

## Comments form

### EUnetHTA JA3 WP4 - Other technologies, OTCA23, Bidodegradable Rectum Spacers for Prostate Cancer Radiotherapy Comments form for manufacturers – Fact Check



<b>Comment from</b>  <i>Insert your name, title and affiliation</i>	<b>Page number</b>  <i>Insert 'general' if your comment relates to the whole document</i>	<b>Line/section number</b>	<b>Comment and suggestion for rewording</b>  <i>Please insert each new comment in a new row.</i>	<b>Character of comment</b>  <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> <i>Please indicate your choice by writing the according number in this field, e.g. for major choose "1".</i>	<b>Author's reply</b>
Boston Scientific	30	1	GENERAL COMMENT	1	<p><b>We will modify accordingly:</b></p> <p>Figure 1 Rectum spacer diagram is an image of SpaceOAR™ Hydrogel and does not illustrate other rectum spacers. Page 30 line 1</p> <p><b>HERE we specify under the figure 1:</b></p> <p>Sources: Adaptation after SpaceOAR diagram, available at link:  <a href="https://www.premiermedicalhv.com/wp-content/uploads/2018/05/LateralwProduct-Callouts.jpg">https://www.premiermedicalhv.com/wp-content/uploads/2018/05/LateralwProduct-Callouts.jpg</a></p>
	30 & 36	21-22 & 33-34	<p>Throughout the document evidence from SpaceOAR™ Hydrogel is cited but applied to all biodegradable spacers. As a result, the evidence may be misinterpreted as being applicable to all rectum spacers.</p> <p>To address this concern, we request the name SpaceOAR™ Hydrogel to be</p>		

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			<p>stated each time evidence is referenced with the use of hydrogel spacers.</p> <p>Some examples:</p> <p>Figure 1 Rectum spacer diagram is an image of SpaceOAR™ Hydrogel and does not illustrate other rectum spacers. Page 30 line 1</p> <p>Statements on SpaceOAR™ Hydrogel evidence which may be misinterpreted to apply to all rectum spacers:</p> <ul style="list-style-type: none"> <li>• <i>A distance of approximately 1.0 to 1.5 cm is usually achieved</i></li> </ul>		<p>Statements on SpaceOAR™ Hydrogel evidence which may be misinterpreted to apply to all rectum spacers:</p> <ul style="list-style-type: none"> <li>• <i>A distance of approximately 1.0 to 1.5 cm is usually achieved between the rectum and prostate, excluding the rectal wall from the high isodoses [3] Page 30 line 19-21.</i></li> <li>• <i>Estimates suggest it takes approximately three months to liquefy by hydrolysis and absorb and clear the body via renal filtration [4] Page 30 line 21-22 and Page 36 line 33-34.</i></li> </ul> <p><b>HERE we add:</b></p> <p><b>For SpaceOAR™ Hydrogel,</b> a distance of approximately 1.0 to 1.5 cm is usually achieved between the rectum and prostate, excluding the rectal wall from the high isodoses [3] <b>and</b> estimates suggest it takes</p>

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			<p><i>between the rectum and prostate, excluding the rectal wall from the high isodoses [3] Page 30 line 19-21.</i></p> <ul style="list-style-type: none"> <li>• <i>Estimates suggest it takes approximately three months to liquefy by hydrolysis and absorb and clear the body via renal filtration [4] Page 30 line 21-22 and Page 36 line 33-34.</i></li> </ul>		<p>approximately three months to liquefy by hydrolysis and absorb and clear the body via renal [4]</p>
Summary					

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Boston Scientific	9	38-45	<b>CLINICAL EFFECTIVENESS</b>  Draft statement:  It is stated that no cases of grade 3 or 4 rectal toxicity were reported through 3 months and between 3-15 months.  Comment:  According to Table 3 in the Mariados paper, there was 1 case of grade 3 toxicity in the Control group at 3 months (see the table footnote). Similar, one late grade 3 event in the Control group between 3-15 months (see the table footnote).	1	We have reviewed the data on both the publication and our draft and modified the information for grade 3 and 4 accordingly

