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Original Article

Radiating Excellence: A Decade of Pioneering Radiotherapy Trials and Collaborative Leadership at Leeds Cancer Research UK Clinical Trials Unit

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Abstract

Recently, there has been considerable development in radiotherapy technologies and novel drug-radiotherapy combinations, with the potential to develop more effective and less toxic treatments for patients. There is a need to evaluate these approaches through clinical trials, and clinical trials units (CTUs) are ideally positioned to design and deliver these studies. Over the past 10 years, the Leeds Cancer Research UK CTU has developed a flagship portfolio of radiotherapy clinical trials, which encompass novel drug-radiotherapy combinations, radiotherapy technologies and optimising radiotherapy dose. Key to the success of the portfolio has been an emphasis on multidisciplinary collaborations, career development of future leaders in clinical trials, understanding the funding landscape, engagement with discovery and translational scientists, and keeping patients at the heart of our research. Moving forward, the priorities of the CTU are to build on this strong foundation with a pipeline of impactful and scientifically rich clinical trials, which will continue to shape the radiotherapy research landscape.

Key words: Clinical trials; clinical trials unit; radiotherapy

Introduction

Radiotherapy has a critically important role in the curative treatment of cancer, often as part of multimodal therapeutic approaches [1]. Recently, there have been considerable developments in radiotherapy technologies, while the potential from novel drug-radiotherapy combinations has been highlighted. These advances present opportunities to develop more effective and less toxic treatments and to integrate radiotherapy into precision medicine approaches. Evaluation of these strategies through impactful clinical trials is essential to optimise standards of care across the UK and internationally [2]. Clinical trials units (CTUs) are ideally positioned to leverage their multidisciplinary expertise in clinical trial design, funding, set-up, conduct and analysis, especially for complex, multicentre studies [3].

This article will focus on the experiences of the Leeds Cancer Research UK (CRUK) CTU (herein referred to as the CTU) over the past decade in developing and delivering an outstanding portfolio of radiotherapy clinical trials, with the aim of providing insights for the wider radiotherapy research community. We outline our portfolio of clinical trials and associated research, discuss key factors contributing to its successful delivery and sustainability, and summarise challenges and future priorities.

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Overview of the Radiotherapy Portfolio

The CTU has over 30 years of experience in the development and delivery of cancer clinical trials. This institutional expertise across multiple disease settings underpinned the development of the radiotherapy portfolio. Since 2014, the portfolio has grown to encompass multiple trials across anal, brain, lung, prostate and rectal cancers, with a focused, strategic pipeline of future trials in development. As illustrated in the Figure, the portfolio encompasses multicentre phase I through to phase III randomised controlled trials (RCTs). Internationally leading trial platforms CONCORDE (ISRCTN10142971) and PLATO (ISRCTN88455282) each contain multiple trials that are addressing specific clinical research questions and/or disease populations. Translational richness is enabled across the portfolio through sample collections that support discovery and translational research. Trial designs are tailored to specific, clinically relevant research questions, with a focus on three key clinical research priorities: novel drug-radiotherapy combinations, radiotherapy technologies and optimising radiotherapy dose.

Novel Drug-Radiotherapy Combinations

In recent years, advances in cancer biology have led to considerable progress in the development of targeted and immunomodulatory systemic therapies [4]. The combination of novel agents with radiotherapy holds great promise to enhance the biological effects of radiation and drive personalisation of therapy using biomarker-based stratification [5,6]. Clinical trials are needed to develop evidence for these approaches and to define the patient populations most likely to benefit. A number of early phase trials of novel agent-radiotherapy combinations are in progress, although few combinations have received clinical approval to date [4]. Key challenges include the need for supporting pre-clinical normal tissue and anti-tumoural activity data to support the application of novel agents in curative-intent settings, the potential for increased or unexpected toxicities and funding barriers. The most appropriate radiotherapy volume, dose and sequencing also require careful consideration. In addition, complex statistical designs for dose-finding studies are required to account for both acute and later onset toxicities while ensuring

