

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Automated digital technologies for supporting sepsis prediction in children: A scoping review protocol
AUTHORS	Tennant, Ryan; Graham, Jennifer; Mercer, Kate; Ansermino, J. Mark; Burns, Catherine

VERSION 1 – REVIEW

REVIEWER	Stefan Candefjord Chalmers University of Technology, Electrical Engineering
REVIEW RETURNED	13-Jul-2022

GENERAL COMMENTS	The authors present the paper "Digital technologies for sepsis prediction in children: A scoping review protocol", which aims to summarize the existing literature on designing paediatric sepsis prediction technologies. This review could potentially bring much value to the research community. The protocol has several strengths, including very good language and high clarity, relatively well explained rationales for the method, valuable references and proper use of citations, a meticulous method for identifying the relevant papers in the literature with reasonable limitations, and a good discussion. I have some concerns that I recommend the authors to address before potential publication, in the following remarks. Introduction: - I find that the first part of the introduction, which clearly explains the challenges with paediatric sepsis and explains the clinical contexts and presents valuable statistics, to be very good. In the following subsection "Prior reviews on sepsis prediction technologies" the authors go into a rather lengthy and detailed explanation about why the review is needed and how it can contribute to the field. This information is valuable, although I think this should be written more concisely to not take up so much space (almost as much as the first part of the Introduction), I would recommend shortening this section to around half of the current word count. It is acceptable that similar reviews have some overlap, so I deem it is unnecessary to go into this level of detail to motivate performing this review. Methods and Analysis: - The research questions in Step 1 are very broad, I am worried that it will be challenging to provide concrete answers to them. I recommend to break them down into some sub-questions or by other means defining some more exact research questions that more likely can be answered with the knowledge compiled in this review. - In step 2 the databases seem pertinent. The search strategy with the example in Table 2 appears to be quite laborious, this should
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	likely capture relevant articles, but with so many OR search strings it will likely mean that a large number of irrelevant articles are found and it seems that the search strategy may be too broad. Indeed, there are 15,531 hits in the PubMed search presented in Table 2. Will the research team go through this large number of hits manually? This appears to not be the best use of resources and may not utilize the strength of the search tools effectively. It will also be more difficult for other research groups to do a new review for a similar topic some years ahead. I recommend the authors to consider developing shorter and more effective search strategies, substantially reducing the complexity of the current search strategy. It may be valuable to do several tests comparing different strategies and their effectiveness in finding relevant papers and exclude irrelevant articles. - In step 3, please provide a rationale for including patients up to 20 years of age (in some countries paediatric care do not include adults, e.g. patients ≥ 18 years of age). There are some relatively broad criteria that may be difficult to judge, e.g. "The article describes how the digital technology was designed, validated for its effectiveness, or evaluated for its usability in the context of a healthcare facility". If strictly applied this may exclude a lot of papers that may have bearing on some or all of the research questions. I recommend the authors to perform some tests to see if the eligibility criteria are suitable and appropriately detailed. If several authors come to different decisions based on disagreement concerning a specific criteria, it may be too inexact / unspecific. This is an important aspect when performing the review. For the exclusion criteria, some criteria may exclude relevant papers, please provide rationales for the three last criteria in the bullet list. - In step 4, a large number of data points are presented. I deem that it is unlikely that included papers provide all this information, and some of the points may suffer from low quantity due to not being reported by many studies. It will also be challenging to present a meaningful summary of all these points in a clear way to the readers that brings much knowledge to the community. I recommend the authors to condense this list into the most important points that are commonly reported in the literature.
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REVIEWER	Sandeep Reddy Deakin University, School of Medicine
REVIEW RETURNED	23-Aug-2022

GENERAL COMMENTS	Thanks for presenting a compelling case to undertake a literature review of a pertinent topic that lacks enough evidence. The protocol is well written, but I am concerned if a protocol by itself, no matter how sound, is enough to justify publication in this journal. As the review methods are not novel, it is unlikely to inform the readership aside from the need for a review of the topic. A more appropriate process would be to publish when you have completed your review.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. S Candefjord, Chalmers University of Technology

Comments to the Author:

- The authors present the paper "Digital technologies for sepsis prediction in children: A scoping review protocol", which aims to summarize the existing literature on designing paediatric sepsis prediction technologies. This review could potentially bring much value to the research community.

The protocol has several strengths, including very good language and high clarity, relatively well explained rationales for the method, valuable references and proper use of citations, a meticulous method for identifying the relevant papers in the literature with reasonable limitations, and a good discussion. I have some concerns that I recommend the authors to address before potential publication, in the following remarks.

