CLINICAL PRIORITIES ADVISORY GROUP
14 April 2021

Agenda Item No	3.1
National Programme	Cancer
Clinical Reference Group	Radiotherapy
URN	1787

Title
Proton Beam Therapy for Breast Cancer

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

Proposition
Not for routine commissioning. The policy proposition recommends that proton beam therapy (PBT) should not be made routinely available for the treatment of breast cancer. The proposition has been developed based on the findings of evidence reviews in line with standard Methods. The review of evidence demonstrated that there was not enough clinical evidence to make the treatment routinely available at this time.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a not for 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 Cancer Programme confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care 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.	Engagement Report
3.	Evidence Summary x 2
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	**Benefit of PBT vs photon based partial breast irradiation (PBI)** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Overall survival was measured as time from diagnosis to time of death or last follow-up (Chowdhary et al 2019). In Chowdhary et al 2019, five-year overall survival was 91.9% for PBT patients (n=871) and 88.9% for photon radiotherapy patients (n=723,621) (95% CI not reported). Overall survival was not associated with PBT in multivariate analysis (HR 0.85 (95%CI 0.68 to 1.07), p=0.168). This analysis adjusted for factors including age, race, insurance status, comorbidity, treatment facility type, income, residence location, education, tumour side, stage, receptor status, chemotherapy, endocrine therapy, type of surgery and year of diagnosis. There was also no significant association between overall survival and PBT for subgroups of patients based on tumour side, quadrant location, type of surgery (mastectomy vs breast conserving), node positivity, N2-N3 positivity or the inclusion of lymph node irradiation. A high overall survival rate is important to clinicians, patients and their families. There was no difference for survival outcomes between different patient groups. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data

		from a national database of patients treated in the US between 2004 and 2014. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. The median follow-up of 62 months (range not reported) may not be long enough to assess the impact of treatment on overall survival.
		Benefit of PBT in non-comparative studies Overall survival was measured from end of treatment to time of death or last follow-up. In Luo et al 2019 (n=42), overall survival was 97.2% (95%CI not reported) at a median follow-up of 35 months (range 1 to 55). The high overall survival rate of 97% will be of importance to clinicians, patients and their families. The results of this small prospective case series should be treated with caution. It does not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted at 1 US centre between 2013 and 2015. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 35 months may not be long enough to assess the impact of treatment on overall survival.
2.	Progression free survival	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Not reported.
3.	Mobility	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Not reported.
4.	Self-care	**Benefit of PBT vs photon based PBI**

		Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Not reported.
5.	Usual activities	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Not reported.
6.	Pain	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Not reported.
7.	Anxiety / Depression	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Not reported.
8.	Replacement of more toxic treatment	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Not reported.

9.	Dependency on care giver / supporting independence	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Not reported.
10.	Safety	**Benefit of PBT vs photon based PBI** A range of safety and adverse events were reported at 5 and 7 years follow-up including breast pain, oedema, fibrosis, fat necrosis, rib pain or fracture as well as physician-assessed skin toxicities which were graded on a 4-point scale (none; mild; moderate; severe). No further definition of the grading categories was provided. In addition, telangiectasia[1] was assessed on a 4-point scale (none; 1-2cm^2; 2-4cm^2; >4cm^2). In Galland-Girodet et al 2014, there was no significant difference between the groups for rates of erythema or dry or moist desquamation (skin toxicities) (figures not provided). There was also no significant difference between the groups in incidence of breast pain, oedema, fibrosis, fat necrosis, rib pain or fracture (figures not provided). Where significant differences existed, these favoured the photon radiotherapy group. For example: • At 5 years there were significantly more patients with moderate skin colour change with PBT (44% vs 2%, p≤0.0001) and significantly more patients developed patchy atrophy in the irradiation portal with PBT (50% vs 5%, p≤0.0001). • At 7 years there was significantly worse[2] skin colour change (p=0.02) and late skin toxicity (p=0.029) with PBT (figures not provided). There were also significantly more patients with telangiectasia >4cm^2 with PBT (38.5% vs 4%, p=0.0013). The skin toxicity and other safety outcomes reported either showed no difference between the groups or showed worse outcomes with PBT. Where figures for the outcomes were reported, the proportion of patients affected was between one third and half of PBT patients compared to 5% or less of photon based partial breast irradiation patients. These results should be treated with caution. These results are based on a small, non-randomised trial which included 79 patients

