



## Original Article

## Radiotherapy quality assurance in paediatric clinical trials: first report from six QUARTET-affiliated trials



Sarah M Kelly<sup>a,b,c,\*</sup>, Andrada Turcas<sup>a,b,d,1</sup>, Coreen Corning<sup>b</sup>, Simon Bailey<sup>e</sup>, Adela Cañete<sup>f</sup>, Enrico Clementel<sup>b</sup>, Andrea di Cataldo<sup>g</sup>, Karin Dieckmann<sup>h,i</sup>, Mark N Gaze<sup>j</sup>, Gail Horan<sup>k</sup>, Meriel Jenney<sup>l</sup>, Ruth Ladenstein<sup>h</sup>, Laetitia Padovani<sup>m</sup>, Dominique Valteau-Couanet<sup>n</sup>, Tom Boterberg<sup>o</sup>, Henry Mandeville<sup>a,p</sup>

<sup>a</sup>The European Society for Paediatric Oncology (SIOP Europe), Clos Chapelle-aux-Champs 30; <sup>b</sup>European Organisation for the Research and Treatment of Cancer (EORTC) Headquarters, Brussels; <sup>c</sup>Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium; <sup>d</sup>Department of Oncology, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Romania; <sup>e</sup>Newcastle Cancer Centre, Newcastle University and Great North Children's Hospital, Newcastle-upon-Tyne, United Kingdom; <sup>f</sup>Pediatric Oncohematology Unit, University and Polytechnic la Fe Hospital, Department of Pediatrics, University of Valencia, Spain; <sup>g</sup>Department of Clinical and Experimental Medicine, Unit of Pediatric Hematology and Oncology, University of Catania, Catania, Italy; <sup>h</sup>Children's Cancer Research Institute, St Anna Children's Hospital; <sup>i</sup>Department of Radiation Oncology, Medical University of Vienna, Vienna, Austria; <sup>j</sup>Department of Oncology, University College London Hospitals NHS Foundation Trust; <sup>k</sup>Oncology Centre, Cambridge University Hospitals NHS Trust, Cambridge; <sup>l</sup>Department of Paediatric Oncology, Children's Hospital for Wales, Heath Park, Cardiff, United Kingdom; <sup>m</sup>Department of Radiation Oncology, Assistance Publique Hôpitaux de Marseille; <sup>n</sup>Gustave Roussy, Villejuif-Grand Paris, France; <sup>o</sup>Department of Radiation Oncology, Ghent University Hospital, Ghent, Belgium; <sup>p</sup>The Royal Marsden Hospital and Institute of Cancer Research, Sutton, United Kingdom

## ARTICLE INFO

## Article history:

Received 30 November 2022  
Received in revised form 2 February 2023  
Accepted 4 February 2023  
Available online 23 February 2023

## Keywords:

Radiotherapy  
Radiation Oncology  
Pediatrics  
Clinical Trial  
Quality Control  
Quality Assurance, Health Care

## ABSTRACT

**Background and Purpose:** SIOP Europe's QUARTET project launched in 2016; aiming to improve access to high-quality radiotherapy for children and adolescents treated within clinical trials across Europe. The aim of this report is to present the profile of institutions participating in six QUARTET-affiliated trials and a description of the initial individual case review (ICR) outcomes.

**Methods:** This is a two-part analysis. Firstly, using facility questionnaires, beam output audit certificates, and advanced technique credentialing records to create a profile of approved institutions, and secondly, collating trial records for ICRs submitted prior to 31/10/2022. Trials included are: SIOPEN HR-NBL1, SIOPEN-LINES, SIOPEN- VERITAS, SIOP-BTG HRMB, EpSSG-FaR-RMS, and SIOPEN HR-NBL2.

**Results:** By 31/10/2022, a total of 103 institutions had commenced QUARTET site approval procedures to participate in QUARTET-affiliated trials; 66 sites across 20 countries were approved. These participating institutions were often paediatric referral sites with intensity modulated radiotherapy or proton beam therapy, designated paediatric radiation oncologists, and paediatric adapted facilities and imaging protocols available. In total, 263 patient plans were submitted for ICR, 254 ICRs from 15 countries were completed. ICRs had a rejection rate of 39.8%, taking an average of 1.4 submissions until approval was achieved. Target delineation was the most frequent reason for rejection.

**Conclusion:** The QUARTET facility questionnaire is a valuable tool for mapping resources, personnel, and technology available to children and adolescents receiving radiotherapy. Prospective ICR is essential for paediatric oncology clinical trials and should be prioritised to reduce protocol violations.

© 2023 The Author(s). Published by Elsevier B.V. Radiotherapy and Oncology 182 (2023) 109549

**Abbreviations:** BOA, Beam Output Audit; CDC, Complex Dosimetry Check; EORTC, The European Organisation for Research and Treatment of Cancer; FQ, Facility Questionnaire; GHG, Global Quality Assurance of Radiation Therapy Clinical Trials Harmonization Group; ICR, Individual Case Review; IMRT, Intensity Modulated Radiotherapy; MDT, Multi-Disciplinary Team; MP, Medical Physicist; PBT, Proton Beam Therapy; QA, Quality Assurance; QUARTET, Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials (Project); RO, Radiation Oncologist; RTQA, Radiotherapy Quality Assurance; RTT, Radiation therapist; SIOP Europe, The European Society for Paediatric Oncology; VMAT, Volumetric Modulated Arc Therapy; VPP, Virtual Phantom Procedure.

\* Corresponding author at: SIOP Europe, Clos Chapelle-aux-Champs 30, Brussels, Belgium.

E-mail address: [Sarah.kelly@eortc.org](mailto:Sarah.kelly@eortc.org) (S.M Kelly).

<sup>1</sup> Sarah M Kelly and Andrada Turcas have contributed equally as co-first authors.

<https://doi.org/10.1016/j.radonc.2023.109549>

0167-8140/© 2023 The Author(s). Published by Elsevier B.V.

In 2016, the European Society for Paediatric Oncology (SIOP Europe) launched a collaborative project with the European Organisation for Research and Treatment of Cancer (EORTC) called Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials (QUARTET). QUARTET contributes to the SIOP Europe aim of improving cure and subsequent quality of life for all children and adolescents receiving anti-cancer therapies, regardless of where they live in Europe [1,2]. The purpose of QUARTET is to deliver a centralised radiotherapy quality assurance (RTQA) program for European clinical trials recruiting children and adolescents with multiple cancer types; the foundation and activity of the project has previously

been described [3]. Aside from creating a co-ordinated resource of paediatric radiotherapy expertise, two of the main QUARTET responsibilities are to assess and approve centres delivering radiotherapy prior to them commencing study recruitment, and to provide prospective Individual Case Review (ICR) of radiotherapy treatment plans for each patient. RTQA procedures are essential within paediatric oncology clinical trials to ensure that dose delivered is as per protocol requirements, or within an acceptable range of variations, and to optimise outcomes for children with cancer [4–6].

