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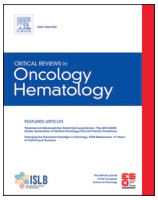

Patient-reported outcomes are under-utilised in evaluating supportive therapies in paediatric oncology – A systematic review of clinical trial registries

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ABSTRACT

Background: Children with cancer suffer from numerous symptoms and side-effects, making supportive interventions indispensable to improve their quality of life. The gold standard for evaluating the latter is patient-reported outcome (PRO) assessment. This systematic review investigates the current practice of clinical outcome assessment (COA) in clinical trials on supportive interventions.

Methods: ClinicalTrials.gov and EudraCT were searched for trials including children and adolescents (≤21 years) with cancer receiving supportive care registered 2007–2020. The use of different types of COAs was analysed, focusing on PRO assessment and the domains measured with PRO measures (PROMs). Associations with trial characteristics were investigated using univariate and multivariable analyses.

Results: Of 4789 identified trials, 229 were included. Among them, 44.1 % relied on PROMs, the most commonly used COA. The proportion of trials using PROMs did not significantly differ over time. In the multivariable analysis, intervention type (higher PROM use in behavioural vs. medical interventional trials) and cancer type (higher PROM use in mixed and solid tumour samples vs. haematological samples) were significant predictors of PROM use. The majority of trials using PROMs (59.6 %) measured more than one health domain. 'Physical health' was the most frequently assessed domain (92.6 %).

Conclusion: Less than half of registered clinical trials investigating supportive interventions for children with cancer used PROMs. This result is striking since supportive care explicitly focuses on patients' quality of life, which is best assessed using PROMs. Our systematic review underlines the need to identify barriers for PROM implementation and to improve PRO research in paediatric oncology.

1. Background

Survival rates in paediatric oncology have been rising over the last decades (Hooke and Linder, 2019; Linder and Hooke, 2019). However, children and adolescents with cancer still experience numerous symptoms and treatment side-effects. These may include pain, nausea, fatigue, impairments in physical activity, insomnia, or changes in taste or appetite (Darcy et al., 2019; Sodergren et al., 2018). Due to an immunosuppressed status patients are also more prone to severe infections or inflammatory responses (e.g., mucositis) (Guilcher et al., 2021). Additionally, the diagnosis of a potentially life-threatening disease is often associated with substantial changes in daily life (Anthony et al., 2014), which may lead to feelings of loneliness, uncertainty, anxiety, and depression and to a decreased quality of life (QOL) (Gatta et al., 2014).

QOL is an umbrella term, covering physical, psychological, and social issues, but also school- or behaviour-related problems as well as body image or self-esteem (Wiener et al., 2015; Kazak et al., 2015) The gold standard to assess patients' quality of life are patient-reported

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outcomes (PROs), defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (Anon, 2009). There are strong recommendations to use PRO measures (PROMs) in clinical practice (Wiener et al., 2015; Kazak et al., 2015) and in clinical trials (Anon, 2007; Appendix, 2016; Regulation (EC), 2006). Nevertheless, a previous review by our research team showed that ~92 % of clinical trials on anti-cancer treatments for children with cancer did not assess any PROs (Riedl et al., 2021a). Additionally, another recent study by the FDA noted that only 4/17 approved paediatric oncology product applications (i.e., trials submitted for regulatory review) reported any PROs, and none of them incorporated them in product labelling (Murugappan et al., 2021).

It seems reasonable to expect that PROs are more commonly assessed in trials investigating supportive interventions, which explicitly have the goal "to improve the quality of life of patients who have a serious or life-threatening disease [… and] to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment." (Anon, 2021) Following this definition, we will use the term 'supportive' for any intervention that is not cancer-directed (i.e., interventions not administered/performed for curative intent), no matter if patients are under anti-cancer treatments, in remission or in palliative care. When we use the term 'palliative', this refers to a specific subgroup of supportive interventions in end-of-life care.

Previous research by Vinches et al. found that 58 % of clinical trials on palliative interventions in oncology applied PROMs (Vinches et al., 2020). However, since only 1 % of the included trials were conducted in paediatric samples, it is not clear if the proportion of PRO assessment is also representative for research in this population. Moreover, there is a delay in the adoption and implementation of PROMs in paediatric compared to adult oncology research (de Rojas et al., 2020; Riedl et al., 2021). The latest review on the use of PROMs in research on supportive interventions for children with cancer was conducted more than a decade ago (Hinds et al., 2007). The authors included studies on palliative treatments published between 2001 and 2006 and found that only 15.4 % (4/26) assessed PROs, while parent- or clinician-reports were more commonly used.

Depending on children's age and cognitive abilities, it is recommended to complement PROs with clinician-rated or observer-rated outcomes by proxies (Arbuckle and Abetz-Webb, 2013; Parsons et al., 2012). For the assessment of neurocognitive or physical functioning, performance-based outcomes play an important role (Söntgerath et al., 2021; Leiss, 2012). However, PROs are the only type of clinical outcome assessment (COA) providing valid insight into unobservable aspects and the subjective experience of patients, whereas proxy-reports tend to underestimate the emotional burden and its impact on children's QOL (Parsons et al., 2012; Yeh et al., 2005; Yoo et al., 2010; Baggott et al., 2014).

The aims of the present review thus were to investigate (a) to what extent the different types of COA and PROMs specifically have been used in clinical trials on supportive interventions in paediatric oncology since 2007; (b) if the proportion of trials using PROMs has increased within the last decade; and (c) if specific trial characteristics were associated with the use of PROMs. Overall, this will provide an insight into the current practice of PRO assessment in the field of paediatric oncology clinical research.

2. Methods

2.1. Search strategy

The present systematic review adds to our previous review focusing on PROM usage in clinical trials on anti-cancer treatments in paediatric oncology (Riedl et al., 2021b). The underlying dataset was retrieved from the National Institutes of Health (NIH) clinical trial database ClinicalTrials.gov (hereafter 'CT'; https://clinicaltrials.gov) and the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT; https://eudract.ema.europa.eu) in July 2020 by using the term "Cancer + (paediatric OR child OR adolescents) + Study Type: Interventional Studies + Age Group: Child (birth - 17) + Study Start Date: 01/01/2007".

For the present review, trials were included if the sample consisted exclusively of children, adolescents, or young adults up to the age of 21 years, who received supportive or palliative care (including medical as well as behavioural or psychosocial interventions). Studies were excluded if they 1) had an upper age limit above 21 years; 2) were conducted in healthy or non-cancer samples; 2) investigated anti-cancer treatment (see (Riedl et al., 2021b) for their analysis); 3) investigated other research aspects (e.g., genetics, pharmacokinetics, diagnostics or organisational issues around care).

