CTRad: national leadership in radiotherapy research

Achievements and vision

NCRI
National
Cancer
Research
Institute

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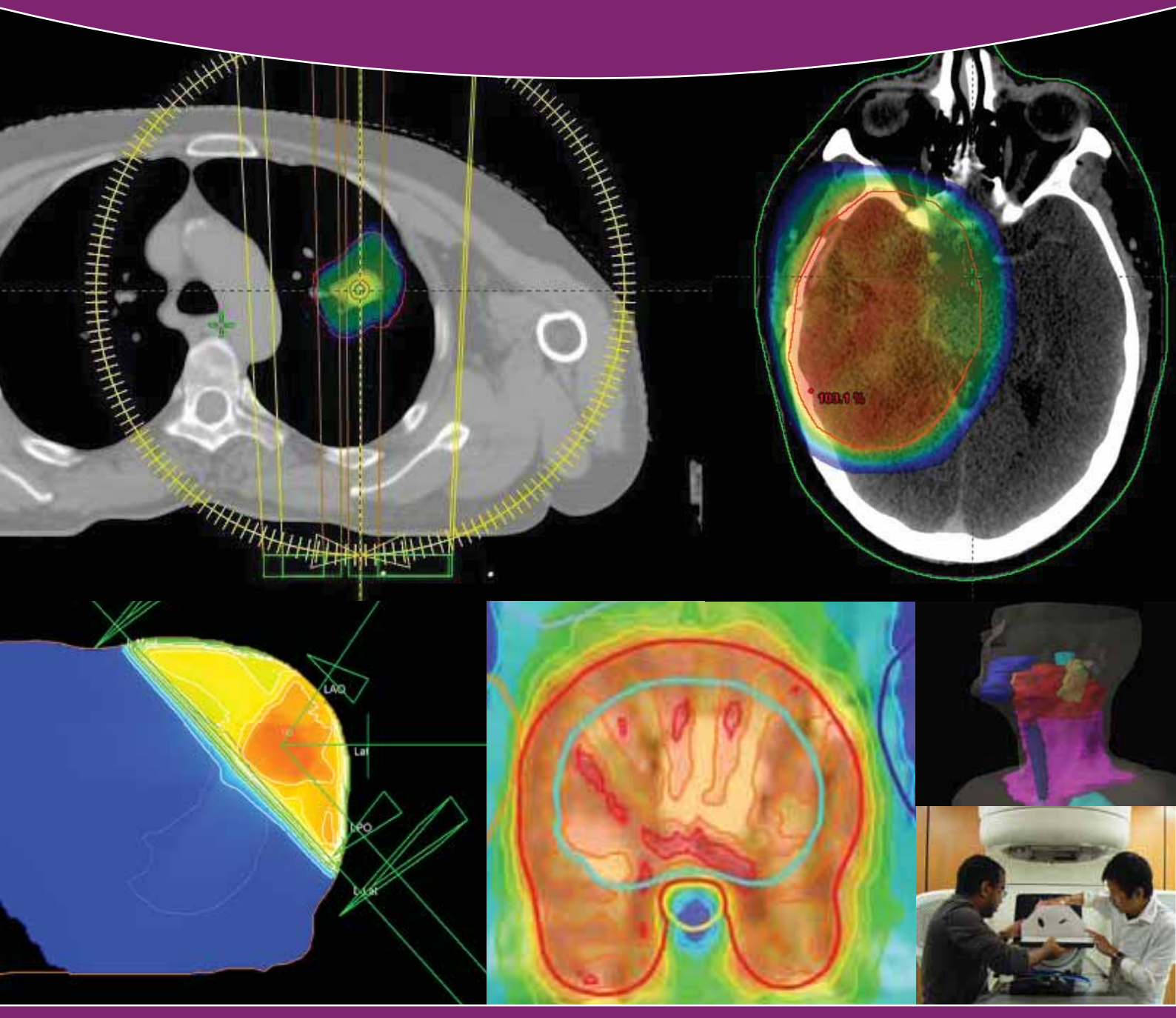

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Cover images (clockwise from top left):

1. Stereotactic Ablative Radiotherapy (SABR) treatment planning image for treating a lung tumour. Photograph used with kind permission of Dr Stephen Harrow.

2. Highly conformal radiation dose distribution achieved by intensity modulated radiotherapy (IMRT) for the treatment of glioblastoma, the most common brain tumour. Photograph used with kind permission of Prof Anthony Chalmers and Aoife Williamson.

3. Three-dimensional image showing anatomical structures in the head and neck region.

4. Members of the NCRI Radiotherapy Trials Quality Assurance (RTTQA) group positioning a phantom before a radiotherapy dose measurement procedure.

(Photographs 3 & 4 used with kind permission of the NCRI RTTQA team).

5. Image-guided intensity modulated radiotherapy (IG-IMRT) for treating chordoma (bone cancer) in the lower thoracic vertebra (middle of the spine). Photograph used with kind permission of Prof Neil Burnet.

6. Intensity modulated radiotherapy (IMRT) treatment planning image for treating a breast tumour. Photograph used with kind permission of Nicola Twyman.

Contents

1. Introduction: the role and potential of radiotherapy in cancer

Radiotherapy (RT) is one of the most potent and cost-effective curative treatments for cancer.[1] In the UK about 300,000 new cancer cases occur each year.[2] Around 50% of patients require radiotherapy at some time during their illness, and 60% are treated with curative intent.[3] Thus over 90,000 patients receive radiotherapy with curative intent in the UK each year, and the potential benefits from improvements in tumour control and reductions in toxicity are considerable. Technical radiotherapy developments can make a major contribution to this strategy, and there are also enormous potential benefits to be gained from combining radiotherapy with chemotherapy and molecularly targeted drugs. Development is typically driven by the academic community, which therefore underpins NHS service delivery.

For most tumours there is a steep dose-cure relationship, both in experimental animal systems and in man. For example, a 5% increase in absolute or biological equivalent dose will typically achieve an increase in tumour cure rate of 5–10%.[4] Thus, small increases in dose can deliver important clinical benefits. Radiotherapy effects can also be enhanced by the addition of drugs that either sensitise the tumour or protect the normal tissues, and again considerable improvements could be achieved by modest biological effects. A tumour-specific radiosensitisation strategy which was applicable to 90,000 patients per annum would therefore have huge potential benefits.

Technical developments including intensity modulated radiotherapy (IMRT), image guided radiotherapy (IGRT) and proton beam therapy (PBT) have demonstrable potential to increase tumour cure and reduce toxicity, with consequent enhancement of both duration and quality of survival. Moreover, simple expedients such as delivering high quality radiotherapy in a timely fashion can improve outcomes. From 2003 to 2012, reductions in radiotherapy waiting times have been shown by computer modelling to have saved around 2,500 lives annually. This is equivalent to one patient per week per radiotherapy centre.[5] Methods to increase work flow efficiency, such as computational radiotherapy techniques in treatment planning and delivery, can support or enhance such improvements.

The last decade has seen exceptional improvements in radiotherapy technology and early evidence that these improvements can improve cancer outcomes. The next decade will bring unprecedented opportunities to translate these advances into increased cure rates for many cancer types. In its first five years, the NCRI Clinical and Translational Radiotherapy Research Working Group (CTRad; ctrad.ncri.org.uk) has coordinated efforts to revitalise the radiotherapy reserach community. CTRad will work with the clinical and scientific communities to ensure that UK cancer patients receive the maximum possible benefit.

