National Proton Beam Therapy Service Development Programme

Value for Money Addendum to Strategic Outline Case

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SOC Addendum: Demonstrating Value for Money of Proton Beam Therapy (PBT)

Summary

Further to Treasury (HMT) and Department of Health formal approval of the Strategic Outline Case (SOC) for the National PBT Service Development Programme, this document develops the economic case set out in the SOC to demonstrate the most cost effective, proposed approach for the delivery of a PBT service in England.

There were three main options considered for this programme, to develop one, two or three proton therapy centres. An option appraisal has been completed using financial modelling from University College London Hospitals NHS Foundation Trust and Monte Carlo simulation modelling to assess the benefits to patients of being treated with protons.

Based on the costs, benefits and risks of each option, developing two proton bean therapy centres in England is shown to be the most cost effective solution. This conclusion is based on the incremental cost effectiveness ratio of each option compared to a baseline, do nothing, position.

1. Introduction

1.1. On 10th February 2012, Her Majesty's Treasury (HMT) and the Department of Health (the DH) formally confirmed full approval of the Strategic Outline Case (SOC) for the National Proton Beam Therapy (PBT) Service Development Programme. SOC approval enabled the programme to move to Outline Business Case (OBC) stage. The Trusts hosting the national service will prepare OBCs, underpinned by a Cooperation Agreement with DH and the NHS Commissioning Board (NHS CB) to ensure the requirements of the national service are addressed.

Purpose of the SOC Addendum

1.2. This document progresses the economic case set out in the SOC. The analysis in the following sections updates and develops the options appraisal in the SOC to reflect the latest position, now including information from the chosen sites. This document will contribute to satisfying the conditions of Treasury approval of the SOC.

The evidence presented here supports the national case for developing PBT services in England, and the economic case in the Trust OBCs will demonstrate the cost effectiveness of the project at Trust level.

Preferred way forward

1.3. The SOC identified the development of two PBT sites in England as the preferred way forward to meet the critical success factors of the project in the near term. The Christie NHS Foundation Trust (The Christie) and University College London Hospitals NHS Foundation Trust (UCLH) are the two organisations chosen to host PBT centres. As demand for proton beam therapy increases, the DH has identified University Hospitals Birmingham NHS Foundation Trust (UHB) as the preferred third site to provide additional capacity.

1.4. The DH selected the host trusts through a market testing exercise concluding in the autumn 2010. The DH had outlined a framework for the development of PBT services in England and invited organisations to submit proposals in response. The Christie and UCLH submitted the highest scoring bids when assessed against the pre-defined criteria. There have been no substantive changes to the scope or requirements for PBT to affect the results of the exercise if it were to be re-run.

Principal related government policies and documents

1.5. In February 2007, The National Radiotherapy Advisory Group (NRAG) made the recommendation for the DH to give NHS patients access to proton therapy (1). NRAG's proton sub-group informed the recommendations for proton therapy to ministers. The report made the following recommendations:

- that the DH develop a business case for a proton facility in England
- that the more immediate needs of patients be met with the access to facilities overseas.

1.6. The following list outlines the additional key related documents to this addendum:

- Proton Beam Therapy Strategic Outline Case
- A Framework for the Development of Proton Beam Therapy Services in England
- Radiotherapy: Developing a world class service for England. Report to Ministers from National Radiotherapy Advisory Group, 26 February 2007
- Proton Treatment for Cancer: A report for the National Radiotherapy Advisory Group. Proton Sub-group, April 2006
- Cancer Reform Strategy, December 2007
- Guidance for the Referral of Patients Abroad for NHS Proton Treatment version 2.3, National Specialised Commissioning Team, July 2007
- Improving Outcomes: A Strategy for Cancer, January 2011.

1 Radiotherapy: Developing a world class service for England. Report to Ministers from National Radiotherapy Advisory Group, 26 February 2007: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_074576.pdf

2. Clinical effectiveness of Proton Therapy

2.1. There are two main advantages of proton therapy compared to photon beams, used in radiotherapy as outlined below. A fuller discussion of the advantages of protons is included in section four of the Proton Sub-Group report to National Radiotherapy Advisory Group (NRAG).

- ### High Precision Targeting

Proton beams offer greater precision than photons, increasing the effectiveness of treatment in affecting the tumour.

- ### Dose Distribution

Conventional radiotherapy cannot be used for all patients needing treatment due to young age or serious risks of toxicity to critical structures. There is evidence that the "dose bath" of radiotherapy increases the long term cancer induction risk. These risks are reduced with proton treatment for patients undergoing treatment when compared to photons.

2.2. The advantages identified above result in:

- improved survival for patients receiving treatment
- reductions in chronic adverse side effects associated with conventional radiotherapy
- reductions in other conventional radiotherapy side effects including deafness and reduced IQ.

2.3. We have used the relative gains in survival and reductions in chronic adverse side effects to compare the benefits of proton therapy and conventional radiotherapy in assessing the cost-effectiveness of these alternative treatments. Further detail of the benefits modelling is in section 3.1 below.

