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# BMJ Open

## Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK

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4 **1 Title page**  
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2 Delphi study to identify consensus on patient selection for  
3 hydrogel rectal spacer use during radiation therapy for prostate  
4 cancer in the UK.

5 **Short title:** Delphi study on hydrogel rectal spacer use (UK)

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4 22 Delphi study to identify consensus on patient selection for  
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9 24 cancer in the UK.  
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14 25 Structured abstract (*Word count: 268, max 300*)  
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## 16 26 **OBJECTIVES**

17  
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19 27 To identify consensus on patient prioritisation for rectal hydrogel spacer use during radiation  
20  
21 28 therapy for the treatment of prostate cancer in the United Kingdom.  
22

## 23 29 **DESIGN**

24  
25  
26 30 Delphi study consisting of two rounds of online questionnaires, two virtual advisory board  
27  
28 31 meetings and a final online questionnaire.  
29

## 30 32 **SETTING**

31  
32  
33 33 Radical radiation therapy for localised and locally advanced prostate cancer in the United  
34  
35 34 Kingdom.  
36  
37

## 38 35 **PARTICIPANTS**

39  
40  
41 36 Six leading clinical oncologists and one urologist from across the UK.  
42

## 43 37 **INTERVENTIONS**

44  
45  
46 38 Rectal hydrogel spacer.  
47  
48

## 49 39 **PRIMARY AND SECONDARY OUTCOME MEASURES**

50  
51 40 NR  
52

## 53 41 **RESULTS**

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56  
57 42 The panel reached consensus on the importance of minimizing toxicity for treatments with  
58  
59 43 curative intent, and that even low-grade toxicity-related adverse events can significantly  
60

1  
2  
3 44 impact quality of life. There was agreement that despite meeting rectal dose constraints, too  
4  
5 45 many patients experience rectal toxicity, and that rectal hydrogel spacers in eligible patients  
6  
7 46 significantly reduces toxicity related adverse events. However, as a consequence of funding  
8  
9 47 limitations, patients need to be prioritized for spacer use. A higher benefit of spacers can be  
10  
11 48 expected in patients on anticoagulation, and in patients with diabetes or inflammatory bowel  
12  
13 49 disease, but consensus could not be reached regarding patient groups expected to benefit  
14  
15 50 less. While radiation therapy regimen is not a main factor determining prioritization, higher  
16  
17 51 benefit is expected in ultra-hypofractionated regimens.

## 21 **CONCLUSION**

23 53 There is a strong and general agreement that all prostate cancer patients undergoing radical  
24  
25 54 radiation therapy have the potential to benefit from hydrogel spacers. Currently, not all patients  
26  
27 55 who could potentially benefit can access hydrogel spacers, and access is unequal.  
28  
29 56 Implementation of the consensus recommendations would likely help prioritise and equalise  
30  
31 57 access to rectal spacers for patients in the UK.  
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## 58 **ARTICLE SUMMARY: STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 59 • The Delphi panel is a recognised method in developing NICE guidelines and is utilised  
60 here to gather insights from a diverse panel of UK radiation oncology and urology  
61 experts who are experienced users of hydrogel spacers.
- 62 • This study included seven panel experts and their experiences may not reflect all users  
63 of hydrogel spacers.
- 64 • To help reduce bias, answers and opinions were assessed by two researchers working  
65 independently.

## 66 **WHAT IS ALREADY KNOWN ON THIS TOPIC?**

- 67 • Radiation toxicity to nearby healthy tissue is a potential problem when undertaking  
68 radical radiotherapy with curative intent for prostate cancer.
- 69 • Biodegradable spacers are used to separate the prostate and the rectum, thus  
70 reducing radiation exposure to a primary dose-limiting organ.
- 71 • Spacer funding and capacity are limited and there is a need to understand which  
72 patients to prioritise for use of a spacer.

## 73 **WHAT DOES THIS STUDY ADD?**

- 74 • Expert consensus opinion can help to guide strategy in areas of care where the  
75 evidence base is lacking.
- 76 • There was consensus that increased benefit from spacers is expected in patients on  
77 anticoagulation and/or with diabetes and/or inflammatory bowel disease.

## 78 INTRODUCTION

### 79 Prostate cancer burden

80 Prostate cancer is the second most common cancer in men globally,<sup>1</sup> and the most common  
81 in the UK.<sup>2</sup> More than 47,500 UK men are diagnosed with prostate cancer every year and over  
82 400,000 men are living with and after prostate cancer.<sup>3</sup> The 5-year survival rate for localized  
83 prostate cancer in the UK is almost 100%,<sup>4</sup> with three quarters of men diagnosed at any stage  
84 expected to survive 10 years.<sup>2</sup> In England, 97%, 87% and 78% of men diagnosed with prostate  
85 cancer survive their disease for more than one, five and ten years, respectively.<sup>2</sup> Given the  
86 high likelihood of curative therapy, a key treatment goal is to prevent potential adverse events  
87 from impacting patient quality of life after treatment.

88 In addition to the patient burden, prostate cancer is a costly disease with the European costs  
89 of care for prostate cancer estimated at EUR 199 billion in 2018.<sup>5</sup>

### 90 Radiation therapy for prostate cancer

91 Choice of treatment for prostate cancer is complex and involves multi-factorial considerations  
92 including presenting cancer stage (localised, locally advanced or metastatic), risk stratification,  
93 life expectancy, comorbidities, and other patient-specific factors, such as lifestyle, patient  
94 preference and treatment goals.<sup>6</sup> For localised and locally advanced prostate cancer,  
95 treatment options include active surveillance, surgery, and radiation therapy (RT), with or  
96 without hormone treatment, as well as multimodality treatment combining surgery or RT with  
97 systemic therapy.<sup>7-9</sup> RT with radical intent is a first-line treatment for localised and locally  
98 advanced prostate cancer.<sup>8</sup> Intensity-modulated RT (IMRT) with image guidance (IGRT) is  
99 considered the gold-standard form of external beam RT (EBRT).<sup>10</sup> Of the circa 18,000 men  
100 identified as having received radical RT for prostate cancer in England and Wales between  
101 April 2018 and March 2019, over 90% were treated with IMRT.<sup>11</sup> Whilst stereotactic body RT  
102 (SBRT) is not currently routine practice in the UK, its use is increasing and it is now delivered



1  
2  
3 103 in several NHS centres.<sup>12</sup> Circa 95% of UK men with intermediate-risk disease receive a  
4  
5 104 hypofractionated radiotherapy regimen.<sup>11</sup>  
6  
7

8 105 The success and clinical outcomes of RT depend on several factors, including radiation dose  
9  
10 106 to the tumour and the extent of irradiation affecting nearby normal-tissue, particularly the  
11  
12 107 rectum.<sup>10</sup> Dose-escalated EBRT is a highly effective curative treatment, with higher doses  
13  
14 108 providing better biochemical control.<sup>13</sup> Higher doses can, however, increase radiation toxicity  
15  
16 109 to nearby tissues. Despite substantial advancements in RT, acute and reversible, as well as  
17  
18 110 rare but severe, long-term adverse effects of radiation toxicity such as urinary and bowel  
19  
20 111 incontinence remain problematic. In 2021, The National Prostate Cancer Audit (NPCA)  
21  
22 112 reported that 11% of prostate cancer patients experienced  $\geq 1$  severe gastrointestinal  
23  
24 113 complication (defined as a confirmed diagnosis of radiation toxicity and requiring a procedure  
25  
26 114 to the large bowel) within two years after radical RT.<sup>11</sup> Due to its proximity to the prostate, the  
27  
28 115 anterior rectal wall is especially vulnerable to irradiation effects and the rectum is a dose-  
29  
30 116 limiting organ at risk.<sup>14</sup>  
31  
32  
33

### 34 117 **Hydrogel spacers**

35  
36  
37 118 One way of reducing the unwanted radiation dose to the rectum is by increasing the space  
38  
39 119 between the prostate and the rectal wall. This can be achieved by use of a rectal spacer, with  
40  
41 120 three currently indicated for use during RT for prostate cancer in the UK: biodegradable  
42  
43 121 balloons, hyaluronic acid gel, and polyethylene glycol (PEG) hydrogel.<sup>15</sup> In the UK, the use of  
44  
45 122 biodegradable spacers to reduce rectal toxicity during RT for prostate cancer is accepted  
46  
47 123 (IPG590) by NICE, based on safety and efficacy data on the use of PEG hydrogel spacers.<sup>15</sup>  
48  
49 124 Use of rectal hydrogel spacers has been evaluated in a single-blind, phase III trial in image  
50  
51 125 guided IMRT (N=222).<sup>16</sup> The spacer-placement success rate was 99%, and no device-related  
52  
53 126 adverse events occurred.<sup>16</sup> Late (three to 15 months) rectal toxicity severity was significantly  
54  
55 127 reduced in the spacer group.<sup>16</sup> At three years follow-up, decreased bowel toxicity and fewer  
56  
57 128 declines in urinary and bowel quality of life were observed in the spacer group.<sup>17</sup>  
58  
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1  
2  
3 129 Lack of routine reimbursement has led to restricted patient access to hydrogel spacers in the  
4  
5 130 UK. Therefore, there is a requirement to prioritise patients for hydrogel spacer use in the UK,  
6  
7 131 and attempts have been made to identify optimal usage. A secondary analysis of the hydrogel  
8  
9 132 spacer trial data tried to identify the patient subgroups most and least likely to benefit from the  
10  
11 133 intervention but found generally homogeneous results in bowel quality of life with benefits in  
12  
13 134 all assessed subgroups.<sup>18</sup>

15  
16 135 The aim of this study was to identify consensus on patient prioritisation for rectal hydrogel  
17  
18 136 spacer use during RT for the treatment of prostate cancer in the UK.

## 19 20 21 137 **METHODS**

### 22 23 24 138 **The Delphi technique and panel experts**

25  
26  
27 139 The Delphi technique is a structured, iterative, multistage process using rounds of  
28  
29 140 questionnaires to collect opinions and to stepwise develop consensus among a pre-defined  
30  
31 141 panel of experts.<sup>19</sup> For this study, experts were approached and asked to participate in the  
32  
33 142 panel based on being a UK radiation oncologist or urologist having experience with rectal  
34  
35 143 hydrogel spacers. To ensure a diverse panel, experts were sought to represent different  
36  
37 144 geographies within the UK and use different types of RT modalities. There is no defined  
38  
39 145 optimal panel size for a Delphi study,<sup>20</sup> but the selection of an odd number of experts ensured  
40  
41 146 that a majority outcome could be reached.

### 42 43 44 45 147 **Steps in the Delphi process**

46  
47  
48 148 There is no fixed number of rounds in a Delphi survey.<sup>20</sup> As depicted in Figure 1, our study  
49  
50 149 adopted a five-stage approach to elicit consensus, consisting of two pre-advisory board  
51  
52 150 questionnaires administered through a web-based survey program, two virtual advisory board  
53  
54 151 discussions, and a final concluding questionnaire.

55  
56  
57 152 The first questionnaire provided some background information on the experts, such as their  
58  
59 153 most used RT modalities and open-ended questions to capture a broad understanding. The

1  
2  
3 154 open-ended questions related to key treatment aims, which patient and treatment  
4  
5 155 characteristics to consider when prioritising hydrogel spacer, factors typically deterring them  
6  
7 156 from recommending hydrogel spacer use, and factors predictive for toxicity. Additionally,  
8  
9 157 experts were asked to rank treatment modalities in order of how much patient benefit they  
10  
11 158 would expect from hydrogel spacer use, on a scale from 0 (no patient benefit) to 100 (maximal  
12  
13 159 patient benefit).

16  
17 160 In the second questionnaire, the responses to the open-ended questions from the previous  
18  
19 161 questionnaire were presented, and the experts asked to rank them by order of importance. In  
20  
21 162 addition to follow-up questions, the second questionnaire included questions on perceived  
22  
23 163 barriers to hydrogel spacer use.

25 164 *Figure 1: Overview of Delphi panel process*

## 27 165 **Analysis and scoring**

30 166 Qualitative content analysis was used to analyse responses to open-ended questions. Two  
31  
32 167 researchers independently analysed responses and interpreted consensus. At the advisory  
33  
34 168 board meetings, results from the questionnaires were presented together with initial drafted  
35  
36 169 consensus statements for discussion. Then followed moderated discussions which led to  
37  
38 170 revisions of the consensus statements. In the final online questionnaire, the consensus  
39  
40 171 statements were presented, and the experts asked to select a level of agreement: "I fully  
41  
42 172 agree", "I partially agree" or "I disagree". Upon selecting "I partially agree", experts were asked  
43  
44 173 to give a comment and/or update the wording of the statement. The responses were linked to  
45  
46 174 an agreement score, based on the answer selected, and the comment given if "I partially  
47  
48 175 agree" was selected (Table 1).

52 176 *Table 1: Consensus statement scoring key*

Score	Answer selected	Description
4	"I fully agree"	
3	"I partially agree"	With minor word change
2	"I partially agree"	With minor change to statement interpretation/meaning
1	"I disagree"	

1  
2  
3 177 Consensus definitions vary between studies<sup>21-25</sup>, with percent agreement being one of the  
4  
5 178 more common approaches.<sup>25</sup> Based on the results of our final online survey, statements were  
6  
7 179 categorised into four levels of consensus (strong, moderate, low, and no consensus). This  
8  
9 180 study scored the level of consensus in terms of percent agreement, and additionally that  
10  
11 181 consensus could not be reached in case any expert disagreed with a statement. Figure 2  
12  
13 182 depicts the consensus statement scoring for this study. Only statements grouped as either  
14  
15 183 **Strong** or **Moderate** are considered statements where consensus was reached. **Weak** or **No**  
16  
17 184 consensus mean that there was still substantial discussion or divergence of opinion among  
18  
19 185 the experts.

20  
21  
22  
23 186 *Figure 2: Consensus statement scoring, decision tree*

## 24 25 187 **Consent, privacy, and data security**

26  
27  
28 188 The panel experts were informed about and consented to the full Delphi process, including  
29  
30 189 length and time of surveys and details on the data collected, stored, and deleted. The retention  
31  
32 190 periods of collected data were pre-defined. Questionnaire responses were anonymised and  
33  
34 191 securely stored on the survey software provider's server in Germany. Audio recordings were  
35  
36 192 stored for 60 days on the conference provider's EU based server. All experts were contracted  
37  
38 193 for this study and reimbursed at fair, local market rates for their time commitment during the  
39  
40 194 Delphi process. The study was approved by an independent review board (HML IRB Review  
41  
42 195 #952SCGC21).

## 43 44 45 196 **Patient and public involvement**

46  
47  
48  
49 197 No patients involved.

## 50 51 52 198 **RESULTS**

### 53 54 55 199 **Panel expert characteristics**

56  
57  
58 200 All approached experts agreed to participate (N=7). Details on the panel experts' treatment  
59  
60 201 practices are presented in Table 2. The majority of the panel (N=6) exclusively use rectal

202 hydrogel spacers in their practices. One uses rectal hydrogel spacers as well as biodegradable  
 203 balloons. Participation rates were high, with only one dropout (one expert did not complete the  
 204 second questionnaire but participated in all other steps).

205 *Table 2: Panel experts treatment practice*

<b>Geographical setting, N (%)</b>	
England	5 (57)
Northern Ireland	1 (14)
Wales	1 (14)
<b>Public or private setting, N (%)</b>	
Public only	1 (14)
Private only	0 (0)
Both	6 (86)
<b>Most frequently used RT modalities, % of patients (N experts using modality)</b>	
IMRT	25–95 (6)
EBRT (not specified)	90 (1)
IMRT and HDR BT boost	15–30 (2)
SBRT	45 (1)
BT monotherapy (LDR)	10–20 (2)
PBT	10 (1)

206 *Key: IMRT, intensity-modulated radiation therapy; EBRT, external beam radiation therapy; HDR, high dose rate;*  
 207 *BT, brachytherapy; SBRT, stereotactic body radiation therapy; LDR, low dose rate; PBT, proton beam therapy.*

208 Key treatment aims, besides curing or controlling cancer and increasing overall survival, were  
 209 to minimise the risk of side effects and toxicity.

## 210 Questionnaire outcomes shaping the consensus statement discussion

211 Questionnaire outcomes showed that the panel estimated considerably less toxicity in patients  
 212 with hydrogel spacer, as compared to those without (Figure 3). All experts agreed that  
 213 hydrogel spacers reduce grade 1 and 2 late rectal toxicity, 86% agreed that it reduces grade  
 214 3 toxicity and 71% grade 4 toxicity.

