline for clinical trials in small populations [92]. The development and better understanding of new innovative methodologies represents a promising potential opportunity for research in pediatrics.

In clinical oncology trials, the gold standard endpoint is overall survival [93]. In pediatric cancer trials, surrogate endpoints such as event-free survival (EFS) are the preferred

endpoint [94]. Surrogate endpoints have the potential advantage to reduce the time to evaluation of an experimental treatment as well as the number of exposed patients, *i.e.*, fewer patients need to be exposed to a treatment in order to determine its efficacy [95]. In the past, the use of surrogate endpoints has been controversial due to the misconception that an association between a true clinical endpoint and an observed biomarker is sufficient to declare a biomarker as a surrogate. What is required is that the effect of the treatment on the surrogate endpoint reliably predicts the effect on the true clinical endpoint. In recent years, statistical methodology has been applied to qualifying surrogate endpoints in adults. However, little work has been done in the pediatric population [96]. In the future, close collaborations between clinicians and statisticians should facilitate the appropriate use of surrogate endpoints in pediatric research with the aim to assess effectively new therapies in children [97].

6 Quality standards

The first step to improve the management of multifaceted diseases such as pediatric cancer is to identify the existing weak areas in patient care [98]. To do so, reviewing past and current clinical practices at different levels (institutional, national, and international) is key. Clinical audits and quality assurance programs constitute a crucial part of good clinical practice [99, 100]. There is a growing interest in assessing the quality of pediatric cancer care with the use of quality indicators (QIs) [101]. Some significant steps have already been taken regarding the definition of the minimal standards of care for pediatric oncology patients. For instance, the SIOPe (European Society of Pediatric Oncology) guideline provides a consensus document recounting the minimum quality requirements for a pediatric cancer facility and describing a general directive [99].

Notwithstanding this example, disease-specific quality assurance systems and guidelines for childhood cancer are still missing. This stands in contrast with the availability of several sets of QI measures for adult cancer (as is the case for testicular cancer [102]). A noteworthy exception to this gap is given by the work of the Pediatric Oncology Group of Ontario (POGO), in which the authors proposed a set of QIs for local pediatric oncology care [103].

Furthermore, the management of many pediatric tumors is particularly challenging due to their aggressiveness and affected organs, the consequent severity of illness, the need for multidisciplinary and highly complex therapies, and the potentially severe acute and long-term toxicities [98]. Therefore, specific QIs for the management of pediatric cancers ought to be developed, which would facilitate the evaluation of patient care at different centers and networks. A recently published real-world research study proposed a set of 34 QIs about the management of children and adolescents with medulloblastoma [98]. Five main areas of quality assurance were identified: diagnosis, global treatment strategy, frontline treatment modalities, outcomes, and long-term and end-of-life care. Lack of central pathology review, delay in the incorporation of novel molecular markers, and absence of a neurocognitive and quality of life evaluation program were some of the audit findings. This set of QIs was developed after a local audit of clinical practice at a Spanish reference center and is yet to be validated, but it constitutes a good start.

Another example of ongoing initiatives about QA in pediatric oncology is given by the recent work by the QUARTET group (QUAlity and excellence in RadioTherapy and imaging for children and adolescents with cancer across Europe in clinical Trials), in which radiotherapy practice for pediatric CNS tumors across Europe and quality assurance initiatives are analyzed [104]. The RTQA aspects of major past and current European trials for pediatric CNS tumors were reviewed based on study protocols and publications, and a survey among radiation oncologists and pediatric oncologists about the practices of RTQA in pediatric CNS tumors across European countries was performed. As a result of the review and survey, the authors proposed five measures: (1) developing international RT guidelines for pediatric CNS tumors, (2) improving the collaboration between pediatric oncologists and pediatric radiation oncologists, (3) building a central storage system for RT data, (4) implementing international prospective RTQA platforms, and (5) promoting European referral networks to reduce inequality.

7 Conclusions

There is a need and an ongoing effort in the pediatric oncology community to adapt research tools for children and AYAs with cancer to facilitate the development of new therapeutic strategies that can be brought to frontline as rapidly as possible and prioritize those therapies with the higher benefit/risk ratio for the patients, including improved survival, reduced toxicity, and enhanced QOL (Fig. 1).

As argued by the RECIST Working Group in a recent article [20], maintaining the applicability of any clinical research tool as a standard evaluation approach is associated with many challenges. Some of these challenges include maintaining a balance between specificity and generalizability, continued validation and innovation, use in early-phase *versus* late-phase drug development, and its relevance in clinical trials *versus* clinical practice. Regarding the former, it is well established that pediatric and AYA cancers present unique challenges, even in the setting of a same tumor type such as soft tissue sarcomas [105], that distinguish them from their adult counterparts. These challenges include differences in

Fig. 1 Visual schematic of the adaptation of research tools for children and AYAs with cancer to facilitate the development of new therapeutic strategies. OS, overall survival; EFS, event-free survival; QOL, quality of life

epidemiology, prognosis, tumor biology, genomics, clinical features, and response to treatments. This has direct consequences for the conduct of clinical research in pediatric patients [8–10]. While the scientific pediatric oncology community has continued to benefit from the adult oncology experience, simply transferring and applying research tools that were originally developed for adults to children and AYAs leads to several shortfalls. In some instances, a pediatric-specific tool may be needed. However, validation research to justify the applicability of adult tools should be conducted in order to avoid unnecessary duplication. In this work, the balance between specificity and generalizability needs to be carefully preserved. In a time when pediatric drug development is advancing rapidly, there is a need to further promote academic research to validate and/or adapt research tools for children and AYAs with cancer.

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Compliance with ethical standards

Conflict of interest Francisco Bautista had a consultant or advisory role for Bayer, Amgen, and EusaPharma, received honoraria for speaking at symposia from Amgen and Jazz Pharmaceuticals and support for attending symposia from Takeda, EusaPharma, Shire, and Jazz Pharmaceuticals. Ana Fernández-Teijeiro has had a consulting or advisory role for Amgen, Novartis, Takeda, SOBI and Bayer. She received honoraria from Takeda and Amgen for educational events and travel expenses from Servier, Shire, and Gilead. Alexander Towbin has received grants from Guerbet and the Cystic Fibrosis Foundation. He receives royalties from Elsevier. He has served as consultant for Applied Radiology, IBM Watson Health Imaging, and KLAS. Lucas Moreno has served in a consulting or advisory role for Novartis, AstraZeneca, Roche Genentech, Bayer, Amgen, and MundiPharma; has received honoraria for educational events from Celgene and Novartis; and has received travel expenses from MundiPharma, Celgene, and Amgen. The rest of the authors declare that they have no conflict of interest.

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