Clinical trial evidence for the effectiveness of protons

2.4. Experience and evidence of proven benefits and long term outcomes is still limited. The main benefits of Proton Beam Therapy (PBT) are to patients with rare and difficult to treat tumours so comparative clinical trial data is difficult to obtain. The NRAG proton sub-group advised that there are no randomised controlled (Phase III) trials of protons vs photons and none are likely to be done in other countries.

All patients treated in English facilities will be defined within clear protocols and enrolled into a prospective programme of evaluation and outcome tracking to provide further evidence of the effectiveness of proton therapy.

2.5. The Proton sub-group considered the latest available evidence to assess the effectiveness of protons over conventional radiotherapy. Citing eleven studies, the group concluded that the evidence was strong for local control rates and lower doses of radiation to critical normal tissues.

3. Clinical demand for proton therapy

3.1. In 2009, National Radiotherapy Advisory Group (NRAG) determined an immediate need for up to 400 high priority patients per annum to have access to proton treatment. To meet this short-term need, patients are referred overseas for treatment. The number of patients treated overseas to date has been less than anticipated but paediatric referrals are escalating as experience grows. This growth in numbers is expected to continue. Currently 160 patients have had their treatment completed, 107 of whom are children. Defined new protocols for rare sacral cancers and a better structure of referral through skull base Multi-Disciplinary Teams (MDTs) will add to the adult numbers.

Table 1: Number of NHS patients treated overseas, 2008-2009 to 2011-2012

Year	Number of patients treated overseas
2008-2009	11
2009-2010	20
2010-2011	50
2011-2012	79

Source: NHS Specialised Services – Proton Beam Therapy (PBT)

3.2. The current guidelines for referring patients overseas are more restricted than those proposed for the UK service. The expanded list (see annex A) includes indications where the international literature is now sufficient to justify protons as the treatment of choice, as confirmed by NRAG and subsequent review by clinical experts. In the USA, significant numbers of prostate cancer patients elect to be treated with protons. There is no evidence of clinical benefit for this and so it is not included in the indications list.

3.3. Each year, between eight and 31 patients per million are affected by the indications for the UK, equating to 1,487 individuals in England and the Devolved Administrations (DAs). Patients from DAs account for 15% of the total. While the DAs accept all current referral guidelines for PBT, the project team are working with them to agree likely future activity. For some indications, the DAs may require evidence from evaluations of patients treated in the UK prior to referring patients. As a result, total UK demand is initially expected to be less than 1,487 patients per annum.

Modelling the health benefits of PBT

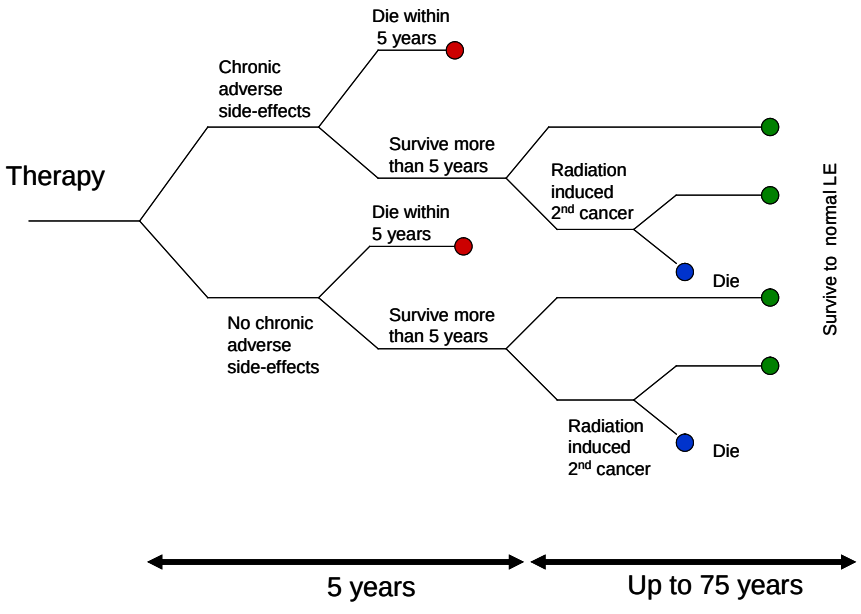
3.4. In the absence of sufficient comparative evidence for PBT, Monte Carlo simulation modelling has been used to assess the benefits of protons for the indications list recommended for the UK. The method and results of this approach are described below.

Method

3.5. Following the general approach used by Lundkvist,(2) a Markov cohort Monte Carlo model was developed to simulate the life of patients subsequent to either current conventional radiation treatment, (if that would normally be offered now,) or PBT. The model simulates the course of events for individual patients from treatment until death (or 100 years of age).

In the Markov model the patients are classified into a number of health states which can change as time progresses, depending on the probability of treatment outcomes. The structure of the Markov model is shown in Figure 1 below.