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			<p>Suggestion for re-wording as stated in Section on Clinical Effectiveness Page 62 line 21-25:</p> <p><i>In the 3 to 15 months follow up period authors reported only small difference in Grade 1 rectal toxicity of 2% vs 5.6% and Grade &gt;2 rectal toxicity of 0% vs 1.4% in the intervention and control groups. No cases of Grade 3 or 4 were reported in the intervention group and one Grade 3 was reported in the controls.</i></p>		

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	9 & 11	38-45, Table 0-1	<p>Comment:</p> <p>The summary section does not capture cumulative incidence from 3 months up to 3 years (Hamstra et al.)</p> <p>Suggestion for additional wording as stated in Section on Clinical Effectiveness Page 62 line 25-28, with the correction on the p-value in bold:</p> <p><i>At 3 years (Hamstra 2017) the 3-year incidence of rectal toxicity greater than grade 1 (2.0% versus 9.0%; <b>p=0.028</b>)</i></p>	1	We have re-structured and re-worded the section to capture cumulative incidence the best way possible.

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			<i>and greater than grade 2 (0% versus 5.7%; p=0.012) was lower in the spacer group than control group.</i>		
	9 & 62	43-44 & 24	<b>CLINICAL EFFECTIVENESS</b>  Comment:  It should be noted that the incidence of late rectal toxicity was statistically lower in the SpaceOAR™ Hydrogel group vs control (p=0.04), (Mariados, Table 3). This has not been captured in the report.	1	New analysis and reporting has been done for the EFF chapter following team feedback, we have aimed to report effect size (RR) and/or HR as per Hamstra 2017

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			<p>Suggestion for rewording (addition of the text in bold):</p> <p><i>Findings report small differences in Grade 1 and Grade ≥2 late toxicity (3 to 15 months) post radiotherapy. Grade 1 of 2% vs 5.6% and Grade ≥2 of 0% vs 1.4% on the spaceOAR vs control group respectively. <b>The lower incidence of late toxicity in the SpaceOAR™ Hydrogel group vs control was statistically significant (p=0.04).</b></i></p>		
	10	9-10	<p>CLINICAL EFFECTIVENESS</p> <p>Draft statement:</p>	1	<p>We have report the rV70 values, but stated there is no comparative data but pre-post within group.</p>



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			<p>It is stated that "After spacer insertion, the rV70 was reduced by 3.3%, while it was 1.7% in controls".</p> <p>Comment and suggestion for rewording:</p> <p>The actual pre-post values were 12.4% to 3.3% with SpaceOAR™ Hydrogel and 12.4% to 11.7% in Controls (Mariados, p. 974, right column text). This clearly demonstrates that SpaceOAR™ Hydrogel reduces radiation exposure to the rectum.</p>		

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			<p>We suggest to re-word this statement as stated in the Section on Clinical Effectiveness, Rectal Dose, Page 63 line 5-7:</p> <p><i>In the RCT (Mariados 2015), there was a statistically significant reduction in mean rectal dose volume within the 70Gy isodose in the spacer group (from baseline 12.4% to 3.3% after injection, <math>p &lt; 0.001</math>) compared to the control group (from baseline 12.4% to 11.7%).</i></p>		

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Boston Scientific	10 & 36	39-41 & 37-41	<b>REIMBURSEMENT STATUS</b>  Draft Statement:  It states 'the technology is reimbursed in 4 (France, Germany, Italy, United Kingdom) out of 12 countries (Austria, Croatia, Hungary, Italy (different region from above), Lithuania, Poland, Scotland, Switzerland, and The Netherlands) for which we have	2	The information from this table include the feedback received from our EunetHTA partners.  <b>We will add and rephrase in:</b>  Page 10...the technology is reimbursed in 4 (France*, Germany, Italy, United Kingdom**) out of <b>13 countries</b> (Austria, Croatia, Hungary, Italy (different region from above), Lithuania, Poland, Scotland, Switzerland, and The Netherlands) for which we have information available.'

