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Introducing the Cancer Research UK Advanced Radiotherapy Technologies Network (ART-NET)

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Institute of Cancer Research[1], Cancer Research UK/MRC Oxford Institute for Radiation Oncology[2], Leeds Teaching Hospitals NHS Trust[3], University of Leeds[4], University of Manchester[5], The Christie NHS Foundation Trust[6], University of Oxford[7], The Royal Marsden NHS Foundation Trust[8], University College London[9], NIHR University College London Hospitals Biomedical Research Centre[10]

We live in a golden age for the development of innovative radiotherapy technologies. Three major new treatment platforms are currently at various stages of being implemented globally: stereotactic ablative radiotherapy (SABR)[1]; MR-guided radiotherapy (MR-Linac)[2]; and proton beam therapy (PBT)[3]. Such technologies offer huge opportunities for clinical benefit, but also present significant challenges for development, assessment and rational implementation within an increasingly financially constrained National Health Service (NHS). However, the apparent restrictions imposed by the structure of the NHS can also be viewed as a benefit for developing and proving the value of new radiotherapy technologies. In large part, this is due to the need to provide robust evidence to support the implementation of new technological developments before they can become widely available nationally. For example, the recent development, assessment and widespread adoption of intensity-modulated radiotherapy (IMRT) in the UK was driven by a programme of preclinical and clinical studies that were led initially by a small number of academic centres, but which progressively involved and finally included the majority of radiotherapy units in the UK[4-7]. A by-product of this research is that the UK has provided the international community with the best evidence-base for the use of IMRT in a variety of indications (e.g. prostate, breast and head and neck cancers).

In a similar vein, there is a drive in the UK to, develop SABR, MR-Linac and PBT as part of a co-ordinated programme of research. This programme can best be delivered through a co-operative network that brings together the leading radiotherapy research centres in the UK. Without such a structure, there is a real danger that new technologies will be introduced piecemeal with variable quality, in a spirit of competition rather than collaboration, being driven by market forces, rather than being based on their potential for achieving clinical benefit. For these reasons, we have established the Advanced Radiotherapy Technologies Network (ART-NET), based at The Institute of

Cancer Research/Royal Marsden Hospital (ICR), Leeds, Manchester Cancer Research Centre (MCRC), Oxford, and University College London (UCL). ART-NET is funded by a Cancer Research UK Network Accelerator Award of £4.3 million.

A key aim of ART-NET is to generate and disseminate national treatment protocols as a means of improving and harmonising practice. This will ultimately result in properly selected patients gaining access to and benefiting from these technologies. Such protocols will also facilitate the subsequent development of collaborative clinical trials in the UK aiming to generate a robust evidence-base on which practice change can be based.

ART-NET is underpinned by the availability of an impressive array of state-of-the-art technologies across the participating centres: all 5 centres have the technological capability to deliver SABR; ICR and the MCRC are members of the global MR-Linac Consortium and have already installed their MR-Linacs; MCRC and UCL are developing proton beam facilities, the first patient to be treated in 2018 in Manchester. A critical aspect of the network is that, even in the absence of the specific hardware, each member will make significant contributions to the physics/planning developments that will be required to translate these technologies for clinical evaluation, because the modalities do have a lot in common, in particular regarding issues related to patient geometry changes. In addition, sharing of expertise in clinical trial methodology (ICR/Leeds) and health economics (MCRC/Oxford) will add significant value to the network. ART-NET will involve a multi-disciplinary group of researchers including clinical oncologists, medical physicists, research radiographers, methodologists and health economists.

In establishing the network, each centre has signed a consortium agreement that was developed in consultation with collaborating centres and with CRUK. The agreement governs decision-making processes, management arrangements, funding, reporting and intellectual property. We have established a Steering Committee (SC) (Table 1) for the Network, comprised of representatives from all partner institutions and a representative from CRUK.