Figure 1 A Markov model of radiotherapy outcomes



Life tables are used to predict the chance of death from all causes as patients get older, no patient is forecast to live beyond 100 years old.

2 Lundkist J., Ekman M., Erucsson S. R., Jonsson B. & Giimelius B., 2005, *Proton therapy of cancer: Potential clinical advantages and cos-effectiveness*, Acta Oncologia, 44, pp 850-861

3.6. The Monte Carlo simulation is conducted in one-year cycles.

In each year of the simulations, new patients are selected on a random basis weighted by the estimated incidence of the disease. Their health status is based on the possible outcomes identified in Figure 1 above and the probability of outcomes in Table 2 below. Each year, the age of the existing patients is incremented by one and their health status (including death) is recalculated, on a probabilistic basis using Table 2 below.

A literature review and expert panel were used to estimate the relative improvement in outcomes that could be expected from treating patients with proton therapy compared to conventional photon radiotherapy. So the model is run twice, once with a non-proton beam therapy pathway and again with PBT. The difference between the two gives the incremental improvement from moving to a PBT based approach.

Table 2: The Markov chain probability values used in the Monte Carlo simulation

			volume	running total	Average age	% Chronic side effects (RT)	children *** = 0.12 ** =0.48 * = 0.72 adults *** = 0.6 ** =0.8	% Chronic side effects (protons)	Ultility loss - QALY (RT)		Ultility loss - QALY (protons)	Five year survival (RT)	***=20% **=10% *= 5%	Five year survival (protons)	2nd cancer from Y 5 (RT) 1.88/1000 years = 2.82% /15 years	*** = 0.1 **=0.5 *=0.25	2nd cancer from Y 5 (protons)	Death from Second cancer (RT) (50% in 5 years)
Chordoma/Chondrosarcoma			15	15	5	53%	***	6%	0.19		**0.19**	90%	***	99%	3%	**	**0.7%**	1.4%
Rhabdomyosarcoma	Orbit		5	20	5	53%	***	6%	0.19		**0.19**	97%	*	99%	3%	***	**0.3%**	1.4%
Parameningeal & Head & Neck			15	35	5	53%	***	6%	0.19		**0.19**	75%	*	79%	3%	***	**0.3%**	1.4%
Pelvis			10	45	5	53%	***	6%	0.19		**0.19**	75%	*	79%	3%	***	**0.3%**	1.4%
Osteosarcoma			3	48	5	53%	***	6%	0.19		**0.19**	25%	***	30%	3%	***	**0.3%**	1.4%
Ewings			9	57	5	53%	***	6%	0.19		**0.19**	55%	**	61%	3%	***	**0.3%**	1.4%
PPNET (Extra-osseous Ewing's)			5	62	5	53%	***	6%	0.19		**0.19**	55%	**	61%	3%	***	**0.3%**	1.4%
Ependymoma			25	87	5	53%	***	6%	0.19		**0.19**	67%	*	70%	3%	**	**0.7%**	1.4%
Low Grade Glioma			5	92	5	53%	**	25%	0.19		**0.19**	92%	*	97%	3%	**	**0.7%**	1.4%
Optic Pathway Glioma			12	104	5	53%	**	25%	0.19		**0.19**	92%	*	97%	3%	***	**0.3%**	1.4%
Craniphayngioma			15	119	5	53%	***	6%	0.19		**0.19**	96%	*	99%	3%	***	**0.3%**	1.4%
Medulloblastoma (PNET)			70	189	5	53%	***	6%	0.19		**0.19**	59%	*	62%	3%	***	**0.3%**	1.4%
Hodgkins			5	194	5	53%	**	25%	0.19		**0.19**	95%	*	99%	3%	***	**0.3%**	1.4%
Retinoblastoma			5	199	5	53%	**	25%	0.19		**0.19**	97%	*	99%	3%	**	**0.7%**	1.4%
Meningioma			3	202	5	53%	***	6%	0.19		**0.19**	92%	**	99%	3%	***	**0.3%**	1.4%
Intracranial Germinoma			10	212	5	53%	***	6%	0.19		**0.19**	91%	*	96%	3%	***	**0.3%**	1.4%
Nasopharynx (Head & Neck)			15	227	5	53%	***	6%	0.19		**0.19**	96%	**	99%	3%	***	**0.3%**	1.4%
Difficult Cases (Esthesioneuroblastoma/Neuroblastoma/Live			5	232	5	53%	***	6%	0.19		**0.19**	25%	**	28%	3%	**	**0.7%**	1.4%
Very Young Age (Side effect for PBT only)			20	252	1	53%	***	6%	0.19		**0.19**	45%	***	54%	3%	***	**0.3%**	1.4%
Choroidal melanoma			100	352	55	70%	***	42%	0.15		**0.15**	50%	***	60%	3%	*	**1.4%**	1.4%
Ocular / Orbital			25	377	55	70%	***	42%	0.10		**0.10**	50%	***	60%	3%	*	**1.4%**	1.4%
Chordoma		Base of Skull	60	437	55	12%	***	7%	0.10		**0.10**	50%	***	60%	3%	*	**1.4%**	1.4%
Chondrosarcoma		Base of Skull	30	467	55	12%	**	10%	0.50		**0.50**	50%	***	60%	3%	*	**1.4%**	1.4%
Para-spinal / Spinal Sarcoma		Including Chordoma	120	587	55	12%	***	5%	0.10		**0.10**	50%	***	60%	3%	*	**1.4%**	1.4%
Sacral Chordoma (chronic side effects of PBT)			60	647	55	90%	***	7%	0.90		**0.90**	50%	*	53%	3%	*	**1.4%**	1.4%
Meningioma			100	747	55	12%	*	11%	0.10		**0.10**	50%	*	53%	3%	*	**1.4%**	1.4%
Acoustic Neuroma			100	847	55	12%	*	11%	0.05		**0.05**	50%	*	53%	3%	*	**1.4%**	1.4%
Craniospinal NOS (Pineal)			10	857	55	12%	***	7%	0.20		**0.20**	50%	**	55%	3%	**	**0.7%**	1.4%
Head & Neck & Paranasal Sinuses		60	300	1157	55	12%	***	7%	0.20		**0.20**	50%	***	60%	3%	**	**0.7%**	1.4%
PNET (medullo/intracranial)			30	1187	55	12%	**	10%	0.10		**0.10**	50%	**	55%	3%	**	**0.7%**	1.4%
Difficult Cases		60	300	1487	55	12%	***	5%	0.20		**0.20**	50%	**	55%	3%	**	**0.7%**	1.4%