215 *Figure 3: Expected level of late (after 3 months) rectal toxicity in patients with and without hydrogel spacer*

216 The panel considered toxicity a considerable issue, and underlined that also low-grade  
 217 toxicity-related adverse events may significantly worsen patient's lives:

1  
2  
3 218 *'I ask them [my patients], when you're out and about, is the first thing you think of where*  
4  
5 219 *the toilet is?... And a remarkable number of patients say yes to that question, and it is*  
6  
7 220 *affecting their quality of life.'*  
8  
9

10 221 In the first questionnaire, the panel estimated that an average of 83% (SD: 13%) patients who  
11  
12 222 could potentially benefit from a hydrogel spacer were denied access. Throughout the  
13  
14 223 discussions, patient access in general and equal access in particular were central themes.  
15  
16 224 The panel voiced their concern, for example regarding differences between NHS and private  
17  
18 225 practice:  
19

20  
21 226 *'In my private practice, every patient gets it [hydrogel spacer] unless there is a reason*  
22  
23 227 *why they should not get it. Whereas in my NHS practice, unfortunately no patient gets*  
24  
25 228 *it, unless there is a reason why they should get it.'*  
26  
27

28 229 The main barrier to hydrogel spacer use was funding and resource constraints, followed by  
29  
30 230 lack of trained staff.  
31

32  
33 231 *'The ideal way to go would be to offer it to every eligible patient. But given that this is*  
34  
35 232 *not currently feasible in our centre, there has to be some kind of categorisation.'*  
36  
37

38 233 As seen in Figure 4, a trend towards hypo-fractionated external-beam regimens, with potential  
39  
40 234 increased bowel dose and toxicity being associated with more potential benefit for spacers  
41  
42 235 was apparent. This was also reflected in the outcome of the conjoint analysis. The absolute  
43  
44 236 variation between expected benefit was, however, relatively low, ranging from 67 (BT  
45  
46 237 monotherapy LDR) to 80 (SBRT/SABR) on average. This was reflected in later discussions,  
47  
48 238 where experts agreed that RT modality is not the main consideration when prioritising patients  
49  
50 239 for hydrogel spacer use.  
51

52  
53 240 *Figure 4: Expected patient benefit from hydrogel spacer use, by treatment modality*  
54

55 241 When asked about patient characteristics to consider when deciding whether to recommend  
56  
57 242 using hydrogel spacer the experts gave a wide range of suggestions, including comorbidities  
58  
59 243 (age, diabetes, high bleeding risk, hip prosthesis, inflammatory bowel disease and rectal and  
60

1  
2  
3 244 bowel problems, normal erectile function), cancer stage, localisation, and heavy smoking. This  
4  
5 245 was narrowed down in subsequent discussion, with general agreement that patients with  
6  
7 246 certain comorbidities (diabetes, inflammatory bowel disease) or on anticoagulation may have  
8  
9 247 higher benefit from hydrogel spacers.  
10

## 11 12 13 248 **Consensus statements** 14 15

16  
17 249 Upon being shown the results of the questionnaires, two rounds of moderated discussion  
18  
19 250 followed, resulting in 13 consensus statements. These statements were subsequently voted  
20  
21 251 on in a final questionnaire, and a final scoring was assigned as described in the method  
22  
23 252 section.  
24  
25

26 253 The following eight statements reached strong consensus:  
27

- 28  
29 254 • Our consensus opinion is that for treatments with curative intent, focus should be on  
30  
31 255 minimising toxicity and the risk of side effects.  
32  
33 256 • Our consensus opinion is that use of spacers in eligible patients significantly reduces  
34  
35 257 radiation dose to the rectum and toxicity-related adverse events.  
36  
37 258 • Our consensus opinion is that despite meeting rectal dose constraints, too many  
38  
39 259 patients continue to experience rectal toxicity.  
40  
41 260 • Our consensus opinion is that certain grade 1 toxicity-related adverse events<sup>1</sup> can still  
42  
43 261 have a significant impact on patient quality of life.  
44  
45 262 • Our consensus opinion is that any toxicity grading system in use should be  
46  
47 263 complemented by patient-reported outcomes.  
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59  
60 <sup>1</sup> Bowel frequency and urgency, diarrhoea, flatulence, radiation cystitis, radiation proctitis, rectal bleeding, rectal mucus.

- 1  
2  
3 264 • Our consensus opinion is that patients receiving long-term anticoagulation therapy with  
4  
5 265 medications such as direct oral anticoagulants (DOACs)<sup>2</sup> should be considered for  
6  
7 266 spacer use if their anticoagulation can be safely paused.  
8  
9 267 • Our consensus opinion is that spacers are useful in eligible patients with T1-T2  
10  
11 268 disease. Spacer use in patients with T2+ disease should not be excluded but should  
12  
13 269 be assessed on an individual basis by a team proficient in inserting spacers.  
14  
15 270 • Our consensus opinion is that patients should have the opportunity to take part in the  
16  
17 271 discussion regarding the use of a spacer.<sup>26</sup>  
18  
19  
20

21 272 For the following two statements, moderate consensus was reached. Each statement is  
22  
23 273 followed by an explanation on why strong consensus was not reached.  
24  
25

- 26 274 • Our consensus opinion is that a higher benefit of spacers is expected in eligible  
27  
28 275 patients with certain comorbidities<sup>3</sup> and/or longer expected overall survival.  
29

30 276 Six experts (86%) fully agreed with the statement. One expert (14%) only partially agreed and  
31  
32 277 suggested removing “and/or longer expected overall survival”. This was deemed a change to  
33  
34 278 the statement interpretation.  
35  
36

- 37 279 • All eligible radiotherapy patients should have equal opportunity to access spacers,  
38  
39 280 independent of socio-economic factors.  
40  
41

42 281 Five experts (71%) fully agreed with the statement. While there was an overall agreement that  
43  
44 282 lack of equality in access to spacers is currently an important issue, two experts (29%) had  
45  
46 283 rewording suggestions that would have impacted the statement interpretation. One proposed  
47  
48 284 to add more detail on eligibility, and to add that patients suitable for a spacer implant should  
49  
50 285 have access, irrespective of whether they can afford it. The other expert expressed some  
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57  
58 <sup>2</sup> The reason for prescribing the DOAC, rather than the medication itself, is more important for the  
59 decision. All patients on DOACs, except for cardiac stent and prosthetic valve replacement patients  
60 may be able to safely pause their anticoagulation.

<sup>3</sup> Anticoagulation, diabetes, inflammatory bowel disease (ulcerative colitis and Crohn's disease)



286 uncertainty regarding the term “socio-economic factors” and would have preferred the wording  
287 “irrespective of post-code”.

## 288 **Statements where no consensus was reached**

289 One statement was categorised as a weak consensus statement:

- 290 • Whilst we support the use of spacers in all eligible patients, our consensus opinion is  
291 that if resource constraints exist, patients receiving ultra-hypofractionated or  
292 hypofractionated radiotherapy should be prioritised for access to a spacer.

293 Four experts (57%) fully agreed with the statement. The remaining three (43%) partially  
294 agreed but had additional comments. One expert expressed that individual risk factors should  
295 be considered, rather than the RT modality. The second expert agreed on the need to identify  
296 a group at higher risk of rectal toxicity, and suggested combination of RT modality  
297 considerations and patient characteristics (e.g., age) and comorbidities. The third respondent  
298 only agreed that patients receiving ultra-hypofractionated RT should be prioritised.

299 For the following two statements, no consensus was reached.

- 300 • Our consensus opinion is that for patients with anticipated short overall survival but  
301 who will receive radical radiotherapy, use of a spacer should only be considered after  
302 careful evaluation of potential benefit.

303 Three experts (43%) fully agreed. Four (57%) partially agreed but had additional comments.

304 Two experts made the point that it is unlikely that patients with short anticipated overall survival  
305 would be indicated for radical radiotherapy. Two experts expressed uncertainty with the  
306 wording “overall survival”. One of them suggested a rewording that some carefully selected  
307 patients with short expected survival who are offered radical radiotherapy may benefit from  
308 spacer use after careful consideration. The second expressed that the statement was too  
309 unclear. Additionally, in subsequent discussions, the experts agreed that the term “anticipated  
310 shorter life expectancy” would have been preferred over “anticipated short overall survival”,

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3 311 so as not to imply that the use of hydrogel spacers affects survival. Upon subsequent  
4  
5 312 discussion, experts agreed that the statement would have been improved by adding “and side  
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7 313 effects” to the end of the statement.  
8  
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- 10 314     • Our consensus opinion is that there are a limited number of patients with risk factors,  
11  
12 315         or combination of risk factors, in which use of a spacer should only be considered after  
13  
14 316         careful evaluation of potential benefits.  
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17 317 Four experts (57%) fully agreed, two (29%) partially agreed, and one (14%) disagreed. Those  
18  
19 318 who partially agreed expressed that an addition should be made to the statement, that the  
20  
21 319 majority of patients who receive radical RT would also be suitable for a spacer, noting that  
22  
23 320 patients who are not fit enough for a spacer, likely are also not fit for RT. The second partially  
24  
25 321 agreeing expert wanted to add a recommendation to discuss such cases with a mentor with  
26  
27 322 extensive experience in spacer insertion. Upon subsequent discussion, experts agreed that  
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29 323 the statement would have been improved by adding “and side effects” to the end of the  
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31 324 statement.  
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## 34 325 **DISCUSSION**

### 36 326 **Statement of principal findings**

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41 327 There was strong consensus that rectal toxicity is a considerable issue, and that minimizing  
42  
43 328 the risk of radiation side effects is an important treatment aim. Rectal hydrogel spacers can  
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45 329 reduce the toxicity burden and benefit patients undergoing radical RT for the treatment of  
46  
47 330 prostate cancer in the UK. Currently, the NHS does not routinely fund hydrogel spacers.  
48  
49 331 Limited funding leads to limited resources, and therefore limited access. Experts estimated  
50  
51 332 that on average, 83% of their patients that could benefit from a spacer are not currently getting  
52  
53 333 access. There was moderate consensus that a higher benefit is expected in patients on  
54  
55 334 anticoagulation, patients with diabetes, and patients with inflammatory bowel disease  
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57 335 (Ulcerative colitis or Crohn’s disease). However, experts expected the majority of patients to  
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59 336 benefit from use of a spacer, and it was not possible to reach consensus on those patients  
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3 337 with lower expected benefit. Key takeaways from discussions around statements where no  
4  
5 338 consensus was reached are that individual patient characteristics are more important for  
6  
7 339 informing the decision on whether to prioritise the use a spacer than the RT regimen selected.  
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9 340 However, a higher level of benefit from spacer use is expected with ultra-hypofractionated RT  
10  
11 341 compared with standard RT, a conclusion in line with current clinical evidence.<sup>27</sup>  
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15 342 **Meaning of the study: possible explanations and implications for clinicians and policy**  
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18 343 **makers**  
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21 344 Currently, patient selection is driven by limitations in the healthcare system rather than patient  
22  
23 345 needs. This highlights the importance of developing guidance on spacer use, to ensure fair  
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25 346 and equal access to healthcare. The COVID-19 pandemic has lengthened already substantial  
26  
27 347 NHS waiting times, further exacerbating issues with access and underscoring the need for  
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29 348 formal guidance. Additionally, practical issues (e.g., availability of trained staff, theatre  
30  
31 349 capacity) need to be considered when preparing a clinic to start using hydrogel spacers. As is  
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33 350 important for all techniques to be introduced, audit of practice and quality improvement is  
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35 351 recommended.  
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39 352 **Strengths and weaknesses**  
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42 353 This study only included seven experts, who are all experienced users of hydrogel spacers  
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44 354 Naturally, a broader selection of experts could have resulted in different answers. However,  
45  
46 355 including non-users as panel experts would not have been feasible for the purposes of this  
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48 356 study, as they would have not possessed the relevant experience required. Additionally, the  
49  
50 357 RT modality used by panel members could influence their view on when to prioritise hydrogel  
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52 358 spacer use. However, the diversity of the panel in terms of modalities used likely safeguarded  
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54 359 the balance of the resulting consensus.  
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58 360 The main strengths of this study are the scientific rigour applied following a well-defined and  
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60 361 proven Delphi methodology, and the experience and diversity of the panel. The Delphi method

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3 362 allowed gathering insights from leading experts in the field from different UK countries utilising  
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5 363 a mix of RT modalities, while reducing bias and separating the evaluation by tasking two  
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7 364 independent researchers with analysis and scoring.  
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### 10 365 **Comparison with other studies**

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12  
13 366 To the best of our knowledge, no previous attempts have been done to establish consensus  
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15 367 for rectal hydrogel spacer use in the UK. One study conducted secondary analyses of a single-  
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17 368 blinded, phase III randomised trial, with the aim of identifying patients benefitting the least from  
18  
19 369 hydrogel rectal spacer during prostate radiation therapy.<sup>18</sup> In line with this study, no subgroup  
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21 370 without potential benefits of hydrogel spacers could be identified. The benefit of hydrogel  
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23 371 spacers perceived by the experts is in line with current clinical evidence.<sup>17</sup>  
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26

### 27 372 **Unanswered questions and future research**

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30 373 This study offers guidance to later adopters of rectal hydrogel spacers, building on the  
31  
32 374 expertise of leading UK radiation oncologists and urologist. Future research should focus on  
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34 375 implementing formal guidance on hydrogel spacer use and strive towards reaching a  
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36 376 consensus on patient prioritisation. A larger follow-up consensus study would be of value,  
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38 377 asking all UK domain experts their opinion on the consensus statements. With growing interest  
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40 378 in hydrogel spacers, it is increasingly important to study the impact of the quality of the implant.  
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42 379 There is an ongoing debate on what a good implant is, and how it is measured. Similarly, it  
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44 380 would be valuable to reach an agreement on which toxicity data to generate and follow up  
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46 381 through including hydrogel spacers in cancer treatment trials, or through the development of  
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48 382 a quality registry. Finally, it is of utmost importance to investigate the availability and equality  
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50 383 in access to spacers.  
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### 54 384 **CONCLUSION**

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56 385 Rectal toxicity is a considerable issue, and focus should be on minimising side effects of  
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58 386 curative treatment. There is a strong and general agreement that all prostate cancer patients  
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3 387 undergoing radical RT have the potential to benefit from hydrogel spacers. Currently, not all  
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5 388 patients who could potentially benefit can access hydrogel spacers, and access is unequal.  
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7 389 Implementation of the ten strong and moderate consensus recommendations would likely help  
8  
9 390 prioritise and equalise access to rectal spacers for patients in the UK. In particular, prioritising  
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11 391 access towards patients on anticoagulation, with diabetes, and/or patients with inflammatory  
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13 392 bowel disease would, in our opinion, be a strong starting position.  
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403 RS is the owner of Coreva Scientific, a health-economics and value-based healthcare  
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## 408 **AUTHOR CONTRIBUTIONS**

409 EW conceptualised the idea. RS and AHH designed and ran the questionnaires and  
410 implemented data protection measures. EW reviewed the study design. AHH and RS analysed  
411 the responses. RS moderated the advisory boards. SJ, AT, AE, AB, PD, CP, and HP  
412 responded to the questionnaires, and participated in the advisory boards. AHH and RS drafted  
413 the manuscript, in collaboration with SJ, AT, AE, AB, PD, CP and HP. All authors critically  
414 reviewed the manuscript outline and manuscript drafts. All authors approved the final  
415 manuscript.

