

QUARTET

the QUARTET Project and the SIOPE Radiation Oncology Working Group

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Current Perspective

QUARTET: A SIOP Europe project for quality and excellence in radiotherapy and imaging for children and adolescents with cancer



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Abbreviations: ECTG, European Clinical Trial Group; EORTC, European Organisation for Research and Treatment of Cancer; GHG, Global Quality Assurance of Radiation Therapy Clinical Trials Harmonization Group; ICR, Individual Case Review; QA, Quality Assurance; QUARTET, Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials; RTQA, Radiotherapy Quality Assurance; SIOPE, European Society for Paediatric Oncology; (SIOPE-) ROWG, SIOPE Radiation Oncology Working Group.

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Abstract The European Society for Paediatric Oncology (SIOPE) Radiation Oncology Working Group presents the QUARTET Project: a centralised quality assurance programme designed to standardise care and improve the quality of radiotherapy and imaging for international clinical trials recruiting children and adolescents with cancer throughout Europe.

QUARTET combines the paediatric radiation oncology expertise of SIOPE with the infrastructure and experience of the European Organisation for Research and Treatment of Cancer to deliver radiotherapy quality assurance programmes for large, prospective, international clinical trials. QUARTET-affiliated trials include children and adolescents with brain tumours, neuroblastoma, sarcomas including rhabdomyosarcoma, and renal tumours including Wilms' tumour.

With nine prospective clinical trials and two retrospective studies within the active portfolio in March 2022, QUARTET will collect one of the largest repositories of paediatric radiotherapy and imaging data, support the clinical assessment of radiotherapy, and evaluate the role and benefit of radiotherapy quality assurance for this cohort of patients within the context of clinical trials.

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1. Introduction

Within multi-centre clinical trials, differences in the quality of treatment across participating institutions may impact the outcome of recruited participants and potentially confound study end-point analysis [1–4]. Quality assurance (QA) has a vital role in ensuring safety and quality of care, as well as verifying protocol compliance.

As rare diseases, childhood cancers are susceptible to suboptimal outcomes, particularly where knowledge and practice sharing initiatives are unavailable or ineffective [5–7]. Once combined with a specialist and ever-advancing treatment modality such as radiotherapy, pooling of resources, and knowledge-sharing are essential to maximise the quality and effectiveness of care. Unfortunately, investment and expertise in paediatric radiotherapy is not uniformly distributed in Europe,

affecting patients treated within and outside of clinical trials [8,9]. A systematic and centralised mechanism for radiotherapy quality assurance (RTQA) can facilitate a standardised approach to radiotherapy planning requirements and their prospective evaluation in clinical practice, thereby reducing variations in implementation and treatment, and improving patient outcomes.

The European Society for Paediatric Oncology (SIOPE) is a pan-European organisation, which represents a network of over 2300 paediatric oncology professionals across 35 countries. SIOPE participates in many collaborations which aim to facilitate equal access to high-quality treatments, ensuring the best possible outcomes for children and adolescents with cancer, regardless of where they receive care [10,11]. In the 'Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials' (QUARTET) project, SIOPE aims to

Establish	Establish standards for plan quality control
Improve	Improve access to high quality radiotherapy for children across Europe
Facilitate	Facilitate prospective RTQA of plans
Evaluate	Evaluate the role of RTQA
Support	Support imaging collection & evaluation

Fig. 1. Aims of QUARTET. RTQA = radiotherapy quality assurance. Image taken with permission from <https://siope.eu/activities/joint-projects/quarter/>.

improve the quality and standardisation of radiotherapy treatment for children and adolescents across Europe.

As a collaborative initiative, QUARTET combines the paediatric oncology expertise of SIOPE with the experience and infrastructure of the European Organisation for Research and Treatment of Cancer (EORTC) to deliver a centralised, prospective, interventional RTQA programme for international clinical trials [12,13]. This project has been realised thanks to Fondation Kriibskrank Kanner, a Luxembourgian foundation that, among other objectives, supports research activities that can improve cure (<https://fondatioun.lu/>).

In this article, we present the QUARTET initiative from the SIOPE Radiation Oncology Working Group (SIOPE-ROWG, <https://siope.eu/siop-europe-radiation-oncology-working-group/>).