As the simulation progresses, the accumulated health gain for all patients, measured in Quality Adjusted Life Years (QALYs) can be identified. For completeness, the loss of QALY due to longevity was attributed at each increment of age but this was common to both pathways and did not significantly influence the incremental cost benefit. Significant QALY loss associated close proximity with death (in effect on a end of life trajectory) was not included as this also is common to both pathways.

New treatments are started each year, for 30 years, the anticipated lifespan of PBT equipment. All the patients are followed until death due to the cancer for which they were being treated, death from a secondary induced cancer as a result of primary treatment or due to natural causes. Loss of health status due to chronic side effects of the primary treatment is carried through until death, either due to cancer or natural causes.

Results

3.7. The simulation modelling was run separately for the high priority indications (accounting for 400 patients) and for the full list of indications, including the high priority cases (1,487 patients).

The high priority patients have greater capacity to benefit from PBT due to the risks associated with radiotherapy treatment. The differences in outcomes by indication are reflected in the probability values used in the model. Based on the possible outcomes following treatment, and the probability of different outcomes by indication, the results of the simulation model are shown in Table 3 below.

Table 3: Average QALY gain per patient following treatment, simulation modelling (QALY discount rate = 1.5% per annum)

QALY/ patient	*Radiotherapy*		*PBT*		*Difference (Gain from PBT)*	
	High priority indications	*All indications*	*High priority indications*	*All indications*	*High priority indications*	*All indications*
Undiscounted	22.9	14.2	27.2	17.1	4.4	2.8
Discounted	14	9.4	16.5	11.2	2.5	1.8

The high priority patients for proton therapy have the capacity to gain an average of 2.5 QALYs over their lifetime relative to conventional treatment. The benefit for the average patient on the indications list is estimated to be 1.8 QALYs over their lifetime. These values are likely to be an underestimate of the total QALY gains per patient as they do not include the non-chronic side effects of conventional radiotherapy such as deafness and reduced IQ.

4. Options for the provision of Proton Therapy in England for NHS patients

4.1. The options for the development of Proton Beam Therapy (PBT) in England, as outlined in the Strategic Outline Case (SOC), are to develop one, two or three facilities.

4.2. There are multiple possible configurations of a PBT facility based on the type and number of rooms. As each room is reliant on the same proton accelerator, the efficiency of different configurations is based on the time taken to switch the beam between rooms, the number of treatment fields used and time to prepare each patient for treatment. All options considered are based on an ideal configuration of three rooms per accelerator, the most cost effective configuration based on international evidence and expert opinion.

4.3. The throughput of each facility will depend on the casemix of patients treated. The high priority cases of adults, and children and the very young will reduce throughput, as they require relatively more complex and longer treatment. There is no facility in the world that treats an equally complex casemix of patients to those proposed for England, so assessments of throughput are based on estimates of the time taken to treat each indication, drawing on international evidence for particular indications where available.

Do nothing

4.4. The do nothing option provides a baseline for comparison. Under this option, all patients are offered the best available alternative treatment in the absence of PBT, usually conventional radiotherapy. There is no national price for radiotherapy treatment per patient, the tariff price per fraction ranges from £85 to £242. Based on the average number of fractions per indication, and associated healthcare appointments, this analysis assumes an average price per paediatric patient of £7,500 and £4,600 for adults. Using the simulation modelling described above, we estimate that the benefits of conventional treatment range from 9.4 to 14.0 discounted Quality Adjusted Life Years (QALYs) per patient over their lifetime.