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			<p>information available.' Page 10 line 39-41.</p> <p>Comment:</p> <p>The technology is reimbursable in Germany and Austria. There is device-specific funding for SpaceOAR™ Hydrogel in England via the NHS ITP programme and a device-specific recommendation for reimbursement of SpaceOAR™ Hydrogel from the HAS in France.</p>		<p>Table3-21 (under the table), we add:</p> <p><b>Table3-21: Overview of countries providing reimbursement for SpaceOAR® Hydrogel System</b></p> <table border="1" data-bbox="1279 938 1995 1345"> <thead> <tr> <th data-bbox="1279 938 1458 1161"> <b>Country and issuing organisation</b> </th> <th data-bbox="1458 938 1749 1161"> <b>Status of recommendation (positive/negative/ongoing/not assessed)</b> </th> <th data-bbox="1749 938 1995 1161"> <b>If positive, level of reimbursement *</b> </th> </tr> </thead> <tbody> <tr> <td data-bbox="1279 1161 1458 1345">Austria</td> <td data-bbox="1458 1161 1749 1345">Positive reimbursement through Diagnosis Related Groups</td> <td data-bbox="1749 1161 1995 1345">Reimbursement not device specific</td> </tr> </tbody> </table>	<b>Country and issuing organisation</b>	<b>Status of recommendation (positive/negative/ongoing/not assessed)</b>	<b>If positive, level of reimbursement *</b>	Austria	Positive reimbursement through Diagnosis Related Groups	Reimbursement not device specific
<b>Country and issuing organisation</b>	<b>Status of recommendation (positive/negative/ongoing/not assessed)</b>	<b>If positive, level of reimbursement *</b>									
Austria	Positive reimbursement through Diagnosis Related Groups	Reimbursement not device specific									

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					Czech Republic	Not assessed	--
					France*	Positive assessment	Not available at this time
					Germany	Positive reimbursement through Diagnosis Related Groups	Reimbursement not device specific
					Italy	Not assessed	
					Spain	Not assessed	
					Sweden	Not assessed	

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					Switzerland	Ongoing assessment	
					England**	Positive funding through Innovation Technology Payment Programme	Full funding of device with volume cap.
<p>*there is a device-specific recommendation for reimbursement of SpaceOAR™ Hydrogel from the HAS in France.</p> <p>**there is device-specific funding for SpaceOAR™ Hydrogel in England via the NHS ITP programme</p>							
Description and technical characteristics of the technology							

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Boston Scientific	34 / 55	26-30 / 23-27	Draft Statement:  It states, 'despite uncertainty, one cost-effectiveness analysis concluded that hydrogel spacers were cost-effective at a willingness to pay threshold of \$100,000 in the United States in 2018 [3]. One decision analysis concluded that spacer use results in a marginal cost increase and a significant reduction in rectal toxicity. For patients receiving high dose stereotactic body radiotherapy, the use of hydrogel spacers was found to be cost-effective.'	1	We deleted the old information:  <del>Despite uncertainty, one cost-effectiveness analysis concluded that hydrogel spacers were cost-effective at a willingness to pay threshold of \$100,000 in the United States in 2018. One decision analysis concluded that spacer use results in a marginal cost increase and a significant reduction in rectal toxicity. For patients receiving high-dose stereotactic body radiotherapy, the use of hydrogel spacers was found to be cost-effective.</del> The guidelines by Cancer Care Ontario, the National Comprehensive Cancer Network, and the National Institute for Health and Care Excellence recommended the use of hydrogel spacers to reduce rectal toxicity and improve quality of life.

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			<p>Comment and suggestion for rewording:</p> <p>A recently published cost effectiveness analysis highlights additional information not captured in this assessment. We request that this study is included in the report.</p> <p>This analysis evaluated hydrogel spacers using real-world cost estimates of treatment complications. Patients were treated with intensity-modulated radiotherapy (IMRT), stereo tactic body radiotherapy (SBRT), and brachytherapy. Under the first model scenario, the increased per-patient cost</p>		<p><del>Despite uncertainty, one cost-effectiveness analysis concluded that hydrogel spacers were cost-effective at a willingness to pay threshold of \$100,000 in the United States in 2018. One decision analysis concluded that spacer use results in a marginal cost increase and a significant reduction in rectal toxicity. For patients receiving high-dose stereotactic body radiotherapy, the use of hydrogel spacers was found to be cost-effective. The guidelines by Cancer Care Ontario, the National Comprehensive Cancer Network, and NICE recommended the use of hydrogel to reduce rectal toxicity and improve QoL (ref)</del></p> <p>AND agree to reword in the suggested phrase.</p>



