

# The utility of routine surveillance screening with magnetic resonance imaging to detect tumour recurrence/progression in children with high-grade central nervous system tumours

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# **The Utility of Routine Surveillance Screening with Magnetic Resonance Imaging (MRI) to Detect Tumor Recurrence / Progression in Children with High-Grade Central Nervous System (CNS) Tumors: A Systematic Review**

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## ABSTRACT

### **The Utility of Routine Surveillance Screening with Magnetic Resonance Imaging (MRI) to Detect Tumor Recurrence / Progression in Children with High-Grade Central Nervous System (CNS) Tumors: A Systematic Review**

Simon P. Stevens,<sup>1</sup> Caroline Main,<sup>1</sup> Simon Bailey,<sup>2</sup> Barry Pizer,<sup>3</sup> Martin English,<sup>5</sup> Bob Phillips,<sup>6</sup> Andrew Peet,<sup>4</sup> Shivaram Avula,<sup>3</sup> Sophie Wilne,<sup>7</sup> Keith Wheatley,<sup>1</sup> Pamela R. Kearns,<sup>1,5</sup> Jayne S. Wilson<sup>1</sup>

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**Background:** Surveillance Magnetic Resonance Imaging (MRI) is routinely used to detect recurrence in children with high-grade central nervous system (CNS) tumors, although no consensus has been reached regarding its effectiveness and whether earlier detection is associated with improved patient outcomes. This review aimed to evaluate this practice and any associated benefits and harms. **Methods:** Systematic searches for relevant studies were undertaken in a number of databases, including MEDLINE and EMBASE, from 1985 to August 2018. Study selection and data extraction was undertaken independently by two reviewers. Due to heterogeneity between studies, no pooling of data was undertaken. Reporting followed PRISMA guidelines. **Results:** No comparative studies were identified. Three retrospective observational studies involving 306 patients were reviewed. All had high risk of bias by virtue of study design. Two studies reported outcomes by symptomatic status - both recurrence rates and overall survival for asymptomatic patients were comparable to those for clinically symptomatic patients. No quality of life outcomes were reported. **Conclusion:** There is a paucity of evidence to guide clinical practice as to the effectiveness

of MRI surveillance in paediatric patients with high grade CNS tumors. These studies do not clearly demonstrate benefit or harm for the practice. With more research needed, there is a role for researchers to build into future trials data collection on surveillance imaging to give more information for the assessment of imaging frequency and duration in asymptomatic patients. This is an important question, not only to clinicians and patients and their families but also from a health service resource perspective.

# 1 Introduction

2

3 Paediatric high-grade central nervous system (CNS) tumors are fast-growing, malignant  
4 tumors with metastatic potential and are commonly associated with poor prognosis even after  
5 multi-modal treatment. Generally classified by the World Health Organization (WHO) as  
6 either grade III or IV tumors, they include glial (anaplastic astrocytoma and glioblastoma  
7 multiforme), ependymal (ependymoma, both WHO grade II and III) and embryonal  
8 (medulloblastoma and tumors previously known as primitive neuroectodermal tumors  
9 (PNET)) tumors, as well as brainstem tumors (diffuse pontine glioma (DIPG)) atypical  
10 teratoid/rhabdoid tumor (AT/RT) and pineoblastoma. Many children with high-grade CNS  
11 tumors will go on to experience recurrence or progression and the likelihood of this will  
12 depend on the histology and location of their first tumor, as well as treatments given.<sup>1,2</sup>

13

14 In recent years, Magnetic Resonance Imaging (MRI) has become the predominant imaging  
15 tool in the management of children with high-grade CNS tumors. The rationale behind  
16 routine imaging, or surveillance, is that recurrence or progressive disease detected at an  
17 earlier stage may be more responsive to treatment and benefit from a wider range of  
18 treatment options than disease diagnosed at a later stage from clinical signs and symptoms.  
19 However, no consensus has been reached as to whether this leads to improved outcomes for  
20 patients and their families.

21

22 The objectives of this review were therefore to:

- 23 1. assess the diagnostic utility of surveillance MRI in detecting tumor recurrence prior  
24 to the emergence of new clinical signs and symptoms compared to the nonroutine use  
25 of MRI upon symptomatic presentation, and assess whether this practice translates to  
26 measurable improvements in clinical outcomes;

- 27 2. consider the effect of differing screening intervals on the diagnostic utility of  
28 surveillance MRI and determine the optimal duration of imaging after initial  
29 diagnosis; and
- 30 3. identify any gaps and methodological weaknesses in the current evidence base and  
31 make recommendations to inform the design and analysis of future studies.