Treat up to 400 patients per annum with PBT at overseas centres

4.5. As an interim solution, while the case for a PBT in England is developed, National Radiotherapy Advisory Group (NRAG) recommended that high priority cases be treated with PBT at international facilities.

The National Specialised Commissioning Team (NSCT) is responsible for the programme to send patients overseas for treatment. In 2010 to 2011, the average cost per patient for treatment at an international facility was £110,000. The additional cost of overseas treatment relative to the weighted average cost of radiotherapy is estimated to be £103,660.

Based on the Monte Carlo simulation modelling, the gains from PBT, relative to the do nothing scenario, for up to 400 high priority patients equates to an average of 2.5 discounted QALYs per patient over their lifetime.

Using the costs and benefits outlined above, each QALY gained by a patient treated overseas costs £41,464.

Provide PBT in England

4.6. NRAG recommended that, subject to a business case led by the Department of Health, at least one modern proton treatment facility is set up in England. The SOC outlines options to develop one, two or three proton therapy centres. An updated assessment of each option is set out below.

Costs

4.7. The per patient cost of providing proton therapy is largely driven by two key elements:

- The capital costs of the project are a significant driver because, based on current estimates approximately 80% of the costs are fixed.
- Throughput, and the extent to which the high proportion of fixed costs can be apportioned across different numbers of patients, will have a significant impact on the cost, and resulting tariff price per patient.

4.8. As all options for the number of PBT sites are based on the same configuration, the capital costs of each site will be the same as far as possible, for example in terms of equipment. Capital costs will differ with regard to features specific to an individual trust or location, such as building costs.

4.9. The subsequent analysis is based on costing by University College London Hospitals NHS Foundation Trust (UCLH). UCLH have undertaken detailed costing where possible and these values are included for the purposes of this analysis. We recognise

that location specific cost variation will affect the total cost of developing PBT at different locations, but we do not expect the differences to materially affect the options analysis. Contingency and optimism bias rates of 25% each have been factored in to the capital costs to reflect current risks given the stage of the project.

4.10. From informal discussions with equipment suppliers, UCLH have provided cost estimates for a PBT facility on their site, as shown in table 4 below. More accurate equipment costs will be available when providers are formally invited to tender for the project. Where options include multiple sites in England, no assumptions have been made to account for economies of scale. Based on evidence from experts, economies of scale for suppliers are likely to arise from management time savings in developing two closely located sites however the scale of savings is unknown.

Table 4: Capital costs of PBT, for one site

Cost type	*Cost (£m)*
Building costs	
Build (inc fees and non-works costs)	61.9
Contingency (25%)	15
Optimism Bias (25%)	19
Total	**96.8**
Core PBT equipment	
Common Beam Infrastructure	18
Compact gantry	16.7
Full gantry	9.5
Training package	0.4
Total	**44.6**
Associated capital costs	
Contingency (5%)	2.23
MRI	1.3
Data Management Information System	1.2
Treatment Planning System	4.2
CT	0.4
Total	**9.33**
GRAND TOTAL	**150.7**

Source: Private correspondence with UCLH

4.11. UCLH have made an assessment of the annual cost base for the project, once fully operational as shown in Table 5. There are still several unknowns that will affect the per patient cost of PBT. Examples include the funding mechanism for capital and the chosen supplier of PBT equipment and associated opportunities for economies of scale.

Table 5: Analysis of annual cost base

Cost type	*Annual cost (£m)*
Staff	5.70
Maintenance	4.20
Other operating costs	3.10
Depreciation	6.20
PDC return	5.25
Income required to offset early year losses	1.10
TOTAL	**25.55**

Source: Private correspondence with UCLH

Develop one PBT centre in England

4.12. One facility in England would provide insufficient capacity to treat all indications for PBT but would enable all those recommended for overseas treatment to be treated in England, at a lower cost. Due to the more intense level of treatment required for high priority patients, current analysis suggests that there would be no additional capacity to treat other cases. Sensitivity analysis is included in Section 6 to assess the impact of different throughput levels.

4.13. The average cost per patient, for a single PBT centre, treating only complex cases would be approximately £61,000. This value is based on the information provided by UCLH. The per patient costs for one site are greater than for multiple site solutions because:

- The fixed costs are the same as for each site in a multi-site solution, but are apportioned over fewer patients
- One site will treat the most complex cases and therefore more resource intensive, both in terms of the length of time taken per fraction and inputs to their care, for example requiring general anaesthetics. These factors increase the per patient cost of a one site solution compared to options with multiple sites.

4.14. Under this option, the patients treated are the same group of high priority patients that would otherwise be sent abroad in option one above. The benefits are equivalent to option one, an average of 2.5 QALYs per patient. Compared to the costs of conventional treatment, the cost per QALY of this option is £21,751.