The study methodology complies with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) statement and guidelines whenever applicable (Moher et al., 2015).

2.2. Data extraction

Data from CT and EudraCT were extracted via a Microsoft Excel sheet [MR]. The data contained the National Clinical Trial (NCT) number and/or EudraCT number, title, start date, status, location(s), funder type, age range, condition, intervention, and defined outcome parameters. To receive information about trial publication, a manual search by NCT or EudraCT number was performed on PubMed.

Three researchers [JL, MR, WM] categorised data as described below and rated the eligibility of trials independently. Conflicts were discussed until consensus was reached, in case of uncertainties further co-authors were consulted [DR, TdR].

2.3. Definition of trial characteristics

If the trial registry entry mentioned that trials were specifically focusing on end-of-life care interventions, they were categorised accordingly as 'palliative'. For all trials, we differentiated medical interventions as 'drugs' (including systemic or topical drugs and biologicals) and 'procedures' (including procedures for pain, radiation, ultrasound, as well as surgical procedures) from behavioural interventions focusing on 'educational/psychological/social' (e.g., coping strategies, resiliency, …) or 'physical' (e.g., physical activity, exercise) aspects. Interventions not fitting into these categories (e.g., non-conventional, or dietary) were categorised as 'other'. These definitions were based on a similar study (Vinches et al., 2020).

In terms of COA, we differentiated between the assessment of PROs, and clinician-reported, observer-rated, and performance-based outcomes as defined in the BEST Glossary (Group F-NBW. BEST, 2021). Additionally, we noted whether qualitative interviews with patients were conducted. For PROs, the specific instruments used in each trial were also extracted. If the instrument was not clearly indicated, the category 'unspecified' was applied. The application of PROMs was categorised as follows: 'assumably as intended' (i.e., a concrete PROM was reported and it was assumably used as intended by the developers), 'made adaptations' (i.e., single subscales or items were chosen/added/modified), 'mixed' (i.e., some used as intended, others adapted).

The domains assessed with PROMs were categorised based on the conceptual framework of QOL in children with cancer provided by Anthony et al. (2014), differentiating 'physical', 'psychological', and 'social' aspects. To account for other contents (e.g., satisfaction with care), the category 'other' was added. If no domain could be identified (e.g., if unspecified instruments were used), domains were categorised as 'unknown'.

Further definitions of other trial characteristics are in line with our first review (Riedl et al., 2021b) and provided in Supplement 1.

2.4. Statistical analyses

The interrater reliability for inclusion and exclusion criteria was calculated for a subsample of ~10 % of the trials. In this subsample, all trials were independently rated by two randomly selected researchers [JL, MR, WM]. Reliability was calculated as intraclass correlation coefficient (ICC, one-way random model, single measures). Intraclass reliability coefficients of > 0.70 were classified as acceptable, > 0.80 as good and > 0.90 as excellent (Koo and Li, 2016).

A descriptive overview of the total sample of included trials is provided. Chi-Square tests or Fisher exact tests were used for a univariate analysis of associations between trial characteristics and PROM usage. A binary logistic regression was run to investigate which trial characteristics are the best predictors of PROM usage within a multivariable model. Odds ratios are given with a 95 % confidence interval. The threshold for significance was set as $p < .05$ in all tests. Calculations were done using IBM SPSS Statistics 27.0.

3. Results

3.1. Trial selection

As shown in Fig. 1, a total of 4789 trials were identified on CT and EudraCT, of which 4473 (711 on anti-cancer treatments and 3726 meeting exclusion criteria) were excluded based on the categorisations made for our previous review focusing on trials on anti-cancer treatments (Riedl et al., 2021b). The 316 trials re-assessed for the present review were those previously categorised as investigating 'other forms of interventions' (i.e., behavioural, dietary, alternative) or guided by 'other intention', i.e., trials focusing on supportive treatments. Of these, 87 (87/316, 27.5 %) were excluded, mostly because they investigated behavioural interventions in a healthy or non-cancer sample (78/87, 89.7 %). The remaining 229 trials were included (229/316, 72.5 %). The ICC for eligibility ratings was determined for a subsample of 30 trials (30/229, 13.1 %) and was 0.93 (95 % CI 0.86–0.97), indicating excellent interrater agreement.

3.2. Characteristics of trials and clinical outcome assessments (COA)

Only 3 trials (3/229, 1.3 %) explicitly mentioned a palliative focus. Thus, we will not further distinguish between trials investigating palliative and other supportive interventions. As shown in Table 1, most trials were conducted in North America (113/229, 49.3 %) and Europe (45/223, 19.7 %). Trials were mainly conducted within academia (202/229, 88.2 %) and largely monocentric (144/229, 62.9 %). Most trials (109/229, 47.6 %) recruited both children with haematological cancers