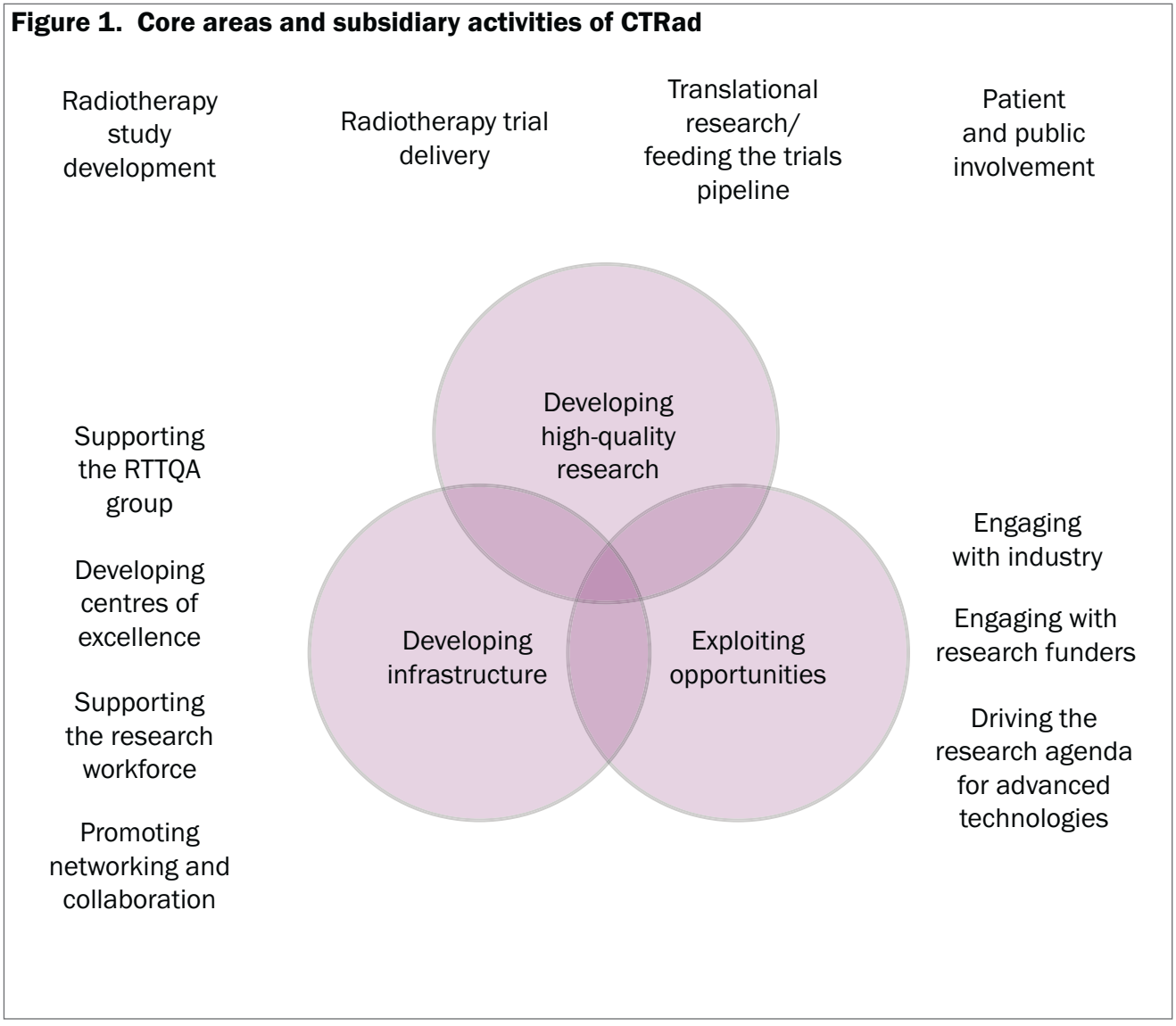
2. CTRad's outputs and achievements

By 2008, radiotherapy research in the UK was recognised to be in crisis. Following the NCRI Rapid Review of Radiotherapy and Associated Radiobiology,[6] CTRad was established in 2009 to provide leadership in the national effort to revitalise radiotherapy research in the UK.

Responding to the 10-point action plan generated by the NCRI Review, CTRad has developed and delivered many different strands of activity over the past five years. 'Working group' is no longer an adequate definition: CTRad has become a broad and multifaceted initiative with 82 members and a number of subgroups embedded within, or supervised by, its Executive Group and four Workstreams (Appendix 1). Representation by CTRad members on relevant national and international groups ensures a joined up and cost-effective approach (Appendix 2), and patient and public involvement has also been instrumental in CTRad's development.

The volume and diversity of CTRad's work is catalogued in Appendix 3. Many of the tasks have evolved into items of core business that are recognised by the community as high quality enterprises that make a significant contribution to the radiotherapy research agenda. While all support the original goals of the 10-point plan, there has been a redefinition of core areas of work, as illustrated in **Figure 1**.

Figure 1. Core areas and subsidiary activities of CTRad



To demonstrate the impact of CTRad, quantitative measures have been captured where possible; these are included in the text and the table of metrics in Appendix 4. CTRad also provides value to the community in ways that are less easily measured. These include re-invigorating the UK radiation research community, providing support to centres and individuals seeking to achieve academic excellence, changing the mindset within the pharmaceutical industry regarding drug-radiation trials, and bringing together investigators and members of the public from diverse disciplines to spark collaboration and generate novel research. Patients and carers have unique experience which enables them to contribute to tackling the challenges faced by researchers. Case studies have been included in an attempt to illustrate these broader aspects of CTRad's work, and the CTRad website (ctrad.ncri.org.uk) hosts many additional documents and meeting reports.

2.1 Radiotherapy clinical trials development

When CTRad was established, there were few UK initiated radiotherapy clinical trials. A core objective for CTRad has been and is to support the development of radiation-related research concepts to enable them to progress through successful funding applications to become active clinical trials.

CTRad's twice-yearly Proposals Guidance Meetings have been instrumental in increasing the quality, number and diversity of radiotherapy studies put forward. These meetings offer investigators (within and beyond CTRad) the chance to present their radiotherapy-related study ideas for peer review and discussion, with the aim of maximising the quality of subsequent funding applications. Each Proposals Guidance Meeting is attended by 75–100 members of the research community, including patient and carer representatives, providing both breadth and depth of critique, and is followed up by post-meeting support for promising concepts from the relevant CTRad Workstream(s). To date more than 120 proposals have been discussed at these meetings, from which 30 studies have been funded, mostly through the CRUK Clinical Trials Awards and Advisory Committee (CTAAC) but also via the NIHR Health Technology Assessment (HTA), CRUK New Agents Committee, NIHR Research for Patient Benefit, and local routes. An impressive diversity of studies has been discussed, in terms of type, phase of research and tumour site (Appendix 5). The success of this model has led to Proposals Guidance Meetings being adopted by some of the NCRI Clinical Studies Groups (CSGs).

These meetings are supplemented by year-round access to CTRad's Radiotherapy Clinical Trials Advisory Service (RADCAS) and a new CTRad Biomarker Support Network, both of which provide tailored advice at the pre-submission stage. CTRad workshops also provide opportunities for investigators to acquire the skills and collaborations required to create high quality clinical studies, and some of these include further opportunities to obtain informal peer review of proposals.

Case study: How CTRad supports proposal ideas through the path to funding

Dr Mererid Evans (Consultant Clinical Oncologist in Cardiff, not currently a CTRad member) first presented her PATHOS study concept at a CTRad Proposals Guidance Meeting in November 2012. It was rated 'amber', meaning it was competitive and had good potential but required further development before applying for funding. She was then invited to present PATHOS as a case study at CTRad's Clinical Trials Workshop in February 2013, where it was discussed in two longer and more detailed sessions, from which additional and deeper guidance was obtained.

Dr Evans reported that CTRad had provided invaluable advice and support during the development of PATHOS. In the early stages, presentation at the Proposals Guidance Meeting had been extremely useful; in particular the positive feedback had encouraged her team to continue with study development. The subsequent Workshop discussions had provided an opportunity to refine endpoints and overall trial design with input from a group of experienced clinical trialists, statisticians and funders; patient representatives also gave advice on how to 'sell' the study to prospective trial participants.

Dr Evans reported that all these aspects had made a major contribution to an eventual funding application to CTAAC that was more focused and included better defined endpoints and evidence of support from centres that could deliver the necessary transoral surgery and radiotherapy. The study received particularly favourable opinions from multiple international reviewers and was approved for funding in November 2013.

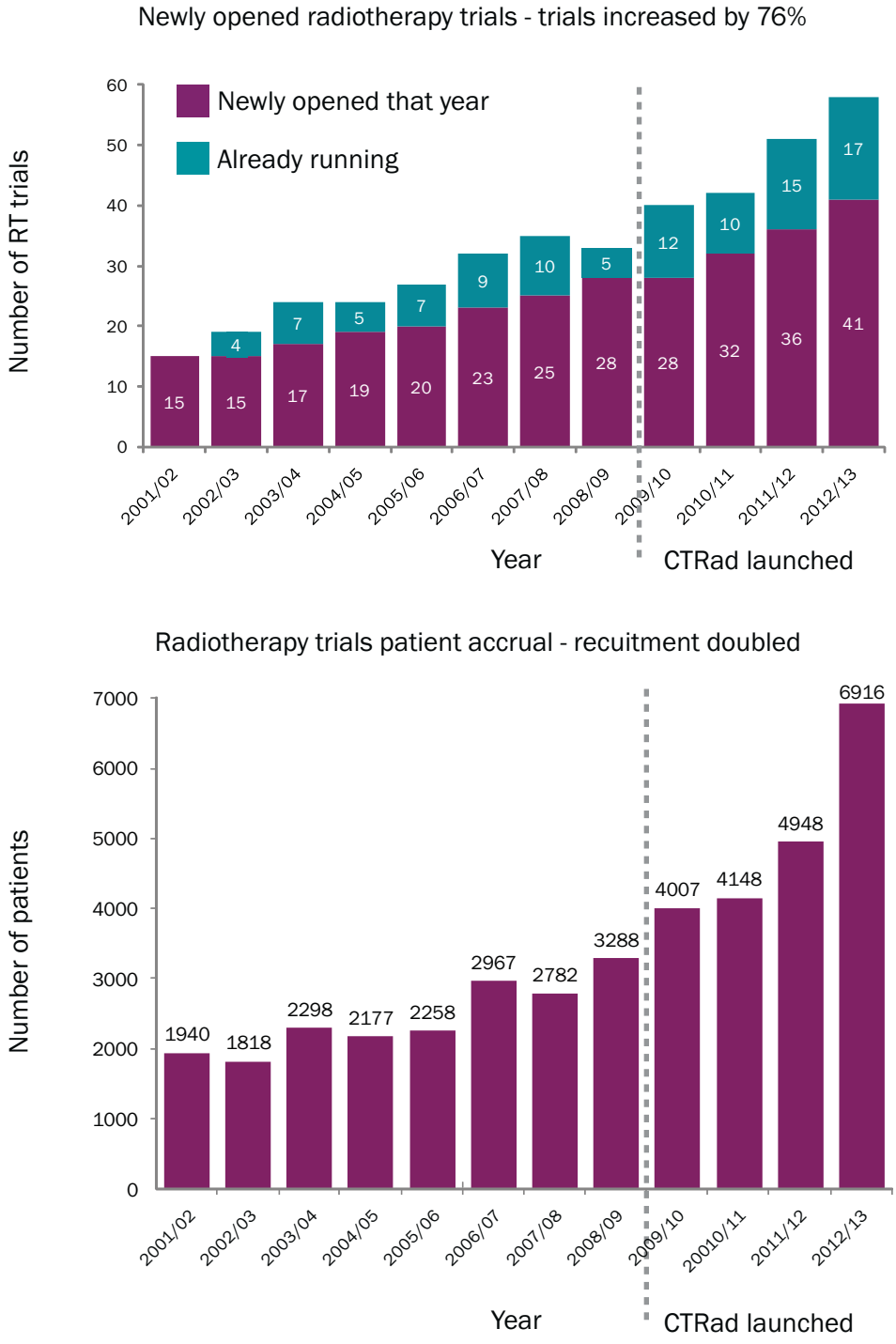
2.2 Radiotherapy trial delivery

Since the start of CTRad's activities in 2009, both the number of radiotherapy studies and the number of patients in trials has risen substantially (**Figure 2**). Patient participation in trials has more than doubled from 3288 in 2008/09 to 6916 in 2012/13. The number of open radiotherapy studies on the NIHR:CRN portfolio has increased from 33 in 2008 to 58 in 2012/13. This is one of CTRad's major achievements.