This analysis shows that the cost per QALY of treating high priority cases in England is less than referring patients overseas, and the difference may be even greater when accounting for non-quantified gains for patients from receiving care closer to home.

Develop two PBT facilities in England

4.15. Based on the most cost-effective configuration of PBT facilities, throughput per site is estimated to be between 600 and 750 patients per annum. This estimate assumes that each facility will receive the same casemix of patients, as agreed by the Throughput, Capacity and Technology Workgroup. The central case for analysis is based on each site being able to treat 675 patients. Sensitivity analysis to assess the impact of achieving different levels of annual throughput given the range of 600-750 patients is included in Section 6 below.

Based on the latest modelling of costs and throughput, with two sites treating a total of 1,350 ([3]) patients per annum, the per patient cost of proton therapy is estimated to be £39,500. The per patient cost of PBT is based on directly apportioning the annual costs of the project across the numbers of patients treated. Further work will be undertaken to derive the tariff price, reflecting appropriate incentives, as the programme develops.

This cost is based on the Devolved Administrations (DAs) utilising capacity beyond that required for English patients. There are currently estimated to be 1,160 English patients requiring treatment. The National Specialised Commissioning Team (NSCT) currently commissions PBT services overseas on behalf of Scotland, Wales and Northern Ireland. The countries have reaffirmed their commitment to offer proton treatment where appropriate and now welcome the opportunity to treat patients within the UK.

Compared to the costs of conventional treatment, the cost per QALY of this option is £19,187.

Develop three PBT facilities in England

4.16. Developing three sites in a single phase, each with three gantries per beam, would provide capacity in excess of current demand for proton therapy in the UK. So, two sub-options to the three site solution are considered:

1. Develop three sites in phase I

Developing three sites in a single phase will provide capacity to treat 2,025 patients (based on the central estimate of the throughput range), 538 more than required to treat all UK indications.

4.17. The PBT Steering Committee has agreed that proton therapy facilities commissioned on behalf of the NHS in England should only offer treatments that would be offered to NHS patients. This approach will ensure that only evidence based treatments are provided at centres in England and supports controlled expansion of the service based

[3] Based on the central estimate of the range of throughput, 675 patients per site, per annum

on evidence review and analysis. There is variability in the list of indications referred for PBT internationally, but the core lists are similar between England and European countries. To achieve maximum efficiency, and meet the above requirement, sites are likely to utilise excess capacity by seeking patients from overseas. However, filling capacity with overseas patients represents a significant risk for English centres: the market is untested and many countries, including Italy, Holland, France and Sweden are already increasing their proton capacity.

4.18. Using the assumption that each site will have the same configuration and receive the same average casemix of patients as the two site option, the cost per NHS patient, will be equivalent to the two-site solution if each site is used to optimal capacity. Because a large proportion of the per patient costs of PBT are fixed (approximately 80%), any under-utilisation of capacity will significantly increase the costs to treat each NHS patient. As an indication of the scale of the risk to increased costs per NHS patient, the spare capacity of three sites represents over a quarter of total capacity.

2. Develop three sites with two rooms each in Phase I, adding third rooms in Phase II

Three organisations may each initially construct and operate two rooms, with scope to install and operate third rooms once there is sufficient demand. Operating two treatment rooms compared to three per cyclotron has consequences for efficiency:

- Clinical efficiency

The time taken to switch the proton beam between rooms affects its marginal utility: as the number of rooms increases, the number of patients treated in a given time period declines. Evidence from operational sites in North America shows that equipment utilisation for two room sites is around 90%, compared to 87% for three rooms. Due to the greater clinical efficiency of two rooms, each site would have 3% more capacity than a three room facility.

- Cost efficiency

Maximum efficiency is achieved with three rooms due to the marginal increase in the number of fractions that can be delivered with a third room and the resulting distribution of fixed costs across more patients.

As three rooms per cyclotron delivers optimal cost-efficiency, under option 3b), each site will be relatively inefficient until third rooms are installed. The majority of the costs of delivering proton therapy are inflexible (estimated to be 80%) so the costs per patient are estimated to be an average of £49,970 until third gantries are utilised at each site.

5. Incremental Cost Effectiveness Ratio per patient

5.1. The incremental cost effectiveness ratio (ICER) measures the difference in costs and benefits of each intervention compared to the do nothing baseline. Table 6 below shows the average difference in costs and benefits per patient of the different proton therapy options, compared to conventional treatment.

Table 6: ICER, per patient treated

Option	*Proportion of capacity used by NHS**	*Incremental cost*	*Incremental QALY gain*	*ICER*
Do nothing				
Treat patients overseas	-	103,660	2.5	41,140
Develop PBT in England				
1 facility	100%	54,808	2.5	21,751
2 facilities	100%	34,359	1.8	19,187
3 facilities:				
a) 3 rooms in phase I	*73%*	34,359	1.8	19,187
b) 2 rooms in phase I, 3 rooms in phase II	*100%*	44,879	1.8	25,062

***includes Devolved Administrations where capacity allows**
†reflects incremental cost for Phase I, in Phase II, costs will be equivalent to option 3a).