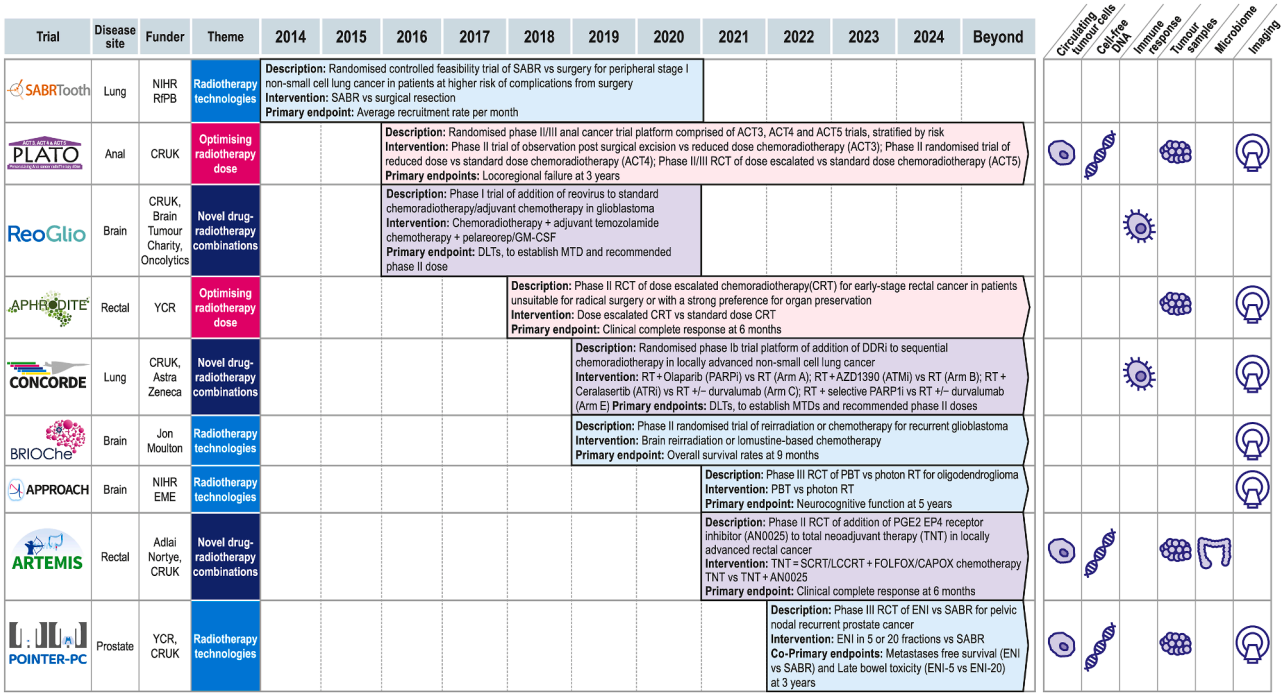

Figure 1. A visual summary of the CTU radiotherapy trials portfolio
ATMi, ataxia telangiectasia mutated protein kinase inhibitor; ATRi, ataxia-telangiectasia and Rad3 related serine/threonine kinase inhibitor; CAPOX, capecitabine and oxaliplatin; CRT, chemoradiotherapy; CRUK, Cancer Research UK; DDRi, DNA damage response inhibitor; DLTs, dose-limiting toxicities; ENI, Extended Nodal Irradiation; FOLFOX, folinic acid, 5-fluorouracil and oxaliplatin; GM-CSF, granulocyte macrophage colony-stimulating factor; LCCRT, long course chemoradiotherapy; MTDs, maximum tolerated doses; NIHR EME, National Institute for Health and Care Research Efficacy and Mechanism Evaluation; NIHR RfPB, National Institute for Health and Care Research for Patient Benefit; PARPi, poly (ADP-ribose) polymerase inhibitor; PARP1i, poly (ADP-ribose) polymerase 1 inhibitor; PBT, proton beam therapy; PGE2 EP4, prostaglandin E2 EP4 receptor; RCT, randomised controlled trial; RT, radiotherapy; SABR, Stereotactic Ablative Radiotherapy; SCRT, short course radiotherapy; TNT, total neoadjuvant therapy; YCR, Yorkshire Cancer Research.

efficient trial accrual. Multidisciplinary expertise and collaboration are required to overcome these challenges. In 2018, the National Cancer Research Institute (NCRI) Clinical and Translational Radiotherapy Research group (CTRad) published recommendations for drug-radiotherapy clinical trials, on which CTU members/staff were co-authors [5,6]. Building on this, CTRad's workstream for early phase clinical trials research, co-led by the CTU Director, developed a roadmap for optimal design of phase I studies of novel drug-radiotherapy combinations, which included consideration of appropriate methodologies [7].

The CTU's phase I drug-radiotherapy expertise is demonstrated with the design, development and delivery of CONCORDE, a CRUK flagship phase I trial platform for novel agent-radiotherapy combinations developed in partnership with AstraZeneca [8]. In unresectable NSCLC, a promising approach is to combine novel DNA damage response inhibitors (DDRi), that target different components of the DNA damage repair pathway, with radiotherapy [6,9]. CONCORDE is the first phase I trial platform in NSCLC to test multiple DDRi-radiotherapy combinations within individual trials to establish toxicity profiles and identify recommended phase II DDRi doses [8]. Use of the Time-To-Event Continual Reassessment Method (TiTE-CRM) for dose finding enables assessment of later onset toxicities which may occur with drug-radiotherapy combinations, while facilitating continuous study accrual [10]. Key to the success of CONCORDE has been extensive, multidisciplinary collaboration and partnership, including medical and clinical oncology, translational scientists, methodologists, patients, funders and industry. Close collaboration with pharmaceutical industry partners has been particularly crucial to add new agents to the platform as they become available.

