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Digital technologies for sepsis prediction in children: A scoping review protocol

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|-------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2022-065429 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 03-Jun-2022 |
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| Keywords: | PAEDIATRICS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Paediatric intensive & critical care < PAEDIATRICS |
| | |

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Manuscripts

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51 29
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53 **30 Word Count: 3333**
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2
3 **31 ABSTRACT**
4

5 **32 Introduction** While there have been several literature reviews on the performance of digital
6
7
8 **33** sepsis prediction technologies and clinical decision-support algorithms for adults, there remains a
9
10 **34** knowledge gap examining the development of technologies for sepsis prediction in children for
11
12 **35** supporting paediatric healthcare. This scoping review will critically analyze the current evidence
13
14 **36** investigating the design, validation, and implementation of digital technologies to predict
15
16 **37** paediatric sepsis to advance the development of new technologies for predicting sepsis in clinical
17
18 **38** settings.
19
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21

22 **39**
23
24 **40 Methods and analysis** This scoping review will follow Arksey and O'Malley's framework. We
25
26 **41** will further develop the protocol using the Preferred Reporting Items for Systematic Review and
27
28 **42** Meta-Analysis extension for scoping reviews (PRISMA-ScR). We plan to search the following
29
30 **43** databases: Association of Computing Machinery (ACM) Digital Library, Cumulative Index to
31
32 **44** Nursing and Allied Health Literature (CINAHL), Embase, Google Scholar, Institute of Electric
33
34 **45** and Electronic Engineers (IEEE), PubMed, Scopus, and Web of Science. Studies will be
35
36 **46** included on children >90 days post-natal to <21 years old, predicted to have or be at risk of
37
38 **47** developing sepsis by a digitalized model or algorithm designed for a clinical setting. Two
39
40 **48** independent reviewers will complete the abstract and full-text screening and the data extraction.
41
42 **49** Thematic analysis will be used to determine themes and present the narrative findings with
43
44 **50** descriptive statistics presented in tabular format.
45
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49 **51**
50
51 **52 Ethics and dissemination** Ethics approval for this scoping review study of the available
52
53 **53** literature is not required. We anticipate that the scoping review will identify the current evidence
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3 54 and design characteristics of digital prediction technologies for the timely and accurate
4
5 55 prediction of paediatric sepsis and factors influencing implementation and usability by clinicians.
6
7
8 56 We plan to disseminate the preliminary findings from this review at national and international
9
10 57 research conferences in global and digital health, gathering critical feedback from multi-
11
12 58 disciplinary stakeholders.
13
14
15 59

60 **Scoping review registration**

61 https://osf.io/nh6qz/?view_only=8c840412a2a44117ac16fdf76e06abd6
62
63

63 **Strengths and limitations of this study**

- 64 • This review is a novel approach to collectively synthesizing current research on designing
65 paediatric sepsis prediction technologies, critically examining the relationships between
66 their design, effectiveness and implementation in clinical settings to identify knowledge
67 gaps requiring further investigation.
- 68 • The chosen review strategy will comprehensively evaluate the vast literature across
69 various study types and research disciplines by a multi-disciplinary research team.
- 70 • The review will exclude digital prediction technologies for sepsis management and
71 treatment after a diagnosis is confirmed and is limited to peer-reviewed literature written
72 in the English language with a full-text version available.
- 73 • Literature focusing on age cohorts <90 days post-natal or >21 years old will be excluded
74 due to significant differences in sepsis etiology and clinical presentation.

75 INTRODUCTION

76 Globally, it is estimated there were a total of 25.2 million cases of sepsis in children (<19) in
 77 2017, imposing significant health care and societal burden (1). Healthcare costs for severe
 78 paediatric sepsis hospitalizations reached approximately \$7.31 billion in the United States in
 79 2016, accounting for almost 20% of total paediatric hospitalization costs (2). However, about
 80 85% of global sepsis cases and 84.5% of sepsis-related deaths among all age groups occur in low
 81 or middle-income countries, specifically sub-Saharan Africa and Southeast Asia (1). Annual
 82 global mortality rates for children (<5) are approximately 2.9 million (Table 1) (3).

83
 84 Table 1. Differences between global neonatal, paediatric, and adult sepsis (3).

| | Neonatal (<90 days) | Paediatric (<5 y/o) | Adult (>20 y/o) |
|-----------------------------------|---------------------|---------------------|-----------------|
| Annual Cases (Million) | 1.3 – 3.9 | 20.3 | 23.7 |
| Annual Mortality (Million) | 0.4 – 0.7 | 2.9 | 7.7 |

85
 86 Early recognition of sepsis in children is challenging. Unlike adult sepsis, children have
 87 different sepsis aetiologies (3). For example, children commonly develop sepsis from
 88 pneumonia, diarrhea, meningitis, or viral infections, whereas abdominal or genitourinary sources
 89 are more common in adults (4). Differences in etiology can also be found between childhood and
 90 neonatal sepsis, with early-onset neonatal sepsis having a distinct microbial pattern (5).
 91 Predicting sepsis in children is also significantly more challenging due to maturation-based
 92 differences in physiology (including immune system response), limitations in the communication
 93 of symptoms, and diagnostic modalities (4,6,7). Sepsis can lead to life-altering organ dysfunction
 94 if not identified quickly in children (8), where mortality rates are reduced two-fold if treated
 95 within the first hour (4). Prediction of sepsis is confounded by the age-based symptom variations
 96 within children, such as their differences in heart rate (4) and commonalities among other

1
2
3 97 childhood conditions and syndromes like Kawasaki syndrome or bronchiolitis (9). This milieu of
4
5 98 complex information combined with significant time pressure provides a significant cognitive
6
7
8 99 burden for healthcare professionals to promptly identify the onset of deterioration that can lead to
9
10 100 this serious medical condition.

11
12 101 In 2020, updated Paediatric Sepsis Survival guidelines were published calling for the
13
14 102 integration of screening standards in healthcare facilities to support rapid identification of sepsis
15
16
17 103 in children (10) and provide the appropriate antimicrobial therapy at the proper time (5,10).
18
19 104 Established screening tools such as the Paediatric Early Warning Score (PEWS) may support the
20
21 105 timeliness of detecting clinical deterioration in children that can lead to sepsis (11). Recently,
22
23 106 adaptations to the Sequential Organ Assessment Score (SOFA) for paediatric patients (pSOFA)
24
25
26 107 and neonates (nSOFA) have shown promise in identifying children at risk for mortality with
27
28 108 sepsis (12); however, it is controversial whether these scores provide value in low-resource
29
30 109 environments (13–15). Development and implementation of algorithms such as the Sepsis
31
32 110 Prediction and Optimization Therapy (SPOT) that can analyze electronic health data in real-time
33
34
35 111 to provide a rule-based approach to initiate a physical sepsis screen have also been reported (16).
36
37 112 With the call from the World Health Organization to improve sepsis identification and the
38
39 113 potential for data-driven and knowledge-based technologies (3,17), digital prediction
40
41 114 technologies are becoming more advanced using mathematical, statistical, and machine learning
42
43 115 techniques to support sepsis prediction utilizing clinical information, symptoms, biomarkers, and
44
45 116 other signs at the bedside (18–21). While recent reviews have explored the literature on the
46
47 117 effectiveness of digital technologies for adult and neonate sepsis prediction (18,19,22–26), there
48
49 118 is currently no review on the design and implementation of these predictive tools for children.
50
51 119 Considering the pathophysiology and etiology of paediatric sepsis are different from that seen in
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3 120 adults and neonates (27), combined with the lack of widely accessible digital technologies for
4
5 121 children compared to adults (28), it is critically important to review the literature on this age
6
7 122 cohort.
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10 123

12 124 **Prior reviews on sepsis prediction technologies**

14 125 Recent narrative reviews discuss machine learning-based technologies for adults and children
15
16 126 (20,29,30). However, the exclusion criteria for these reviews result in most of the included
17
18 127 literature focusing on technologies to predict adult sepsis, with only two (20) or three (29)
19
20 128 articles on paediatric sepsis. Some reviews excluded digital technologies that were not based on
21
22 129 “modern” machine learning models (21,30) or involved a broad search on infectious disease
23
24 130 prediction beyond sepsis (29). Recent narrative reviews have also limited their investigations to
25
26 131 PubMed/Medline, excluding other scientific or engineering databases, which may provide
27
28 132 greater insight into the design of digital technologies (20,26,30–32). One narrative review has
29
30 133 described the design, implementation, and performance of paediatric sepsis screening
31
32 134 technologies (30). However, the review included limited results on technologies based on
33
34 135 machine learning while focusing exclusively on US hospitals (30).
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40 136 Many systematic and scoping reviews have been rigorous in their search strategy but
41
42 137 similarly, report on screening tools and technologies for adult patients while excluding
43
44 138 paediatrics in their full-review criteria (24,25,28,33–36). They also do not include databases
45
46 139 among the engineering disciplines (19,23,37–39), as the objective of these reviews is generally
47
48 140 towards understanding the clinical effectiveness of these technologies and not the design
49
50 141 methodology. While previously published protocols for systematic reviews do not specify a
51
52 142 patient population inclusion or exclusion, some plan to exclude literature on the application of
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3 143 machine learning models (38,40). This approach may not capture research on certain algorithm
4
5 144 types depending on the authors' definitions of artificial intelligence/machine learning. However,
6
7
8 145 the completed reviews from these protocols (38,40) have not been found. While there have been
9
10 146 systematic reviews on the performance of neonatal sepsis prediction technologies providing
11
12 147 insight into their capabilities (19,23), none are focusing on the specifics of paediatric sepsis,
13
14 148 including their design and implementation.

15
16
17 149 Finally, current systematic reviews that include the paediatric literature as part of their
18
19 150 search strategy are limited in their search scope and do not focus on the design and
20
21 151 implementation requirements for this specific patient population (22,28,37). Two reviews
22
23 152 examine early warning systems for paediatric clinical deterioration, focusing on reporting
24
25 153 effectiveness in reducing adverse outcomes and identifying that there remains limited evidence
26
27 154 supporting the mandated use of these systems in hospitals (41,42). For sepsis specifically,
28
29 155 systematic reviews on automated prediction and decision-support systems have only identified
30
31 156 one (37) or three (22,28) related articles specific to children due to the period searched or
32
33 157 exclusion restrictions for how the technology was evaluated. One published protocol aims to
34
35 158 capture strategies for early recognition of paediatric sepsis from clinical deterioration (39).
36
37
38 159 However, the review focuses on general strategy effectiveness and does not explicitly include
39
40 160 engineering databases such as IEEE or ACM Digital Library (39). While the systematic review
41
42 161 associated with the protocol mentioned above has not been found, the search strategy approach
43
44 162 may not completely capture the breadth of digital technologies developed for paediatric sepsis
45
46 163 (39). There is a need for a comprehensive scoping review, understanding the design and
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48 164 evaluation of technologies for sepsis prediction in children, and highlighting where knowledge
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3 165 gaps exist to inform future development and implementation that supports clinical decision-
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10 168 **Purpose of the study**

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12 169 Given the limitations of recent literature reviews and the lack of reviews focused on paediatric
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14 170 sepsis, it is necessary to scope the literature to identify the current evidence describing the
15
16 171 development of digital sepsis prediction technologies for this age cohort. The scoping review
17
18 172 defined by this protocol will identify and summarize the existing literature on the design,
19
20 173 effectiveness, and usability of digital sepsis prediction technologies in the paediatric population.
21
22 174 The scoping review, a methodology focusing on answering broader research questions through a
23
24 175 systematic search and presenting tabular findings along with a narrative integration (43), was
25
26 176 identified as the best approach for this review. We anticipate that this methodology will warrant
27
28 177 a meaningful summary of the current development of digital technologies for sepsis prediction
29
30 178 that can inform future research towards improving their performance and evidence-based clinical
31
32 179 implementation to improve the lives of children globally.
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40 181 **METHODS AND ANALYSIS**

41
42 182 The reviewers on this scoping review consist of a multi-disciplinary team of engineers, a health
43
44 183 researcher/biomedical engineering research librarian, a psychology student, and a paediatric
45
46 184 clinician. Our methodology will be guided by the framework developed by Arksey and O'Malley
47
48 185 (43), which iterates through six steps: (i) identifying the research question; (ii) searching for
49
50 186 relevant studies; (iii) selecting the studies; (iv) charting the data; (v) collating, summarizing, and
51
52 187 reporting the results; and (vi) consulting with stakeholders to inform or validate findings. The
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3 188 sixth step is optional, and we will modify this step to consult with experts specifically around
4
5 189 finding technologies used in hospital or industry settings. Levac's recommendations for
6
7 190 independent full-text reviews by at least two reviewers will also be followed (44). This study
8
9 191 protocol will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis
10
11 192 extension for a scoping review (PRISMA-ScR) (45), with any gaps being filled by the Preferred
12
13 193 Reporting Items for Systematic Review and Meta-Analysis extension for protocols (PRISMA-P)
14
15 194 [see Additional file 1]. This protocol has been registered on the Open Science Framework
16
17 195 (https://osf.io/nh6qz/?view_only=8c840412a2a44117ac16fdf76e06abd6).
18
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24 197 **Step 1: identifying the research question**

25
26 198 The research questions were identified through an initial search of the literature on predictive
27
28 199 electronic clinical prediction technologies for sepsis and gaps identified in current systematic and
29
30 200 narrative reviews. The following questions maintain a broad scope for understanding the existing
31
32 201 evidence on digital sepsis prediction technologies and their clinical implementation in the
33
34 202 paediatric context:

- 35 203 1. How are digital sepsis prediction technologies currently designed and developed?
- 36 204 2. What is the effectiveness and usability of digital technologies in predicting sepsis in
37 205 clinical settings?
- 38 206 3. What gaps exist in understanding how to effectively improve the design and
39 207 implementation of digital technologies for sepsis prediction?