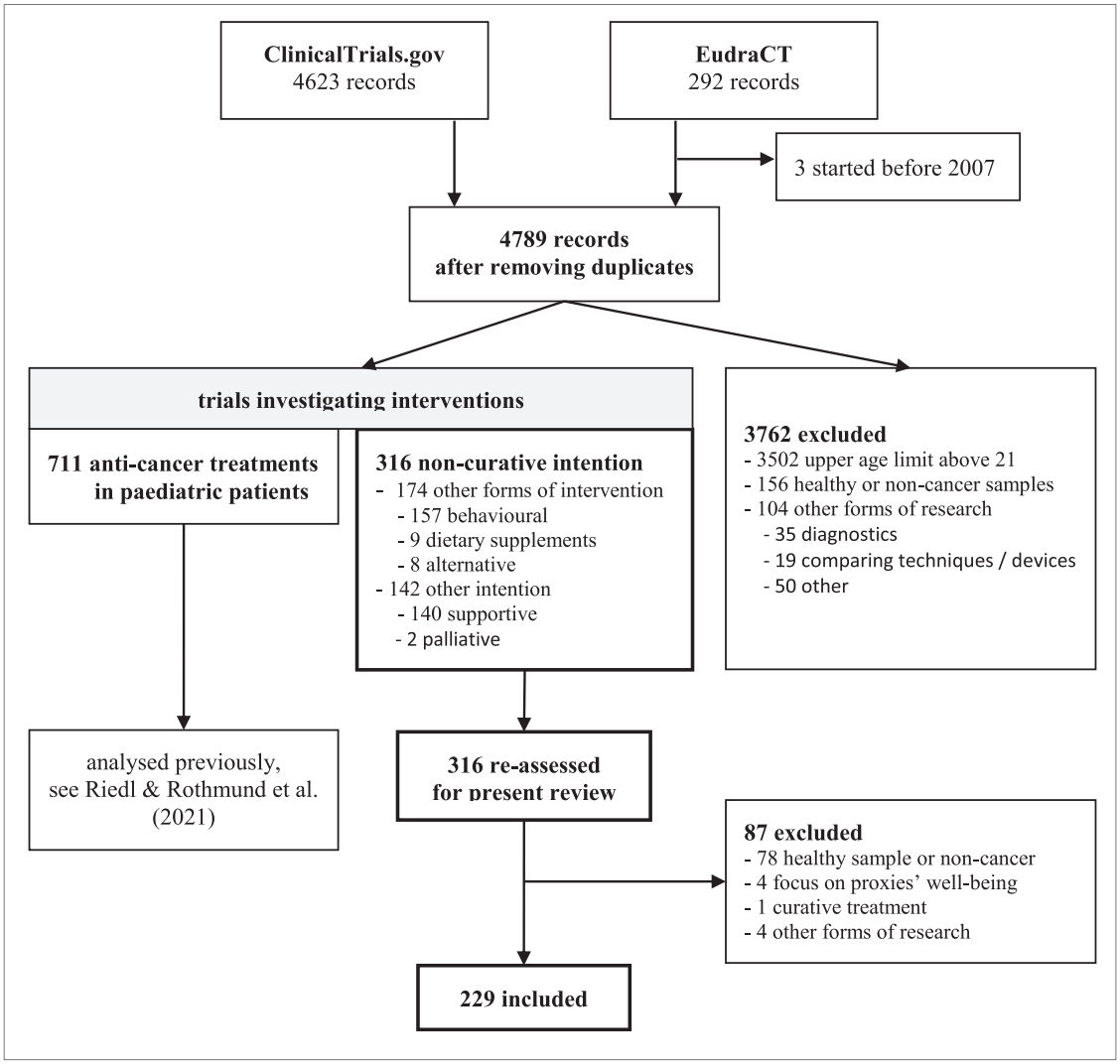

Fig. 1. Trial selection procedure. The underlying search on ClinicalTrials.gov and EudraCT was conducted for a previous review of trials investigating anti-cancer treatments (Riedl et al., 2021). From this previous review, 316 trials were excluded as following a 'non-curative intention'. These 316 trials have been re-assessed for the present review of trials investigating supportive interventions. The re-assessment revealed that 87 met other exclusion criteria, leaving 229 trials for inclusion.

Table 1
Main characteristics of clinical trials.

	Total		No PROM		Any PROM		Comparative statistics		
	N	C%	N	R%	N	R%	X^2 (df)	*p*	ϕ/V
All Trials	229	100.0	128	55.9	101	44.1			
Region							9.354 (4)	.053	.209
North America	113	49.3	58	51.3	55	48.7			
Europe	45	19.7	20	44.4	25	55.6			
Asia	17	7.4	11	64.7	6	35.3			
intercontinental	14	6.1	11	78.6	3	21.4			
other	25	10.9	18	72.0	7	28.0			
missing data[a]	15	6.6	10	66.7	5	33.3			
Number of Centres							6.876 (2)	.032	.180
monocentric	144	62.9	76	52.8	68	47.2			
multicentric national	44	19.2	21	47.7	23	52.3			
multicentric international	24	10.5	19	79.2	5	20.8			
missing data[a]	17	7.4	12	70.6	5	29.4			
Funder Type							8.128 (1)	.004	.188
academic	202	88.2	106	52.5	96	47.5			
industry-driven	27	11.8	22	81.5	5	18.5			
Time Period							1.353 (2)	.508	.077
2007–2011	58	25.3	35	60.3	23	39.7			
2012–2016	85	37.1	49	57.6	36	42.4			
since 2017	86	37.6	44	51.2	42	48.8			
Status							.608 (3)	.895	.053
not yet recruiting	19	8.3	12	63.2	7	36.8			
ongoing	64	27.9	34	53.1	30	46.9			
closed	118	51.5	65	55.1	53	44.9			
withdrawn	13	5.7	7	53.8	6	46.2			
unknown[a]	15	6.6	10	66.7	5	33.3			
Results available on PubMed for closed trials (n = 118)							6.125 (1)	.013	.228
yes	20	16.9	6	30.0	14	70.0			
no	98	83.1	59	60.2	39	39.8			
Phase							1.606 (2)	.448	.116
early phase	25	11.0	21	84.0	4	16.0			
phase 2	36	15.7	26	72.2	10	27.8			
late phase	59	25.8	42	71.2	17	28.8			
not applicable[a]	109	47.6	39	35.8	70	64.2			
Cancer Type							11.247 (2)	.004	.222
solid tumour	53	23.1	32	60.4	21	39.6			
haematological	67	29.3	47	70.1	20	29.9			
mixed	109	47.6	49	45.0	60	55.0			
Intervention Type							60.411 (6)[F]	<.001	.507
drugs	107	46.7	83	77.6	24	22.4			
procedures	14	6.1	10	71.4	4	28.6			
behavioural – physical	40	17.5	13	32.5	27	67.5			
behavioural – edu/psy/soc	48	21.0	10	20.8	38	79.2			
other	20	8.7	12	60.0	8	40.0			

C% = column-percentages. R% = row-percentages. C% / R% may not total 100% due to rounding errors.
edu/psy/soc = educational, psychological, social.
[F] Fisher Exact Test; [a] excluded for comparative statistics.

and solid tumours. The most common interventions were drugs (107/229, 46.7%), followed by behavioural interventions with an educational/psychological/social (48/229, 21.0 %) or physical (40/229, 17.5 %) focus.

The most frequently used COA was PRO, which was assessed in 101/229 (44.1 %) of trials, followed by performance-based (39/229, 17.0 %), clinician-reported (37/229, 16.2 %) and observer-reported outcomes (34/229, 14.8 %). Fourteen trials (14/229, 6.1 %) had no clear COA. As PROs were of primary interest for this study, the further analyses focus on PROM usage and potential associations with various trial characteristics.