Each QUARTET-affiliated trial has an RTQA guideline which supplements the main trial protocol; aiming to support investigators to meet protocol requirements and any established best-practice for planning and delivery. This document defines the pre-recruitment site RTQA approval procedures as well as a comprehensive overview of planning objectives; wherever appropriate the components are standardised across trials. Pre-recruitment site RTQA procedures and on-trial ICRs are performed in order to minimise variations in infrastructure, personnel, radiotherapy planning, and dose delivery which could influence trial or patient outcomes [7]. Site RTQA approval procedures are based upon those previously described by the Global Quality Assurance of Radiation Therapy Clinical Trials Harmonization Group (GHG) [8], are typically the same as for adult trials, and can incorporate any combination of the following: facility questionnaire (FQ), beam output audit (BOA), advanced technique credentialing (CDC, complex dosimetry check or VPP, virtual phantom procedure), dummy run, or benchmark case exercise. An ICR is an on-trial activity to review both structure delineations and dosimetry against the RTQA guidelines/trial protocol. The trial quality assurance procedures, including site RTQA approval and ICR definitions, are briefly outlined within Fig. 1.

Within this paper we describe the initial experience of QUARTET regarding site RTQA approvals and ICRs performed since the project launch in May 2016 until 31/10/2022. This report aims to provide a profile of radiotherapy centres treating children and adolescents within clinical trials and information regarding treatment techniques, planning practices, and compliance to trial protocols for this diverse cohort of patients.

## Patients and methods

All site RTQA approvals and ICRs are tracked on an individual trial basis.

All QUARTET FQs, BOA certificates, and CDC reports submitted for the purposes of site RTQA approval within the European paediatric Soft tissue Sarcoma Group FaR-RMS<sup>2</sup> (EUDRACT 2018–000515–24); SIOP Europe Neuroblastoma group VERITAS<sup>3</sup> (EUDRACT 2015–003130–27) and HR-NBL2<sup>4</sup> (EUDRACT 2019–001068–31), and SIOP Brain Tumour Group HRMB<sup>5</sup> (EUDRACT 2018–004250–17) trials were collated, and a descriptive analysis of participating institutions performed. Institutions with site RTQA approval completed by 31/10/2022 were included.

Individual trial trackers and database records for ICR case submission and review forms for all cases submitted for ICR between 01/05/2016 and 31/10/2022, within the HR-NBL1<sup>6</sup> (EUDRACT 2006–001489–17), LINES<sup>7</sup> (EUDRACT 2010–021396–81), HR-NBL2,

<sup>2</sup> An overarching study for children and adults with frontline and relapsed rhabdomyosarcoma.

<sup>3</sup> An international multicentre phase II randomised trial evaluating and comparing two intensification treatment strategies for metastatic neuroblastoma patients with a poor response to induction chemotherapy. A SIOPEN Study.

<sup>4</sup> High-Risk Neuroblastoma Study 2 of SIOP-Europe-Neuroblastoma (SIOPEN).

<sup>5</sup> An international prospective trial on high-risk medulloblastoma in patients older than 3 years.

<sup>6</sup> High risk neuroblastoma study 1 of SIOP-Europe (SIOPEN).

<sup>7</sup> European Low and Intermediate Risk Neuroblastoma.

VERITAS, HRMB, and FaR-RMS trials were reviewed and collated for descriptive analysis. Minimum inclusion criteria were trial, patient, and site identifiers, initial submission date, treatment modality, and treatment technique.

## Results

A total of 103 institutions had begun site RTQA approval procedures (defined as date of FQ submission), for at least one QUARTET-affiliated trial by 31/10/2022. After opening of the first trials with integrated prospective ICR, the first site approval took place on 03/01/2020. Sixty-six centres from across 20 countries were approved to participate in QUARTET-affiliated trials during the evaluation period. The 37 remaining sites have BOA and/or advanced technique credentialing procedures underway; no sites have failed to meet RTQA approval requirements to date.

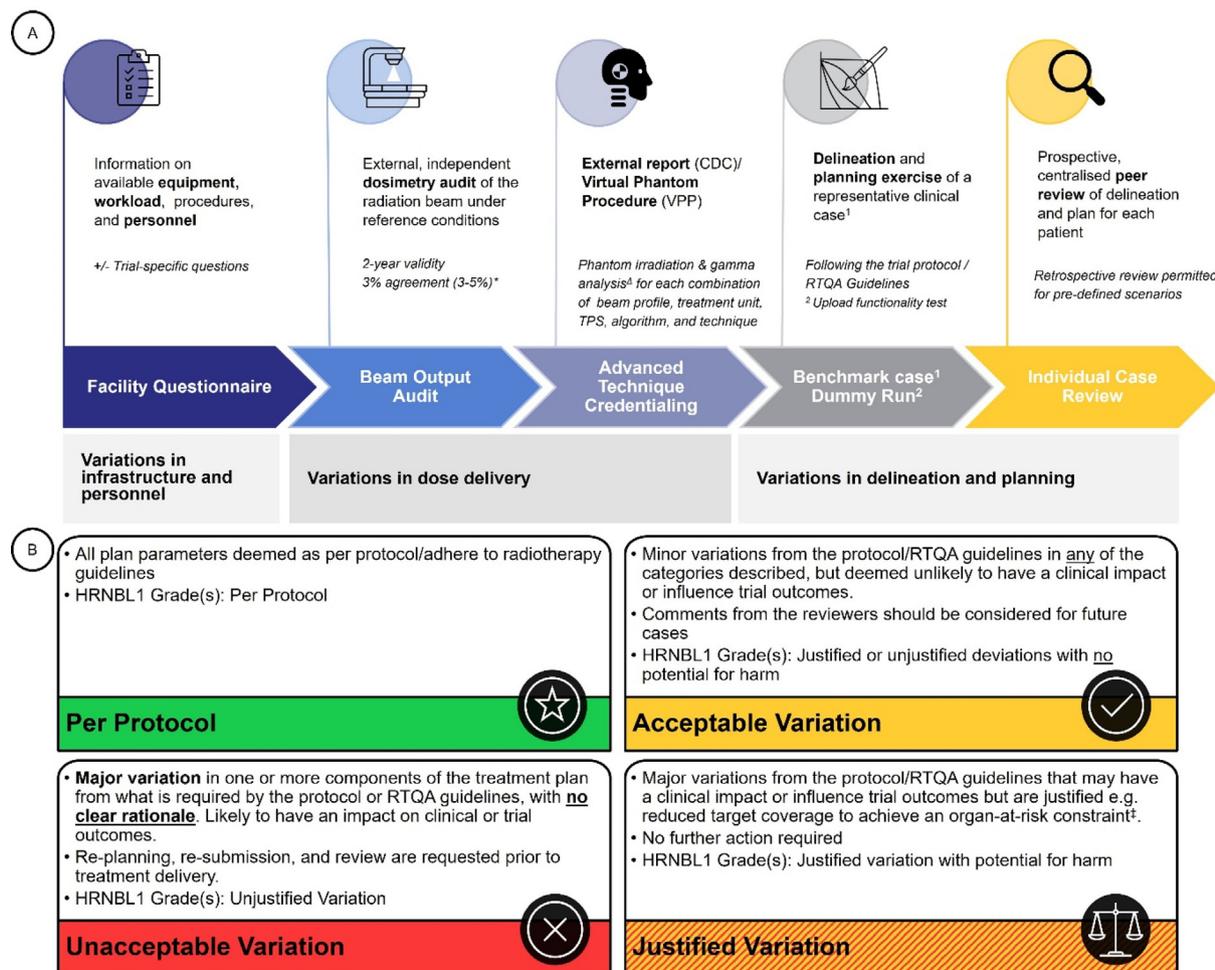
Fig. 2 shows the distribution of approved sites and the number of completed ICRs for each country currently, or planned, to participate in QUARTET-affiliated trials.

