

Impact case study (REF3)

Institution: The University of Manchester		
Unit of Assessment: 9 (Physics and Astronomy)		
Title of case study: Establishing the UK's first high-energy proton-therapy service at the Christie Hospital Manchester and University College London Hospital		
Period when the underpinning research was undertaken: 2002 – 2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Hywel Owen	Lecturer	2008 – 2021
Robert Appleby	Lecturer/Reader/Professor	2005 onwards
Ranald Mackay	Professor	2006 onwards
Karen Kirkby	Professor	2015 onwards
Roger Barlow	Professor	2005 – 2011
Period when the claimed impact occurred: August 2013 – July 2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact		
<p>Proton-beam therapy offers improved patient-dose deposition over conventional radiotherapy, improving outcomes for patients through reduced side effects and making it particularly suited for paediatric treatments. University of Manchester (UoM) research underpinned the design, procurement plan and ongoing operation of the two bespoke, flexible and future-proof NHS proton-beam therapy treatment centres in Manchester and London, procured for a combined sum in excess of GBP250,000,000.</p> <p>Commencing treatment in November 2018, the Christie Proton Therapy Centre at Manchester has treated approximately 400 patients, offering an estimated average 11.2 quality-adjusted life-years (QALY) per patient; 1.8 QALYs per patient greater than conventional radiotherapy.</p> <p>These UK state-of-the-art treatments have reduced the need for the previous provision of 200 annual overseas referrals, at a greatly reduced cost. This saved the NHS at least GBP60,000 per patient; it also opened up treatment to patients from a much wider demographic, including those too ill to travel.</p>		
2. Underpinning research		
<p>UoM's research programme has advanced proton therapy through a series of research projects. The 2012 Electron Model for Many Applications (EMMA) prototype particle accelerator GBP8,300,000 Basic Technology, led by Barlow with Owen and Kirkby) developed a key technology needed for future rapid patient radiotherapy treatment [1] – the so-called non-scaling FFAG (Fixed-Field, Alternating Gradient) accelerator. EMMA was the first demonstration of this technology, and improves upon industry-standard cyclotrons by giving pulse-by-pulse energy variation of the accelerated particles (and thereby depth variation). Owen's group made the key measurements that proved successful extraction and delivery of particle bunches.</p> <p>The follow-on Particle Accelerator for MEDical Applications (PAMELA) study (Barlow, Owen, Kirkby) [2] used the EMMA results to develop an FFAG-based treatment facility proposal. Barlow led this study, which produced a comprehensive design for dual-particle treatment (protons or carbon ions) and which developed a coherent specification for treatments in the UK, including the key attributes of fast energy switching and high-energy availability (see features (3), (6) and (7) in the impact section). Whilst industry-standard cyclotrons are limited to 250 MeV protons (that can treat adult patients), PAMELA is capable of 350 MeV proton delivery that enables more accurate proton-based imaging of patients for more accurate treatment targeting (see NHS specification [A]).</p> <p>The NOrmal-conducting Racetrack Medical Accelerator (NORMA) project (led by UoM – Owen and Appleby) [3] developed the first design of an economic, proton-only, 30–350 MeV FFAG accelerator, again to satisfy the NHS specification for proton imaging of patients; proton imaging allows more accurate imaging than conventional CT scans, leading to lower patient irradiation during treatment. The NORMA design used UoM-developed computationally intensive code, which led to a more precise optimisation of the accelerator design than previously possible. This</p>		

Impact case study (REF3)

allowed the use of conventional normal-conducting magnets (maximum field <1.8 T), offering an operationally simpler and cheaper alternative to superconducting designs such as the previous PAMELA.

Aitkenhead and Mackay [4] developed a Monte-Carlo model to estimate quantitatively the throughput and waiting times of a single accelerator multi-treatment-room proton therapy facility. The model was validated against the MD Anderson Cancer Centre (MDACC, USA), demonstrating its accuracy and sensitivity to variance in parameters such as beam switch time, the number of treatment rooms, and patient set-up times. The model studied the UK-specific scenario of a more complex patient caseload (greater number of paediatric patients requiring general anaesthesia), specifying a 19% lower throughput than MDACC but maintaining an eventual capacity of 750 patients per year.

Burnet, Mackay and Kirkby, as part of the National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group (CTRad) [5], developed an eight-point framework to assist the development and delivery of high-quality Proton-Beam Therapy (PBT) clinical trials. This involved identifying the most appropriate endpoints, methodologies and translational elements for each clinical trial. The work also defined the need to involve patients and carers as well as key government and funder stakeholders from the outset and to establish a multidisciplinary framework involving researchers from the clinic and academia.

Mee and Kirkby [6] conducted an in-depth review of the available modelling approaches for estimating service demand, patient numbers, and individual patient selection, highlighting areas of under-referral. Using Office of National Statistics (ONS) national cancer incidence data and population data, it enabled NHS scenario planning and an assessment of the heterogeneity of cancer incidence and referral. For example, it assessed the effect of changing clinical indications upon PBT demand, and the impact on radiotherapy and surgery if regional screening programmes were rolled out nationally. It is also being used to identify the bottlenecks that lead to increased waiting times for cancer care.