3.3. Characteristics of PRO assessment

Among the trials relying on PROMs, PROMs were considered as a primary outcome in 57/101 (56.4%) and as a secondary outcome measure in 40/101 (39.6 %) trials. In 4/101 (4.0 %) cases, PROMs were listed as neither a primary nor secondary, but 'other' outcome. Mostly, PROM use was classified as 'assumably as intended' (70/101, 69.3 %); only few trials reported to have adapted all (2/101, 2.0 %) or some (13/101, 12.9 %) of the PROMs used.

The most commonly used PROMs were modules of the PedsQL Inventory (Varni and Limbers, 2009) (36/101, 35.6 %). Among them, the Generic Module (27/36, 75.0 %) was most often used, followed by the Cancer Module (16/36, 44.4 %) and Fatigue Module (14/36, 38.9 %), while the Brain Tumor Module was least commonly used (3/36, 8.3 %). The second most commonly used inventory was the Patient-Reported Outcomes Measurement Information System (PROMIS) (PROMIS, 2021)(8/101, 7.9 %), which provides numerous subscales. Among them, the most often administered scales were the Pediatric PROMIS Anxiety short form (4/8, 50 %), the Pediatric PROMIS Psychological Stress Experience scale (4/8, 50 %), and the Pediatric PROMIS Pain Behavior short form (2/8, 25 %). Other PROMIS scales (i.e., Anger, Depressive Symptoms, Fatigue, Pain Interference, Physical Stress Experience, Positive Affect, Social Isolation) were used once. One trial (NCT03778658) mentioned to use the PROMIS Profile 29, which is an adult tool. The third most commonly used instrument was the Memorial Symptom Assessment Scale (Portenoy et al., 1994) (6/101, 5.9 %). For 7/101 (6.9

%) of trials none of the PROMs used could be identified, i.e., no validated or specified PROM was listed. Qualitative interviews were conducted in only 8 trials (8/229, 3.5 %), always in combination with a PROM.

3.4. Trial characteristics associated with PROM use

PROM use was strongly associated with intervention type (effect size.51, $p < .001$), indicating that trials on behavioural interventions – physical or educational/psychological/social – are significantly more likely to integrate PROMs (Fig. 2). Among trials on medical interventions (i.e., drugs and procedures), the proportion of trials using PROMs was only 28/121 (23.1 %). In comparison, 65/88 (73.9 %) of trials on behavioural interventions (i.e., physical and educational/psychological/social combined) used PROMs.

Furthermore, PROMs were significantly more often used in clinical trials conducted in mixed samples with both cancer types ($p = .004$, Table 1), which more commonly investigated behavioural (47/88, 53.4 %) compared to medical interventions (51/121, 42.1 %).

Another significant association was found for number of centres, indicating that international multicentre trials were less likely to administer PROMs than trials conducted in single centres or within single countries ($p = .032$, Table 1).

PROMs were significantly more often used in academic trials than in industry-driven trials ($p = .004$, Table 1). Industry-driven trials were more commonly focusing on medical interventions (24/25, 96.0 %; compared to 97/184, 52.7 % in academic trials) and more likely to be conducted at multiple centres in different countries (10/27, 37.0 %, compared to 14/202, 6.9 % in academic trials).

For closed trials, there was a significant positive association between PROM use and available publications on PubMed ($p = .013$, Table 1).

3.5. Domains assessed with PROMs

For 94 (93.1 %) of the 101 trials relying on PROMs, the domains assessed could be identified unambiguously. The majority of trials (56/94, 59.6 %) measured more than one domain and, in many cases, even three or more domains were measured (34/94, 45.8 %). The domain most frequently assessed was 'physical' (87/94, 92.6 %), followed by 'psychological' (58/94, 61.7 %), and 'social' (41/94, 43.6 %).

Table 2 shows the PRO domains assessed in trials investigating different intervention types. For all intervention types, physical aspects were assessed most frequently. However, trials on drugs and procedures predominantly focused on physical outcomes, while trials investigating behavioural interventions (either physical or educational/psychological/social) had a more comprehensive approach and included psychological and social aspects more often.

3.6. PROM usage over time

The comparison of PROM usage over time did not indicate any significant change across the years ($p = .508$, Table 1). Fig. 3 shows the number of clinical trials per year and the percentage of PROM usage. While in 2007, PROMs were only included in 1/7 (14 %) of registered

Table 2
PRO domains assessed in trials on different intervention type.

Intervention type	Domains measured			
	Physical N (%)	Psychological N (%)	Social N (%)	Other N (%)
drugs (n = 24)	22 (91.7)	5 (20.8)	3 (12.5)	1 (4.2)
procedures (n = 4)	4 (100.0)	1 (25.0)	0 (0.0)	0 (0.0)
behavioural – physical (n = 27)	23 (85.2)	19 (70.4)	18 (66.7)	3 (11.1)
behavioural – edu/psych/soc (n = 38)	32 (84.2)	29 (76.3)	18 (47.4)	8 (21.1)
other (n = 8)	6 (75.0)	4 (50.0)	2 (25.0)	1 (12.5)
Total (N = 94)	87 (92.6)	58 (61.7)	41 (43.6)	13 (13.8)

Note. *edu/psych/soc* = educational, psychological or social.
N = 94 because domains could only be identified for 94 out of 101 trials using PROMs.