ReoGlio (ISRCTN70044565) and ARTEMIS (ISRCTN15384496) are further examples of trials that leveraged industry and additional funding sources to enable evaluation of novel strategies to enhance the efficacy of radiotherapy-based treatments. ReoGlio is a phase I trial, supported by charitable and industry funding, which explored safety and dose finding for an oncolytic virus palareorep combined with standard chemoradiotherapy for glioblastoma [11,12]. In rectal cancer, there is increasing interest in organ preservation with the potential to avoid radical surgery, either opportunistically or pre-planned, where a clinical complete response (cCR) to neoadjuvant systemic anti-cancer therapies and/or (chemo)radiotherapy is obtained [13]. In the phase II RCT ARTEMIS, industry partnership with Adlai Nortye has enabled evaluation of the addition of a novel prostaglandin E2 EP4 inhibitor (AN0025) to standard total neoadjuvant treatment for locally advanced rectal cancer to assess its impact on cCR rates.

Radiotherapy Technologies

The focus on radiotherapy technologies aims to improve efficacy/reduce toxicity from radiotherapy in primary and recurrent disease settings. This includes delivery of further radiotherapy close to/within a previously irradiated volume, known as reirradiation. Key to successful delivery of these studies has been collaboration between the CTU and radiotherapy research teams in Leeds.

APPROACH (ISRCTN13390479) is a phase III RCT of Proton Beam Therapy (PBT) versus photon radiotherapy in oligodendroglioma (ODG) [14]. It was one of three initial UK PBT RCTs alongside the Institute of Cancer Research Clinical Trials and Statistics Unit-led TORPEdO and PARABLE trials, and represents a collaboration between the CTU, multidisciplinary radiotherapy teams, neuroscientists, the two UK NHS PBT centres and the National Radiotherapy Trials Quality Assurance (RTTQA) Group. APPROACH also benefitted from support of the NCRI CTRad PBT Clinical Trials Strategy group and experience gained within the UK radiotherapy clinical trials community in developing TORPEdO and PARABLE, shared through a national PBT trials "buddy group" established across institutions within CRUK's Advanced Radiotherapy Technologies Network (ART-NET) [15].

POINTER-PC (ISRCTN11089334) is a phase III RCT evaluating the impact of different radiotherapy volumes in pelvic nodal recurrent prostate cancer [16,17]. Prostate cancer pelvic nodal recurrences typically occur close to/within previously delivered primary/post-operative radiotherapy volumes, and the trial design, including the radiotherapy planning guidelines developed in combination with RTTQA, built on reirradiation research at Leeds within CRUK ART-NET and CRUK Radiation Research Centre of Excellence (RadNet) [18,19].

The CTU is also delivering the phase II randomised BRIOChe trial (ISRCTN16052954) of brain reirradiation or chemotherapy for recurrent glioblastoma following prior chemoradiotherapy [20]. Treatment planning for reirradiation is complex, with challenges in accounting for anatomical change, fraction size effects and accumulated radiation doses to normal tissues across two courses of radiotherapy [21,22]. POINTER-PC and BRIOChe reflect internationally recognised expertise in reirradiation in Leeds, with reirradiation a core theme of the Leeds CRUK Radiation Research Centre of Excellence (RadNet Leeds). The radiotherapy planning guidelines and quality assurance (QA) programmes for POINTER-PC and BRIOChe will facilitate consistent approaches to reirradiation planning and treatment delivery, provide much-needed evidence regarding safety and efficacy of reirradiation and potentially support its wider clinical implementation. Building on this, the CTU is supporting development of further clinical trials in reirradiation through Second-Time Around: Reirradiation Treatment Using Protons or Photons (STA:RTUPP), a National Institute for Health and Care Research (NIHR) Programme Development Grant (NIHR206942).

Optimising Radiotherapy Dose

The portfolio contains two studies investigating radiotherapy dose, including strategies of dose escalation to improve disease outcomes and de-escalation to reduce

toxicity. PLATO is a world-leading anal cancer trial platform comprised of three separate phase II/III trials (ACT3, ACT4, ACT5) with endpoints of 3-year locoregional failure and toxicity [23]. PLATO is investigating treatment intensification/de-intensification, stratified by disease risk to allow inclusion of the full spectrum of localised/locally advanced anal cancer. ACT3 and ACT4 are phase II trials in patients with low and intermediate-risk anal cancer investigating whether lower dose chemoradiotherapy (ACT3 and ACT4) and, for ACT3, the selective use of a smaller target volume, result in reduced toxicity without compromising locoregional failure rates. Promising initial 6-month outcomes were recently reported for ACT4 [24]. cCR rates for standard and lower dose chemoradiotherapy were 84% versus 85%, respectively. Severe acute toxicity rates were 46% versus 35%, respectively. ACT5 is a phase II/III trial in patients with locally advanced anal cancer, investigating whether dose escalated chemoradiotherapy improves locoregional failure rates with acceptable toxicity. APHRODITE (ISRCTN16158514) is a phase II RCT in rectal cancer, which is investigating whether radiotherapy dose escalation improves cCR rates at 6 months compared with standard long course (chemo)radiotherapy [25]. Little is known about whether patients would accept increased risk of radiotherapy toxicity for a better chance of tumour response. APHRODITE therefore incorporates a sub-study using discrete choice experiments to examine trade-offs that participants make when considering these factors.