40 208 41 209 **Step 2: identifying relevant studies**

210 We will conduct a comprehensive scoping review that includes a multi-disciplinary group of
 211 scholarly databases: Association of Computing Machinery (ACM) Digital Library, Cumulative
 212 Index to Nursing and Allied Health Literature (CINAHL), Embase, Google Scholar, Institute of
 213 Electric and Electronic Engineers (IEEE), PubMed, Scopus, and Web of Science. Articles will
 214 also be identified using the snowballing technique (46), to identify relevant literature among the
 215 references and citations of articles included for the full review. We will additionally hand-search
 216 for literature on the design, validation, and implementation of commercial digital technologies
 217 for sepsis prediction, which may be approved by governing bodies such as Health Canada
 218 (health-products.canada.ca/mdall-limh/), the Food and Drug Administration
 219 (accessdata.fda.gov/scripts/cdrh/cfdocs/cfml/textsearch.cfm), and the European Union Medical
 220 Device Regulation (ec.europa.eu/tools/eudamed/#/screen/home).

221 We have developed a search strategy for each database to support our comprehensive
 222 literature search. Our approach employs keywords, medical subject headings (MeSH), key
 223 concept subject headings, and Boolean terms. A sample search strategy for PubMed is presented
 224 in Table 2.

225 Table 2. Sample search strategy and results.

| Database | Search Terms | Results | Date |
|---------------|---|---------|------------|
| PubMed | ("decision support"[All Fields] OR "decision-support"[All Fields] OR "early warning score"[MeSH Terms] OR "early warning score"[All Fields] OR "smart system*"[All Fields] OR "electronic alert*"[All Fields] OR "artificial intelligence"[All Fields] OR "artificial intelligence"[MeSH Terms] "machine learning"[All Fields] OR "deep learning"[All Fields] OR "neural network*"[All Fields] OR "support vector machine"[All Fields] OR "hidden markov model"[All Fields] OR "statistical learning"[All Fields] OR "predictive function"[All Fields] OR "algorithm"[All Fields] OR "algorithms"[MeSH Terms] OR "automat*"[All Fields] OR "comput*"[All Fields] OR "decision making, computer assisted"[MeSH Terms] OR | 15,531 | 02/15/2022 |

"electronic*" [All Fields] OR "representation learning" [All Fields] OR "conformal prediction" [All Fields] OR "random forest" [All Fields] OR "naïve bayes" [All Fields] OR "regression" OR "regression analysis" [MeSH Terms] OR "gradient boosting" [All Fields] OR "artificial learning" [All Fields] OR "machine intelligence" [All Fields] OR "probabilistic network*" [All Fields] OR "knowledge representation" [All Fields] OR "bayesian learning" [All Fields] OR "expert system*" [All Fields] OR "technology assisted" [All Fields] OR "computer assisted" [All Fields] OR "statistical" [All Fields] OR "mathematical" [All Fields]) AND ("system" [All Fields] OR "tool" [All Fields] OR "alert*" [All Fields] OR "technology" [All Fields] OR "software" [All Fields] OR "model*" [All Fields] OR "engine" [All Fields] OR "approach*" [All Fields] OR "algorithm" [All Fields] OR "platform" [All Fields] OR "method*" [All Fields] OR "scor*" [All Fields] OR "device" [All Fields]) AND ("sepsis" [All Fields] OR "sepsis" [MeSH Terms] OR "septic shock" [All Fields] OR "systemic inflammatory response syndrome" [All Fields] OR "acute deterioration" [All Fields] OR "patient deterioration" [All Fields] OR "clinical deterioration" [MeSH Terms] OR "clinical deterioration" [All Fields] OR "severe infection" [All Fields] OR "severe bacterial infection" [All Fields] OR "bacterial infections" [MeSH Terms] OR "febrile illness" [All Fields] OR "non-malarial febrile illness" [All Fields] OR "bacteremia" [All Fields] OR "bacteremia" [MeSH Terms]) AND ("diagnos*" [All Fields] OR "detect*" [All Fields] OR "predict*" [All Fields] OR "prognosticate" [All Fields] OR "identif*" [All Fields] OR "infer*" [All Fields] OR "warn*" [All Fields] OR "alert*" [All Fields] OR "recog*" [All Fields] OR "screen*" [All Fields] OR "monitor*" [All Fields] OR "assess*" [All Fields] OR "surveillance" [All Fields] OR "classif*" [All Fields]) AND ("evaluat*" [All Fields] OR "implement*" [All Fields] OR "perform*" [All Fields] OR "design" [All Fields] OR "validat*" [All Fields] OR "usability" [All Fields] OR "effectiveness" [All Fields] OR "efficiency" [All Fields] OR "satisfaction" [All Fields] OR "safety" [All Fields] OR "acceptance" [All Fields] OR "clinical value" [All Fields] OR "interpret*" [All Fields] OR "perception" [All Fields] OR "perspective" [All Fields] OR "opinion" [All Fields] OR "error" [All Fields]) AND ("child*" [All Fields] OR "paediatric" [All Fields] OR "pediatric" [All Fields] OR "pediatrics" [MeSH Terms] OR

"toddler*"[All Fields] OR "teen*"[All Fields] OR
"youth*"[All Fields] OR "adolescen*"[All Fields] OR
"adolescent"[MeSH Terms] OR "infan*"[All Fields] OR
"infant"[MeSH Terms] OR "school age*"[All Fields] OR
"PICU"[All Fields])

226
227 The search results will be imported to Mendeley's reference management software for
228 future referencing and organization (Mendeley Ltd.). A systematic review management software,
229 Covidence (Veritas Health Innovation Ltd.), will be used to identify and merge duplicate articles.
230 A sample of 20 abstracts will be initially screened by two reviewers (RT and JG), ensuring the
231 inclusion-exclusion requirements are robust in capturing relevant articles related to the design
232 and evaluation of digital prediction technologies for paediatric sepsis. Both reviewers will also
233 ensure that the data extraction items capture valuable and appropriate study details from the
234 articles included in the full-text review, which will be shared with the research team.

235

236 **Step 3: study selection**

237 ***Inclusion criteria***

238 The proposed review will include articles that meet the following inclusion criteria:

- 239 • The article is written in English
- 240 • The article is a peer-reviewed journal article, full conference proceeding, or research
241 published on a commercially available digital technology which may be approved by a
242 medical device regulatory body
- 243 • The article includes the description of a digital prediction technology indicative of at least
244 one aspect of clinical deterioration that may lead to sepsis in children (>90 days post-
245 natal to <21 years old)

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2
3 246 • The article describes how the digital technology was designed, validated for its
4
5 247 effectiveness, or evaluated for its usability in the context of a healthcare facility
6
7
8 248 • The article discusses the features and, if applicable, the dataset used in its design
9
10 249 • There is no specification for publication years
11
12
13 250

14
15 251 ***Exclusion criteria***

16
17 252 Screened that include any of the following factors will be excluded from this review:
18

- 19 253 • Commentaries
20
21 254 • Dissertations
22
23 255 • Editorials
24
25 256 • Books and book chapters
26
27 257 • Lectures and addresses
28
29 258 • Study protocols
30
31 259 • Review articles
32
33 260 • Articles inaccessible for full-text review
34
35 261 • Digital technologies informing sepsis treatment strategies
36
37 262 • Digital technologies with proposed use outside a healthcare facility
38
39 263 • Digital technologies that predict mortality risk from sepsis
40
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47
48 265 ***Selection process***

49
50 266 This review will follow the reporting checklist in the Preferred Reporting Items for Systematic
51
52 267 reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR), provided by Tricco
53
54 268 et al. (45). First, all relevant articles will be imported into Covidence. Second, two reviewers (RT
55
56
57
58
59
60

1
2
3 269 and JG) will independently perform the title and abstract screening using the developed
4
5 270 eligibility criteria by classifying them as “Yes,” “No.” Any article classified as “Yes” by RT or
6
7 271 JG will be included in the full-text review during this stage by adding them to an Excel
8
9 272 spreadsheet for access by all authors. If a full-text article cannot be accessed, the reviewers will
10
11 273 seek assistance from library services at the institution or directly contact the article’s
12
13 274 corresponding author. Third, two investigators (RT and JG) will independently perform the full-
14
15 275 text screening for eligibility using the listed inclusion-exclusion criteria. A third member of the
16
17 276 research team will resolve any disagreements on eligibility that occur during the full-text review.
18
19 277 After the full-text review, an inter-rater agreement will be calculated using Cohen’s kappa
20
21 278 coefficient (κ) statistic.
22
23
24
25

26 279

28 280 **Step 4: charting the data**

29
30 281 The data extraction form will be developed in Covidence and exported to Excel to capture the
31
32 282 relevant information from each article. Two reviewers (RT, JG) will individually extract the
33
34 283 relevant data from a sample of eligible articles screened for inclusion in the full-text review to
35
36 284 ensure consistency of recording data. Any disagreements on extracted data will be resolved
37
38 285 through discussion between the reviewers. The form will be iteratively updated until the authors
39
40 286 reach a consensus on the relevant data to extract. We will begin by pulling the following type of
41
42 287 data into the form, with additional data included as we screen more articles:
43
44
45