2. Materials and methods

QUARTET provides a platform for centralised, on-line, prospective QA of radiotherapy and imaging data. The aims of QUARTET are presented in Fig. 1.

2.1. RTQA for clinical trials

A standard approach to delivering RTQA within clinical trials has been described by the Global Quality Assurance of Radiation Therapy Clinical Trials Harmonization Group (GHG, <https://rtqaharmonization.org/>) [14]. The GHG aims to harmonise approaches to trial RTQA globally; with participation from groups in Europe

(EORTC³ and RTTQA⁴), North America (IROC⁵), Japan (JCOG⁶), and Australia and New Zealand (TROG⁷) [15]. In 2019, QUARTET joined as an observing member, enabling a voice for paediatric considerations within the GHG. These recommendations inform RTQA programme design for QUARTET-affiliated trials and are intended to provide confidence of accurate dose calculation and delivery according to protocol requirements.

The QUARTET RTQA programme design considers legal, logistical, and technical requirements for each trial. Following contractual agreement between SIOPE/EORTC and the trial sponsor, procedures for institutional RTQA approval and individual case review (ICR) are agreed with the trial radiotherapy committee. RTQA guidelines that elaborate the protocol-stated requirements and provide a detailed resource to support radiation oncologists are a key component of each trial. All RTQA guidelines are subject to ongoing review and are amended as required to be most useful. Additionally, training packages, facilities for record keeping and tracking, and engagement and training of reviewers are provided.

2.1.1. Institutional RTQA approval

Institutional RTQA approval encompasses the activities put into place to provide confidence that all participating institutions are able to meet protocol treatment requirements accurately and safely. These activities are undertaken as defined by the GHG [14] and include collection of a facility questionnaire, beam output audit(s), dummy run, and advanced technique credentialing for IMRT and proton delivery techniques. A benchmark case may also be incorporated when determined essential by the trial team to test protocol compliance before recruiting a patient. Approvals are essential but streamlined across QUARTET studies, avoiding the duplication of effort by institutions.

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⁴ Radiation Therapy Trial Quality Assurance, United Kingdom.

⁵ Imaging and Radiation Oncology Core, North America.

⁶ Japanese Clinical Oncology Group, Japan.

⁷ Trans-Tasman Radiation Oncology Group, Australia and New Zealand.

2.1.2. Individual case review

The ICR describes the plan evaluation stage of RTQA: both delineation and dosimetry are assessed by at least one expert reviewer. All QUARTET-affiliated trials have an ICR requirement. As prospective review and feedback is the only mechanism that can ensure treatment errors are corrected prior to delivery, this is the method of choice for QUARTET and is highly recommended for all patients. ICR timing may be adapted depending on the treatment modalities employed and trial requirements. For example, brachytherapy cases are reviewed retrospectively out of necessity and non-randomised cases may not have a mandatory prospective ICR; nevertheless, submission is strongly encouraged for all cases to ensure consistency in quality across cohorts. Regular case discussion sessions among

reviewers are held to align decision-making and encourage feedback among reviewers.

QUARTET uses the existing infrastructure at the EORTC to collect all required DICOM and supporting data. The data flow for receiving a case and completing the ICR process can be seen in Fig. 2. Cases are submitted using the EORTC RTQA Uploader (<http://www.eortc.be/Uploader>) or AQUILAB OncoPlace (AQUILAB SAS, France) in France where QUARTET submissions have been integrated into their national review programme and their French database PediaRT. ICRs are performed using Velocity (Version 4.1, Varian Medical Systems Inc.) via an online Citrix Gateway (Citrix Solutions Inc.). Ownership of all patient data remains with the trial sponsor, with QUARTET acting as a Data Processor under GDPR [16].