32

33 The authors have also undertaken a systematic review on the effectiveness of surveillance  
34 MRI in paediatric low-grade tumors, which forms a companion piece to this review paper.<sup>3</sup>

35

## 36 **Methods**

37

38 Standard systematic review methodology was employed and reporting followed the Preferred  
39 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>4</sup> A  
40 detailed account of the methodology employed in this review can be found in the published  
41 protocol, which is also registered with PROSPERO (CRD42016036802).<sup>5</sup> A summary of the  
42 methods are described below.

43

### 44 *Search strategy*

45

46 This review formed part of a wider NIHR-funded work programme of systematic reviews  
47 aimed at assessing the effects of different interventions for the treatment of paediatric CNS  
48 tumors and therefore searches were not restricted to studies concerned solely with  
49 surveillance imaging in children with high-grade tumors. Searches for published studies from  
50 1985 to August 2018 were undertaken in several databases, including MEDLINE and  
51 EMBASE. (See Supplementary File S1). No language, publication restrictions or study  
52 design filters were applied.

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Study selection

The following inclusion and exclusion criteria were applied:

**Population:** Children and young adults (up to age 25 years) with diagnoses of any type of high-grade CNS tumor who were asymptomatic at the time of study recruitment. Given that children undergoing surveillance may have some neurologic sequelae from their tumor and/or its treatment, it would be more accurate to characterise patients as exhibiting no new, stable or improved neurological signs or symptoms.

**Interventions:** Routine or surveillance MRI. Studies employing computed tomography (CT) as the sole surveillance imaging modality were excluded.

**Outcome Measures:** Recurrence rates (by study, tumor type, location and extent of resection), diagnostic yield of imaging, timing of recurrence, change in patient management post-recurrence, overall survival (OS), surrogate survival measures (e.g. recurrence-free survival (RFS), progression-free survival (PFS)) and quality of survival. Studies reporting outcomes from aggregated CT and MRI scans were excluded.

**Study designs:** As randomized controlled trials (RCTs) and nonrandomized comparative studies were initially sought but not identified, the review was extended to include observational studies such as case series.

Study selection was undertaken by two independent reviewers, with disagreements resolved by discussion.

79

80 Data extraction and risk of bias assessment

81

82 Data, extracted by one reviewer and checked by a second, were recorded on a standardised  
83 proforma developed in Microsoft Word (See Supplementary File S2). Risk of bias was  
84 assessed at the study level by two reviewers using a six-point tool devised by the Centre for  
85 Reviews and Dissemination (York; CRD)<sup>6</sup> designed to assess bias in case series studies.

86

87 Statistical analysis

88

89 Due to the design of the included studies and the heterogeneity of outcomes reported, only a  
90 descriptive analysis was undertaken.

91

## 92 **Results**

93

94 Quantity and description of included studies

95

96 From the electronic database searches, 28 potentially relevant publications were identified

97 with an additional 13 publications identified from citation-checking. On full text

98 examination, 38 were excluded including 11 studies which employed both CT and MRI as

99 surveillance imaging modalities but failed to report results separately for MRI. (See

100 Supplementary File S3). No RCTs or prospective comparative studies were identified. Three

101 retrospective case series studies<sup>7-9</sup> were included in the review. (See Figure 1).

102

103 The three studies were conducted between 2001 and 2014 and undertaken at single centre  
104 institutions. Two studies<sup>8,9</sup> included patients with high-grade tumors only, with one<sup>7</sup>  
105 including a mix of low- and high-grade tumor patients. (See Table 1).