- 46 288 • Author(s) and date published
 - 47 289 • Study location
 - 48 290 • Document type
 - 49 291 • Discipline
- 50
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3 292 • Objective
4
5
6 293 • Use setting type
7
8 294 ○ Prevalence of sepsis in the use setting
9
10 295 • Age cohort
11
12 296 • Number of participants
13
14
15 297 • Research methodology: retrospective, prospective
16
17 298 • Study design
18
19
20 299 • Sepsis prediction approach/method
21
22 300 • Design of the digital prediction technology
23
24 301 ○ Data source
25
26 302 ○ Model type: data-driven, knowledge-based
27
28
29 303 ○ Interface/Platform
30
31 304 ○ Data flow: continuous, discrete
32
33 305 ○ Prediction objective: sepsis, severe sepsis, septic shock, sepsis severity
34
35
36 306 ○ Definition of the prediction objective
37
38 307 ○ Design process/approach
39
40 308 ■ Workflow integration: triage, monitoring, discharge
41
42
43 309 ○ Clinical predictors
44
45 310 ■ Vital signs
46
47 311 ■ Biomarkers
48
49
50 312 ■ Anthropometric data
51
52 313 ■ Sociodemographic information
53
54 314 ■ Administrative variables
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- 1
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3 315 ▪ Medical history variables
4
5 316 ○ Equity considerations (47,48)
6
7 317 ▪ Bias: quantitative or qualitative misrepresentations of particular patient
8
9 groups
10 318
11
12 319 ▪ Fairness: impacts on various demographic groups
13
14 ▪ Appropriateness: adaptations for specific patient groups or use contexts
15 320
16
17 321 • Measures used for validating the performance and implementation of the digital
18
19 322 prediction technology
20
21 ○ Confirmation method for a true positive sepsis case
22 323
23
24 324 ○ Quantitative values
25
26 325 ▪ Firing rate/Proportion positive
27
28 ▪ Specificity
29 326
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31 327 ▪ Sensitivity
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33 328 ▪ Area under the receiver operating curve
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35 329 ▪ Positive predictive value
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37 ▪ Negative predictive value
38 330
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40 331 ▪ Risk ratio
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42 332 ▪ Machine learning performance measures
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44 ▪ Prediction timing
45 333
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47 334 ▪ Mortality rates
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49 335 ▪ Intervention/Treatment outcomes
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51 336 ▪ Method for handling missing data
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53 ▪ Comparison to other sepsis prediction algorithms
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- 338 ○ User focused outcomes
 - 339 ■ Usability: effectiveness, efficiency, satisfaction, safety
 - 340 ■ User feedback
 - 341 ■ User error
 - 342 ■ User acceptance and trust
- 343 ○ Clinical value provided
- 344 ○ Evaluation of bias, fairness or appropriateness
- 345 ● Conclusion/Primary Findings
 - 346 ○ Future steps/research

347

348 **Step 5: collating, summarizing, and reporting the results**

349 The extracted data will be synthesized within tables that summarize the current digital
350 technology landscape in predicting paediatric sepsis, including characteristics that describe their
351 effectiveness and implementation by health care providers. We will quantitatively identify the
352 number of similar approaches toward model and algorithm development for digital sepsis
353 prediction technologies and their interface and delivery platform. We will also report their
354 quantitative performance and implementation outcomes such as sensitivity and specificity,
355 mortality rates, and impacts on earlier intervention times through descriptive statistics. We will
356 then perform a thematic analysis to identify relevant themes and sub-themes related to our
357 scoping review objectives. The analysis will include an organization of themes on the usability
358 and implementation of digital prediction technologies in clinical contexts related to clinician-
359 system interaction and gaps in improving clinical integration, which will be presented as a
360 narrative. Diagrams will be developed to visualize the relationships and themes between the

1
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3 361 design of digital technologies for paediatric sepsis prediction and their influence on system
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5 362 effectiveness and implementation throughout time to highlight further knowledge gaps and
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7 363 opportunities for future investigation.
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11 365 **Step 6: methodological quality appraisal**

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14 366 We will consult with experts in paediatric sepsis prediction digital technologies for this review to
15
16 367 identify those applied in clinical settings. While critical appraisal of the identified articles is not
17
18 368 mandatory in the scoping review methodology, we will consult with stakeholders to inform and
19
20 369 validate our findings.
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25 371 **Patient and public involvement**

26
27 372 There were no patients or public involvement in the development of this protocol.
28
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32 374 **ETHICS AND DISSEMINATION**

33
34
35 375 Approval from an ethics review committee is not required for this study because it is a scoping
36
37 376 review of previously published literature. Once the review is completed, we plan to disseminate
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39 377 the preliminary findings at national and international research conferences in global and digital
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41 378 health to gather critical feedback from researchers and the public. The finalized results from the
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43 379 review will be submitted for publication in an open access peer-reviewed journal.
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48 381 **DISCUSSION**

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51 382 This scoping review will provide a comprehensive and structured understanding of the digital
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53 383 technologies that have been developed to support the timely prediction of paediatric sepsis. The
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3 384 results will focus on design, validation, and implementation, which will be analyzed thematically
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5 385 and reported in data summary tables, indicating how the development of these technologies is
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7 386 evolving throughout time. It is anticipated that the outcomes will reveal the current challenges in
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9 387 designing and implementing clinically meaningful digital prediction technologies for paediatric
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11 388 sepsis across various clinical environments. Furthermore, the results are expected to identify
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13 389 critical research aspects requiring further investigation that may contribute toward developing
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15 390 future successful technologies.
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19 391 Compared to previous reviews, this scoping review focuses on the complexities of
20
21 392 paediatric sepsis, with a methodological strength in taking a comprehensive and systematic
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23 393 approach that will provide an overview of the evidence in this digital technology landscape.
24
25 394 Inherent in this approach is the limitation of its objective: to summarize the literature and
26
27 395 identify meaningful gaps for further research. As this study will include articles with various
28
29 396 study designs, it does not aim to answer specific questions about recommending the use or
30
31 397 application of certain sepsis prediction technologies for paediatrics. With the results of the pilot
32
33 398 search (Table 2), this review is also limited in its scope, where non-English articles or articles
34
35 399 without a full-text version will not be included. Finally, digital technologies informing treatment
36
37 400 strategies for sepsis and studies looking at age cohorts <90 days post-natal or >21 years old will
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39 401 be excluded because of significant differences in sepsis etiology and clinical presentation. We
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41 402 plan to adequately convey the overall strengths and limitations once the review is completed,
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43 403 including any deviations from the protocol.
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49 404 In conclusion, by mapping the attributes of paediatric sepsis prediction technologies to
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51 405 outcomes related to clinical implementation and performance, we anticipate that our results will
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53 406 highlight critical research gaps among the medical, engineering, and computer science
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3 407 disciplines. The results may inform research on identifying relevant predictive indicators best
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5 408 suited for the design of digital technologies in specific use contexts and environments,
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7 409 improvements towards model development for sepsis prediction, and factors supporting the
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9 410 optimal workflow integration of digital prediction systems by clinicians. Ultimately, this review
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11 411 will be critical for advancing knowledge to improve sepsis prediction for children globally.
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15 412

16 17 413 **List of abbreviations**

18
19 414 ACM: Association of Computing Machinery

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21 415 CINAHL: Cumulative Index to Nursing and Allied Health Literature

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23 416 IEEE: Institute of Electric and Electronic Engineers

24
25 417 nSOFA: neonatal Sequential Organ Assessment Score

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27 418 PEWS: Paediatric Early Warning Score

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29 419 PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for
30
31 420 protocols

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33 421 PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis extension
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35 422 for scoping reviews

36
37 423 pSOFA: paediatric Sequential Organ Assessment Score

38
39 424 SOFA: Sequential Organ Assessment Score

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41 425 SPOT: Sepsis Prediction and Optimization Therapy

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43 426

44 45 427 **Author contributions**

46
47 428 RT is the guarantor of the review and drafted the initial manuscript. All authors contributed to
48
49 429 the development of the search strategy, selection criteria, and data extraction template. MA
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1
2
3 430 provided expertise on paediatric sepsis. All authors critically reviewed the protocol for
4
5 431 intellectual content, subsequently revised it for publication, and read and approved the final
6
7
8 432 version.
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11
12 434 **Availability of data and materials**

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14 435 The datasets used and analyzed during the current study will be available in the Pediatric Sepsis
15
16
17 436 Data CoLab repository: https://dataverse.scholarsportal.info/dataverse/Pedi_SepsisCoLab.
18

19 437

20
21 438 **Funding statement**

22
23
24 439 Not applicable.
25

26 440

27
28 441 **Competing interests statement**

29
30
31 442 The authors declare that they have no competing interests.
32

33 443

34
35 444 **Acknowledgements**

36
37
38 445 RT is supported by an Engineering Excellence Doctoral Fellowship from the University of
39
40 446 Waterloo Faculty of Engineering.
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PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|-----------------------------------|----|---|-------------------------------------|-------------------------------------|----------------|
| | | | Yes | No | |
| ADMINISTRATIVE INFORMATION | | | | | |
| Title | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| Registration | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 61, 195 |
| Authors | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 3-28 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 427-432 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| Support | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 438-439 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 438-439 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 438-446 |
| INTRODUCTION | | | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 86-166 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|-----|---|-------------------------------------|-------------------------------------|------------------|
| | | | Yes | No | |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 203-207 |
| METHODS | | | | | |
| Eligibility criteria | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 237-263 |
| Information sources | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 210-220 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 221-226 |
| STUDY RECORDS | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 227-229, 268-273 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 266-278 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 232-234, 281-287 |
| Data items | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 288-346 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| DATA | | | | | |
| Synthesis | 15a | Describe criteria under which study data will be quantitatively synthesized | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 349-357, |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|--|-----|---|-------------------------------------|-------------------------------------|----------------|
| | | | Yes | No | |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 357-363 |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 366-369 |

BMJ Open

Automated digital technologies for supporting sepsis prediction in children: A scoping review protocol

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2022-065429.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 29-Sep-2022 |
| Complete List of Authors: | Tennant, Ryan; University of Waterloo Faculty of Engineering, Department of Systems Design Engineering Graham, Jennifer; University of Waterloo Faculty of Arts, Department of Psychology Mercer, Kate; University of Waterloo Faculty of Engineering, Department of Systems Design Engineering; University of Waterloo, Library Ansermino, J. Mark; The University of British Columbia, Department of Anesthesiology Burns, Catherine; University of Waterloo Faculty of Engineering, Department of Systems Design Engineering |
| Primary Subject Heading: | Health informatics |
| Secondary Subject Heading: | Paediatrics, Research methods |
| Keywords: | PAEDIATRICS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Paediatric intensive & critical care < PAEDIATRICS |
| | |

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Manuscripts

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3 1 **Automated digital technologies for supporting sepsis prediction in children: A scoping**
4 **review protocol**
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55 31 **Word Count:** 3223
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32 **ABSTRACT**

33 **Introduction** While there have been several literature reviews on the performance of digital
34 sepsis prediction technologies and clinical decision-support algorithms for adults, there remains a
35 knowledge gap in examining the development of automated technologies for sepsis prediction in
36 children. This scoping review will critically analyze the current evidence on the design and
37 performance of automated digital technologies to predict paediatric sepsis, to advance their
38 development and integration within clinical settings.

39
40 **Methods and analysis** This scoping review will follow Arksey and O'Malley's framework,
41 conducted between February to December 2022. We will further develop the protocol using the
42 Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping
43 reviews (PRISMA-ScR). We plan to search the following databases: Association of Computing
44 Machinery (ACM) Digital Library, Cumulative Index to Nursing and Allied Health Literature
45 (CINAHL), Embase, Google Scholar, Institute of Electric and Electronic Engineers (IEEE),
46 PubMed, Scopus, and Web of Science. Studies will be included on children >90 days post-natal
47 to <21 years old, predicted to have or be at risk of developing sepsis by a digitalized model or
48 algorithm designed for a clinical setting. Two independent reviewers will complete the abstract
49 and full-text screening and the data extraction. Thematic analysis will be used to develop
50 overarching concepts and present the narrative findings with quantitative results and descriptive
51 statistics displayed in data tables.

52
53 **Ethics and dissemination** Ethics approval for this scoping review study of the available
54 literature is not required. We anticipate that the scoping review will identify the current evidence

1
2
3 55 and design characteristics of digital prediction technologies for the timely and accurate
4
5 56 prediction of paediatric sepsis and factors influencing clinical integration. We plan to
6
7 57 disseminate the preliminary findings from this review at national and international research
8
9 58 conferences in global and digital health, gathering critical feedback from multi-disciplinary
10
11 59 stakeholders.
12
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15
16

17 61 **Scoping review registration**

18
19 62 https://osf.io/nh6qz/?view_only=8c840412a2a44117ac16fdf76e06abd6
20
21
22
23

24 64 **Strengths and limitations of this study**

- 25
26 65 • This review is a rigorous approach to collectively synthesizing current research on
27
28 66 automated paediatric sepsis prediction technologies, critically examining the relationships
29
30 67 between their design, performance, and clinical integration to identify sociotechnical
31
32 68 challenges and research gaps.
33
34
35 69 • The chosen review strategy will comprehensively evaluate the vast literature across
36
37 70 various study types and research disciplines by a multi-disciplinary research team.
38
39
40 71 • The review will exclude digital prediction technologies for paediatric sepsis treatment
41
42 72 decisions and is limited to peer-reviewed literature written in the English language with a
43
44 73 full-text version available.
45
46
47 74 • Articles focusing on age cohorts <90 days post-natal or >21 years old will be excluded
48
49 75 due to significant differences in sepsis etiology and clinical presentation.
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76 INTRODUCTION

77 Globally, it is estimated there were a total of 25.2 million cases of sepsis in children (<19) in
 78 2017, imposing significant health care and societal burden (1). Healthcare costs for severe
 79 paediatric sepsis hospitalizations reached approximately \$7.31 billion in the United States in
 80 2016, accounting for almost 20% of total paediatric hospitalization costs (2). However, about
 81 85% of global sepsis cases and 84.5% of sepsis-related deaths among all age groups occur in
 82 low-middle income countries, specifically those in sub-Saharan Africa and South-East Asia (1).
 83 Annual global mortality rates for children (<5) are approximately 2.9 million (Table 1) (3).