3. References to the research

The papers below exemplify the body of research on which the impact is based, and are published in both leading physics and medical journals. Citation data come from Scopus, and are accurate as of 7 March 2021.

[1] "Acceleration in the linear non-scaling fixed-field alternating-gradient accelerator EMMA, Electron Model for Many Applications", S. Machida *et al.* *Nature Physics*, 8, 243-247 (2012). DOI: [10.1038/NPHYS2179](https://doi.org/10.1038/NPHYS2179) (71 citations)

[2] "Conceptual design of a nonscaling fixed field alternating gradient accelerator for protons and carbon ions for charged particle therapy", K. Peach *et al.* *Phys. Rev. S.T. Accel. Beams*, 16, 030101 (2013). DOI: [10.1103/PhysRevSTAB.16.030101](https://doi.org/10.1103/PhysRevSTAB.16.030101) (20 citations)

[3] "Normal-conducting scaling fixed field alternating gradient accelerator for proton therapy", J. Garland, R. Appleby, H. Owen, S. Tygier, *Phys. Rev. S.T. Accel. Beams*, 18, 094701 (2015). DOI: [10.1103/PhysRevSTAB.18.094701](https://doi.org/10.1103/PhysRevSTAB.18.094701) (5 citations)

[4] "Modelling the throughput capacity of a single-accelerator multitreatment room proton therapy centre", A. Aitkenhead, D. Bugg, C. Rowbottom, E. Smith, R. Mackay, *Brit. J. Radiol.*, 85, 1263-1272 (2012). DOI: [10.1259/bjr/27428078](https://doi.org/10.1259/bjr/27428078) (14 citations)

[5] "Proton Beam Therapy - the Challenges of Delivering High-quality Evidence of Clinical Benefit", CTRad Proton Beam Clinical Trial Strategy Group & Kirkby, K, *Clin. Oncol.*, 30, 280-284 (2018). DOI: [10.1016/j.clon.2018.02.031](https://doi.org/10.1016/j.clon.2018.02.031) (12 citations)

[6] "Mathematical Modelling for Patient Selection in Proton Therapy", Mee, T, Kirkby, N & Kirkby, K, *Clin. Oncol.*, 30, 299-306 (2018). DOI: [10.1016/j.clon.2018.01.007](https://doi.org/10.1016/j.clon.2018.01.007) (4 citations)

4. Details of the impact

Pathway to impact

In 2010, the NHS began a review of the technical case to bring proton-beam therapy (PBT) to the UK. In 2011, by virtue of the successes of 2006-2012 EMMA [1] and 2006-2013 PAMELA [2] projects, Owen was invited to write a review with the Science and Technology Facilities Council (STFC) for the then Department of Health (DoH), which formed part of the technical specification for the UK proton therapy service [A, B]. Building on his research in biological

modelling of conformal therapy and capacity planning, Mackay was appointed technical director for the Christie PBT service [C]. Christie Hospital and the NHS decided the procured PBT system should come from established suppliers to obtain short timescales for commencing a treatment service. They also wanted to purchase a bespoke set-up suitable for the broadest range of complex treatments, which would remain state-of-the-art [D]. Between 2013 and 2018, Owen (as part of a three-person advisory group) co-wrote the technical specification for the non-standard FFAG accelerator system [D]. An FFA (Fixed Field Accelerator) allows rapid cycling of the beam energy to permit fast energy layer changes in beam delivery, and hence greater patient throughput. The team wrote the specification based on their research expertise [1-4] and the DoH review; Mackay led the procurement with Owen acting as advisor.

Impacts on policy and the delivery of professional services

In December 2013, the NHS Review on bringing PBT to the UK was published [A]. The input of advisors Owen and Mackay to the Review was crucial in defining the specifications of the PBT facilities that the NHS procured. Owen and Mackay specified future delivery of higher-energy protons for treatment with imaging [3]. The strength of their arguments, backed up by their research [1-4], made clear the benefits of investing heavily in non-standard features ((1) to (7) below), each of which were included in the final specifications and are now part of the two completed facilities: The Christie Hospital Manchester and University College London Hospital (UCLH). These non-standard features included:

- 1) Fast scanning and fast (ideally sub-second) energy switching for Intensity-Modulated Proton Therapy (IMPT) [1, 2, 3, 4];
- 2) Use of gantries (to assist IMPT) over fixed treatment lines [4];
- 3) Spot scanning (to assist IMPT) over ordinary passive scattering [3];
- 4) Using a cyclotron source, which has allowed high-intensity treatment upgrades as originally foreseen [4][D, E];
- 5) Construction of a research beamline at the Christie centre to support and develop facility and treatment upgrades (future-proofing the facility);
- 6) High-energy options for imaging and proton radiography/tomography [1, 2, 3];
- 7) High-intensity and high-energy compact proton accelerators [1, 2, 3].

