CLINICAL PRIORITIES ADVISORY GROUP
10 May 2021

Agenda Item No	3.2
National Programme	Cancer
Clinical Reference Group	Radiotherapy
URN	1831

Title
High dose rate brachytherapy boost and low dose rate brachytherapy boost for intermediate- and high-risk localised prostate cancer.

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

Proposition
The policy proposition recommends that brachytherapy dose escalation, added to treatment with external beam radiotherapy, is routinely commissioned as a treatment option for intermediate- and high-risk localised prostate cancer. Development of the policy proposition is supported by a review of the latest available clinical evidence in line with standard processes.

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 Cancer Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement 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.	Engagement Report
3.	Evidence Summary (2)
4.	Clinical Panel Report (3)
5.	Equality Impact and Assessment Report

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Overall survival (OS) is the proportion of subjects still alive at a defined time point. Hoskin et al (2012) reported OS at 5, 7 and 10 years respectively of 88%, 81% and 67% in the group receiving HDRPB and 89%, 88% and 79% in those receiving EBRT. There was no statistically significant difference between the groups (p=0.2). An improvement in OS would extremely important for patients, their families and clinicians. Both treatment groups had reasonably high rates of OS, but the study did not demonstrate that either radiotherapy treatment was more beneficial. This appears to have been a well-conducted RCT whose results can be regarded as reliable. However it was not powered to detect differences in OS. The EBRT dose used for the comparator group (55Gy) is below the current NICE recommendation of a minimum of 74Gy or the NHS England recommended dose of 60Gy in 20 fractions, and only 76% of all patients received ADT.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.

		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Overall survival (OS) is the proportion of subjects still alive at a defined time point. Kishan et al (2017) reported estimated OS at 5 and 10 years respectively of 84.7% and 59.2% in the group receiving HDRPB, 79.9% and 65.3% in the group receiving EBRT, and 90.3% and 72.1% in the group receiving RP. There was no statistically significant difference in OS between the group receiving HDRPB and either of the other two treatment groups (HDRPB vs EBRT: HR=0.99 (95%CI 0.58-1.98), p=0.98; HDRPB vs RP: HR=1.06 (95%CI 0.53-2.12), p=0.8688). An improvement in OS would extremely important for patients, their families and clinicians. The study did not demonstrate any difference in OS up to 10 years after treatment between patients receiving HDRPB and those receiving either EBRT alone or RP. This was a retrospective analysis of 3 treatment cohorts treated at 3 different centres. All patients were high risk. There were a number of potential sources of bias, including the retrospective design, differences between treatment groups in clinical stage and receipt of ADT, and differences in treatment approaches and follow-up between treatment centres. Patients in the HDRPB group included 84 who received HDRBT and 3 who received LDRBT. The findings can therefore be regarded as only moderately reliable.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high-risk prostate cancer Overall survival (OS) is the proportion of patients still alive at a defined time point after baseline. Morris et al (2017) found no significant difference in OS for patients randomised to low dose rate prostate brachytherapy boost with external beam radiotherapy (LDRPB) compared with dose-escalated external beam radiotherapy (DE-EBRT) at 5 years (91.3% vs 88.7%), 7 years (85.7% vs 81.5%) and 9 years (77.9% vs 73.6%) after starting treatment with ADT (log-rank p=0.293). Overall survival is an extremely important outcome for patients, their families and clinicians. A gain in overall survival would extend the lives of patients. There was no statistically significant difference in OS between patients randomised to LDRPB compared with DE-EBRT. This was a well-conducted randomised controlled trial (RCT) and the findings can be regarded as reliable but the study was not powered to detect differences in OS[1].

[1] The study was designed to be large enough to detect expected differences in biochemical progression-free survival but not in survival outcomes.

2.	Progression free survival	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** See below.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high-risk prostate cancer Biochemical progression-free survival is the percentage of people who are alive and free of biochemical progression in a defined period of time. Being free of biochemical progression was defined as a prostate specific antigen (PSA) level which rose <2 ng/mL above the nadir level for that patient. Morris et al (2017) also included in their definition the absence of any imaging or clinical recurrence and no receipt of any form of secondary treatment for prostate cancer after completion of protocol interventions. Morris et al found significantly better biochemical progression-free survival (bPFS) in patients randomised to LDRPB compared with DE-EBRT, up to 9 years post-treatment. For LDRPB the % bPFS (+/- SD) at 5, 7 and 9 years was 88.7 +/- 4.8, 86.2 +/- 5.4 and 83.3 +/- 6.6 respectively compared with 83.8 +/- 5.6, 75.0 +/- 7.2 and 62.4 +/- 9.8 respectively for DE-EBRT (log-rank p<0.001). Biochemical progression is an important outcome for patients, their families and clinicians as it relates to progression of prostate cancer. Around 20% fewer patients randomised to LDRPB had biochemical progression of disease 9 years after treatment compared with those randomised to DE-EBRT. This was a well conducted RCT and the findings can be regarded as reliable. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on bPFS compared with what might be expected from current treatment regimes.
3.	Mobility	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.

		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high-risk prostate cancer Not reported.
4.	Self-care	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high- risk prostate cancer Not reported.
5.	Usual activities	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high- risk prostate cancer Not reported.
6.	Pain	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.

		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high-risk prostate cancer Not reported.
7.	Anxiety / Depression	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high-risk prostate cancer Not reported.
8.	Replacement of more toxic treatment	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high-risk prostate cancer Not reported.

9.	Dependency on care giver / supporting independence	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high-risk prostate cancer Not reported.
10.	Safety	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** See below.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high-risk prostate cancer See below.
11.	Delivery of intervention	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.

		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high-risk prostate cancer Not reported.

