MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
04 June 2019

Agenda Item No	04.2
National Programme	Cancer
Clinical Reference Group	Radiotherapy
URN	1783

Title
Proton Beam Therapy for Children, Teenagers and Young Adults in the treatment of malignant and non-malignant tumours

Actions Requested	1. Support the adoption of the policy proposition.
	2. Recommend its approval as an IYSD.

Proposition
This policy proposition recommends that proton beam therapy (PBT), a form of radiotherapy, should be routinely commissioned for the treatment of children, teenagers and young adults with malignant (cancerous) and non-malignant tumours. In 2015, NHS England published two clinical commissioning policies to enable children, teenagers and young adults to access PBT services via the NHS Overseas Programme. This proposition amalgamates these existing policies into one single policy in preparation for the ramp-up of the NHS PBT service in England. In addition to the existing eligibility criteria, the policy proposition expands the current eligibility criteria for use of PBT in the treatment of children, teenagers and young people, enabling wider access to the treatment within this age range. It is estimated that, at full capacity, approximately 550 children, teenagers and young adults will benefit from treatment with PBT under this policy. To date, this policy proposition has only undergone stakeholder testing. It has been brought to CPAG ahead of public consultation in order to enable patients to access PBT services in England as soon as possible, with the first centre now open in Manchester. Public consultation on this policy proposition is expected to take place in June 2019 for a period of 30 days and is expected to be received positively by stakeholders.

Clinical Panel recommendation

The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes / Head of Mental Health Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

1. The Benefits of the Proposition – Proton beam therapy (PBT) versus photon x-ray radiotherapy (PRT) in <u>medulloblastoma</u>

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	This outcome was out of the scope of this evidence review (and this is the same for all the indications in this review)
2.	Progression free survival	This outcome was out of the scope of this evidence review (and this is the same for all the indications in this review)
3.	Mobility	This outcome was out of the scope of this evidence review (and this is the same for all the indications in this review)
4.	Self-care	This outcome was out of the scope of this evidence review (and this is the same for all the indications in this review)
5.	Usual activities	This outcome was out of the scope of this evidence review (and this is the same for all the indications in this review)

6.	Pain	This outcome was out of the scope of this evidence review (and this is the same for all the indications in this review)
7.	Anxiety / Depression	This outcome was out of the scope of this evidence review (and this is the same for all the indications in this review)
8.	Replacement of more toxic treatment	This outcome was out of the scope of this evidence review (and this is the same for all the indications in this review)
9.	Dependency on care giver / supporting independence	This outcome was out of the scope of this evidence review (and this is the same for all the indications in this review)
10.	Safety	**Hearing loss of grade 3 or 4 on the SIOP Boston scale[1]** Hearing loss of grade 3 means more than 20 dB sensorineural hearing loss at or above 2 kHz; grade 4 mean more than 40 dB sensorineural hearing loss at or above 2 kHz. Paulino et al 2018 reported that the prevalence of hearing loss of grade 3 or 4 did not differ significantly between children who had PBT and PRT. Rates of hearing loss are an objective measure of otological damage. However, they do not indicate the impact of hearing loss on the ability to carry out normal activities or on quality of life. This result indicates that there is no clinical benefit on hearing preservation from the use of PBT rather than PRT. Although the study was unrandomized, the biases were in favour of PBT, so the result is reliable. **Sex hormone deficiency** Eaton et al 2016 defined sex hormone deficiency as a clinical diagnosis of and/or initiation of treatment for abnormally low levels of sex hormones. Eaton et al 2016 reported a multivariable odds ratio, adjusted for gender, date of diagnosis, histology, location of radiotherapy boost, age at diagnosis and craniospinal radiation dose, of 0.06, 95% CI 0.01 to 0.55, p=0.013. An absence of sex hormone deficiency is more likely to be associated with normal sexual development. However, the authors do not report whether participants differed in rates of symptoms or in quality of life.

[1] A hearing loss scale: grade 0= ≤20dB loss at all frequencies, grade 1 = > 20dB sensorineural hearing loss (SNHL) above 4 kHz, Grade 2 = > 20dB SNHL at 4 kHz, Grade 3 = > 20 dB SNHL at or above 2 kHz, Grade 4 = Grade 2 = >40 dB SNHL at or above 2 kHz.