84
 85 Table 1. Differences between global neonatal, paediatric, and adult sepsis (3).

| | Neonatal (<90 days) | Paediatric (<5 y/o) | Adult (>20 y/o) |
|-----------------------------|---------------------|---------------------|-----------------|
| Annual Cases (M) | 1.3 – 3.9 | 20.3 | 23.7 |
| Annual Mortality (M) | 0.4 – 0.7 | 2.9 | 7.7 |

86
 87 Early recognition of sepsis in children is challenging. Unlike adult sepsis, children have
 88 different sepsis aetiologies (3). For example, children commonly develop sepsis from
 89 pneumonia, diarrhea, meningitis, or viral infections, where abdominal or genitourinary sources
 90 are more common in adults (4). Differences in aetiology can also be found between childhood
 91 and neonatal sepsis, with early-onset neonatal sepsis having a distinct microbial pattern (5).
 92 Recognizing sepsis in children is also significantly more challenging due to maturation-based
 93 differences in physiology (including immune system response), limitations in the communication
 94 of symptoms, and diagnostic modalities (4,6,7). Sepsis can lead to life-altering organ dysfunction
 95 if not identified quickly in children (8), where mortality rates are reduced two-fold if treated
 96 within the first hour (4). Recognition of sepsis is confounded by the age-based symptom
 97 variations within children, such as their differences in blood pressure response, serum lactate

1
2
3 98 levels (4), and commonalities among other childhood conditions and syndromes like Kawasaki
4
5 99 syndrome or bronchiolitis (9). This milieu of complex information combined with significant
6
7
8 100 time pressure provides a significant cognitive burden for healthcare professionals to promptly
9
10 101 identify the onset of deterioration that can lead to this serious medical condition.

12 102 In 2020, updated Paediatric Sepsis Survival guidelines were published calling for the
13
14 103 integration of screening standards in healthcare facilities to support rapid identification of sepsis
15
16 104 in children (10) and provide the appropriate antimicrobial therapy at the proper time (5,10).
17
18 105 Established screening tools such as the Paediatric Early Warning Score (PEWS) may support the
19
20 106 timeliness of detecting clinical deterioration in children that can lead to sepsis (11). Recently,
21
22 107 adaptations to the Sequential Organ Assessment Score (SOFA) for paediatric patients (pSOFA)
23
24 108 and neonates (nSOFA) have shown promise in identifying children at risk for mortality with
25
26 109 sepsis (12); however, it is controversial whether these scores provide value in low-resource
27
28 110 environments (13–15). Development and implementation of algorithms such as the Sepsis
29
30 111 Prediction and Optimization Therapy (SPOT) that can analyze electronic health data in real-time
31
32 112 to provide a rule-based approach to initiate a physical sepsis screen have also been reported (16).
33
34 113 With the call from the World Health Organization to improve sepsis identification and the
35
36 114 potential for data-driven and knowledge-based technologies (3,17), digital prediction
37
38 115 technologies are becoming more advanced using mathematical, statistical, and machine learning
39
40 116 techniques to support sepsis prediction utilizing clinical information, symptoms, biomarkers, and
41
42 117 other signs at the bedside (18–21). While recent reviews have explored the literature on the
43
44 118 effectiveness of digital technologies for adult and neonate sepsis prediction (18,19,22–26), there
45
46 119 is currently no review on the design and implementation of these predictive technologies for
47
48 120 children. Considering the pathophysiology and aetiology for paediatric sepsis are different from
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3 121 that seen in adults and neonates (27), combined with the lack of widely accessible digital
4
5 122 technologies for children compared to adults (28), it is critically important to review the
6
7
8 123 literature on this age cohort.
9

10 124

12 125 **Prior reviews on sepsis prediction technologies**

14
15 126 Recent narrative reviews discuss machine learning-based technologies for adult and paediatric
16
17 127 sepsis (20,29,30). However, their eligibility criteria focus primarily on adults, with only two (20)
18
19 128 or three (29) articles on children. Some reviews excluded digital technologies that were not
20
21 129 based on “modern” machine learning models (21,30), or involved a broad search on infectious
22
23 130 disease prediction beyond sepsis (29). Others have also limited their investigations to
24
25
26 131 PubMed/Medline, excluding engineering databases, which may provide greater insight into the
27
28 132 design characteristics of digital technologies (20,26,31–33), or they focus exclusively on US
29
30
31 133 hospitals (33).
32

33 134 Many systematic and scoping reviews have been rigorous in their search strategy but
34
35 135 similar to the identified narrative reviews, report on screening tools and technologies for adult
36
37 136 patients while excluding children (24,25,28,34–37), and the engineering disciplines (19,23,38–
38
39 137 40). Currently published protocols plan to exclude literature on the application of machine
40
41
42 138 learning (39,41), which may not capture research on certain relevant technologies. While there
43
44
45 139 have been systematic reviews on the performance of neonatal sepsis prediction and recognition
46
47 140 technologies providing insight into their capabilities (19,23), none focus on the specifics of
48
49 141 paediatric sepsis.
50

51 142 Current systematic reviews that include the paediatric literature as part of their search
52
53
54 143 strategy are not strictly focused on this patient population (22,28,38), having only identified one
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1
2
3 144 (38) or three (22,28) related articles specific to children. Other reviews broadly examine early
4
5 145 warning systems for paediatric clinical deterioration (42,43). We have not identified any
6
7
8 146 systematic or scoping reviews that accurately scope the literature on digital paediatric sepsis
9
10 147 prediction technology. While one identified protocol aims to capture strategies for early
11
12 148 recognition of paediatric sepsis from clinical deterioration, the focus of the review is general
13
14
15 149 strategy effectiveness and does not explicitly include engineering databases which would
16
17 150 describe technical design aspects (40).
18

19 151

21 152 **Purpose of the study**

23
24 153 Given the limitations of recent literature reviews and the lack of reviews focused on paediatric
25
26 154 sepsis, it is necessary to synthesize the current research describing the development and
27
28 155 evaluation of automated sepsis prediction technologies for this underrepresented age cohort. The
29
30 156 scoping review defined by this protocol will identify and summarize the existing literature on the
31
32
33 157 design characteristics, performance, and integration of automated sepsis prediction technologies
34
35 158 in paediatric contexts. The scoping review, a methodology focusing on answering broader
36
37
38 159 research questions through a systematic search and presenting tabular findings along with a
39
40 160 narrative integration (44), was identified as the best approach for this study. We anticipate that
41
42 161 the rigorous methodology will warrant a meaningful summary about the current development of
43
44
45 162 digital technologies for sepsis prediction that can inform future research toward improving their
46
47 163 performance and evidence-based clinical implementation to ultimately improve the lives of
48
49 164 children globally.
50

51 165

54 166 **METHODS AND ANALYSIS**

1
2
3 167 The reviewers on this scoping review consist of a multi-disciplinary team of engineers, a health
4
5 168 researcher/biomedical engineering research librarian, a psychology student, and a paediatric
6
7 169 clinician. Our methodology will be guided by the framework developed by Arksey and O'Mally
8
9
10 170 (44), which iterates through six steps: (i) identifying the research questions; (ii) searching for
11
12 171 relevant studies; (iii) selecting the studies; (iv) charting the data; (v) collating, summarizing, and
13
14 172 reporting the results; and (vi) consulting with stakeholders to inform or validate findings. The
15
16 173 sixth step is optional, and we will modify this step to consult with experts specifically around
17
18 174 finding technologies used in hospital or industry settings. Levac's recommendations for
19
20 175 independent full-text reviews by at least two reviewers will also be followed (45). This study
21
22 176 protocol will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
23
24 177 extension for a scoping review (PRISMA-ScR) (46) with any gaps being filled by the Preferred
25
26 178 Reporting Items for Systematic Reviews and Meta-Analyses extension for protocols (PRISMA-
27
28 179 P) [see Additional file 1]. This protocol has been registered on the Open Science Framework
29
30
31 180 (https://osf.io/nh6qz/?view_only=8c840412a2a44117ac16fdf76e06abd6).
32
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38 **Step 1: identifying the research questions**

39
40 183 The research questions were developed through an initial search of the literature on automated
41
42 184 digital technologies for paediatric sepsis recognition and gaps identified in current systematic
43
44 185 and narrative reviews in the neonatal and adult context. The Joanna Briggs Institute
45
46 186 recommendations of the Population, Concept, and Context model were followed (47),
47
48 187 maintaining a broad scope for understanding the existing evidence on paediatric sepsis prediction
49
50 188 technologies with respect to their current performance, identified outcome measures, and
51
52
53 189 existing research gaps:
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- 1
2
3 190 1. How do the design characteristics of automated paediatric sepsis prediction technologies
4
5 191 for healthcare facilities (e.g., the recognition task, type, method, demographics, and
6
7 192 indicators) influence their performance?
8
9
10 193 2. What are the impacts of clinically implemented automated paediatric sepsis prediction
11
12 194 technologies on decision-making and patient outcome measures?
13
14 195 3. What challenges and research gaps (e.g., evidence, practical knowledge, population,
15
16 196 theoretical, methodological) exist for improving the sociotechnical integration of
17
18 197 knowledge-based algorithms and data-driven models for predicting paediatric sepsis in
19
20 198 healthcare facilities?
21
22
23
24 199

25
26 200 **Step 2: identifying relevant studies**

27
28 201 We will conduct a comprehensive scoping review that includes a multi-disciplinary group of
29
30 202 scholarly databases: Association of Computing Machinery (ACM) Digital Library, Cumulative
31
32 203 Index to Nursing and Allied Health Literature (CINAHL), Embase, Google Scholar, Institute of
33
34 204 Electric and Electronic Engineers (IEEE), PubMed, Scopus, and Web of Science. Articles will
35
36 205 further be identified using the snowballing technique (48), to identify relevant literature among
37
38 206 the references and citations of articles included for the full review. We will also hand-search for
39
40 207 reports on the design, validation, and implementation of commercial digital technologies for
41
42 208 sepsis prediction, which may be approved by governing bodies such as Health Canada (health-
43
44 209 products.canada.ca/mdall-limh/), the Food and Drug Administration
45
46 210 (accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/textsearch.cfm), and the European Union Medical
47
48 211 Device Regulation (ec.europa.eu/tools/eudamed/#/screen/home).

212 Guided by a University of Waterloo biomedical engineering research librarian, we
 213 developed a comprehensive search strategy for each database. The approach employs keywords,
 214 medical subject headings (MeSH), key concept subject headings, and Boolean terms broken
 215 down into the following parts: the recognition algorithm or model, type of digital technology,
 216 health condition, alert type, implementation or validation factors, and patient population. A
 217 sample search strategy for PubMed is presented in Table 2.