Most approved sites are in Europe, predominantly the UK (18) and France (10), followed by Australia (7). There are 59 photon and 7 proton beam therapy (PBT) centres. Fifty-six are public/university centres, four are privately operated, and data is missing for 6 centres. Sixty-two sites report previous participation in clinical trials; the majority (47) active in both paediatric and adult studies. Two sites were not previously involved in clinical trials and two did not comment. The majority (61) are paediatric referral centres, with 20 receiving national referrals, 36 regional, and 5 international; patients are referred to these sites to receive photon radiotherapy (55), molecular radiotherapy<sup>8</sup> (11), brachytherapy (10), and PBT (7). Paediatric specialised radiotherapy professionals are present in many centres, with designated radiation oncologists (RO, n = 50 sites), medical physicists (MP, n = 22), and radiation therapists (RTT, n = 19) available. The median number of treatment units per photon centre is six (range 3–16), with 38 centres reporting at least one unit designated for paediatric patients; PBT centres have a median of 3 treatment rooms (range 2–5). Molecular radiotherapy/radioisotope therapy and brachytherapy are available in 13 and 20 centres, respectively. Electron beams are used in 47 departments. All 59 photon centres use advanced techniques (IMRT/VMAT), 54 can deliver stereotactic radiotherapy, and all 7 PBT centres have pencil beam scanning technology and intensity modulated proton therapy.

In terms of treatment planning systems, 28 sites use one, while others have two (n = 21) or three (n = 14) available. Dose calculation algorithms in use are type A (Pencil Beam Convolution-based) (n = 3 centres), type B (Convolution-Superposition-based: Anisotropic Analytical Algorithm or Collapsed Cone Convolution)(n = 30), and type C (Boltzmann transport dose computation: Monte Carlo, Accuros XB) (n = 40). Centres using multiple treatment planning systems often do so for the availability of alternative dose calculation algorithms due to varying accuracy, with type C algorithms being the gold standard [9,10], or for technology-specific optimisation. All systems allow for image registration and plan summation, while robustness analysis and/or optimisation are possible in 43 and 36 departments, respectively.

To validate calculated doses, secondary monitor unit calculation is used in 48/66 centres for 3-dimensional conformal radiotherapy (n = 46), static and rotational IMRT delivery (n = 30), stereotactic radiotherapy (n = 22), PBT (n = 2), and brachytherapy (n = 6).

<sup>8</sup> Molecular radiotherapy, also known as radionuclide or radioisotope therapy, uses unsealed sources of radiation administered orally or intravenously, to treat tumours in a targeted way. Within the paediatric population this is mainly used for children with neuroblastoma. This is relevant to children treated within the SIOPEN HR-NBL2 and VERITAS trials.



**Fig. 1. QUARTET clinical trial radiotherapy quality assurance procedures** A: Schematic representation of the main steps for site approval, both in QUARTET and EORTC Radiotherapy Quality Assurance (RTQA) site screening process. \*All beam output audit measurements should preferably be within 3 % agreement, but 3 %-5% is acceptable. Advanced Technique Credentialing performed by either CDC = Complex Dosimetry Check, physical phantom measurements or VPP (Virtual Phantom Procedure); valid for up to 5 years unless there is a change in planning or delivery technology. <sup>‡</sup> Typical pass criteria for gamma analysis are 95 % within 3 % dose and 3 mm distance to agreement. The timing of the individual case review is defined on a trial-by-trial basis; prospective review is prioritised but may not be possible (e.g., for brachytherapy treatments) or feasible to enforce (e.g., for non-randomised patients). B: Individual case review outcomes and definitions. The HR-NBL1/SIOPEN trial used a different grading system, how this relates to the current system is included. <sup>‡</sup> The order of prioritisation of dose objectives, in case of conflict, are described within the RTQA guidelines whenever possible.