[1] Dilation of the capillaries causing red or purple clusters on the skin or other organs, often spidery in appearance (https://en.oxforddictionaries.com/definition/telangiectasia)
[2] Not further defined. It is not clear from the published study if this refers to the severity of the skin condition or the proportion of patients experiencing either skin colour change or late skin toxicity

		who received photon radiotherapy and 19 patients who received PBT and had a median follow-up of 82.5 months. The study was conducted at 3 US centres over a 3 year period from 2003 to 2006 which may limit the applicability to current UK practice. The use of PBT was determined by proton-beam availability rather than randomised patient selection. There were no significant differences between the treatment groups at baseline. Some details on safety outcomes were only reported graphically without precise figures.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Skin toxicity was assessed by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. On this scale Grade 1 = '*mild*', Grade 2 = '*moderate*', Grade 3 = '*severe or medically significant but not immediately life-threatening*', Grade 4 = '*life-threatening consequences*' and Grade 5 = '*death related to adverse event*'[3]. Two specific skin toxicity adverse events were assessed by DeCesaris et al 2019: radiation dermatitis[4] and skin hyperpigmentation[5]. *Radiation dermatitis*: There were no Grade 4 or 5 cases. There was no significant difference in Grade 3 radiation dermatitis between PBT (n=39) and photon (n=47) radiotherapy (5.1% vs 4.3%, p=0.848). Acute radiation dermatitis ≥ Grade 2 was statistically significantly higher with PBT (69.2% vs 29.8%, p<0.01). The highest recorded grade of radiation dermatitis was also statistically significantly higher with PBT (p=0.002). *Skin hyperpigmentation*: There was no significant difference between PBT and photon radiation for skin hyperpigmentation ≥ Grade 2 (7.7% vs 12.8%, p=0.502). There was also no significant difference in the highest recorded grade of skin hyperpigmentation (p=0.413). At first clinical follow-up (within 8 weeks of treatment completion) there was no difference in sustained skin reactions between PBT (n=29) and photon radiotherapy (n=41) (Grade 1 radiation dermatitis 17.2% vs 19.5%, p=0.810; Grade 1 skin hyperpigmentation 65.5% vs 61.0%, p=0.698).

[3] https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf

[4] Radiation dermatitis was scored as grade 1 = '*faint erythema or dry desquamation*'; grade 2 = '*moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema*'; grade 3 = '*moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion*'; grade 4 = '*life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated*'; grade 5 = '*death*'

[5] Skin hyperpigmentation was scored as grade 1 = '*hyperpigmentation covering <10% body service area; no psychological impact*'; grade 2 = '*hyperpigmentation covering >10% body service area; psychological impact*'. Grades 3 to 5 not applicable for this adverse event

		Skin toxicity adverse events are important outcomes as they may affect function and quality of life. There was more Grade 2 (moderate) acute radiation dermatitis with PBT but there was no significant difference at clinical follow-up. There was no difference between the treatment groups in skin hyperpigmentation. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data from patients treated at 1 US centre between 2015 and 2017. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. Only patients with weekly on-treatment visit documentation of acute treatment related toxicities were included. Data from first clinical follow-up were only available for 74% and 87% of PBT and photon patients respectively. Toxicities were primarily scored by the same physician for both treatments.
		Benefit of PBT in non-comparative studies In the two highest scoring studies (Luo et al 2019, Verma et al 2017), adverse events were assessed by the CTCAE Version 4.0. On this scale Grade 1 = '*mild*', Grade 2 = '*moderate*', Grade 3 = '*severe or medically significant but not immediately life-threatening*', Grade 4 = '*life-threatening consequences*' and Grade 5 = '*death related to adverse event*'[3]. In Luo et al 2019 (n=42), there were no acute adverse events (<90 days after radiotherapy) of Grade 3 or higher. Grade 2 (moderate) acute adverse events included dermatitis (74%), skin pain (24%), oesophagitis (17%) and fatigue (2%). There was 1 (2%) Grade 3 (severe) chronic adverse event (pneumonitis) >90 days after radiotherapy. There were no Grade 2 chronic adverse events. The authors reported that no acute or chronic cardiac toxicities were reported. Median follow-up was 35 months (range 1 to 55). In Verma et al 2017 (n=91), there were no Grade 4 or 5 adverse events. Grade 3 (severe) adverse events included dermatitis (5%) and breast/ chest wall pain (1%). Grade 2 (moderate) adverse events included dermatitis (72%), breast/ chest wall pain (29%), oesophagitis (33%) and fatigue (15%). In addition, 8% developed a skin infection, 2% had uncomplicated rib fracture, and 3% had clinically evident lymphoedema. Adverse events were also separately reported for patients who received radiotherapy to the breast (n=27) and chest wall (n=66). The only Grade 3 adverse event for breast radiotherapy patients