		This result is not clear or reliable. The PBT participants were on average more than two years younger than those who received PRT. This may have affected the susceptibility of adjacent tissue to irradiation and biased the study, for which multivariate analysis may not have fully adjusted, or affected the diagnostic rates of sex hormone deficiency. The authors suggest that the differences that they report may be due to biases in diagnostic testing and acceptance of treatment at the two hospitals. Differences in the timing and purpose of data collection may also have introduced bias. It is uncertain whether the reported differences would have a material impact on participants' symptoms and quality of life. The result's reliability is undermined by the non-randomised nature of the study and the differences between the two groups of participants. **Hypothyroidism** Eaton et al 2016 defined hypothyroidism as a clinical diagnosis of and/or initiation of treatment for an underactive thyroid. Eaton et al 2016 reported a multivariable odds ratio, adjusted for gender, date of diagnosis, histology, location of radiotherapy boost, age at diagnosis and craniospinal radiation dose, of 0.13, 95% CI 0.04 to 0.41, p<0.001. Normal thyroid function is more likely to be associated with normal health and development. However, the authors do not report whether participants differed in rates of symptoms or in quality of life. This result is not clear or reliable as per previous comment. **Endocrine replacement therapy** Eaton et al 2016 defined endocrine replacement therapy as the initiation of treatment for an endocrine abnormality. Eaton et al 2016 reported a multivariable odds ratio, adjusted for gender, date of diagnosis, histology, location of radiotherapy boost, age at diagnosis and craniospinal radiation dose, of 0.30, 95% CI 0.09 to 0.99, p=0.047. An absence of endocrine deficiency is more likely to be associated with normal health and development. However, the authors do not report whether participants differed in rates of symptoms or in quality of life. This result is not clear or reliable as per previous comment.. **Lower height**

		Eaton et al 2016 defined lower height as having a lower standard deviation score, a measure of difference in height. Eaton et al 2016 reported a parameter score, adjusted for gender, date of diagnosis, histology, location of radiotherapy boost, age at diagnosis and craniospinal radiation dose, of 0.89 (indicating greater height with PBT), 95% CI 0.24 to 1.54, p=0.008. Less than normal height is not desirable. However, the authors do not report how much shorter PRT participants were in absolute terms and whether this affected their quality of life. This result is not clear or reliable as per previous comment.
11.	Delivery of intervention	This outcome was out of the scope of this evidence review.

Other health metrics determined by the evidence review: Proton beam therapy versus photon x-ray radiotherapy in <u>medulloblastoma</u>		
No	Metric	Summary from evidence review
1.	Cost per quality-adjusted life year (QALY)	Cost per QALY is the incremental cost of one treatment over a less expensive one, divided by the extra QALYs which it yields. Hirano et al 2014 reported three different measures of quality of life, with these costs per QALY: EQ-5D[2] £16,100, HUI3[3] £8,710 and SF-6D[4] £14,900. A lower incremental cost effectiveness ratio indicates better value for money. This does not directly benefit individual patients but means that more patients can be treated with the resources available. All three metrics of quality of life give estimates of cost utility well below the threshold of acceptable value of money for the NHS. The results were robust to sensitivity analysis, but costs in Japan may differ from those in the NHS. Hirano et al 2014 used estimated risks of grade 3 or 4 hearing loss of: PRT average-risk 39% (sensitivity range 37% to 41%), PRT high-risk 47.1% (sensitivity range 44.6% to 49.7%), PBT average-risk 15.6% (sensitivity range 4.97% to 26.1%), PBT high-risk 26.5% (sensitivity range 18.4% to 34.7%). The PBT

[2] A standardised instrument for measuring health status
[3] The Health Utilities Index 3, a rating scale used to measure general health status and health-related quality of life
[4] Short form 6 dimension is a measure of health utility

		rates are similar to those reported in Paulino et al 2018, but the PRT rates are much higher. This may be because of improvements in radiotherapy techniques since the 1980s, when one of the studies (Schell MJ et al 1989) on which Hirano et al 2014 relied was published. So, hearing loss rates supported by modern evidence lie outside the sensitivity ranges used by Hirano et al 2014, casting doubt on the reliability of their conclusions.