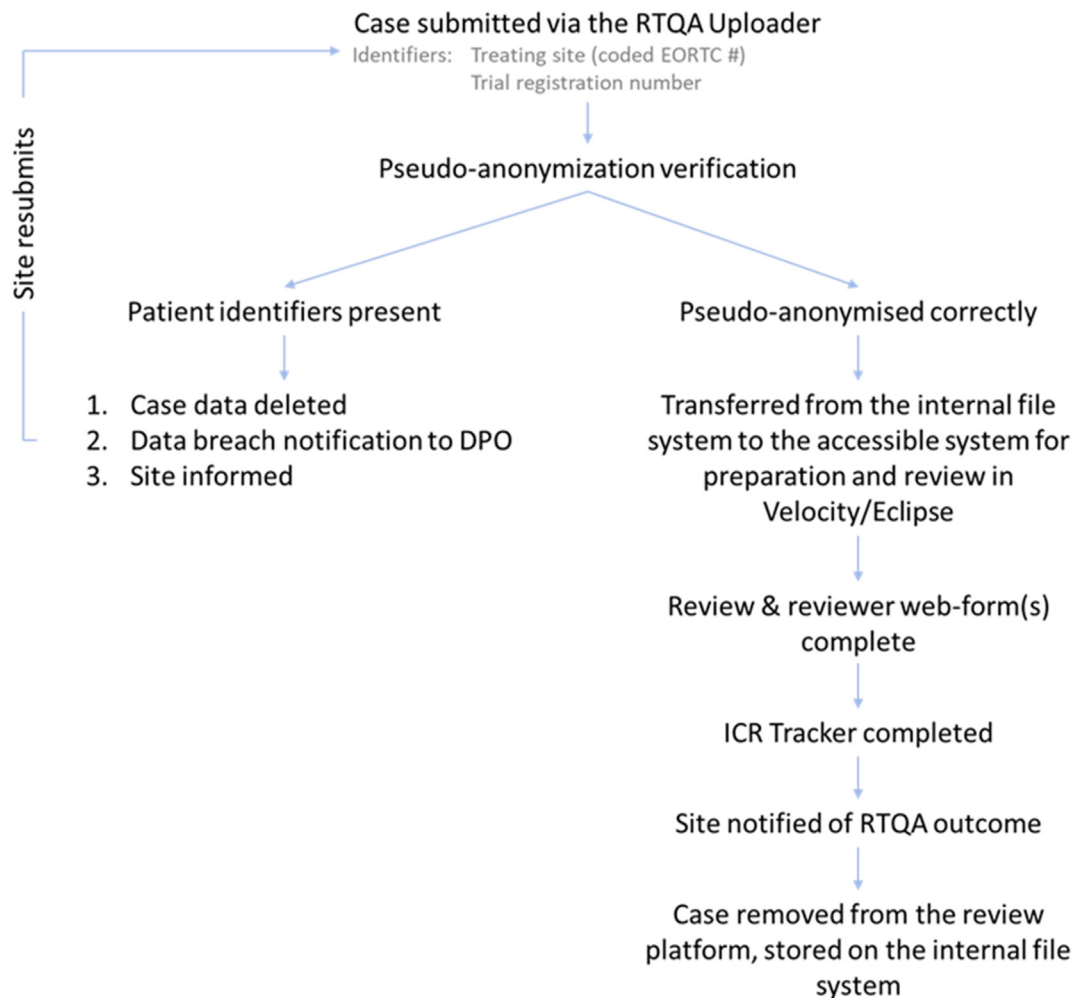


Fig. 2. Data flow for individual case review submission. DPO = data protection officer, ICR = individual case review, RTQA = radiotherapy quality assurance. All participating treatment sites are registered with a coded EORTC number (#). Pseudo-anonymisation: DICOM and supporting patient data are anonymised as far as possible but re-coded with a trial-specific patient registration number.

2.2. Reviewers

Clinician and medical physicist reviewers are identified by the QUARTET working groups in collaboration with the trial radiotherapy lead and associated European Clinical Trial Group (ECTG). Reviewers have significant experience in both paediatric radiation oncology and the relevant tumour type for each trial. Reviewer information is collected by QUARTET and processed and stored at EORTC Headquarters in accordance with GDPR [16]. The trial sponsor is responsible for formally contracting the reviewers, for which a template agreement is available.