ART-NET's mission is to:

- build a national co-operative group drawn from UK centres of excellence that will provide leadership for the development, assessment and clinical implementation of new radiotherapy technologies;
- develop and disseminate the essential expertise in Medical Physics to lead the development of planning and image-guided solutions for SABR, MR-Linac and PBT;

- co-ordinate crucial methodological developments in the design and conduct of clinical trials to streamline health technology assessments of new technologies in specific tumour types;
- lead on health economic assessments that will estimate cost savings that will be achieved through these technologies and guide the scope of investment that will be necessary across the NHS;
- conduct in silico modelling and prospective cohort studies of new technologies that will provide the rationale for subsequent response mode-funded randomised evaluations that will be disseminated across the UK;
- disseminate national treatment protocols developed through this award to other UK centres;
- train clinical researchers of the future in the field of advanced radiotherapy.

ART-NET will initially focus on a number of disease sites including prostate, rectal, lung and oesophageal cancers and central nervous system, but will subsequently establish mechanisms for ongoing research on these technology platforms in a range of other tumour types. One central, unifying theme of the network is to evaluate the new technological platforms as a means of delivering *hypofractionated radiotherapy* in a range of clinical indications. In recent years, the orthodox view that curative radiotherapy must be administered in conventional fractions of around 2 Gy, in order to limit normal tissue toxicities, has been overturned[8,9]. As a result, there has been a drive towards testing hypofractionated regimens and, thus far, this has been particularly successful in lung, breast and prostate cancers[10-12]. Investigators at the ICR have led research in breast and prostate cancer that has shown that good tumour control rates can be maintained (or even improved) with equivalent levels of normal tissue damage when delivering a smaller number of larger doses of radiation. In addition to significant clinical benefits that will arise from increased use of hypofractionation, there are huge implications for the NHS, because reducing the number of treatment fractions delivered is a large cost saving. These savings will, to some extent, be offset by additional costs of delivering advanced radiotherapy. Assessment of the balance between these competing effects will be a central component of ART-NET and will provide guidance for the implementation and dissemination of the advanced treatment platforms that we are assessing.

Each platform each offer great opportunities to develop optimised hypofractionated radiation approaches, with both generic and platform-specific challenges that will need to be addressed and solved by the ART-NET investigators. Individual research workstreams (Table 2) will be based on providing the solutions to a number of key challenges for advanced radiotherapy technologies. The

strength of the ART-NET approach is that, for each of these challenges, leadership will be provided by at least 2 of the network members, with the ability to draw on expertise from each of the other centres. Importantly, the structure that we establish will be based on sharing information across the network, but it will also facilitate education and skill transfer between centres and, eventually, beyond ART-NET to the wider UK radiotherapy community.

Although the individual technologies each present their own specific challenges, we believe that there is considerable scope for lessons to be shared across the network in order to maximise research outputs and accelerate clinical translation. This collaborative framework will allow us to move away from the historical approach of single-centre early development and will significantly accelerate the process of translating each of the new technologies into the clinic. Specific workstreams will address problems relating to advanced treatment delivery, including MR-based planning (Workstream 1) and fast/adaptive treatment (re)planning and interactive dose-shaping (Workstream 2), management of organ motion (Workstream 3), the delivery of functional MR image-guided radiotherapy (Workstream 4) and the development of effective image-guidance and dose verification for PBT (Workstream 5). In addition, health economics methodology will be employed to assess the cost effectiveness of new treatment approaches and this information will be used as a component of the overall health technology assessment to inform plans for implementation and dissemination across the UK (Workstream 6). Finally, specific activity will also include consideration of methodological aspects of evaluating new radiotherapy technologies and how to assess their clinical utility (Workstream 7). This is particularly important, given the fact that traditional phase III clinical trials may not be the most effective means of assessing some indications for these technologies.