106

#### 107 Quality of the research

108

109 Studies were clinically heterogeneous with study populations varying in terms of both tumor  
110 type and disease severity. Study samples were small but patients appeared to be  
111 representative of the target population, although it was unclear whether patients were at a  
112 similar timepoint in the disease progression. Inclusion and exclusion criteria for each study  
113 were explicitly stated. Generally details of previous treatments were not reported. (See  
114 Supplementary File S4). There was also variability in terms of reporting and defining of  
115 outcomes. The terms ‘recurrence’ and ‘progression’ were defined in all three studies,  
116 although only two reported recurrences as ‘symptomatic’ and ‘asymptomatic’ and defined  
117 these terms.<sup>7,9</sup> All three studies reported OS, although only Kornreich<sup>8</sup> defined the term. (See  
118 Table S5). This was also the only study to report PFS. Korones<sup>7</sup> did not report average  
119 duration of follow-up.

120

#### 121 Included studies

122

#### 123 Korones (2001)<sup>7</sup>

124

125 Korones<sup>7</sup> was a mixed tumor grade study with 112 children at study commencement. Patient  
126 details were provided only for the 46 patients who went on to experience  
127 recurrence/progression. Of these, 33 had high-grade tumors. Eight tumor types were

128 included. The median age of these patients at recurrence was six years (range 0.25 – 21)  
129 although this was not reported by tumor type.

130

131 All patients underwent surgery as the primary treatment, although this was not further  
132 specified by extent of resection (i.e., gross total resection (GTR) versus sub-total resection  
133 (STR)). At the commencement of surveillance imaging, none of the patients had relapsed  
134 disease.

135

136 With respect to imaging frequency, patients received a median of one scan every 2.5 months  
137 (range 1/1 – 1/6.7 months) irrespective of whether they were symptomatic or asymptomatic at  
138 recurrence. Frequency of scanning was not reported by tumor type.

139

140 As only data on recurrent patients was reported, it was not possible to calculate the recurrence  
141 rate for the 33 high-grade tumor patients as a whole, nor by tumor type. The rate of  
142 recurrence/progression by symptomatic status was reported, with 17 patients (52%)  
143 asymptomatic at recurrence. Recurrence by symptomatic status was also reported by tumor  
144 type, with asymptomatic and symptomatic recurrences comparable in number, although the  
145 numbers in each category were very small (ranging from 1-6). (See Table 2). Recurrence by  
146 extent of resection was not reported.

147

148 The diagnostic yield of imaging for all seventeen asymptomatic patients was 4.4%, i.e., one  
149 asymptomatic recurrence detected every 23 MRI scans. (See Table 2). With respect to CPC,  
150 GCT and AT/RT, there were two asymptomatic recurrences among these tumor types and the  
151 diagnostic yield of imaging was 6.5%.

152

153 Median time to recurrence from initial diagnosis for all 33 patients was 0.75 years with no  
154 significant difference in median time to recurrence between symptomatic and asymptomatic  
155 patients at recurrence (0.66 and 0.77 years respectively). Median time to recurrence was not  
156 reported by individual tumor type, nor by extent of resection.

157

158 Information regarding local therapy received following recurrence/progression was provided  
159 for 26 patients (79%), with eight of 14 asymptomatic patients (57%) undergoing local therapy  
160 (surgery with or without stereotactic radiosurgery) compared to only three of 12 symptomatic  
161 patients (25%) ( $p = 0.13$ ). Again, change in patient management was not reported by tumor  
162 type.

163

164 Overall survival from recurrence for all 33 patients was reported but only by symptomatic  
165 status at recurrence, with median OS for the 17 asymptomatic patients (0.58 years)  
166 marginally and nonstatistically significantly greater ( $p=0.25$ ) than that for the 16  
167 symptomatic patients (0.42 years). Median OS was not reported by tumor type.

168

169 Kornreich (2005)<sup>8</sup>

170

171 Kornreich<sup>8</sup> was a retrospective case series study looking at the role of surveillance MRI in the  
172 management of 15 paediatric patients with DIPG. While the frequency of imaging was not  
173 reported, the mean number of MRI scans per patient was six. Thirteen patients (87%)  
174 experienced tumor progression while two patients remained stable. Symptomatic status of  
175 patients at progression was not reported.

176

177 Median PFS was 0.83 years, ranging from 0 months (in 4 patients who deteriorated  
178 immediately from diagnosis without any prior period of stability) to nine years. Treatment

179 (radiotherapy and/or chemotherapy) was planned and not consequent to changes in scans or  
180 recurrence. Median OS was 1.67 years, with three patients (20%) alive at the time of  
181 reporting.