2.3. Group membership and organisation

QUARTET is managed by a steering group comprised of a chair, past-chair, research fellows, and project co-ordinator. QUARTET working groups then provide a forum for the development and monitoring of QUARTET-affiliated trials and research projects. Other project collaborators, SIOPE administration, and EORTC technical support also facilitate project delivery, details of which can be found in Fig. 3. The chair is designated as a radiation oncologist, whereas other

contributors are from multi-professional backgrounds (Fig. 4). Responsibility for the project direction and decision-making ultimately lies with the chair and SIOPE Board. Fondatioun Kriibskrank Kanner provides funding with no direct influence on research activities.

2.4. Dissemination

QUARTET collaborates closely with the ECTGs, the relevant trial management groups, national and regional paediatric radiotherapy groups, and SIOPE membership to encourage engagement with the RTQA process and support understanding and adherence to the trial protocol requirements. QUARTET shares its experience and progress through (inter)national paediatric radiotherapy conferences and meetings, the SIOPE website, as well as the SIOPE and SIOPE-ROWG newsletters, and open-access peer-reviewed publication.

3. Results

In June 2014, 10 radiation oncologists and one radiologist from nine European countries created a SIOPE

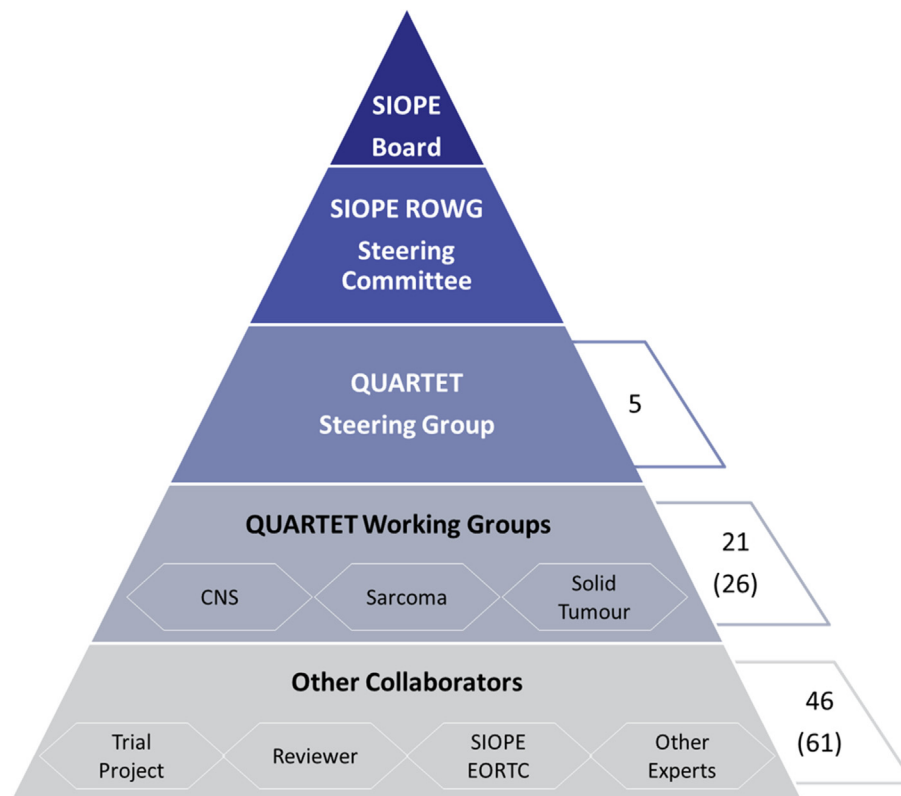


Fig. 3. QUARTET organisation and membership showing the 80 contributors' roles within the project. Number of members are indicated on the right. Members may contribute to multiple components; this is indicated by the additional number in brackets. For example, the QUARTET steering group members (QUARTET chair, past chair, current research fellows, and project coordinator) contribute to the working groups; the members of which may also act as trial leads or reviewers. "Other collaborators" incorporates all contributors including trial sponsor representatives and the radiotherapy primary investigator, SIOPE/EORTC support staff, and other experts in paediatric radiotherapy and/or (trial) RTQA like medical physicists, radiation therapists, and paediatric oncologists.