2. The Benefits of the Proposition – Proton beam therapy versus photon x-ray radiotherapy in <u>ependymoma</u>		
No	*Outcome measures*	*Summary from evidence review*
10.	Safety	**Toxicity** Sato et al 2017 defined toxicity as any adverse reaction to treatment. Toxicity rates after PBT were 3/41 (7.3%), and after PRT 5/38 (13.2%), $\chi^2 = 0.237$, p=0.626 with Yates' correction (calculated by SPH). Three children treated with PBT developed radiation necrosis (2 in the 4th ventricle and 1 in the temporal lobe). Of the 5 adverse reactions to PRT, 3 children developed radiation necrosis (2 in the 4th ventricle and 1 in the frontoparietal region), 1 had a stroke and 1 developed a cavernoma. The avoidance of adverse treatment effects is valuable to patients, but Sato et al 2017 do not report the effect of these on symptoms or quality of life. This study does not indicate a difference between PBT and PRT in rates of adverse treatment effects. Children receiving PBT had a median age less than half that of the PRT group, being on average 3.2 years younger. Their follow-up was also on average 2.3 years shorter, which may have biased the study in favour of PBT, as there was less time for late adverse effects to emerge. The study had little power to detect differences in symptomatic adverse effects of treatment, reducing its reliability. **MRI abnormalities with associated symptoms** Gunther et al 2015 reported participants who had both an abnormality seen on MRI and an associated symptom. Reported asymptomatic radiological abnormalities were out-of-scope. Reported symptoms after radiotherapy included hemiplegia, ataxia, seizures and dysarthria.

		Rates of MRI abnormalities with associated symptoms after PBT were 4/37 (11%) and after PRT 3/35 (8.6%), $\chi^2 = 0.006$, p=0.938 with Yate's correction (calculated by SPH). Reductions in rates of symptomatic adverse treatment events would benefit patients. This study does not indicate that PRT is any safer than PRT. Patients with radiological abnormalities (mostly asymptomatic) were younger than those without (median age at treatment 2.7 years versus 4.2 years, p=0.2). Because the PBT patients were also on average younger, it is difficult to determine whether any reported differences between the two treatment groups are valid, or the result of confounding by age. The study had little power to detect differences in symptomatic adverse effects of treatment, reducing its reliability.
11.	Delivery of intervention	This outcome was out of the scope of this evidence review.

3. The Benefits of the Proposition – Proton beam therapy versus photon x-ray radiotherapy in <u>craniopharyngioma</u>		
No	*Outcome measures*	*Summary from evidence review*
10.	Safety	**Vascular morbidity** Vascular morbidity included moyamoya, stroke and vessel malformations. Bishop et al 2014 report that rates of vascular morbidity after PBT were 2/21 (10%), and after PRT were 3/31 (10%), p=1.0. Reductions in rates of symptomatic adverse treatment events would benefit patients. This study does not indicate that PBT is any safer than PRT. The median length of follow-up for participants treated with PRT was more than 3 times that in those who received PBT. However, the reporting of adverse effects was a simple count, not an annual rate, and the authors made no adjustment for duration of follow-up. The annual rate of adverse events may have been significantly higher among the PBT group, which limits the study's reliability. **Visual morbidity** Bishop et al 2014 defined visual morbidity as any deviation in baseline vision (field cuts or acuity) on physical and ophthalmologic examination.

		Bishop et al 2014 report that rates of visual morbidity after PBT were 1/21 (5%), and after PRT were 4/31 (13%), p=0.637. Reductions in rates of symptomatic adverse treatment events would benefit patients. This study does not indicate that PBT is any safer than PRT – as previous comment in this section. **Hypothalamic obesity** Bishop et al 2014 defined hypothalamic obesity "on the primary clinician's diagnosis of morbid or hypothalamic obesity during follow-up". Bishop et al 2014 report that rates of hypothalamic obesity after PBT were 4/21 (19%), and after PRT were 9/31 (29%), p=0.523. Reductions in rates of symptomatic adverse treatment events would benefit patients. This study does not indicate that PBT is any safer than PRT – as previous comment in this section. **Endocrinopathy** Endocrinopathy means disorders of the endocrine system; it is not defined by Bishop et al 2014. Bishop et al 2014 report that rates of endocrinopathy after PBT were 16/21 (76%), and after PRT were 24/31 (77%), p=1.0 Reductions in rates of symptomatic adverse treatment events would benefit patients. This study does not indicate that PBT is any safer than PRT – as previous comment in this section.
11.	Delivery of intervention	This outcome was out of the scope of this evidence review.