The complexity of the radiotherapy in trials has also been increasing, as discussed below, making quality assurance even more important. Through the Proposals Guidance Meetings CTRad also provides a mechanism for providing expert comment on technical details of radiotherapy for trials in development.

An important trend in trial activity has been the evaluation of treatment schedules with fewer fractions (hypofractionation), such as START-B and CHHiP. Some centres have experienced difficulties in opening hypofractionation trials because of issues related to NHS reimbursement. CTRad has worked with NCRI and NHS England to clarify how centres can overcome these.

Figure 2. NIHR:CRN portfolio radiotherapy trials, and patients recruited to them, by year



2.3 Translational research/feeding the trials pipeline

One of the key aims of CTRad has been to facilitate efficient translation of basic radiobiological and radiation-related research findings into early phase clinical trials. The original 10-point plan identified improving connections with the pharmaceutical industry to make it easier and faster to perform combination trials of radiotherapy with novel agents as a critical objective. A unique feature of CTRad that differentiates it from the CSGs and has enabled it to make significant progress in this area is the integral involvement of basic science. Twelve Workstream 1 members are non-clinical scientists and many of CTRad's oncologists are clinician scientists. The success of this philosophy and the enthusiastic and collaborative contribution of these members is reflected in numerous translational activities and outputs, including national and international workshops and peer-reviewed publications (ctrad.ncri.org.uk/resources/publications-and-recommended-reads).

CTRad has also set up a Biomarker Support Network (ctrad.ncri.org.uk/research-support/biomarker-support-network) as a national resource to facilitate routine incorporation of high quality biomarker research into UK radiotherapy clinical trials. This stemmed from a workshop entitled 'Current and future biomarkers for inclusion in radiotherapy trials' that took place at the University of Leicester in April 2012. Of note, 27 radiotherapy-novel agent combination studies, four preclinical and two translational research proposals have been presented at CTRad Proposals Guidance Meetings, of which 13 have subsequently been funded.

The challenges of persuading pharmaceutical companies to engage with radiotherapy researchers and initiate early phase trials of novel compounds in combination with radiotherapy has been a particularly difficult area in which to make progress. Over the past three years CTRad has made a major step forward by proposing and subsequently establishing the Radiotherapy-Drug Combinations Consortium (RaDCom). This innovative initiative is a collaborative network of laboratories working in partnership with industry and funders to deliver high quality preclinical data in a timely and efficient manner, providing the necessary evidence base for early phase clinical trials. The positive responses from funding organisations and pharmaceutical companies and the successful funding of the first Consortium proposal in autumn 2013 demonstrate the value of such an approach and illustrate the potential scope and impact of RaDCom's future activities.

Case study: The Radiotherapy-Drug Combinations Consortium

This is another example where a national need was identified by CTRad and a unique strategy developed, resulting in innovative partnership activity. In 2011, CTRad organised a Drug-Radiation Conference in conjunction with the LH Gray Foundation, at which a lack of engagement with pharmaceutical companies was identified as the major factor responsible for the lack of drug-radiation combination studies in the clinical trials portfolio. It was apparent that pharmaceutical companies lacked both awareness and expertise in this area, and that conventional early phase clinical trial designs were not well suited to evaluating radiotherapy-drug combinations. To address these issues, Workstreams 1 and 2 of CTRad initiated discussions with the ECMC Combinations Alliance in May 2012 and subsequently produced a discussion paper entitled 'Streamlining new drugs in combination with RT from lab to clinic'. After meeting with senior CRUK and Drug Development Office (DDO) managers in November 2012, CTRad suggested establishing a collaborative network of laboratories that would work in partnership with industry and funders to deliver high quality preclinical data on radiation-drug combinations in a timely and efficient manner. The overall aim would be to provide the necessary evidence base to initiate early phase clinical trials.

The DDO agreed to fund a project manager to support the Consortium, and the Radiotherapy-Drug Combinations Consortium (RaDCom) was established in April 2013. RaDCom is chaired by CTRad's Deputy Chair, Professor Anthony Chalmers, and a project manager has been in post since November 2013. Within a few months, the first new collaborative project was selected for development by the RaDCom Steering Committee and this was subsequently funded through the NAC's Preclinical Funding scheme. Further applications will be submitted to the next round of this scheme in April 2014. The Consortium is also engaging directly with a number of pharmaceutical companies with the aim of overcoming barriers to the development of radiotherapy-drug combinations and streamlining routes to the clinic.

By establishing RaDCom CTRad has overcome the most significant barrier to the clinical development of radiotherapy-drug combinations, and is providing an important resource for industry and the UK radiation biology community. The positive responses from pharmaceutical companies, funders and academia confirm the value of this approach.

2.4 Patient and public involvement in trial development

Consumers play an active role within CTRad, having a strong presence both within the Workstreams and on the Executive Group. The contribution of this dedicated and experienced group of consumer members has been highly influential. The consumers' input has been significant in reviewing trials but their reach goes far beyond this. They have developed the scope of the consumer's role within CTRad, providing perspectives on trial design, service delivery, qualitative and quantitative evaluation, applications for funding and dissemination.

The CTRad consumers have created and disseminated documents giving guidance to researchers on how to write lay abstracts and how to benefit from patients and consumers in the process of radiotherapy trial development (ctrad.ncri.org.uk/research-support/patient-and-public-involvement). Both of these have a much wider reach across other research groups.

Initially, the pace and complexity of work within the CTRad workstreams made it difficult for consumer members to engage, so these members initiated a new model whereby they meet as a group and work flexibly across CTRad activities according to their interests and expertise. This is proving to be a successful approach and may be a useful model for other cross-cutting working groups.

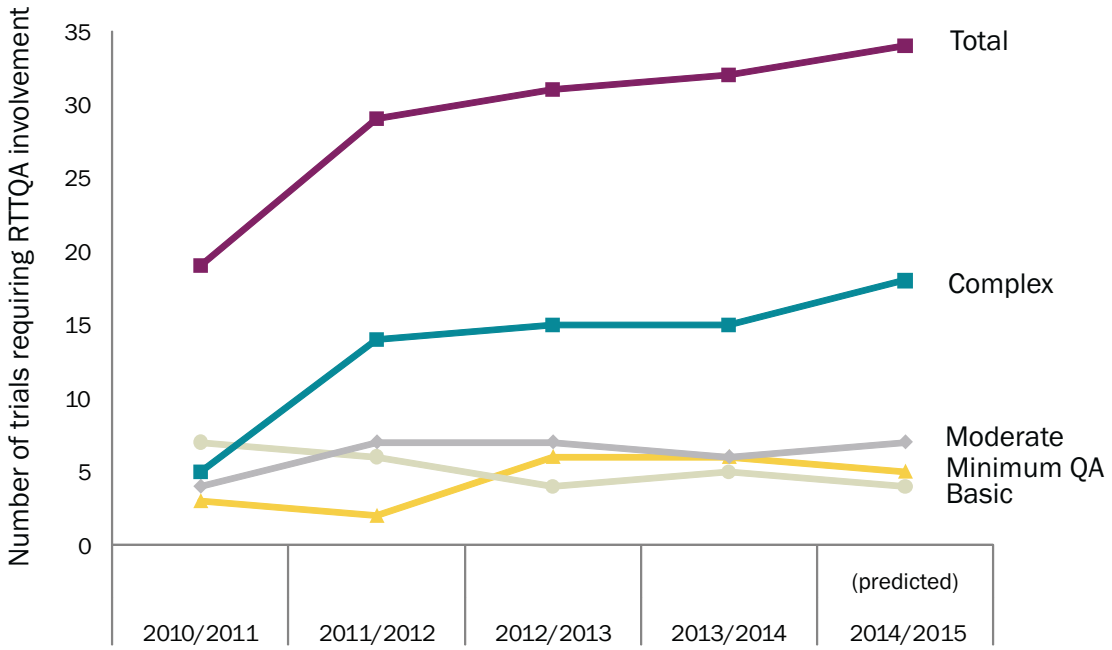
2.5 Leadership in radiotherapy quality assurance

Radiotherapy quality assurance (QA) plays an essential role in providing both high quality patient care and robust research data. It has been clearly shown that poor quality of radiotherapy delivery adversely affects treatment outcomes for patients. Similarly poor or variable quality radiotherapy in clinical trials can adversely affect study outcomes by overwhelming the treatment effect being investigated.[7]

The Radiotherapy Trials Quality Assurance (RTTQA) team, funded by the NIHR, has benefited from CTRad oversight and senior clinical and managerial support at a crucial time. Not only is the number of radiotherapy trials increasing (**Figure 2**), but with the widespread introduction of advanced technologies, the complexity of radiotherapy within clinical trials is growing (**Figure 3**). The number of complex radiotherapy trials has almost doubled since the group obtained central funding in 2010, and by 2012/13 the total number of radiotherapy trials on the group's portfolio had also increased by 74%. The increase in RTTQA input to trials applies to those of a complex nature (**Figure 3**). This trend indicates a rising sophistication in radiotherapy planning and delivery techniques, especially the use of IGRT, IMRT and stereotactic ablative radiotherapy (SABR). The RTTQA team has made a major contribution to the implementation of these techniques in radiotherapy centres around the country, providing benefit for patients receiving routine clinical care as well as those participating in trials.