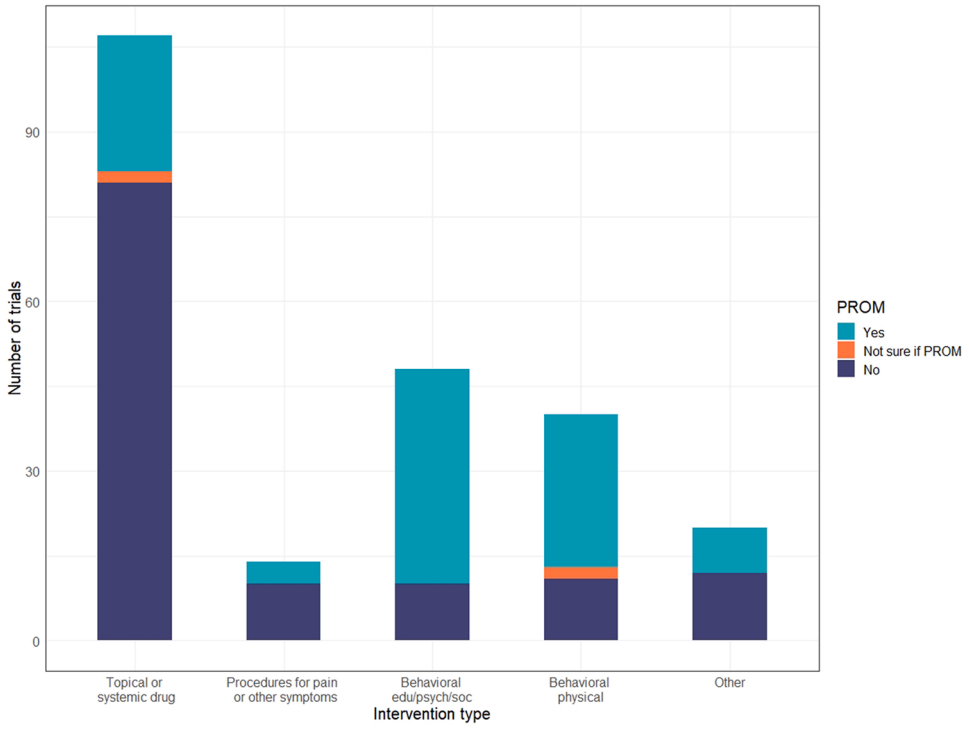

Fig. 2. Use of PROMs in paediatric cancer clinical trials investigating different intervention types.

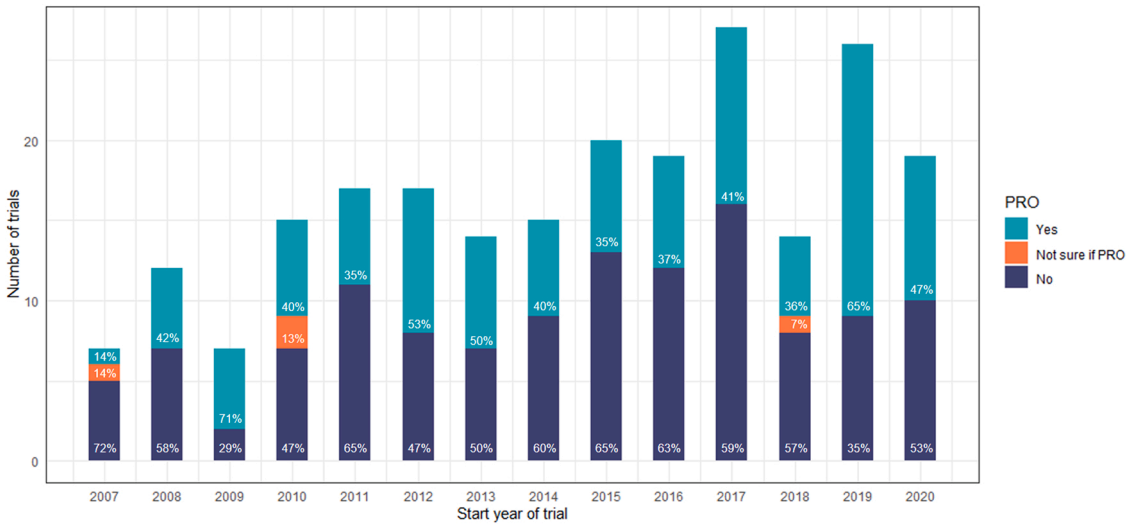

Fig. 3. Number of clinical trials per year and the proportion of trials relying on PROMs.

trials, the share of trials using PROMs ranged between 6/17 (35 %, 2011) and 5/7 (71 %, 2009) for the subsequent years. However, there is no consistent trend towards increased PROM usage over time.

3.7. Multivariable model to predict PROM usage by trial characteristics

In a multivariable model based on a binary logistic regression, intervention and cancer type remained significant predictors of PROM usage (see Table 3). On the contrary, industry involvement and number of centres were no longer significant. The regression model explains 39.6 % of variance (Nagelkerke R^2) and is statistically significant (Omnibus: χ^2 =68.189 (de Rojas et al., 2020), $p < .001$).

The phase of trials could not be included as a predictor because for too many trials it was 'not applicable' (109/229, 47.6 %). The variable 'published results' was not included, as it was only assessed for subsamples of the data (i.e., closed trials).

Table 3
Binary logistic regression model to predict PROM usage by status, cancer type, intervention type, industry involvement, time period, region, and number of centres.

		CI 95 %		
	OR	LL	UL	*p*
Status (reference: not yet recruiting)				.653
ongoing	2.557	.569	11.497	.221
closed	2.670	.534	13.362	.232
withdrawn	3.006	.326	27.688	.331
Type of cancer (reference: haematological)				**.003**
solid tumour	2.831	1.036	7.731	**.042**
mixed	4.861	1.976	11.958	**.001**
Intervention type (reference: drugs)				**.000**
procedures	.780	.173	3.512	.746
behavioural – physical	9.663	3.407	27.406	**.000**
behavioural – edu/psy/soc	9.421	3.344	26.541	**.000**
other	1.781	.543	5.839	.341
Industry-driven (reference: academic)	.338	.060	1.903	.219
Time Period (reference: 2007–2011)				.387
2012–2016	.629	.241	1.639	.342
since 2017	1.181	.368	3.793	.779
Region (reference: Other)				.862
Asia	.618	.109	3.489	.585
Europe	1.241	.319	4.828	.755
North-America	1.187	.346	4.073	.786
intercontinental	2.925	.155	55.297	.474
Number of centres (reference: monocentric)				.357
multicentric – national	1.342	.542	3.321	.525
multicentric – international	.306	.043	2.179	.237
Constant	.055			.011

N = 194. OR = odds ratio, CI = confidence interval, LL = lower limit, UL = upper limit.
edu/psy/soc = educational, psychological, social.
Phase of trials could not be included as predictor, because it was 'not applicable' for most trials.

4. Discussion

Our review shows that less than half of clinical trials on supportive interventions for children and adolescents with cancer used PROMs (44.1 %, 101/229) and only one out of four trials considered PROMs as primary outcome (23.6 %, 57/229). These proportions indicate that clinical trials substantially fail to appropriately assess the core outcome of supportive interventions: patients' perspective on their QOL and health state. Additionally, these results highlight a delay of PRO research in paediatric compared to adult oncology, which is especially apparent in clinical trials investigating drugs and medical procedures.