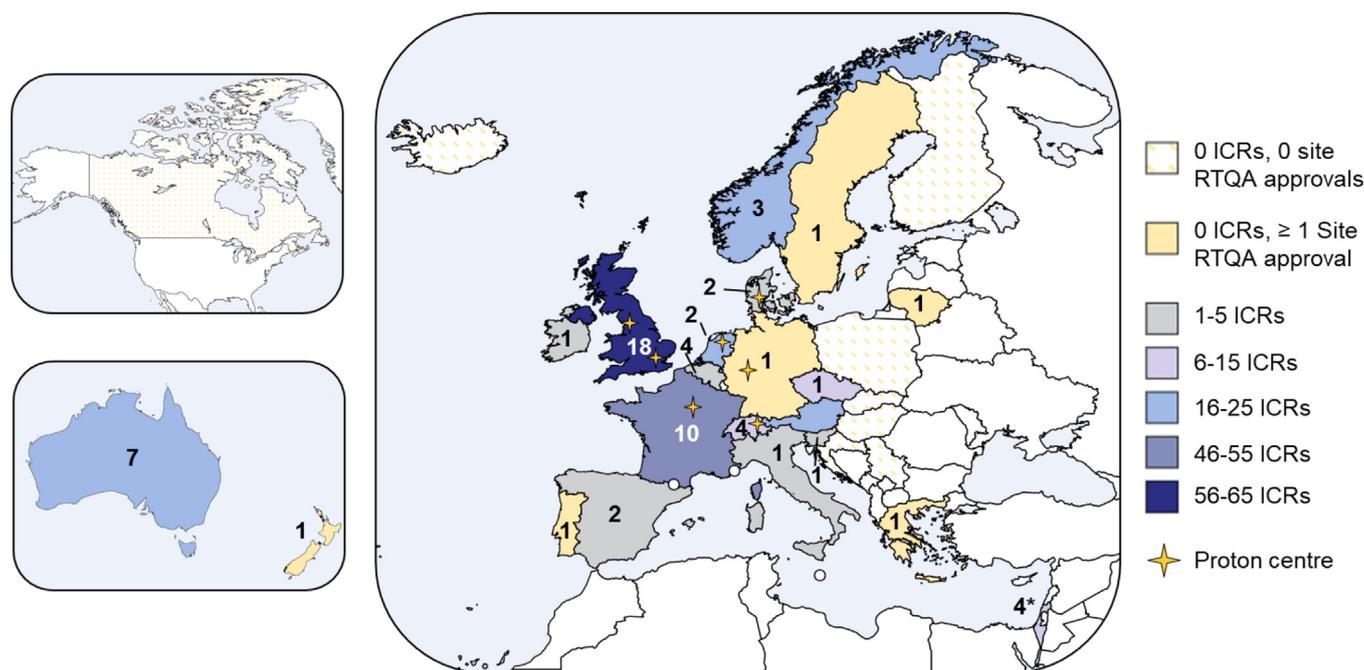
The most frequently used individual patient plan QA method for IMRT is 3D diode/chamber array (31 sites), followed by 2D diode/chamber array (25 sites), single ionisation chamber (12 sites), electronic portal image dosimetry (11 sites), or film-based dosimetry (1 site). For stereotactic radiotherapy, the individual patient plan QA methods used are 3D diode/chamber array (25 sites), ionisation chamber measurement (20 sites), 2D diode/chamber array (16 sites), film dosimetry (11 sites), and electronic portal image dosimetry (8 sites). Six PBT centres use 2D diode/chamber array and 3 use ionisation chamber measurements.

A total number of 84 BOA submissions were recorded: 71 for photons (55 c-arm Linac, 9 rotational/Tomotherapy, 2 MR-Linac, 5 Cyberknife), 4 for electrons, and 7 for proton beams. Most sites (50) provided proof of audit for one treatment modality, 10 for two modalities, and 4 sites provided BOAs for three different treatment modalities. The 84 BOA submissions encompassed a total of 231 beams measured. The majority of measurements were for 6MV flattened beams (93), followed by 10MV flattened beams (49), 6MV flattening-filter-free (37), 18MV flattened (15), and 10MV flattening-filter-free (14). BOA measurements were performed using thermo-luminescent dosimeters (30 %), optically stimulated luminescent dosimeters (28 %), or ionisation chamber

(19 %). Other methods such as alanine film, radio-photoluminescence dosimetry, or synthetic single crystal diamond dosimeters were used less frequently (9%, 5%, and 2% respectively).

Regarding advanced technique credentialing, i.e., delivery verification for IMRT and proton plans, CDC reports detailing the results of physical measurements from external credentialing services were submitted for 55 scenarios, and 70 VPPs were completed. The VPP is the EORTC solution to advanced technique credentialing when on-site certification is unavailable. The VPP involves submission of an institution's planning and individual patient QA files for independent gamma analysis [11]. The majority of VPPs were performed for rotational IMRT (28), followed by stereotactic (small fields with a prescription greater than 2 Gy per fraction using fixed-field or rotational techniques; 20), and static IMRT (13). Approvals for 52 dummy runs were provided, 40 of which were transferred from other EORTC trials. The scenarios tested are not specific to paediatric treatments.

Table 1 shows the workload and available human resources for approved sites. Paediatric cases are managed within organised multi-disciplinary teams (MDTs) in 53 sites (13 national, 25 regional, 14 single-institution, 1 not specified), with 42 having access to



**Fig. 2. Map of the countries participating or expressing the intention of participating in QUARTET-affiliated trials.** Colour shades indicate the number of individual case reviews (ICRs) completed, numeric labels show the total number of sites approved by 31/10/2022 in each country, including proton centres (shown by the yellow stars). “0 ICRs, 0 site RTQA approvals” indicates countries which are planned to participate in QUARTET-affiliated trials but are yet to begin any site approval procedures, “0 ICRs, ≥ 1 site RTQA approval” indicates countries where at least one site has been approved to recruit patients but is yet to submit a case for ICR. Please note that Austria shows ICRs completed without any site RTQA approvals due to contribution of cases from HR-NBL1.\* One site approved for brachytherapy only with photon approval underway.

specialist support for unusual or rare cases such as SIOP<sup>9</sup>/PROS<sup>10</sup>/COG<sup>11</sup> discussion forums, peer-review meetings, or international e-mail networks.

Within the period 01/05/2016–31/10/2022, a total of 263 patient cases were submitted from 56 institutions across 15 countries. ICRs were performed prospectively for 133 cases (52.4%), retrospectively for 121 cases (47.6%), and were pending for 9 cases. Fig. 3 demonstrates the distribution of reviews over time, with an increasing proportion of prospective plan reviews, reflecting the shift to new prospective trials opening and actively recruiting patients. ICR was deemed as “prospective” for multiple sub-categories according to protocol specifications: approval of all plan components (delineation and dosimetry) prior to fraction one (n = 107, 80.5%), delineation approved prior to fraction one and dose approved within five fractions (n = 16, 12.0%), delineation approved prior to fraction one and dose approved after fraction five (n = 3, 2.3%), or all components approved within the first five fractions (n = 7, 5.7%). Retrospective reviews were performed due to planned retrospective analysis, according to protocol-specific allowances, a lack of awareness of trial requirements, or feasibility within patient pathways.

IMRT was used in 50.2% of cases submitted, with the majority treated with rotational IMRT (96/132). For the remaining plans either 3DCRT (28.1%) or PBT (20.5%) were used. Fig. 4 demonstrates the use of different techniques over time. Since 2021, cases submitted for ICR are 64.1% IMRT (75/100 rotational IMRT), 34.6% PBT, and only a small portion using 3DCRT (3.0%). Stereotactic treatments have limited indications across the trials, but one was submitted for ICR. The prevalence of PBT use varies by trial, ranging from 9.8–53.1% among the four trials with at least one PBT case

submitted. No electron, brachytherapy, or molecular radiotherapy cases have been submitted to date.