More recently, Workstream 1 has investigated the previously 'hidden' issue of quality assurance in preclinical radiotherapy research, surveying centres with preclinical radiation equipment to determine the range of equipment, methods of calibration used and the most recent dates of calibration. Preliminary findings indicate, as suspected, that preclinical radiotherapy QA is extremely variable and might be compromising the quality of research outputs. CTRad is now leading a unique initiative to provide all preclinical laboratories with access to standardised QA and to monitor its implementation on a regular basis. This programme will increase the quality of preclinical radiation research in the UK, promote networking and facilitate collaborative, complementary research across multiple laboratories, and is an integral component of the RaDCom initiative described above.

Figure 3. Change over time in the complexity of radiotherapy trials requiring input from the RTTQA team. This includes a substantial commitment to preparation for trials, especially those with greater complexity, as well as QA during the active recruitment phase.



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2.6 Developing centres of excellence

One of the over-arching goals of CTRad is to support UK centres in developing activity in academic radiation biology and radiotherapy, as they aspire to become radiotherapy centres of excellence. CTRad's 'Academic Think Tank' meetings provide a constructive environment within which centres can share experiences and openly discuss problem areas that are limiting local progress. The candour and generosity displayed at these meetings has been important in generating mutual support and trust. Several centres have reported an increase in local research activity, engagement at more senior levels, and development of a more research-active culture. In 2013, seven centres bidding for CRUK Centres funding identified radiotherapy as a priority area; only four centres were known by CTRad members to have done so in 2008.

Securing programmatic funding was identified as a major but necessary step in the path to becoming a centre of excellence. Of the 32 outline applications submitted to the CRUK Clinical and Translational Research programme funding stream in 2011, 10 were radiotherapy-themed, and two of the four programmes awarded focused entirely on enhancing radiotherapy outcomes. This was rightly seen as a major achievement and it had an enormously positive impact on the UK radiotherapy research community. CTRad recognises that the transition from project grants to programmatic funding is a significant challenge for up-and-coming centres and is committed to encouraging these centres to apply for high level funding. CTRad also works with researchers to maximise the quality of grant applications through mentoring and by sharing the experiences of leading centres.

Case study: Helping centres to expand academic radiotherapy

Belfast is an example of a centre that has made considerable progress since the establishment of CTRad, and has a clearly stated aim to become recognised as a centre of excellence in radiotherapy. Professor Joe O'Sullivan, a member of Workstream 3, now holds an academic chair of radiation oncology at Queen's University Belfast, and the department has two new clinical senior lecturers and 1.5 academic physicists. The team was recently awarded a programme grant from 'Movember' in partnership with Prostate Cancer UK, investigating mechanisms of radiation resistance in prostate cancer in the contexts of external beam, brachytherapy and molecular radiotherapy (Appendix 6).

Professor O'Sullivan reported that involvement with CTRad enabled his department to understand what was required to become a centre of excellence, and provided opportunities to learn from other centres (the Royal Marsden and the Christie in particular) about how to construct a successful programme grant. Attendance at a number of CTRad workshops also helped the team to establish radiotherapy as the clear focus of their prostate cancer research programme.

Case study: Multidisciplinary programme grants in radiotherapy

Professor Neil Burnet's VoxTox programme 'Linking radiation dose at the voxel level with toxicity' was one of the two successful radiotherapy programme applications in the 2011 CRUK Clinical and Translational research funding round. Professor Burnet reported that the success of this programme application has built a foundation for radiotherapy research in Cambridge, which has been an essential step in gaining recognition for academic radiotherapy in Cambridge. Although CTRad was not directly involved in the application process, it actively encouraged centres to submit proposals, and Professor Burnet noted that the practical encouragement provided by CTRad leaders was a significant factor in his success. He presented VoXTox at CTRad's third clinical oncology Academic Think Tank meeting in 2013, to help others consider how to approach a multidisciplinary programme grant application.

2.7 Supporting the research workforce

Ensuring a strong academic workforce is a necessarily collaborative endeavour, and CTRad has played a major part in this endeavour by engaging proactively with professional bodies and by promoting involvement of new as well as established researchers. Radiotherapy research is particularly dependent on multiple professional groups and for a centre to succeed it must nurture research-active individuals from all the relevant disciplines. Our website provides a resource for all researchers, with a wide range of materials published for easy access.

The CRUK/MRC Oxford Institute for Radiation Oncology (formerly the Gray Institute for Radiation Oncology and Biology) is at the centre of radiation biology research in the UK, and has begun to feed new researchers into the community. CTRad has strong links with the Oxford Institute, both at Executive Group and membership levels and through jointly-hosted events. CTRad also runs educational workshops aimed at newer investigators from Oxford and beyond who may be taking their first steps into research. To date, at least 14 junior investigators from across the UK have submitted trials for CTRad review.

CTRad has also developed productive relationships with professional bodies including the Royal College of Radiologists (RCR) and the Society and College of Radiographers (SCoR). Both have taken part in CTRad Academic Think Tank meetings that include a focus on developing academic careers for clinical oncologists, radiation physicists and radiographers, respectively.

Case study: Workshops to help newer investigators to develop radiotherapy research skills

Some of the workshops run by CTRad have a skill-building focus, as part of the broader objective to build capacity in radiation-related research by supporting newer investigators. One example is the CTRad Clinical Trials Workshop, first designed and run by Workstream 3 member Professor David Sebag-Montefiore in 2012, and now into its third annual reiteration. Pitched at newer investigators, it includes 'how to' presentations that deal directly with radiotherapy-specific challenges such as designing studies using a complex intervention such as radiotherapy, and how to involve the RTTQA team. The Workshop also incorporates intensive 'real-world example' sessions that serve the dual purposes of advancing a particular proposal idea in a group setting and teaching others about the process. With this model now established and consistently well received, it has been possible to devolve the delivery of future workshops to CTRad members at their own centres.

Case study: Supporting emerging leaders in radiotherapy research

Dr Corinne Faivre-Finn (Consultant Clinical Oncologist in Manchester, member of Workstream 3) is a respected clinical researcher in the field of lung cancer. Originally a Consultant Clinical Oncologist at the Christie NHS Foundation Trust, she made the transition to an academic post in November 2013 when she was appointed Reader in Clinical Oncology at the University of Manchester.

Leading up to this transition, Dr Faivre-Finn received guidance and informal mentoring from senior CTRad members, which enabled her to make an informed choice regarding the transition to an academic post, and reassured her that she was well-positioned to become a successful academic. She reported that the CTRad Academic Think Tank meetings were also valuable, and praised the role of CTRad in providing useful feedback and support on her clinical trial concepts at Proposals Guidance Meetings. All of her studies received the 'green' grading, meaning they were judged to be 'highly competitive', and three were subsequently funded (2 CTAAC and 1 NIHR). She is now Chief Investigator of several phase I, II and III trials both nationally and internationally, acts as site Principal Investigator for major national and international lung trials, and has become the European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group's Radiotherapy chair.

2.8 Promoting networking and collaboration

A number of collaborative workshops have been run by CTRad each year, and are promoted and reported through the CTRad website (ctrad.ncri.org.uk/resources/reports-and-tumour-site-reviews), as well as other channels. The aims of these workshops are to facilitate networking and collaborative working, encourage and support activity from individual centres and consortia in the relevant areas, and create critical mass. In a broader sense they support the important aim of building a multidisciplinary radiotherapy research community in the UK.

CTRad members have also demonstrated leadership and participation in international programmes. These include RAPPER, which is a key partner in the international Radiogenomics Consortium, and involvement with a European working group on linking radiotherapy dose plans into outcome databanks. Where appropriate international experts have been invited to speak at or participate in workshops.

Collaboration between organisations is also helping to support the goal of increasing radiotherapy and radiation biology research. For instance, with CTRad leaders supporting negotiations in 2012, the RCR now hosts a 1-day joint programme of radiation oncology-specific content at the NCRI Cancer Conference each year. On the technology side, CTRad has also begun building links with the Institute of Physics and Engineering in Medicine (IPEM) and the Institute of Physics (IoP), which it hopes to strengthen in coming years.

2.9 Engagement with industry

The use of novel targeted agents to sensitise tumours to radiation is a rapidly growing research area, and the potential clinical benefits of this approach are enormous. Until recently, however, very few radiotherapy-novel agent combinations had progressed to the clinic, for the reasons described in section 2.3. Since its inception, CTRad has engaged with major pharmaceutical companies, initially through workshops and conferences, but with the notable exception of AstraZeneca (AZ), the response has been limited. Recognising the impact of this bottleneck, and with additional support from the CRUK DDO, CTRad established RaDCom as a novel approach to accelerating preclinical research into drug-radiation combinations. Through its close connections with the ECMC Combinations Alliance, RaDCom has become an integral part of the drive towards more productive collaboration with industry, and has already benefited from the existing relationship with AZ. New Combinations Alliance partnerships with Lilly and Astex, and the acquisition by AZ of MedImmune, have greatly enhanced the opportunities for collaboration and indicate a growing enthusiasm of pharmaceutical and biotechnology companies to work in partnership with NCRI affiliated organisations. This area promises to be a major focus of activity for CTRad in the years to come.