No	Outcome measure	Summary from evidence review
1.	Prostate cancer-specific mortality	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Prostate cancer-specific mortality (PCSM) is the proportion of patients who have died due to prostate cancer at a defined time point. Wedde et al (2018) reported that PCSM at 5 and 10 years was 1% and 2.5% (7/325) respectively in the group receiving HDR-EBRT and 3.1% and 8.2% (25/296) respectively in the group receiving EBRT alone, a statistically significant difference ($p<0.01$). Reducing deaths due to prostate cancer would be extremely important for patients, their families and clinicians. This study suggests that the group receiving HDR-EBRT were over three times less likely to have died due to prostate cancer than those receiving EBRT alone. This was a retrospective analysis of 2 treatment cohorts treated at a number of different treatment centres. All patients were high risk. There were a number of potential sources of bias, including the retrospective design, differences in approach between treatment centres, differences between the treatment groups in provision of ADT, and baseline differences between the cohorts. The findings can therefore be regarded as only moderately reliable.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Prostate cancer-specific mortality (PCSM) is the proportion of patients who have died due to prostate cancer at a defined time point. Kishan et al (2017) reported estimated PCSM at 5 and 10 years respectively of 4.4% and 11.9% in the group receiving HDRPB, 8.4% and 19.5% in the group receiving EBRT, and 8.3% and 21.5% in the group receiving RP. There was no statistically significant difference in PCSM between the group receiving HDRPB and either of the other two treatment groups (HDRPB vs EBRT: HR=0.64 (95%CI 0.24-1.71), p=0.37; HDRPB vs RP: HR=0.48 (95%CI 0.16-1.4), p=0.18). A reduction in deaths due to prostate cancer would be extremely important for patients, their families and clinicians. The study did not

		demonstrate any difference in deaths due to prostate cancer up to 10 years after treatment between patients receiving HDRPB and those receiving either EBRT alone or RP. This was a retrospective analysis of 3 treatment cohorts treated at 3 different centres. All patients were high risk. There were a number of potential sources of bias, including the retrospective design, differences between treatment groups in clinical stage and receipt of ADT, and differences in treatment approaches and follow-up between treatment centres. Patients in the HDRPB group included 84 who received HDRBT and 3 who received LDRBT. The findings can therefore be regarded as only moderately reliable.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high-risk prostate cancer Prostate cancer-specific survival is the proportion of people who have not died from prostate cancer in a defined period of time, for example between date of diagnosis or date or first treatment and death; the term was not further defined by Morris et al. Deaths were classified as being due to prostate cancer if this was identified as the cause of death, or if men were recorded as having been treated with systemic agents for metastatic prostate cancer at or before their death, regardless of the proximate cause of death. Morris et al (2017) found no significant difference between treatment arms in prostate cancer-specific survival (PCSS), which at 9 years follow-up was 94.8% +/-SD 4.0 in the LDRPB group, and 92.1% +/-SD 5.6 in the DE-EBRT group. Avoiding death due to prostate cancer is an extremely important outcome for patients, their families and clinicians. This study found that patients treated with LDRPB had the same risk of death due to prostate cancer as those treated with DE-EBRT. Morris et al was a well-conducted RCT and the findings are likely to be reliable. However the study was not powered to detect differences in PCSS[2].
2.	Overall mortality/ Mortality	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Overall mortality (OM) is the proportion of patients who have died from any cause at a defined time point. Wedde et al (2018) reported that OM at 10 years was 12.92% (42/325) in the group receiving HDR-EBRT and 23.31% (69/296) in the group receiving EBRT alone, a significant difference (p=0.02). The main contributor to the difference between groups was the number of prostate cancer deaths (see above).

[2] The study was designed to be large enough to detect expected differences in biochemical progression-free survival but not in survival outcomes.

		Reducing OM would be extremely important for patients, their families and clinicians. This study suggests the group receiving HDR-EBRT were around half as likely to have died due to any cause than those receiving EBRT alone. This was a retrospective analysis of 2 treatment cohorts treated at a number of different treatment centres. All patients were high risk. There were a number of potential sources of bias, including the retrospective design, differences in approach between treatment centres, differences between the treatment groups in provision of ADT, and baseline differences between the cohorts. The findings can therefore be regarded as only moderately reliable.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Mortality includes deaths due to all causes. Lennernas et al (2015) reported that at least 10 years after randomisation there had been 2 deaths due to prostate cancer in the group treated with HDRPB and 6 in those treated with RP. At the same point there had been 7 deaths due to other causes in the group treated with HDRPB and 6 in those treated with RP. The significance of differences between groups was not reported. A reduction in mortality would be extremely important to patients, their families and clinicians. This study reported 9 deaths (2 due to prostate cancer) in the 44 subjects treated with HDRPB and 12 deaths (6 due to prostate cancer) in the 45 subjects treated with RP at least 10 years after randomisation. They did not report whether the differences between the groups were significant. This appears to have been a well-conducted RCT but recruited only 89 subjects, about a quarter of the total originally planned, and was significantly underpowered to detect differences between treatment groups. The subjects' risk groups were not stated. It is not possible to draw any conclusions about mortality associated with the different treatment approaches from the results presented.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high-risk prostate cancer Not reported.
3.	Biochemical relapse-free survival	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Biochemical relapse-free survival (RFS) is the proportion of patients without relapse at a defined time point. Relapse was defined as biochemical recurrence (patients with a rise of 2ng/ml or more above nadir PSA, and those not meeting this criterion but who underwent