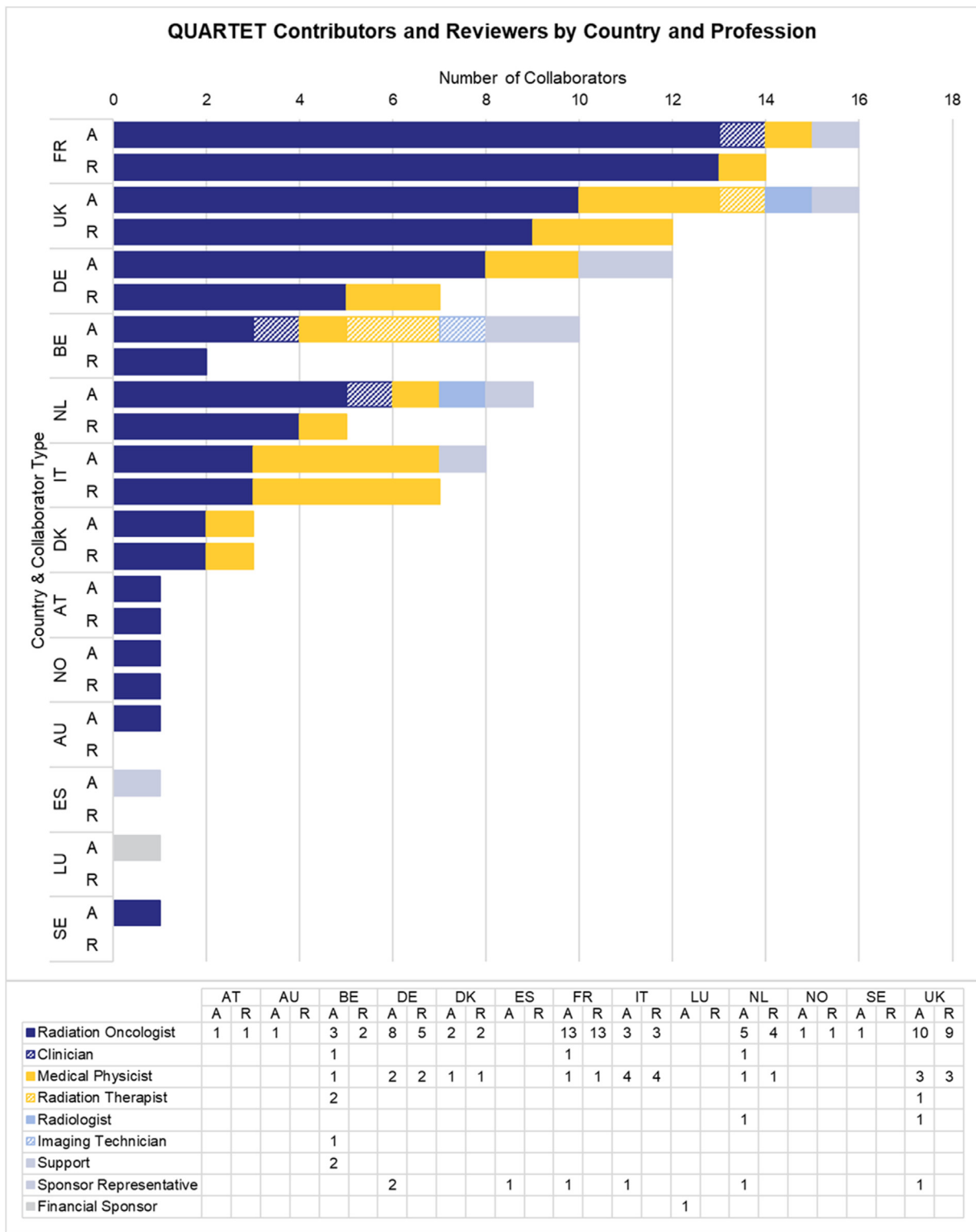


Fig. 4. QUARTET collaborators and reviewers according to country of practice and profession. EORTC and SIOPE headquarters are located in Belgium. Country codes: AT, Austria; AU, Australia; BE, Belgium; DE, Germany; DK, Denmark; ES, Spain; FR, France; IT, Italy; LU, Luxembourg; NL, The Netherlands; NO, Norway; SE, Sweden; UK, United Kingdom. Collaborator: A, All collaborators; R, Reviewers.