## 416 **DATA SHARING STATEMENT**

417 No additional data available.

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3 418 **LEAD AUTHOR TRANSPARENCY STATEMENT**  
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5 419 I confirm that the manuscript is an honest, accurate, and transparent account of the study  
6  
7 420 being reported; that no important aspects of the study have been omitted; and that any  
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9 421 discrepancies from the study as originally planned have been explained.  
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12 422 Prof. Heather Ann Payne  
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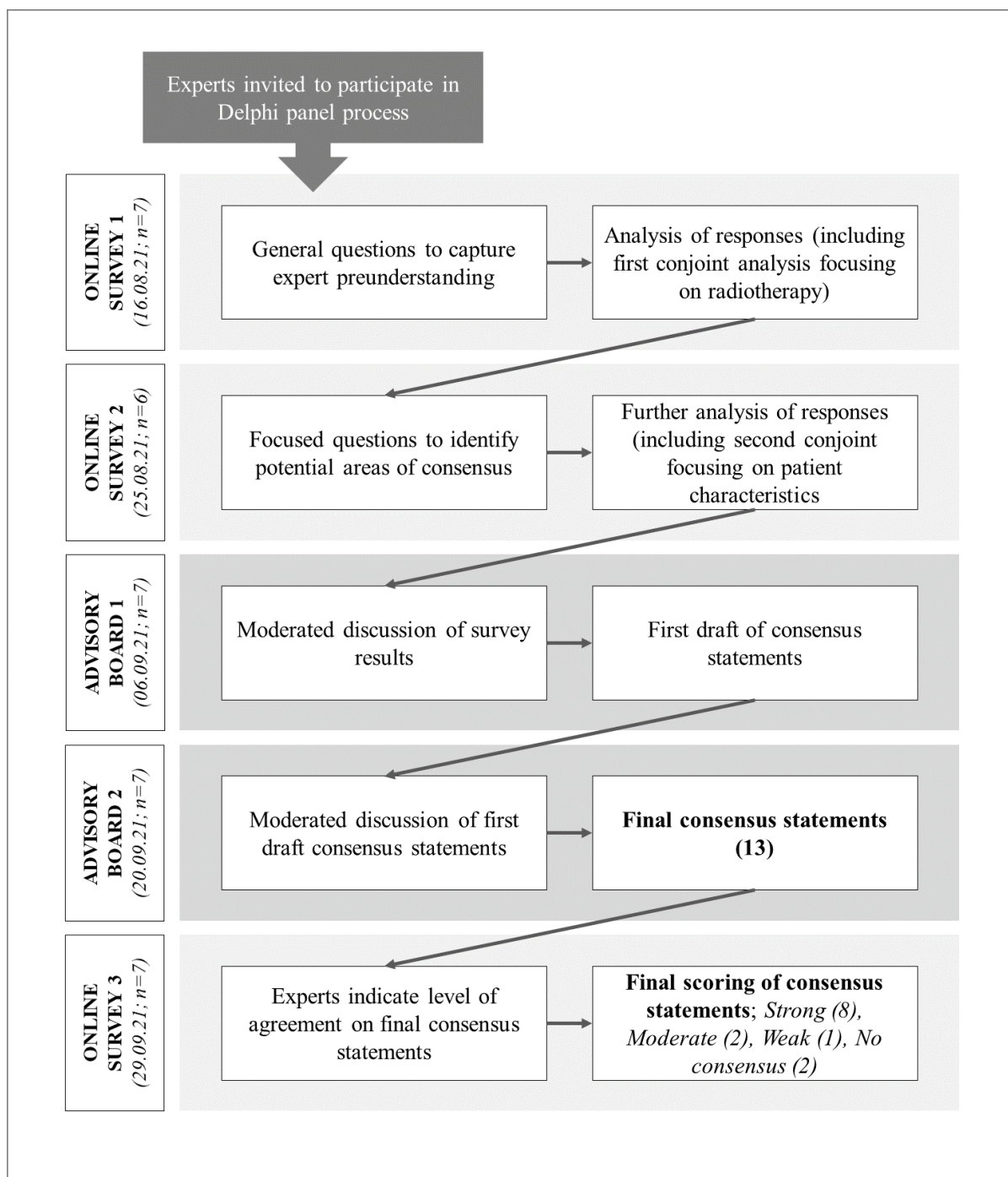
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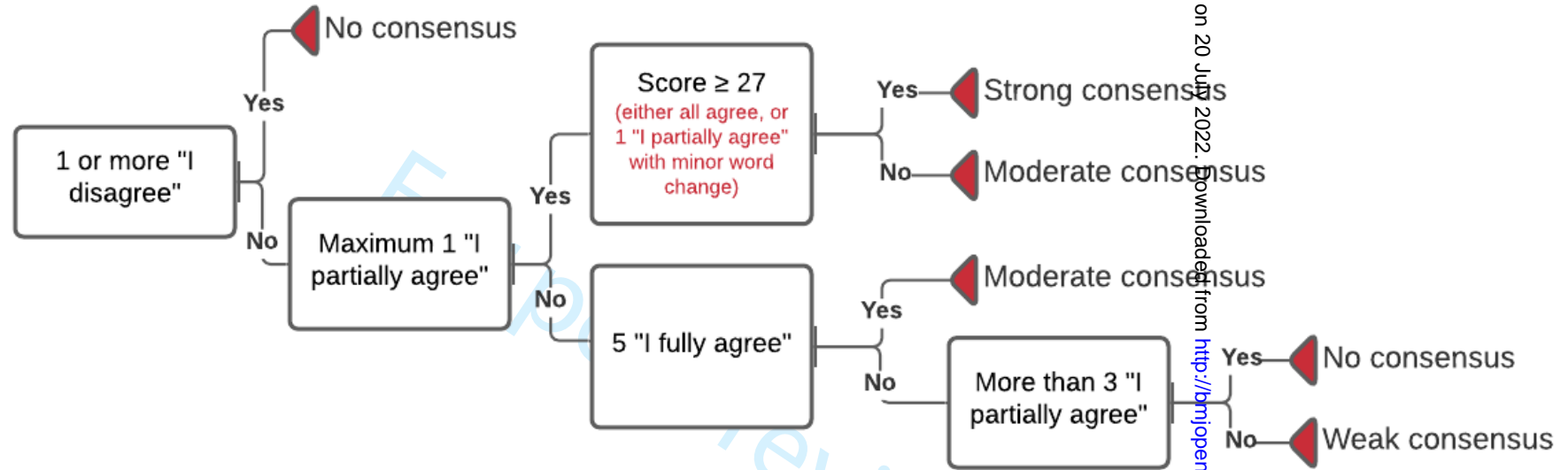
### 27 532 **FIGURE 2:**

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30 533 Strong consensus could only be reached if all experts indicated that they “Fully agree” or all  
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32 534 except one “Fully agree”, with the last respondent “Partially agree” with only a minor word  
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34 535 change (score  $\geq 27$ ). Moderate consensus could only be reached if at least five respondents  
35  
36 536 “Fully agree”, and with no “Disagree”. Weak consensus was reached where a maximum of  
37  
38 537 three respondents “Partially agree”, and with no “Disagree”. No consensus was indicated  
39  
40 538 where at least one respondent “Disagree”, or if four or more respondents “Partially agree”.  
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### 45 539 **FIGURE 4:**

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48 540 Key: BT, brachytherapy; LDR, low dose rate; HDR, high dose rate; PBT, proton beam therapy,  
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50 541 IMRT, intensity-modulated radiation therapy; IGRT, image guided radiation therapy, SBRT,  
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52 542 stereotactic body radiation therapy; SABR, stereotactic ablative radiotherapy  
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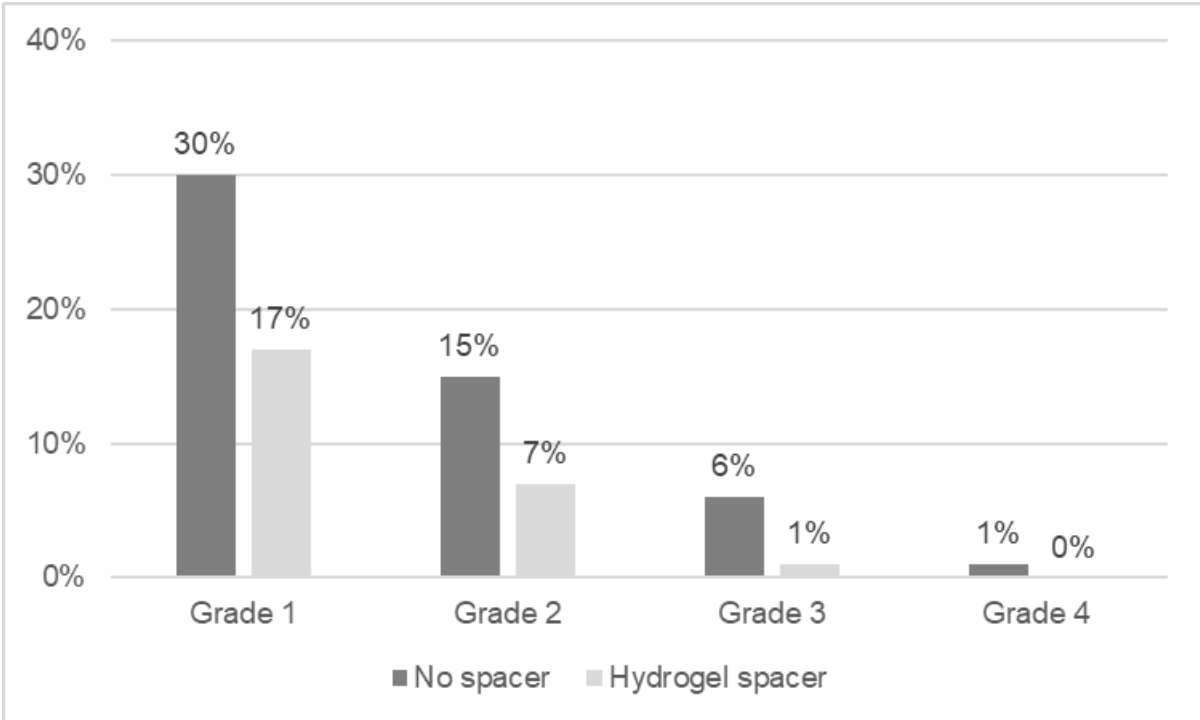




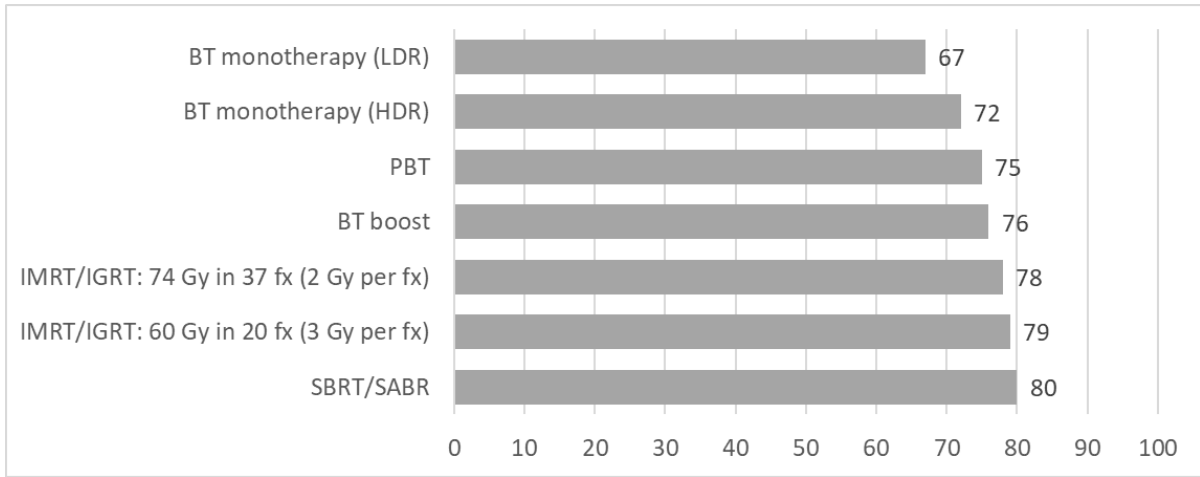
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# BMJ Open

## Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK

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4 **1 Title page**  
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2 Delphi study to identify consensus on patient selection for  
3 hydrogel rectal spacer use during radiation therapy for prostate  
4 cancer in the UK.

5 **Short title:** Delphi study on hydrogel rectal spacer use (UK)

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14 25 Structured abstract (*Word count: 268, max 300*)

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17 26 **OBJECTIVES**

18  
19 27 To identify consensus on patient prioritisation for rectal hydrogel spacer use during radiation  
20  
21 28 therapy for the treatment of prostate cancer in the United Kingdom.

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24 29 **DESIGN**

25  
26 30 Delphi study consisting of two rounds of online questionnaires, two virtual advisory board  
27  
28 31 meetings and a final online questionnaire.

29  
30  
31 32 **SETTING**

32  
33 33 Radical radiation therapy for localised and locally advanced prostate cancer in the United  
34  
35 34 Kingdom.

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37  
38 39 **PARTICIPANTS**

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40  
41 40 Six leading clinical oncologists and one urologist from across the UK.

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44 41 **INTERVENTIONS**

45  
46 42 Rectal hydrogel spacer.

47  
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49 43 **PRIMARY AND SECONDARY OUTCOME MEASURES**

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51 40 NR

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53  
54 41 **RESULTS**

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56  
57 42 The panel reached consensus on the importance of minimizing toxicity for treatments with  
58  
59 43 curative intent, and that even low-grade toxicity-related adverse events can significantly  
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3 44 impact quality of life. There was agreement that despite meeting rectal dose constraints, too  
4  
5 45 many patients experience rectal toxicity, and that rectal hydrogel spacers in eligible patients  
6  
7 46 significantly reduces toxicity related adverse events. However, as a consequence of funding  
8  
9 47 limitations, patients need to be prioritized for spacer use. A higher benefit of spacers can be  
10  
11 48 expected in patients on anticoagulation, and in patients with diabetes or inflammatory bowel  
12  
13 49 disease, but consensus could not be reached regarding patient groups expected to benefit  
14  
15 50 less. While radiation therapy regimen is not a main factor determining prioritization, higher  
16  
17 51 benefit is expected in ultra-hypofractionated regimens.

## 52 **CONCLUSION**

53 There is a strong and general agreement that all prostate cancer patients undergoing radical  
54 radiation therapy have the potential to benefit from hydrogel spacers. Currently, not all patients  
55 who could potentially benefit can access hydrogel spacers, and access is unequal.  
56 Implementation of the consensus recommendations would likely help prioritise and equalise  
57 access to rectal spacers for patients in the UK.

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2  
3 58 **ARTICLE SUMMARY: STRENGTHS AND LIMITATIONS OF THIS STUDY**  
4

- 5  
6 59 • The Delphi panel is a recognised method in developing NICE guidelines and is utilised  
7  
8 60 here to gather insights from a diverse panel of UK radiation oncology and urology  
9  
10 61 experts who are experienced users of hydrogel spacers.  
11  
12 62 • This study included seven panel experts and their experiences may not reflect all users  
13  
14 63 of hydrogel spacers.  
15  
16 64 • To help reduce bias, answers and opinions were assessed by two researchers working  
17  
18 65 independently.  
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## 66 INTRODUCTION

### 67 Prostate cancer burden

68 Prostate cancer is the second most common cancer in men globally,<sup>1</sup> and the most common  
69 in the UK.<sup>2</sup> More than 47,500 UK men are diagnosed with prostate cancer every year and over  
70 400,000 men are living with and after prostate cancer.<sup>3</sup> The 5-year survival rate for localized  
71 prostate cancer in the UK is almost 100%,<sup>4</sup> with three quarters of men diagnosed at any stage  
72 expected to survive 10 years.<sup>2</sup> In England, 97%, 87% and 78% of men diagnosed with prostate  
73 cancer survive their disease for more than one, five and ten years, respectively.<sup>2</sup> Given the  
74 high likelihood of curative therapy, a key treatment goal is to prevent potential adverse events  
75 from impacting patient quality of life after treatment.

76 In addition to the patient burden, prostate cancer is a costly disease with the European costs  
77 of care for prostate cancer estimated at EUR 199 billion in 2018.<sup>5</sup>

### 78 Radiation therapy for prostate cancer

79 Choice of treatment for prostate cancer is complex and involves multi-factorial considerations  
80 including presenting cancer stage (localised, locally advanced or metastatic), risk stratification,  
81 life expectancy, comorbidities, and other patient-specific factors, such as lifestyle, patient  
82 preference and treatment goals.<sup>6</sup> For localised and locally advanced prostate cancer,  
83 treatment options include active surveillance, surgery, brachytherapy and radiation therapy  
84 (RT), with or without hormone treatment, as well as multimodality treatment combining surgery  
85 or RT with systemic therapy.<sup>7-9</sup> RT with radical intent is a first-line treatment for localised and  
86 locally advanced prostate cancer.<sup>8</sup> Intensity-modulated RT (IMRT) with image guidance  
87 (IGRT) is considered the gold-standard form of external beam RT (EBRT).<sup>10</sup> Of the circa  
88 18,000 men identified as having received radical RT for prostate cancer in England and Wales  
89 between April 2018 and March 2019, over 90% were treated with IMRT.<sup>11</sup> Whilst stereotactic  
90 body RT (SBRT) is not currently routine practice in the UK, its use is increasing and it is now

1  
2  
3 91 delivered in several NHS centres.<sup>12</sup> Circa 95% of UK men with intermediate-risk disease  
4  
5 92 receive a hypofractionated radiotherapy regimen.<sup>11</sup>  
6  
7

8 93 The success and clinical outcomes of RT depend on several factors, including radiation dose  
9  
10 94 to the tumour and the extent of irradiation affecting nearby normal-tissue, particularly the  
11  
12 95 rectum.<sup>10</sup> Dose-escalated EBRT is a highly effective curative treatment, with higher doses  
13  
14 96 providing better biochemical control.<sup>13</sup> Higher doses can, however, increase radiation toxicity  
15  
16 97 to nearby tissues. Despite substantial advancements in RT, acute and reversible, as well as  
17  
18 98 rare but severe, long-term adverse effects of radiation toxicity such as urinary and bowel  
19  
20 99 incontinence remain problematic. The National Prostate Cancer Audit (NPCA) reported that  
21  
22 100 11% of prostate cancer patients experienced  $\geq 1$  severe gastrointestinal complication within  
23  
24 101 two years after radical RT. This outcome factor derived from hospital records data is defined  
25  
26 102 as a confirmed diagnosis of radiation toxicity  $\geq$  grade 2 according to National Cancer Institute  
27  
28 103 Common Toxicity Criteria for Adverse Events [CTCAE] in addition to a documented procedure  
29  
30 104 to the large bowel.<sup>11 14</sup> Late  $\geq$  grade 2 gastrointestinal toxicity has been explored in numerous  
31  
32 105 randomized clinical trials. The 2016 Hypofractionated versus conventionally fractionated  
33  
34 106 radiotherapy for patients with prostate cancer (HYPRO) trial found an incidence of  
35  
36 107 gastrointestinal toxicity at three years of 17.7% in standard fractionation and 21.9% in  
37  
38 108 hypofractionation.<sup>15</sup> In 2017, results from the ASCENDE-RT trial showed a cumulative  
39  
40 109 incidence of 5-year gastrointestinal side effects ranging from 20.2% (dose-escalated external  
41  
42 110 beam radiation therapy) to 31.3% (low-dose-rate prostate brachytherapy).<sup>16</sup> Due to its  
43  
44 111 proximity to the prostate, the anterior rectal wall is especially vulnerable to irradiation effects  
45  
46 112 and the rectum is a dose-limiting organ at risk.<sup>17</sup>  
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### 51 113 **Hydrogel spacers**

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54 114 One way of reducing the unwanted radiation dose to the rectum is by increasing the space  
55  
56 115 between the prostate and the rectal wall. This can be achieved by use of a rectal spacer, with  
57  
58 116 three currently indicated for use during RT for prostate cancer in the UK: biodegradable  
59  
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3 117 balloons, hyaluronic acid gel, and polyethylene glycol (PEG) hydrogel.<sup>18</sup> In the UK, the use of  
4  
5 118 biodegradable spacers to reduce rectal toxicity during RT for prostate cancer is accepted  
6  
7 119 (IPG590) by NICE, based on safety and efficacy data on the use of PEG hydrogel spacers.<sup>18</sup>  
8  
9 120 Use of rectal hydrogel spacers has been evaluated in a single-blind, phase III trial in image  
10  
11 121 guided IMRT (N=222).<sup>19</sup> The spacer-placement success rate was 99%, and no device-related  
12  
13 122 adverse events occurred.<sup>19</sup> Late (three to 15 months) rectal toxicity severity was significantly  
14  
15 123 reduced in the spacer group.<sup>19</sup> At three years follow-up, decreased bowel toxicity and fewer  
16  
17 124 declines in urinary and bowel quality of life were observed in the spacer group (41% men in  
18  
19 125 the control group experienced a minimally important difference (MID) in decline in bowel  
20  
21 126 quality of life vs 14% in the spacer group; P=0.002). The risk of large decline (twice the MID)  
22  
23 127 was 21% (control) vs 5% (spacer; P=0.02) in bowel quality of life and 23% (control) vs 8%  
24  
25 128 (spacer; P=0.02) in urinary quality of life respectively.<sup>20</sup>

26  
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28  
29 129 Lack of routine reimbursement has led to restricted patient access to hydrogel spacers in the  
30  
31 130 UK. Therefore, there is a requirement to prioritise patients for hydrogel spacer use in the UK,  
32  
33 131 and attempts have been made to identify optimal usage. A secondary analysis of the hydrogel  
34  
35 132 spacer trial data tried to identify the patient subgroups most and least likely to benefit from the  
36  
37 133 intervention but found generally homogeneous results in bowel quality of life with benefits in  
38  
39 134 all assessed subgroups.<sup>21</sup>

40  
41  
42 135 The aim of this study was to identify consensus on patient prioritisation for rectal hydrogel  
43  
44 136 spacer use during RT for the treatment of prostate cancer in the UK.