		salvage therapies such as ADT, radical prostatectomy, brachytherapy, or cryosurgery); clinical evidence of local disease (confirmed by imaging which was initiated in patients with rising PSA levels or with pelvic or musculoskeletal symptoms); or death from any cause. Hoskin et al (2012) reported RFS at 5, 7 and 10 years respectively of 75%, 66% and 46% in the group receiving HDRPB and 61%, 48% and 39% in those receiving EBRT alone. The difference between the groups was statistically significant (p=0.04). An improvement in RFS would be extremely important for patients, their families and clinicians as biochemical relapse reflects disease progression and is likely to be associated with greater morbidity and mortality. This study suggests that around a third more patients receiving HDRPB were likely to have avoided biochemical relapse at 7 years than those receiving EBRT alone, but the difference had narrowed by 10 years. This appears to have been a well-conducted RCT whose results can be regarded as reliable. The EBRT dose used for the comparator group (55Gy) is below the current NICE recommendation of a minimum of 74Gy or the NHS England recommended dose of 60Gy in 20 fractions, and only 76% of all patients received ADT.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate- or high-risk prostate cancer Not reported.
4.	Freedom from biochemical failure/ Biochemical failure-free control rate	**Benefit of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Freedom from biochemical failure (FFBF) is the proportion of patients without biochemical failure (defined as a rise of 2ng/ml or more above PSA nadir) at a defined time point. Khor et al (2013) reported FFBF at 5 and 10 years respectively of 79.8% and 69.2% in the group receiving HDRPB and 70.9% and 32.8% in the group receiving EBRT alone. The difference between treatment groups was statistically significant (p=0.0011). An improvement in FFBF would be extremely important for patients, their families and clinicians as biochemical failure reflects disease progression and is likely to be associated with greater morbidity and mortality. This study suggests that over twice as many patients treated with HDRPB

		were free from biochemical failure at 10 years compared with those treated with EBRT alone. This was a retrospective analysis of 2 matched cohorts. All patients were intermediate or high risk. The EBRT dose received by the EBRT-alone group was in line with the current NICE recommendation, but only 59% of all patients received ADT. There were a number of potential sources of bias, including the retrospective design, changes in treatment approaches over time, and baseline differences between the cohorts in age and length of follow-up, although there were no significant differences in the indicators of risk or comorbidity reported. The findings can therefore be regarded as only moderately reliable.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Biochemical failure-free control rate (BFFCR) is the proportion of subjects who are free of biochemical failure (defined as a rise of 2ng/ml or more above the nadir PSA level) at a defined time point. Noda et al (2011) reported a BFFCR at 3 years and 5 years respectively of 92% and 85% for patients receiving HDRPB and 72% and 72% for those receiving RP. This difference was statistically significant ($p<0.0012$). This was the result for their whole cohort which included an unspecified number of low risk patients. They reported a BFFCR for the intermediate risk patients only at 3 years and 5 years respectively of 92% and 92% for patients receiving HDRPB and 73% and 73% for those receiving RP. This difference was statistically significant ($p<0.0492$). They also reported a BFFCR for the high risk patients only at 3 years and 5 years respectively of 94% and 72% for patients receiving HDRPB and 45% and 45% for those receiving RP. This difference was statistically significant ($p<0.0073$). An improvement in BFFCR would be extremely important for patients, their families and clinicians as biochemical failure reflects disease progression and is likely to be associated with greater morbidity and mortality. Noda et al reported significant improvements in BFFCR for patients receiving HDRPB compared with those receiving RP for their whole cohort, and for intermediate and high risk subgroups. At 5 years, about 13% more of the whole cohort of HDRPB patients, 19% more of the intermediate risk HDRPB patients, and 27% more of the high risk HDRPB patients did not have biochemical failure compared with the RP patients in the same risk groups. This study was a retrospective comparison of 2 treatment cohorts. There were significant differences between them at baseline in T stage, but no other significant differences reported. The 2 groups were managed and assessed by different groups of clinicians and very little information was provided about the RP group. Risk groups did not correspond to NCCN or NICE definitions and the numbers in each risk group were not stated. There were therefore a number of sources of potential bias and the findings of this study should be viewed with caution.

		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Not reported.
5.	Biochemical recurrence/ Biochemical failure	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Biochemical recurrence was defined for RP patients as a postoperative PSA of ≥0.2ng/ml or initiation of salvage therapy, and for HDRPB and EBRT patients, a PSA ≥2ng/ml above the nadir for that patient or the initiation of salvage therapy. Kishan et al (2017) reported biochemical recurrence at 5 and 10 years respectively of 17.1% and 30.0% in the group receiving HDRPB, 28.2% and 39.7% in the group receiving EBRT, and 73.6% and 83.8% in the group receiving RP. There was no statistically significant difference in biochemical recurrence between the group receiving HDRPB and those receiving EBRT (HR=0.76 (95%CI 0.44-1.32), p=0.33). The rate of biochemical recurrence was statistically significantly lower in the group receiving HDRPB than the group receiving RP (HR=0.16 (95%CI 0.09-0.28), p<0.0001). A reduction in biochemical recurrence would be extremely important for patients, their families and clinicians as biochemical recurrence reflects disease progression and is likely to be associated with greater morbidity and mortality. Kishan et al found that patients receiving HDRPB were about one-sixth as likely to experience biochemical recurrence up to 10 years after treatment as those receiving RP. There was no difference in biochemical recurrence between those receiving HDRPB and EBRT alone. The authors considered that the findings were subject to bias because of differences between groups in the definition of biochemical recurrence and did not include this finding in their conclusions. This finding should be viewed with extreme caution as biochemical recurrence was defined at a lower threshold for RP patients than for patients receiving HDRPB or EBRT. This was a retrospective analysis of 3 treatment cohorts treated at 3 different centres. All patients were high risk. There were a number of potential sources of bias, including the retrospective design, differences between treatment groups in clinical