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			<p>of \$3,311 achieved an additional 0.1317 QALYs over two years and an overall incremental cost-effectiveness ratio (ICER) of \$21,898 per QALY. The second scenario showed an increased per-patient cost of \$2,759 and an additional 0.2148 QALYs over two years, with an overall ICER of \$12,841 per QALY. This study concluded over a two-year period, hydrogel spacer use reduced gastrointestinal, genitourinary, and sexual dysfunction complications and yielded QALY gains deemed to be cost effective.</p> <p>REFERENCE: Brooks E, Hu J, Yu J, et al. Cost Effectiveness of the Insertion of Hydrogel Spacer in Men Treated With</p>		<p>A recent analysis evaluated hydrogel spacers using real-world cost estimates of treatment complications. Patients were treated with intensity-modulated radiotherapy (IMRT), stereo tactic body radiotherapy (SBRT), and brachytherapy. Under the first model scenario, the increased per-patient cost of \$3,311 achieved an additional 0.1317 QALYs over two years and an overall incremental cost-effectiveness ratio (ICER) of \$21,898 per QALY. The second scenario showed an increased per-patient cost of \$2,759 and an additional 0.2148 QALYs over two years, with an overall ICER of \$12,841 per QALY. This study concluded over a two-year period, hydrogel spacer use reduced gastrointestinal, genitourinary, and sexual dysfunction complications and yielded QALY gains deemed to be cost effective.</p> <p>REFERENCE: Brooks E, Hu J, Yu J, et al. Cost Effectiveness of the Insertion of Hydrogel Spacer in Men Treated With Radiation Therapy for ProstateCancer. <i>Managed Care</i>; <a href="https://www.managedcaremag.com/archives/2019/12/cost-">https://www.managedcaremag.com/archives/2019/12/cost-</a></p>

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			Radiation Therapy for ProstateCancer. <i>Managed Care</i> ; <a href="https://www.managedcaremag.com/archives/2019/12/cost-effectiveness-insertion-hydrogel-spacer-men-treated-radiation-therapy-prostate">https://www.managedcaremag.com/archives/2019/12/cost-effectiveness-insertion-hydrogel-spacer-men-treated-radiation-therapy-prostate</a> . Accessed February 18, 2020.		<a href="#">effectiveness-insertion-hydrogel-spacer-men-treated-radiation-therapy-prostate</a> . Accessed February 18, 2020.
Health problem and current use					
Clinical effectiveness					
Boston Scientific	62	25-26	Draft Statement  It states 'at 3 years (Hamstra 2017) the 3-year incidence of rectal toxicity greater	1	Section re-worded and re-structured with 3x2 tables and effect sizes (RR and HR) for what p-values are not longer presented

<b>Comment from</b>  <i>Insert your name, title and affiliation</i>	<b>Page number</b>  <i>Insert 'general' if your comment relates to the whole document</i>	<b>Line/ section number</b>	<b>Comment and suggestion for rewording</b>  <i>Please insert each new comment in a new row.</i>	<b>Character of comment</b>  <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> <i>Please indicate your choice by writing the according number in this field, e.g. for major choose "1".</i>	<b>Author's reply</b>
			<p>than grade 1 (2.0% versus 9.0%; p=0.28)'</p> <p>Comment and suggestion for re-wording:</p> <p>There is an error on this outcome as it reached statistical significance p=0.028. Please re-word the sentence to update the p-value:</p>		

<p><b>Comment from</b></p> <p><i>Insert your name, title and affiliation</i></p>	<p><b>Page number</b></p> <p><i>Insert 'general' if your comment relates to the whole document</i></p>	<p><b>Line/ section number</b></p>	<p><b>Comment and suggestion for rewording</b></p> <p><i>Please insert each new comment in a new row.</i></p>	<p><b>Character of comment</b></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><b>Author's reply</b></p>
			<p><i>At 3 years (Hamstra 2017) the 3-year incidence of rectal toxicity greater than grade 1 (2.0% versus 9.0%; <b>p=0.028</b>)</i></p>		
	63	Table 5-1	<p>Draft Statement</p> <p>In the Table 5-1 it states 'Rectal Toxicity (Mariados 2015) Late (3 to 15 months)' the p-value is only applied to Grade 0 adverse events.</p> <p>Comment and suggestion for re-wording:</p>	1	<p>We have now provided effect sizes (RR or HR) for the 3x2 tables the p values mentioned have been removed to ensure clarity of information presented.</p>