CTRad has also made efforts to engage with manufacturers of RT equipment over a number of years. Unfortunately the major manufacturers have been largely unresponsive, and supporting research activity in the UK does not appear to be a commercial priority. Manufacturers do support research through agreements with individual centres, but have not sought to extend this to a national level. Useful routes of dialogue have been opened, but this area has been deprioritised by CTRad in favour of more productive activities.

2.10 Engagement with research funders

CTRad has been able to bring the radiation research community into closer contact with research funders. The main aims have been to improve researchers' understanding of proposal fit within existing funding streams, to explore opportunities to improve funding opportunities for radiation related research, and to identify and ameliorate barriers to funding.

CTRad's programme of workshops and meetings creates opportunities for researchers to hear directly from funders on the available streams and where best to target radiation research of different kinds. The leadership structure also allows CTRad to act on behalf of the wider research community to raise issues with funders and identify gaps. In 2010, CTRad highlighted a major gap in CRUK funding for multidisciplinary, translational programmes, and CRUK's Scientific Executive Board (SEB) subsequently approved a new funding stream in late 2010. More recently, CTRad worked with the MRC to revise its wording of the 'Radiation Oncology and Biology Highlight' notice, to more clearly encompass therapeutic as well as adverse aspects of radiation research, and arranged a presentation of the new Highlight and associated translational funding streams at a CTRad Proposals Guidance Meeting. CTRad works continuously to identify funding calls of potential relevance and to encourage researchers to develop and submit proposals.

CTRad has also been able to provide expertise to enhance other aspects of work delivered by research funders. For instance, CTRad leaders presented to CRUK's SEB on opportunities and areas of unmet need in radiotherapy research at a time when the new CRUK strategy was being developed. CTRad has also contributed to national consultations led by the Department of Health (DH), sometimes independently and sometimes with the assistance of the CRUK policy team. CTRad worked closely with the former DH National Radiotherapy Implementation Group (NRIG) and is currently working with the DH National Clinical Lead for PBT on developing the proton research agenda.

2.11 Driving the research agenda for advanced technologies: Protons and SABR

CTRad takes a national view of the research and development requirements for new technologies, a role which has become even more important since the demise of NRIG. Two current areas of focus are PBT and SABR.

CTRad provides a platform for bringing together the different parties with a stake in the development of an evidence base for PBT. The Christie and UCLH were selected by DH to be NHS PBT facilities, and the Oxford Institute is also intending to develop a proton beam research facility. While programmes of research will ultimately be driven by the treating centres, the wider research community also has a vested interest in what research questions might be a priority for UK patients. CTRad has convened three meetings to date; these have been attended by representatives from the proposed proton centres as well as a wider pool of researchers. The overall intention is to support the development of a nationally-focused proton research agenda across four research domains (biology; physics; clinical trials; methodology and outcome data collection).

SABR represents an exciting new development in radiotherapy in which technological advances in imaging and accuracy enable the administration of very high, curative (ablative) doses of radiotherapy in a small number of fractions (typically 3–5). Promising preliminary data have prompted early adoption of this technique in many centres internationally resulting in a lack of high quality evidence to support and inform its use. The UK is uniquely placed to conduct randomised controlled clinical trials in this area and CTRad has worked with the UK SABR Consortium to identify opportunities and develop high quality trial protocols. Very recently CTRad effectively influenced a discussion between NHS England, funding bodies including CRUK and members of the clinical community to ensure that clinical trials should take precedence over commissioning through evaluation (CtE) as the most effective method of evaluating SABR in a variety of tumour settings. Central to this argument was the ability to demonstrate that a number of high quality, multicentre trials were either already recruiting or in the advanced stages of development. Of the eight studies cited, six had been developed via CTRad Proposals Guidance Meetings.

3. Vision for 2015–2018 and beyond

The UK needs a high quality and internationally-competitive radiotherapy research community with academic centres of excellence in order to complement and drive future development of an efficient radiotherapy clinical service. Indeed, academic development, evaluation and implementation of new technology underpins the NHS service. For example, the MRC RT01 trial provided the mechanism to roll out conformal radiotherapy nationally, and the CTAAC-funded PARSPORT trial facilitated the adoption of IMRT; both trials were academically driven. The DH set a target of delivering 24% of radical RT fractions by inverse-planned IMRT for 2013,[5] the service in England has achieved a more than 10-fold increase from 2% in 2008 to exceed 24% in the second half of 2013.[8] This outstanding achievement was dependent on significant support from the CTRad community. CTRad is in the forefront of coordinating ongoing implementation of new radiotherapy technologies across the UK, a process that needs to be viewed as a long term and continuously evolving project.

CTRad has delivered substantial output against multiple objectives, compared both to its original starting point and to the objectives established in the 2011 funding application. Successes include increasing the number of trials and patients entering trials, the number of early phase trials involving RT, ensuring RT quality assurance in trials, developing mechanisms to aid the embedding of translational research into trials, establishing alternative trial designs for RT studies, co-ordinating preclinical development of drug-RT combinations, and facilitating discussion of the PBT research agenda. CTRad has also supported academic centres, provided mentoring for young investigators and budding academics, and facilitated successful programmatic grant funding.

Given the starting point for this work, and the challenges associated with expanding the size of the academic radiation oncology research base, a timeframe of 10–15 years is likely to be required to develop a strong, robust and collaborative community. This is analogous to the objectives of the CRUK/MRC Oxford Institute for Radiation Oncology to re-seed and grow the radiation biology research base for the UK. Ultimately, it is envisaged that leadership and some aspects of the work of CTRad may be migrated gradually to established senior members of the community and to the professional bodies and Colleges.

Radiotherapy is a treatment specialty which depends heavily on technology for treatment preparation and delivery. Technology develops over time, predominantly by evolution, occasionally by revolution, and these changes require refinement, evaluation and safe introduction into clinical practice. The place of technology developments also requires careful evaluation in clinical trials. All of these processes are typically driven by academic radiation oncologists, physicists and radiographers. In this way, there is a direct effect of academic radiation oncology on the clinical service which can be offered by the NHS.

Leadership and coordination need dedicated time to enable strategic development, liaison across the community, and timely execution of significant packages of work. Securing dedicated clinicians' time for leadership has been crucial to the success of CTRad and to achieving the necessary momentum in the community. The small size of the academic radiation oncology research community in the UK necessitates significant cooperation to achieve successful research outputs, as well as a commitment to mutual support. CTRad has played a key part in these processes.

Major challenges remain, and the scale of work that we want to undertake means that CTRad will be seeking to continue working at a similar level for 2015–2018. The four-workstream structure is serving us well for the breadth of activity, and we also need to support the projects that stem from them.

Over the next 3–5 years we envisage significant effort in the following areas:

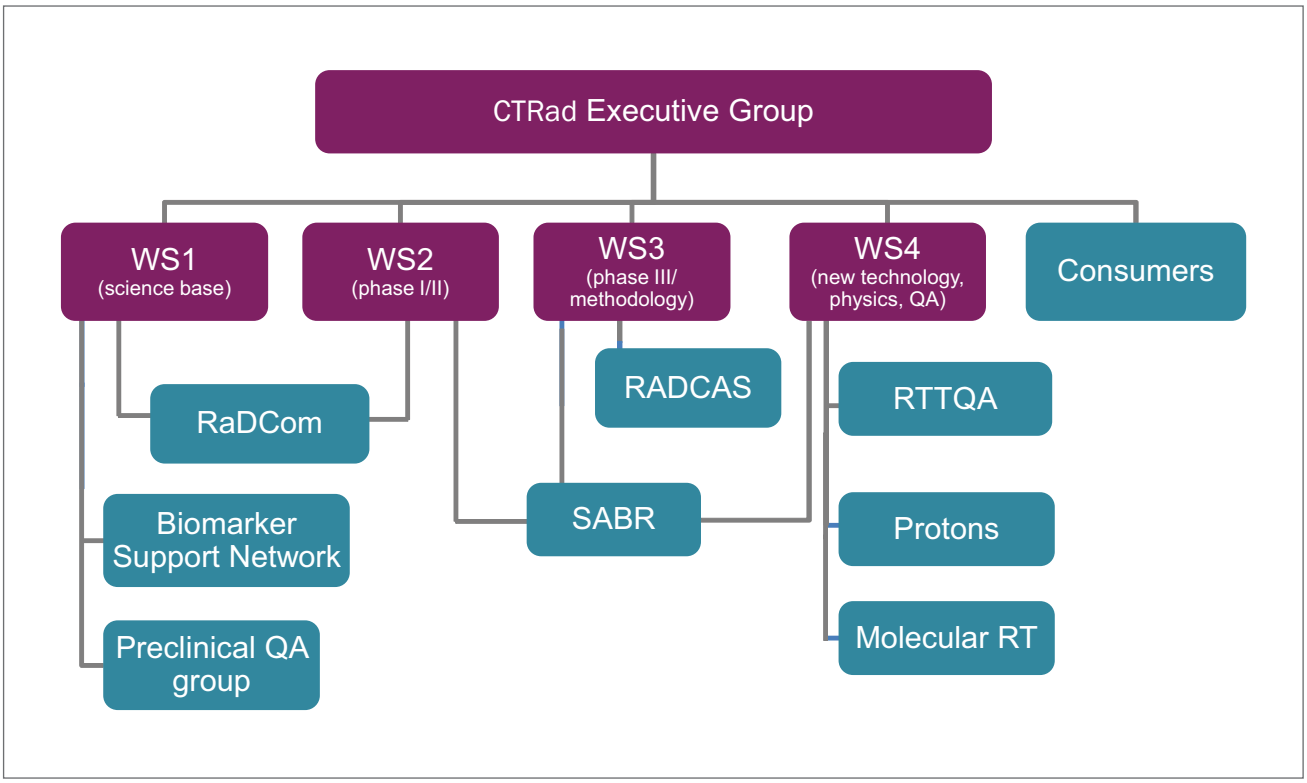
- continuing the rise in trial recruitment
- expanding early phase studies of drug-RT combinations
- supporting an increase in the number of centres of excellence
- proton beam therapy
- molecular radiotherapy (see Appendix 6)
- developing and appraising new technologies (e.g. SABR, MR linear accelerators)
- large scale data collection, within the 'Big Data' arena, considering ethical issues
- expanding international collaborations.