For prospective ICRs, an average of 1.4 (average range 1–1.75) submissions were completed until plan acceptance by reviewers (range 1–3, median 1.0), 62.4% of cases were accepted at first submission. For all ICRs, there was an (initial) plan rejection rate of 39.8% (101/254), ranging from 0–60.8% (0/2 and 45/74) for individual trials. The initial plan rejection rate is similar between prospectively and retrospectively reviewed cases (38.4% vs 41.3%, respectively). Time taken from initial plan submission to plan acceptance ranged from 0–35 days for prospective cases (mean 6 days, median 4 days); excluding those cases requiring re-submissions the time taken was 0–17 days (mean 4 days, median 3 days).

Retrospective cases graded as unacceptable variation cannot be corrected to meet protocol requirements - affecting 50 patients within this cohort. For cases with an ICR performed prospectively, unacceptable variations were corrected in 92% (47/51) of cases. The plans which remained unacceptable were due to target delineation and/or dose coverage, with investigators declining to make amendments. Justified variations (n = 22) were most often due to dose compromises in areas where there were conflicts in dose objectives between the normal tissue and target volumes, two cases had clinically justified target volume modifications when compared against protocol recommendations. Fig. 5 provides further information regarding ICR outcomes and reasons for plan rejection for the 254 completed cases.

## Discussion

Radiotherapy for children and young people is a highly complex treatment delivered using a wide range of technologies and techniques. Consistency in both target and normal structure delineation has been demonstrated to be challenging and have the potential to impact patient outcomes for adult and paediatric

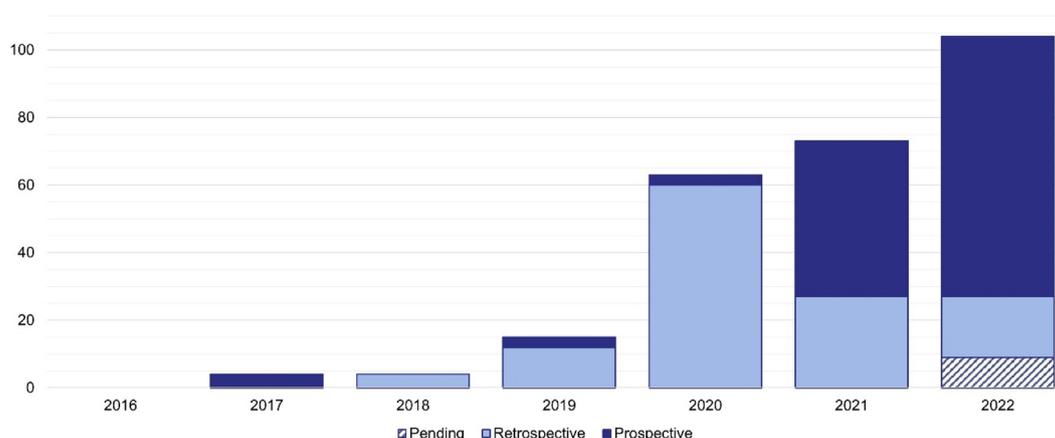
<sup>9</sup> International Society for Pediatric Oncology.

<sup>10</sup> Paediatric Radiation Oncology Society.

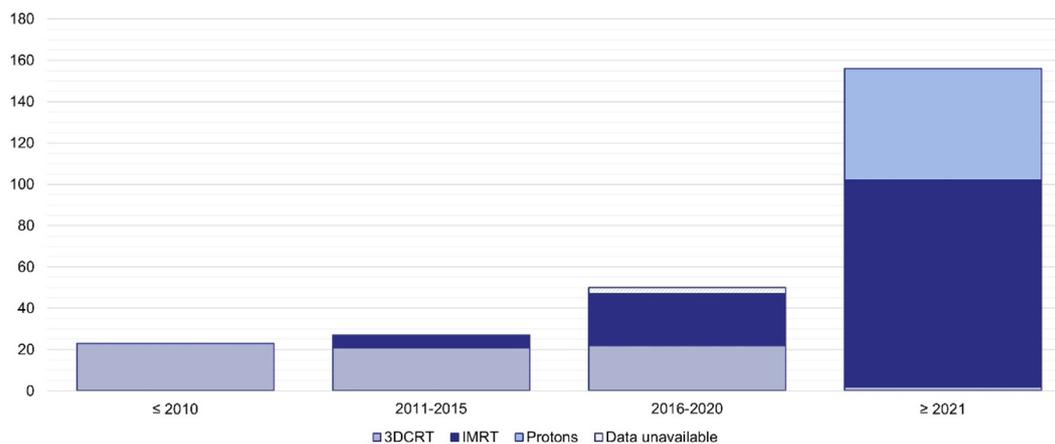
<sup>11</sup> Children’s Oncology Group.

**Table 1**  
Workload and personnel in radiotherapy departments participating in QUARTET-affiliated trials.

	Median	Mean	SD	Range
Total no. of patients per year	2700.0	2841.0	1661.88	350–10200
Paediatric patients per year	35.5	46.1	45.84	0* (4)–272
Radical	25.0	38.4	44.20	0* (2)–270
Palliative	5.0	8.0	7.39	0–30
Re-treatment	4.0	9.0	10.90	0* (1)–40
ROs per centre	15.0	17.5	11.44	3–63
Annual no. of patients per RO	177.8	191.7	97.14	44–650
Designated Paediatric ROs	1.7	1.8	1.99	0–13.5
Annual no. of paediatric patients per Designated RO	20.1	37.4	40.10	0* (1.4)–200
MPs per centre	10.0	13.2	7.97	5–40
Annual no. of patients per MP	224.7	242.2	116.50	47.3–760
Designated Paediatric MPs	0.0	1.0	1.86	0–10.6
RTTs per centre	41.0	51.2	35.79	13.9–192
Annual no. of patients per RTT	59.6	63.6	28.17	10.2–134.5
Designated Paediatric RTTs	0.0	1.8	4.47	0–26.9
Patients per treatment unit	436.6	444.6	138.10	221.9–925