		was dermatitis (7%). Grade 3 adverse events for chest wall radiotherapy patients included dermatitis (5%) and pain (2%). Grade 2 adverse events for breast radiotherapy patients included dermatitis (56%), pain (52%), oesophagitis (30%) and fatigue (7%). Grade 2 adverse events for chest wall radiotherapy patients included dermatitis (79%), pain (20%), oesophagitis (33%) and fatigue (5%). Median follow-up 15.5 months (range not reported). Adverse events are important outcomes as they may impact on quality of life. A small proportion of patients had Grade 3 (severe) adverse events in both studies. The proportion of patients experiencing Grade 2 (moderate) adverse events was higher, particularly for dermatitis. The results of these two small case series should be treated with caution and do not provide any information on the effectiveness of PBT compared to photon radiotherapy. The retrospective design of Verma et al 2017 introduces the possibility of selection bias in the completeness of the information reported. Both studies were conducted in the US, Luo et al between 2013 and 2015 and Verma et al between 2011 and 2015. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 35 and 15.5 months respectively may not be long enough to assess the impact of longer term toxicities.
11.	Delivery of intervention	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Not reported.

Other health metrics determined by the evidence review		
No	*Outcome measure*	*Summary from evidence review*
1.	Mortality	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.

		Benefit of PBT in non-comparative studies Mortality records the number of patients that had died at last follow-up. In Verma et al 2017 (n=91), 6 patients (7%) had died at a median follow-up of 15.5 months (range not reported). A low mortality rate of 7% will be of importance to clinicians, patients and their families. The results of this small retrospective case series should be treated with caution and do not provide any information on the effectiveness of PBT compared to photon radiotherapy. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. The study was conducted at 1 US centre between 2011 and 2016. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 15.5 months may not be long enough to assess the impact of treatment on mortality.
2.	Disease-free survival	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Disease free survival was not defined by Bush et al 2014 but is generally the time period without any signs or symptoms of disease (local, regional or distant), measured from the end of treatment. In Bush et al 2014 (n=100), disease-free survival was 94% (95%CI not reported) with a median follow-up of 5 years (range not reported). Disease-free survival assesses the success of treatment and is important to clinicians, patients and their families. 94% of patients were disease free at 5 years follow-up. The results of this small prospective case series should be treated with caution and do not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted in the US but the number of participating centres and year of treatment were not reported. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 5 years may not be long enough to assess the impact of treatment on disease free survival.

3.	Loco-regional disease free survival	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Loco-regional disease free survival was measured from end of treatment to time of loco-regional recurrence or last follow-up (Luo et al 2019). In Luo et al 2019 (n=42), loco-regional disease free survival was 96.3% (95%CI not reported) at a median follow-up of 35 months (range 1 to 55). Loco-regional disease free survival assesses the success of treatment and is important to clinicians, patients and their families. 96% of patients had not developed loco-regional recurrence at 35 months follow-up. See above for limitations of Luo et al 2019. The median follow-up of 35 months may not be long enough to assess the impact of treatment on loco-regional disease free survival.
4.	Metastasis free survival	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Metastasis free survival was measured from end of treatment to time of metastasis or last follow-up (Luo et al 2019). In Luo et al 2019 (n=42), metastasis free survival was 84.1% (95%CI not reported) at a median follow-up of 35 months (range 1 to 55). Metastatic disease indicates a progression of disease and is important to clinicians, patients and their families. 84% had not developed metastasis at 35 months follow-up. See above for limitations of Luo et al 2019.

