PIVOTALboost **Sponsor Number: CCR 4643**
MREC Ref: 17/LO/0731
Amendment 4 – Summary of proposed amendment dated 24th May 2019

Protocol Amendment:

See tracked changes protocol (v5.0 dated 24 May 2019) for full details of changes

Protocol Page No.	**Section:**	***Comments* (new wording in blue):**
	Administration Clinical Coordination	*Brendan Carey has now retired and a suitable replacement is currently being sought by the PIVOTALboost TMG.* ~~Dr Brendan Carey~~ ~~Imaging lead~~ ~~St James's University Hospital,~~ ~~Leeds, LS9 7TF~~ ~~0113 206 7630~~ ~~Brendan.Carey@nhs.net~~
	Section 1.2.2 & Section 13.1	*1) Wording clarified to indicate that toxicity will be assessed in each experimental group separately.* *2) Correction to numbers of patients to be reviewed for acute toxicity follow up.* *1.2.2* *"Acute toxicity will be reviewed in each of the experimental arms (B, C and D) ~~This and the toxicity of prostate and pelvic IMRT combined with prostate boost (arm D) will be reviewed~~ once a minimum of 119 ~~94~~ patients per arm have completed the 18 weeks acute toxicity follow up assessment (see section 13)~~,~~. As the recruitment pattern for arm B is different to arms C and D this analysis will be carried out as the data for each of the experimental arms matures. Adverse event data will be collected prospectively and rates will be monitored by the IDMC throughout the study."* *13.1* *"The study is powered to detect a 7% difference in 5-year FFS ~~for any of the~~ each experimental arms compared to A (B, C or D) from 80% to 87%."*
	Section 3	*Wording clarified with regards to randomisation options, to reflect that some patients may not be suitable for focal IMRT:* "Randomisation into arms C and D will depend on the boost volume identified by MRI (suitable for focal boost or not), availability of focal HDR or IMRT, and patient suitability for focal IMRT ~~or in case~~ of HDR (see section 10 for further details)."
	Section 8.1 & Section 9	*The requirement for testosterone to be assessed prior to randomisation has been removed. Not all sites routinely assess testosterone levels prior to commencement of ADT; TMG agreed that testosterone assessment at baseline is not a necessity. (Note - pre-treatment testosterone assessment to monitor ADT efficacy prior to start of radiotherapy is still required):* "Full blood count, Urea & Electrolytes ~~, Testosterone~~." Baseline testosterone (X) deleted from schedule of assessments table.

	Section 10.1 & Figure 1	*New wording added to randomisation options to include patients who have a suitable boost volume but do not want to be treated with a focal boost or not well enough to receive a focal boost.* *"*Patients will be eligible for entry into one of the following randomisation options according to: … • Suitability and availability of focal IMRT boost."
	Section 10.1 & Figure 1	*New wording added to randomisation option 2a (Pelvic node and whole gland boost) to reflect standard practice for sites where whole gland HDR would be used to treat a suitable boost volume. Not all sites will be able to offer focal boost HDR and are currently unable to offer the 4 arms of the trial to potential patients.* "*this also includes patients who have a suitable boost volume on MRI at a HDR centre where only **whole gland HDR** is RTQA is approved" Decision tree algorithm figure amended to reflect change.
	Section 10.4	*Change of wording to imaging requirements to reflect TMG decision to allow soft tissue imaging to be used as an alternative to fiducial markers for IGRT.* *It was previously mandatory for fiducial markers to be inserted for focal boost IMRT. Following feedback from sites and discussion at the PIVOTALboost TMG it has been agreed that the RTQA guidance document will be updated in order that soft tissue matching may be used. For some sites they are unable to take part in C2/D2 because fiducial marker insertion is not their standard of care and some patients refuse trial entry because fiducial marker insertion is mandated in C2/D2.* *Different types of markers are in use at different sites and the interval should be appropriate to the type of marker used.* "Daily imaging and online correction (kV, CBCT, CT on rails, tomotherapy or MR-guided RT) are mandatory for all arms. Fiducial markers or soft tissue imaging can be used for IGRT. ~~Fiducial markers can be used for IGRT in all arms and are mandatory for focal boost IMRT (arm C2 and D2).~~ For fiducial marker insertion ~~A~~a minimum of three fiducial markers are inserted into the prostate as per standard care. Markers should ideally be separated 20mm apart. This can be undertaken before the HDR implant if appropriate, depending on the type of marker, an appropriate time prior to external beam planning should be scheduled. ~~but should be done more than 1 week prior to external beam planning.~~"