<b>Comment from</b>  <i>Insert your name, title and affiliation</i>	<b>Page number</b>  <i>Insert 'general' if your comment relates to the whole document</i>	<b>Line/ section number</b>	<b>Comment and suggestion for rewording</b>  <i>Please insert each new comment in a new row.</i>	<b>Character of comment</b>  <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> <i>Please indicate your choice by writing the according number in this field, e.g. for major choose "1".</i>	<b>Author's reply</b>								
			<p>The p-value is for the overall trend, not for each grade individually.</p> <p>Please re-word Table 5-1 to reflect this change (correction in bold).</p> <table border="1" data-bbox="651 1070 1093 1377"> <thead> <tr> <th data-bbox="651 1070 875 1265">Intervention</th> <th data-bbox="875 1070 1093 1265">Group Control</th> </tr> </thead> <tbody> <tr> <td data-bbox="651 1265 875 1321">SpaceOAR/balloon (n=148) %</td> <td data-bbox="875 1265 1093 1321">(n=72) %</td> </tr> <tr> <td colspan="2" data-bbox="651 1321 1093 1377">Variados 2015) Late (3 to 15 months)</td> </tr> <tr> <td data-bbox="651 1377 875 1433">98%</td> <td data-bbox="875 1377 1093 1433">93%</td> </tr> </tbody> </table>	Intervention	Group Control	SpaceOAR/balloon (n=148) %	(n=72) %	Variados 2015) Late (3 to 15 months)		98%	93%		
Intervention	Group Control												
SpaceOAR/balloon (n=148) %	(n=72) %												
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<b>Comment from</b>  <i>Insert your name, title and affiliation</i>	<b>Page number</b>  <i>Insert 'general' if your comment relates to the whole document</i>	<b>Line/ section number</b>	<b>Comment and suggestion for rewording</b>  <i>Please insert each new comment in a new row.</i>	<b>Character of comment</b>  <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> <i>Please indicate your choice by writing the according number in this field, e.g. for major choose "1".</i>	<b>Author's reply</b>									
		<table border="1"> <tr> <td data-bbox="517 772 638 826">Grade 1</td> <td data-bbox="651 772 869 826">2%</td> <td data-bbox="882 772 1077 826">5.6%</td> </tr> <tr> <td data-bbox="517 826 638 880">Grade 2</td> <td data-bbox="651 826 869 880">0%</td> <td data-bbox="882 826 1077 880">0%</td> </tr> <tr> <td data-bbox="517 880 638 935">Grade 3</td> <td data-bbox="651 880 869 935">0%</td> <td data-bbox="882 880 1077 935">1.4%</td> </tr> </table>	Grade 1	2%	5.6%	Grade 2	0%	0%	Grade 3	0%	1.4%	<p>Draft Statement</p> <p>In the Table 5-1 it states 'Late (Hamstra 2017) cumulative incidence from 3 months up to 3 years' the p-value is only applied to Grade 0 adverse events.</p> <p>Comment and suggestion for re-wording:</p>		
Grade 1	2%	5.6%												
Grade 2	0%	0%												
Grade 3	0%	1.4%												

<b>Comment from</b>  <i>Insert your name, title and affiliation</i>	<b>Page number</b>  <i>Insert 'general' if your comment relates to the whole document</i>	<b>Line/ section number</b>	<b>Comment and suggestion for rewording</b>  <i>Please insert each new comment in a new row.</i>	<b>Character of comment</b>  <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> <i>Please indicate your choice by writing the according number in this field, e.g. for major choose "1".</i>	<b>Author's reply</b>										
			<p>There is an error on Grade <math>\geq 1</math> adverse events outcome as it reached statistical significance <math>p=0.028</math>. Please re-word Table 5-1 to reflect the correct p-value (correction in bold).</p> <table border="1" data-bbox="640 1027 1104 1391"> <thead> <tr> <th data-bbox="640 1027 871 1225">Intervention</th> <th data-bbox="871 1027 1104 1225">Group Control</th> </tr> </thead> <tbody> <tr> <td data-bbox="640 1027 871 1225">SpaceOAR/balloon (n=148) %</td> <td data-bbox="871 1027 1104 1225">(n=72) %</td> </tr> <tr> <td colspan="2" data-bbox="640 1225 1104 1273">ra 2017) – cumulative incidence from 3 months u</td> </tr> <tr> <td data-bbox="640 1273 871 1337">98%</td> <td data-bbox="871 1273 1104 1337">91%</td> </tr> <tr> <td data-bbox="640 1337 871 1391">2%</td> <td data-bbox="871 1337 1104 1391">9%</td> </tr> </tbody> </table>	Intervention	Group Control	SpaceOAR/balloon (n=148) %	(n=72) %	ra 2017) – cumulative incidence from 3 months u		98%	91%	2%	9%		
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		Grade ≥2	0%	6%	<0.015	
	69	4	Comment and suggestion for rewording:  In the Table 6-2 clinical effectiveness outcomes, according to Table 3 in the Mariados paper, there was 1 case of grade 3 toxicity in the Control group at 3 months (see the table footnote). Similar, one late grade 3 event in the Control group between 3-15 months (see the table footnote).	1	Numbers checked and tables re-worked	