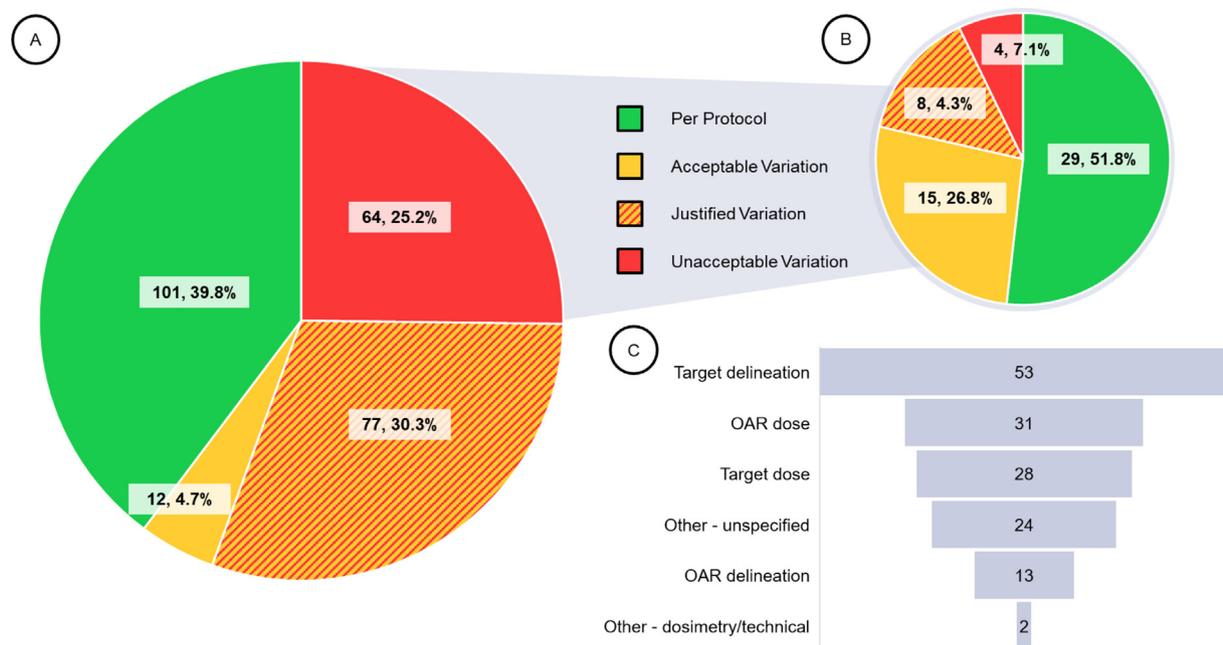
**Fig. 3. Individual Case Review timing by year that the review was completed.** Pending cases did not yet have a final review outcome at the time of analysis.



**Fig. 4. Treatment technique by year of treatment.** Treatment period covered 2003–2022. 3DCRT = 3D conformal radiotherapy, IMRT = intensity modulated radiotherapy by any delivery method (fixed gantry, rotational).

cohorts [6,12–15]. However, this data for childhood cancers is limited, therefore QUARTET objectives include evaluating the role and benefit of RTQA in this cohort of patients. Especially within the context of clinical trials, significant variations in radiotherapy quality could influence reported trial outcomes, which could ultimately affect treatment recommendations for radiotherapy as well as other treatment modalities including systemic therapy [5,6,16].

Increased uniformity in radiotherapy delivery within clinical trials has been encouraged globally, with the GHG bringing together trial RTQA organisations to better harmonise site requirements, screening procedures, and on-trial ICR activities [8]. Weber *et al.* [5] previously reported the importance of institutional experience, workload, and infrastructure to the likelihood of meeting protocol requirements for planning and delivery. This QUARTET report for the 2016–2022 period, demonstrates a large variability



**Fig. 5. ICR outcomes and reasons for plan rejection.**A: ICR outcome for submission one B: ICR outcome for the final submission – cases submitted prospectively but submission 1 graded as unacceptable variation C: Main components which resulted in a grade of unacceptable variation. “Other – unspecified” indicates multiple plan components, which may include those specified here, resulted in the plan being deemed unacceptable. OAR = organ at risk.

between institutions treating children and young people. As encouraged within paediatric radiotherapy good-practice guidelines [17,18], centres participating in QUARTET-affiliated trials show some centralisation of services, with most operating as referral sites. Yet, there are sites with no designated paediatric radiation oncologist and that do not participate in paediatric MDT discussions. QUARTET-affiliated sites have a median of 1.7 FTE paediatric designated radiation oncologists compared to the minimum of two recommended, and designated paediatric RTTs are not yet commonplace, with only 19/66 sites reporting their availability.

The establishment of this centralised, international RTQA platform was reliant on the timelines and contributions of all collaborative partners, including the logistical and regulatory challenges of opening new, international, prospective clinical trials. This is evident in the reported dates for first site approvals and ICRs completed in relation to the official launch of QUARTET in May 2016. After an initial period allowing for the setup of procedures, the first ICR was completed in February 2017 for a pre-established trial where site approval procedures were not enforced. The first site approvals only took place once the new prospective trials opened, which were delayed from their original planned start dates.

The implementation of the QUARTET FQ has allowed collection of a significant volume of data regarding the organisation and availability of resources for paediatric radiotherapy in Europe, although this is limited to centres participating in clinical trials. There have previously been efforts to map paediatric radiotherapy services [17,19] in order to better understand access and quality inequity. SIOP Europe continues to contribute to this work and has identified 250 radiotherapy centres providing treatment to children and adolescents across Europe [20]. Four countries associated with the SIOP Europe Radiation Oncology Working Group are not currently planned to participate within QUARTET-affiliated trials, indicative of continued barriers in access to clinical trials in eastern Europe. It is encouraging to observe that all other countries in eastern Europe have at least one centre planned to participate.

Large technological shifts have been seen over the past decade, both institutions and trial RTQA groups need to adapt to technologi-

cal advances [21–24]. All photon sites in this report have IMRT delivery techniques available and it is clear that this has become the standard of care for paediatric patients treated in QUARTET-affiliated centres. Stereotactic deliveries are also available but are less frequently used in younger patients, probably due to limited evidence available in a paediatric population and uncertainty about the long-term side effects of high dose fractions in children. All QUARTET approved PBT facilities have pencil beam scanning available, this is in contrast to previous reports where 66 % used passive scattering [23]. The data presented in Fig. 4 shows how technique use over time changed but is influenced by the historic data set from HR-NBL1 which had a dominance of 3DCRT treatments delivered between 2003 and 2019. The limitations of older conventional techniques increase the proportion of justified variations seen. By comparison, 2017 is the earliest treatment year for all other QUARTET-affiliated trials and 3DCRT is rarely used. The rise in retrospective reviews in 2020 is also explained by the HR-NBL1 cohort because it was at this time that the radiotherapy committee made an additional effort to expand the dataset, profiting from the technical advantages of the QUARTET platform over the SIOPEN R-NET system [3,25].

