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

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**Short bios**

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**Wiebke Moser**, MSc, MSc, is a clinical psychologist at the University Hospital of Innsbruck, Austria, working in the field of psycho-oncology and psychosomatics. She and her team are currently setting up an oncological long-term follow-up care project ('ZONE') at the Comprehensive Cancer Center Innsbruck, where she is responsible for the screening, care and treatment of young cancer survivors.

**Teresa de Rojas**, MD-PhD, is currently working as Scientific Coordinator of ACCELERATE, an academic platiforme promoting drug development in childhood cancer. Her main research areas include oncogenomics, real-world data science and quality of life. Dr. de Rojas is experienced in the field of clinical research, having been clinical investigator in more than 20 pediatric trials as member of the FIB-HNJ Clinical Research Unit, in Madrid (2015-2016). Dr. de Rojas worked at the EORTC (European Organisation for Research and Treatment of Cancer), in Brussels, Belgium, as medical research fellow (2017-2020) and wasinvolved in and/or led several research projects about childhood and AYA cancer. Dr. de Rojas worked as post-doc researcher at the Children's University Hospital Niño Jesús in Madrid, Spain, in the Pediatric Oncology Department, as co-lead of the OncoGenomics & Innovation Unit (2020). Dr. de Rojas is Clinical Expert for the Adolescent Medicine Expert Group of the Conect4Children (c4c) Consortium, the collaborative network for European clinical trials for children. She is also member of several scientific societies, such as SIOPE and SEHOP. She is member of the Steering Committee of Young SIOPE.Finally, Dr. de Rojas has an interest in non-for-profit, international cooperation projects and is faculty member of the Pediatric Oncology Training Program at the Uganda Cancer Institute, Kampala, Uganda, to help in the development of a solid pediatric oncology expertise network in East Africa.

**Samantha C. Sodergren**, Dr, is a Chartered Health Psychologist and Senior Research Fellow at the University of Southampton in the UK. She specialises in quality of life assessment in people living with and beyond cancer with a particular interest in young people with cancer. She is an active member of the European Organisation for Research and Treatment of Cancer Quality of Life Group (EORTC QLG) and leads the development of several EORTC QLG questionnaire modules including the development of a quality of life measure for Children and Adolescents and Young Adults with cancer.

**Anne-Sophie Darlington**, Prof, is a Professor of Child and Family Psychological Health, at the University of Southampton, in the UK, specialising in Health/Paediatric Psychology. Her programme of work focuses measuring and improving Quality of Life of children and young people with a chronic illness, through developing and testing interventions. She is an expert on quality of life for Adolescents and Young Adults with cancer.

**David Riedl**, PhD, is a clinical psychologist and senior researcher at the Medical University Innsbruck. He specialized in patient-reported outcome research with a focus on the assessment of health-related quality of life in children with cancer. He is an active member of the European Organisation for Research and Treatment of Cancer Quality of Life Group (EORTC QLG), and leads the module development for children with cancer.

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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.

# Background

Survival rates in paediatric oncology have been rising over the last decades (1, 2). 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 (3, 4). Due to an immunosuppressed status patients are also more prone to severe infections or inflammatory responses (e.g., mucositis) (5). Additionally, the diagnosis of a potentially life-threatening disease is often associated with substantial changes in daily life (6), which may lead to feelings of loneliness, uncertainty, anxiety, and depression and to a decreased quality of life (QOL) (7).

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 (8, 9) The gold standard to assess patients’ quality of life are patient-reported 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” (10). There are strong recommendations to use PRO measures (PROMs) in clinical practice (8, 9) and in clinical trials (11-13). 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 (14). 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 (15).

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.” (16) 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 (17). 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 (18, 19). The latest review on the use of PROMs in research on supportive interventions for children with cancer was conducted more than a decade ago (20). 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 (21, 22). For the assessment of neurocognitive or physical functioning, performance-based outcomes play an important role (23, 24). 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 (22, 25-27).