Radiotherapy Group, forming the foundation for QUARTET and the current SIOPE-ROWG. Since the official launch in May 2016, QUARTET has grown

considerably, reaching a total of 80 collaborators (Figs. 3 and 4) practising across 13 countries. The reviewer pool is now composed of 40 radiation oncologists, 12

Table 1

QUARTET-affiliated trials March 2022. European Clinical Trial Groups (ECTG): BTG – SIOPE Brain Tumour Group; EEC - Euro-Ewing Consortium; EpSSG - European Paediatric Soft-tissue sarcoma Study Group; SIOP RT-SG - SIOP Renal Tumour Study Group; SIOPEN – SIOP-Europe-Neuroblastoma.

Trial	Disease	ECTG	Sponsor NCT/EUDRACT #	Planned # of RT patients	Cases received*	Role of QUARTET	Status
Prospective radiotherapy quality assurance							
FaR-RMS An overarching study for children and adults with frontline and relapsed rhabdomyosarcoma	Rhabdomyosarcoma	EpSSG	University of Birmingham 2018-000515-24	1260–1690	27	Prospective RTQA	Open
HRMB An international prospective trial on high-risk medulloblastoma in patients older than 3 years	Medulloblastoma	BTG	University of Birmingham 2018-004250-17	850		Prospective RTQA	Open
HR-NBL2 High-Risk Neuroblastoma Study 2 of SIOP-Europe-Neuroblastoma (SIOPEN)	Neuroblastoma	SIOPEN	Gustave Roussy 2019-001068-31	800	22	Prospective RTQA	Open
LINES European Low and Intermediate Risk Neuroblastoma	Neuroblastoma	SIOPEN	Instituto de Investigación Sanitaria La Fe de Valencia 2010-021396-81	100	10	Prospective RTQA	Open
VERITAS 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.	Neuroblastoma	SIOPEN	Gustave Roussy 2015-003130-27	150	1	Prospective RTQA	Open
ATRT01 An international prospective umbrella trial for children with atypical teratoid/ rhabdoid tumours	Atypical-Teratoid Rhabdoid Tumours	BTG	German Paediatric Oncology Group, GPOH 2018-003335-29	152		Prospective RTQA	In development

(continued on next page)

Table 1 (continued)

Trial	Disease	ECTG	Sponsor NCT/EUDRACT #	Planned # of RT patients	Cases received*	Role of QUARTET	Status
(ATRT) including a randomised phase III study evaluating the non-inferiority of three courses of high dose chemotherapy compared to focal radiotherapy as consolidation therapy							
INTER-EWING-1	Ewing Sarcoma	EEC	University of Birmingham –	420–900		Prospective RTQA	In development
MYKIDS Molecular identification and characterisation of non-rhabdomyosarcoma soft tissue sarcoma in kids, adolescents, and young adults: an EpSSG NRSTS study	Non-Rhabdomyosarcoma Soft Tissue Sarcomas	EpSSG	UMC Utrecht –	270		Prospective RTQA	In development
UMBRELLA The UMBRELLA SIOP-RTSG 2016 Protocol	Wilms' Tumour	SIOP RT-SG	UKS Universitätsklinikum des Saarlandes [17]	150		Prospective RTQA	In development
Retrospective Radiotherapy Quality Assurance HR-NBL1 High risk neuroblastoma study 1 of SIOP-Europe (SIOPEN)	Neuroblastoma	SIOPEN	St. Anna Kinderkrebsforschung e.V. 2006-001489-17	250–300	97 (242) [‡]	Retrospective RTQA	Closed to new submissions
Prospective Imaging FaR-RMS (DW-MRI & PET sub-studies)	Rhabdomyosarcoma	EpSSG	University of Birmingham 2018-000515-24	750		Provide required infrastructure for imaging collection. Imaging QA	Open
NB-SCI Prospective study registry of peripheral neuroblastic tumours presenting with spinal canal involvement (SCI)	Neuroblastoma	SIOPEN	Associazione Italiana Ematologia Oncologia Pediatrica NCT02559804	150	59	Provide required infrastructure for imaging collection	Closed

Retrospective Imaging
 RMS 2005
 EpSSG RMS 2005: a protocol for non-metastatic rhabdomyosarcoma.
 Combination chemotherapy in treating young patients with nonmetastatic rhabdomyosarcoma (diffusion weighted MRI study)

Open

Provide required infrastructure for imaging collection

96

150

Rikshospitalet-Radiumhospitalet HF 2005-000217-35

EpSSG

Rhabdomyosarcoma

† 97 cases submitted via the QUARTET platform, a total of 242 cases collected for review and analysis. # = number. i.e. planned number of radiotherapy (RT) patients.
 * Cases received by 31/12/2021.

medical physicists, and 1 radiologist practicing across nine countries. The geographical distribution of contributors can be seen in Fig. 4.