4. The Benefits of the Proposition – Proton beam therapy versus photon x-ray radiotherapy in <u>salivary gland tumours</u>		
No	*Outcome measures*	*Summary from evidence review*
10.	Safety	**Dermatitis**

		Grant al 2015 defined dermatitis as brisk erythema, moderate oedema or moist desquamation. Grant al 2015 report that rates of dermatitis after PBT were 7/13 (54%), and after PRT were 6/11 (55%), p=1.0 The avoidance of dermatitis would be of benefit to patients. This study does not indicate that PBT is less likely to cause dermatitis than PRT. The median length of follow-up for participants treated with PRT was more than 10 times that in those who received PBT. However, the reporting of adverse effects was a simple count, not an annual rate, and the authors made no adjustment for duration of follow-up. The annual rate of adverse events may have been significantly higher among the PBT group. The study was small and underpowered, so its results are less reliable. **Dysphagia** Grant al 2015 defined dysphagia as pain requiring change in diet and/or nutritional support. Grant al 2015 report that rates of dysphagia after PBT were 0/13 (0%), and after PRT were 3/11 (27%), p=0.08. The avoidance of dysphagia would be of benefit to patients. This study does not indicate that PBT is any less likely to cause dysphagia than PRT. The median length of follow-up for participants treated with PRT was more than 10 times that in those who received PBT. However, the reporting of adverse effects was a simple count, not an annual rate, and the authors made no adjustment for duration of follow-up. The annual rate of adverse events may have been significantly higher among the PBT group. The study was small and underpowered, so its results are less reliable. **Otitis externa** Otitis externa was defined by Bishop et al 2014 as discharge from ear canal. Bishop et al 2014 report that rates of otitis externa after PBT were 1/13 (8%), and after PRT were 2/11 (18%), p=0.58. The avoidance of otitis externa would be of benefit to patients. This study does not indicate that PBT is any less likely to cause otitis externa than PRT. The median length of follow-up for participants treated with PRT was more than 3 times that in those who received PBT. However, the reporting of adverse

		effects was a simple count, not an annual rate, and the authors made no adjustment for duration of follow-up. The annual rate of adverse events may have been significantly higher among the PBT group. The study was small and underpowered, so its results are less reliable. **Mucositis** Mucositis was defined by Bishop et al 2014 as patchy or confluent ulcerations. Bishop et al 2014 report that rates of mucositis after PBT were 6/13 (46%), and after PRT were 10/11 (91%), p<0.05 reported by authors, p=0.0335 calculated by SPH The avoidance of mucositis would be of benefit to patients. This study does not indicate that PBT is any less likely to cause mucositis than PRT. The median length of follow-up for participants treated with PRT was more than 3 times that in those who received PBT. However, the reporting of adverse effects was a simple count, not an annual rate, and the authors made no adjustment for duration of follow-up. The annual rate of adverse events may have been significantly higher among the PBT group. The study was small and underpowered, so its results are less reliable.
11.	Delivery of intervention	This outcome was out of the scope of this evidence review.

5. The Benefits of the Proposition – Proton beam therapy versus photon x-ray radiotherapy in <u>retinoblastoma</u>		
No	*Outcome measures*	*Summary from evidence review*
10.	Safety	**Second malignancies in the radiation field, 10-year incidence** Second malignancies arising in the field irradiated to treat the retinoblastoma are new tumours in the brain, orbits, facial sinuses, temporal bones or soft tissue overlying the temporal bones. Sethi et al 2014 report that rates of second malignancies after PBT were 0/55 (0%), 95% CI not reported, and after PRT were 4/31 (14%), 95% CI 3% to 31%; p=0.015. A reduced risk of secondary malignancies would be of great benefit to patients.

		This study does not indicate a benefit from PBT. The median length of follow-up for participants treated with PRT was nearly twice that in those who received PBT. However, the reporting of adverse effects was a cumulative total over ten years, not an annual rate, and the authors made no adjustment for duration of follow-up. The annual rate of adverse events may have been significantly higher among the PBT group. PBT participants were also older when treated, another potential source of bias. The study was small and underpowered, so its results are less reliable. **Second malignancies anywhere, 10-year incidence** Second malignancies are new tumours arising anywhere in the body. Sethi et al 2014 report that rates of second malignancies after PBT were [figure not reported]/55 (5%), 95% CI 0% to 21%, and after PRT were 4/31 (13%), 95% CI 3% to 31%; p=0.120. A reduced risk of secondary malignancies would be of great benefit to patients. This study does not indicate a benefit from PBT – as previous comment in this section.
11.	Delivery of intervention	This outcome was out of the scope of this evidence review.