182

183 Perreault (2014)<sup>9</sup>

184

185 Perreault<sup>9</sup> was a retrospective case series study which sought to assess the benefits of  
186 surveillance MRI in a cohort of 258 high-grade tumor patients. There were seven tumor types  
187 included. (See Table 1). All patients underwent surgery as the primary treatment although  
188 this was not further specified by extent of resection. At commencement of surveillance  
189 imaging, none of the patients had relapsed disease.

190

191 While frequency of scanning was not reported, the median number of MRI scans per patient  
192 across all tumor types was 13, ten of the brain and three spinal. (See Table 3). The interval  
193 since last MRI for symptomatic patients was not longer for symptomatic compared to  
194 asymptomatic patients (mean 3.9 versus 4.8 months).

195

196 Rates of recurrence/progression were also reported by symptomatic status. (See Table 3).

197 With respect to first recurrences (n=113), there was a slight predominance of asymptomatic  
198 (46%) compared to symptomatic recurrences (42%), whereas for subsequent recurrences  
199 (n=125) the converse was the case (29% versus 58%). Recurrences (both first and

200 subsequent) by symptomatic status were also reported by tumor type where, in the case of

201 medulloblastoma and ependymoma, this trend continued with the majority of first recurrences  
202 asymptomatic and second symptomatic. Conversely, for sPNET, the majority of first

203 recurrences were symptomatic and second asymptomatic. For HGG, the majority of both first  
204 and second recurrences were symptomatic. For the remaining tumor types (GCT, AT/RT and

205 pineoblastoma), the number of recurrences was so small that caution should be exercised  
206 when comparing recurrences by symptomatic status (most notably AT/RT, with 100% of first  
207 recurrences asymptomatic based on only four patients). Recurrences among glioma patients  
208 were more frequently symptomatic compared to those patients with other tumor types (68  
209 versus 38 % respectively;  $p=0.003$ ). The rate of recurrence by extent of resection was not  
210 reported.

211

212 A breakdown of MRI scans by both tumor type and site of imaging was reported, with  
213 diagnostic yield across all tumor types of 8.3% for brain recurrence only (range 2.1% to  
214 21.6%), 3.8% for combined brain-spine recurrence (range 1.6% to 19.7%) and 0.9% for spine  
215 recurrence only (range 0.7% to 4.9%). (See Table 3).

216

217 Median time to recurrence from initial diagnosis was 1 year, although it is unclear whether  
218 this relates to first or all recurrences. Median time to recurrence by tumor type was reported  
219 but, again, it is unclear if this relates to first or all recurrences. (See Table 3). No significant  
220 difference in median time to recurrence was reported between symptomatic and  
221 asymptomatic patients at recurrence (1.0 and 0.92 years respectively;  $p>0.8$ ). The time by  
222 which greater than 90% of recurrences had occurred for each individual tumor type was also  
223 reported. (See Table 3). Median time to recurrence by extent of resection was not reported.

224

225 Change in patient management following first recurrence was reported for 93% of patients,  
226 with 59% of patients undergoing new treatments, 11% continuing with existing treatment,  
227 16% scheduled for palliative care and 7% undergoing closer interval surveillance MRI. New  
228 treatments consisted of chemotherapy (22% standard dose and 4% high dose with stem cell  
229 support), radiotherapy (6%), radiosurgery (2%), surgery (5%) and unspecified multi-modal

230 therapy (20%). Change in patient management post-recurrence by tumor type was not  
231 reported.

232

233 There was no significant difference ( $p > 0.3$ ) in median OS from recurrence between  
234 symptomatic and asymptomatic patients (1.92 years and 2.25 years respectively). Median OS  
235 by tumor type was not reported.

236

## 237 **Discussion**

238

239 This systematic review is one of a series evaluating treatments for children with CNS tumors.  
240 Underpinning the reviews was consultation with clinical experts and a Patient and Public  
241 Involvement (PPI) group, consisting of mothers of children with CNS tumors. The PPI group  
242 in particular expressed concerns about over-scanning, especially in situations where scanning  
243 is no longer able to influence prognosis as in the case of patients for which nothing further  
244 can be clinically done. As well as the unknown risks associated with repeated administration  
245 of contrast materials such as Gadolinium,<sup>10</sup> anaesthesia and sedatives, the PPI group spoke of  
246 what has come to be termed ‘scanxiety’, i.e. an overwhelming feeling of stress experienced  
247 by both patient and family around the time of scanning. As one parent put it “At times, it  
248 seems like life and all its decisions revolve around scanning, which serves as a constant  
249 reminder of the cancer and acts as an obstacle to resuming normal behaviour.”