The initial QUARTET ICR outcomes show that inconsistency in planning, particularly due to (target) delineation remains a challenge, impacting the quality of radiotherapy treatments for children. This echoes the previous reports of protocol non-compliance rates and the importance of peer-review [5,6,13,14,26–28] to this population of patients as well as adults. Prospective ICR will continue to be prioritised, but regular amendments to the RTQA guidelines and implementation of additional education resources will also be necessary to better support investigators to meet protocol requirements at first submission, and to monitor and standardise decision making in areas of conflict which result in justified variations. This is particularly relevant when we consider the additional resource and time-burden for investigators when multiple submissions are required – engagement with prospective ICR is reliant on efficient implementation and clear, constructive communication. The initial ICR rejection rates vary

significantly from trial to trial (0–60.8 %), with some cases requiring three submissions until deemed acceptable. Although individual trial RTQA results are not presented here, the results of this and future individual and cross-trial analyses will be used to inform QUARTET procedures, provision of education resource, and the role of RTQA across different cancers affecting children and adolescents. In relation to OARs, the most frequently occurring variation relates to the vertebrae which should be approached in accordance with the SIOP Europe consensus guidelines published by Hoeben *et al* [29], the results of which have been presented separately [30].

## Conclusion

QUARTET is a platform designed to improve the quality of radiotherapy treatments delivered to children and understand resource distribution for the paediatric oncology population. Despite being founded as an initiative for European clinical trials, its reach extends well beyond, with clinical trials embracing inter-continental collaborations which extends the data pool for these rare diseases.

Paediatric radiotherapy has seen significant changes in technical practice, which, when coupled with unequal distribution of expertise, could contribute to sizeable plan rejection rates. QUARTET will continue to engage with clinical trial sponsors and treating institutions to improve quality and standardisation of radiotherapy; both key factors for producing valid, meaningful trial outcomes. SIOP Europe will maintain its commitment addressing inequalities, to allow for better cure rates and consequent quality of life no matter where young people receive treatment.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

The authors would like to acknowledge the support of Gilles Vassal, Pam Kearns, and others at SIOP Europe in establishing the QUARTET project, and the international trial sponsors who have integrated QUARTET into their clinical trials: Dominique Valteau-Couanet (CI) with Habiba Lynda Attalah and colleagues at Gustave Roussy (France) for the High Risk Neuroblastoma 2 study; Meriel Jenney (CI), Nicola Fenwick and colleagues at CRCTU and the University of Birmingham (UK) for the Frontline and Relapsed Rhabdomyosarcoma study, Vanessa Segura and Instituto de Investigación Sanitaria La Fe de Valencia, and St. Anna Kinderkrebsforschung. Thanks too to Lorenza Gandola for her contributions to High Risk Medulloblastoma, Daniel Portik for data collection relating to the beam output audits, Nick Reynaert for supporting site approval activities, James Talbot and all of the QUARTET reviewers, the SIOPEN and EpSSG radiotherapy committees, all QUARTET collaborators, and especially to all patients or parents for their consent to participate in these clinical trials.

MNG is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre and by the Radiation Research Unit at the Cancer Research UK City of London Centre Award [C7893/A28990]. HCM is supported by the National Institute for Health and Care Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. QUARTET and the work of SMK and AT as research fellows at EORTC headquarters are funded thanks to the generosity of Fondatioun Kriibskrank Kanner

(FKK), Luxembourg (SIOP Europe Grant). FKK provides funding for QUARTET activities, including research fellowships, with no direct influence on research activities.

## References

- [1] Vassal G, Schrappe M, Pritchard-Jones K, Arnold F, Basset L, Biondi A, et al. The SIOPEN strategic plan: A European cancer plan for children and adolescents. vol. 8. Elsevier Ltd; 2016. <https://doi.org/10.1016/j.jpco.2016.03.007>.
- [2] European Society for Paediatric Oncology. SIOP Europe Strategic Plan Update (2021–2026). 2021 <https://siopen.eu/news/siop-europe-strategic-plan-update-2021-2026/>.
- [3] Kelly SM, Effefey R, Gaze MN, Bernier-Chastagner V, Blondeel A, Clementel E, et al. QUARTET: a SIOP Europe project for quality and excellence in radiotherapy and imaging for children and adolescents with cancer. *Eur J Cancer* 2022;172:209–20. <https://doi.org/10.1016/j.ejca.2022.05.037>.
- [4] FitzGerald TJ, Bishop-Jodoin M, Bosch WR, Curran WJ, Followill DS, Galvin JM, et al. Future vision for the quality assurance of oncology clinical trials. *Front Oncol* 2013;3. <https://doi.org/10.3389/fonc.2013.00031>.
- [5] Weber DC, Tomsej M, Melidis C, Hurkmans CW. QA makes a clinical trial stronger: evidence-based medicine in radiation therapy. *Radiother Oncol* 2012;105:4–8. <https://doi.org/10.1016/j.radonc.2012.08.008>.
- [6] Peters LJ, O'Sullivan B, Giralt J, Fitzgerald TJ, Trotti A, Bernier J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. *J Clin Oncol* 2010;28:2996–3001. <https://doi.org/10.1200/JCO.2009.27.4498>.
- [7] Bentzen SM, Bernier J, Davis JB, Horiot JC, Garavaglia G, Chavaudra J, et al. Clinical impact of dosimetry quality assurance programmes assessed by radiobiological modelling of data from the thermoluminescent dosimetry study of the European Organization for Research and Treatment of Cancer. *Eur J Cancer* 2000;36:615–20. [https://doi.org/10.1016/S0959-8049\(99\)00336-6](https://doi.org/10.1016/S0959-8049(99)00336-6).
- [8] Melidis C, Bosch WR, Izewska J, Fidarova E, Zubizarreta E, Ulin K, et al. Global harmonization of quality assurance naming conventions in radiation therapy clinical trials. *Int J Radiat Oncol Biol Phys* 2014;90:1242–9. <https://doi.org/10.1016/j.ijrobp.2014.08.348>.
- [9] Knöös T, Wieslander E, Cozzi L, Brink C, Fogliata A, Albers D, et al. Comparison of dose calculation algorithms for treatment planning in external photon beam therapy for clinical situations. *Phys Med Biol* 2006;51:5785–807. <https://doi.org/10.1088/0031-9155/51/22/005>.
- [10] de Martino F, Clemente S, Graeff C, Palma G, Cella L. Dose calculation algorithms for external radiation therapy: an overview for practitioners. *Appl Sci* 2021;11. <https://doi.org/10.3390/app11156806>.
- [11] Weber DC, Vallet V, Molineu A, Melidis C, Teglas V, Naudy S, et al. IMRT credentialing for prospective trials using institutional virtual phantoms: results of a joint European Organization for the Research and Treatment of Cancer and Radiological Physics Center project. *Radiat Oncol* 2014;9:1–8. <https://doi.org/10.1186/1748-717X-9-123/TABLES/3>.
- [12] Cox S, Cleves A, Clementel E, Miles E, Staffurth J, Gwynne S. Impact of deviations in target volume delineation – time for a new RTQA approach? *Radiother Oncol* 2019;137:1–8. <https://doi.org/10.1016/j.radonc.2019.04.012>.
- [13] Carrie C, Hoffstetter S, Gomez F, Moncho V, Doz F, Alapetite C, et al. Impact of targeting deviations on outcome in medulloblastoma: study of the French society of pediatric oncology (SFOP). *Int J Radiat Oncol* 1999;45:435–9. [https://doi.org/10.1016/S0360-3016\(99\)00200-X](https://doi.org/10.1016/S0360-3016(99)00200-X).
- [14] Ohri N, Shen X, Dicker AP, Doyle LA, Harrison AS, Showalter TN. Radiotherapy protocol deviations and clinical outcomes: a meta-analysis of cooperative group clinical trials. *J Natl Cancer Inst* 2013;105:387–93. <https://doi.org/10.1093/jnci/djt001>.
- [15] Kelly SM, Pötschger U, Arndt HB, Boterberg T, Dieckmann K, Beck Popovic M, et al. Radiotherapy quality assurance outcome and its correlation with survival in the SIOPEN High-Risk Neuroblastoma trial (HR-NBL1/SIOPEN). A report from the radiotherapy committee [PROS 2022 Abstract 1074]. *Int J Radiat Oncol* 2022;114:1074. <https://doi.org/10.1016/j.ijrobp.2022.09.041>.
- [16] FitzGerald TJ, Urie M, Ulin K, Laurie F, Yorty J, Hanusik R, et al. Processes for quality improvements in radiation oncology clinical trials. *Int J Radiat Oncol Biol Phys* 2008;71:S76–9. <https://doi.org/10.1016/j.ijrobp.2007.07.2387>.
- [17] Janssens GO, Timmermann B, Laprie A, Mandeville H, Padovani L, Chargari C, et al. Recommendations for the organisation of care in paediatric radiation oncology across Europe: a SIOPEN–ESTRO–PROS–CCI–Europe collaborative project in the framework of the JARC. *Eur J Cancer* 2019;114:47–54. <https://doi.org/10.1016/j.ejca.2019.03.003>.
- [18] [18] Royal College of Radiologists, Society and College of Radiographers, Institute of Physics and Engineering in Medicine, Children's Cancer and Leukaemia Group. Good practice guide for paediatric radiotherapy. Second edition. *R Coll Radiol* 2018.
- [19] Demoor-Goldschmidt C, Carrie C, Whitfield G, Meijnders P, Dieckmann K, Timmermann B, et al. Paediatric radiation therapy across Europe: a European questionnaire survey supported by the SIOPEN, ESTRO, PROS and several national paediatric hematology-oncology societies (NAPHOS). *Ann Oncol* 2017;28. <https://doi.org/10.1093/annonc/mdx440.067>.
- [20] [20] European Society for Paediatric Oncology, SIOP Europe Radiation Oncology Working Group. SIOPEN Radiation Oncology Departments :: SIOP Europe n.d. <https://siopen.eu/Radiation-Oncology-Centres> (accessed November 26, 2022).