The original portfolio of QUARTET-affiliated trials planned in 2016 consisted of nine studies recruiting a total of 1900 patients over 5 years. There have been significant delays, in part due to complex regulatory requirements, delays beginning new clinical trials, and more recently the COVID-19 pandemic; however, integration of QUARTET within paediatric clinical trials has overall been very successful. In March 2022, nine trials with prospective RTQA, one retrospective RTQA study, one molecular radiotherapy dosimetry central review programme, two prospective imaging projects, and one retrospective imaging project are either open to recruitment or in development. Further details of the trials affiliated with a QUARTET RTQA or imaging programme are detailed in Table 1. Integration of QUARTET within open trials with few patients remaining to recruit proved to be overly complex so plans to provide RTQA via QUARTET for SIOP PNET-5 and SIOP-Ependymoma-II for limited countries were halted.

Five trials (FaR-RMS, HRMB, HR-NBL2, LINES, and VERITAS) are open to site RTQA approvals and prospective ICR submissions (Table 1). Within the period May 2016–December 2021, 123 institutions commenced site RTQA approval procedures, with 61 now RTQA approved; and 157 ICRs completed. Fig. 5 depicts the ICR submissions, showing the increasing submissions and proportion of prospective reviews over time. In addition, two imaging studies are open and have so far collected data for 155 patients.

4. Discussion

As rare diseases, cancers affecting children and young people often require multi-national trials to recruit sufficient participants. In addition to answering a protocol's principal question, clinical trials can bring added benefits such as standardisation of care, safety monitoring, and access to new treatments. However, they can also present financial and infrastructural challenges. Uneven distribution of expertise and limited access to clinical trials likely contribute to reduced survival in central and eastern Europe [8,9,18–20].

Inconsistencies in treatment have been reported across adult and paediatric cohorts [1–4,21–23], with poor radiotherapy protocol compliance demonstrating reduced local control [2,4,22,24] and confounding of trial end-point analyses [3,25]. The meta-analysis by Ohri *et al* [4] revealed radiotherapy protocol deviation rates as high as 71% occur and are associated with an approximately 75% increased risk of treatment failure and mortality risk compared to compliant treatment. Prospective review of target volume delineation and