In summary, improvements in radiotherapy technology and molecular radiation biology will continue to create unprecedented opportunities to increase cure rates for many cancer types. CTRad has demonstrated the ability to bring together clinical and scientific researchers across the UK to increase the quantity and quality of radiotherapy research activity. Emerging treatment modalities include, but are not limited to, SABR, protons and radiotherapy-drug combinations. Continued funding is required to strengthen and expand the research infrastructure to support these and other emerging treatment modalities, and to provide rigorous evaluation at the preclinical and clinical stages of development. CTRad is uniquely placed to develop its extensive portfolio of activities to ensure that UK cancer patients receive the maximum possible benefit from these exciting new treatments.

Appendix 1. The evolved structure of CTRad

The Executive Group and four-workstream structure still forms the core framework under which CTRad operates (purple).

As CTRad has grown, new groups have emerged that sit within this structure (blue) to allow CTRad to focus in more depth on areas of high priority.



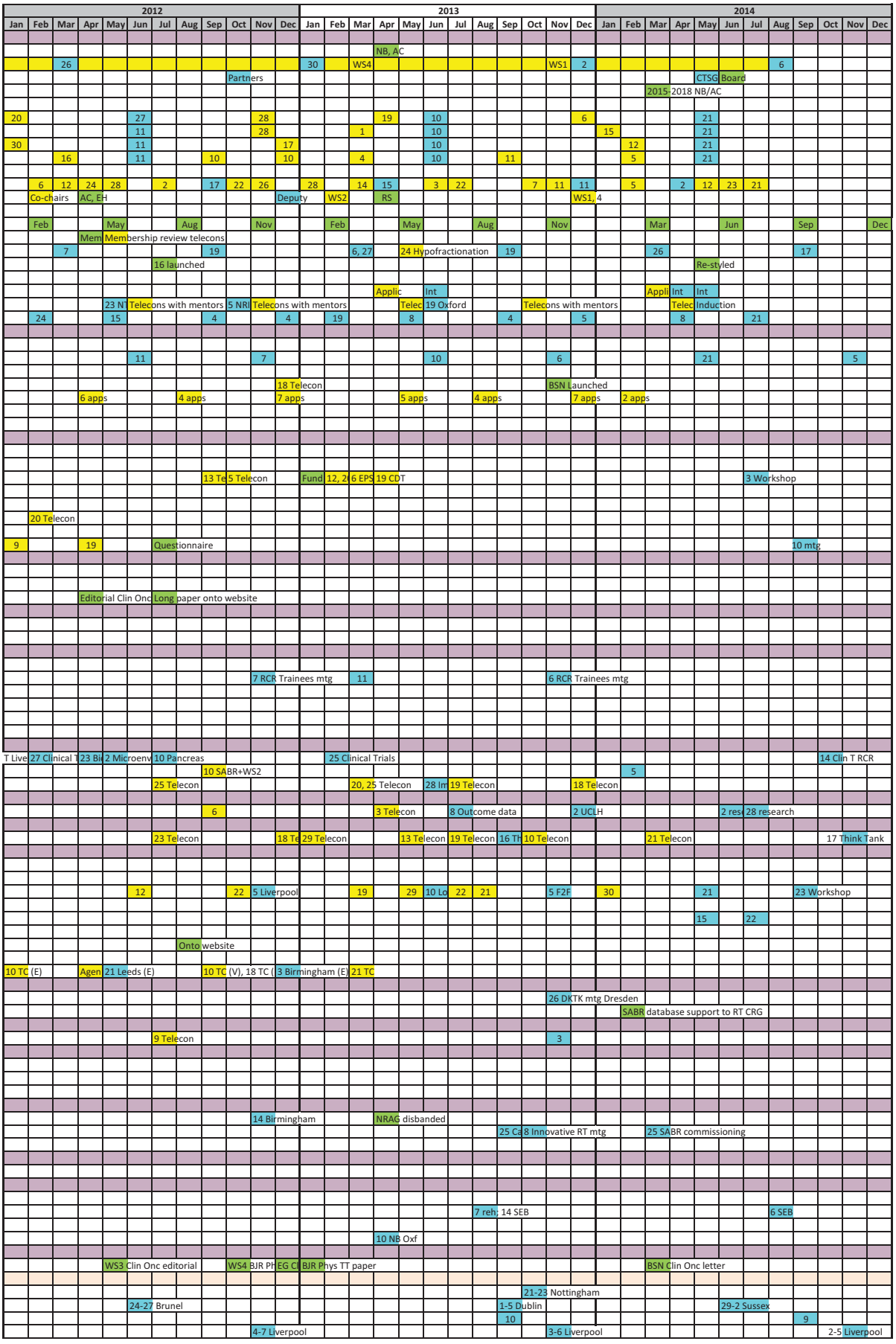
Appendix 2. CTRad Executive Group members and their links to other national radiotherapy/research initiatives

Chair	**Prof. Neil Burnet**	Member of National Commissioning Group Clinical Reference Panel for Proton Therapy; Department of Health Proton Special Interest Group; co-director of ESTRO Course on Advanced Treatment Planning
Deputy chair	**Prof. Anthony Chalmers**	Chair of RaDCom (CTRad and CRUK DDO); Deputy Chair of CTAAC; member of Brain CSG; Chair of Novel Agents Subgroup of Brain CSG; Scientific Committees of the European Association for Neuro-Oncology (EANO) and the European Society for Therapeutic Radiation Oncology (ESTRO); Chair of Scottish Radiotherapy Research Forum (SCoRRF)
Ex officio	**Prof. Tim Illidge**	Member of NCRI Clinical and Translational Strategy Group
Ex officio	**Prof. Tim Maughan**	Clinical Director of the CRUK/MRC Oxford Institute for Radiation Oncology; member of RCR Council
Ex officio	**Prof. Gillies McKenna**	Director of the CRUK/MRC Oxford Institute for Radiation Oncology
Ex officio	**Prof. Ian Stratford**	Member, Committee of Medical Aspects of Radiation in the Environment (COMARE), Department of Health; Council Member, International Association for Radiation Research
Workstream 1 co-chair	**Prof. Kaye Williams**	Past Chair of the Association for Radiation Research (2012-14)
Workstream 1 co-chair	**Prof. Kevin Harrington**	Member of Head and Neck CSG; Chair of Systematic Therapy and Radiotherapy Subgroup of Head and Neck CSG; CTRad's link for the CRUK National Radiotherapy Awareness Initiative
Workstream 2 co-chair	**Prof. Ruth Plummer**	Chair of CRUK New Agents Committee; member of Skin Cancer CSG
Workstream 2 co-chair	**Dr Ricky Sharma**	Member of Colorectal CSG; member of NHS England Selective Internal Radiotherapy Implementation Group for Commissioning through Evaluation; member of RCR Faculty Board; member of NCRI Cancer Conference Scientific Committee
Workstream 3 co-chair	**Prof. Chris Nutting**	Member of Head and Neck CSG; member of the RCR Professional Board and organises the national oncology meeting programme; member of the Board of British Association of Head and Neck Oncologists
Workstream 3 co-chair	**Dr Emma Hall**	Member of Prostate CSG; member of CRUK CTAAC
Workstream 4 co-chair	**Dr Ran Mackay**	Member of NCRI RTTQA Management Group
Workstream 4 co-chair	**Dr John Staffurth**	Member of the RCR/IPEM/SCoR Radiotherapy Board; Chair of the IMRT working group; member of Prostate CSG; member of RTTQA Management Group; member of SABR Consortium
Consumer	**Dr Helen Bulbeck**	Member of Brain CSG; member of Consumer Liaison Group; member of Specialised Services CNS tumour Clinical Reference Group
Consumer (outgoing)	**Mr Alfred Oliver**	Member of Colorectal CSG; member of Consumer Liaison Group
Consumer (incoming)	**Mrs Hilary Stobart**	Member of Gynaecological Cancer CSG; member of Consumer Liaison Group
Funder representative	**Ms Kate Law**	Responsible for CRUK CTAAC; member of NCRI CTSG; CRUK representative on UKCRC Board; observer on NIHR HTA Clinical Evaluation and Trials Board.