Multidisciplinary Expertise and Collaborations

Radiotherapy is a complex intervention, and radiotherapy clinical trials require multidisciplinary approaches to set up, and rigorous QA of treatment pathways. This can lengthen setup times and create barriers to site activation and participant recruitment, exacerbated by challenges in availability and resources for dedicated research staff and an increasingly competitive funding landscape [2,3,26–29]. Multidisciplinary working across academic and NHS institutions, in combination with pharmaceutical industry, has been key to addressing these challenges and to build the radiotherapy portfolio. Shared learning and collaboration across each of the trials has enabled refinement of processes for efficient trial design, conduct and analysis. The portfolio has developed around clinical and technical expertise of the chief investigators (CIs) who clinically lead individual trials, which reflects the focus on particular disease sites and radiotherapy techniques. In addition, methodological expertise within the CTU has informed use of specific trial designs, including trial platforms and adaptive designs, with assigned methodological leadership for each trial. The CTU comprises specialist teams of trial managers, methodologists, statisticians, data managers, information specialists and patient and public involvement and engagement (PPIE) experts. There are, however, challenges in recruitment and retention of individuals within these professions [30]. Building the multidisciplinary team, leveraging its skills and expertise and supporting career development, has been a key focus.

CTU collaborations with clinical oncology and medical physics leads and RTTQA to develop trial radiotherapy guidelines and benchmarking and credentialling have been a critical part of trial development within the portfolio, especially for studies using advanced radiotherapy techniques [28]. Consideration of how RTTQA can be integrated into trial delivery is essential. For CONCORDE, RTTQA representatives attend safety review committee (SRC) meetings to present radiotherapy planning data, which can aid with novel agent versus radiotherapy toxicity attribution.

Radiotherapy is frequently part of multimodality therapeutic approaches, and expertise regarding these therapies is reflected within trial management groups (TMGs) and independent oversight committees. Selection of study CIs is also important, and several CTU radiotherapy trials have co-CIs who bring specific expertise to these roles. PLATO and CONCORDE are complex trial platforms, with different patient populations eligible for ACT3, ACT4 and ACT5 in PLATO and different novel agent-radiotherapy combinations in CONCORDE. Both PLATO and CONCORDE benefit from co-leads, drawn from multiple institutions, for individual trials within each platform, which provides specific expertise and enables sharing of workload. APHRODITE, examining radiotherapy dose escalation, has co-CIs with clinical oncology and medical physics expertise, respectively. CONCORDE and ARTEMIS, investigating radiotherapy-novel drug combinations, have co-CIs from clinical oncology and medical oncology. This collaborative approach supports development of trial protocols, ensures comprehensive oversight and aids interpretation and attribution of radiotherapy- and drug-related toxicities.

Developing Strong Clinical Researchers and Future Leaders in Trials

The CTU is focused on developing and nurturing staff across disciplines, which has been central to the success of the portfolio. POINTER-PC has co-CIs, with a senior CI supporting a junior CI who is a CRUK Clinical Trial Fellow, an approach that enablest he sharing of responsibilities for trial activities and provides an important mentoring relationship. The CTU has a track record in successful CRUK Clinical Trial Fellowships, with six current or previous fellows in clinical and medical oncology and clinical radiology. Few UK clinical oncologists hold clinical academic posts, and these fellowships provide important practical experience and training opportunities for developing the next generation of CIs [31]. Clinical trial fellows have played a central role in multiple aspects of the trial process, including trial design, funding applications, set-up (including protocol and radiotherapy guideline development), conduct, analysis and translational sub-studies. CRUK's Leeds-Manchester ARCTIC Clinical PhD Programme has enabled research that informed the design of new trials and development of sub-studies to add value to existing trials [32,33]. Recently appointed clinical radiology

clinical trial fellows demonstrate the strengthening of collaborative links with academic radiology and interventional oncology, with the potential to enhance imaging-related translational research within the portfolio. The CTU is also dedicated to nurturing future leaders in methodology and trial and data management. The CTU director's PhD, focused on phase II oncology trials, was instrumental in developing earlier phase trials within the CTU and, subsequently, the radiotherapy portfolio [34]. Building directly on experiences in CONCORDE, a CRUK-funded PhD student is currently investigating dose escalation methodologies within phase I dose-finding studies of novel drug-radiotherapy combinations.

