

Fact Check Guidance Document:

## Comments Form

**EUnetHTA JA3 WP4 – Other Technologies**

**OTCA23 - Biodegradable rectum spacers to reduce toxicity for prostate cancer.**

**Comments form for Manufacturers – Fact Check**

**Comments should be submitted no later than *Weekday 04/10/2019***

**Please use this form for submitting your comments to the project manager: [Julia.bidonde@fhi.no](mailto:Julia.bidonde@fhi.no)**

1. Please use the checklist for fact check and follow the instruction provided via e-mail when checking the document.
2. Please put each new comment in a new row.
3. Please insert the page number and section number to which your comment applies.
4. Please provide a description of your comment as specific as possible and provide a suggestion for amendment.
5. All comments (either on your own product or on the product of a competitor) must be validated by published sources (full reference).
6. Please **do not** comment on typos or wording as long as they do not lead to inaccuracy.

**All comments will be formally responded to in a combined document that will be published on the EUnetHTA website, with company names disclosed.  
Comments that are outside the scope of a fact check are neither considered nor answered by the authors.**

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<p>Comment from</p> <p><i>Insert your company's name</i></p>	<p>Page number</p>	<p>Line or section number</p>	<p>Description of factual inaccuracy and proposed amendment</p> <p><i>Please insert each new comment in a new row.</i></p>	<p>Character of comment</p> <ul style="list-style-type: none"> <li>• 'major'<sup>a</sup>=1</li> <li>• 'minor'<sup>b</sup>= 2</li> <li>• 'linguistic'<sup>c</sup>=3</li> </ul> <p><i>Please indicate your choice by writing the according number in this field, e.g. for major choose "1"</i></p>	<p>Author's reply</p>
<p>Boston Scientific</p>	<p>9</p>	<p>Paragraph 4, 5, 6, 7.</p>	<p>The text describes a number of approaches to review the evidence pertaining to rectum spacers including meta-analysis and network meta-analysis. It is important to be aware that the level of evidence available on the different spacers listed in the project plan varies significantly. Therefore, it is our view that each spacer should be evaluated upon the merits of the clinical evidence that pertains to it, and attempts to group spacers together may lead to erroneous conclusions. For example the results of the SpaceOAR randomised controlled trial cannot be generalised to other spacers that have not undergone such rigorous evaluation, have less supporting evidence, different characteristics, materials, insertion techniques etc.</p>	<p>1</p>	<p>We are aware that the level of evidence available on the different spacers listed in the project plan varies significantly.</p> <p>Sentence added for clarification</p>
<p>Boston Scientific</p>	<p>10</p>	<p>Paragraph 2</p>	<p>The text states that one of the exploratory subgroups is 'Fractionation and dose of radiotherapy: normo vs moderately hypo fractionated vs hypofractionated; standard dose vs high dose)'.  As ultra-hypofractionation delivering over <math>\geq 5</math> Gy per fraction (e.g. 36.25 Gy in 5 fractions) is an emerging therapy and is being used increasingly across Europe (e.g. in the UK, France, Switzerland, Sweden, Netherlands), and for which studies including rectal spacers have been initiated, we suggest that the exploratory subgroups are expanded to include ultra-hypofractionation. Preliminary findings, for example, are available for <i>King et al. 2018 - Efficacy of a rectal spacer with prostate SABR-first UK experience</i> as well as the <i>Folkert et al. 2017 - Multi-Institutional Phase 2 Trial of High-Dose Stereotactic Body Radiation Therapy</i></p>	<p>1</p>	<p>Ultra-hypofractionation added as per suggestion</p> <p>We will cross-check references suggested with our search to be able to include them</p>

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			<p><i>with Temporary Hydrogel Spacer for Low and intermediate-Risk Prostate Cancer (Fokert 2017).</i> These studies are expected to be published within the next 12 months.</p>		
Boston Scientific	11	Paragraph 9	As rectum spacers are only used during radiotherapy, we suggest adding radiotherapy search terms to the search strategy.	2	We will add radiotherapy to the search strategy.
Boston Scientific	13	Paragraph 1 of 'intervention' section	The text states: 'There are several treatment options for prostate cancer including among others radiotherapy, chemotherapy, and hormonal (i.e. androgen deprivation therapy)'. It may also be helpful to note that other standard options include radical prostatectomy, active surveillance and watchful waiting.	2	There were initially included, and later on removed to avoid having to much information in this section. Have added "other standard options include radical prostatectomy, active surveillance and watchful waiting." Further details will be provided in the final report
Boston Scientific	13	Paragraph 3 of 'intervention' section	As stated in the project plan, DuraSeal (Integra) is off-label for prostate-rectum sparing. To our knowledge, hyaluronic acid and human collagen are also off label for use as prostate-rectum spacers and we would therefore question whether it is appropriate to include them as comparators in the project plan.	1	Your concern/question was discussed with EUnetHTA secretariat. Off label product DuraSeal (Integra) is now removed from the assessment, but Hyaluronic Acid (Barrigel) has CE marked and is label for the condition, so it remains as part of the assessment.
Boston Scientific	13, 14	Paragraph 4 of 'intervention' section on page 13 and line 1 of 'comparator' section on page 14	<p>In the intervention section, the text states 'the above technologies will be assessed when used when in combination with one or more of the following: a) radiotherapy [.....], b) hormone therapy [.....], c) chemotherapy. In the 'comparator' section, the text states 'Management pathway without the technology (e.g. hormone therapy and/or radiotherapy)'.</p> <p>As rectum spacers are indicated for use during prostate radiotherapy, we wanted to clarify that radiotherapy will always be part of the treatment when spacers are used, and this may impact the search strategy.</p>	2	<p>Chemotherapy removed.</p> <p>Radiotherapy will be included in the search strategy.</p>
Boston Scientific	13	Paragraph 5 of 'intervention' section	The text states that 'Low dose rate brachytherapy may be used alone or in combination with EBRT.'. Please note that HDR (high dose rate) brachytherapy may also be used in combination with EBRT.	2	Changed as suggested