4.1. Insufficient PRO assessment to evaluate supportive interventions

The observed proportion of 44.1 % of trials using PROMs is substantially higher than the 8.2 % found for clinical trials investigating anti-cancer treatments (Riedl et al., 2021a). However, these numbers still show that the majority of trials has not used PROMs for the evaluation of supportive interventions. This is striking because at its core, supportive care aims to improve patients' functioning, well-being, and QOL (Anon, 2021). To assess these outcomes, PROMs should be the essential COA in clinical trials on interventions targeting those domains. Especially for clinical trials examining experimental interventions, PRO assessment is recommended by regulatory agencies (Patient-Reported, 2009; Appendix, 2016).

Clinical trials on supportive interventions are also currently limited by their uncomprehensive assessment of different domains of QOL. While we found that most trials followed a multidimensional assessment approach, we observed a strong focus on physical symptoms. Psychological or social domains were far less frequently measured, especially in trials investigating drugs or medical procedures. This is not only problematic as these are the aspects especially prioritised by children and adolescents (Sodergren et al., 2018; Jones et al., 2018; Anthony et al., 2017). The focus on physical symptoms also negates the fact that symptoms and adverse events are often inseparable from psychological distress (Hinds et al., 2021). Moreover, a review of clinical trials in adult oncology found that differences in HRQOL were most frequently found not only in global QOL and the physical domain, but also for role

functioning (Giesinger et al., 2020). This highlights the significance of social health aspects and the need for a more multidimensional assessment of QOL using PROMs.

4.2. PRO research in childhood cancer lags behind adult oncology

Our results indicate that PROM use for the evaluation of supportive interventions has become more commonplace compared to the results of Hinds et al. (2007), who found that only 15.4 % of included studies used PROMs at that time. However, while the overall use increased, we did not observe any significant or consistent increase in PRO assessment within the last 13 years.

The current share of 44.1 % of trials using PROMs to evaluate supportive interventions for paediatric cancer patients is considerably lower than the 58 % observed by Vinches et al (Vinches et al., 2020). in adult oncology research. This difference mirrors a trend that we also observed in our previous review (Riedl et al., 2021a) and which has been noted by other studies: PRO assessment in paediatric oncology lags behind adult oncology (Riedl et al., 2021a; de Rojas et al., 2020).

Factors contributing to this delay in paediatric PRO research and barriers for PROM use in general have been discussed elsewhere (de Rojas et al., 2020; Efficace et al., 2014). Besides missing guidelines for the implementation, analysis, and interpretation of PROMs, the most important obstacle in paediatric settings is probably a persistent hesitation to actively involve children in research and shared decision-making (Coyne et al., 2016). It seems as if there is a remaining scepticism towards children's ability to speak for themselves, even though research has shown that they are capable to provide valid and reliable self-report from the age of ~8 years (Arbuckle and Abetz-Webb, 2013; Varni et al., 2007).

Another obstacle might be that the currently available PROMs for children and adolescents with cancer have been criticised for partly insufficient psychometric properties (Coombes et al., 2016; Solans et al., 2008; Pinheiro et al., 2018; Cremeens et al., 2006). Most instruments were developed without any patient involvement (Klassen et al., 2010) and it is questionable if they cover and represent children's priorities well (Anthony et al., 2017; Hinds et al., 2004; Davis et al., 2006). They have further been criticised for insufficiently assessing social aspects (Anthony et al., 2017) and exclusively focusing on negative health, what might have an impact on patients' self-perception (Fayed et al., 2011).

4.3. Trial characteristics associated with PROM use

The type of intervention investigated in a trial was a significant predictor of PROM use in the multivariable model. Behavioural (both physical and educational/psychological/social) interventions were associated with higher PROM use compared to medical intervention types. A possible explanation would be that, in contrast to drug or procedural interventions, behavioural interventions by nature depend on the active participation of patients. In these settings, patients are probably rather perceived as active co-creators than only as recipients of care. Assessing their perspective might be more self-evident in trials investigating behavioural interventions.

Previous studies suggest that adult oncology trials with academic involvement show a higher use of PROMs compared to industry-driven trials (Vodicka et al., 2015; Scoggins and Patrick, 2009). We observed the same association in the univariate analysis. However, funder type was no significant predictor for PROM use in the multivariable model, which likely can be traced back to differing trial characteristics. Industry-driven trials investigated primarily medical interventions, where overall fewer PROMs were used than in trials on behavioural interventions, which are more commonly conducted by academia.

We observed that closed trials relying on PROMs were more commonly published in peer-reviewed journals compared to trials which do not assess any PROs. This is in line with previous findings (Riedl et al., 2021a) and might indicate that trials using PROMs are of higher quality in general, which makes them more likely to be published.

4.4. Limitations and strengths of reviewing clinical trial registries

Due to changing regulations, the registration of trials and information submitted vary over time and may provide a somewhat biased picture of clinical research as a whole (Tse et al., 2018). The quality of reporting was highly heterogeneous across trials. This also concerned the level of detail provided on PROM usage. Often, the description of PROM administration was vague. Only 14.9 % of trials using PROMs reportedly modified some or all administered PROMs. However, it is possible that more trials used modified PROMs without explicitly reporting so. Thus, our review probably overestimates the complete use of PROMs.

Despite this limitation, the analysis of clinical trial registries provides very valuable information if the research question is adequate. They provide a more comprehensive picture of research compared to literature databases: There is a considerable gap between registered and published trials, as only a fraction is published in peer-reviewed journals (Vinches et al., 2020; Ramsey and Scoggins, 2008). This under-reporting of trial results may be the result of different kinds of bias, such as publication bias or outcome reporting bias (Dwan et al., 2013; Hopewell et al., 2009). If we had based our study on published trials only, we would have overestimated the use of PROMs since it was much higher (70 %) in published closed trials.

4.5. Conclusion and implications for research

Our review shows that PROMs are used in less than half of registered clinical trials investigating supportive interventions for children and adolescents with cancer. While this proportion is higher than in trials on anti-cancer treatments for paediatrics, it is inferior to that in adult oncology research. Overall, it is strikingly low given that supportive care at its core aims to improve QOL, which is best assessed using PROMs. PRO assessment in clinical trials evaluating supportive interventions should therefore be the norm rather than the exception. Therefore, we recommend that the use of PROMs should be carefully considered during trial design. Future studies should critically evaluate whether existing PROMs are suitable to accurately assess PROs in paediatric oncology or whether there is a need for new tools. Additionally, we need to better understand what hinders PROM implementation in paediatric oncology in order to overcome these barriers and to make children's voices heard.