## 45 46 47 137 **METHODS**

### 48 49 50 138 **The Delphi technique and panel experts**

51  
52  
53 139 The Delphi technique is a structured, iterative, multistage process using rounds of  
54  
55 140 questionnaires to collect opinions and to stepwise develop consensus among a pre-defined  
56  
57 141 panel of experts.<sup>22</sup> For this study, experts were approached and asked to participate in the  
58  
59 142 panel based on being a UK radiation oncologist or urologist having experience with rectal

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3 143 hydrogel spacers. To ensure a diverse panel, experts were sought to represent different  
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5 144 geographies within the UK and use different types of RT modalities. There is no defined  
6  
7 145 optimal panel size for a Delphi study,<sup>23</sup> but the selection of an odd number of experts ensured  
8  
9 146 that a majority outcome could be reached.  
10

### 11 12 13 147 **Steps in the Delphi process**

14  
15  
16 148 There is no fixed number of rounds in a Delphi survey.<sup>23</sup> As depicted in Figure 1, our study  
17  
18 149 adopted a five-stage approach to elicit consensus, consisting of two pre-advisory board  
19  
20 150 questionnaires administered through a web-based survey program, two virtual advisory board  
21  
22 151 discussions, and a final concluding questionnaire.  
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24  
25 152 The first questionnaire provided some background information on the experts, such as their  
26  
27 153 most used RT modalities and open-ended questions to capture a broad understanding. The  
28  
29 154 open-ended questions related to key treatment aims, which patient and treatment  
30  
31 155 characteristics to consider when prioritising hydrogel spacer, factors typically deterring them  
32  
33 156 from recommending hydrogel spacer use, and factors predictive for toxicity. Additionally,  
34  
35 157 experts were asked to rank treatment modalities in order of how much patient benefit they  
36  
37 158 would expect from hydrogel spacer use, on a scale from 0 (no patient benefit) to 100 (maximal  
38  
39 159 patient benefit).  
40

41  
42 160 In the second questionnaire, the responses to the open-ended questions from the previous  
43  
44 161 questionnaire were presented, and the experts asked to rank them by order of importance. In  
45  
46 162 addition to follow-up questions, the second questionnaire included questions on perceived  
47  
48 163 barriers to hydrogel spacer use.  
49

50  
51 164 *Figure 1: Overview of Delphi panel process*  
52

### 53 165 **Analysis and scoring**

54  
55  
56 166 Qualitative content analysis was used to analyse responses to open-ended questions. Two  
57  
58 167 researchers independently analysed responses and interpreted consensus. At the advisory  
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3 168 board meetings, results from the questionnaires were presented together with initial drafted  
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5 169 consensus statements for discussion. Then followed moderated discussions which led to  
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7 170 revisions of the consensus statements. In the final online questionnaire, the consensus  
8  
9 171 statements were presented, and the experts asked to select a level of agreement: "I fully  
10  
11 172 agree", "I partially agree" or "I disagree". Upon selecting "I partially agree", experts were asked  
12  
13 173 to give a comment and/or update the wording of the statement. The responses were linked to  
14  
15 174 an agreement score, based on the answer selected, and the comment given if "I partially  
16  
17 175 agree" was selected (Table 1).

176 *Table 1: Consensus statement scoring key*

Score	Answer selected	Description
4	"I fully agree"	
3	"I partially agree"	With minor word change
2	"I partially agree"	With minor change to statement interpretation/meaning
1	"I disagree"	

177 Consensus definitions vary between studies<sup>24-28</sup>, with percent agreement being one of the  
178 more common approaches.<sup>28</sup> Based on the results of our final online survey, statements were  
179 categorised into four levels of consensus (strong, moderate, low, and no consensus). This  
180 study scored the level of consensus in terms of percent agreement, and additionally that  
181 consensus could not be reached in case any expert disagreed with a statement. Figure 2  
182 depicts the consensus statement scoring for this study. Only statements grouped as either  
183 **Strong** or **Moderate** are considered statements where consensus was reached. **Weak** or **No**  
184 consensus mean that there was still substantial discussion or divergence of opinion among  
185 the experts.

186 *Figure 2: Consensus statement scoring, decision tree*

## 187 **Consent, privacy, and data security**

188 The panel experts were informed about and consented to the full Delphi process, including  
189 length and time of surveys and details on the data collected, stored, and deleted. The retention  
190 periods of collected data were pre-defined. Questionnaire responses were anonymised and  
191 securely stored on the survey software provider's server in Germany. Audio recordings were

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3 192 stored for 60 days on the conference provider's EU based server. All experts were contracted  
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5 193 for this study and reimbursed at fair, local market rates for their time commitment during the  
6  
7 194 Delphi process. The study was approved by an independent review board (HML IRB Review  
8  
9 195 #952SCGC21).

## 12 196 Patient and public involvement

15 197 No patients involved.

## 18 198 RESULTS

### 21 199 Panel expert characteristics

24 200 All approached experts agreed to participate (N=7). Details on the panel experts' treatment  
25  
26 201 practices are presented in Table 2. The majority of the panel (N=6) exclusively use rectal  
27  
28 202 hydrogel spacers in their practices. One uses rectal hydrogel spacers as well as biodegradable  
29  
30 203 balloons. Participation rates were high, with only one dropout (one expert did not complete the  
31  
32 204 second questionnaire but participated in all other steps).

35 205 *Table 2: Panel experts treatment practice*

<b>Geographical setting, N (%)</b>	
England	5 (57)
Northern Ireland	1 (14)
Wales	1 (14)
<b>Public or private setting, N (%)</b>	
Public only	1 (14)
Private only	0 (0)
Both	6 (86)
<b>Most frequently used RT modalities, % of patients (N experts using modality)</b>	
IMRT	25–95 (6)
EBRT (not specified)	90 (1)
IMRT and HDR BT boost	15–30 (2)
SBRT	45 (1)
BT monotherapy (LDR)	10–20 (2)
PBT	10 (1)

57 206 **Key:** IMRT, intensity-modulated radiation therapy; EBRT, external beam radiation therapy; HDR, high dose rate;  
58 207 BT, brachytherapy; SBRT, stereotactic body radiation therapy; LDR, low dose rate; PBT, proton beam therapy.

208 Key treatment aims, besides curing or controlling cancer and increasing overall survival, were  
209 to minimise the risk of side effects and toxicity.

## 210 Questionnaire outcomes shaping the consensus statement discussion

211 Questionnaire outcomes showed that the panel estimated considerably less toxicity in patients  
212 with hydrogel spacer, as compared to those without (Figure 3). All experts agreed that  
213 hydrogel spacers reduce grade 1 and 2 late rectal toxicity, 86% agreed that it reduces grade  
214 3 toxicity and 71% grade 4 toxicity.

215 *Figure 3: Expected level of late (after 3 months) rectal toxicity in patients with and without hydrogel spacer*

216 The panel considered toxicity a considerable issue, and underlined that also low-grade  
217 toxicity-related adverse events may significantly worsen patient's lives:

218 *'I ask them [my patients], when you're out and about, is the first thing you think of where*  
219 *the toilet is?... And a remarkable number of patients say yes to that question, and it is*  
220 *affecting their quality of life.'*

221 In the first questionnaire, the panel estimated that an average of 83% (SD: 13%) patients who  
222 could potentially benefit from a hydrogel spacer were denied access. Throughout the  
223 discussions, patient access in general and equal access in particular were central themes.  
224 The panel voiced their concern, for example regarding differences between NHS and private  
225 practice:

226 *'In my private practice, every patient gets it [hydrogel spacer] unless there is a reason*  
227 *why they should not get it. Whereas in my NHS practice, unfortunately no patient gets*  
228 *it, unless there is a reason why they should get it.'*

229 The main barrier to hydrogel spacer use was funding and resource constraints, followed by  
230 lack of trained staff.

1  
2  
3 231 *'The ideal way to go would be to offer it to every eligible patient. But given that this is*  
4  
5 232 *not currently feasible in our centre, there has to be some kind of categorisation.'*  
6  
7

8 233 As seen in Figure 4, a trend towards hypo-fractionated external-beam regimens, with potential  
9  
10 234 increased bowel dose and toxicity being associated with more potential benefit for spacers  
11  
12 235 was apparent. This was also reflected in the outcome of the conjoint analysis. The absolute  
13  
14 236 variation between expected benefit was, however, relatively low, ranging from 67 (BT  
15  
16 237 monotherapy LDR) to 80 (SBRT/SABR) on average. This was reflected in later discussions,  
17  
18 238 where experts agreed that RT modality is not the main consideration when prioritising patients  
19  
20 239 for hydrogel spacer use.  
21  
22

23 240 *Figure 4: Expected patient benefit from hydrogel spacer use, by treatment modality*  
24

25 241 When asked about patient characteristics to consider when deciding whether to recommend  
26  
27 242 using hydrogel spacer the experts gave a wide range of suggestions, including comorbidities  
28  
29 243 (age, diabetes, high bleeding risk, hip prosthesis, inflammatory bowel disease and rectal and  
30  
31 244 bowel problems, normal erectile function), cancer stage, localisation, and heavy smoking. This  
32  
33 245 was narrowed down in subsequent discussion, with general agreement that patients with  
34  
35 246 certain comorbidities (diabetes, inflammatory bowel disease) or on anticoagulation may have  
36  
37 247 higher benefit from hydrogel spacers.  
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## 40 41 248 **Consensus statements**

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45 249 Upon being shown the results of the questionnaires, two rounds of moderated discussion  
46  
47 250 followed, resulting in 13 consensus statements. These statements were subsequently voted  
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49 251 on in a final questionnaire, and a final scoring was assigned as described in the method  
50  
51 252 section.  
52  
53

54 253 The following eight statements reached strong consensus:

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57 254
  - Our consensus opinion is that for treatments with curative intent, focus should be on  
58  
59 255 minimising toxicity and the risk of side effects.  
60

- 1  
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3 256 • Our consensus opinion is that use of spacers in eligible patients significantly reduces  
4  
5 257 radiation dose to the rectum and toxicity-related adverse events.  
6  
7 258 • Our consensus opinion is that despite meeting rectal dose constraints, too many  
8  
9 259 patients continue to experience rectal toxicity.  
10  
11 260 • Our consensus opinion is that certain grade 1 toxicity-related adverse events<sup>1</sup> can still  
12  
13 261 have a significant impact on patient quality of life.  
14  
15 262 • Our consensus opinion is that any toxicity grading system in use should be  
16  
17 263 complemented by patient-reported outcomes.  
18  
19 264 • Our consensus opinion is that patients receiving long-term anticoagulation therapy with  
20  
21 265 medications such as direct oral anticoagulants (DOACs)<sup>2</sup> should be considered for  
22  
23 266 spacer use if their anticoagulation can be safely paused.  
24  
25 267 • Our consensus opinion is that spacers are useful in eligible patients with T1-T2  
26  
27 268 disease. Spacer use in patients with T2+ disease should not be excluded but should  
28  
29 269 be assessed on an individual basis by a team proficient in inserting spacers.  
30  
31 270 • Our consensus opinion is that patients should have the opportunity to take part in the  
32  
33 271 discussion regarding the use of a spacer.<sup>29</sup>  
34  
35  
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37

38 272 For the following two statements, moderate consensus was reached. Each statement is  
39  
40 273 followed by an explanation on why strong consensus was not reached.

- 41  
42  
43 274 • Our consensus opinion is that a higher benefit of spacers is expected in eligible  
44  
45 275 patients with certain comorbidities<sup>3</sup> and/or longer expected overall survival.  
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55  
56 <sup>1</sup> Bowel frequency and urgency, diarrhoea, flatulence, radiation cystitis, radiation proctitis, rectal  
57 bleeding, rectal mucus.

58 <sup>2</sup> The reason for prescribing the DOAC, rather than the medication itself, is more important for the  
59 decision. All patients on DOACs, except for cardiac stent and prosthetic valve replacement patients  
60 may be able to safely pause their anticoagulation.

<sup>3</sup> Anticoagulation, diabetes, inflammatory bowel disease (ulcerative colitis and Crohn's disease)

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2  
3 276 Six experts (86%) fully agreed with the statement. One expert (14%) only partially agreed and  
4  
5 277 suggested removing “and/or longer expected overall survival”. This was deemed a change to  
6  
7 278 the statement interpretation.

- 8  
9  
10 279
  - All eligible radiotherapy patients should have equal opportunity to access spacers,  
11  
12 280 independent of socio-economic factors.

13  
14  
15 281 Five experts (71%) fully agreed with the statement. While there was an overall agreement that  
16  
17 282 lack of equality in access to spacers is currently an important issue, two experts (29%) had  
18  
19 283 rewording suggestions that would have impacted the statement interpretation. One proposed  
20  
21 284 to add more detail on eligibility, and to add that patients suitable for a spacer implant should  
22  
23 285 have access, irrespective of whether they can afford it. The other expert expressed some  
24  
25 286 uncertainty regarding the term “socio-economic factors” and would have preferred the wording  
26  
27 287 “irrespective of post-code”.

### 28 288 **Statements where no consensus was reached**

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34 289 One statement was categorised as a weak consensus statement:

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37 290
  - Whilst we support the use of spacers in all eligible patients, our consensus opinion is  
38  
39 291 that if resource constraints exist, patients receiving ultra-hypofractionated or  
40  
41 292 hypofractionated radiotherapy should be prioritised for access to a spacer.

42  
43  
44 293 Four experts (57%) fully agreed with the statement. The remaining three (43%) partially  
45  
46 294 agreed but had additional comments. One expert expressed that individual risk factors should  
47  
48 295 be considered, rather than the RT modality. The second expert agreed on the need to identify  
49  
50 296 a group at higher risk of rectal toxicity, and suggested combination of RT modality  
51  
52 297 considerations and patient characteristics (e.g., age) and comorbidities. The third respondent  
53  
54 298 only agreed that patients receiving ultra-hypofractionated RT should be prioritised.