<b>Comment from</b>  <i>Insert your name, title and affiliation</i>	<b>Page number</b>  <i>Insert 'general' if your comment relates to the whole document</i>	<b>Line/ section number</b>	<b>Comment and suggestion for rewording</b>  <i>Please insert each new comment in a new row.</i>	<b>Character of comment</b>  <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> <i>Please indicate your choice by writing the according number in this field, e.g. for major choose "1".</i>	<b>Author's reply</b>						
			Please include in Table 6-2 the two cases of grade 3-4 rectal toxicity in the comparator group, as illustrated below:  <table border="1" data-bbox="640 890 1104 1093"> <tr> <td data-bbox="640 890 831 1034">s/adverse events</td> <td data-bbox="831 890 1104 1034">Grade 3-4</td> </tr> <tr> <td></td> <td data-bbox="831 951 1104 1034">SpaceOAR™ Hydrogel (148)</td> </tr> <tr> <td data-bbox="640 1034 831 1093">Adverse events</td> <td data-bbox="831 1034 1104 1093">None reported</td> </tr> </table>	s/adverse events	Grade 3-4		SpaceOAR™ Hydrogel (148)	Adverse events	None reported		
s/adverse events	Grade 3-4										
	SpaceOAR™ Hydrogel (148)										
Adverse events	None reported										
<b>Safety</b>											
<b>Appendix</b>											

<b>Comment from</b>  <i>Insert your name, title and affiliation</i>	<b>Page number</b>  <i>Insert 'general' if your comment relates to the whole document</i>	<b>Line/section number</b>	<b>Comment and suggestion for rewording</b>  <i>Please insert each new comment in a new row.</i>	<b>Character of comment</b>  <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> <i>Please indicate your choice by writing the according number in this field, e.g. for major choose "1".</i>	<b>Author's reply</b>

Comment from <i>Insert your company's name</i>	Page number	Line or section number	Description of factual inaccuracy and proposed amendment <i>Please insert each new comment in a new row.</i>	Character of comment  • 'major' <sup>a</sup> =1 • 'minor' <sup>b</sup> = 2 • 'linguistic' <sup>c</sup> =3 <i>Please indicate your choice by writing the according number in this field, e.g. for major choose "1".</i>	Authors' reply
Palette Life Sciences	General	General	Where the name Barrigel is used please use the descriptor Barrigel™	2	Changes in all instances the name shows in the report
Palette Life Sciences	3	16	Please amend "Barrigel manufactured by Galderma/Palette Science" to "Barrigel™ manufactured by Palette Life Sciences"	2	Galderma removed as requested
Palette Life Sciences	8	13	Please amend:  „At present there are three CE-marked biodegradable spacers in Europe: SpaceOAR, ProSpace Balloon, and Hyaluronic Acid (HA).“  to  „At present there are three CE-marked biodegradable spacers in Europe: SpaceOAR, ProSpace Balloon, and Barrigel™“	2	Change das requested
Palette Life Sciences	10	30.33.34, 46-48, 51	Typos/incomplete sentences/missing characters	3	Reviewed – rectal dose paragraph, perirectal distance, and PSA
Palette Life Sciences	11	2	Typos	3	Reviewed - safety
Palette Life Sciences	26-27	2	In the intervention section of the scope, please amend: „Barrigel manufactured by Galderma/Palette Life Sciences Material: Hyaluronic acid, also named Non-Animal Stabilized Hyaluronic Acid (NASHA)“ to „Barrigel, manufactured by Palette Life Sciences Material: Stabilised sodium hyaluronate also named Non-Animal Stabilized Hyaluronic Acid (NASHA)“	2	Changed as requested