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CRediT authorship contribution statement

RD; Conceptualization, **MR, JL, RD**; Methodology, **MR, JL, WM, TdR, DR**; Writing – original draft, **MR, JL,RD**; Writing – review & editing, **MR, JL, WM, TdR, SS, ASD, RD**; Visualization, **MR, JL**; Supervision, **TdR, SS, ASD, RD**. All authors have read and agreed to the published version of the manuscript. The EORTC Quality of Life Group has provided funding and endorsed the final manuscript based on an internal peer-review procedure.

Conflicts of interest

Apart from the funding, we have no conflicts of interest to declare

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2022.103755.

References

Anon, (IV) Pediatric ResearchEquity Act and (V) Best Pharmaceuticals in Children Act of 2007. In: Food and Drug Administration Amendments Act (FDAAA) of 2007, Food and Drug Administration (FDA). ⟨http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/html/PLAW-110publ85.htm⟩.

Anon, NCI Dictionary of Cancer Terms. 2021. supportive care.

Anon, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, Food and Drug Administration (FDA), Rockville, 2009. ⟨https://www.fda.gov/media/77832/download⟩.

Anthony, S.J., Selkirk, E., Sung, L., Klaassen, R.J., Dix, D., Klassen, A.F., 2017. Quality of life of pediatric oncology patients: do patient-reported outcome instruments measure what matters to patients? Qual. Life Res. 26 (2), 273–281.

Anthony, S.J., Selkirk, E., Sung, L., Klaassen, R.J., Dix, D., Scheinemann, K., et al., 2014. Considering quality of life for children with cancer: a systematic review of patient-reported outcome measures and the development of a conceptual model. Qual. Life Res. 23 (3), 771–789.

Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man: The use of patient-reported outcome (PRO) measures in oncology studies. London European Medicines Agency (EMA); 2016. ⟨https://www.ema.europa.eu/en/documents/other/appendix-2-guideline-evaluation-anticancer-medicinal-products-man_en.pdf⟩.

Arbuckle, R., Abetz-Webb, L., 2013. "Not just little adults": qualitative methods to support the development of pediatric patient-reported outcomes. Patient 6 (3), 143–159.

Baggott, C., Cooper, B.A., Marina, N., Matthay, K.K., Miaskowski, C., 2014. Symptom assessment in pediatric oncology: how should concordance between children's and parents' reports be evaluated? Cancer Nurs. 37 (4), 252–262.

Coombes, L.H., Wiseman, T., Lucas, G., Sangha, A., Murtagh, F.E., 2016. Health-related quality-of-life outcome measures in paediatric palliative care: a systematic review of psychometric properties and feasibility of use. Palliat. Med. 30 (10), 935–949.

Coyne, I., O'Mathúna, D.P., Gibson, F., Shields, L., Leclercq, E., Sheaf, G., 2016. Interventions for promoting participation in shared decision-making for children with cancer. Cochrane Database Syst. Rev. 11, CD008970.

Cremeens, J., Eiser, C., Blades, M., 2006. Characteristics of health-related self-report measures for children aged three to eight years: a review of the literature. Qual. Life Res 15 (4), 739–754.

Darcy, L., Enskar, K., Bjork, M., 2019. Young children's experiences of living an everyday life with cancer - a three year interview study. Eur. J. Oncol. Nurs. 39, 1–9.

Davis, E., Waters, E., Mackinnon, A., Reddihough, D., Graham, H.K., Mehmet-Radji, O., 2006. Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes. Dev. Med. Child Neurol. 48 (4), 311–318.

Dwan, K., Gamble, C., Williamson, P.R., Kirkham, J.J., Group, R.B., 2013. Systematic review of the empirical evidence of study publication bias and outcome reporting bias - an updated review. PLoS One 8 (7), e66844.

Efficace, F., Rees, J., Fayers, P., Pusic, A., Taphoorn, M., Greimel, E., 2014. Overcoming barriers to the implementation of patient-reported outcomes in cancer clinical trials: the PROMOTION Registry. Health Qual. Life Outcomes 12, 86.

Fayed, N., Schiariti, V., Bostan, C., Cieza, A., Klassen, A., 2011. Health status and QOL instruments used in childhood cancer research: deciphering conceptual content using World Health Organization definitions. Qual. Life Res. 20 (8), 1247–1258.

Gatta, G., Botta, L., Rossi, S., Aareleid, T., Bielska-Lasota, M., Clavel, J., et al., 2014. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5–a population-based study. Lancet Oncol. 15 (1), 35–47.

Giesinger, J.M., Blazeby, J., Aaronson, N.K., Sprangers, M., Fayers, P., Sparano, F., 2020. Differences in patient-reported outcomes that are most frequently detected in randomized controlled trials in patients with solid tumors: a pooled analysis of 229 trials. Value Health 23 (5), 666–673.

Group F-NBW. BEST , (Biomarkers, EndpointS, and other Tools) Resource. Food and Drug Administration (US), National Institutes of Health (US), Silver Spring (MD), Bethesda (MD), 2021.

Guilcher, G.M.T., Rivard, L., Huang, J.T., Wright, N.A.M., Anderson, L., Eissa, H., 2021. Immune function in childhood cancer survivors: a Children's Oncology Group review. Lancet Child Adolesc. Health 5 (4), 284–294.

Hinds, P.S., Brandon, J., Allen, C., Hijiya, N., Newsome, R., Kane, J.R., 2007. Patient-reported outcomes in end-of-life research in pediatric oncology. J. Pediatr. Psychol. 32 (9), 1079–1088.

Hinds, P.S., Gattuso, J.S., Fletcher, A., Baker, E., Coleman, B., Jackson, T., 2004. Quality of life as conveyed by pediatric patients with cancer. Qual. Life Res. 13 (4), 761–772.

Hinds, P.S., Weaver, M.S., Withycombe, J.S., Baker, J.N., Jacobs, S.S., Mack, J.W., 2021. Subjective toxicity profiles of children in treatment for cancer: a new guide to supportive care? J. Pain. Symptom Manag. 61 (6), 1188–1195 e2.

Hooke, M.C., Linder, L.A., 2019. Symptoms in children receiving treatment for cancer-part i: fatigue, sleep disturbance, and nausea/vomiting. J. Pediatr. Oncol. Nurs. 36 (4), 244–261.

Hopewell, S., Loudon, K., Clarke, M.J., Oxman, A.D., Dickersin, K., 2009. Publication bias in clinical trials due to statistical significance or direction of trial results. Cochrane Database Syst. Rev. 1, MR000006.