		The median follow-up of 35 months may not be long enough to assess the impact of treatment on metastasis free survival.
5.	Disease failure	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Disease failure included loco-regional recurrence and distant disease. Loco-regional failure was defined as imaging evidence of tumour in the ipsilateral breast or chest wall and/ or ipsilateral lymphatics. Other failures were categorised as distant. In Verma et al 2017 (n=91), 12 patients (13%) had disease failure at a median follow-up of 15.5 months (range not reported). 10 patients (11%) had distant recurrence and 4 patients (4%) had loco-regional recurrence (2 patients had both distant and loco-regional recurrence). Median time to any disease failure was 8 months (range not reported). Disease failure assesses the success of treatment and is important to clinicians, patients and their families. Most of the disease failures observed were distant disease. See above for limitations of Verma et al 2017. The median follow-up of 15.5 months may not be long enough to assess disease failure.
6.	Local failure rate	**Benefit of PBT vs photon based PBI** Local failure generally means recurrence of disease at the treatment site or surrounding area. In Galland-Girodet et al 2014, all recurrences occurred outside the treatment original site. In Galland-Girodet et al 2014, there was no significant difference in the 7-year local failure rate between the PBT (11%) and photon groups (4%) (p=0.22). The significance of local failure rate outside of the original treatment site is not clear. However, the results indicate that patients treated with PBT were no more or less likely to experience this outcome. See above for limitations of Galland-Girodet et al 2014.
		Benefit of PBT vs photon radiotherapy (excluding PBI)

		Not reported.
		Benefit of PBT in non-comparative studies Not reported.
7.	Loco-regional recurrence	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Loco-regional recurrence was measured from end of treatment to time of loco-regional recurrence or last follow-up. In Chang et al 2013 (n=30), there were no cases of loco-regional recurrence at a median follow-up of 59 months (range 43 to 70). Loco-regional recurrence assesses the success of treatment and is important to clinicians, patients and their families. No patients had developed loco-regional recurrence at 59 months follow-up. The results of this very small prospective case series should be treated with caution and do not provide any information on the effectiveness of PBT compared to photon radiotherapy. The study was conducted at 1 centre in Korea between 2007 and 2009. The applicability to current UK NHS clinical practice is unclear. The median follow-up of 59 months may not be long enough to assess the impact of treatment on loco-regional recurrence.
8.	Distant metastasis	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Distant metastasis was measured from end of treatment to time of distant metastasis or last follow-up. In Chang et al 2013 (n=30), there were no cases of distant metastasis at a median follow-up of 59 months (range 43 to 70). Distant metastasis indicated a progression of disease and is important to clinicians, patients and their families. No patients had developed distant metastasis at 59 months follow-up.

		See above for limitations of Chang et al 2013. The median follow-up of 59 months may not be long enough to assess the impact of treatment on distant metastasis.
9.	Physician-rated cosmetic outcome	**Benefit of PBT vs photon based PBI** The proportion of physicians who rated the cosmetic outcome after partial breast irradiation as good or excellent was reported annually between 1 and 7 years follow-up using the Harvard 4-point cosmetic scoring system. This subjective scale has 4 response options: excellent (treated breast nearly identical to untreated breast); good (treated breast slightly different from untreated breast); fair (treated breast clearly different from untreated breast but not seriously distorted) and poor (treated breast seriously distorted)[6]. In Galland-Girodet et al 2014, at 1 year follow-up the proportion of physicians rating overall cosmetic outcome as good or excellent was similar for PBT (100%) and photon radiotherapy (97%). The study authors reported this as a non-significant result but did not provide a p-value. At 7 years, the proportion of physicians rating overall cosmetic outcome as good or excellent was significantly lower for PBT (62%) than photon radiotherapy (94%) (p=0.03). Relative to clinical outcomes, it is not clear what the importance of cosmetic outcome following partial breast irradiation is to physicians. See above for limitations of Galland-Girodet et al 2014. There is no indication that physician assessors were blinded to treatment group when assessing cosmetic outcomes which introduces the risk of bias. The study authors did not provide precise figures or p values for all of the time points assessed.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Physician-rated cosmetic outcome assessed global cosmetic result, appearance of the surgical scar, breast size, breast shape, skin colour and location and shape of the areola and nipple. This was assessed on a 4-point scale where 0 = '*excellent result (no difference)*', 1 = '*good result (small difference)*', 2 = '*fair result (moderate difference)*', 3 = '*poor result (large difference)*'. Percentage of breast retraction was also assessed by comparing