218 Table 2. Sample search strategy and results.

| Database | Search Terms | Results | Date |
|---------------|---|---------|------------|
| PubMed | ("decision support"[All Fields] OR "decision-support"[All Fields] OR "early warning score"[MeSH Terms] OR "early warning score"[All Fields] OR "smart system*"[All Fields] OR "electronic alert*"[All Fields] OR "artificial intelligence"[All Fields] OR "artificial intelligence"[MeSH Terms] "machine learning"[All Fields] OR "deep learning"[All Fields] OR "neural network*"[All Fields] OR "support vector machine"[All Fields] OR "hidden markov model"[All Fields] OR "statistical learning"[All Fields] OR "predictive function"[All Fields] OR "algorithm"[All Fields] OR "algorithms"[MeSH Terms] OR "automat*"[All Fields] OR "comput*"[All Fields] OR "decision making, computer assisted"[MeSH Terms] OR "electronic*"[All Fields] OR "representation learning"[All Fields] OR "conformal prediction"[All Fields] OR "random forest"[All Fields] OR "naïve bayes"[All Fields] OR "regression" OR "regression analysis"[MeSH Terms] OR "gradient boosting"[All Fields] OR "artificial learning"[All Fields] OR "machine intelligence"[All Fields] OR "probabilistic network*"[All Fields] OR "knowledge representation"[All Fields] OR "bayesian learning"[All Fields] OR "expert system*"[All Fields] OR "technology assisted"[All Fields] OR "computer assisted"[All Fields] OR "statistical"[All Fields] OR "mathematical"[All Fields]) AND ("system"[All Fields] OR "tool"[All Fields] OR "alert*"[All Fields] OR "technology"[All Fields] OR "software"[All Fields] OR "model*"[All Fields] OR "engine"[All Fields] OR "approach*"[All Fields] OR "algorithm"[All Fields] OR "platform"[All Fields] OR "method*"[All Fields] OR "scor*"[All Fields] OR "device"[All Fields]) AND (| 15,531 | 02/15/2022 |

"sepsis"[All Fields] OR "sepsis"[MeSH Terms] OR "septic shock"[All Fields] OR "systemic inflammatory response syndrome"[All Fields] OR "acute deterioration"[All Fields] OR "patient deterioration"[All Fields] OR "clinical deterioration"[MeSH Terms] OR "clinical deterioration"[All Fields] OR "severe infection"[All Fields] OR "severe bacterial infection"[All Fields] OR "bacterial infections"[MeSH Terms] OR "febrile illness"[All Fields] OR "non-malarial febrile illness"[All Fields] OR "bacteremia"[All Fields]) AND ("diagnos*"[All Fields] OR "detect*"[All Fields] OR "predict*"[All Fields] OR "prognosticate"[All Fields] OR "identif*"[All Fields] OR "infer*"[All Fields] OR "warn*"[All Fields] OR "alert*"[All Fields] OR "recog*"[All Fields] OR "screen*"[All Fields] OR "monitor*"[All Fields] OR "assess*"[All Fields] OR "surveillance"[All Fields] OR "classif*"[All Fields]) AND ("evaluat*"[All Fields] OR "implement*"[All Fields] OR "perform*"[All Fields] OR "design"[All Fields] OR "validat*"[All Fields] OR "usability"[All Fields] OR "effectiveness"[All Fields] OR "efficiency"[All Fields] OR "satisfaction"[All Fields] OR "safety"[All Fields] OR "acceptance"[All Fields] OR "clinical value"[All Fields] OR "interpret*"[All Fields] OR "perception"[All Fields] OR "perspective"[All Fields] OR "opinion"[All Fields] OR "error"[All Fields]) AND ("child*"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields] OR "pediatrics"[MeSH Terms] OR "toddler*"[All Fields] OR "teen*"[All Fields] OR "youth*"[All Fields] OR "adolescenc*"[All Fields] OR "adolescent"[MeSH Terms] OR "infan*"[All Fields] OR "infant"[MeSH Terms] OR "school age*"[All Fields] OR "PICU"[All Fields]) LIMIT TO: [Text Availability]: Full text, [Language]: English, [Species]: Human

219
 220 The search results will be imported to Mendeley's reference management software for
 221 future referencing and organization (Mendeley Ltd.). A systematic review management software,
 222 Covidence (Veritas Health Innovation Ltd.), will be used to identify and merge duplicate articles.
 223 A sample of 20 abstracts will be initially screened by two reviewers (RT and JG), ensuring the
 224 inclusion-exclusion requirements are robust in capturing relevant articles related to the design
 225 and evaluation of automated prediction technologies for paediatric sepsis. Both reviewers will

226 also ensure that the data extraction items capture valuable and appropriate study details from the
227 articles included in the full-text review, which will be shared with the research team.

228

229 **Step 3: study selection**

230 *Inclusion criteria*

231 The proposed review will include articles that meet the following inclusion criteria:

- 232 • The article is about an automated data-driven or knowledge-based approach toward
233 paediatric sepsis prediction in a healthcare setting, including sepsis, severe sepsis, and
234 septic shock.
- 235 • The digital technology is evaluated for its performance through validation testing,
236 experiments, or an observational study.
- 237 • Following the American Academy of Pediatrics' definition for late adolescence, more
238 than the majority of data reported will include children aged >90 days post-natal to <21
239 years old (49).
- 240 • The article is written in English.
- 241 • The article is a peer-reviewed journal article, full conference proceeding, or research
242 published on a commercially available digital technology which may be approved by a
243 medical device regulatory body.
- 244 • There is no specification for publication years.

245

246 *Exclusion Criteria*

247 Screened articles that fit within the following categories will be excluded from this review:

248 Commentaries, dissertations, editorials, books and book chapters, lectures and addresses, study

1
2
3 249 protocols, review articles, and articles inaccessible for full-text review after utilizing library
4
5 250 resources. Cohort studies where paediatric sepsis has already been clinically identified, such as
6
7
8 251 articles describing prediction technologies for subsequent sepsis treatment or mortality risk, are
9
10 252 outside the scope of this review if predicting sepsis, severe sepsis or septic shock is not a facet of
11
12 253 the technology. Also, digital technologies developed for at-home use are also outside the scope
13
14
15 254 of this review, as the context of the protocol is to review the evidence on automated sepsis
16
17 255 prediction technologies in regulated healthcare settings.
18
19
20 256

21 257 *Selection process*

22
23
24 258 This review will follow the reporting checklist in the Preferred Reporting Items for Systematic
25
26 259 reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR), provided by Tricco
27
28 260 et al. (46). First, all relevant articles will be imported into Covidence. Second, two reviewers (RT
29
30
31 261 and JG) will independently perform the title and abstract screening using the developed
32
33 262 eligibility criteria by classifying them as “Yes,” “No,” or “Maybe.” Any article classified as
34
35 263 “Yes” or “Maybe” by RT or JG will be included in the full-text review during this stage by
36
37
38 264 adding them to an Excel spreadsheet for access by all authors. If a full-text article cannot be
39
40 265 accessed, the reviewers will seek assistance from library services at the institution or directly
41
42 266 contact the article’s corresponding author. Third, two investigators (RT and JG) will
43
44
45 267 independently perform the full-text screening for eligibility using the listed inclusion-exclusion
46
47 268 criteria. A third member of the research team will resolve any disagreements on eligibility that
48
49 269 occur during the full-text review. After the full-text review, an inter-rater agreement will be
50
51 270 calculated using Cohen’s kappa coefficient (κ) statistic.
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1
2
3 271 The first step in identifying relevant studies was performed on February 15, 2022. The
4
5 272 planned end date for completing the full-text screening and analysis is December 30th, 2022. We
6
7
8 273 have maintained search alerts for potentially eligible articles to ensure our review remains
9
10 274 updated before dissemination through publication.
11

12 275

14 276 **Step 4: charting the data**

16
17 277 The data extraction form will be developed in Covidence and exported to Excel to capture the
18
19 278 relevant information from each article. Two reviewers (RT, JG) will individually extract the
20
21 279 relevant data from a sample of eligible articles screened for inclusion in the full-text review to
22
23 280 ensure consistency of recording data. Any disagreements on extracted data will be resolved
24
25 281 through discussion between the reviewers. The form will be iteratively updated until the authors
26
27 282 reach a consensus on the relevant data to extract. We will begin by pulling the following type of
28
29
30 283 data into the form, with additional data included as we screen more articles:

- 31
32
33 284 • Article information: author(s), year published, city, country, discipline(s).
34
35 285 • Prediction task: the definition of sepsis being identified and the use context for
36
37 286 recognition in paediatrics.
38
39
40 287 • Prediction task type:
41
42 288 ○ Alerting automation that provides a notification that a patient has met the
43
44 289 objective sepsis recognition criteria.
45
46 290 ○ Decision support automation that provides assistance in the diagnosis of sepsis.
47
48 291 ○ Data automation that collects clinically relevant cues and information on behalf of
49
50 292 the user(s), which may be used in combination with alerting and decision support.
51
52
53 293 • Prediction method:

- 294 ○ Data-driven methods that use retrospective datasets to build a statistical or
- 295 machine learning-based model.
- 296 ○ Knowledge-based methods that use consensus criteria to build an algorithm with
- 297 threshold-based criteria.
- 298 ● Participant demographics: age cohort, number of participants.
- 299 ● Prediction indicators: vital signs, biomarkers, socio-demographics, treatment, medical
- 300 history.
- 301 ● Prediction interface: audible alert, dialog box, provided information
- 302 ● Validation measures:
 - 303 ○ Reported number of true positives, false positives, and false negatives.
 - 304 ○ Reported sensitivity and specificity.
 - 305 ○ Time to accurate sepsis recognition by the technology and/or the clinician.
 - 306 ○ Measured or expected impact on clinical decisions and patient outcomes.
 - 307 ○ Generalizability of the digital technology in the context of bias, fairness, and
 - 308 appropriateness (50,51).

310 **Step 5: collating, summarizing, and reporting the results**

311 The extracted data will be synthesized within tables that summarize the current digital
312 technology landscape in predicting paediatric sepsis, including characteristics that describe their
313 performance and the sociotechnical factors of their integration by health care providers on
314 patient outcomes. Within summary tables, we will present the current approaches toward model
315 and algorithm development for automated sepsis prediction technologies, including the
316 predictive indicators, the prediction timing objective, and how they interface with clinicians.

1
2
3 317 Quantitative performance and implementation measures such as sensitivity and specificity, and
4
5 318 the impacts on intervention timing will also be reported in data tables, including calculations of
6
7 319 precision, recall, and F1 score, when possible.
8
9

10 320 We will then perform a thematic analysis to identify concepts related to our research
11
12 321 questions. This analysis will be presented as a narrative, including an organization of themes on
13
14 322 the identified design characteristics of automated prediction technologies integrated within
15
16 323 clinical contexts. The purpose of the analysis will be to identify the types of research gaps that
17
18 324 exist for knowledge-based algorithms and data-driven models to improve sociotechnical
19
20 325 integration (i.e., supporting clinical decision-making) and patient outcomes. Challenges with
21
22 326 bias, fairness, and appropriateness will also be qualitatively examined with respect to potential
23
24 327 generalizability barriers. Diagrams will be developed for the identified relationships and themes
25
26 328 among the design characteristics of the automated technologies for paediatric sepsis prediction
27
28 329 and their influence on system performance and implementation throughout time to visually
29
30 330 highlight the opportunities for future investigations.
31
32
33
34

35 331

36 332 **Step 6: methodological quality appraisal**

37
38 333 We will consult with experts in automated paediatric sepsis prediction technologies for this
39
40 334 review to identify those applied in clinical settings. While critical appraisal of the identified
41
42 335 articles is not mandatory in the scoping review methodology, we will consult with stakeholders
43
44 336 to inform and validate our findings.
45
46
47
48

49 337

50 338 **Patient and public involvement**

51
52 339 There were no patients or public involvement in the development of this protocol.
53
54
55
56
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58

340

341 ETHICS AND DISSEMINATION

342 Approval from an ethics review committee is not required for this study because it is a scoping
343 review of previously published literature. Once the review is completed, we plan to disseminate
344 the preliminary findings at national and international research conferences in global and digital
345 health to gather critical feedback from researchers and the public. The finalized results from the
346 review will be submitted for publication in an open access peer-reviewed journal.

347

348 DISCUSSION

349 This scoping review will provide a comprehensive and structured understanding of the
350 automated digital technologies that have been developed to support the timely prediction of
351 paediatric sepsis. At a high-level, the results will focus on design characteristics, performance
352 validation, and current sociotechnical integration factors, which will be analyzed thematically
353 and reported in data summary tables, indicating how the development of these technologies is
354 evolving throughout time. It is anticipated that the outcomes will reveal the current challenges in
355 developing and implementing clinically meaningful digital prediction technologies for paediatric
356 sepsis across various clinical environments. Furthermore, the results are expected to identify
357 critical research aspects requiring further investigation.