6. The Benefits of the Proposition – Proton beam therapy versus photon x-ray radiotherapy tumours of <u>several primary sites</u>		
No	*Outcome measures*	*Summary from evidence review*
10.	Safety	**Decline in intelligence quotient, all participants** Intelligence quotient is an age-adjusted measure of reasoning skills. After PBT, Kahalley at al 2017 report “no statistically significant decline” in IQ, though the absolute value is not reported, 95% CI for gradient -1.6 to 0.2, p= 0.130. After PRT, there was a loss of 1.1 IQ points per year, 95% CI -1.8 to -0.4; p= 0.004. The change in IQ over time in the PBT and PRT groups was -0.7 and -1.1 points per year respectively, p= 0.509. A reduced risk of loss of intelligence would be of benefit to patients.

		This result does not indicate a benefit in intelligence preservation from PBT, because the results are inconsistent and indicate at best a small difference in intelligence quotients between the two treatments. The authors conclude that “this study does not provide clear evidence that [PBT] results in clinically meaningful sparing of global IQ significantly exceeding that of modern [PRT] protocols.” They also note that “it is difficult to ascribe clinical meaningfulness to a difference in IQ change as small as that observed in this sample.” They suggest that “modern [PRT] protocols may be so successful at limiting exposure to healthy surrounding brain tissue that patients treated since 2002 are not experiencing the extent of neurocognitive decline reported in previous studies”. The study’s results appear reliable. **Decline in intelligence quotient, participants who received cranio-spinal irradiation** Intelligence quotient is an age-adjusted measure of reasoning skills. After PBT, Kahalley at al 2017 report “no statistically significant decline” in intelligence quotient, though the absolute value and 95% CI for gradient are not reported. After PRT, there was “no statistically significant decline”, absolute value and 95% CIs not reported, p=0.060. The change in IQ over time in the PBT and PRT groups was -0.8 and -0.9 points per year respectively, p= 0.890. A reduced risk of loss of intelligence would be of benefit to patients. This result does not indicate a benefit in intelligence preservation from PBT participants who received cranio-spinal irradiation. The result appears reliable. **Decline in intelligence quotient, participants who received focal irradiation** Intelligence quotient is an age-adjusted measure of reasoning skills. After PBT, Kahalley at al 2017 report “no statistically significant decline” in IQ, though the absolute value is not reported, 95% CI for gradient 95% CI -2.0 to 0.8, p=0.401. After PRT, there was a loss of 1.6 points per year, 95% CI -3.0 to -0.2, p= 0.026. The change in IQ over time in the PBT and PRT groups was -0.6 and -1.6 points per year respectively, p= 0.342. A reduced risk of loss of intelligence would be of benefit to patients.

		This result does not indicate a benefit in intelligence preservation from PBT - as previous comment in this section. **Health-related quality of life (QoL)** Yock et al 2014 assessed health-related QoL with the parent-proxy report versions of the PedsQL Core Module. It assesses QoL in two domains: physical (concerned with active daily living) and psychosocial (concerned with mood and interpersonal relationships). Yock et al 2014 report mean PedsQL total core scores of 75.9 after PBT, and 65.4 after PRT, unadjusted p=0.002, not significant. An improvement in QoL of meaningful size would be of great benefit to patients. However, this result is neither reliable nor statistically significant. Since family income and quality of life may differ between people of different ethnicities, the significantly higher proportion of children treated with PBT who were white may explain the effects reported here. The authors say that "The proton cohort likely includes a larger proportion of patients from a higher socio-economic status". They also note that "The more recently treated proton cohort … may have benefited from improved techniques over time in all the treatment arenas, including surgery, chemotherapy and radiation therapy, which would skew the results to favor the proton cohort." The authors report "As the marginal error rates are of primary interest, rather than an experiment-wise rate, the data analysis … has not been adjusted for multiple comparisons." This unorthodox approach raises the risk of differences being deemed significant when they were the result of the many comparisons being made. We have therefore calculated Bonferroni-corrected P-values, dividing the standard significance level of 0.05 by the number of QoL comparisons in the paper (35) to yield an adjusted p-value of 0.00143. So, the reported difference is not statistically significant. Parents' scores may be less valid because of lack of first-hand knowledge of the benefits and adverse effects of treatment. **Health-related QoL, physical summary score** Yock et al 2014 assessed health-related QoL with the parent-proxy report versions of the PedsQL Core Module. The physical summary score is concerned with active daily living. Yock et al 2014 report mean PedsQL physical summary scores of 78.4 after PBT, and 68.1 after PRT, unadjusted p=0.015, not significant.