[6] https://www.researchgate.net/figure/Harvard-scale-4-point-Likert-scale_tbl1_267101566

		the lateral and vertical displacement of the nipple in the treated breast compared to the untreated breast. In Chang et al 2013, the proportion of outcomes rated '*excellent*' or '*good*' were: 84% at the end of radiotherapy (n=30), 80% at 2 months (n=80), 84% at 6 months (n=30), 77% at 1 year (n=30), 75% at 2 years (n=27) and 69% at 3 years (n=23). Mean percentage breast retraction increased statistically significantly over time from 10.5% at the end of treatment to 15.3% at 3 years (p=0.002). Cosmetic outcome is important as it may impact quality of life. Physician-rated cosmetic outcome was generally positive but worsened over time. See above for limitations of Chang et al 2013. Cosmetic outcome was assessed by 1 radiation oncologist.
10.	Patient-rated cosmetic outcome	**Benefit of PBT vs photon based PBI** The proportion of patients rating cosmetic outcome after partial breast irradiation as good or excellent was reported annually between 1 and 7 years follow-up using the Harvard 4-point cosmetic scoring system. This subjective scale has 4 response options: excellent (treated breast nearly identical to untreated breast); good (treated breast slightly different from untreated breast); fair (treated breast clearly different from untreated breast but not seriously distorted) and poor (treated breast seriously distorted)[7]. In Galland-Girodet et al 2014, at 1 year follow-up the proportion of patients rating overall cosmetic outcome as good or excellent was similar for PBT (100%) and photon radiotherapy (93%). The study authors reported this as a non-significant result but did not provide a p-value. At 7 years, there was no significant difference in this outcome between PBT (92%) and photon radiotherapy (96%) (p=0.95). Relative to clinical outcomes, it is not clear what the importance of cosmetic outcome following partial breast irradiation is to patients. See above for limitations of Galland-Girodet et al 2014. The study authors did not provide precise figures or p values for all of the time points assessed.
		Benefit of PBT vs photon radiotherapy (excluding PBI)

[7] https://www.researchgate.net/figure/Harvard-scale-4-point-Likert-scale_tbl1_267101566

		Patient-reported cosmetic result was assessed by the Harvard Cosmesis Scale. This single-item question rates cosmetic result as 4 = '*excellent*', 3 = '*good*', 2 = '*fair*' or 1 = '*poor*'. Teichman et al 2018 reported a statistically significantly better mean (standard deviation (SD)) result for PBT (n=69) vs photon radiotherapy (n=56) (3.40 (0.75) vs 2.44 (0.96), p<0.001). Data were collected at a median of 6.5 years post-diagnosis. Cosmetic outcome is an important outcome as this may impact quality of life. Cosmetic result was judged more positively by patients who were treated with PBT. These results need to be interpreted with caution because of the limitations of the study. This retrospective comparison used data from patients treated at 1 US centre between 2003 and 2012 who responded to a survey. The survey was sent to patients who were alive and disease-free 5 years or more after diagnosis. The response rate was 79%. The data may be subject to response bias as the people who responded to the survey may not reflect all patients treated. The proportion of non-responders who received PBT or photon radiotherapy was not specified. The applicability to current UK NHS clinical practice is unclear. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. All but 2 of the 69 PBT patients received their treatment during a clinical trial. The photon radiotherapy patients received the conventional treatment at the time. This may have had a confounding effect on attitudes to the treatment received or perceptions of outcomes. The differences in treated volume (partial breast PBT vs whole breast photon radiotherapy) and delivery of radiotherapy (10 days vs 6 weeks) for the 2 groups may also have had a confounding effect.
		Benefit of PBT in non-comparative studies Patient-reported cosmetic result for the treated breast was assessed by the Harvard Cosmesis Scale. This single-item question rates cosmetic result as 4 = '*excellent*', 3 = '*good*', 2 = '*fair*' or 1 = '*poor*'. The proportion of patients who rated the cosmetic outcome as '*excellent*' or '*good*' was reported by Bush et al (2014). In Bush et al 2014 (n=100), the proportion of patients reporting an '*excellent*' or '*good*' result was between approximately 90% and 95% at baseline and at median 5 year follow-up (range not reported). The authors reported that no annual assessment was significantly different from baseline (figures not reported).