		stage and receipt of ADT, and differences in treatment approaches and follow-up between treatment centres. Patients in the HDRPB group included 84 who received HDRBT and 3 who received LDRBT.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Biochemical failure was defined as a PSA level which rose ≥2 ng/mL above the nadir level for that patient. Morris et al (2017) found that patients randomised to LDRPB were significantly less likely to experience biochemical failure than those randomised to DE-EBRT. On multivariable analysis (MVA) the hazard ratio (HR) of the difference was 2.04, 95% CI 1.25-3.33, p=0.004. Biochemical failure is an important outcome for patients, their families and clinicians as it relates to progression of prostate cancer. Patients randomised to LDRPB had about half the risk of biochemical failure of those randomised to DE-EBRT. This was a well-conducted RCT and the findings can be regarded as reliable. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on biochemical failure compared with what might be expected from current treatment regimes.
6.	Median time to biochemical progression	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Median time to biochemical progression was defined as the time taken for the PSA level to rise ≥2 ng/mL above the nadir level for patients in the study population, or (for cases with no previous PSA level decrease), a more than 1.25-fold elevation compared to baseline values. Luo et al (2018) reported that, in follow-up to 15 years, the median time to biochemical progression was 9.8 years (95%CI 8.5-10.7) for patients receiving LDRPB compared with 6.5years (95%CI 4.8-8.1) for DE-EBRT, a statistically significant difference (HR: 5.126 (95% CI 4.251-6.306), p < 0.001).

		Biochemical progression is an important outcome for patients, their families and clinicians as it relates to progression of prostate cancer. Patients receiving LDRPB experienced biochemical progression more than 3 years later on average than those receiving DE-EBRT. This can be regarded as moderately reliable as it is based on a retrospective data review in which treatment groups appeared comparable but which lacked details on treatment allocation and data completeness which increase the risk of bias.
7.	Health-related quality of life	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Health-related quality of life (HRQoL) was measured using the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire C33 (EORTC QLQ-C33). This comprises 33 items incorporating five single-item scales and nine multi-item scales evaluating function (physical, role, cognitive, emotional, and social), symptoms (fatigue, pain, nausea/vomiting, sleeping problems, constipation, appetite loss, dyspnoea, diarrhoea), and global health and QoL. Lennernas et al (2015) reported scores for a number of the scales at randomisation and at 12 and 24 months. They found no significant difference between treatment groups in scores for physical, role, emotional, cognitive or social functioning or in global QoL. They found an overall significant improvement over time in emotional functioning (p=0.0005) and an overall significant deterioration over time in social functioning (p=0.0051). In the symptom scores, they found no significant differences between groups or over time in fatigue, pain, insomnia, constipation or diarrhoea. HRQoL is an extremely important outcome for patients, their families and clinicians. This study found no significant differences between treatment groups in any measures of HRQoL up to 24 months after randomisation, although there was a worsening of social functioning and improvement in emotional functioning for the whole study population over time. This appears to have been a well-conducted RCT but recruited only 89 subjects, about a quarter of the total originally planned, and was significantly underpowered to detect differences between treatment groups. The subjects' risk groups were not stated. It is not possible to draw any conclusions about differences in HRQoL associated with the different treatment approaches from the results presented.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.

		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Health-related quality of life (HRQoL) was measured using the SF36v2, a validated 8-scale profile of functional health and well-being scores. It has 36 items organized into 8 scales: physical function, vitality, general health, bodily pain, role physical, social functioning, role emotional and mental health. Items were also added for urinary function, bowel function, and sexual function. Scales are scored from 0 to 100, with higher scores representing better HRQoL Patients were asked to complete the HRQoL measure at each clinic visit. Rodda et al (2017b) reported change in SF36v2 domain scores from baseline at 12 months and up to 6 years. Baseline scores were between 80-90 for most domains (physical function, bodily pain, role physical, social function, role emotional, urinary function), between 70-80 for vitality, general health and mental health, >90 for bowel function, and 58-60 for sexual function. At 12 months there had been a decline in all domains except mental health (which had increased +0.8 in the LDRPB group and +6.2 in the DE-EBRT group). The decline was significantly greater in the LDRPB group compared with the DE-EBRT group for physical health (p=0.04), vitality (p=0.02), role physical (p=0.01), bowel function (p=0.01) and sexual function (p=0.02). For other domains there was no significant difference in score change between treatment groups. The largest decline (LDRPB vs DE-EBRT) was for sexual function (-30.6 vs -23.8), with larger declines also for physical function (-11.6 vs -7.4), role physical (-20.9 vs -13.1) and vitality (-12.2 vs -7.4), and bowel function (-12.2 vs -0.1). At 6 years scores for most domains had improved compared with 12 month scores (except urinary function for both groups). However, scores for most domains were still worse than baseline, except for mental health for which scores had improved further in both groups (LDRPB +2.3 vs DE-EBRT +8.3). The decline in scores was significantly greater in the LDRPB group compared with the DE-EBRT group for physical function and urinary function. The domains with the greatest decline in scores at 6 years (LDRPB vs DE-EBRT) were physical function (-15.3 vs -6.9), role physical (-15.3 vs -11.4) and sexual function (-19.2 vs -15.1). HRQoL is an extremely important outcome for patients, their families and clinicians. The largest declines in physical, social and general health measures of HRQoL at 12 months after treatment were in domains relating to sexual function, physical function and vitality. Declines were significantly worse in the LDRPB treatment group than the DE-EBRT group for domains relating to physical health, vitality, role physical, bowel function and sexual function. At 6 years after treatment most scores had improved but HRQOL remained worse than at baseline for most areas which were measured, particularly for physical function, role physical and sexual function, and declines remained significantly greater in the LDRPB group for physical function and urinary function. Scores improved in the mental health domain at both 12 months and 6 years in both groups. This analysis was carried out as part of a well-conducted RCT, although was not one of the originally planned analyses. The numbers included in HRQoL measures were not stated, but based on baseline and later response rates provided were likely to be 67-81% patients in the first 4