The Funding Landscape

The CTU has established an important strategic partnership with CRUK, which has provided institutional investment and enabled the development of the radiotherapy portfolio as a core theme for CRUK CTU infrastructure funding. It also strongly aligns with other CRUK investments into radiation research at Leeds, including ART-NET and RadNet. The portfolio is supported through a broad range of funders, reflecting individual research priorities and enabling a sustainable, multifaceted suite of trials and associated translational elements. Trial funders include UK government funding (NIHR, e.g. Efficacy and Mechanism Evaluation (EME) for APPROACH), charitable organisations (CRUK for PLATO and CONCORDE, Yorkshire Cancer Research for APHRODITE and POINTER-PC and Jon Moulton Charity Trust for BRIOChe) and pharmaceutical industry (AstraZeneca for CONCORDE and Adlai Nortye for ARTEMIS).

The decision of where to seek funding is influenced by the strategic priorities of each funding body. For example, PLATO contains an embedded CRUK-funded Biomarker Project Award which aligns with CRUK's strategic objective to learn as much as possible from participants recruited to the trial [35]. APPROACH, funded by the NIHR's EME programme, contains a mechanistic component to improve the understanding of relationships between the spatial distribution of radiation dose and the development of neurocognitive dysfunction. CONCORDE's CRUK funding enabled the trial platform to be established, while industry funding was leveraged for DDRi agents within individual study arms.

The CTU radiotherapy portfolio continues to successfully fund and conduct trials despite the small proportion of cancer research funding spent on radiotherapy (2.8% of global cancer research funding and ~5% of CRUK's research spend) [36,37].

Discovery and Translational Science

The portfolio trials contain a variety of embedded discovery and translational science, typically funded through additional grants. Collaboration with scientists across biology, pathology and imaging has been critically important in enabling this research, which will explore questions regarding treatment personalisation and mechanisms of toxicity.

As part of PLATO's CRUK Biomarker Project Award, digital pathology and next-generation sequencing for biopsy specimens will facilitate analysis of prognostic p16/tumour infiltrating lymphocyte biomarkers across ACT3, ACT4 and ACT5, with an aspiration to inform future treatment escalation/de-escalation stratification [38]. Collaboration with CRUK's National Biomarker Centre will also enable analysis of circulating tumour DNA and circulating tumour cells as potential biomarkers of response assessment and early detection of disease relapse. In POINTER-PC and ARTEMIS, CRUK Sample Collection Awards will facilitate future translational research into the prognostic value of circulating biomarkers pre and post-radiotherapy, to identify patients who may benefit from treatment intensification. Across the portfolio, there is a strong focus on digital pathology in collaboration with the Leeds Institute of Medical Research Division of Pathology and Data Analytics.

Investigation of underlying mechanisms of radiotherapy-related toxicity and potential biomarkers are a focus for other trials. In APPROACH, analyses of PBT and photon radiotherapy plans to understand how the spatial distribution of radiation dose across brain sub-regions, and radiotherapy technique, is associated with neurocognitive dysfunction, could inform future personalisation of radiotherapy planning to spare dose-sensitive sub-regions [39]. In POINTER-PC, longitudinal analysis of tissue-specific DNA methylation will be performed to identify biomarkers of normal tissue toxicity post-radiotherapy [40]. In CONCORDE, a translational programme (Trans-CONCORDE) will investigate underlying pathophysiology mechanisms of DDRi-radiotherapy toxicity and the impact of patient factors including frailty.

A key consideration is maintaining a line of sight to patient benefit from translational research. Biomarkers identified in PLATO will be further developed during the follow-on PLATO-2 trial platform. Similarly, insights into DDRi-radiotherapy toxicity gained during Trans-CONCORDE hold the potential for future stratification by particular DDRi agents and individualised dosing.

A major challenge to clinical trial-driven translational research is that it is often not funded alongside the main study, especially for biological sample collection, storage and analysis. Obtaining separate funding for sub-studies may delay trial set-up. Key to overcoming this is early engagement with discovery and translational collaborators, to embed these elements at an early time point and ensure that separate funding applications, if needed, can be aligned with the main study applications. The streamlining of this process by funders to meet clinical and scientific objectives, ideally within single applications, is needed. This is reflected in CRUK's new Clinical Research Funding Scheme, providing a modular approach to funding high-quality clinical research and associated translational research within the same scheme.

Patients at the Heart of Radiotherapy Trials

A key priority is to better understand patients' perspectives regarding treatments and their impact. The ability to use participant-reported instruments to provide more nuanced insights regarding toxicity and its impact has been well described, and all portfolio trials include Patient-Report Outcome Measure (PROM)-based toxicity endpoints and evaluation of Health-Related Quality of Life (HRQoL) [41].

PPIE has played a central role in shaping the portfolio, and the CTU has dedicated leadership roles for PPIE and equality, diversity and inclusion. Each study received a variety of PPIE inputs during the design phases, including from local PPIE groups, national research advisory meetings and dedicated workshops with patients and caregivers. In APPROACH, for example, a focus group with 15 patients previously treated with radiotherapy for ODG and their caregivers resulted in the modification of HRQoL assessments to ensure that greater information would be obtained regarding fatigue, and daily wellbeing, and caregiver perspectives were incorporated [42].