Jones, C.M., Baker, J.N., Keesey, R.M., Eliason, R.J., Lanctot, J.Q., Clegg, J.L., 2018. Importance ratings on patient-reported outcome items for survivorship care: comparison between pediatric cancer survivors, parents, and clinicians. Qual. Life Res. 27 (7), 1877–1884.

Kazak, A.E., Abrams, A.N., Banks, J., Christofferson, J., DiDonato, S., Grootenhuis, M.A., et al., 2015. Psychosocial assessment as a standard of care in pediatric cancer. Pediatr. Blood Cancer 62 (Suppl 5), S426–S459.

Klassen, A.F., Strohm, S.J., Maurice-Stam, H., Grootenhuis, M.A., 2010. Quality of life questionnaires for children with cancer and childhood cancer survivors: a review of the development of available measures. Support Care Cancer 18 (9), 1207–1217.

Koo, T.K., Li, M.Y., 2016. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J. Chiropr. Med. 15 (2), 155–163.

Leiss, U., 2012. Neuropsychological assessment and intervention in pediatric neuro-oncology. memo - magazine of European. Med. Oncol. 4, 24–25.

Linder, L.A., Hooke, M.C., 2019. Symptoms in children receiving treatment for cancer-part II: pain, sadness, and symptom clusters. J. Pediatr. Oncol. Nurs. 36 (4), 262–279.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 4, 1.

Murugappan, M.N., King-Kallimanis, B.L., Reaman, G.H., Bhatnagar, V., Horodniceanu, E.G., Bouchkouj, N., et al., 2021. Patient reported outcomes in pediatric cancer registration trials: a U.S. Food and Drug Administration perspective. J. Natl. Cancer Inst.

Parsons, S.K., Fairclough, D.L., Wang, J., Hinds, P.S., 2012. Comparing longitudinal assessments of quality of life by patient and parent in newly diagnosed children with cancer: the value of both raters' perspectives. Qual. Life Res. 21 (5), 915–923.

Pinheiro, L.C., McFatrich, M., Lucas, N., Walker, J.S., Withycombe, J.S., Hinds, P.S., 2018. Child and adolescent self-report symptom measurement in pediatric oncology research: a systematic literature review. Qual. Life Res. 27 (2), 291–319.

Portenoy, R.K., Thaler, H.T., Kornblith, A.B., Lepore, J.M., Friedlander-Klar, H., Kiyasu, E., et al., 1994. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur. J. Cancer 30A (9), 1326–1336.

PROMIS, HealthMeasures, 2021 ⟨https://www.healthmeasures.net/explore-measurement-systems/promis⟩.

Ramsey, S., Scoggins, J., 2008. Commentary: practicing on the tip of an information iceberg? Evidence of underpublication of registered clinical trials in oncology. Oncologist 13 (9), 925–929.

Regulation (EC), 2006. No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medical products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004: European Parliament; Counsil of the European Union. ⟨https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf⟩.

Riedl, D., Rothmund, M., Darlington, A.S., Sodergren, S., Crazzolara, R., de Rojas, T., et al., 2021a. Rare use of patient-reported outcomes in childhood cancer clinical trials - a systematic review of clinical trial registries. Eur. J. Cancer 152, 90–99.

de Rojas, T., Neven, A., Towbin, A., Carceller, F., Bautista, F., Riedl, D., et al., 2020. Clinical research tools in pediatric oncology: challenges and opportunities. Cancer Metastas Rev.

Scoggins, J.F., Patrick, D.L., 2009. The use of patient-reported outcomes instruments in registered clinical trials: evidence from ClinicalTrials.gov. Contemp. Clin. Trials 30 (4), 289–292.

Sodergren, S.C., Husson, O., Rohde, G.E., Tomaszewska, I.M., Vivat, B., Yarom, N., et al., 2018. A life put on pause: an exploration of the health-related quality of life issues relevant to adolescents and young adults with cancer. J. Adolesc. Young Adult Oncol. 7 (4), 453–464.

Solans, M., Pane, S., Estrada, M.D., Serra-Sutton, V., Berra, S., Herdman, M., et al., 2008. Health-related quality of life measurement in children and adolescents: a systematic review of generic and disease-specific instruments. Value Health 11 (4), 742–764.

Söntgerath, R., Däggelmann, J., Kesting, S.V., Rueegg, C.S., Wittke, T.C., Reich, S., et al., 2021. Physical and functional performance assessment in pediatric oncology: a systematic review. Pediatr. Res.

Tse, T., Fain, K.M., Zarin, D.A., 2018. How to avoid common problems when using ClinicalTrials.gov in research: 10 issues to consider. BMJ 361, k1452.

Varni, J.W., Limbers, C.A., 2009. The pediatric quality of life inventory: measuring pediatric health-related quality of life from the perspective of children and their parents. Pediatr. Clin. North Am. 56 (4), 843–863.

Varni, J.W., Limbers, C.A., Burwinkle, T.M., 2007. How young can children reliably and validly self-report their health-related quality of life?: an analysis of 8,591 children across age subgroups with the PedsQL 4.0 Generic Core Scales. Health Qual. Life Outcomes 5, 1.

Vinches, M., Neven, A., Fenwarth, L., Terada, M., Rossi, G., Kelly, S., et al., 2020. Clinical research in cancer palliative care: a metaresearch analysis. BMJ Support Palliat. Care 10 (2), 249-58.

Vodicka, E., Kim, K., Devine, E.B., Gnanasakthy, A., Scoggins, J.F., Patrick, D.L., 2015. Inclusion of patient-reported outcome measures in registered clinical trials: Evidence from ClinicalTrials.gov (2007-2013). Conte Clin. Trials 43, 1–9.

Wiener, L., Kazak, A.E., Noll, R.B., Patenaude, A.F., Kupst, M.J., 2015. Standards for the psychosocial care of children with cancer and their families: an introduction to the special issue. Pediatr. Blood Cancer 62 (Suppl 5), S419–424.
Yeh, C.H., Chang, C.W., Chang, P.C., 2005. Evaluating quality of life in children with cancer using children's self-reports and parent-proxy reports. Nurs. Res. 54 (5), 354–362.
Yoo, H.J., Ra, Y.S., Park, H.J., Lai, J.S., Cella, D., Shin, H.Y., et al., 2010. Agreement between pediatric brain tumor patients and parent proxy reports regarding the Pediatric Functional Assessment of Cancer Therapy-Childhood Brain Tumor Survivors questionnaire, version 2. Cancer 116 (15), 3674–3682.

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