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57 299 For the following two statements, no consensus was reached.  
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3 300 • Our consensus opinion is that for patients with anticipated short overall survival but  
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5 301 who will receive radical radiotherapy, use of a spacer should only be considered after  
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7 302 careful evaluation of potential benefit.  
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10 303 Three experts (43%) fully agreed. Four (57%) partially agreed but had additional comments.  
11  
12 304 Two experts made the point that it is unlikely that patients with short anticipated overall survival  
13  
14 305 would be indicated for radical radiotherapy. Two experts expressed uncertainty with the  
15  
16 306 wording “overall survival”. One of them suggested a rewording that some carefully selected  
17  
18 307 patients with short expected survival who are offered radical radiotherapy may benefit from  
19  
20 308 spacer use after careful consideration. The second expressed that the statement was too  
21  
22 309 unclear. Additionally, in subsequent discussions, the experts agreed that the term “anticipated  
23  
24 310 shorter life expectancy” would have been preferred over “anticipated short overall survival”,  
25  
26 311 so as not to imply that the use of hydrogel spacers affects survival. Upon subsequent  
27  
28 312 discussion, experts agreed that the statement would have been improved by adding “and side  
29  
30 313 effects” to the end of the statement.  
31  
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- 34 314 • Our consensus opinion is that there are a limited number of patients with risk factors,  
35  
36 315 or combination of risk factors, in which use of a spacer should only be considered after  
37  
38 316 careful evaluation of potential benefits.  
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41 317 Four experts (57%) fully agreed, two (29%) partially agreed, and one (14%) disagreed. Those  
42  
43 318 who partially agreed expressed that an addition should be made to the statement, that the  
44  
45 319 majority of patients who receive radical RT would also be suitable for a spacer, noting that  
46  
47 320 patients who are not fit enough for a spacer, likely are also not fit for RT. The second partially  
48  
49 321 agreeing expert wanted to add a recommendation to discuss such cases with a mentor with  
50  
51 322 extensive experience in spacer insertion. Upon subsequent discussion, experts agreed that  
52  
53 323 the statement would have been improved by adding “and side effects” to the end of the  
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55 324 statement.  
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## 325 **DISCUSSION**

### 326 **Statement of principal findings**

327 There was strong consensus that rectal toxicity is a considerable issue, and that minimizing  
328 the risk of radiation side effects is an important treatment aim. Rectal hydrogel spacers can  
329 reduce the toxicity burden and benefit patients undergoing radical RT for the treatment of  
330 prostate cancer in the UK. Currently, the NHS does not routinely fund hydrogel spacers.  
331 Limited funding leads to limited resources, and therefore limited access. Experts estimated  
332 that on average, 83% of their patients that could benefit from a spacer are not currently getting  
333 access. There was moderate consensus that a higher benefit is expected in patients on  
334 anticoagulation, patients with diabetes, and patients with inflammatory bowel disease  
335 (Ulcerative colitis or Crohn's disease). However, experts expected the majority of patients to  
336 benefit from use of a spacer, and it was not possible to reach consensus on those patients  
337 with lower expected benefit. Key takeaways from discussions around statements where no  
338 consensus was reached are that individual patient characteristics are more important for  
339 informing the decision on whether to prioritise the use a spacer than the RT regimen selected.  
340 However, a higher level of benefit from spacer use is expected with ultra-hypofractionated RT  
341 compared with standard RT, a conclusion in line with current clinical evidence.<sup>30</sup>

### 342 **Meaning of the study: possible explanations and implications for clinicians and policy**

#### 343 **makers**

344 Currently, patient selection is driven by limitations in the healthcare system rather than patient  
345 needs. This highlights the importance of developing guidance on spacer use, to ensure fair  
346 and equal access to healthcare. The COVID-19 pandemic has lengthened already substantial  
347 NHS waiting times, further exacerbating issues with access and underscoring the need for  
348 formal guidance. Additionally, practical issues (e.g., availability of trained staff, theatre  
349 capacity) need to be considered when preparing a clinic to start using hydrogel spacers. As is



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3 350 important for all techniques to be introduced, audit of practice and quality improvement is  
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5 351 recommended.  
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## 8 352 **Strengths and weaknesses**

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11 353 This study only included seven experts, who are all experienced users of hydrogel spacers  
12  
13 354 Naturally, a broader selection of experts could have resulted in different answers. However,  
14  
15 355 including non-users as panel experts would not have been feasible for the purposes of this  
16  
17 356 study, as they would have not possessed the relevant experience required. Additionally, the  
18  
19 357 RT modality used by panel members could influence their view on when to prioritise hydrogel  
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21 358 spacer use. However, the diversity of the panel in terms of modalities used likely safeguarded  
22  
23 359 the balance of the resulting consensus.  
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26  
27 360 The main strengths of this study are the scientific rigour applied following a well-defined and  
28  
29 361 proven Delphi methodology, and the experience and diversity of the panel. The Delphi method  
30  
31 362 allowed gathering insights from leading experts in the field from different UK countries utilising  
32  
33 363 a mix of RT modalities, while reducing bias and separating the evaluation by tasking two  
34  
35 364 independent researchers with analysis and scoring.  
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## 38 365 **Comparison with other studies**

39  
40  
41 366 To the best of our knowledge, no previous attempts have been done to establish consensus  
42  
43 367 for rectal hydrogel spacer use in the UK. A study published in 2016 used a model-based  
44  
45 368 approach to identify patients expected to benefit the most from implantable rectum spacers  
46  
47 369 among 26 patients with localized prostate cancer treated at a German hospital. The clinical  
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49 370 risk factors found relevant were anticoagulant use, hormonal therapy, antihypertensive use,  
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51 371 diabetes, haemorrhoids, pelvic nodal RT, and prior abdominal surgery.<sup>31</sup> Single-centre studies  
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53 372 of rectal spacers in Crohn's and ulcerative colitis patients suggest benefit of spacers.<sup>32 33</sup> One  
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55 373 study conducted secondary analyses of a single-blinded, phase III randomised trial, with the  
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57 374 aim of identifying patients benefitting the least from hydrogel rectal spacer during prostate  
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3 375 radiation therapy.<sup>21</sup> In line with this study, no subgroup without potential benefits of hydrogel  
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5 376 spacers could be identified. The benefit of hydrogel spacers perceived by the experts is in line  
6  
7 377 with current clinical evidence.<sup>20</sup>  
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## 10 378 **Unanswered questions and future research**

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12  
13 379 This study offers guidance to later adopters of rectal hydrogel spacers, building on the  
14  
15 380 expertise of leading UK radiation oncologists and urologist. Future research should focus on  
16  
17 381 implementing formal guidance on hydrogel spacer use and strive towards reaching a  
18  
19 382 consensus on patient prioritisation. A larger follow-up consensus study would be of value,  
20  
21 383 asking all UK domain experts their opinion on the consensus statements. With growing interest  
22  
23 384 in hydrogel spacers, it is increasingly important to study the impact of the quality of the implant.  
24  
25 385 There is an ongoing debate on what a good implant is, and how it is measured. Similarly, it  
26  
27 386 would be valuable to reach an agreement on which toxicity data to generate and follow up  
28  
29 387 through including hydrogel spacers in cancer treatment trials, or through the development of  
30  
31 388 a quality registry. Finally, it is of utmost importance to investigate the availability and equality  
32  
33 389 in access to spacers. For this aim to be reached, further cost-effectiveness research and a  
34  
35 390 continued discussion on willingness to pay should be undertaken. Analyses of spacers in  
36  
37 391 prostate cancers have shown cost-effectiveness in certain radiation modalities in US<sup>34 35</sup> and  
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39 392 Dutch<sup>36</sup> contexts.  
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## 44 393 **CONCLUSION**

45  
46 394 Rectal toxicity is a considerable issue, and focus should be on minimising side effects of  
47  
48 395 curative treatment. There is a strong and general agreement that all prostate cancer patients  
49  
50 396 undergoing radical RT have the potential to benefit from hydrogel spacers. Currently, not all  
51  
52 397 patients who could potentially benefit can access hydrogel spacers, and access is unequal.  
53  
54 398 Implementation of the ten strong and moderate consensus recommendations would likely help  
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56 399 prioritise and equalise access to rectal spacers for patients in the UK. In particular, prioritising  
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3 400 access towards patients on anticoagulation, with diabetes, and/or patients with inflammatory  
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5 401 bowel disease would, in our opinion, be a strong starting position.  
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412 RS is the owner of Coreva Scientific, a health-economics and value-based healthcare  
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## 417 **AUTHOR CONTRIBUTIONS**

418 EW conceptualised the idea. RS and AHH designed and ran the questionnaires and  
419 implemented data protection measures. EW reviewed the study design. AHH and RS analysed  
420 the responses. RS moderated the advisory boards. SJ, AT, AE, AB, PD, CP, and HP  
421 responded to the questionnaires, and participated in the advisory boards. AHH and RS drafted  
422 the manuscript, in collaboration with SJ, AT, AE, AB, PD, CP and HP. All authors critically  
423 reviewed the manuscript outline and manuscript drafts. All authors approved the final  
424 manuscript.

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3 425 **ETHICS APPROVAL STATEMENT**  
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5  
6 426 The study was approved by an independent review board (HML IRB Review #952SCGC21).  
7

8 427 All participants gave informed consent before taking part.  
9

10 428 **DATA SHARING STATEMENT**  
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12  
13 429 No additional data available.  
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16 430 **LEAD AUTHOR TRANSPARENCY STATEMENT**  
17

18 431 I confirm that the manuscript is an honest, accurate, and transparent account of the study  
19

20 432 being reported; that no important aspects of the study have been omitted; and that any  
21

22 433 discrepancies from the study as originally planned have been explained.  
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25 434 Prof. Heather Ann Payne  
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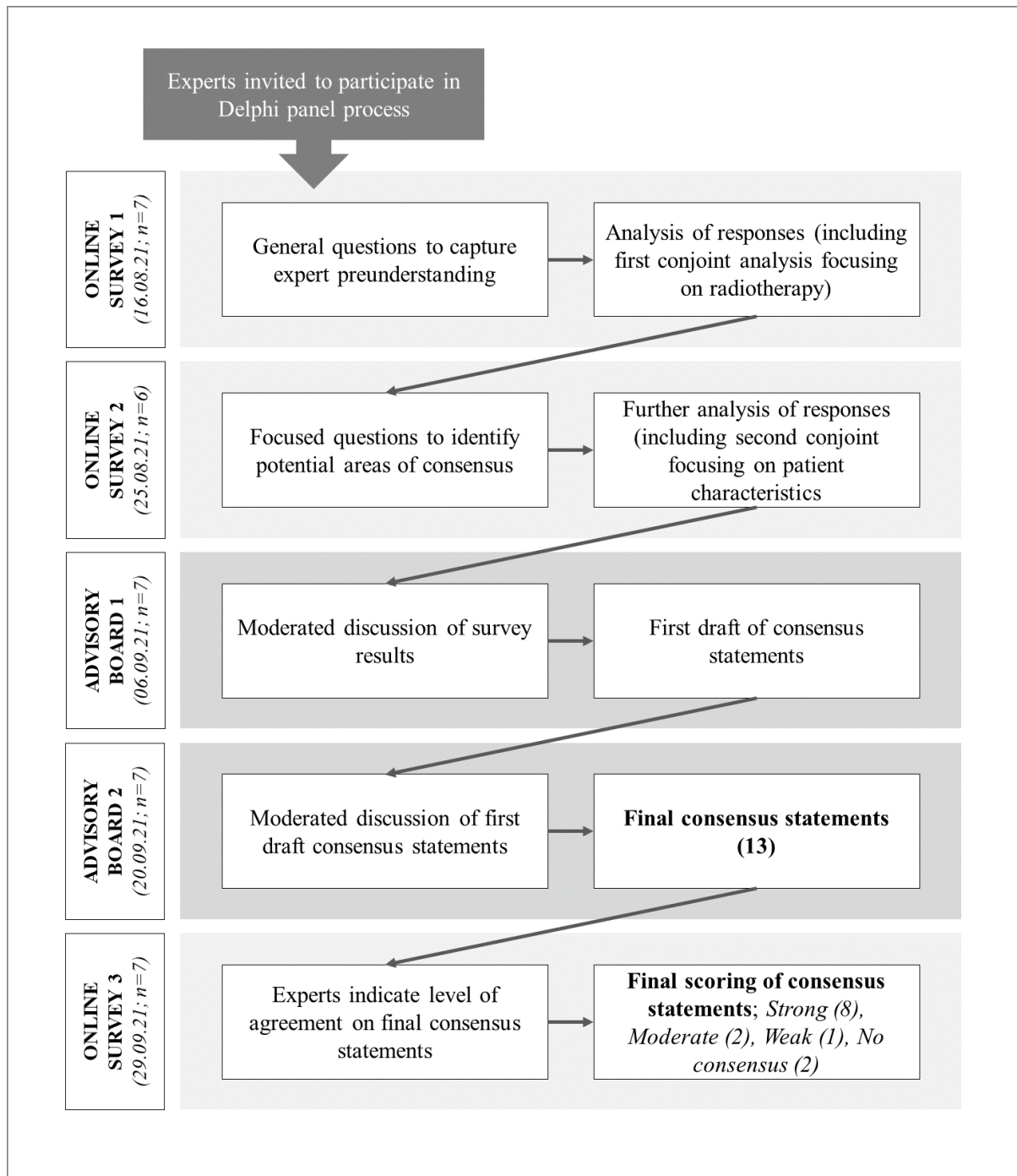
## 20 21 584 Figure legends

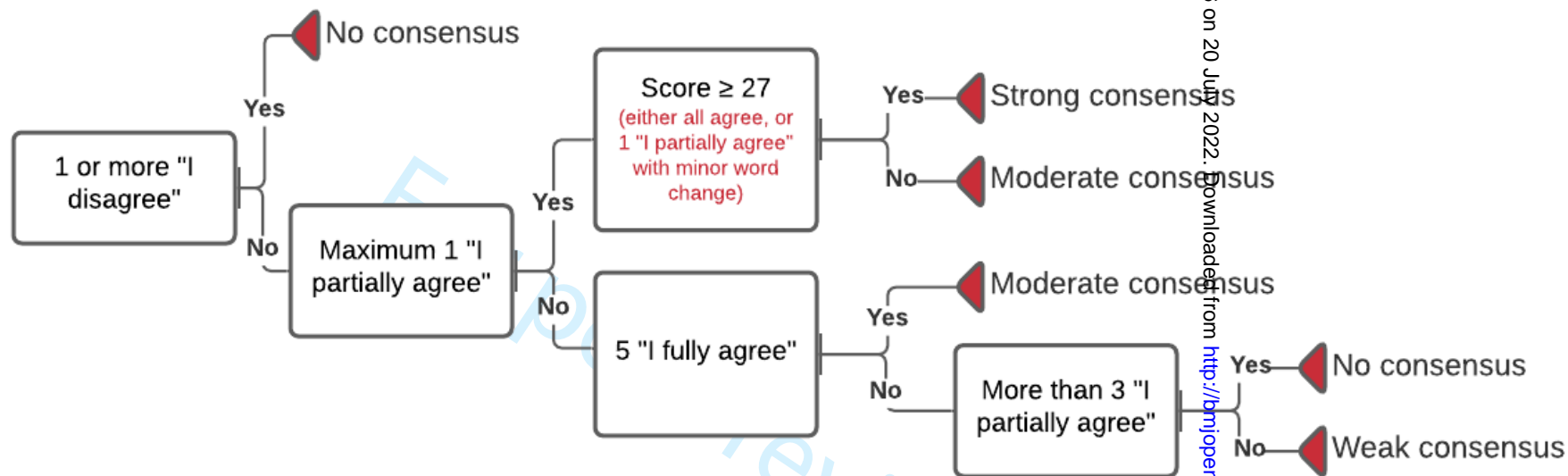
### 22 23 24 585 **FIGURE 2:**

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26 586 Strong consensus could only be reached if all experts indicated that they “Fully agree” or all  
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28 587 except one “Fully agree”, with the last respondent “Partially agree” with only a minor word  
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30 588 change (score  $\geq 27$ ). Moderate consensus could only be reached if at least five respondents  
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32 589 “Fully agree”, and with no “Disagree”. Weak consensus was reached where a maximum of  
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34 590 three respondents “Partially agree”, and with no “Disagree”. No consensus was indicated  
35  
36 591 where at least one respondent “Disagree”, or if four or more respondents “Partially agree”.  
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### 39 592 **FIGURE 4:**

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42 593 Key: BT, brachytherapy; LDR, low dose rate; HDR, high dose rate; PBT, proton beam therapy,  
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44 594 IMRT, intensity-modulated radiation therapy; IGRT, image guided radiation therapy, SBRT,  
45  
46 595 stereotactic body radiation therapy; SABR, stereotactic ablative radiotherapy  
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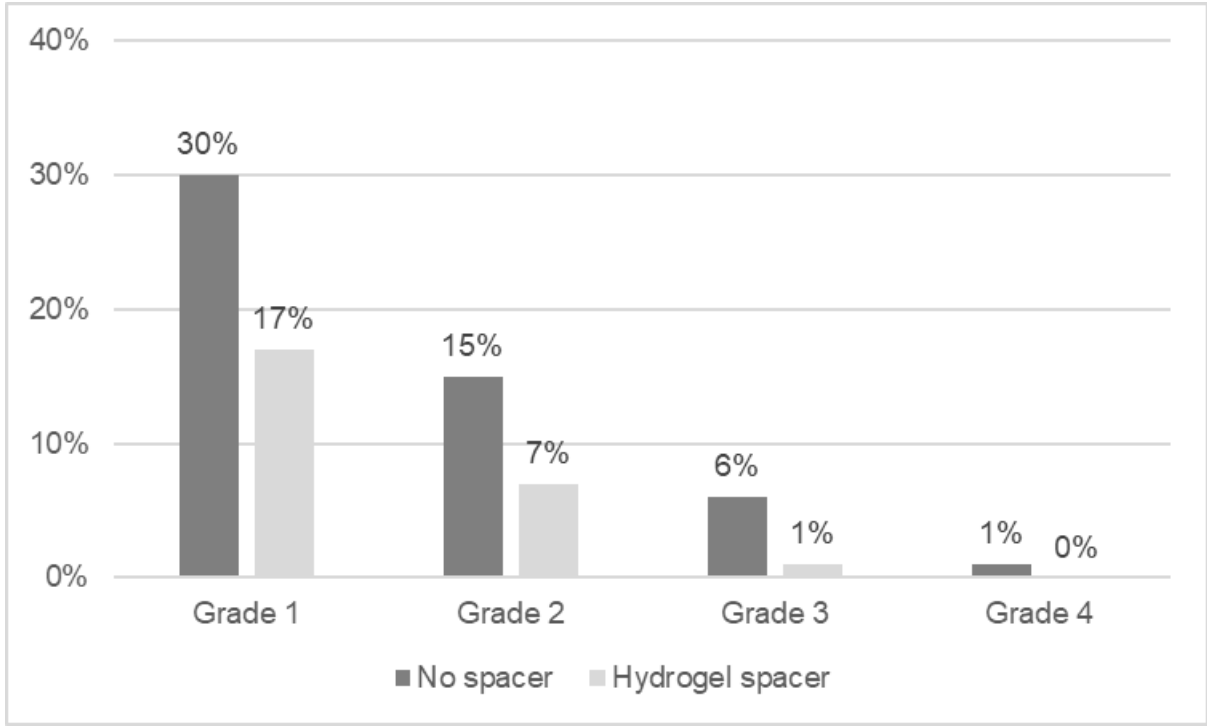