		Cosmetic outcome is an important outcome as this may impact on quality of life. Patient-rated cosmetic outcome was generally positive. See above for limitations of Bush et al 2014. Precise figures for this outcome were not available as the results were only presented graphically.
11.	Patient-reported treatment outcome	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Patient-reported treatment outcome was assessed by the Breast Cancer Treatment Outcome Scale. This 22-item questionnaire evaluates functional and cosmetic outcome, reported as 4 subdomains: cosmetic, breast specific pain, functionality and oedema. Items are scored from 1 to 4 based on any difference between the treated and untreated breast where 1 = '*none*', 2 = '*slight*', 3 = '*moderate*' and 4 = '*large (major)*'. Teichman et al 2018 reported a statistically significantly better mean cosmetic score for PBT (n=72) vs photon radiotherapy (n=57) 1.45 vs 1.88, p<0.001). However, the mean pain score was statistically significantly worse with PBT (1.42 vs 1.25, p<0.005). There was no significant difference in functionality (1.11 vs 1.17, p=0.311) or oedema (1.07 vs 1.12, p=0.526). The authors also created a weighted score based on the average of the 3 questions that patients thought were most important. This was statistically significantly better for PBT (1.84 vs 2.55, p<0.001). Standard deviation was not reported for this outcome. Data were collected at a median of 6.5 years post-diagnosis. Treatment outcome is an important outcome as it may impact quality of life. However, the clinical significance of this composite result is not clear as patients treated with PBT had statistically significant better cosmetic outcome but reported statistically significant worse pain. See above for limitations of Teichman et al 2018.
		Benefit of PBT in non-comparative studies Not reported.
12.	Quality of life	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI)

		Not reported.
		Benefit of PBT in non-comparative studies Quality of life was assessed by the European Organization for Research and Treatment of Cancer 30 Quality of Life Questionnaire (EORTC QLQ-C30) and the EORTC breast cancer specific questionnaire (EORTC QLQ-BR23). These are scored out of 100 with higher functional scores and lower symptoms scores indicating better quality of life. The EORTC QLQ-C30 includes 6 functional subscales (global health status, physical, role, emotional cognitive and social functioning) and 9 symptom subscales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The EORTC QLQ-BR23 includes 3 functional subscales (body image, sexual function and future perspective) and 3 symptom subscales (systemic therapy side effects, breast symptoms and arm symptoms). In Chang et al 2013 (n=30), there were no significant differences before treatment and after the last day of radiotherapy for any of the 6 functional subscales or 9 symptom subscales on the general quality of life questionnaire. There were also no significant differences for any of the 3 functional subscales or 3 symptom subscales on the breast cancer specific quality of life questionnaire. Impact of treatment on quality of life is important to clinicians, patients and their families. There was no difference in quality of life before and after treatment. See above for limitations of Chang et al 2013.
13.	Body image	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Body image was assessed by the Body Image Scale. This 10-item self-reported questionnaire assesses feelings about appearance and changes which may have resulted from a disease or treatment during the prior week. Each item is scored from 1 to 4 with higher scores indicating more dissatisfaction/ negative feelings, where 1 = '*not at all*', 2 = '*a little*', 3 = '*quite a bit*' and 4 = '*very much*'. Teichman et al 2018 reported a statistically significantly better mean (SD) result for PBT (n=72) vs photon radiotherapy (n=57) (12.04 (3.75) vs 13.91 (5.25), p<0.03). Data were collected at a median of 6.5 years post-diagnosis.