Based on the ICERs above, developing two sites, or developing three sites with three rooms in Phase I deliver each Quality Adjusted Life Years (QALY) gained for the lowest cost (£19,187). However, the three site solution (3a)) is reliant on all excess capacity being utilised by non-NHS patients, after accounting for NHS demand. NHS patients will account for 73% of total capacity under this option, placing a heavy reliance on income from non-NHS patients to make up the shortfall. Operating at any less than full capacity increases the per patient cost of this options, leaving the two-site solution as the most cost effective option.

The significant risk associated with securing large numbers of non-NHS patients for treatment cannot be quantified at this stage, but is considered to be sufficiently large to negatively impact the cost effectiveness of fully developing three sites in a single phase.

Based on the analysis above and the risks considered, the preferred option for the development of PBT services in England is the provision of two facilities, each with three rooms and an anticipated throughput of 600-750 patients per annum.

Future demand increases

5.2. The anticipated throughput of the two-site solution will provide sufficient capacity to treat the current list of indications. Subject to future increases in demand, a second phase of the project, delivering a third site may be required.

The following list highlights the main factors that will determine the need for further capacity:

- evidence from the English sites, once operational, of throughput capacity
- demand from the Republic of Ireland to offer proton therapy to their patients
- the referral rates and resulting casemix of adult patients with valid indications
- further international evidence of the benefits of proton therapy for different indications.

5.3. DH will develop a strategy that identifies the trigger point for a third site as the programme develops. Subsequent cost-effectiveness analysis will inform decisions for future phases of the project.

6. Sensitivity Analysis

The following sensitivity analyses consider the impact of patient throughput on the highest scoring options, as indicated by the Incremental Cost Effectiveness ratio (ICERs) in Table 6 above.

Range of throughput per site

6.1. There is no international evidence of Proton beam Therapy (PBT) facilities providing treatment to an equivalent casemix of patients as that proposed for the UK. Due to the uncertainty of throughput capacity, a range of 25% between the minimum and maximum anticipated patient number per year is applied for all options for PBT facilities in England.

Option 1: One site

6.2. With only one facility available, patients with the highest need would be prioritised for treatment. The baseline assumption for one site is throughput of 400 patients per annum. The estimated range of patients treated per year is between 360 and 450.

Site capacity affects the ICER of each option. As shown in Table 7 below, the range of ICER values is from £20,105 to £25,761 at the upper and lower limits of throughput capacity.

Table 7: Impact of throughput range on cost per QALY (ICER) for one site

Assumption	*Patients per site*	*Average cost/patient*	*Incremental cost*	*QALY gain*	*ICER*
Baseline	400	61,148	54,808	2.5	21,751
Lower bound	360	67,942	61,602	2.5	24,448
Upper bound	450	54,353	48,013	2.5	19,055

Option 2: Two sites

6.3. With multiple sites providing capacity to treat the full casemix of patients, the Programme Board estimate that 600-750 patients per annum can be treated at a single PBT facility, assuming each receives an average casemix of patients from the list of indications. The central estimate of 675 patients per annum is used in the analysis above.

As shown in Table 8 below, treating 600 patients per annum would give a per patient cost of £42,047, compared to £33,638 if throughput is 750 patients per site per year. Annual throughput of 750 patients per site is greater than the current expected demand from the UK. So, as with the option to develop three sites in a single phase, to maintain a low cost per NHS patient, sites would need to seek patients from abroad. Failure to utilise capacity would increase the unit costs of treatment.

Table 8: Impact of throughput range on cost per QALY (ICER) for two sites

Assumption	*Patients per site*	*Average cost/patient*	*Incremental cost*	*QALY gain*	*ICER*
Baseline	675	39,450	34,359	1.8	19,187
Lower bound	600	44,381	39,290	1.8	21,941
Upper bound	750	35,505	30,414	1.8	16,984

If throughput is at the lower limit of the range, 600 patients per site per annum, the one-site solution becomes the preferred option: based on the ICERs, one QALY can be generated at a cost of £21,751 under the one site solution compared to £21,941 if the maximum annual throughput at two sites is 600 patients. To be at least as cost-effective as the one site-solution, at least 610 patients must be treated per site per year under the two site option. 610 patients per site per year is close to the lower limit of the patient range and it is anticipated that sites will achieve this rate.

Option 3a) Three sites, single phase

6.4. Using the assumption that any spare capacity will be utilised by treating patients from overseas, the impact of differences in throughput will be the same under this option as the two-site option above. However, with overall capacity for fewer patients, the risk of utilising spare capacity is reduced. At the lower bound (600 patients per site per annum), there will only be spare capacity for 313 patients, compared to 538 at the baseline and 763 at the maximum.