- [21] Grant W, Hurkmans CW, Poortmans PM, Maingon P, Monti AF, Van Os MJH, et al. Quality assurance standards drive improvements in the profile of radiation therapy departments participating in trials of the EORTC Radiation Oncology Group. *Radiother Oncol* 2014;112:376–80. <https://doi.org/10.1016/j.radonc.2014.09.003>.
- [22] Willmann J, Poortmans P, Monti AF, Grant W, Clementel E, Corning C, et al. Development of staffing, workload and infrastructure in member departments of the European Organisation for Research and Treatment of Cancer (EORTC) radiation oncology group. *Radiother Oncol* 2021;155:226–31. <https://doi.org/10.1016/j.radonc.2020.11.009>.
- [23] Weber DC, Abrunhosa-Branquinho A, Bolsi A, Kacperek A, Dendale R, Geismar D, et al. Profile of European proton and carbon ion therapy centers assessed by the EORTC facility questionnaire. *Radiother Oncol* 2017;124:185–9. <https://doi.org/10.1016/j.radonc.2017.07.012>.
- [24] Budiharto T, Musat E, Poortmans P, Hurkmans C, Monti A, Bar-Deroma R, et al. Profile of European radiotherapy departments contributing to the EORTC Radiation Oncology Group (ROG) in the 21st century. *Radiother Oncol* 2008;88:403–10. <https://doi.org/10.1016/j.radonc.2008.05.013>.
- [25] Gaze MN, Boterberg T, Dieckmann K, Habrand JL, Helfré S, Peylan-Ramu N, et al. Development of an electronic database for quality assurance of radiotherapy in the International Society of Paediatric Oncology (Europe) high risk neuroblastoma study. *Radiother Oncol* 2010;97:593–5. <https://doi.org/10.1016/j.radonc.2010.08.017>.
- [26] Gaze MN, Boterberg T, Dieckmann K, Hörmann M, Gains JE, Sullivan KP, et al. Results of a quality assurance review of external beam radiation therapy in the international society of paediatric oncology (Europe) neuroblastoma group's high-risk neuroblastoma trial: a SIOPE study. *Int J Radiat Oncol Biol Phys* 2013;85:170–4. <https://doi.org/10.1016/j.ijrobp.2012.05.004>.
- [27] Dietzsch S, Braesigk A, Seidel C, Remmele J, Kitzing R, Schlender T, et al. Pretreatment central quality control for craniospinal irradiation in non-metastatic medulloblastoma : first experiences of the German radiotherapy quality control panel in the SIOPE PNET5 MB trial. *Strahlentherapie Und Onkol* 2021;197:674–82. <https://doi.org/10.1007/s00066-020-01707-8>.
- [28] Meroni S, Cavatorta C, Barra S, Cavagnetto F, Scarzello G, Scaggion A, et al. A dedicated cloud system for real-time upfront quality assurance in pediatric radiation therapy. *Strahlentherapie Und Onkol* 2019;843–50. <https://doi.org/10.1007/s00066-019-01469-y>.
- [29] Hoebe BA, Carrie C, Timmermann B, Mandeville HC, Gandola L, Dieckmann K, et al. Management of vertebral radiotherapy dose in paediatric patients with cancer: consensus recommendations from the SIOPE radiotherapy working group. *Lancet Oncol* 2019;20:e155–66. [https://doi.org/10.1016/S1470-2045\(19\)30034-8](https://doi.org/10.1016/S1470-2045(19)30034-8).
- [30] Turcas A, Kelly S, Tom B, Mandeville H. The vertebrae as OARs in paediatric radiotherapy clinical trials: initial QUARTET experience [PROS 2022 Abstract 1073]. *Int J Radiat Oncol* 2022;114:1073. <https://doi.org/10.1016/j.ijrobp.2022.09.039>.