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Boston Scientific	14	Paragraph 1 of 'intervention' section, cont'd from pg 13	The text states that: 'State of the art radiotherapy (with or without spacer) will be allowed (IMRT, IGRT, minimal absolute dose) for inclusion. Older techniques might produce higher rectal toxicity and a benefit for spacers that cannot be transferred to modern techniques.' While there has been a marked shift in recent years to modern techniques, it is important to note that older technologies such as 3D-conformal are still used in a community setting. For example the most recent National Prostate Cancer Audit 2018, reporting on data from 1st April 2016 to 31st March 2017 from England and Wales states that 11% of all cases in the period were performed with 3D-conformal.(National Prostate Cancer Audit) As such, we ask that studies related to older technologies are not specifically excluded from the evaluation. It is also important to note that not all centres are using image-guided IMRT.	1	Paragraph changed to address comment: „Older techniques (e.g. 3D conformal) will also be included, with the acknowledgement that they might produce higher rectal toxicity“
Boston Scientific	14	Line 2 of 'comparator' section	The text states that in addition to management without spacing, the second comparator is 'another rectum spacer'. As the standard of care in Europe is radiotherapy without spacer, we believe that this is the appropriate comparator. We do not believe that it is appropriate to compare spacers with one another, as this is not a comparison against standard-of-care. Furthermore, there is no high-level comparative evidence available between spacers, and to our knowledge only SpaceOAR has been evaluated in a randomised controlled trial (against standard of care of radiotherapy without spacer).	1	Another rectum spacer as a comparator removed
Boston Scientific	14	Paragraph 2 of 'outcomes' section	In the 'outcomes' paragraph, we would suggest to also look at: <ul style="list-style-type: none"> <li>• reduction in rectal radiation dose (V70)</li> <li>• bowel quality of life</li> <li>• procedural success rate</li> <li>• spacer stability over time</li> </ul>	1	In consultation with Co-authors and Dedicated Reviewers, we have included a statement indicating quality of life as an outcome and sub-endpoints (bowel, sexual, etc) and we will extract it if found in the literature. Procedural success rate and spacer stability over time are not of interest to patients, clinicians, authors and co-authors of this assessment and therefore not included

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Boston Scientific	14	Paragraph 2 of outcomes section	There is a question as to whether PSA should be included as an outcome. We suggest that PSA is collected, but not as a toxicity-related outcome, as it is not related to toxicity, which is the focus of the review.	2	In consultation with co-authors and dedicated reviewers, we have included this outcome
Boston Scientific	15	Paragraph 3 of 'study design' section on effectiveness	'Retrospective studies' are excluded in the study design under 'effectiveness'. We suggest that retrospective studies may provide a good insight into the 'real-world' usage of rectal spacers and their benefits, and would suggest that the project plan allows the for inclusion of retrospective studies.	1	Although retrospective studies may have some value, the biases associated to them are high and typically are under the observational design (i.e. association not effectiveness).  We do not consider this suggestion as there are prospective studies available.

**References**

King RB, Osman SO, Fairmichael C, Irvine DM, Lyons CA, Ravi A, et al. Efficacy of a rectal spacer with prostate SABR-first UK experience. The British journal of radiology. 2018;91(1083):20170672.

Folkert, M.R. et al., 2017. Multi-Institutional Phase 2 Trial of High-Dose Stereotactic Body Radiation Therapy with Temporary Hydrogel Spacer for Low- and Intermediate-Risk Prostate Cancer. International Journal of Radiation Oncology\*Biography\*Physics, 99(5), pp.1319–1320.

National Prostate Cancer Audit – Annual Report 2018 <https://www.npca.org.uk/reports/?audience%5B%5D=professional>