Listing of PORTEC-4a Protocol Amendments (version 2.5, 18 February 2020)

1. Administrative changes in the protocol

- Front page and page 2: Some changes in local PIs at sites (due to retirement and/or change of tasks); addition of the international participating group and sites with their PIs and pathologists.
- Study synopsis (page 5) and Trial design (page 12) and for consistency also in Statistical considerations (12.1, page 23): specification that 500 eligible and evaluable patients are to be included (including 50 recruited in pilot phase and ~38 of those included in previous PORTEC-4 design).
- Study synopsis (page 5): specification that the total study duration will be the duration of the inclusion period and 7 year follow-up after the last included patient.
- Some added information to study synopsis (page 5) to resolve inconsistencies with the Patient selection (paragraph 5, page 13), and specification that eligible patients should be adults (aged 18 or over)
- An update on the pilot phase in the last part of paragraph 2.4 of the introduction and reference to the publication (also included in the references, ref 39, page 30).
- Patient selection (page 13) and Surgery (7.2, page 14): inclusion of sentinel node procedure when addressing lymph node staging procedures (unchanged is that these are allowed if used as per centre's standard protocol but not recommended as standard).
- Vaginal brachytherapy (7.3.1 and 7.3.2, pages 14-15): specification that the CTV is the proximal 3.5-4 cm to resolve minor inconsistency with the next paragraph; specification that only if the patient's local anatomy is not suitable for use of a cylinder, other applicators such as vaginal ovoids are permitted; clarification that the CTV should be contoured from the surface to 3 mm depth and is thus a ring structure.
- Quality assurance (7.3.3, page 15): based on previous QA, it is specified here that QA of the brachytherapy will be performed for each centre once at least once every second year, or annually based on the previous QA evaluation, and that a dummy run should be done again if a centre acquires new brachytherapy equipment or planning system.
- External beam radiotherapy (7.4.1, page 16): specification that a "library of plans technique" with daily selection of the most appropriate treatment plan is permitted and in that case it is not mandatory to use an ITV.
- Follow-up (9.1, page 18 and Appendix H): Specification that in case of observation the 1st appointment should be around 6 weeks after randomization (about the same time as for those who had VBT or EBRT and at a QoL timepoint); specification that the QoL questionnaires are sent to the patient's home address only in the Netherlands; in other groups and sites the questionnaires will be handed out by the centre's staff. Moved and deleted some text to clarify that depending on the local routine, follow-up can be done by the gynaecological oncologist and/or the radiation oncologist at the centre. For consistency, deleted the text mentioning a 10-year follow-up point (as had already been changed in previous protocol version)
- Registration (10.1, page 21): Specification that informed consent can be obtained by telephone, provided that the patient has signed and dated the Informed consent form and has completed the baseline QoL questionnaire (both prior to or on that same date), and the radiation oncologist has written a note in the patient file that informed consent has been received on that day
- Data handling, monitoring and quality control (10.3, page 21-22): Specification that data handling will be done according to the data protection and data transfer regulations

(GPDR – European regulation on data protection). Central and on-site monitoring: Specification that on-site monitoring is done in the Netherlands, but that participating international groups and sites will have on-site monitoring only if required by their group and/or centre and/or according to local law.

- List of participating groups, centres and local investigators (16, pages 27-28): same updates on active sites, PIs, and participating international sites and groups as on front pages. Site Medical Spectre Twente has been closed as it has never started recruitement. Site Radiotherapy Group Deventer has been closed as after the merger with Arnhem the gynaecology patients are only treated in Arnhem.
- Appendix E: some clarifications in the instructions for vaginal brachytherapy planning (based on previous dummy runs and QA)

2. Administrative changes in the patient information sheet

- Date of birth of patient deleted from consent form
- Update of contact Dr Remi Nout

3. Changes in ABR form:

- Sections E4 and K: 10-year time point for QoL questionnaire deleted for consistency with the previous protocol amendments.
- Section C: deleted centres Medical Spectre Twente (as it has not activated the trial in the centre and not started recruitment) and Site Deventer of Radiotherapy Group (after merger with Arnhem patients are only included in Arnhem), changed specification 'Radiotherapy Group Arnhem' to "Radiotherapy Group Arnhem/Deventer"
- Section C: changed C6 to 'within European Union': added countries Austria (in setup) and Switzerland (preparing ethics submission); deleted Australia and New Zealand as they have not been able to secure funding and initiate the trial. Belgium, Germany, Ireland, France and Czech Republic had already been included in the previous amendments.
- Number of patients in the trial: clarified total as 465 patients (as about 35 will be included from the previous PORTEC-4 design depending on the profile), and inserted *expected* numbers of 415 from the Netherlands and about 50 from the other European participating groups and centres.