		An improvement in physical summary score QoL of meaningful size would be of great benefit to patients. However, this result is neither reliable nor statistically significant – as per previous comment in this section. **Health-related QoL, psychosocial summary score** Yock et al 2014 assessed health-related QoL with the parent-proxy report versions of the PedsQL Core Module. The psychosocial summary score is concerned with mood and interpersonal relationships. Yock et al 2014 report mean PedsQL psychosocial summary score of 74.5 after PBT, and 64.0 after PRT, unadjusted p=0.001, borderline significant depending on rounding. An improvement in psychosocial QoL of meaningful size would be of great benefit to patients. However, this result is neither reliable nor of clear statistical significance – as per previous comment in this section. **Leukopaenia** Leukopaenia is an abnormally low level of white cells in the bloodstream. Song et al 2014 report rates of grade 3 leukopaenia after PBT of 14/30 (57%), and after PRT of 6/13 (46%); rates of grade 4 leukopaenia were 2/30 (7%) and 4/13 (31%); p=0.069. A reduced risk of leukopaenia would be of benefit to patients if it led to a lower incidence of infection. This result does not indicate a significant reduction in the risk of leukopaenia from the use of PBT. It is based on small numbers and therefore not reliable. **Anaemia** Anaemia is an abnormally low level of haemoglobin in the bloodstream. Song et al 2014 report rates of grade 3 anaemia after PBT of 0/30 (0%), and after PRT of 2/13 (15%), p=0.493. A reduced risk of anaemia would be of benefit to patients if it led to reduced symptoms. This result does not indicate a significant reduction in the risk of anaemia from the use of PBT. It is based on small numbers and therefore not reliable.

		Thrombocytopaenia Thrombocytopaenia is an abnormally low number of platelets in the bloodstream. Song et al 2014 report rates of grade 3 thrombocytopaenia after PBT of 6/30 (20%), and after PRT of 4/13 (31%); rates of grade 4 thrombocytopaenia were 1/30 (3%) and 3/13 (23%); p=0.012. A reduced risk of thrombocytopaenia would be of benefit to patients if it led to reduced symptoms. This result does not indicate a significant reduction in the risk of thrombocytopaenia from the use of PBT. The authors carried out 15 tests of statistical significance but did not adjust the level of statistical significance to reflect this. Bonferroni correction of their significance threshold of p=0.05 gives an adjusted P-value of 0.05/15=0.0033. So, the reported difference is not statistically significant. It is also based on small numbers and therefore not reliable. **Platelet transfusion** Platelet transfusion is a treatment of thrombocytopaenia, an abnormally low number of platelets in the bloodstream. Song et al 2014 report rates of platelet transfusion after PBT of 5/30 (17%), and after PRT of 6/13 (46%), p=0.042. A reduced risk of thrombocytopaenia would be of benefit to patients if it led to reduced need for platelet transfusion. This result does not indicate a significant reduction in the risk of platelet transfusion from the use of PBT. The authors carried out 15 tests of statistical significance but did not adjust the level of statistical significance to reflect this. Bonferroni correction of their significance threshold of p=0.05 gives an adjusted P-value of 0.05/15=0.0033. So, the reported difference is not statistically significant. It is also based on small numbers and therefore not reliable. **Dysphagia** Dysphagia is difficulty with or pain on swallowing. Song et al 2014 report rates of dysphagia after PBT of 14/30 (47%), and after PRT of 2/13 (15%), p=0.086. A reduced risk of dysphagia would be of benefit to patients.

		This result does not indicate a significant reduction in the risk of dysphagia from the use of PBT. It is based on small numbers and therefore not reliable. **Diarrhoea** Diarrhoea is the passage of frequent loose bowel movements. Song et al 2014 report rates of diarrhoea after PBT of 0/30 (0%), and after PRT of 3/13 (23%), p=0.023. A reduced risk of diarrhoea would be of benefit to patients. This result does not indicate a significant reduction in the risk of diarrhoea from the use of PBT. The authors carried out 15 tests of statistical significance but did not adjust the level of statistical significance to reflect this. Bonferroni correction of their significance threshold of p=0.05 gives an adjusted P-value of 0.05/15=0.0033. So, the reported difference is not statistically significant. It is also based on small numbers and therefore not reliable. It is also based on small numbers and therefore not reliable.
11.	Delivery of intervention	This outcome was out of the scope of this evidence review.

CI = confidence interval, HR = hazard ratio, ICER = incremental cost-effectiveness ratio, IQ = intelligence quotient, OR = odds ratio, PBT = proton beam therapy, PRT = photon radiotherapy, QALY = quality-adjusted life

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
The draft proposal received the full support of the Cancer PoC Board on 28th March 2019, who recommended that the policy undergo a 30 day public consultation.