		years, and 60-70% subsequently. There was no information comparing patients included and excluded from the analysis. Data completeness was high at 98.3% and clear rules were followed for missing data. The findings appear to be moderately reliable and suggest that most measures of HRQoL decline both in the shorter and longer term after treatment with both LDRPB and DE-EBRT, but declines in some domains particularly relating to physical health and functions are greater for the LDRPB group. Conversely, a measure of Mental Health improved for both groups, but particularly the DE-EBRT group. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on HRQoL outcomes compared with what might be expected from current treatment regimes. Understanding the risk of decline in HRQoL would be important for patients, and would need to be weighed against the risk of other outcomes such as mortality.
8.	Local progression-free survival	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Local progression-free survival is the proportion of people alive without local progression of disease. Local progression was confirmed pathologically. In Abugharib et al (2017), local progression-free survival (LPFS) at 5yrs was 100.0% (95%CI 100.0-100.0) in the LDRPB group and 99.4% (95%CI 98.6-100.0) in the DE-EBRT group, and at 10 years was 100.0% (95% CI 100.0-100.0) in the LDRPB group and 94.9% (95%CI 92.2-97.6) in the DE-EBRT group (p=0.042). Avoiding local progression of disease is an important outcome for patients, their families and clinicians. Ten years after treatment, no patient receiving LDRPB had experienced local progression of disease while around 5% of those receiving DE-EBRT had done so. This finding can be regarded as only moderately reliable, as this was a retrospective analysis with significant differences between treatment groups, and included only intermediate risk patients.
9.		**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer**

	Freedom from metastases/ Metastasis-free survival	Freedom from metastases (FFM) is the proportion of patients without metastases (not further defined in this study) at a defined time point. Khor et al (2013) reported FFM at 5 years of 90.0% in the group receiving HDRPB and 91.0% in the group receiving EBRT alone. The difference between treatment groups was not statistically significant (p=0.27). A reduction in metastases would be extremely important for patients, their families and clinicians as they reflect disease progression and are likely to be associated with greater morbidity and mortality. This study suggests no difference between the groups treated with HDRPB or EBRT alone in the proportion free from metastases at 5 years. This was a retrospective analysis of 2 matched cohorts. All patients were intermediate or high risk. The EBRT dose received by the EBRT-alone group was in line with the current NICE recommendation, but only 59% of all patients received ADT. There were a number of potential sources of bias, including the retrospective design, changes in treatment approaches over time, and baseline differences between the cohorts in age and length of follow-up, although there were no significant differences in the indicators of risk or comorbidity reported. The findings can therefore be regarded as only moderately reliable.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Metastasis-free survival (MFS) is the proportion of people alive who have not developed a metastasis in a defined period of time. Morris et al (2017) did not provide details of how metastases were determined. Morris et al found no significant difference in MFS between treatment groups. In patients randomised to LRDPB vs DE-EBRT, MFS was 88.6% +/- SD 5.6 vs 84.8% +/- SD 7.6 at 9yrs. Survival without metastases is extremely important to patients, their families and clinicians as metastases indicate disease progression and may be associated with increased morbidity. This study found that patients treated with LDRPB were likely to live for the same length of time without the development of metastatic disease as those treated with DE-EBRT.

		Morris et al was a well-conducted RCT and the findings can be regarded as reliable. However the study was not powered to detect differences in MFS[3].
10.	Distant metastases	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Distant metastases (DM) were classified as imaging evidence of lesions that were clinically or pathologically diagnosed as metastatic. Kishan et al (2017) reported a rate of DM at 5 and 10 years respectively of 5.4% and 10.2% in the group receiving HDRPB, 20.9% and 33.3% in the group receiving EBRT, and 20.9% and 38.5% in the group receiving RP. The rate of DM was statistically significantly lower in the group receiving HDRPB than in both the group receiving EBRT (HR=0.30 (95%CI 0.12-0.72), p=0.008) and the group receiving RP (HR=0.23 (95%CI 0.09-0.6), p=0.003). A reduction in metastases would be extremely important for patients, their families and clinicians as they reflect disease progression and are likely to be associated with greater morbidity and mortality. Kishan et al found that up to 10 years after treatment, patients receiving HDRPB were about a third as likely to experience DM as those receiving EBRT alone, and about a quarter as likely to experience DM as those receiving RP. This was a retrospective analysis of 3 treatment cohorts treated at 3 different centres. All patients were high risk. There were a number of potential sources of bias, including the retrospective design, differences between treatment groups in clinical stage and receipt of ADT, and differences in treatment approaches and follow-up between treatment centres. Patients in the HDRPB group included 84 who received HDRBT and 3 who received LDRBT. The findings can therefore be regarded as only moderately reliable
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Not reported.

[3] The study was designed to be large enough to detect expected differences in biochemical progression-free survival but not in survival outcomes.

11.	Median time to first skeletal-related event	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Median time to first SRE is the median time to presentation of first SRE amongst people in the study population. Skeletal-related events (SREs) were defined as radiotherapy or bone surgery, pathologic bone fractures, spinal cord compression, and antineoplastic treatment changes for bone pain alleviation. Patients underwent annual radioisotope scan of the bone and computed tomography of the pelvis, lung, and skull, which suggests that ascertainment of SREs was likely to be accurate. Median time to first SRE was significantly longer in those receiving LDRPB (10.4 years (95% CI 8.9-12.2)) compared with DE-EBRT (8.2 years (95% CI 7.1-10.5)), HR 3.361 (95% CI 2.925-3.815), $p < 0.001$. Skeletal-related events are important outcomes for patients, their families and clinicians as they are likely to be related to progression of prostate cancer and may cause significant morbidity. Patients receiving LDRPB experienced their first skeletal-related event more than 2 years later on average than those receiving DE-EBRT, and this difference was statistically significant. This finding is moderately reliable as it is based on a retrospective data review in which treatment groups appeared comparable but which lacked details on treatment allocation and data completeness which increase the risk of bias. The patients in this study were stated to be high risk but appear to be both intermediate and high risk according to the NCCN classification used in other studies.
12.	Median time to cytotoxic chemotherapy	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.