250

251 Although the use of surveillance MRI is standard practice throughout the developed world in  
252 the management of children with high-grade CNS tumors, this systematic review did not  
253 identify any RCTs evaluating this intervention. After excluding 11 high-grade tumor  
254 surveillance imaging studies which employed both CT and MRI but did not report results  
255 separately by imaging modality,<sup>11-21</sup> the review included three retrospective, single arm

256 studies (n=306 patients) with MRI employed as the sole imaging modality. It could be argued  
257 that in excluding studies employing CT imaging, the review has lost valuable data on  
258 surveillance. However, the reason for focussing on MRI, other than its superior sensitivity, is  
259 that MRI studies are more recent than CT studies and therefore encompass an era of  
260 improved survival and greater salvageability of patients due to improved treatments.

261

262 The findings of the review were mixed. Korones<sup>7</sup> concluded that "asymptomatic recurrences  
263 were detected in only a small proportion of surveillance scans and had no impact on survival  
264 in children with high-grade tumors." Kornreich<sup>8</sup> reported on 15 patients with DIPG and  
265 compared the findings of 51 surveillance scans with those from clinical examination and  
266 reported a high degree of concordance (87%), suggesting that for DIPG, surveillance MRI is  
267 providing little information over and above that conveyed by clinical symptoms and signs  
268 and therefore its utility may be limited. Ultimately, surveillance imaging did not affect the  
269 treatment given, nor the outcome. Based on this evidence, it could be argued, albeit  
270 tentatively, that certain tumor types may be more amenable to surveillance MRI than others  
271 and that for aggressive tumors such as DIPG, where often any period of clinical stability is  
272 extremely limited, there is a very short window of opportunity for surveillance imaging to  
273 exploit. In support of this, Kornreich<sup>8</sup> reported four patients with zero time to progression.  
274 However, with other, less aggressive high-grade tumor types, the use of MRI surveillance  
275 may be of value. For example, with Perreault<sup>9</sup> asymptomatic recurrence rates were higher for  
276 ependymoma and medulloblastoma compared to other tumor types, suggesting that  
277 surveillance might potentially be beneficial to these patients, although in this study  
278 asymptomatic patients across all tumor types did not benefit from improved overall survival  
279 compared to symptomatic patients. Unfortunately, the potential for bias within case series is  
280 considerable and therefore conclusions from this review are tentative and should be viewed  
281 with extreme caution.

282

283 There were several reporting problems that made comparison across the studies problematic.  
284 Korones failed to report frequency of MRI imaging by tumor grade or type thereby rendering  
285 a cross-study comparison of the effect of differing imaging schedules on the rate of  
286 asymptomatic recurrence for different tumor types impossible.<sup>7</sup> Similarly, Kornreich<sup>8</sup> did not  
287 report patients by symptomatic status at time of progression. Only Perreault<sup>9</sup> reported patients  
288 and recurrences by tumor type and symptomatic status, enabling observations to be drawn  
289 which could potentially inform the design of future trials. However, it is important to  
290 appreciate that the data analysed in these studies were acquired for clinical purposes for  
291 which assessment of surveillance imaging protocols was not an objective.

292

293 The initial aim of this review was to assess the effectiveness of surveillance MRI. RCTs were  
294 required to do this but as none were found, focus was switched to finding studies that were  
295 specifically conducted to describe surveillance scanning. With just three studies meeting the  
296 inclusion criteria, one criticism of this review which emerged from the peer review process  
297 was that the co-operative trials should have been hand-searched for information on  
298 surveillance. This does raise an interesting point about the best way to systematically review  
299 paediatric oncology trials. Systematic reviewing (especially employing Cochrane  
300 methodology) was developed with single question trials involving more common diseases in  
301 mind, i.e. A versus B, whereas paediatric oncology trials tend to be co-operative, multi-modal  
302 trials that attempt to answer a variety of questions within a single trial due to the rarity of the  
303 diseases. In response to the peer review feedback, a search of co-operative trials in  
304 medulloblastoma was undertaken to determine whether there was data within these trials to  
305 inform the review question. Of 27 trials, surveillance MRI scanning intervals appeared to be  
306 arbitrary and variable, with few reasons given for the surveillance schedules. (See  
307 Supplementary File S6). Only one study, not identified in our systematic review searches