	Section 10.6	*Update to wording to EBRT treatment scheduling and gaps, in light of Royal College of Radiologists (RCR) update and feedback from sites.* "A gap of up to 5 days is acceptable in the event of machine service ~~or~~, breakdown or re-planning but further delays should be avoided."
	Section 12.8	*Correction of error to correctly link SAE review to interim analysis and stopping rules (IDMC).* "SAEs assessed as having a causal relationship to study treatment and as being unexpected will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see section 13.7~~14~~)."
	Section 13.1 & Section 13.2	*Text added and clarifications made in relation to treatment allocation wording, and reordering of the statistical design and sample size section for clarity.* 13.1 "Treatment allocation will be by minimisation using a 2:2:3:3 ratio initially as it is expected fewer sites will be able to offer boost treatment groups (C and D). Recruitment will be closely monitored and allocation ratio may be adjusted to ensure 9:9:8:8 final relative numbers. Overall, 1952 patients are required: 517 allocated to Arm A, 517 to Arm B, 459 to Arm C and 459 to Arm D. ~~Therefore the relative numbers between treatment groups are 9:9:8:8.~~ The sample size calculation is based on the log-rank test using the 'artsurv' command in STATA, incorporating 4.5 years of staggered recruitment and a minimum of 5 years of follow-up." 13.2 "During the design of the study, it was acknowledged that recruitment and allocation into the different treatment arms could evolve during the trial, given the number of sites open, and the type of boost available at each site. We ran simulations to explore how this would affect time to complete overall recruitment. Following this, we decided to start the trial using an allocation ratio of 2:2:3:3, so it favours the boost groups C or D in a period where it is expected less sites would be offering the boost treatment groups. The allocation ratio may be adjusted during the trial to ensure 9:9:8:8 final relative numbers.We also plan to change it to 1:1:1:1 once the experimental groups C and D are more broadly available. ~~Treatment allocation will be on a 9:9:8:8 ratio (following simulations run to explore how recruitment and allocation to the different treatment arms would evolve during the trial given the number of sites open, and the type of boost available at each site).~~ Recruitment will be closely monitored and allocation ratios will be monitored annually. ~~The allocation ratio may be adjusted during the trial should imbalances occur."~~

	Section 13.7	*Clarification of wording relating the interim analysis recognising that recruitment patterns will be different across the trial arms.* "Once 119 patients have been recruited to each of the experimental arms (B, C, and D) and completed their week 18 toxicity assessment an interim safety analysis will be conducted to rule out 30% (or more) patients with RTOG grade 2 or worse bladder or bowel complications. ~~We will conduct a pre- planned interim safety analysis after 476 patients have completed their week 18 toxicity assessment, (119 per treatment group) to rule out 30% patients with RTOG grade 2 or worse bladder or bowel complications at 18 weeks (acute toxicity) for each experimental group.~~ The figure has been estimated ~~inferred~~ assuming an expected rate of 20% in the control group (inferred from data for all patients in the PIVOTAL study) and powered (80% power, 0.05 one-sided α) with a one-stage A'Hern design. If 27 or more patients out of 119 in one group developed bladder or bowel complications of grade 2 or more at 18 weeks, consideration will be given to modifying the trial design by dropping the treatment arm. As the recruitment pattern for arm B is different to arms C and D this analysis will be carried out as the data for each of the experimental arms matures."