All portfolio studies include PPIE representation on the Trial Management Group (TMG) and oversight committees, providing ongoing perspectives and inputs on trial conduct, recruitment and key trial decisions. In CONCORDE, PPIE perspectives on toxicities have aided decision-making at SRC meetings. CONCORDE has supported PPIE partners by providing training on statistical models for dose finding and expected toxicities, along with debriefs before and after TMG/SRC meetings. Additionally, CONCORDE has six active PPIE members, which has improved meeting attendance and facilitated the distribution of workload [43].

PPIE partners also co-develop participant facing materials and support engagement activities to publicise trials. In PLATO, PPIE partners worked with the CI and trial manager to develop a summary of the ACT5 short term results for dissemination to participants. Across the portfolio, ongoing involvement of PPIE representatives throughout all stages of the trial process will be crucial in the interpretation and dissemination of trial results.

Lessons Learned and Future Opportunities

The radiotherapy portfolio is built on the CTU's established expertise in cancer clinical trials and its deep understanding of complex and innovative designs and the practicalities of delivery. The portfolio has significantly benefitted from strong engagement with radiotherapy research teams in Leeds and across national networks (CTRad, ART-NET, RadNet). Additionally, the CTU actively contributes to the wider radiotherapy research community through participation in working groups to develop guidelines and methodological recommendations, such as the phase I trial roadmap, and engaging in proposal review and knowledge-sharing across multiple institutions [7]. Multidisciplinary collaborations have been fundamental in the development of the portfolio, especially to engage with CIs with specific disease site/treatment expertise, to develop radiotherapy QA programmes and to maximise learning through discovery and translational research elements. Career development and training for clinicians, methodologists and other CTU specialists has and will continue to be a key priority, to ensure successful trial delivery now and in the future. Meaningful and supported PPIE, guided by PPIE experts, will remain critically important to keep patients at the heart of our trial design and conduct.

Moving forward, the CTU remains committed to increasing inclusivity of trials to improve participation and ensure findings are relevant to broader populations. The integration of real-world and clinical trial data also presents an opportunity to understand the impact of radiotherapy in broader populations and to gain longer-term insights. The portfolio's translational research will deepen the understanding of cancer biology, mechanisms of treatment and toxicities and support future precision medicine approaches.

The CTU strategy for the next 10 years is to develop a pipeline of impactful and scientifically rich trials aligned with our priorities of novel drug-radiotherapy combinations, radiotherapy technologies and optimisation of radiotherapy dose. By developing and nurturing the next generation of leaders, building and strengthening multidisciplinary partnerships, and keeping patients at the heart of our research, we will continue to shape the national and international radiotherapy research landscape and the treatments of the future.

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Author Contribution

1. guarantor of integrity of the entire study FS
2. study concepts and design FS, EMH, JK, SN, JBO, AS, JCW, DSM, SRB
3. literature research FS, EMH
4. clinical studies N/A
5. experimental studies/data analysis N/A
6. statistical analysis N/A
7. manuscript preparation FS, EMH, JK, SN, JBO, AS, JCW
8. manuscript editing FS, EMH, AH, JK, SN, JBO, AS, JCW, DSM, SRB

Conflict of 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.