During the 5-year funding period, we will establish an enduring UK-wide culture of collaborative working. Initially, this will be based within the 5 founding centres of ART-NET and the selected radiotherapy technology platforms. However, by the time of the completion of the Network Award, we will have engaged large sections of the UK RT community in ART-NET and will have established a framework that will drive nationwide improvements in RT. By disseminating national protocols, ART-NET will allow all centres in the UK to offer their patients state-of-the-art treatment, either in clinical trials or as standard-of-care. We anticipate that ART-NET will solve key problems relating to SABR, MR-Linac and PBT, but will also define residual problems that will need to be addressed through further funding applications beyond the period of the Network Award. We expect to be able to attract ongoing grant funding from CRUK and non-CRUK sources (e.g. MRC, NIHR) and support from industrial partners. Furthermore, the clinical research fellows in ART-NET will help to develop a

skilled workforce that will be a huge asset for future radiotherapy research in the UK. Finally, the enhanced network-wide working that we will have established will ensure that future studies will be rapid and streamlined, which will benefit funders, researchers and, most importantly, patients.

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Table 1: ART-NET Steering Committee Members

Centre	Committee member	Deputies
ICR/RM	Kevin Harrington (Chair)	Uwe Oelfke / Chris Nutting / Emma Hall
Leeds	David Sebag-Montefiore	Ann Henry / Vivian Cosgrove
MCRC	Marcel van Herk	Corinne Faivre-Finn / Ranald MacKay
Oxford	Maria Hawkins	Frank Van den Heuvel / Tim Maughan / Alistair Gray
UCL	Gary Royle	Dave Hawkes / Ricky Sharma

ICR/RM – Institute of Cancer Research/Royal Marsden
MCRC – Manchester Cancer Research Centre
UCL – University College London

Table 2: ART-NET Workstreams & Specific Objectives

Workstream		Objectives
1	MR-based treatment planning	Provide guidance on QA of MR and image registration software to implement MR in routine clinical practice for SABR.
		Standardise algorithms that generate synthetic CT images (syCTs) from treatment-integrated MR images for all selected clinical treatment sites and the spectrum of applied imaging protocols.
		Implement image processing tools to allow verification of the geometrical accuracy of the acquired MR images by comparison with prior information.
2	Fast/adaptive re-planning	Share tools to generate images suitable for dose calculations from online images (CBCT, MR).
		Implement fast segmentation tools across the network.
		Disseminate ultra-fast Monte-Carlo dose algorithms for photon and proton beams.
		Multi-site implementation of a high-performance inverse planning tool exploiting modern computational CPU and GPU hardware architectures.
3	Motion management	Image library-based (3-D, 4-D) quantification of organ motion and anatomical changes in tumour and adjacent critical structures.
		Evaluation of novel 4-D acquisition, reconstruction, and motion modelling approaches and determine their suitability for clinical use.

		Quantification of treatment platform-independent uncertainties (eg delineation variability and short term organ motion) and their effect on predictions of tumour/normal organs motion.
		Evaluation of the accuracy of image-guidance methodologies for each treatment platform.
4	Functional imaging	Development of MRI-based early predictors of radiotherapy response.
		Design of one prospective validation study to demonstrate that predictors of response have utility in a multi-site and multi-vendor trial.
5	Proton image-guidance and dose verification	Protocol for correction of range differences at all PBT centres.
		In silico validation of protocol of determination of proton range using motion management system.
		Evaluate proton range verification techniques and identify margins for complex treatments.
6	Health economics	Development of health economic methodology.
		Comparative assessment of SABR, PBT and MR-Linac for prostate cancer.
		Comparative assessment of SABR, PBT and MR-Linac for second site (e.g. lung, oesophagus).
7	Trial methodology	Recommendations for development pathways for new RT technologies into practice-changing clinical trials. Assess feasibility/delivery of PBT and MR-Linac clinical trials including assessment of logistics and equipoise.
		Development of core outcome set – treatment, dosimetry, safety, efficacy, effectiveness, including electronic platforms for patient-reported outcomes.
		Support for clinical trial grant applications in core TSGs.

3-D	3-Dimensional
4-D	4-Dimensional
CBCT	Cone Beam Computed Tomography
CPU	Central Processing Unit
CT	Computed Tomography
GPU	Graphics Processing Unit
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
PBT	Proton Beam Therapy
QA	Quality Assurance
RT	Radiotherapy
SABR	Stereotactic Ablative Radiotherapy
TSG	Trial Steering Groups