Appendix 3. Record of CTRad activities

	2008	2009												2010												2011										
	Nov	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
National leadership (1) and repeat funding																																				
Chair and programme manager appointment	TM	CSG	CC					TI									JM							TI, NB												
Chair and Deputy weekly telecons and F2F								22	3		12, 2	12 V	3 W	12 WS1				25		13	16	8, 16				17							16				
Board, Partners, Subgroup/CTSG meetings											Board											BSG	Board														
Extension proposal																												2012-2015 TI/NB									
Workstreams																																				
WS1 meetings								7						12					30						16						28					
WS2 meetings								7		18		9		18		12				16				1					13						1	
WS3 meetings								3, 7			6				1				21					8					21					3		
WS4 meetings								7			20		9		11					8						26					24				17		
Exec Group																																				
Exec Group telecon, F2F meetings					29	19	16	7, 28		28	29		11	11	22	16	12	20	29	15		9	18		20		7	15	18	23	20			6	10	28	
Deputy and co-chair rotations					Deputy and co-cha			TB,	S, KH, RP, CN, CB, NB, RM											Deputy			WS1,	KW, JS													
Members																																				
CTRad bulletin																												Mar							Oct	
Membership rotation					Members			7 LAUNCH																							Manuf					
Link with CSGs - CSG Chairs Forum												24				1								21			17			30					11	
CTRad website																																				
Consumers																																				
Consumer recruitment round					App	Ints						App	Ints													Appli	Ints									
CTRad-specific training / Educational visit						14 Cance		2 Briefin	23 B	5 Bi	24 Intro clin trials				8 Networki			18-19	10 Networking			RT Update RMH							18-19 Intro Cance		15 Manchester				
Consumer group meeting																																		18		12
Trial development support																																				
Peer review & development																																				
Proposals guidance meetings															12									10											9	
RADCAS																																				
Biomarker / Support Network																																				
CTAAC and funders reviews																	3 apps				3 apps				4 apps				1 app				5 apps			2 apps
Information & resources																																				
CaRD review; funding stream document																																				
Physics and RT support (2)																																				
Academic radiotherapy physics																																				
Physics think tank - meeting and paper																		28 Te	14 SH		26 TC									9 Tele	4 Thi	22 Telecon		20 Te	28 funders	
Physics grants / educational																																				
RTTQA																																				
Accountability report to WS4																																				
Funding bids / renewal					28 SS	DC		1 Planning													31 Planning															
Preclinical QA support (WS1+WS4)																																				
Telecon, questionnaire and meetings																																				
Trial methodology (3)																																				
MRC methodology workshop																		27																		
Planning telecon										14			8			31																				
MRC methodology editorial / paper																																				
Data on patterns of RT practice - NCIN national RT dataset (RTDS) (4)																																				
Planning of RT research questions																																				
Database outputs become available																													RTDS							
Academic career development (5)																																				
Academic radiation oncology think tank meeting																																				
Meeting, pre-work/SWOTs															15				17 RCR Acad Tr com									9	13 RCR Trainees mtg						
RCR Mentoring scheme																												Launched								
FSF evaluation																																				
Collection of data																										x										
Liaison with DH FSF scheme													3 DC														x									
National collaboration workshops																																				
Nationwide																							4, 29	(Tume	2, 13,	17 (Signal Transduction, Molecular RT, Biotherapy)										5 SBR
SABR																																				
Imaging																																		4 Imaging		
Proton therapy research																																				
Telecons, meetings																																				
Radiographers - Training, career development & resources (6)																																				
Think Tank meeting																																				
Industry engagement / drug-RT combinations (7)																																				
Radiotherapy-Drug combinations																																				
Radiotherapy-Drug Conference + preparation															29 Telecon											13 Te	3-5 Manchester									
RaDCom, DDO, ECMC CA																																				
Industry meetings																																				
Pharma								6																												
Tumour site review papers																																				
Printed copies and onto CTRad website																													Printed copies							
Meeting with RT equipment manufacturers																																				
General and companies																										31 Telecon			20							
Databases																																				
Discussion meetings (national and international)															11		8																			
Support for national database																																				
Molecular radiotherapy																																				
Committee / discussion / workshop															11 F2F									2 Telecon										21 Telecon		
NHS clinical oncologist engagement (8)																																				
FSF																																				
FSF results - requested from members	x																								x											
FSF outcomes - information to NCAT														x												x										
NHS implementation of research advances (9)																																				
NCAT NRAG NRIG NRAI							8					13							11 NRAI			10	8, 12		21 TI	2011	Year of RT		18 Workforce						2 Birm	
NHS England / CRUK (post-April 2013)																																				
Case to DH			23			18				28																										
Metrics																																				
Patient accrual analyses from NIHR:CRN portfolio data																																				
Building on CR-UK/MRC investment (10)																																				
Interaction with CR-UK																																				
Telecon/F2F meetings																																				
Meeting with MRC																																				
Meeting with centres																																				
CTRad publications																																				
Peer-reviewed journals					TM	Clin Onc editorial																	EG	Clin Onc editorial							EG	BJC Preclin guidelines			
Relevant external meetings, workshops and conferences not organised by CTRad																																				
UKRO					6-8 Cardiff																									11-13 Manchester						
ARR							22-24 Glasgow												28-30 Oxford											28-1 Nottingham						
RCR Annual meeting																						14											19			
NCRI											4-7 Birmingham													7-10 Liverpool											6-9 Liverpool	

Key
Face-to-face
Teleconference
Highlighted boxes without numbers meant multiple meetings that month
Other events or activities

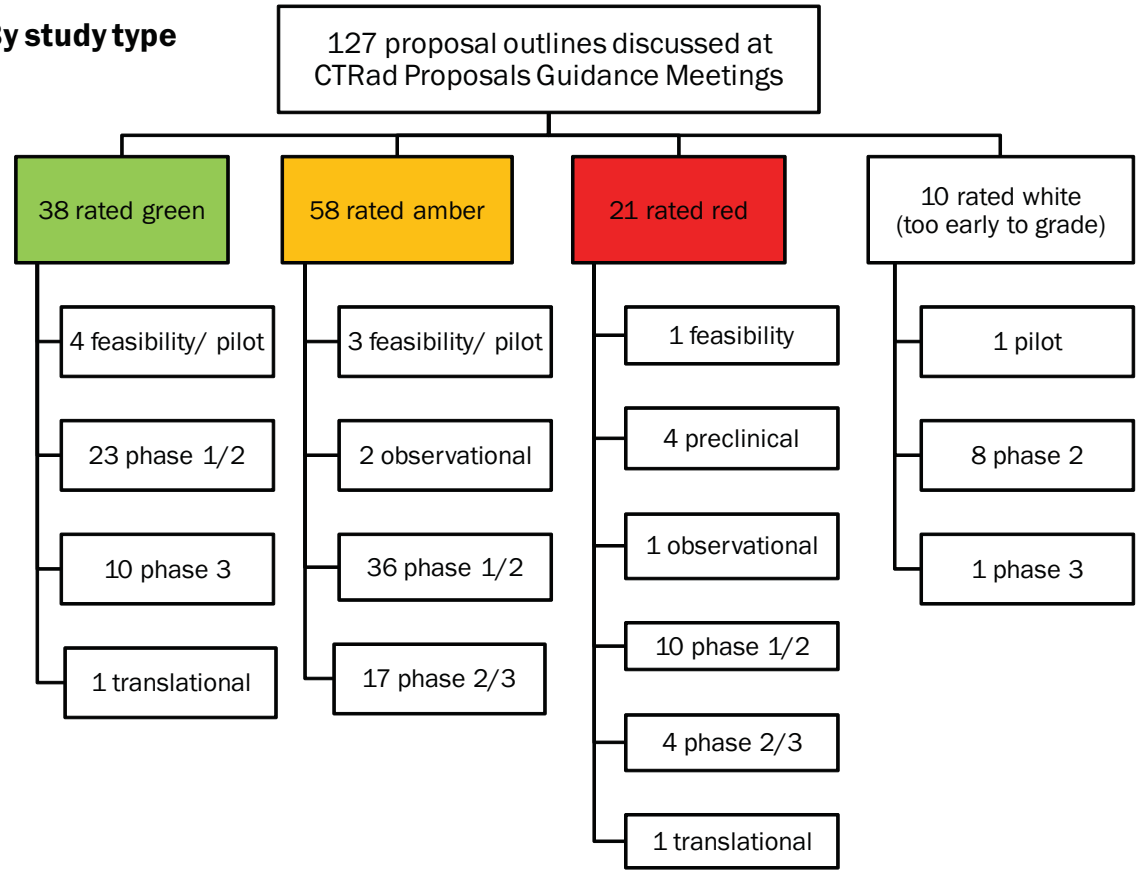


Appendix 4. Metrics as agreed with CTRad funders at the start of the second funding period