Section 6.5. following includes sensitivity analysis for the impact of under-utilisation rates for the baseline capacity case.

Option 3b) Three sites, two phases

6.5. The sensitivity analysis for this option considers the range of throughput for Phase I of development as shown in Table 9 below.

Table 9: Impact of throughput range on cost per QALY (ICER) for three sites

Assumption	*Patients per site*	*Average cost/patient*	*Incremental cost*	*QALY gain*	*ICER*
Baseline	450	49,800	44,709	1.8	24,967
Lower bound	400	56,025	50,934	1.8	28,443
Upper bound	500	44,820	39,729	1.8	22,186

Under the most optimistic scenario, with throughput of 500 patients per site, the cost per QALY gain under this option is higher than the least optimistic level of throughput (600 patients per annum) under the two site option, or option 3a).

6.6. Impact of under-utilisation of three site capacity under option 3a)

Under the three site option, if all sites can utilise their full capacity, the costs per NHS patient will be the same as under the two site option. However, there is a significant risk that sites will fail to meet this requirement due to the necessary reliance on income from non-NHS patients. Any capacity utilisation less than 100% will increase the average cost per NHS patient, reducing the favourability of this option. As shown in Table 10 below, with no treatment of non-NHS patients, the incremental cost-effectiveness of fully developing three sites in one phase makes this the least preferred option for developing PBT in England.

Table 10: Impact of capacity utilisation rates on ICER, three sites fully developed in phase I

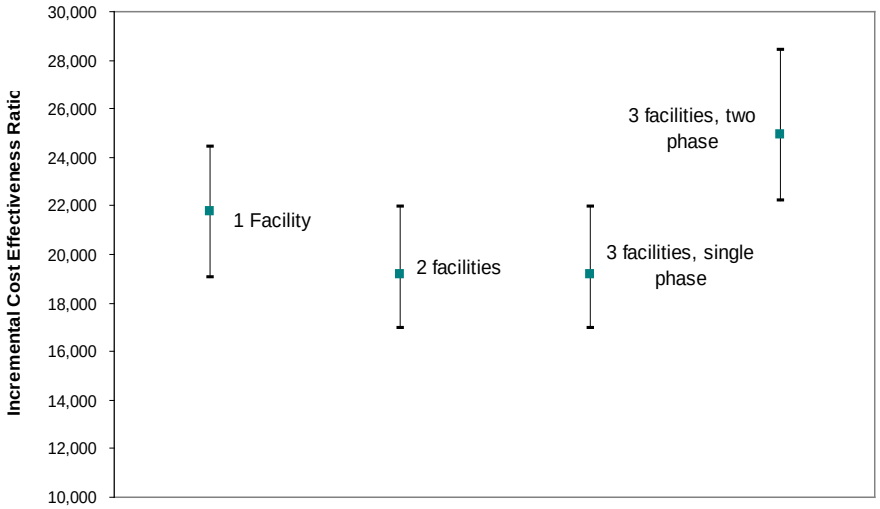
Capacity utilisation	*Average cost/ patient*	*Incremental cost*	*Incremental QALY gain*	*ICER*
Full capacity (100%)	39,450	34,359	1.8	19,187
NHS patients only (73%)	53,687	48,596	1.8	27,137

6.7. Results

Comparing the ICER for each option at different levels of throughput does not alter the preferred option from the results of the baseline analysis.

As illustrated in Figure 2 below, the baseline assumption for the one site solution has an ICER below the least optimistic case (lowest throughput) for the preferred option. At the maximum of the throughput range for one-site, the ICER will be below the central estimate for the two-site option.

Figure 2: Comparison of the impact of throughput ranges on the ICER of each option



Annex A: List of indications for UK patients

	Indication	Number of patients
Paediatric	Chordoma/ Chondrosacoma	15
	Rhabdomyosarcoma (Orbit)	5
	Rhabdomyosarcoma (Prameningeal and H&N)	15
	Rhabdomysarcoma(Pelvis)	10
	Osteosarcoma	3
	Ewings	9
	PPNET	5
	Ependymoma	25
	Low Grade Glioma	5
	Optic Pathway Glioma	12
	Craniphayngioma	15
	Medulloblastoma (PNET)	70
	Hodgkins	5
	Retinoblastoma	5
	Meninggioma	3
	Intracranial germinoma	10
	Nasopharynx (H&N)	15
	Difficult Cases Esthe/Neuro/Liver)	5
	Very Young Age	20
	Total	**252**
Adult	**Choroidial Melanoma**	100
	Ocular/Orbital	25
	Chordoma	60
	Chondrosarcoma	30
	Para- Spinal / Spinal Sarcoma	120
	Sacral Chordoma	60
	Meningoma	100
	Acoustic Neuroma	100
	Craniospinal NOS (Pineal)	10
	Head & Neck & Paranasal Sinuses	300
	PNET(medulloblastoma Intracranial)	30
	Difficult cases	300
	Total	**1,235**
	GRAND TOTAL	**1,487**