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References

[1] Liu X, Zhang Y, Tang L-L, Le QT, Chua MLK, Wee JTS, *et al*. Characteristics of Radiotherapy Trials Compared With Other Oncological Clinical Trials in the Past 10 Years. *JAMA Oncol* 2018;4(8):1073–1079.
[2] Chalmers AJ, Chan C, Sebag-Montefiore D, Sebag-Montefiore D, Evans M, Chalmers A, *et al*. CTRad 10 Years On: From 10-point Plan to Top 10 Achievements. *Clin Oncol* 2020;32(1):9–12.
[3] Duley L, Gillman A, Duggan M, Belson S, Knox J, McDonald A, *et al*. What are the main inefficiencies in trial conduct: a survey of UKCRC registered clinical trials units in the UK. *Trials* 2018;19(1):15.
[4] Levy A, Massard C, Michiels S, Deutsch E. Innovative, early-phase clinical trials of drug–radiotherapy combinations. *Lancet Oncol* 2025;26(4):e190–e202.
[5] Ahmad SS, Crittenden MR, Tran PT, Kluetz PG, Blumenthal GM, Bulbeck H, *et al*. Clinical Development of Novel Drug-Radiotherapy Combinations. *Clin Cancer Res* 2019;25(5):1455–1461.
[6] Sharma RA, Plummer R, Stock JK, Greenhalgh TA, Ataman O, Kelly S, *et al*. Clinical development of new drug–radiotherapy combinations. *Nat Rev Clin Oncol* 2016;13(10):627–642.
[7] Brown SR, Hinsley S, Hall E, Hurt C, Baird RD, Forster M, *et al*. A Road Map for Designing Phase I Clinical Trials of Radiotherapy-Novel Agent Combinations. *Clin Cancer Res* 2022;28(17):3639–3651.
[8] Walls GM, Oughton JB, Chalmers AJ, Brown S, Collinson F, Forster MD, *et al*. CONCORDE: A phase I platform study of novel agents in combination with conventional radiotherapy in non-small-cell lung cancer. *Clin Translational Radiat Oncol* 2020;25:61–66.
[9] Harrow S, Hanna GG, Faivre-Finn C, McDonald F, Chalmers AJ. The Challenges Faced in Developing Novel Drug Radiation Combinations in Non-small Cell Lung Cancer. *Clin Oncol (R Coll Radiol)* 2016;28(11):720–725.
[10] Walker K, Hinsley S, Phillip R, Oughton JB, Murden G, Chalmers AJ, *et al*. Implementation of the Time-to-Event Continuous Reassessment Method Design in a Phase I Platform Trial Testing Novel Radiotherapy-Drug Combinations-CONCORDE. In: *JCO precis oncol* 2022:e2200133.
[11] Bagley SJ, Kothari S, Rahman R, Lee EQ, Dunn GP, Galanis E, *et al*. Glioblastoma Clinical Trials: Current Landscape and Opportunities for Improvement. *Clin Cancer Res* 2022;28(4):594–602.
[12] Short S, Kendall J, West E, Chalmers A, McBain C, Melcher A, *et al*. P11.64.A Long-term follow up and translational data from the ReoGlio phase Ib trial of GM-CSF and intravenous pelareorep (Reovirus) alongside standard of care in GBM. *Neuro-Oncol* 2022;24. ii73-ii73.
[13] Verrijssen AE, Ketelaers SHJ, Rutten HJT, Theuws J, Burger JWA, Cnossen JS. Organ Preservation in Rectal Cancer: An Overview of the Dutch Perspective and Recent Developments. *Clin Oncol (R Coll Radiol)* 2023;35(2):107–116.
[14] Slevin F, Hudson EM, Boele FW, Powell JR, Noutch S, Borland M, *et al*. APPROACH: Analysis of Proton versus Photon Radiotherapy in Oligodendroglioma and Assessment of Cognitive Health - study protocol paper for a phase III multicentre, open-label randomised controlled trial. *BMJ Open* 2025;15(2):e097810.
[15] Hudson EM, Slevin F, Biscombe K, Brown SR, Haviland JS, Murray L, *et al*. Hitting the Target: Developing High-quality Evidence for Proton Beam Therapy Through Randomised Controlled Trials. *Clin Oncol (R Coll Radiol)* 2024;36(2):70–79.
[16] Slevin F, Alexander S, Brown SR, Carter M, Choudhury A, Clipson A, *et al*. Pelvis Or Involved Node Treatment: Eradicating Recurrence in Prostate Cancer (POINTER-PC) - study protocol paper for a phase III multicentre, open-label randomised controlled trial. *BMJ Open* 2024;14(12):e095560.
[17] Slevin F, Brown SR, Ost P, Henry AM. The POINTER-PC Study-determining Optimal Radiotherapy for Pelvic Nodal Recurrence in Prostate Cancer. *Clin Oncol (R Coll Radiol)* 2025;46:103912.
[18] Slevin F, Aitken K, Alongi F, Arcangeli S, Chadwick E, Chang AR, *et al*. An international Delphi consensus for pelvic stereotactic ablative radiotherapy re-irradiation. *Radiother Oncol* 2021;164:104–114.
[19] Slevin F, Thompson CM, Speight R, Murray LJ, Lilley J, Henry AM. Ultra hypofractionated extended nodal irradiation using volumetric modulated arc therapy for oligorecurrent pelvic nodal prostate cancer. *Med Dosim* 2021;46(4):411–418.
[20] Hudson EM, Noutch S, Webster J, Brown SR, Boele FW, Al-Salihi O, *et al*. Brain Re-Irradiation Or Chemotherapy: a phase II randomised trial of re-irradiation and chemotherapy in patients with recurrent glioblastoma (BRIOChe) - protocol for a multi-centre open-label randomised trial. *BMJ Open* 2024;14(3):e078926.
[21] Kamran SC, Zelefsky M, Nguyen PL, Lawton CAF. To Radiate or Not to Radiate-The Challenges of Pelvic Reirradiation. *Semin Radiat Oncol* 2020;30(3):238–241.
[22] Murray LJ, Lilley J, Hawkins MA, Henry AM, Dickinson P, Sebag-Montefiore D. Pelvic re-irradiation using stereotactic ablative radiotherapy (SABR): A systematic review. *Radiother Oncol* 2017;125(2):213–222.
[23] Sebag-Montefiore D, Adams R, Bell S, Berkman L, Gilbert DC, Glynne-Jones R, *et al*. The Development of an Umbrella Trial (PLATO) to Address Radiation Therapy Dose Questions in the Locoregional Management of Squamous Cell Carcinoma of the Anus. In: *International journal of radiation oncology, biology, physics*. Elsevier; 2016. p. E164–E165.
[24] Gilbert A, Adams R, Webster J, Gilbert DC, Abbott NL, Berkman L, *et al*. Standard versus reduced-dose chemoradiotherapy in anal cancer (PLATO-ACT4): short-term results of a phase 2 randomised controlled trial. *Lancet Oncol* 2025;26(6):707–718.
[25] Hudson EM, Noutch S, Brown S, Adapala R, Bach SP, Burnett C, *et al*. A Phase II trial of Higher RadiOtherapy Dose In The Eradication of early rectal cancer (APHRODITE): protocol for a multicentre, open-label randomised controlled trial. *BMJ Open* 2022;12(4):e049119.
[26] Hancock A, Hutton D, Roberts D, Whiteside L, Golby C, Eccles CL, *et al*. Barriers and facilitators to conducting radiotherapy clinical trials: Findings from a UK survey. *Radiography* 2023;29(2):369–378.