		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Median time to cytotoxic chemotherapy is the median time between baseline and commencement of cytotoxic chemotherapy amongst people within the study population. Time to commencement of cytotoxic chemotherapy was identified retrospectively from patient records. Luo et al (2018) reported that median time was significantly longer in those receiving LDRPB (11.6 years (95% CI 9.8-12.7)) compared with DE-EBRT (8.8 years (95% CI 6.3-10.9)), HR 1.627 (95% CI 1.311-1.809), p = 0.007. Not requiring cytotoxic chemotherapy is an important outcome for patients, their families and clinicians as chemotherapy would be required for progression of prostate (or other) cancer and is likely to be associated with significant morbidity. Patients receiving LDRPB commenced cytotoxic chemotherapy almost 3 years later on average than those receiving DE-EBRT, and this difference was statistically significant. This finding is moderately reliable as it is based on a retrospective data review in which treatment groups appeared comparable but which lacked details on treatment allocation and data completeness which increase the risk of bias. The patients in this study were stated to be high risk but appear to be both intermediate and high risk according to the NCCN classification used in other studies.
13.	Genitourinary adverse events	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Genitourinary (GU) adverse events as reported in this outcome were defined as: urinary diversion; frequency at night ≥6 times; intermittent or persistent incontinence; intermittent or daily haematuria, blood clots; score 3 for urgency or dysuria. Hoskin et al (2102) reported the cumulative incidence of GU adverse events by 5 and 7 years respectively of 26% and 31% in the group receiving HDRPB and 26% and 30% in those receiving EBRT alone. The difference between the groups was not statistically significant (p=0.5). They also reported the prevalence of GU adverse events at 5 and 7 years respectively of 8% and 11% in the group receiving HDRPB and 9% and 4% in those receiving EBRT alone. The differences were not statistically significant (p=1.0 (5 years), p=0.4 (7 years)). Almost a third of all patients experienced GU adverse events which can cause significant morbidity and reduction in quality of life, so a reduction would be important for patients, their families and clinicians. This study suggests no difference in GU adverse events between patients receiving HDRPB and those receiving EBRT alone.

		This appears to have been a well-conducted RCT whose results can be regarded as reliable. The adverse event outcomes reported here were analysed by treatment received rather than intention-to treat. The EBRT dose used for the comparator group (55Gy) is below the current NICE recommendation of a minimum of 74Gy or the NHS England recommended dose of 60Gy in 20 fractions, and only 76% of all patients received ADT.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Not reported.
14.	Acute genitourinary (GU) morbidity	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Acute genitourinary morbidity refers to the proportion of people who had early onset GU symptoms. Rodda et al (2017a) scored GU morbidity using the LENTSOMA Scale. Each grade is defined according to specific symptoms, representing 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death). The maximum LENTSOMA score up to 6 months after starting pelvic irradiation was recorded as acute morbidity. Rodda et al found that up to 6 months after starting radiotherapy, 19.1% of LDRPB patients were symptom-free, compared with 40.5% of DE-EBRT patients ($p<0.0001$), and 30.0% of LDRPB patients had moderate symptoms, compared with 15.8% of DE-EBRT patients ($p<0.0001$).There

		was no difference between groups in the proportions with mild or moderately severe symptoms. Acute GU morbidity is an important outcome for patients, their families and clinicians. While many symptoms resolve over time or with treatment, they can seriously impair quality of life and require further interventions. Half as many LDRPB patients were free of acute GU symptoms compared with DE-EBRT patients, and twice as many LDRPB patients had moderate acute GU symptoms compared with DE-EBRT patients. Rodda et al was a well-designed RCT whose findings are likely to be reliable. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on acute GU morbidity compared with what might be expected from current treatment regimes. Avoiding acute GU symptoms would be important for patients, though would need to be weighed against the risk of other outcomes such as longer-term morbidity and mortality.
15.	Late genitourinary (GU) morbidity	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Late genitourinary morbidity refers to the proportion of people who had late onset GU symptoms Rodda et al (2017a) scored GU morbidity using the LENTSOMA Scale. Each grade is defined according to specific symptoms, representing 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death). The cumulative incidence of each maximum LENTSOMA score more than 6 month and up to 5 years after starting pelvic irradiation was recorded as late morbidity. Rodda et al found that significantly more DE-EBRT patients had no late GU symptoms (LDRPB vs DE-EBRT: 20.6% vs 29.6%, p=0.003), and significantly more LDRPB patients had moderate (32.8% vs 20.6%, p=0.002) or moderately severe (18.4% vs 5.2%, p<0.001) late GU symptoms up to 5 years after starting pelvic irradiation. The prevalence of late grade ≥3 GU adverse events at 2 years was LDRPB 7.0% vs DE-EBRT 1.1% (p=0.005), and at 5 years was LDRPB 8.6% vs DE-EBRT 2.2% (p=0.058).

		Late GU morbidity is an important outcome for patients, their families and clinicians as it can seriously impair longer-term quality of life and may require further interventions. Patients treated with LDRPB were one-third less likely to be free of late GU symptoms, 50% more likely to have moderate late GU symptoms and three times more likely to have moderately severe late GU symptoms compared with patients treated with DE-EBRT. Rodda et al was a well-designed RCT whose findings are likely to be reliable. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on late GU morbidity compared with what might be expected from current treatment regimes. Avoiding late GU morbidity would be important for patients, and would need to be weighed against the risk of other outcomes such as mortality.
16.	Urinary and sexual function	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Urinary, bowel and sexual function were assessed using a prostate cancer-specific questionnaire, but no further details were provided about this measure. Lennernas et al (2015) reported scores for a number of items from the questionnaire at randomisation and at 12 and 24 months. They reported no significant difference between treatment groups in any of the measures, although p values were not reported. The scores for urinary incontinence and erectile problems showed an overall significant deterioration over time (urinary incontinence p=0.0011; erectile problems p<0.0001). Urinary and sexual function are important outcomes for patients, their families and clinicians. This study found no significant differences between treatment groups, but a worsening of urinary incontinence and erectile problems for the whole study population up to 24 months after randomisation. This appears to have been a well-conducted RCT but recruited only 89 subjects, about a quarter of the total originally planned, and was significantly underpowered to detect differences between treatment groups. The subjects' risk groups were not stated. It is not possible to draw any conclusions about differences in urinary and sexual function associated with the different treatment approaches from the results presented.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.