		Body image is an important outcome as this may impact quality of life. A statistical difference favouring PBT was reported. However, the means reported suggest the difference may not be clinically significant. See above for limitations of Teichman et al 2018.
		Benefit of PBT in non-comparative studies Not reported.
14.	General perspective	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) General perspective was assessed by 9 questions generated by the study authors which were scored on a 5-point scale from 1 = '*not at all*' to 5 = '*very much*'. Teichman et al 2018 reported statistically significantly better mean scores for PBT (n=72) vs photon radiotherapy patients (n=57) for the following questions: '*happy with treatment choice*' (4.92 vs 4.20, p<0.001), '*skin "felt different" since treatment*' (1.22 vs 1.95, p<0.001), '*changed attitude about sex*' (1.41 vs 1.94, p=0.012), '*breast cancer changed views of "myself and body*"' (1.57 vs 2.16, p=0.008) and '*worry about "disease coming back*"' (2.31 vs 3.27, p<0.001). The mean score was statistically significantly worse with PBT for the question: '*skin quality during treatment*' (1.50 vs 2.82, p<0.001). There was no significant difference for the following questions: '*changed how I live my daily life*' (2.00 vs 2.30, p=0.197), '*role of spirituality/ religion*' (4.35 vs 4.00, p=0.116) and '*upper arms/ mobility issues*' (1.19 vs 1.30, p=0.348). Standard deviation was not reported for this outcome. Data were collected at a median of 6.5 years post-diagnosis. General perspective covers a range of areas that could impact quality of life. Some of the results favoured PBT. However, these did not translate to a difference between the groups for questions about change in daily life or upper arm/ mobility issues. See above for limitations of Teichman et al 2018.
		Benefit of PBT in non-comparative studies Not reported.
15.	Fatigue	**Benefit of PBT vs photon based PBI** Not reported.

		Benefit of PBT vs photon radiotherapy (excluding PBI) Fatigue was assessed by the Brief Fatigue Inventory. This 9-item self-reported questionnaire is scored on a scale of 0 '*no fatigue*' to 10 '*as bad as you can imagine*'. An average total score was calculated for 8 of the 9 items. The 9th item (see below) was reported separately. Teichman et al 2018 reported a statistically significantly better mean (SD) result for PBT (n=72) vs photon radiotherapy patients (n=57) (15.3 (17.11) vs 27.25 (22.26), p<0.002). The authors also created a weighted score based on the average of the 3 questions that patients thought were most important. There was no significant difference between the groups (1.84 vs 2.55, p<0.001). Standard deviation was not reported for this outcome. The proportion of patients responding '*yes*' to the question '*have you felt unusually tired or fatigued in the last week*' was 25% for PBT (n=71) and 63% (n=51) for photon radiotherapy. No significance test was reported. Data were collected at a median of 6.5 years post-diagnosis. Fatigue is an important outcome as this may impact quality of life. A statistical difference favouring PBT was reported. However, there was no difference for the weighted mean, focusing on what patients thought was most important. The significance of the difference in recent tiredness is not clear. See above for limitations of Teichman et al 2018.
		Benefit of PBT in non-comparative studies Not reported.
16.	Patient satisfaction with partial breast irradiation	**Benefit of PBT vs photon based PBI** This outcome assessed patient's satisfaction with the partial breast irradiation (PBI) (as PBT or photon radiotherapy) that they had been treated with rather than whole breast irradiation (WBI). The response categories were '*totally satisfied*'; '*not totally satisfied but would choose PBI again*'; '*not totally satisfied and would choose WBI*'. In Galland-Girodet et al 2014, the proportion of patients who were 'totally satisfied' was 94% for PBT and 98% for photon radiotherapy at 1 year follow-up. At 7 years this was 85% for PBT and 96% for photon radiotherapy. No comparative analysis was reported for these time points. Patient satisfaction with PBI (as opposed to WBI) was high for both treatment groups. The importance of this outcome to patients is not clear.