[27] Hanna CR, Lynskey DM, Wadsley J, Appleyard SE, Anwar S, Miles E, *et al*. Radiotherapy Trial Set-up in the UK: Identifying Inefficiencies and Potential Solutions. *Clin Oncol* 2020;32(4):266–275.
[28] Miles E, Wadsley J, Diez P, Patel R, Gwynne S. The National Radiotherapy Trials Quality Assurance Group – Driving up Quality in Clinical Research and Clinical Care. *Clin Oncol* 2024;36(5):273–277.
[29] Veronica N, Richard TB, Anne MP, Ana H, Kieran J, James WFC, *et al*. Boosting and broadening recruitment to UK cancer trials: towards a blueprint for action. *BMJ Oncol* 2023;2(1):e000092.
[30] Mitchell EJ, Goodman K, Wakefield N, Cochran C, Cockayne S, Connolly S, *et al*. Clinical trial management: a profession in crisis? *Trials* 2022;23(1):357.
[31] Royal College of Radiologists. *Clinical oncology UK workforce census report 2020* 2021.
[32] NHS Health Research Authority. *NOC-rad: neurocognition in oropharyngeal cancer following radiotherapy* 2023. 14/11/2024] Available from: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/noc-rad/.
[33] Zhong J, Brown S, Serra M, Shuttleworth P, Bownes P, Thompson C, *et al*. Reirradiation Options for Previously Irradiated Prostate cancer (RO-PIP): Feasibility study investigating toxicity outcomes following reirradiation with stereotactic body radiotherapy (SBRT) versus high-dose-rate brachytherapy (HDR-BT). *BMJ Open* 2022;12(11):e068580.
[34] Brown S, Gregory WM, Twelves C. A practical guide to designing phase II trials in oncology, 1st ed. Hoboken, New Jersey: John Wiley & Sons; 2014.
[35] Cancer Research UK. *Clinical research statement of intent* 2024. 01/10/2024] Available from: https://www.cancerresearchuk.org/sites/default/files/clinical_research_statement_of_intent_1.pdf.
[36] Cancer Research UK. *Strategic review of CRUK's investment in radiation biology and radiation oncology* 2018.
[37] McIntosh SA, Alam F, Adams L, Boon IS, Callaghan J, Conti I, *et al*. Global funding for cancer research between 2016 and 2020: a content analysis of public and philanthropic investments. *Lancet Oncol* 2023;24(6):636–645.
[38] Jones CM, Goh V, Sebag-Montefiore D, Gilbert DC. Biomarkers in anal cancer: from biological understanding to stratified treatment. *Br J Cancer* 2017;116(2):156–162.
[39] Monti S, Paganelli C, Buizza G, Preda L, Valvo F, Baroni G, *et al*. A novel framework for spatial normalization of dose distributions in voxel-based analyses of brain irradiation outcomes. *Phys Med* 2020;69:164–169.
[40] Conway A-M, Pearce SP, Clipson A, Hill SM, Chemi F, Slane-Tan D, *et al*. A cfDNA methylation-based tissue-of-origin classifier for cancers of unknown primary. *Nat Commun* 2024;15(1):3292.
[41] Fairweather D, Taylor RM, Simões R. Choosing the right questions - A systematic review of patient reported outcome measures used in radiotherapy and proton beam therapy. *Radiother Oncol* 2024;191:110071.
[42] Powell JR, Murray L, Burnet NG, Fernandez S, Lingard Z, McParland L, *et al*. Patient Involvement in the Design of a Randomised Trial of Proton Beam Radiotherapy Versus Standard Radiotherapy for Good Prognosis Glioma. *Clin Oncol (R Coll Radiol)* 2020;32(2):89–92.
[43] Walker F, Wharram E, Oughton JB, Brown S, Phillip R, Norris M, *et al*. Enhancing Patient and Public Involvement and Engagement (PPIE): Insights from the CONCORDE Phase I Platform Trial. In: *International clinical trials methodology conference* 2024.