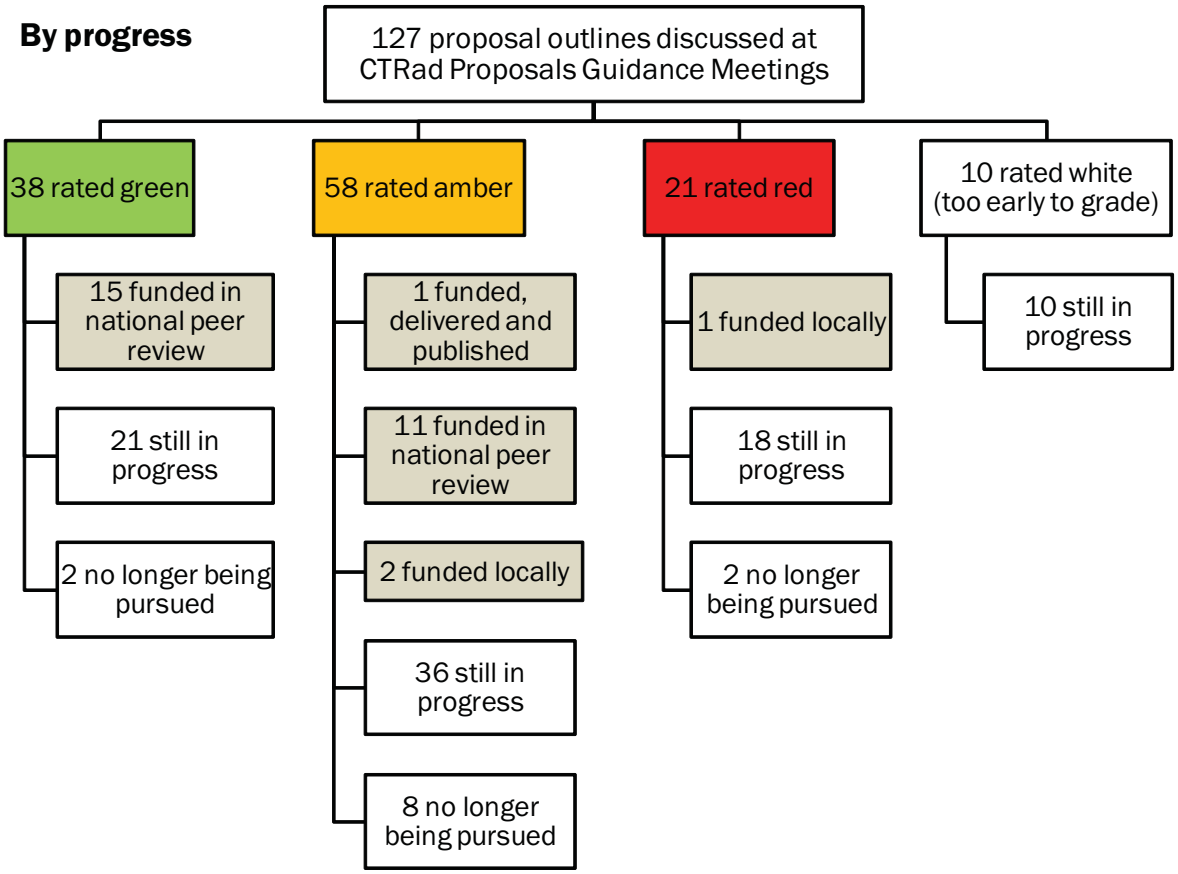
	Data source	2008–09	2009–10	2010–11	2011–12	2012–13	2013–14
Patient accrual in radiotherapy trials in the four countries of the UK	Cancer portfolio spreadsheet from NIHR:CRN (by financial year; searching by radiotherapy CSG or associated keyword)	England: 2855 Scotland: 208 Wales: 196 N Ireland: 29 Total: 3288	England: 3443 (+21%) Scotland: 227 (+16%) Wales: 132 (-32%) N Ireland: 55 (+90%) Total: 3857 (+17%)	England: 3729 (+8%) Scotland: 229 (+1%) Wales: 156 (+18%) N Ireland: 34 (-38%) Total: 4148 (+8%)	England: 4307 (+16%) Scotland: 330 (+44%) Wales: 183 (+17%) N Ireland: 128 (+276%) Total: 4948 (+19%)	England: 6174 (+43%) Scotland: 311 (-6%) Wales: 371 (+103%) N Ireland: 60 (-53%) Total: 6916 (+40%)	(Data not yet available)
Proportion of radiotherapy trial applications awarded by CTAAC	CRUK Trials Team; includes trials funded and endorsed; excludes extension applications	5/13 RT applications accepted (38%) (Overall CTAAC acceptance rate: 54%)	10/13 RT applications accepted (77%) (Overall CTAAC acceptance rate: 59%)	5/14 RT applications accepted (35%) (Overall CTAAC acceptance rate: 72%)	4/10 RT applications accepted (40%) (Overall CTAAC acceptance rate: 53%)	15/22 RT applications accepted (68%) (Overall CTAAC acceptance rate: 66%)	(Data incomplete for year)
Proportion of radiotherapy programme grants at CTRC	CRUK Trials Team; funding stream available from 2011 onwards	–	–	10/32 applications were RT-related (31%) 2/8 proposals invited to full application were RT-related (25%)	[Scheme no longer open]	[Scheme no longer open]	[Scheme no longer open]
Proportion of new radiation-related grants awarded by the MRC	MRC Cancer Programme Manager	Not available	1/14 RT research grants successful 1/3 RT fellowships successful	2/16 RT research grants successful 3/7 RT fellowships successful	3/13 RT research grants successful 1/6 RT fellowships successful	2/11 RT research grants successful 0/3 RT fellowships successful	3/17 RT research grants successful 0/4 RT fellowships successful
Number of radiation-related programme grants awarded by NCRI Partners	NCRI CaRD; by financial year	–	7 fully related 2 partly related	9 fully related 2 partly related	6 fully related 1 partly related	7 fully related 1 partly related	(Data not yet available)
Radiation-related grant spend in the UK by NCRI Partners (excludes core/centre funding and equipment)	NCRI CaRD; by financial year	–	£5.9m	£6.7m	£7.9m	£7.9m	(Data not yet available)
Number of new outline proposals reviewed by CTRad workstream	CTRad all-workstream meetings (data on trials funded to be added based on investigator feedback, once received)	N/A	Preclinical: 2 Phase I/II: 17 Phase III: 9 Translational: 1 Total: 29	Phase I/II: 16 Phase III: 2 Total: 18	Feasibility / pilot: 2 Phase I/II: 21 Phase III: 7 Prospective study: 1 Total: 31	Observational: 1 Feasibility: 2 Phase I/II: 14 Phase III: 7 Translational: 1 Total: 25	
Published radiotherapy/radiobiology papers from CTRad members	Annual reporting from CTRad members (editorials, reviews and original research)	[Resources limit capture; would require automated data collection]	[Resources limit capture; would require automated data collection]	[Resources limit capture; would require automated data collection]	[Resources limit capture; would require automated data collection]	[Resources limit capture; would require automated data collection]	[Resources limit capture; would require automated data collection]

Appendix 5. Proposals reviewed at CTRad Proposals Guidance Meetings to date (April 2014)

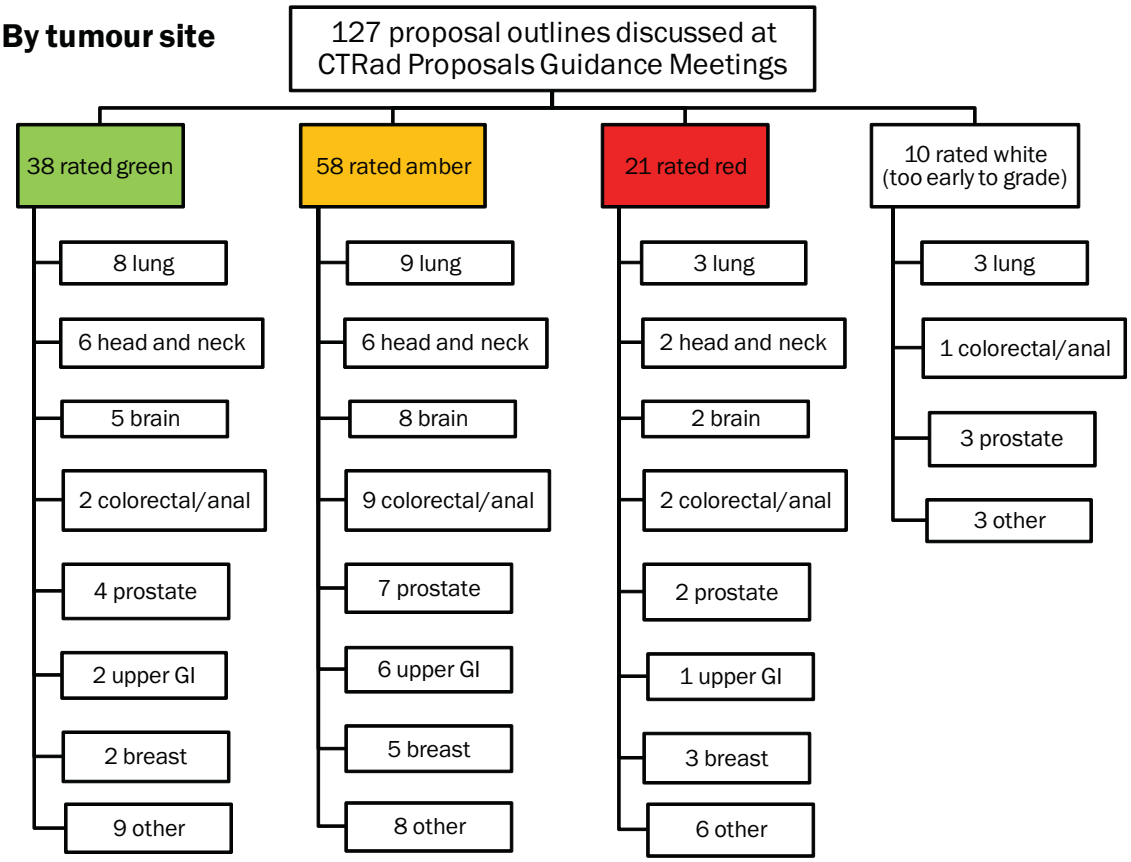
By study type



By progress



By tumour site



Appendix 6. Description of molecular radiotherapy

Molecular radiotherapy, or molecular radionuclide therapy (MRT), is the selective delivery of radioactive nuclides that emit energetic particles to target and destroy cancer cells.

Innovations in recombinant protein engineering, targeted therapies, conjugation chemistry and nanotechnology are providing new methods for more effective delivery of MRTs to cancer cells. When properly combined with tailored patient dose selection and new applications of dosimetry, MRT is a model for personalised anti-cancer therapy based on state-of-the-art imaging.

Although the delivery of MRT has many technical, logistical and regulatory challenges, further development in this area is likely to make an important contribution to patient care. Indeed, breakthrough innovations such as radium-223 dichloride are already changing clinical practice in the NHS.

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Clinical and Translational Radiotherapy
Research Working Group

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