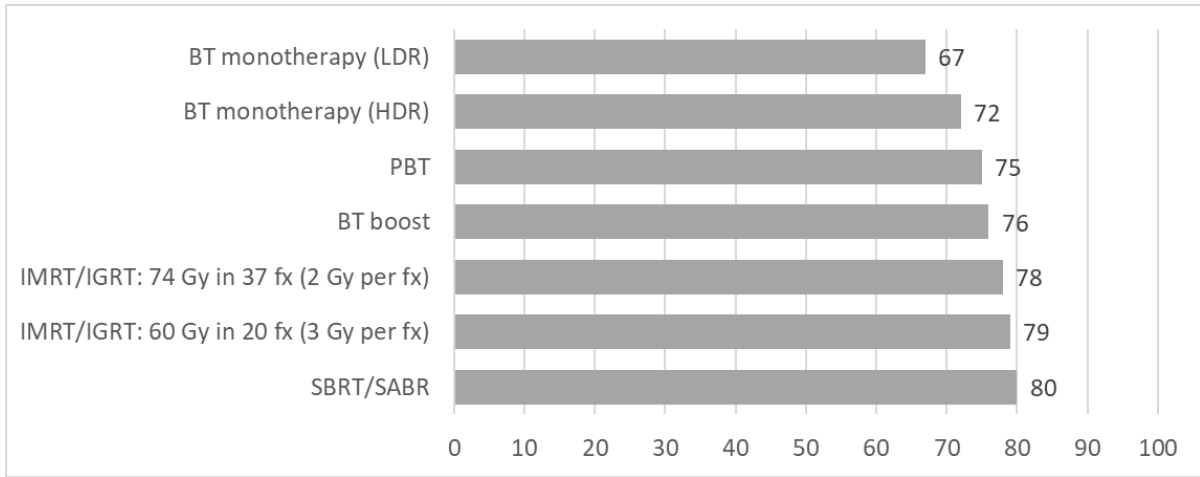
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O'Brien, Bridget C.; Harris, Ilene B.; Beckman, Thomas J.; Reed, Darcy A.; Cook, David A. Academic Medicine 89(9):1245-1251, September 2014. doi: 10.1097/ACM.0000000000000388

No.	Topic	Item
<b>Title and abstract</b>		
S1	Title	Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended
S2	Abstract	Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions
<b>Introduction</b>		
S3	Problem formulation	Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work, problem statement
S4	Purpose or research question	Purpose of the study and specific objectives or questions
<b>Methods</b>		
S5	Qualitative approach and research paradigm	Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/interpretivist) is also recommended; rationale <sup>a</sup>
S6	Researcher characteristics and reflexivity	Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability
S7	Context	Setting/site and salient contextual factors; rationale <sup>b</sup>
S8	Sampling strategy	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale <sup>b</sup>
S9	Ethical issues pertaining to human subjects	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues
S10	Data collection methods	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale <sup>b</sup>
S11	Data collection instruments and technologies	Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study
S12	Units of study	Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)
S13	Data processing	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/identification of excerpts
S14	Data analysis	Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale <sup>b</sup>
S15	Techniques to enhance trustworthiness	Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale <sup>b</sup>
<b>Results/findings</b>		
S16	Synthesis and interpretation	Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory
S17	Links to empirical data	Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings
<b>Discussion</b>		
S18	Integration with prior work, implications, transferability, and contribution(s) to the field	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field
S19	Limitations	Trustworthiness and limitations of findings
<b>Other</b>		
S20	Conflicts of interest	Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed
S21	Funding	Sources of funding and other support; role of funders in data collection, interpretation, and reporting

<sup>a</sup>The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.  
<sup>b</sup>The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Indication where relevant information can be found in manuscript

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# BMJ Open

## Delphi study to identify consensus on patient selection for hydrogel rectal spacer use during radiation therapy for prostate cancer in the UK

Journal:	<i>BMJ Open</i>
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Date Submitted by the Author:	23-Jun-2022
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<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Radiology and imaging, Urology
Keywords:	Prostate disease < UROLOGY, Radiation oncology < RADIOLOGY & IMAGING, RADIOTHERAPY, Toxicity < THERAPEUTICS

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4 **1 Title page**  
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9 **2 Delphi study to identify consensus on patient selection for**  
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11 **3 hydrogel rectal spacer use during radiation therapy for prostate**  
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13 **4 cancer in the UK.**  
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17 **5 Short title:** Delphi study on hydrogel rectal spacer use (UK)  
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20 **6 Authors:** Heather Ann Payne<sup>1</sup>, Suneil Jain<sup>2</sup>, Clive Peedell<sup>3</sup>, Albert Edwards<sup>4</sup>, James Andrew  
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14 25 Structured abstract (*Word count: 268, max 300*)  
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## 16 26 **OBJECTIVES**

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19 27 To identify consensus on patient prioritisation for rectal hydrogel spacer use during radiation  
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21 28 therapy for the treatment of prostate cancer in the United Kingdom.  
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## 23 29 **DESIGN**

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26 30 Delphi study consisting of two rounds of online questionnaires, two virtual advisory board  
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28 31 meetings and a final online questionnaire.  
29

## 30 32 **SETTING**

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33 33 Radical radiation therapy for localised and locally advanced prostate cancer in the United  
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35 34 Kingdom.  
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## 38 35 **PARTICIPANTS**

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41 36 Six leading clinical oncologists and one urologist from across the UK.  
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## 43 37 **INTERVENTIONS**

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46 38 Rectal hydrogel spacer.  
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## 49 39 **PRIMARY AND SECONDARY OUTCOME MEASURES**

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## 54 41 **RESULTS**

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57 42 The panel reached consensus on the importance of minimizing toxicity for treatments with  
58  
59 43 curative intent, and that even low-grade toxicity-related adverse events can significantly  
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3 44 impact quality of life. There was agreement that despite meeting rectal dose constraints, too  
4  
5 45 many patients experience rectal toxicity, and that rectal hydrogel spacers in eligible patients  
6  
7 46 significantly reduces toxicity related adverse events. However, as a consequence of funding  
8  
9 47 limitations, patients need to be prioritized for spacer use. A higher benefit of spacers can be  
10  
11 48 expected in patients on anticoagulation, and in patients with diabetes or inflammatory bowel  
12  
13 49 disease, but consensus could not be reached regarding patient groups expected to benefit  
14  
15 50 less. While radiation therapy regimen is not a main factor determining prioritization, higher  
16  
17 51 benefit is expected in ultra-hypofractionated regimens.

## 21 **CONCLUSION**

23 53 There is a strong and general agreement that all prostate cancer patients undergoing radical  
24  
25 54 radiation therapy have the potential to benefit from hydrogel spacers. Currently, not all patients  
26  
27 55 who could potentially benefit can access hydrogel spacers, and access is unequal.  
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29 56 Implementation of the consensus recommendations would likely help prioritise and equalise  
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31 57 access to rectal spacers for patients in the UK.  
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3 **58 ARTICLE SUMMARY: STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 5  
6 **59**       • The Delphi panel is a recognised method in developing NICE guidelines and is utilised  
7  
8 **60**           here to gather insights from a diverse panel of UK radiation oncology and urology  
9  
10 **61**           experts who are experienced users of hydrogel spacers.  
11  
12 **62**       • This study included seven panel experts and their experiences may not reflect all users  
13  
14 **63**           of hydrogel spacers.  
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16 **64**       • To help reduce bias, answers and opinions were assessed by two researchers working  
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18 **65**           independently.  
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## 66 INTRODUCTION

### 67 Prostate cancer burden

68 Prostate cancer is the second most common cancer in men globally,<sup>1</sup> and the most common  
69 in the UK.<sup>2</sup> More than 47,500 UK men are diagnosed with prostate cancer every year and over  
70 400,000 men are living with and after prostate cancer.<sup>3</sup> The 5-year survival rate for localized  
71 prostate cancer in the UK is almost 100%,<sup>4</sup> with three quarters of men diagnosed at any stage  
72 expected to survive 10 years.<sup>2</sup> In England, 97%, 87% and 78% of men diagnosed with prostate  
73 cancer survive their disease for more than one, five and ten years, respectively.<sup>2</sup> Given the  
74 high likelihood of curative therapy, a key treatment goal is to prevent potential adverse events  
75 from impacting patient quality of life after treatment.

76 In addition to the patient burden, prostate cancer is a costly disease with the European costs  
77 of care for prostate cancer estimated at EUR 199 billion in 2018.<sup>5</sup>

### 78 Radiation therapy for prostate cancer

79 Choice of treatment for prostate cancer is complex and involves multi-factorial considerations  
80 including presenting cancer stage (localised, locally advanced or metastatic), risk stratification,  
81 life expectancy, comorbidities, and other patient-specific factors, such as lifestyle, patient  
82 preference and treatment goals.<sup>6</sup> For localised and locally advanced prostate cancer,  
83 treatment options include active surveillance, surgery, brachytherapy and radiation therapy  
84 (RT), with or without hormone treatment, as well as multimodality treatment combining surgery  
85 or RT with systemic therapy.<sup>7-9</sup> RT with radical intent is a first-line treatment for localised and  
86 locally advanced prostate cancer.<sup>8</sup> Intensity-modulated RT (IMRT) with image guidance  
87 (IGRT) is considered the gold-standard form of external beam RT (EBRT).<sup>10</sup> Of the circa  
88 18,000 men identified as having received radical RT for prostate cancer in England and Wales  
89 between April 2018 and March 2019, over 90% were treated with IMRT.<sup>11</sup> Whilst stereotactic  
90 body RT (SBRT) is not currently routine practice in the UK, its use is increasing and it is now

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3 91 delivered in several NHS centres.<sup>12</sup> Circa 95% of UK men with intermediate-risk disease  
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5 92 receive a hypofractionated radiotherapy regimen.<sup>11</sup>  
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8 93 The success and clinical outcomes of RT depend on several factors, including radiation dose  
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10 94 to the tumour and the extent of irradiation affecting nearby normal-tissue, particularly the  
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12 95 rectum.<sup>10</sup> Dose-escalated EBRT is a highly effective curative treatment, with higher doses  
13  
14 96 providing better biochemical control.<sup>13</sup> Higher doses can, however, increase radiation toxicity  
15  
16 97 to nearby tissues. Despite substantial advancements in RT, acute and reversible, as well as  
17  
18 98 rare but severe, long-term adverse effects of radiation toxicity such as urinary and bowel  
19  
20 99 incontinence remain problematic. The National Prostate Cancer Audit (NPCA) reported that  
21  
22 100 11% of prostate cancer patients experienced  $\geq 1$  severe gastrointestinal complication within  
23  
24 101 two years after radical RT. This outcome factor derived from hospital records data is defined  
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26 102 as a confirmed diagnosis of radiation toxicity  $\geq$  grade 2 according to National Cancer Institute  
27  
28 103 Common Toxicity Criteria for Adverse Events [CTCAE] in addition to a documented procedure  
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30 104 to the large bowel.<sup>11 14</sup> Late  $\geq$  grade 2 gastrointestinal toxicity has been explored in numerous  
31  
32 105 randomized clinical trials. The 2016 Hypofractionated versus conventionally fractionated  
33  
34 106 radiotherapy for patients with prostate cancer (HYPRO) trial found an incidence of  
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36 107 gastrointestinal toxicity at three years of 17.7% in standard fractionation and 21.9% in  
37  
38 108 hypofractionation.<sup>15</sup> In 2017, results from the ASCENDE-RT trial showed a cumulative  
39  
40 109 incidence of 5-year gastrointestinal side effects ranging from 20.2% (dose-escalated external  
41  
42 110 beam radiation therapy) to 31.3% (low-dose-rate prostate brachytherapy).<sup>16</sup> Due to its  
43  
44 111 proximity to the prostate, the anterior rectal wall is especially vulnerable to irradiation effects  
45  
46 112 and the rectum is a dose-limiting organ at risk.<sup>17</sup>  
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### 51 113 **Hydrogel spacers**

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54 114 One way of reducing the unwanted radiation dose to the rectum is by increasing the space  
55  
56 115 between the prostate and the rectal wall. This can be achieved by use of a rectal spacer, with  
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58 116 three currently indicated for use during RT for prostate cancer in the UK: biodegradable  
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3 117 balloons, hyaluronic acid gel, and polyethylene glycol (PEG) hydrogel.<sup>18</sup> In the UK, the use of  
4  
5 118 biodegradable spacers to reduce rectal toxicity during RT for prostate cancer is accepted  
6  
7 119 (IPG590) by NICE, based on safety and efficacy data on the use of PEG hydrogel spacers.<sup>18</sup>  
8  
9 120 Use of rectal hydrogel spacers has been evaluated in a single-blind, phase III trial in image  
10  
11 121 guided IMRT (N=222).<sup>19</sup> The spacer-placement success rate was 99%, and no device-related  
12  
13 122 adverse events occurred.<sup>19</sup> Late (three to 15 months) rectal toxicity severity was significantly  
14  
15 123 reduced in the spacer group.<sup>19</sup> At three years follow-up, decreased bowel toxicity and fewer  
16  
17 124 declines in urinary and bowel quality of life were observed in the spacer group (41% men in  
18  
19 125 the control group experienced a minimally important difference (MID) in decline in bowel  
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21 126 quality of life vs 14% in the spacer group; P=0.002). The risk of large decline (twice the MID)  
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23 127 was 21% (control) vs 5% (spacer; P=0.02) in bowel quality of life and 23% (control) vs 8%  
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25 128 (spacer; P=0.02) in urinary quality of life respectively.<sup>20</sup>

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28  
29 129 Lack of routine reimbursement has led to restricted patient access to hydrogel spacers in the  
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31 130 UK. Therefore, there is a requirement to prioritise patients for hydrogel spacer use in the UK,  
32  
33 131 and attempts have been made to identify optimal usage. A secondary analysis of the hydrogel  
34  
35 132 spacer trial data tried to identify the patient subgroups most and least likely to benefit from the  
36  
37 133 intervention but found generally homogeneous results in bowel quality of life with benefits in  
38  
39 134 all assessed subgroups.<sup>21</sup>

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41  
42 135 The aim of this study was to identify consensus on patient prioritisation for rectal hydrogel  
43  
44 136 spacer use during RT for the treatment of prostate cancer in the UK.

## 45 46 47 137 **METHODS**

### 48 49 50 138 **The Delphi technique and panel experts**

51  
52  
53 139 The Delphi technique is a structured, iterative, multistage process using rounds of  
54  
55 140 questionnaires to collect opinions and to stepwise develop consensus among a pre-defined  
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57 141 panel of experts.<sup>22</sup> For this study, experts were approached and asked to participate in the  
58  
59 142 panel based on being a UK radiation oncologist or urologist having experience with rectal



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3 143 hydrogel spacers. To ensure a diverse panel, experts were sought to represent different  
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5 144 geographies within the UK and use different types of RT modalities. There is no defined  
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7 145 optimal panel size for a Delphi study,<sup>23</sup> but the selection of an odd number of experts ensured  
8  
9 146 that a majority outcome could be reached.  
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### 11 12 13 147 **Steps in the Delphi process**

14  
15  
16 148 There is no fixed number of rounds in a Delphi survey.<sup>23</sup> As depicted in Figure 1, our study  
17  
18 149 adopted a five-stage approach to elicit consensus, consisting of two pre-advisory board  
19  
20 150 questionnaires administered through a web-based survey program, two virtual advisory board  
21  
22 151 discussions, and a final concluding questionnaire.  
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24  
25 152 The first questionnaire provided some background information on the experts, such as their  
26  
27 153 most used RT modalities and open-ended questions to capture a broad understanding. The  
28  
29 154 open-ended questions related to key treatment aims, which patient and treatment  
30  
31 155 characteristics to consider when prioritising hydrogel spacer, factors typically deterring them  
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33 156 from recommending hydrogel spacer use, and factors predictive for toxicity. Additionally,  
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35 157 experts were asked to rank treatment modalities in order of how much patient benefit they  
36  
37 158 would expect from hydrogel spacer use, on a scale from 0 (no patient benefit) to 100 (maximal  
38  
39 159 patient benefit).  
40

41  
42 160 In the second questionnaire, the responses to the open-ended questions from the previous  
43  
44 161 questionnaire were presented, and the experts asked to rank them by order of importance. In  
45  
46 162 addition to follow-up questions, the second questionnaire included questions on perceived  
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48 163 barriers to hydrogel spacer use.  
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51 164 *Figure 1: Overview of Delphi panel process*  
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### 53 165 **Analysis and scoring**

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55  
56 166 Qualitative content analysis was used to analyse responses to open-ended questions. Two  
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58 167 researchers independently analysed responses and interpreted consensus. At the advisory  
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3 168 board meetings, results from the questionnaires were presented together with initial drafted  
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5 169 consensus statements for discussion. Then followed moderated discussions which led to  
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7 170 revisions of the consensus statements. In the final online questionnaire, the consensus  
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9 171 statements were presented, and the experts asked to select a level of agreement: "I fully  
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11 172 agree", "I partially agree" or "I disagree". Upon selecting "I partially agree", experts were asked  
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13 173 to give a comment and/or update the wording of the statement. The responses were linked to  
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15 174 an agreement score, based on the answer selected, and the comment given if "I partially  
16  
17 175 agree" was selected (Table 1).