358 Compared to previous articles, this scoping review focuses on the complexities of
359 paediatric sepsis, with a methodological strength in taking a comprehensive and systematic
360 approach that will provide an overview of the evidence in this digital technology landscape.
361 Inherent in the approach of a scoping review is the limitation of its objective: to summarize the
362 literature and identify meaningful gaps for further research. As this study will include articles

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3 363 with various study designs, it does not aim to answer specific questions about recommending the
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5 364 use or application of certain sepsis prediction technologies for paediatrics. With the results of the
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7 365 pilot search (Table 2), this review is also limited in its scope, where non-English articles or
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9 366 articles without a full-text version will not be included. Finally, digital technologies informing
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11 367 treatment strategies for sepsis and studies looking at age cohorts <90 days post-natal or >21
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13 368 years old will be excluded because of significant differences in sepsis etiology and clinical
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15 369 presentation, while capturing literature from geographic areas that provide paediatric healthcare
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17 370 services to this age range. We plan to adequately convey the overall strengths and limitations
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19 371 once the full-text review is completed, including any deviations from the protocol, in the final
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21 372 review.
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26 373 In conclusion, by mapping the attributes of paediatric sepsis prediction technologies to
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28 374 outcomes related to clinical integration and performance, we anticipate that our results will
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30 375 highlight critical research gaps among the medical, engineering, and computer science
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32 376 disciplines. The results may inform research on identifying relevant predictive indicators best
33
34 377 suited for the design of digital technologies in specific use contexts and environments,
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36 378 improvements towards model development for sepsis prediction, and factors supporting the
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38 379 optimal workflow integration of digital prediction systems by clinicians. Ultimately, this review
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40 380 will be critical for advancing knowledge to improve sepsis prediction for children globally.
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46 382 **List of abbreviations**

47 383 ACM: Association of Computing Machinery

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49 384 CINAHL: Cumulative Index to Nursing and Allied Health Literature

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51 385 IEEE: Institute of Electric and Electronic Engineers
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3 386 nSOFA: neonatal Sequential Organ Assessment Score

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5 387 PEWS: Paediatric Early Warning Score

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7 388 PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for

8
9 389 protocols

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11 390 PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis extension

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13 391 for scoping reviews

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15 392 pSOFA: paediatric Sequential Organ Assessment Score

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17 393 SOFA: Sequential Organ Assessment Score

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19 394 SPOT: Sepsis Prediction and Optimization Therapy

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26 396 **Author contributions**

27
28 397 RT, JG, KM, CMB, and JMA contributed to the development of this manuscript. RT is the

29
30 398 guarantor of the review, conceptualized the research questions and methods, and drafted the

31
32 399 initial manuscript. All authors contributed to the development of the search strategy, selection

33
34 400 criteria, and data extraction template. JMA provided expertise on paediatric sepsis and search

35
36 401 terms. All authors critically reviewed the protocol for intellectual content, subsequently revised it

37
38 402 for publication, and read and approved the final version for submission.

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44 404 **Availability of data and materials**

45
46 405 Not applicable.

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51 407 **Funding statement**

52
53 408 Not applicable.

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5 410 **Competing interests statement**
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7
8 411 The authors declare that they have no competing interests.
9

10 412
11

12 413 **Acknowledgements**
13

14 414 RT is supported by an Engineering Excellence Doctoral Fellowship from the University of
15

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17 415 Waterloo Faculty of Engineering.
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PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted – Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|-----------------------------------|----|---|-------------------------------------|-------------------------------------|----------------|
| | | | Yes | No | |
| ADMINISTRATIVE INFORMATION | | | | | |
| Title | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| Registration | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 62, 180 |
| Authors | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 4-29 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 396-401 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| Support | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 414-415 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 408, 414-415 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 408, 414-415 |
| INTRODUCTION | | | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 87-164 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|------------------------------------|-----|---|-------------------------------------|-------------------------------------|------------------|
| | | | Yes | No | |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 183-198 |
| METHODS | | | | | |
| Eligibility criteria | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 230-255 |
| Information sources | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 201-211 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 218-219, 231-255 |
| STUDY RECORDS | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 220-227, 260-264 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 260-274 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 220-227, 231-255 |
| Data items | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 277-308 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| DATA | | | | | |
| Synthesis | 15a | Describe criteria under which study data will be quantitatively synthesized | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 311-319 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 320-330 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|--|----|---|-------------------------------------|-------------------------------------|----------------|
| | | | Yes | No | |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 333-336 |

For peer review only

BMJ Open

Automated digital technologies for supporting sepsis prediction in children: A scoping review protocol

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2022-065429.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 02-Nov-2022 |
| Complete List of Authors: | Tennant, Ryan; University of Waterloo Faculty of Engineering, Department of Systems Design Engineering Graham, Jennifer; University of Waterloo Faculty of Arts, Department of Psychology Mercer, Kate; University of Waterloo Faculty of Engineering, Department of Systems Design Engineering; University of Waterloo, Library Ansermino, J. Mark; The University of British Columbia, Department of Anesthesiology Burns, Catherine; University of Waterloo Faculty of Engineering, Department of Systems Design Engineering |
| Primary Subject Heading: | Health informatics |
| Secondary Subject Heading: | Paediatrics, Research methods |
| Keywords: | PAEDIATRICS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Paediatric intensive & critical care < PAEDIATRICS |
| | |

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Manuscripts

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3 1 **Automated digital technologies for supporting sepsis prediction in children: A scoping**
4 **review protocol**
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55 31 **Word Count:** 3217
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32 **ABSTRACT**

33 **Introduction** While there have been several literature reviews on the performance of digital
34 sepsis prediction technologies and clinical decision-support algorithms for adults, there remains a
35 knowledge gap in examining the development of automated technologies for sepsis prediction in
36 children. This scoping review will critically analyze the current evidence on the design and
37 performance of automated digital technologies to predict paediatric sepsis, to advance their
38 development and integration within clinical settings.

39
40 **Methods and analysis** This scoping review will follow Arksey and O'Malley's framework,
41 conducted between February to December 2022. We will further develop the protocol using the
42 Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping
43 reviews (PRISMA-ScR). We plan to search the following databases: Association of Computing
44 Machinery (ACM) Digital Library, Cumulative Index to Nursing and Allied Health Literature
45 (CINAHL), Embase, Google Scholar, Institute of Electric and Electronic Engineers (IEEE),
46 PubMed, Scopus, and Web of Science. Studies will be included on children >90 days post-natal
47 to <21 years old, predicted to have or be at risk of developing sepsis by a digitalized model or
48 algorithm designed for a clinical setting. Two independent reviewers will complete the abstract
49 and full-text screening and the data extraction. Thematic analysis will be used to develop
50 overarching concepts and present the narrative findings with quantitative results and descriptive
51 statistics displayed in data tables.

52
53 **Ethics and dissemination** Ethics approval for this scoping review study of the available
54 literature is not required. We anticipate that the scoping review will identify the current evidence

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2
3 55 and design characteristics of digital prediction technologies for the timely and accurate
4
5 56 prediction of paediatric sepsis and factors influencing clinical integration. We plan to
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7 57 disseminate the preliminary findings from this review at national and international research
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9 58 conferences in global and digital health, gathering critical feedback from multi-disciplinary
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11 59 stakeholders.
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17 61 **Scoping review registration**

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19 62 https://osf.io/veqha/?view_only=f560d4892d7c459ea4cff6dcdfacb086
20
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22 63

23 64 **Strengths and limitations of this study**

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26 65 • This review is a rigorous approach to collectively synthesizing current research on
27
28 66 automated paediatric sepsis prediction technologies, critically examining the relationships
29
30 67 between their design, performance, and clinical integration to identify sociotechnical
31
32 68 challenges and research gaps.
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34
35 69 • The chosen review strategy will comprehensively evaluate the vast literature across
36
37 70 various study types and research disciplines by a multi-disciplinary research team.
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40 71 • The review will exclude digital prediction technologies for paediatric sepsis treatment
41
42 72 decisions and is limited to peer-reviewed literature written in the English language with a
43
44 73 full-text version available.
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47 74 • Articles focusing on age cohorts <90 days post-natal or >21 years old will be excluded
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49 75 due to significant differences in sepsis etiology and clinical presentation.
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76 INTRODUCTION

77 Globally, it is estimated there were a total of 25.2 million cases of sepsis in children (<19) in
 78 2017, imposing significant health care and societal burden (1). Healthcare costs for severe
 79 paediatric sepsis hospitalizations reached approximately \$7.31 billion in the United States in
 80 2016, accounting for almost 20% of total paediatric hospitalization costs (2). However, about
 81 85% of global sepsis cases and 84.5% of sepsis-related deaths among all age groups occur in
 82 low-middle income countries, specifically those in sub-Saharan Africa and South-East Asia (1).
 83 Annual global mortality rates for children (<5) are approximately 2.9 million (Table 1) (3).

84
 85 Table 1. Differences between global neonatal, paediatric, and adult sepsis (3).

| | Neonatal (<90 days) | Paediatric (<5 y/o) | Adult (>20 y/o) |
|-----------------------------|---------------------|---------------------|-----------------|
| Annual Cases (M) | 1.3 – 3.9 | 20.3 | 23.7 |
| Annual Mortality (M) | 0.4 – 0.7 | 2.9 | 7.7 |

86
 87 Early recognition of sepsis in children is challenging. Unlike adult sepsis, children have
 88 different sepsis aetiologies (3). For example, children commonly develop sepsis from
 89 pneumonia, diarrhea, meningitis, or viral infections, where abdominal or genitourinary sources
 90 are more common in adults (4). Differences in aetiology can also be found between childhood
 91 and neonatal sepsis, with early-onset neonatal sepsis having a distinct microbial pattern (5).
 92 Recognizing sepsis in children is also significantly more challenging due to maturation-based
 93 differences in physiology (including immune system response), limitations in the communication
 94 of symptoms, and diagnostic modalities (4,6,7). Sepsis can lead to life-altering organ dysfunction
 95 if not identified quickly in children (8), where mortality rates are reduced two-fold if treated
 96 within the first hour (4). Recognition of sepsis is confounded by the age-based symptom
 97 variations within children, such as their differences in blood pressure response, serum lactate

1
2
3 98 levels (4), and commonalities among other childhood conditions and syndromes like Kawasaki
4
5 99 syndrome or bronchiolitis (9). This milieu of complex information combined with significant
6
7
8 100 time pressure provides a significant cognitive burden for healthcare professionals to promptly
9
10 101 identify the onset of deterioration that can lead to this serious medical condition.