308 likely due to indexing, evaluated the number of patients who had relapse detected through  
309 surveillance MRI compared to symptom-based relapse.<sup>22</sup> (This study reported that 45 relapses  
310 were detected on surveillance MRI, with 20 detected from symptoms alone. Of these, patients  
311 detected from symptoms had a significantly shorter survival post-relapse than those detected  
312 by surveillance MRI ( $p < 0.01$ ), although OS post-primary diagnosis was not statistically  
313 significantly different. This could be due to lead time bias or that patients in the symptomatic  
314 relapse group possibly have more aggressive tumors). Finding the evidence in a systematic  
315 way, from identifying the relevant publications to finding the information within the trial  
316 publications (often results are written into the discussions) can be challenging in these large  
317 co-operative trials. In future, we recommend that systematic reviewers consider hand-  
318 searching relevant co-operative trials, whilst bearing in mind that the main aim of these trials  
319 might differ from that of the systematic review. We also urge authors of co-operative trials to  
320 improve the transparency of their publications, especially with respect to database indexing  
321 as well as signposting and organization of information within the papers.

322

323 The paucity of data evidenced in this review may be due to the complexity of surveillance in  
324 these patients, with frequency of monitoring depending on tumor type, disease status (newly  
325 diagnosed, resistant or relapsed), extent of metastatic spread and previous treatments. Other  
326 factors such as pseudo-progression and radiation necrosis can also complicate the  
327 interpretation of scans, making it a difficult area to investigate. However, there is a need to  
328 examine this question further in order to guide clinicians in developing optimal evidence-  
329 based surveillance strategies, to help parents and children understand the need for  
330 surveillance and to optimise the use of health service resources. There is a role for researchers  
331 to build into future, large co-operative trials methodology that investigates the role of  
332 surveillance MRI or at the very minimum, collects and reports data on the trial surveillance

333 MRI practice, as well as incorporating quality of life data collection, particularly regarding  
334 anxiety around surveillance and the reassurance that it may also afford.

335

336 Conclusion

337

338 Only three retrospective observational studies with a high risk of bias were identified to guide  
339 clinical practice of surveillance MRI for children with high-grade CNS tumors.<sup>7-9</sup> These  
340 studies do not clearly demonstrate benefit or harm for this practice, nor do they define  
341 methods or intervals for maximal effectiveness. To resolve this, more research is needed with  
342 the ultimate endpoints of surveillance relating to survival and quality of life, as opposed to  
343 surrogate outcomes such as the detection of tumor growth. As most of the patients within this  
344 group are treated within the context of a co-operative clinical trial, this research could be built  
345 into trial protocols for very little extra investment. It is an important question, not only to  
346 clinicians and patients and their families but also as a health service resource question.

347

348

349 Figure 1: PRISMA diagram of flow of studies through the selection process

350 Supplementary file S1: Search strategy

351 Supplementary file S2: Data extraction and quality assessment proforma

352 Supplementary file S3: List of excluded studies

353 Supplementary file S4: Quality assessment of included studies

354 Supplementary file S5: Definitions of recurrence / progression and symptomatic /  
355 asymptomatic provided by study authors

356 Supplementary file S6: MRI imaging schedules in co-operative trials in paediatric  
357 medulloblastoma

## **Compliance with ethical standards**

Disclosure of potential conflicts of interest: The authors declare that they have no conflict of interest.

Informed consent: Not required for this type of study (i.e. systematic review).

Ethical approval: Not required for this type of study (i.e. systematic review).

Research involving Human Participants and/or animals: This article does not contain any studies with human participants or animals performed by any of the authors.

## **Authors' contributions**

SPS conceived and designed the study and wrote the article. CM conceived and designed the study and read and commented on the article. SB, BP, ME, RP conceived the study concept, provided clinical input and read and commented on the article. AP, SA, SW and PRK provided clinical input and read and commented on the article. KW conceived and designed the study, provided methodological and statistical input and read and commented on the article. JSW conceived and designed the study, revised the article and is the guarantor of the review. All authors read and approved the final manuscript.

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