176 *Table 1: Consensus statement scoring key*

Score	Answer selected	Description
4	"I fully agree"	
3	"I partially agree"	With minor word change
2	"I partially agree"	With minor change to statement interpretation/meaning
1	"I disagree"	

177 Consensus definitions vary between studies<sup>24-28</sup>, with percent agreement being one of the  
178 more common approaches.<sup>28</sup> Based on the results of our final online survey, statements were  
179 categorised into four levels of consensus (strong, moderate, low, and no consensus). This  
180 study scored the level of consensus in terms of percent agreement, and additionally that  
181 consensus could not be reached in case any expert disagreed with a statement. Figure 2  
182 depicts the consensus statement scoring for this study. Only statements grouped as either  
183 **Strong** or **Moderate** are considered statements where consensus was reached. **Weak** or **No**  
184 consensus mean that there was still substantial discussion or divergence of opinion among  
185 the experts.

186 *Figure 2: Consensus statement scoring, decision tree*

## 187 **Consent, privacy, and data security**

188 The panel experts were informed about and consented to the full Delphi process, including  
189 length and time of surveys and details on the data collected, stored, and deleted. The retention  
190 periods of collected data were pre-defined. Questionnaire responses were anonymised and  
191 securely stored on the survey software provider's server in Germany. Audio recordings were

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3 192 stored for 60 days on the conference provider's EU based server. All experts were contracted  
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5 193 for this study and reimbursed at fair, local market rates for their time commitment during the  
6  
7 194 Delphi process. The study was approved by an independent review board (HML IRB Review  
8  
9 195 #952SCGC21).

## 12 196 Patient and public involvement

15 197 No patients involved.

## 18 198 RESULTS

### 21 199 Panel expert characteristics

24 200 All approached experts agreed to participate (N=7). Details on the panel experts' treatment  
25  
26 201 practices are presented in Table 2. The majority of the panel (N=6) exclusively use rectal  
27  
28 202 hydrogel spacers in their practices. One uses rectal hydrogel spacers as well as biodegradable  
29  
30 203 balloons. Participation rates were high, with only one dropout (one expert did not complete the  
31  
32 204 second questionnaire but participated in all other steps).

35 205 *Table 2: Panel experts treatment practice*

<b>Geographical setting, N (%)</b>	
England	5 (57)
Northern Ireland	1 (14)
Wales	1 (14)
<b>Public or private setting, N (%)</b>	
Public only	1 (14)
Private only	0 (0)
Both	6 (86)
<b>Most frequently used RT modalities, % of patients (N experts using modality)</b>	
IMRT	25–95 (6)
EBRT (not specified)	90 (1)
IMRT and HDR BT boost	15–30 (2)
SBRT	45 (1)
BT monotherapy (LDR)	10–20 (2)
PBT	10 (1)

57 206 **Key:** IMRT, intensity-modulated radiation therapy; EBRT, external beam radiation therapy; HDR, high dose rate;  
58 207 BT, brachytherapy; SBRT, stereotactic body radiation therapy; LDR, low dose rate; PBT, proton beam therapy.

208 Key treatment aims, besides curing or controlling cancer and increasing overall survival, were  
209 to minimise the risk of side effects and toxicity.

## 210 Questionnaire outcomes shaping the consensus statement discussion

211 Questionnaire outcomes showed that the panel estimated considerably less toxicity in patients  
212 with hydrogel spacer, as compared to those without (Figure 3). All experts agreed that  
213 hydrogel spacers reduce grade 1 and 2 late rectal toxicity, 86% agreed that it reduces grade  
214 3 toxicity and 71% grade 4 toxicity.

215 *Figure 3: Expected level of late (after 3 months) rectal toxicity in patients with and without hydrogel spacer*

216 The panel considered toxicity a considerable issue, and underlined that also low-grade  
217 toxicity-related adverse events may significantly worsen patient's lives:

218 *'I ask them [my patients], when you're out and about, is the first thing you think of where*  
219 *the toilet is?... And a remarkable number of patients say yes to that question, and it is*  
220 *affecting their quality of life.'*

221 In the first questionnaire, the panel estimated that an average of 83% (SD: 13%) patients who  
222 could potentially benefit from a hydrogel spacer were denied access. Throughout the  
223 discussions, patient access in general and equal access in particular were central themes.  
224 The panel voiced their concern, for example regarding differences between NHS and private  
225 practice:

226 *'In my private practice, every patient gets it [hydrogel spacer] unless there is a reason*  
227 *why they should not get it. Whereas in my NHS practice, unfortunately no patient gets*  
228 *it, unless there is a reason why they should get it.'*

229 The main barrier to hydrogel spacer use was funding and resource constraints, followed by  
230 lack of trained staff.

1  
2  
3 231 *'The ideal way to go would be to offer it to every eligible patient. But given that this is*  
4  
5 232 *not currently feasible in our centre, there has to be some kind of categorisation.'*  
6  
7

8 233 As seen in Figure 4, a trend towards hypo-fractionated external-beam regimens, with potential  
9  
10 234 increased bowel dose and toxicity being associated with more potential benefit for spacers  
11  
12 235 was apparent. This was also reflected in the outcome of the conjoint analysis. The absolute  
13  
14 236 variation between expected benefit was, however, relatively low, ranging from 67 (BT  
15  
16 237 monotherapy LDR) to 80 (SBRT/SABR) on average. This was reflected in later discussions,  
17  
18 238 where experts agreed that RT modality is not the main consideration when prioritising patients  
19  
20 239 for hydrogel spacer use.  
21  
22

23 240 *Figure 4: Expected patient benefit from hydrogel spacer use, by treatment modality*  
24

25 241 When asked about patient characteristics to consider when deciding whether to recommend  
26  
27 242 using hydrogel spacer the experts gave a wide range of suggestions, including comorbidities  
28  
29 243 (age, diabetes, high bleeding risk, hip prosthesis, inflammatory bowel disease and rectal and  
30  
31 244 bowel problems, normal erectile function), cancer stage, localisation, and heavy smoking. This  
32  
33 245 was narrowed down in subsequent discussion, with general agreement that patients with  
34  
35 246 certain comorbidities (diabetes, inflammatory bowel disease) or on anticoagulation may have  
36  
37 247 higher benefit from hydrogel spacers.  
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## 40 41 248 **Consensus statements**

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45 249 Upon being shown the results of the questionnaires, two rounds of moderated discussion  
46  
47 250 followed, resulting in 13 consensus statements. These statements were subsequently voted  
48  
49 251 on in a final questionnaire, and a final scoring was assigned as described in the method  
50  
51 252 section.  
52  
53

54 253 The following eight statements reached strong consensus:

- 55  
56  
57 254 • Our consensus opinion is that for treatments with curative intent, focus should be on  
58  
59 255 minimising toxicity and the risk of side effects.  
60

- 1  
2  
3 256 • Our consensus opinion is that use of spacers in eligible patients significantly reduces  
4  
5 257 radiation dose to the rectum and toxicity-related adverse events.  
6  
7 258 • Our consensus opinion is that despite meeting rectal dose constraints, too many  
8  
9 259 patients continue to experience rectal toxicity.  
10  
11 260 • Our consensus opinion is that certain grade 1 toxicity-related adverse events<sup>1</sup> can still  
12  
13 261 have a significant impact on patient quality of life.  
14  
15 262 • Our consensus opinion is that any toxicity grading system in use should be  
16  
17 263 complemented by patient-reported outcomes.  
18  
19 264 • Our consensus opinion is that patients receiving long-term anticoagulation therapy with  
20  
21 265 medications such as direct oral anticoagulants (DOACs)<sup>2</sup> should be considered for  
22  
23 266 spacer use if their anticoagulation can be safely paused.  
24  
25 267 • Our consensus opinion is that spacers are useful in eligible patients with T1-T2  
26  
27 268 disease. Spacer use in patients with T2+ disease should not be excluded but should  
28  
29 269 be assessed on an individual basis by a team proficient in inserting spacers.  
30  
31 270 • Our consensus opinion is that patients should have the opportunity to take part in the  
32  
33 271 discussion regarding the use of a spacer.<sup>29</sup>  
34  
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36  
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38 272 For the following two statements, moderate consensus was reached. Each statement is  
39  
40 273 followed by an explanation on why strong consensus was not reached.

- 41  
42  
43 274 • Our consensus opinion is that a higher benefit of spacers is expected in eligible  
44  
45 275 patients with certain comorbidities<sup>3</sup> and/or longer expected overall survival.  
46  
47  
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55  
56 <sup>1</sup> Bowel frequency and urgency, diarrhoea, flatulence, radiation cystitis, radiation proctitis, rectal  
57 bleeding, rectal mucus.

58 <sup>2</sup> The reason for prescribing the DOAC, rather than the medication itself, is more important for the  
59 decision. All patients on DOACs, except for cardiac stent and prosthetic valve replacement patients  
60 may be able to safely pause their anticoagulation.

<sup>3</sup> Anticoagulation, diabetes, inflammatory bowel disease (ulcerative colitis and Crohn's disease)

1  
2  
3 276 Six experts (86%) fully agreed with the statement. One expert (14%) only partially agreed and  
4  
5 277 suggested removing “and/or longer expected overall survival”. This was deemed a change to  
6  
7 278 the statement interpretation.

- 8  
9  
10 279
  - All eligible radiotherapy patients should have equal opportunity to access spacers,  
11  
12 280 independent of socio-economic factors.

13  
14  
15 281 Five experts (71%) fully agreed with the statement. While there was an overall agreement that  
16  
17 282 lack of equality in access to spacers is currently an important issue, two experts (29%) had  
18  
19 283 rewording suggestions that would have impacted the statement interpretation. One proposed  
20  
21 284 to add more detail on eligibility, and to add that patients suitable for a spacer implant should  
22  
23 285 have access, irrespective of whether they can afford it. The other expert expressed some  
24  
25 286 uncertainty regarding the term “socio-economic factors” and would have preferred the wording  
26  
27 287 “irrespective of post-code”.

### 28 288 **Statements where no consensus was reached**

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33  
34 289 One statement was categorised as a weak consensus statement:

- 35  
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37 290
  - Whilst we support the use of spacers in all eligible patients, our consensus opinion is  
38  
39 291 that if resource constraints exist, patients receiving ultra-hypofractionated or  
40  
41 292 hypofractionated radiotherapy should be prioritised for access to a spacer.

42  
43  
44 293 Four experts (57%) fully agreed with the statement. The remaining three (43%) partially  
45  
46 294 agreed but had additional comments. One expert expressed that individual risk factors should  
47  
48 295 be considered, rather than the RT modality. The second expert agreed on the need to identify  
49  
50 296 a group at higher risk of rectal toxicity, and suggested combination of RT modality  
51  
52 297 considerations and patient characteristics (e.g., age) and comorbidities. The third respondent  
53  
54 298 only agreed that patients receiving ultra-hypofractionated RT should be prioritised.

55  
56  
57 299 For the following two statements, no consensus was reached.  
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59  
60

- 1  
2  
3 300 • Our consensus opinion is that for patients with anticipated short overall survival but  
4  
5 301 who will receive radical radiotherapy, use of a spacer should only be considered after  
6  
7 302 careful evaluation of potential benefit.  
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10 303 Three experts (43%) fully agreed. Four (57%) partially agreed but had additional comments.  
11  
12 304 Two experts made the point that it is unlikely that patients with short anticipated overall survival  
13  
14 305 would be indicated for radical radiotherapy. Two experts expressed uncertainty with the  
15  
16 306 wording “overall survival”. One of them suggested a rewording that some carefully selected  
17  
18 307 patients with short expected survival who are offered radical radiotherapy may benefit from  
19  
20 308 spacer use after careful consideration. The second expressed that the statement was too  
21  
22 309 unclear. Additionally, in subsequent discussions, the experts agreed that the term “anticipated  
23  
24 310 shorter life expectancy” would have been preferred over “anticipated short overall survival”,  
25  
26 311 so as not to imply that the use of hydrogel spacers affects survival. Upon subsequent  
27  
28 312 discussion, experts agreed that the statement would have been improved by adding “and side  
29  
30 313 effects” to the end of the statement.  
31  
32  
33

- 34 314 • Our consensus opinion is that there are a limited number of patients with risk factors,  
35  
36 315 or combination of risk factors, in which use of a spacer should only be considered after  
37  
38 316 careful evaluation of potential benefits.  
39  
40

41 317 Four experts (57%) fully agreed, two (29%) partially agreed, and one (14%) disagreed. Those  
42  
43 318 who partially agreed expressed that an addition should be made to the statement, that the  
44  
45 319 majority of patients who receive radical RT would also be suitable for a spacer, noting that  
46  
47 320 patients who are not fit enough for a spacer, likely are also not fit for RT. The second partially  
48  
49 321 agreeing expert wanted to add a recommendation to discuss such cases with a mentor with  
50  
51 322 extensive experience in spacer insertion. Upon subsequent discussion, experts agreed that  
52  
53 323 the statement would have been improved by adding “and side effects” to the end of the  
54  
55 324 statement.  
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## 325 **DISCUSSION**

### 326 **Statement of principal findings**

327 There was strong consensus that rectal toxicity is a considerable issue, and that minimizing  
328 the risk of radiation side effects is an important treatment aim. Rectal hydrogel spacers can  
329 reduce the toxicity burden and benefit patients undergoing radical RT for the treatment of  
330 prostate cancer in the UK. Currently, the NHS does not routinely fund hydrogel spacers.  
331 Limited funding leads to limited resources, and therefore limited access. Experts estimated  
332 that on average, 83% of their patients that could benefit from a spacer are not currently getting  
333 access. There was moderate consensus that a higher benefit is expected in patients on  
334 anticoagulation, patients with diabetes, and patients with inflammatory bowel disease  
335 (Ulcerative colitis or Crohn's disease). However, experts expected the majority of patients to  
336 benefit from use of a spacer, and it was not possible to reach consensus on those patients  
337 with lower expected benefit. Key takeaways from discussions around statements where no  
338 consensus was reached are that individual patient characteristics are more important for  
339 informing the decision on whether to prioritise the use a spacer than the RT regimen selected.  
340 However, a higher level of benefit from spacer use is expected with ultra-hypofractionated RT  
341 compared with standard RT, a conclusion in line with current clinical evidence.<sup>30</sup>

### 342 **Meaning of the study: possible explanations and implications for clinicians and policy** 343 **makers**

344 Currently, patient selection is driven by limitations in the healthcare system rather than patient  
345 needs. This highlights the importance of developing guidance on spacer use, to ensure fair  
346 and equal access to healthcare. The COVID-19 pandemic has lengthened already substantial  
347 NHS waiting times, further exacerbating issues with access and underscoring the need for  
348 formal guidance. Additionally, practical issues (e.g., availability of trained staff, theatre  
349 capacity) need to be considered when preparing a clinic to start using hydrogel spacers. As is

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2  
3 350 important for all techniques to be introduced, audit of practice and quality improvement is  
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5 351 recommended.  
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## 8 352 **Strengths and weaknesses**

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11 353 This study only included seven experts, who are all experienced users of hydrogel spacers  
12  
13 354 Naturally, a broader selection of experts could have resulted in different answers. However,  
14  
15 355 including non-users as panel experts would not have been feasible for the purposes of this  
16  
17 356 study, as they would have not possessed the relevant experience required. Additionally, the  
18  
19 357 RT modality used by panel members could influence their view on when to prioritise hydrogel  
20  
21 358 spacer use. However, the diversity of the panel in terms of modalities used likely safeguarded  
22  
23 359 the balance of the resulting consensus.  
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26  
27 360 The main strengths of this study are the scientific rigour applied following a well-defined and  
28  
29 361 proven Delphi methodology, and the experience and diversity of the panel. The Delphi method  
30  
31 362 allowed gathering insights from leading experts in the field from different UK countries utilising  
32  
33 363 a mix of RT modalities, while reducing bias and separating the evaluation by tasking two  
34  
35 364 independent researchers with analysis and scoring.  
36  
37

## 38 365 **Comparison with other studies**

39  
40  
41 366 To the best of our knowledge, no previous attempts have been done to establish consensus  
42  
43 367 for rectal hydrogel spacer use in the UK. A study published in 2016 used a model-based  
44  
45 368 approach to identify patients expected to benefit the most from implantable rectum spacers  
46  
47 369 among 26 patients with localized prostate cancer treated at a German hospital. The clinical  
48  
49 370 risk factors found relevant were anticoagulant use, hormonal therapy, antihypertensive use,  
50  
51 371 diabetes, haemorrhoids, pelvic nodal RT, and prior abdominal surgery.<sup>31</sup> Single-centre studies  
52  
53 372 of rectal spacers in Crohn's and ulcerative colitis patients suggest benefit of spacers.<sup>32 33</sup> One  
54  
55 373 study conducted secondary analyses of a single-blinded, phase III randomised trial, with the  
56  
57 374 aim of identifying patients benefitting the least from hydrogel rectal spacer during prostate  
58  
59  
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2  
3 375 radiation therapy.<sup>21</sup> In line with this study, no subgroup without potential benefits of hydrogel  
4  
5 376 spacers could be identified. The benefit of hydrogel spacers perceived by the experts is in line  
6  
7 377 with current clinical evidence.<sup>20</sup>  
8  
9

## 10 378 **Unanswered questions and future research**

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12  
13 379 As well as hydrogel rectal spacers, other materials including hyaluronic acid, saline-filled  
14  
15 380 balloon, and human collagen have been used to create space between the rectum and  
16  
17 381 prostate. Readers should familiarize themselves with the available evidence on each product  
18  
19 382 when considering between the different options. This study offers guidance to later adopters  
20  
21 383 of rectal hydrogel spacers, building on the expertise of leading UK radiation oncologists and  
22  
23 384 urologist. Future research should focus on implementing formal guidance on hydrogel spacer  
24  
25 385 use and strive towards reaching a consensus on patient prioritisation. A larger follow-up  
26  
27 386 consensus study would be of value, asking all UK domain experts their opinion on the  
28  
29 387 consensus statements. With growing interest in hydrogel spacers, it is increasingly important  
30  
31 388 to study the impact of the quality of the implant. There is an ongoing debate on what a good  
32  
33 389 implant is, and how it is measured. Similarly, it would be valuable to reach an agreement on  
34  
35 390 which toxicity data to generate and follow up through including hydrogel spacers in cancer  
36  
37 391 treatment trials, or through the development of a quality registry. Finally, it is of utmost  
38  
39 392 importance to investigate the availability and equality in access to spacers. For this aim to be  
40  
41 393 reached, further cost-effectiveness research and a continued discussion on willingness to pay  
42  
43 394 should be undertaken. Analyses of spacers in prostate cancers have shown cost-effectiveness  
44  
45 395 in certain radiation modalities in US<sup>34 35</sup> and Dutch<sup>36</sup> contexts.  
46  
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## 50 396 **CONCLUSION**

51  
52 397 Rectal toxicity is a considerable issue, and focus should be on minimising side effects of  
53  
54 398 curative treatment. There is a strong and general agreement that all prostate cancer patients  
55  
56 399 undergoing radical RT have the potential to benefit from hydrogel spacers. Currently, not all  
57  
58 400 patients who could potentially benefit can access hydrogel spacers, and access is unequal.  
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3 401 Implementation of the ten strong and moderate consensus recommendations would likely help  
4  
5 402 prioritise and equalise access to rectal spacers for patients in the UK. In particular, prioritising  
6  
7 403 access towards patients on anticoagulation, with diabetes, and/or patients with inflammatory  
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9 404 bowel disease would, in our opinion, be a strong starting position.  
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411 AE, AB, PD, CP, and HP were contracted for this study and reimbursed at fair, local market  
412 rates for their time commitment during the Delphi process but received no reimbursement for  
413 their participation in the manuscript development.