12 102 In 2020, updated Paediatric Sepsis Survival guidelines were published calling for the
13
14 103 integration of screening standards in healthcare facilities to support rapid identification of sepsis
15
16 104 in children (10) and provide the appropriate antimicrobial therapy at the proper time (5,10).
17
18 105 Established screening tools such as the Paediatric Early Warning Score (PEWS) may support the
19
20 106 timeliness of detecting clinical deterioration in children that can lead to sepsis (11). Recently,
21
22 107 adaptations to the Sequential Organ Assessment Score (SOFA) for paediatric patients (pSOFA)
23
24 108 and neonates (nSOFA) have shown promise in identifying children at risk for mortality with
25
26 109 sepsis (12); however, it is controversial whether these scores provide value in low-resource
27
28 110 environments (13–15). Development and implementation of algorithms such as the Sepsis
29
30 111 Prediction and Optimization Therapy (SPOT) that can analyze electronic health data in real-time
31
32 112 to provide a rule-based approach to initiate a physical sepsis screen have also been reported (16).
33
34 113 With the call from the World Health Organization to improve sepsis identification and the
35
36 114 potential for data-driven and knowledge-based technologies (3,17), digital prediction
37
38 115 technologies are becoming more advanced using mathematical, statistical, and machine learning
39
40 116 techniques to support sepsis prediction utilizing clinical information, symptoms, biomarkers, and
41
42 117 other signs at the bedside (18–21). While recent reviews have explored the literature on the
43
44 118 effectiveness of digital technologies for adult and neonate sepsis prediction (18,19,22–26), there
45
46 119 is currently no review on the design and implementation of these predictive technologies for
47
48 120 children. Considering the pathophysiology and aetiology for paediatric sepsis are different from
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3 121 that seen in adults and neonates (27), combined with the lack of widely accessible digital
4
5 122 technologies for children compared to adults (28), it is critically important to review the
6
7
8 123 literature on this age cohort.
9

10 124

12 125 **Prior reviews on sepsis prediction technologies**

14
15 126 Recent narrative reviews discuss machine learning-based technologies for adult and paediatric
16
17 127 sepsis (20,29,30). However, their eligibility criteria focus primarily on adults, with only two (20)
18
19 128 or three (29) articles on children. Some reviews excluded digital technologies that were not
20
21 129 based on “modern” machine learning models (21,30), or involved a broad search on infectious
22
23 130 disease prediction beyond sepsis (29). Others have also limited their investigations to
24
25 131 PubMed/Medline, excluding engineering databases, which may provide greater insight into the
26
27 132 design characteristics of digital technologies (20,26,31–33), or they focus exclusively on US
28
29 133 hospitals (33).
30
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32

33 134 Many systematic and scoping reviews have been rigorous in their search strategy but
34
35 135 similar to the identified narrative reviews, report on screening tools and technologies for adult
36
37 136 patients while excluding children (24,25,28,34–37), and the engineering disciplines (19,23,38–
38
39 137 40). Currently published protocols plan to exclude literature on the application of machine
40
41 138 learning (39,41), which may not capture research on certain relevant technologies. While there
42
43 139 have been systematic reviews on the performance of neonatal sepsis prediction and recognition
44
45 140 technologies providing insight into their capabilities (19,23), none focus on the specifics of
46
47 141 paediatric sepsis.
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51 142 Current systematic reviews that include the paediatric literature as part of their search
52
53 143 strategy are not strictly focused on this patient population (22,28,38), having only identified one
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3 144 (38) or three (22,28) related articles specific to children. Other reviews broadly examine early
4
5 145 warning systems for paediatric clinical deterioration (42,43). We have not identified any
6
7
8 146 systematic or scoping reviews that accurately scope the literature on digital paediatric sepsis
9
10 147 prediction technology. While one identified protocol aims to capture strategies for early
11
12 148 recognition of paediatric sepsis from clinical deterioration, the focus of the review is general
13
14
15 149 strategy effectiveness and does not explicitly include engineering databases which would
16
17 150 describe technical design aspects (40).
18

19 151

21 152 **Purpose of the study**

23
24 153 Given the limitations of recent literature reviews and the lack of reviews focused on paediatric
25
26 154 sepsis, it is necessary to synthesize the current research describing the development and
27
28 155 evaluation of automated sepsis prediction technologies for this underrepresented age cohort. The
29
30 156 scoping review defined by this protocol will identify and summarize the existing literature on the
31
32
33 157 design characteristics, performance, and integration of automated sepsis prediction technologies
34
35 158 in paediatric contexts. The scoping review, a methodology focusing on answering broader
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38 159 research questions through a systematic search and presenting tabular findings along with a
39
40 160 narrative integration (44), was identified as the best approach for this study. We anticipate that
41
42 161 the rigorous methodology will warrant a meaningful summary about the current development of
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45 162 digital technologies for sepsis prediction that can inform future research toward improving their
46
47 163 performance and evidence-based clinical implementation to ultimately improve the lives of
48
49 164 children globally.
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54 166 **METHODS AND ANALYSIS**

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3 167 The reviewers on this scoping review consist of a multi-disciplinary team of engineers, a health
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5 168 researcher/biomedical engineering research librarian, a psychology student, and a paediatric
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7
8 169 clinician. Our methodology will be guided by the framework developed by Arksey and O'Mally
9
10 170 (44), which iterates through six steps: (i) identifying the research questions; (ii) searching for
11
12 171 relevant studies; (iii) selecting the studies; (iv) charting the data; (v) collating, summarizing, and
13
14 172 reporting the results; and (vi) consulting with stakeholders to inform or validate findings. The
15
16 173 sixth step is optional, and we will modify this step to consult with experts specifically around
17
18 174 finding technologies used in hospital or industry settings. Levac's recommendations for
19
20 175 independent full-text reviews by at least two reviewers will also be followed (45). This study
21
22 176 protocol will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
23
24 177 extension for a scoping review (PRISMA-ScR) (46) with any gaps being filled by the Preferred
25
26 178 Reporting Items for Systematic Reviews and Meta-Analyses extension for protocols (PRISMA-
27
28 179 P) (47). This protocol has been registered on the Open Science Framework
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32 180 (https://osf.io/nh6qz/?view_only=8c840412a2a44117ac16fdf76e06abd6).
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38 **Step 1: identifying the research questions**

39
40 183 The research questions were developed through an initial search of the literature on automated
41
42 184 digital technologies for paediatric sepsis recognition and gaps identified in current systematic
43
44 185 and narrative reviews in the neonatal and adult context. The Joanna Briggs Institute
45
46 186 recommendations of the Population, Concept, and Context model were followed (48),
47
48 187 maintaining a broad scope for understanding the existing evidence on paediatric sepsis prediction
49
50 188 technologies with respect to their current performance, identified outcome measures, and
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53 189 existing research gaps:
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- 190 1. How do the design characteristics of automated paediatric sepsis prediction technologies
191 for healthcare facilities (e.g., the recognition task, type, method, demographics, and
192 indicators) influence their performance?
- 193 2. What are the impacts of clinically implemented automated paediatric sepsis prediction
194 technologies on decision-making and patient outcome measures?
- 195 3. What challenges and research gaps (e.g., evidence, practical knowledge, population,
196 theoretical, methodological) exist for improving the sociotechnical integration of
197 knowledge-based algorithms and data-driven models for predicting paediatric sepsis in
198 healthcare facilities?

200 **Step 2: identifying relevant studies**

201 We will conduct a comprehensive scoping review that includes a multi-disciplinary group of
202 scholarly databases: Association of Computing Machinery (ACM) Digital Library, Cumulative
203 Index to Nursing and Allied Health Literature (CINAHL), Embase, Google Scholar, Institute of
204 Electric and Electronic Engineers (IEEE), PubMed, Scopus, and Web of Science. Articles will
205 further be identified using the snowballing technique (49), to identify relevant literature among
206 the references and citations of articles included for the full review. We will also hand-search for
207 reports on the design, validation, and implementation of commercial digital technologies for
208 sepsis prediction, which may be approved by governing bodies such as Health Canada (health-
209 products.canada.ca/mdall-limh/), the Food and Drug Administration
210 (accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/textsearch.cfm), and the European Union Medical
211 Device Regulation (ec.europa.eu/tools/eudamed/#/screen/home).

212 Guided by a University of Waterloo biomedical engineering research librarian, we
 213 developed a comprehensive search strategy for each database. The approach employs keywords,
 214 medical subject headings (MeSH), key concept subject headings, and Boolean terms broken
 215 down into the following parts: the recognition algorithm or model, type of digital technology,
 216 health condition, alert type, implementation or validation factors, and patient population. A
 217 sample search strategy for PubMed is presented in Table 2.

218 Table 2. Sample search strategy and results.

| Database | Search Terms | Results | Date |
|---------------|---|---------|------------|
| PubMed | ("decision support"[All Fields] OR "decision-support"[All Fields] OR "early warning score"[MeSH Terms] OR "early warning score"[All Fields] OR "smart system*"[All Fields] OR "electronic alert*"[All Fields] OR "artificial intelligence"[All Fields] OR "artificial intelligence"[MeSH Terms] "machine learning"[All Fields] OR "deep learning"[All Fields] OR "neural network*"[All Fields] OR "support vector machine"[All Fields] OR "hidden markov model"[All Fields] OR "statistical learning"[All Fields] OR "predictive function"[All Fields] OR "algorithm"[All Fields] OR "algorithms"[MeSH Terms] OR "automat*"[All Fields] OR "comput*"[All Fields] OR "decision making, computer assisted"[MeSH Terms] OR "electronic*"[All Fields] OR "representation learning"[All Fields] OR "conformal prediction"[All Fields] OR "random forest"[All Fields] OR "naïve bayes"[All Fields] OR "regression" OR "regression analysis"[MeSH Terms] OR "gradient boosting"[All Fields] OR "artificial learning"[All Fields] OR "machine intelligence"[All Fields] OR "probabilistic network*"[All Fields] OR "knowledge representation"[All Fields] OR "bayesian learning"[All Fields] OR "expert system*"[All Fields] OR "technology assisted"[All Fields] OR "computer assisted"[All Fields] OR "statistical"[All Fields] OR "mathematical"[All Fields]) AND ("system"[All Fields] OR "tool"[All Fields] OR "alert*"[All Fields] OR "technology"[All Fields] OR "software"[All Fields] OR "model*"[All Fields] OR "engine"[All Fields] OR "approach*"[All Fields] OR "algorithm"[All Fields] OR "platform"[All Fields] OR "method*"[All Fields] OR "scor*"[All Fields] OR "device"[All Fields]) AND (| 15,531 | 02/15/2022 |

"sepsis"[All Fields] OR "sepsis"[MeSH Terms] OR "septic shock"[All Fields] OR "systemic inflammatory response syndrome"[All Fields] OR "acute deterioration"[All Fields] OR "patient deterioration"[All Fields] OR "clinical deterioration"[MeSH Terms] OR "clinical deterioration"[All Fields] OR "severe infection"[All Fields] OR "severe bacterial infection"[All Fields] OR "bacterial infections"[MeSH Terms] OR "febrile illness"[All Fields] OR "non-malarial febrile illness"[All Fields] OR "bacteremia"[All Fields]) AND ("diagnos*"[All Fields] OR "detect*"[All Fields] OR "predict*"[All Fields] OR "prognosticate"[All Fields] OR "identif*"[All Fields] OR "infer*"[All Fields] OR "warn*"[All Fields] OR "alert*"[All Fields] OR "recog*"[All Fields] OR "screen*"[All Fields] OR "monitor*"[All Fields] OR "assess*"[All Fields] OR "surveillance"[All Fields] OR "classif*"[All Fields]) AND ("evaluat*"[All Fields] OR "implement*"[All Fields] OR "perform*"[All Fields] OR "design"[All Fields] OR "validat*"[All Fields] OR "usability"[All Fields] OR "effectiveness"[All Fields] OR "efficiency"[All Fields] OR "satisfaction"[All Fields] OR "safety"[All Fields] OR "acceptance"[All Fields] OR "clinical value"[All Fields] OR "interpret*"[All Fields] OR "perception"[All Fields] OR "perspective"[All Fields] OR "opinion"[All Fields] OR "error"[All Fields]) AND ("child*"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields] OR "pediatrics"[MeSH Terms] OR "toddler*"[All Fields] OR "teen*"[All Fields] OR "youth*"[All Fields] OR "adolescenc*"[All Fields] OR "adolescent"[MeSH Terms] OR "infan*"[All Fields] OR "infant"[MeSH Terms] OR "school age*"[All Fields] OR "PICU"[All Fields]) LIMIT TO: [Text Availability]: Full text, [Language]: English, [Species]: Human

219
 220 The search results will be imported to Mendeley's reference management software for
 221 future referencing and organization (Mendeley Ltd.). A systematic review management software,
 222 Covidence (Veritas Health Innovation Ltd.), will be used to identify and merge duplicate articles.
 223 A sample of 20 abstracts will be initially screened by two reviewers (RT and JG), ensuring the
 224 inclusion-exclusion requirements are robust in capturing relevant articles related to the design
 225 and evaluation of automated prediction technologies for paediatric sepsis. Both reviewers will

226 also ensure that the data extraction items capture valuable and appropriate study details from the
227 articles included in the full-text review, which will be shared with the research team.