		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Not reported.
17.	Erectile function	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Erectile function was defined as the proportion of patients reporting erections adequate for penetration at 1 and 5years after starting ADT. In Rodda et al (2017a), 63.8% men in the LDRPB group and 61% men in the DE-EBRT group reported adequate erectile function before treatment. This declined to 5.2% vs 7.1% one year after starting treatment, recovering to 33.9% vs 30.6% after 5 years. There was no statistically significant difference between treatment groups. Erectile function is an important outcome for quality of life for patients and their partners. Rodda et al found that about 50% of men who had adequate erectile function before treatment reported having lost it after 5 years, regardless of type of radiotherapy, with no differences between treatment groups. This study was well-conducted but this finding is based on a self-reported measure therefore may be subject to bias.
18.	Gastrointestinal adverse events	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Gastrointestinal (GI) adverse events as reported in this outcome were defined as frequency ≥6 times/day; faecal consistency liquid; blood loss intermittent or daily, gross haemorrhage; rectal discharge intermittent or persistent requiring surgical treatment. Hoskin et al (2012) reported the cumulative incidence of GI adverse events by 5 and 7 years respectively of 7% and 7% in the group receiving HDRPB and 6% and 6% in those receiving EBRT alone. The difference between the groups was not statistically significant (p=0.8). They also reported the prevalence of GI adverse events at 5 and 7 years respectively of 0% and 0% in the group receiving HDRPB and 0% and

		2% in those receiving EBRT alone. The differences were not statistically significant (p=1.0). While the overall incidence of GI adverse events was relatively low in both groups, a reduction would be important for patients, their families and clinicians as they can cause significant morbidity and reduction in quality of life. This study suggests no difference in GI adverse events between patients receiving HDRPB and those receiving EBRT alone. This appears to have been a well-conducted RCT whose results can be regarded as reliable. The adverse event outcomes reported here were analysed by treatment received rather than intent-to treat. The EBRT dose used for the comparator group (55Gy) is below the current NICE recommendation of a minimum of 74Gy or the NHS England recommended dose of 60Gy in 20 fractions, and only 76% of all patients received ADT.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Not reported.
19.	Urethral stricture	**Benefit of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** A urethral stricture is a narrowing of the urethra which may result in difficulty in passing urine and may require management by catheterisation or surgical intervention. Hoskin et al (2012) reported the cumulative incidence of urethral stricture requiring surgical management by 5 and 7 years respectively of 6% and 8% in the group receiving HDRPB and 2% and 2% in those receiving EBRT alone. The difference between the groups was not statistically significant (p=0.1). While the overall incidence of urethral stricture was relatively low in both groups, a reduction would be important for patients, their families and clinicians as they can cause significant morbidity and reduction in quality of life and require surgical intervention. This study suggests no difference in the incidence of urethral stricture requiring surgical management between patients receiving HDRPB and those receiving EBRT alone. This appears to have been a well-conducted RCT whose results can be regarded as reliable. The adverse event outcomes reported here were

		analysed by treatment received rather than intent-to treat. The EBRT dose used for the comparator group (55Gy) is below the current NICE recommendation of a minimum of 74Gy or the NHS England recommended dose of 60Gy in 20 fractions, and only 76% of all patients received ADT.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Not reported.
20.	Acute gastrointestinal (GI) morbidity	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Acute gastrointestinal morbidity refers to the proportion of people who had early onset GI symptoms. Rodda et al (2017a) scored GI morbidity using the LENTSOMA Scale. Each grade is defined according to specific symptoms, representing 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death). The maximum LENTSOMA score up to 6 months after starting pelvic irradiation was recorded as acute morbidity. Rodda et al found no statistically significant difference in acute GI morbidity between the treatment groups. In the LDRPB vs DE-EBRT groups 46.2% vs 45.1% of patients had no symptoms, 39.3% vs 33.3% had grade 1 symptoms, 9% vs 14.3% had grade 2 symptoms and none had worse than Grade 2 symptoms.

		Acute GI morbidity is an important outcome for patients, their families and clinicians. While symptoms may resolve over time or with treatment, they can seriously impair quality of life and may require further interventions. There was no difference in acute GI morbidity between patients receiving LDRPB compared with DE-EBRT. Rodda et al was a well-designed RCT whose findings are likely to be reliable. Avoiding acute GI symptoms would be important for patients, though would need to be weighed against the risk of other outcomes such as longer-term morbidity and mortality.
.21.	Late gastrointestinal (GI) morbidity	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Late gastrointestinal morbidity refers to the proportion of people who had late onset GI symptoms Rodda et al (2017a) scored GI morbidity using the LENTSOMA Scale. Each grade is defined according to specific symptoms, representing 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death). The cumulative incidence of each maximum LENTSOMA score more than 6 months and up to 5 years after starting pelvic irradiation was recorded as late morbidity. Rodda et al found no statistically significant difference between treatment groups in late GI morbidity. In the LDRPB vs DE-EBRT groups, 31.3% vs 35.8% of patients had no symptoms, 42% vs 48.2% had mild symptoms, 31.3% vs 20.2% had moderate and 8.1% vs 3.2% moderately severe symptoms. The prevalence of late grade ≥3 GI adverse events was 1.7% vs 1.1% at 2 years and 1.0% vs 2.2% at 5 years, with no significant differences between groups. Late GI morbidity is an important outcome for patients, their families and clinicians as it can seriously impair longer-term quality of life and may require further interventions. There was no difference in late GI morbidity between patients receiving LDRPB compared with DE-EBRT. Rodda et al was a well-designed RCT whose findings are likely to be reliable. Avoiding late GI morbidity would be important for patients, and would need to be weighed against the risk of other outcomes such as mortality.