		See above for limitations of Galland-Girodet et al 2014. The study authors did not provide precise figures or p values for all of the time points assessed.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Not reported.
17.	Skin toxicity	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.
		Benefit of PBT in non-comparative studies Skin toxicity was assessed by the CTCAE Version 4.0. On this scale Grade 1 = '*mild*', Grade 2 = '*moderate*', Grade 3 = '*severe or medically significant but not immediately life-threatening*', Grade 4 = '*life-threatening consequences*' and Grade 5 = '*death related to adverse event*'[3]. In Liang et al 2018 (n=23), 10 patients (43%) had Grade 3 radiation dermatitis. 23 patients (100%) had ≥ Grade 2 skin reactions including erythema or patchy moist desquamation confined to skin folds. Median follow-up was not reported. Skin toxicity adverse events are important outcomes as they may impact on quality of life. All patients had Grade 2 (moderate) toxicities and 43% had Grade 3 (severe) toxicities. The results of this very small retrospective case series should be treated with caution and do not provide any information on the effectiveness of PBT compared to photon radiotherapy. The retrospective design introduces the possibility of selection bias in the completeness of the information reported. The study was conducted at 1 US centre between 2012 and 2016. The applicability to current UK NHS clinical practice is unclear.
18.	Reconstruction complications	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) Not reported.

		Benefit of PBT in non-comparative studies Reconstruction complications were reported for patients who received PBT after a mastectomy with immediate reconstruction. In Luo et al 2019 (n=42), 7 of 26 patients (27%) who underwent PBT after immediate reconstruction developed complications. This included 6 capsular contractures and 1 implant infection. Implants were removed in 5 patients. Reconstruction complications are important as they could lead to further surgery and impact quality of life. 27% of patients had complications and 19% had an implant removed. See above for limitations of Luo et al 2019.
19.	Incremental cost effectiveness ratio (ICER)	**Benefit of PBT vs photon based PBI** Not reported.
		Benefit of PBT vs photon radiotherapy (excluding PBI) ICER[8] was reported for a range of different scenarios based on the woman's age and mean radiotherapy heart dose. A treatment strategy was assessed for cost effectiveness against a willingness to pay threshold of either $50,000/ quality-adjusted life year (QALY) (£40,102) or $100,000/ QALY (£80,205). In Mailhot Vega et al 2017, PBT was not cost effective for women without cardiac risk factors compared to photon radiotherapy at a threshold of $50,000/ QALY. This remained the case following sensitivity analysis. • At a threshold of $50,000/QALY PBT was cost effective compared to photon radiotherapy for women with 1 or more cardiac risk factors for 50 year old women receiving a mean heart dose of 9Gy and 60 year old women receiving a mean heart dose of 10Gy • At a threshold of $100,000/ QALY there were scenarios (based on woman's age and mean radiotherapy heart dose) where PBT was cost effective compared to photon radiotherapy for both women with and without cardiac risk factors. This study indicates that for some women with 1 or more cardiac risk factors, there may be patient selection factors (based on age and mean heart dose) for which PBT would potentially be more cost effective than photon radiotherapy at a willingness to pay threshold of $50,000.

[8] Mailhot Vega et al (2017) described the ICER as the ratio of the difference in costs between PBT and photon radiotherapy and the difference in effectiveness between PBT and photon radiotherapy

		These results are not generalisable to a UK NHS context because the willingness to pay thresholds used were higher than the threshold that is commonly used by NICE (£20,000 to £30,000). Additional concerns include the use of a societal perspective for 2012 US dollars. This overestimates the duration of the effect and underestimates the ICER value. The study also used of a lifetime horizon ending at patient death or age 100 years which may make the intervention appear more cost effective than if a lower, more realistic, age cut-off had been used. Conversions from US dollars to UK pounds were calculated in September 2019.
		Benefit of PBT in non-comparative studies Not reported.

Abbreviations: CHD – Coronary Heart Disease; CI - Confidence Interval; CTCAE - Criteria for Adverse Events; EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer 30 Quality of Life Questionnaire; EORTC QLQ-BR23- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer specific questionnaire; Gy – Gray; HR – Hazard Ratio; ICER - Incremental Cost Effectiveness Ratio; PBI – Partial Breast Irradiation; PBT – Proton Beam Therapy; PCI - Percutaneous Coronary Intervention; QALY - Quality-Adjusted Life Year; SD – Standard Deviation

Patient Impact Summary
Details of impact upon patients: This is a not for routine commissioning policy proposition and will not impact on patients as patients will continue to receive currently commissioned services. **Details of impact upon carers:** This is a not for routine commissioning policy proposition and will not impact on carers as patients will continue to receive currently commissioned services.

Considerations from review by Rare Disease Advisory Group
RDAG has been informed of this policy proposition and indicated its support on 14/10/20.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Cancer PoC on the 18th March 2021.