## 414 **COMPETING INTERESTS**

415 RS is the owner of Coreva Scientific, a health-economics and value-based healthcare  
416 consultancy that focuses on medical devices. AHH is an employee of Coreva Scientific.  
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418 manuscript. The authors did not receive direct payment as a result of this work outside of their  
419 normal salary payments. EW is an employee of Boston Scientific.

## 420 **AUTHOR CONTRIBUTIONS**

421 EW conceptualised the idea. RS and AHH designed and ran the questionnaires and  
422 implemented data protection measures. EW reviewed the study design. AHH and RS analysed  
423 the responses. RS moderated the advisory boards. SJ, AT, AE, AB, PD, CP, and HP  
424 responded to the questionnaires, and participated in the advisory boards. AHH and RS drafted  
425 the manuscript, in collaboration with SJ, AT, AE, AB, PD, CP and HP. All authors critically  
426 reviewed the manuscript outline and manuscript drafts. All authors approved the final  
427 manuscript.

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2  
3 428 **ETHICS APPROVAL STATEMENT**  
4

5  
6 429 The study was approved by an independent review board (HML IRB Review #952SCGC21).  
7

8 430 All participants gave informed consent before taking part.  
9

10 431 **DATA SHARING STATEMENT**  
11

12  
13 432 No additional data available.  
14

15  
16 433 **LEAD AUTHOR TRANSPARENCY STATEMENT**  
17

18 434 I confirm that the manuscript is an honest, accurate, and transparent account of the study  
19

20 435 being reported; that no important aspects of the study have been omitted; and that any  
21

22 436 discrepancies from the study as originally planned have been explained.  
23  
24

25 437 Prof. Heather Ann Payne  
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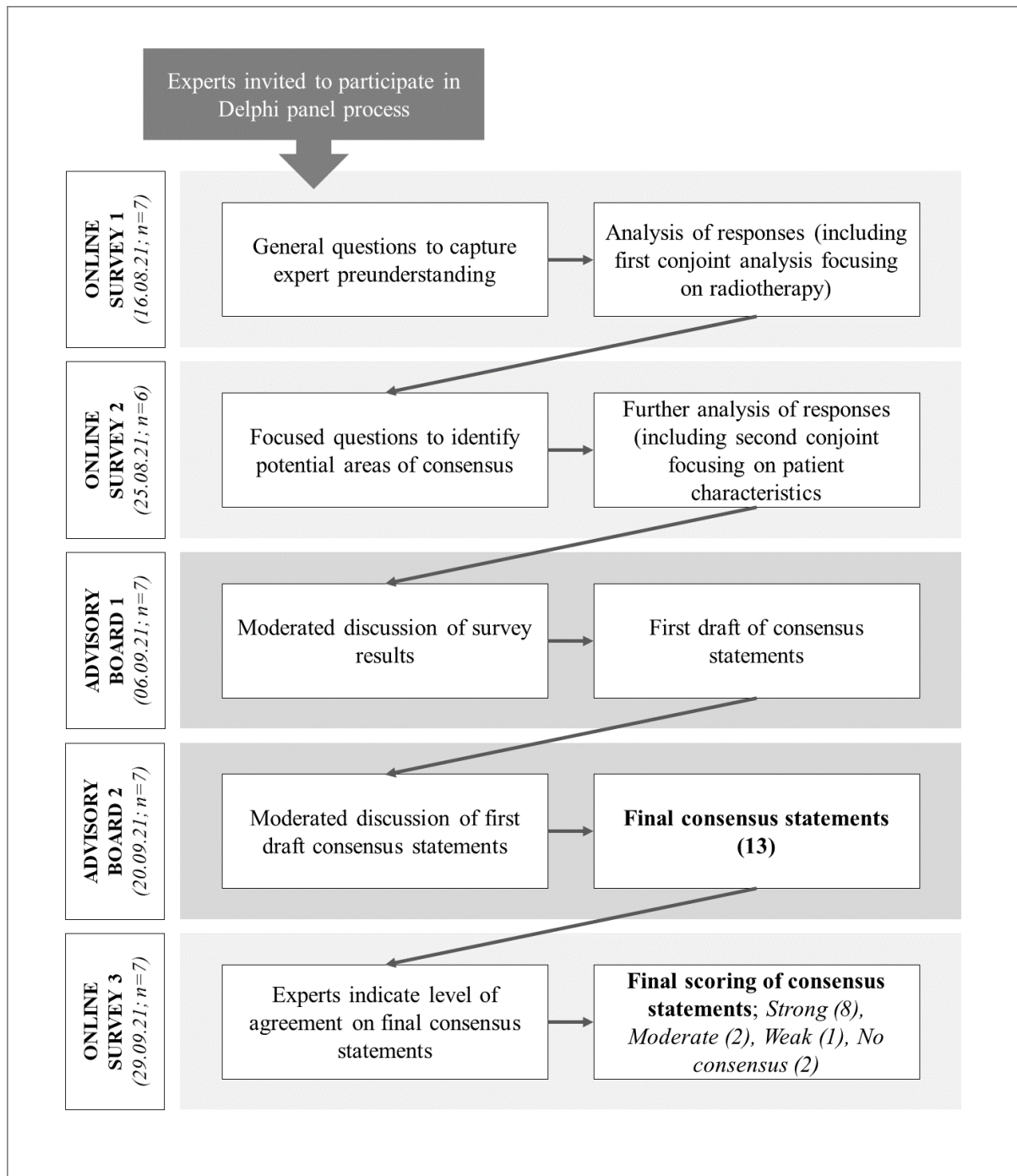
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21 587 **Figure legends**

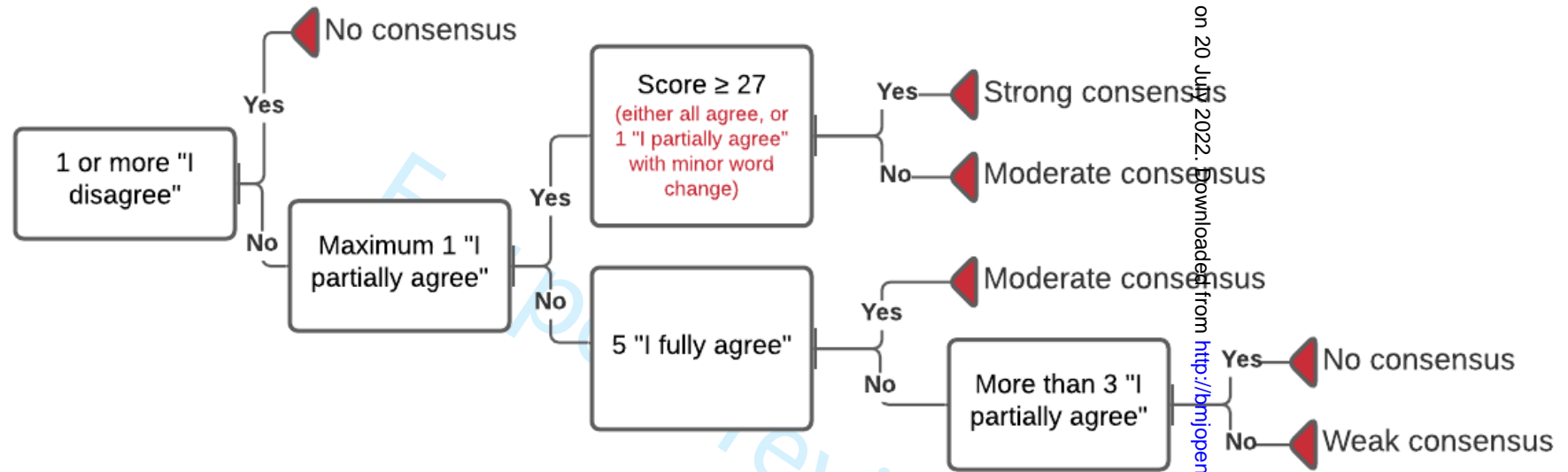
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24 588 **FIGURE 2:**

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26 589 Strong consensus could only be reached if all experts indicated that they “Fully agree” or all  
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28 590 except one “Fully agree”, with the last respondent “Partially agree” with only a minor word  
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30 591 change (score  $\geq 27$ ). Moderate consensus could only be reached if at least five respondents  
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32 592 “Fully agree”, and with no “Disagree”. Weak consensus was reached where a maximum of  
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34 593 three respondents “Partially agree”, and with no “Disagree”. No consensus was indicated  
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36 594 where at least one respondent “Disagree”, or if four or more respondents “Partially agree”.  
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39 595 **FIGURE 4:**

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42 596 Key: BT, brachytherapy; LDR, low dose rate; HDR, high dose rate; PBT, proton beam therapy,  
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44 597 IMRT, intensity-modulated radiation therapy; IGRT, image guided radiation therapy, SBRT,  
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46 598 stereotactic body radiation therapy; SABR, stereotactic ablative radiotherapy  
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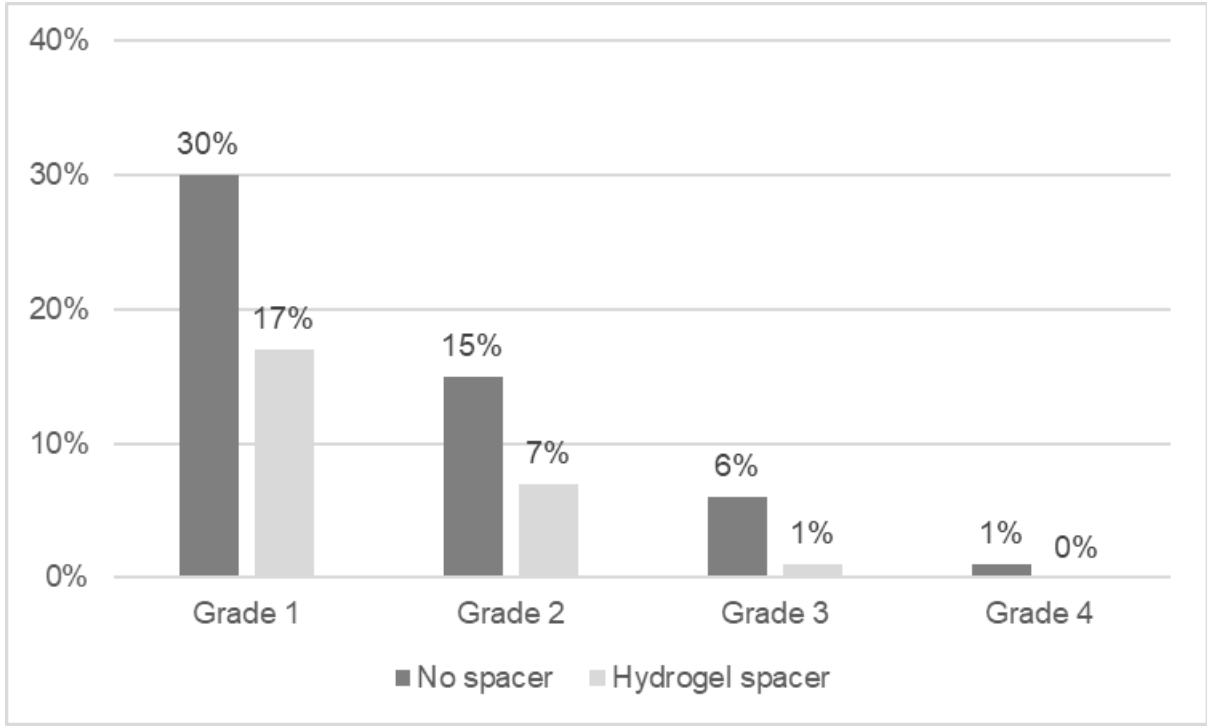




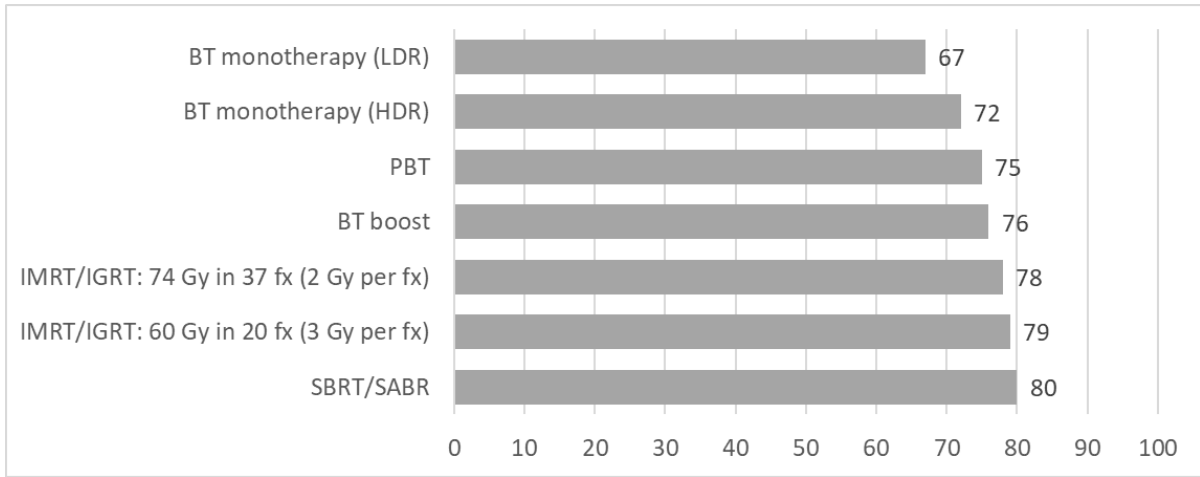
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O'Brien, Bridget C.; Harris, Ilene B.; Beckman, Thomas J.; Reed, Darcy A.; Cook, David A. Academic Medicine 89(9):1245-1251, September 2014. doi: 10.1097/ACM.0000000000000388

No.	Topic	Item
<b>Title and abstract</b>		
S1	Title	Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended
S2	Abstract	Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions
<b>Introduction</b>		
S3	Problem formulation	Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work, problem statement
S4	Purpose or research question	Purpose of the study and specific objectives or questions
<b>Methods</b>		
S5	Qualitative approach and research paradigm	Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/interpretivist) is also recommended; rationale <sup>a</sup>
S6	Researcher characteristics and reflexivity	Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability
S7	Context	Setting/site and salient contextual factors; rationale <sup>b</sup>
S8	Sampling strategy	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale <sup>b</sup>
S9	Ethical issues pertaining to human subjects	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues
S10	Data collection methods	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale <sup>b</sup>
S11	Data collection instruments and technologies	Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study
S12	Units of study	Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)
S13	Data processing	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/identification of excerpts
S14	Data analysis	Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale <sup>b</sup>
S15	Techniques to enhance trustworthiness	Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale <sup>b</sup>
<b>Results/findings</b>		
S16	Synthesis and interpretation	Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory
S17	Links to empirical data	Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings
<b>Discussion</b>		
S18	Integration with prior work, implications, transferability, and contribution(s) to the field	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field
S19	Limitations	Trustworthiness and limitations of findings
<b>Other</b>		
S20	Conflicts of interest	Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed
S21	Funding	Sources of funding and other support; role of funders in data collection, interpretation, and reporting

<sup>a</sup>The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.  
<sup>b</sup>The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Indication where relevant information can be found in manuscript

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