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.

# Methods

## 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 (19). 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 (19) for their analysis); 3) investigated other research aspects (e.g., genetics, pharmacokinetics, diagnostics or organizational issues around care).

The study methodology complies with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) statement and guidelines whenever applicable (28).

## 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] categorized 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].

## Definition of Trial Characteristics

If the trial registry entry mentioned that trials were specifically focusing on end-of-life care interventions, they were categorized 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 (17).

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 (29). 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 categorized 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 categorized based on the conceptual framework of QOL in children with cancer provided by Anthony et al. (6), 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 categorized as ‘unknown’.

Further definitions of other trial characteristics are in line with our first review (19) and provided in Supplement 1.

## 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 >.70 were classified as acceptable, >.80 as good and >.90 as excellent (30).

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.

# Results

## 3.1 Trial Selection

As shown in Figure 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 categorizations made for our previous review focusing on trials on anti-cancer treatments (19). The 316 trials re-assessed for the present review were those previously categorized 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 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.

Table 1: Main characteristics of clinical trials.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **total**  | **no PROM**  | **any PROM**   |  **comparative statistics** |
|   | **N**  | **C%**  | **N**  | **R%**  | **N**  | **R%** | **Χ2 (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.  |

## 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 (31) (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) (32) (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 (33) (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 (Figure 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.

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

|  |  |
| --- | --- |
|  | **Domains measured** |
| **Intervention type** | **Physical** | **Psychological** | **Social** | **Other** |
| **N (%)** | **N (%)** | **N (%)** | **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.

## 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). Figure 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 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 R2) and is statistically significant (Omnibus: χ2=68.189 (18), *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.  |

# 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 (14). 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 (16). 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 (10, 12).

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 prioritized by children and adolescents (4, 34, 35). The focus on physical symptoms also negates the fact that symptoms and adverse events are often inseparable from psychological distress (36). 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 (37). 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. (20), 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. (17) in adult oncology research. This difference mirrors a trend that we also observed in our previous review (14) and which has been noted by other studies: PRO assessment in paediatric oncology lags behind adult oncology (14, 18).

Factors contributing to this delay in paediatric PRO research and barriers for PROM use in general have been discussed elsewhere (18, 38). 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 (39). 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 (21, 40).

Another obstacle might be that the currently available PROMs for children and adolescents with cancer have been criticized for partly insufficient psychometric properties (41-44). Most instruments were developed without any patient involvement (45) and it is questionable if they cover and represent children’s priorities well (35, 46, 47). They have further been criticized for insufficiently assessing social aspects (35) and exclusively focusing on negative health, what might have an impact on patients’ self-perception (48).

## 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 (49, 50). 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 (14) 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 (51). 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 (17, 52). This under-reporting of trial results may be the result of different kinds of bias, such as publication bias or outcome reporting bias (53, 54). 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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**Figure Captions**

Figure 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 & Rothmund 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.

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

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

Figure 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 & Rothmund 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.

**ClinicalTrials.gov**
4623 records

**4789 records**

**after removing duplicates**

**711 anti-cancer treatments in paediatric patients**

**EudraCT**
292 records

3 started before 2007

**316 re-assessed
for present review**

**229 included**

**87 excluded**

- 78 healthy sample or non-cancer

- 4 focus on proxies’ well-being

- 1 curative treatment

- 4 other forms of research

**316 non-curative intention**

- 174 other forms of intervention
 - 157 behavioural

 - 9 dietary supplements

 - 8 alternative

- 142 other intention
 - 140 supportive

 - 2 palliative

**trials investigating interventions**

**3762 excluded**

- 3502 upper age limit above 21

- 156 healthy or non-cancer samples

- 104 other forms of research

 - 35 diagnostics
 - 19 comparing techniques / devices
 - 50 other

analysed previously,

see Riedl & Rothmund et al. (2021)