22.	Expected QALYs	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** QALYs (quality adjusted life years) are a way of assessing treatment benefits taking into account both length and quality of life. Vu et al (2018) reported the estimated QALYs for their base case estimates to be 10.8 years for patients receiving HDRPB and 9.3 years for patients receiving IMRT alone. For alternative case 1 (assuming worse outcomes, higher toxicity and greater costs for brachytherapy than the base case) their estimated QALYs were 9.49 years for HDRPB and 9.3 years for IMRT alone. For alternative case 2 (assuming better outcomes, lower toxicity and lower costs for brachytherapy than the base case) their estimated QALYs were 12.07 years for HDRPB and 9.3 years for IMRT alone. The statistical significance of differences was not reported. Cost-effectiveness was not reported for the base case. An improvement in both length and quality of life as a result of treatment would be extremely important for patients, their families and clinicians, although this would need to be linked with an analysis of treatment costs to ascertain cost-effectiveness. The authors concluded that using their assumptions based on a standard approach to treatment, patients receiving HDRPB could expect 1.5 more QALYs than those receiving IMRT alone. This suggests a benefit in both length and quality of life for the HDRPB group. They did not report the cost-effectiveness (i.e. the cost per QALY) of the standard approach to treatment. The difference between the treatment groups changed when they changed the assumptions they made about approaches to treatment and treatment outcomes. This study used a cost-effectiveness model based on assumptions which were drawn from a range of sources. Assumptions about disease progression, outcomes and toxicity were based on the findings of the ASCENDE-RT trial (Morris et al 2017). ASCENDE-RT compared LDRPB with DE-EBRT while Vu et al aimed to compare HDRPB with IMRT, and no evidence was provided demonstrating that outcomes of these treatment approaches would be the same. The use of ASCENDE-RT as a source for model assumptions therefore appears questionable. Other published studies were also used for other model assumptions. The findings of this study should therefore be regarded as unreliable.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.
		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Not reported.

23.	Expected lifetime cost of treatment	**Benefit of high dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer** The expected lifetime cost of treatment as reported in Vu et al (2018) included estimates of the US cost of initial treatment and of treatment required for disease progression and complications. Vu et al reported the estimated lifetime cost of treatment for their base case estimates to be US$68,696 for patients receiving HDRPB and US$114,944 for patients receiving IMRT alone. For alternative case 1 (assuming worse outcomes, higher toxicity and greater costs for brachytherapy than the base case) their estimated lifetime costs were US$106,143 for HDRPB and US$102.238 for IMRT alone. For alternative case 2 (assuming better outcomes, lower toxicity and lower costs for brachytherapy than the base case) their estimated lifetime costs were US$42,817 for HDRPB and US$111,738 for IMRT alone. The statistical significance of differences was not reported. Cost-effectiveness was not reported. for the base case. A reduction in treatment costs would be important for those paying for care, although this would need to be linked with an analysis of treatment outcomes to ascertain cost-effectiveness. The authors concluded that the lifetime treatment cost of their standard approach to treatment was over 50% higher for patients receiving IMRT alone compared with HDRPB. However, this relative difference changed when they changed the assumptions they made about approaches to treatment and treatment outcomes. This study used a cost-effectiveness model based on assumptions which were drawn from a range of sources. Assumptions about disease progression, outcomes and toxicity were based on the findings of the ASCENDE-RT trial (Morris et al 2017). ASCENDE-RT compared LDRPB with DE-EBRT while Vu et al aimed to compare HDRPB with IMRT, and no evidence was provided demonstrating that outcomes of these treatment approaches would be the same. The use of ASCENDE-RT as a source for model assumptions therefore appears questionable. Other published studies were also used for other model assumptions. Costs were US costs, using Medicare reimbursement and other sources, so may not reflect actual treatment costs and are not generalisable to the UK. The findings of this study should therefore be regarded as unreliable.
		Benefit of high dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer Not reported.
		Benefit of high dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer Not reported.

		Benefit of dose-escalated external beam radiation therapy boost vs low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer Not reported.

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** Patients have slight problems in walking about. • **ability to provide self-care:** Patients have slight problems in washing or dressing. • **undertaking usual activities:** Patients have moderate problems in doing their usual activities. • **experience of pain/discomfort:** Patients have moderate pain or discomfort. • **experience of anxiety/depression:** Patients are slightly to moderately anxious or depressed.
Further details of impact upon patients: Prostate cancer can have a wide range of impact on patients depending on severity. As the cancer grows, symptoms develop and common problems include developing urinary symptoms, sleep disturbance and sexual dysfunction. Morbidity can increase during treatment periods (surgery, chemotherapy, hormone therapy and radiotherapy). Those in older age groups are likely to have co-morbidities, so their problems are cumulative. There is also a mental health burden of living with a cancer, patients may feel anxious or depressed. Sleeplessness and hot flushes can add to discomfort, fatigue and irritability. **Further details of impact upon carers:** Patients may need to be cared for depending on disease burden, especially around the treatment periods. Carers will often accompany patients to all appointments, scans and share the emotional burden and worry of disease uncertainty with the patient. Sleep disturbance may be an issue if the carer is a spouse/partner.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
The proposal received the full support of the Cancer Programme of Care on the 10th February 2021.