Mackay's Monte-Carlo (MC) model [4] specified the installed one-accelerator/three-treatment-room setup, optimised to ensure the highest possible patient throughput with UK treatment protocols (a world-leading 250 patients per year per room). The reliability of the MC model has further served to mitigate financial risk and consequent successful operation of the facility and has facilitated the world's fastest patient-service ramp-up of paediatric capacity [D]. Additionally, the patient selection research [6] sets the policy framework for patients at Christie. CTRad has similarly set a policy for clinical trials [5] within which the Christie will be working. Together, these papers set the overall UK method for NHS patient selection and treatment used currently [F].

Economic impact

The inclusion by Owen and Mackay of each non-standard feature (1-7) represented an overall GBP13,000,000 addition to each of the Christie and ULCH project budgets, contributed heavily to the NHS's total investment into their two PBT facilities exceeding GBP250,000,000, but guaranteed future-proofed treatments. This was the largest single financial investment in NHS history [D].

Unlike comparable procurements, no legal challenges by competing manufacturers were levied against their decision. The unique detail of the facilities' specifications, developed in part by Owen and Mackay, left no ambiguity about the criteria for selection of supplier. This was central to NHS England's strategy to avoid costly and time-consuming legal challenges. Such challenges typically cost upwards of GBP500,000 and can delay the beginning of a project by at least 12 months.

Unlike most PBT facilities, where service provision of equipment is effectively frozen at the point of purchase, each non-standard feature has ensured capability for future treatment, effectively future-proofing the service provision by facilitating adaptation or modification of the infrastructure, to introduce or pioneer innovative treatments at the clinical forefront. Previous

generation patient-specific hardware cost typically over GBP2,000 per patient; specifying spot scanning (3) eliminates this to save over GBP800,000 so far on 400 patients [D]. It also reduces average per-patient overseas costs from over GBP100,000 to less than GBP45,000 [D]. Whilst the procurement of these facilities represented the largest investment in NHS history, we (with the NHS) are confident that the purchase of a future-proofed facility represents a better investment long term than constructing new facilities for each subsequent generation of PBT treatment.

The research beamline facility (point 5 above), led by Kirkby, contains a clinically-equivalent scanned proton beamline representing a GBP15,000,000 investment split between infrastructure, equipment and staff time (a full time staff complement of over 30 people [G]). In May 2020, as the only infrastructure of its type, the research line demonstrated the feasibility of radiation oncology treatment manufacturer Varian's new dosimetry instrument key to enabling FLASH (Ultra-High Dose Rate) therapy, an approach seen as the next-generation proton treatment and a paradigm shift in radiotherapy [E]. As a result of this development Varian have increased spending in this field by [text removed for publication] [E].

Impact on health and wellbeing

Inclusion of the non-standard features has allowed the NHS to offer state-of-the-art treatments not available with a 'standard' facility. For example, features (1) and (2) have allowed for treatment of craniospinal cancers on paediatric patients under anaesthesia, accommodating for movement in the patient, which is not possible using older passive scanning methods. Specification of spot-scanning (3) eliminated the need for costly patient-specific hardware and offers personalised, adaptive and more conformal treatments than would otherwise have been available.

The first NHS centre to offer full-body proton therapy started treatments in November 2018 at Christie, to be joined by a second centre at UCLH in summer 2021. After the first two years, over 400 patients have received treatment [H] at Christie as operation ramps up as planned to 750 per year. Whilst long-term analysis of this cohort is not yet available, the literature suggests an improvement of 11.2 quality-adjusted life-years (QALY) per patient from proton therapy; 1.8 additional QALYs to each patient compared to conventional radiotherapy [A]. The NHS previously referred patients overseas for PBT: approximately 200 per year. The provision of domestic treatment allows for more PBT referrals as it offers the opportunity for treatment to a range of patients who would be ineligible for treatment abroad due to the health and wellbeing challenges posed by international travel [A, D]. Of the patients treated at the Christie facility, 20% would not have received equivalent quality treatment at alternative international centres because of different provisions of service, and 10% would have been ineligible for treatment due to restrictions on travel [C, H]. The efficient procurement of a high-capacity, domestic service has preserved PBT of UK patients during the unprecedented time of restricted international travel caused by COVID-19.

5. Sources to corroborate the impact

[A] National Proton Beam Therapy Service Development Programme: 'Strategic Outline Case', and 'Value for Money Addendum to Strategic Outline Case' (October 2012), UK DoH

[B] Letter from the Head of GFS, Agri-Tech and Water, STFC, 7 July 2020

[C] Letter from the Chief Executive, The Christie NHS Foundation Trust, undated

[D] Letter from NHS England National Clinical Lead Proton Beam Therapy, undated

[E] Letter from the FLASH Communications Director, Varian, 22 June 2020

[F] Letter from the Chair of CTRad, undated

[G] List of research staff associated with Christie Research Beamline

[H] Letter from The Christie NHS Foundation Trust's Clinical Director for Proton Beam Therapy, undated