Palette Life Sciences	40	20 Table 3-1	<p>Please delete reference to Galderma in Barrigel manufacturer row of Table 3-1.</p> <p>Please amend headquarter for Barrigel to Santa Barbara, California, US</p>	2	Change das requested
Palette Life Sciences	41	3 Table 3-2	<p>Please add the following information for Barrigel:</p> <p>CE mark: YES</p> <p>Date of approval: 23 January 2014</p> <p>FDA approval: Undergoing clinical investigation prior to FDA approval.</p> <p>Other regulatory approvals:</p> <p>TGA Clearance (Australia)</p> <p>Date of Approval: 3 July 2020</p> <p>Intended use: Barrigel is used to increase the distance between the prostate and the anterior rectal wall, with the intent to decrease radiation dose delivered to the rectum when treating prostate cancer with radiation.</p>	1	Added as requested
Palette Life Sciences	43	Starting at line 26	<p>Line 28: Please amend: "Is approved in Europe and will be further developed for future market introduction in the United States" To „is approved in Europe and Australia and is being investigated for market clearance in the United States“</p> <p>After the sentence ending on Line 30 please add the following: "Barrigel uniquely allows for an image-guided trans-rectal ultrasound (TRUS) implant that can be sculpted to individual patient anatomy without time constraints. Barrigel is provided as a pre-packaged, sterile, uniform gel within a syringe and requires to additional mixing or preparation prior to injection."</p>	1	Changed and added as requested.
Palette Life Sciences	45	9-10	<p>,The guidelines by CCO, the National Comprehensive Cancer Network, and NICE recommended the use of</p>	1	NICE reference removed

			hydrogel spacers to reduce rectal toxicity and improve quality of life.' This sentence is incorrect and misleading with reference to the NICE Interventional Procedures Guidance 590 which made recommendations about the <b>procedure</b> by which biodegradable spacers are placed. Specifically, the guidance, which was not restricted to hydrogel spacers, recommended that there was sufficient evidence of safety and efficacy to be used with standard governance arrangements. Please reword to make this clear.		
Palette Life Sciences	45	15	Please make line 15 a sub-heading, clarifying that text is about 1 proprietary product as in line 36.	3	Su-heading made as suggested
Palette Life Sciences	45 46	47-8 1-3	Please amend p45, lines 47-48 and p46, lines 1-3, to  "The benefits claimed for <b>Barrigel</b> :  <ol style="list-style-type: none"> <li>1. Reduces rectal toxicity from prostate radiotherapy, allowing hypofractionation regimens, improving patient outcomes and reducing healthcare utilisation</li> <li>2. Premixed and ready to use (no chance of mixing disasters or early polymerisation and clogging)</li> <li>3. Does not polymerise and therefore gives the injector the ability to sculpt the rectal spacing, including the ability to achieve homogenous spacing from base to apex and from L to R</li> <li>4. Controlled insertion that can be easily visualised within the perirectal space, limiting the risk of inadvertent insertion into rectum</li> <li>5. Barrigel remains stable for up to 12 months</li> <li>6. Barrigel can be reversed with hyaluronidase, a well-known enzyme on formulary at institutions"</li> </ol>	1	I have replaced the previously written with the suggestions here. Hope that is ok.
Palette Life Sciences	46	22	Please amend: „CE information for BioProtect Balloon and HA gel is not available beyond what is stated in Table 3-1 above.“ To:	2	Changed as requested