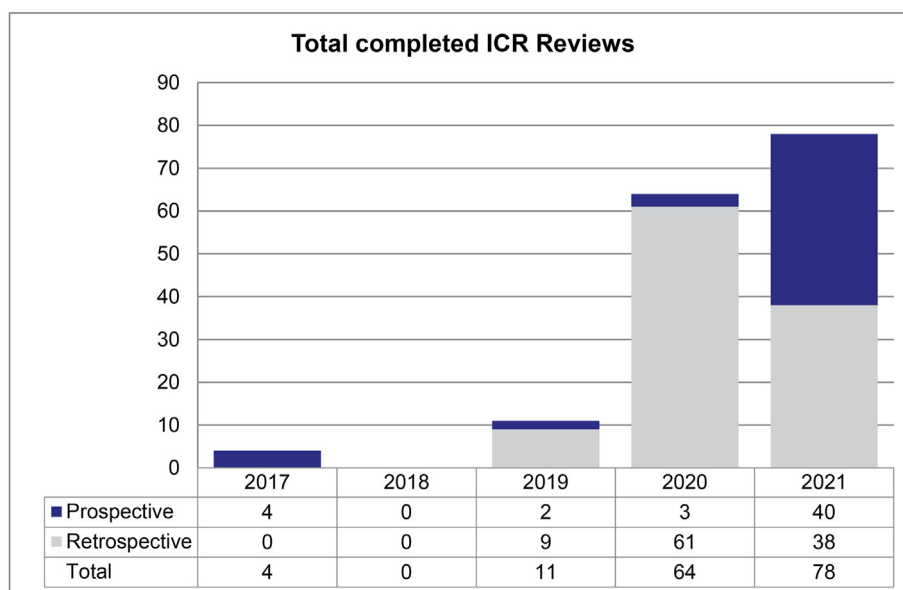


Fig. 5. Total individual case reviews completed for the period May 2016–December 2021. Includes case reviews completed for FaR-RMS (27), HR-NBL1 (97), HR-NBL2 (22), LINES (10), and VERITAS (1).

treatment plans, within and outside the context of clinical trials, is considered best practice to reduce the risk of systematic errors and support ongoing improvement [4,8,26–29]. Unfortunately, uneven distribution of expertise and resources extends to the provision of RTQA initiatives [8,9], which have demonstrated an ability to mitigate planning errors [21–23]. As an independent, centralised platform, QUARTET provides the expertise, infrastructure, and funding for RTQA activities so that it is not dependent on, nor borne by, national providers. Without improved national or cross-border access to clinical trials in Europe, QUARTET may need to explore feasibility to extend services beyond clinical trials in order to reach those with the greatest need, for example, in eastern Europe and other lower income countries.

The regulatory and logistical complexity of introducing an international, centralised RTQA platform for clinical trials cannot be underestimated. QUARTET is reliant on engagement from international trial sponsors, the participation of sufficient and dedicated expert reviewers to provide a timely evaluation, and the commitment of participating institutions to submit all required data, allowing for sufficient time for review and implementation of any recommended changes prior to treatment delivery. Early experience indicates promising engagement with institutions; QUARTET is working closely with trial sponsors to maximise participation.

QUARTET fulfils the SIOPE strategic research goal to create and run sustainable cross-disease platforms which support high-quality clinical research within the ECTGs. QUARTET will facilitate one of the largest repositories of paediatric radiotherapy and imaging data: supporting uniform data collection and reporting.

This resource will facilitate evaluation of the role of RTQA within this cohort of patients and the interrogation of normal tissue constraints and tumour control probabilities within and across different tumours.

5. Conclusions and future work

SIOPE is invested in the betterment of paediatric oncology; supporting improvements in access to high-quality effective treatments to reduce inequality and provide the best possible control of disease and quality of life after treatment, for children and adolescents across Europe. QUARTET supports this mission through the provision of a centralised, online, interventional RTQA platform which helps to reduce the administrative and logistical burdens of implementing national or individual trial RTQA programmes and equalises access to expertise. Initiatives to improve access to advanced radiotherapy techniques and clinical trials are required to ensure that those countries most in need will benefit.

Prospective QA of paediatric radiotherapy treatment planning is highly recommended, particularly within the context of clinical trials where both treatment compliance and dataset uniformity are essential. SIOPE is committed to converting QUARTET into a long-term, sustainable programme, and the SIOPE-ROWG encourages use of QUARTET for clinical trials recruiting children and adolescents across SIOPE-affiliated ECTGs.

QUARTET will continue to collaborate closely with trial sponsors to ensure data completeness, disseminate findings and share its experience with the paediatric radiation oncology community, and invest in education

activities to support institutions in delivering optimal radiotherapy. SIOPE is exploring further initiatives to support imaging and surgical QA. Any professionals with an interest in paediatric radiation oncology, or indeed quality assurance in clinical trials, are welcome to contribute and encouraged to contact QUARTET and also join the SIOPE-ROWG, especially those from countries without current representation. For further information, see the QUARTET website <https://siope.eu/activities/joint-projects/quartet/> or contact us via email quartet@siope.eu.

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Role of funding source

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Author contributions

TB, HCM, MNG, GV, SMK: Study concepts; SMK, RE, AB, CC: Data acquisition; SMK, CC: Quality control of data and algorithms; SMK, HCM: Data analysis and interpretation; SMK, HCM: Statistical analysis; SMK, RE, HCM, TB, MNG, EC: Manuscript preparation; All authors: Study design, Manuscript editing, Manuscript review.

Conflict of interest statement

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.

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