228

229 **Step 3: study selection**

230 *Inclusion criteria*

231 The proposed review will include articles that meet the following inclusion criteria:

- 232 • The article is written in English.
- 233 • The article is a peer-reviewed journal article, full conference proceeding, or research
234 published on a commercially available digital technology which may be approved by a
235 medical device regulatory body.
- 236 • Following the American Academy of Pediatrics' definition for late adolescence, more
237 than the majority of data reported will include children aged >90 days post-natal to <21
238 years old (50).
- 239 • The article is about an automated data-driven or knowledge-based approach toward
240 paediatric sepsis prediction in a healthcare setting, including sepsis risk, severe sepsis,
241 septic shock, or sepsis mortality risk.
- 242 • The digital technology is evaluated for its performance through validation testing,
243 experiments, or an observational study.
- 244 • There is no specification for publication years.

245

246 *Exclusion Criteria*

247 Screened articles that fit within the following categories will be excluded from this review:

248 Commentaries, dissertations, editorials, books and book chapters, lectures and addresses, study

1
2
3 249 protocols, review articles, and articles inaccessible for full-text review after utilizing library
4
5 250 resources. Articles that describe digital technologies informing sepsis treatment strategy
6
7
8 251 selection are outside the scope of this review, because this study is focused on technologies
9
10 252 supporting clinical decision-making and screening that occurs before fluid resuscitation or
11
12 253 antibiotic selection for confirmed sepsis patients. Digital technologies developed for at-home use
13
14
15 254 are also outside the scope of this review, as the context of the protocol is to review the evidence
16
17 255 on automated sepsis prediction technologies in regulated healthcare settings.
18
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21

256

257 ***Selection process***

258 This review will follow the reporting checklist in the Preferred Reporting Items for Systematic
259 reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR), provided by Tricco
260 et al. (46). First, all relevant articles will be imported into Covidence. Second, two reviewers (RT
261 and JG) will independently perform the title and abstract screening using the developed
262 eligibility criteria by classifying them as “Yes,” “No,” or “Maybe.” Any article classified as
263 “Yes” or “Maybe” by RT or JG will be included in the full-text review during this stage by
264 adding them to an Excel spreadsheet for access by all authors. If a full-text article cannot be
265 accessed, the reviewers will seek assistance from library services at the institution or directly
266 contact the article’s corresponding author. Third, two investigators (RT and JG) will
267 independently perform the full-text screening for eligibility using the listed inclusion-exclusion
268 criteria. A third member of the research team will resolve any disagreements on eligibility that
269 occur during the full-text review. After the full-text review, an inter-rater agreement will be
270 calculated using Cohen’s kappa coefficient (κ) statistic.

1
2
3 271 The first step in identifying relevant studies was performed on February 15, 2022. The
4
5 272 planned end date for completing the full-text screening and analysis is December 30th, 2022. We
6
7
8 273 have maintained search alerts for potentially eligible articles to ensure our review remains
9
10 274 updated before dissemination through publication.
11

12 275

14 276 **Step 4: charting the data**

16
17 277 The data extraction form will be developed in Covidence and exported to Excel to capture the
18
19 278 relevant information from each article. Two reviewers (RT, JG) will individually extract the
20
21 279 relevant data from a sample of eligible articles screened for inclusion in the full-text review to
22
23 280 ensure consistency of recording data. Any disagreements on extracted data will be resolved
24
25 281 through discussion between the reviewers. The form will be iteratively updated until the authors
26
27 282 reach a consensus on the relevant data to extract. We will begin by pulling the following type of
28
29
30 283 data into the form, with additional data included as we screen more articles:

- 31
32
33 284 • Article information: author(s), year published, city, country, discipline(s).
34
35 285 • Prediction task: the definition of sepsis being identified and the use context for
36
37 286 recognition in paediatrics.
38
39
40 287 • Prediction task type:
41
42 288 ○ Alerting automation that provides a notification that a patient has met the
43
44 289 objective sepsis recognition criteria.
45
46 290 ○ Decision support automation that provides assistance in the diagnosis of sepsis.
47
48 291 ○ Data automation that collects clinically relevant cues and information on behalf of
49
50 292 the user(s), which may be used in combination with alerting and decision support.
51
52
53 293 • Prediction method:

- 294 ○ Data-driven methods that use retrospective datasets to build a statistical or
- 295 machine learning-based model.
- 296 ○ Knowledge-based methods that use consensus criteria to build an algorithm with
- 297 threshold-based criteria.
- 298 ● Participant demographics: age cohort, number of participants.
- 299 ● Prediction indicators: vital signs, biomarkers, socio-demographics, prior treatments,
- 300 medical history.
- 301 ● Prediction interface: audible alert, dialog box, provided information
- 302 ● Validation measures:
 - 303 ○ Reported number of true positives, false positives, and false negatives.
 - 304 ○ Reported sensitivity and specificity.
 - 305 ○ Time to accurate sepsis recognition by the technology and/or the clinician.
 - 306 ○ Measured or expected impact on clinical decisions and patient outcomes.
 - 307 ○ Generalizability of the digital technology in the context of bias, fairness, and
 - 308 appropriateness (51,52).

310 **Step 5: collating, summarizing, and reporting the results**

311 The extracted data will be synthesized within tables that summarize the current digital
312 technology landscape in predicting paediatric sepsis, including characteristics that describe their
313 performance and the sociotechnical factors of their integration by health care providers on
314 patient outcomes. Within summary tables, we will present the current approaches toward model
315 and algorithm development for automated sepsis prediction technologies, including the
316 predictive indicators, the prediction timing objective, and how they interface with clinicians.

1
2
3 317 Quantitative performance and implementation measures such as sensitivity and specificity, and
4
5 318 the impacts on intervention timing will also be reported in data tables, including calculations of
6
7 319 precision, recall, and F1 score, when possible.
8
9

10 320 We will then perform a thematic analysis to identify concepts related to our research
11
12 321 questions. This analysis will be presented as a narrative, including an organization of themes on
13
14 322 the identified design characteristics of automated prediction technologies integrated within
15
16 323 clinical contexts. The purpose of the analysis will be to identify the types of research gaps that
17
18 324 exist for knowledge-based algorithms and data-driven models to improve sociotechnical
19
20 325 integration (i.e., supporting clinical decision-making) and patient outcomes. Challenges with
21
22 326 bias, fairness, and appropriateness will also be qualitatively examined with respect to potential
23
24 327 generalizability barriers. Diagrams will be developed for the identified relationships and themes
25
26 328 among the design characteristics of the automated technologies for paediatric sepsis prediction
27
28 329 and their influence on system performance and implementation throughout time to visually
29
30 330 highlight the opportunities for future investigations.
31
32
33
34

35 331

36 332 **Step 6: methodological quality appraisal**

37
38 333 We will consult with experts in automated paediatric sepsis prediction technologies for this
39
40 334 review to identify those applied in clinical settings. While critical appraisal of the identified
41
42 335 articles is not mandatory in the scoping review methodology, we will consult with stakeholders
43
44 336 to inform and validate our findings.
45
46
47
48

49 337

50 338 **Patient and public involvement**

51
52 339 There were no patients or public involvement in the development of this protocol.
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340

341 ETHICS AND DISSEMINATION

342 Approval from an ethics review committee is not required for this study because it is a scoping
343 review of previously published literature. Once the review is completed, we plan to disseminate
344 the preliminary findings at national and international research conferences in global and digital
345 health to gather critical feedback from researchers and the public. The finalized results from the
346 review will be submitted for publication in an open access peer-reviewed journal.

347

348 DISCUSSION

349 This scoping review will provide a comprehensive and structured understanding of the
350 automated digital technologies that have been developed to support the timely prediction of
351 paediatric sepsis. At a high-level, the results will focus on design characteristics, performance
352 validation, and current sociotechnical integration factors, which will be analyzed thematically
353 and reported in data summary tables, indicating how the development of these technologies is
354 evolving throughout time. It is anticipated that the outcomes will reveal the current challenges in
355 developing and implementing clinically meaningful digital prediction technologies for paediatric
356 sepsis across various clinical environments. Furthermore, the results are expected to identify
357 critical research aspects requiring further investigation.

358 Compared to previous articles, this scoping review focuses on the complexities of
359 paediatric sepsis, with a methodological strength in taking a comprehensive and systematic
360 approach that will provide an overview of the evidence in this digital technology landscape.
361 Inherent in the approach of a scoping review is the limitation of its objective: to summarize the
362 literature and identify meaningful gaps for further research. As this study will include articles

1
2
3 363 with various study designs, it does not aim to answer specific questions about recommending the
4
5 364 use or application of certain sepsis prediction technologies for paediatrics. With the results of the
6
7 365 pilot search (Table 2), this review is also limited in its scope, where non-English articles or
8
9
10 366 articles without a full-text version will not be included. Finally, digital technologies informing
11
12 367 treatment strategies for sepsis and studies looking at age cohorts <90 days post-natal or >21
13
14 368 years old will be excluded because of significant differences in sepsis etiology and clinical
15
16 369 presentation, while capturing literature from geographic areas that provide paediatric healthcare
17
18
19 370 services to this age range. We plan to adequately convey the overall strengths and limitations
20
21 371 once the full-text review is completed, including any deviations from the protocol, in the final
22
23 372 review.

24
25
26 373 In conclusion, by mapping the attributes of paediatric sepsis prediction technologies to
27
28 374 outcomes related to clinical integration and performance, we anticipate that our results will
29
30 375 highlight critical research gaps among the medical, engineering, and computer science
31
32 376 disciplines. The results may inform research on identifying relevant predictive indicators best
33
34 377 suited for the design of digital technologies in specific use contexts and environments,
35
36 378 improvements towards model development for sepsis prediction, and factors supporting the
37
38 379 optimal workflow integration of digital prediction systems by clinicians. Ultimately, this review
39
40 380 will be critical for advancing knowledge to improve sepsis prediction for children globally.
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45 381

46 382 **List of abbreviations**

47 383 ACM: Association of Computing Machinery

48
49 384 CINAHL: Cumulative Index to Nursing and Allied Health Literature

50
51 385 IEEE: Institute of Electric and Electronic Engineers
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3 386 nSOFA: neonatal Sequential Organ Assessment Score
4

5 387 PEWS: Paediatric Early Warning Score
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8 388 PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for
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10 389 protocols
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12 390 PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis extension
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14 391 for scoping reviews
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17 392 pSOFA: paediatric Sequential Organ Assessment Score
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19 393 SOFA: Sequential Organ Assessment Score
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21 394 SPOT: Sepsis Prediction and Optimization Therapy
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26 396 **Author contributions**
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28 397 RT, JG, KM, CMB, and JMA contributed to the development of this manuscript. RT is the
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30
31 398 guarantor of the review, conceptualized the research questions and methods, and drafted the
32

33 399 initial manuscript. All authors contributed to the development of the search strategy, selection
34

35 400 criteria, and data extraction template. JMA provided expertise on paediatric sepsis and search
36

37 401 terms. All authors critically reviewed the protocol for intellectual content, subsequently revised it
38

39
40 402 for publication, and read and approved the final version for submission.
41

42 403
43

44 404 **Availability of data and materials**
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46
47 405 Not applicable.
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49 406
50

51 407 **Funding statement**
52

53
54 408 Not applicable.
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5 410 **Competing interests statement**
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7
8 411 The authors declare that they have no competing interests.
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11

12 413 **Acknowledgements**
13

14 414 RT is supported by an Engineering Excellence Doctoral Fellowship from the University of
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17 415 Waterloo Faculty of Engineering.
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PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|-----------------------------------|----|---|-------------------------------------|-------------------------------------|----------------|
| | | | Yes | No | |
| ADMINISTRATIVE INFORMATION | | | | | |
| Title | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| Registration | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 62, 180 |
| Authors | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 4-29 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 396-401 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| Support | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 414-415 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 408, 414-415 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 408, 414-415 |
| INTRODUCTION | | | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 87-164 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|-----|---|-------------------------------------|-------------------------------------|------------------|
| | | | Yes | No | |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 183-198 |
| METHODS | | | | | |
| Eligibility criteria | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 230-255 |
| Information sources | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 201-211 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 218-219, 231-255 |
| STUDY RECORDS | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 220-227, 260-264 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 260-274 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 220-227, 231-255 |
| Data items | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 277-308 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| DATA | | | | | |
| Synthesis | 15a | Describe criteria under which study data will be quantitatively synthesized | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 311-319 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|--|-----|---|-------------------------------------|-------------------------------------|----------------|
| | | | Yes | No | |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 320-330 |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | N/A |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 333-336 |