			„CE information for BioProtect Balloon is not available beyond what is stated in Table 3-1 above. The CE marking of conformity categorises Barrigel as ‘Stabilized non-animal hyaluronic acid-based implants for protection of the rectal wall when treating prostate cancer with radiation‘“		
	47	5	Please substitute „Barrigel“ for „HA spacers“	2	Done
Palette Life Sciences	63	10	Please add the following sentence: „The target population for Barrigel is patients receiving radical radiotherapy for prostate cancer.“	2	Added as per request
Palette Life Sciences	63	Line 15	„[A0023] – How many people belong to the target population?“ Please amend to clarify that the figures are a reasonable estimate of size of the potential benefitting population for a biodegradable rectal spacer which need not necessarily be the SpaceOAR product.	2	Check with co-authors
Palette Life Sciences	65	5 onwards	Included studies: The randomised controlled study by Prada et al 2009 [ Brachytherapy 8(2): 210-207]) was not included in the evidence review – possibly it was outside the 2010-19 search strategy timeframe - despite a relevant population and including rectal toxicity outcomes.	1	Indeed. The searches were executed on 11,12 and 18 November 2019 with a year limit of 2010-2019 in the following databases:
Palette Life Sciences	83	31-32	Typos	3	Thanks, the medical editor will catch those
Palette Life Sciences	86	27-28	Please amend: ‘According to the 2019 document, NICE is currently evaluating the cost-efficacy and safety of SpaceOAR‘  To  ‘The development of NICE medical technologies guidance on Space OAR was suspended in 2019 because, after development of the final scope, NICE determined that the topic was no longer suitable for medical technologies guidance. The topic will now be considered for selection by the technology appraisals programme.’	1	Changed as per suggestion

			( <a href="https://www.nice.org.uk/guidance/indevelopment/gid-mt526">https://www.nice.org.uk/guidance/indevelopment/gid-mt526</a> ) ‘		
Palette Life Sciences	87	4-16	<p>„We found an overwhelming number of single-arm studies..... we acknowledge that device-14 related safety results (or results as a whole) may have been different had we been able to 15 consider that information“</p> <p>This is an important observation which also appears elsewhere in the report and we understand the technical challenges of analysis and synthesis of such a data set. Nevertheless, it would have been helpful to include well-described single arm studies/case series where these report relevant safety/toxicity outcomes. For example, the Chapet et al 2015 paper (<a href="https://doi.org/10.1016/j.ijrobp.2014.11.027">https://doi.org/10.1016/j.ijrobp.2014.11.027</a>), which was included in the NICE Interventional Procedures Guidance Overview document, reported acute toxicities in 36 patients treated with a hyaluronic acid spacer and hypofractionation.</p>	1	Indeed. We agree processing this information would have been useful and added an important aspect to the assessment but there were few hurdles that prevented us to make any further work on this dataset.
Palette Life Sciences	105	3	<p>P105 line 3 Table A4. The following Barrigel studies report relevant outcomes in appropriate populations.. Please add them to Table A4 to ensure that it is a comprehensive list of relevant citations:</p> <p>Prada et al Int. J. Radiation Oncology Biol. Phys., Vol. 69, No. 1, pp. 95–102, 2007</p> <p>Prada et al. Brachytherapy 8(2): 210-207, 2009</p> <p>Prada et al BJUI International 106 (1), 2010,32-36, <a href="https://doi.org/10.1111/j.1464-410X.2009.09096.x">https://doi.org/10.1111/j.1464-410X.2009.09096.x</a></p> <p>Boissier et al. <a href="http://dx.doi.org/doi:10.1016/j.urology.2016.09.045">http://dx.doi.org/doi:10.1016/j.urology.2016.09.045</a>.</p>	1	<p>2007 and 2009 would not have been caught by our literature review.</p> <p>Prada 2010 does not include HA in title, abstract or keywords, so IF the search captured it, it would not have been included.</p> <p>Boissier 2017 included in the list</p>
Palette Life Sciences	108	4	<p>The study in Table A5 by Chapet et al 2013, which we assume to be <a href="http://dx.doi.org/10.1016/j.ijrobp.2012.11.027">http://dx.doi.org/10.1016/j.ijrobp.2012.11.027</a>, reports rectal toxicity outcomes in a relevant population and has</p>	1	Single arm study -we were looking for safety outcomes only. Study does not meet criterion

			been incorrectly included in this table. Please move the reference to Table A4.		
Palette Life Sciences	119	2	In Table A10, please apply the same changes as suggested above on p41, Table 3-2.	2	Changes made as suggested

Please add extra rows as needed.

<sup>1</sup> a "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)

b "minor": the comment does not necessarily have to be answered in a detailed manner

c "linguistic": grammar, wording, spelling or comprehensibility, only if they lead to inaccuracy.