Thank you for your positive and critical review of our protocol paper. Please see our responses to your concerns and the subsequent changes made to our manuscript below.

Introduction:

- I find that the first part of the introduction, which clearly explains the challenges with paediatric sepsis and explains the clinical contexts and presents valuable statistics, to be very good. In the following subsection "Prior reviews on sepsis prediction technologies" the authors go into a rather lengthy and detailed explanation about why the review is needed and how it can contribute to the field. This information is valuable, although I think this should be written more concisely to not take up so much space (almost as much as the first part of the Introduction), I would recommend shortening this section to around half of the current word count. It is acceptable that similar reviews have some overlap, so I deem it is unnecessary to go into this level of detail to motivate performing this review.

Thank you for your suggestion. We have reviewed this section of our manuscript and while retaining the identified reviews, reduced the word count from 517 to 272 words to highlight the most significant limitations. The updated version of this section better situates the relevancy and need for our scoping review protocol within the current literature:

"Recent narrative reviews discuss machine learning-based technologies for adult and paediatric sepsis (20,29,30). However, their eligibility criteria focus primarily on adults, with only two (20) or three (29) articles on children. Some reviews excluded digital technologies that were not based on "modern" machine learning models (21,30), or involved a broad search on infectious disease prediction beyond sepsis (29). Others have also limited their investigations to PubMed/Medline, excluding engineering databases, which may provide greater insight into the design characteristics of digital technologies (20,26,31–33), or they focus exclusively on US hospitals (33).

Many systematic and scoping reviews have been rigorous in their search strategy but similar to the identified narrative reviews, report on screening tools and technologies for adult patients while excluding children (24,25,28,34–37), and the engineering disciplines (19,23,38–40). Currently published protocols plan to exclude literature on the application of machine learning (39,41), which may not capture research on certain relevant technologies. While there have been systematic reviews on the performance of neonatal sepsis prediction and recognition technologies providing insight into their capabilities (19,23), none focus on the specifics of paediatric sepsis.

Current systematic reviews that include the paediatric literature as part of their search strategy are not strictly focused on this patient population (22,28,38), having only identified one (38) or three (22,28) related articles specific to children. Other reviews broadly examine early warning systems for paediatric clinical deterioration (42,43). We have not identified any systematic or scoping reviews that accurately scope the literature on digital paediatric sepsis prediction technology. One identified protocol aims to capture strategies for early recognition of paediatric sepsis from clinical deterioration (40). However, the focus of the review is general strategy effectiveness and does not explicitly include engineering databases which would describe technical design aspects (40)."

Methods and Analysis:

- The research questions in Step 1 are very broad, I am worried that it will be challenging to provide concrete answers to them. I recommend to break them down into some sub-questions or by other

means defining some more exact research questions that more likely can be answered with the knowledge compiled in this review.

We appreciate your comment on our research questions. For scoping reviews, the typical goal is to identify gaps in the literature, or scope an area of literature, which often results in broader research questions compared to other types of literature reviews [1]. Broad research questions, including questions that aim to understand what has already been done, what gaps exist, which populations have been explored, are appropriate [2]. While keeping with our broader objectives, we have refined our research questions to make them more concretely answerable.

1. How do the design characteristics of automated paediatric sepsis recognition technologies for healthcare facilities (e.g., the recognition task, type, method, demographics, and indicators) influence their performance?
2. What are the impacts of clinically implemented automated sepsis recognition technologies on decision-making and patient outcome measures?
3. What challenges and research gaps exist (e.g., evidence, practical knowledge, population, theoretical, methodological) exist for improving the sociotechnical integration of knowledge-based algorithms and data-driven models for clinical recognition of paediatric sepsis in healthcare facilities?

[1] Munn, Z., Peters, M. D. J., Stern, C., Tufanaru, C., McArthur, A., & Aromataris, E. (2018). Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Medical Research Methodology*, 18(1), 143. <https://doi.org/10.1186/s12874-018-0611-x>

[2] Peters, M. D. J., Godfrey, C., McInerney, P., Khalil, H., Larsen, P., Marnie, C., Pollock, D., Tricco, A. C., & Munn, Z. (2022). Best practice guidance and reporting items for the development of scoping review protocols. *JBIM Evidence Synthesis*, 20(4), 953–968. <https://doi.org/10.11124/JBIES-21-00242>

- In step 2 the databases seem pertinent. The search strategy with the example in Table 2 appears to be quite laborious, this should likely capture relevant articles, but with so many OR search strings it will likely mean that a large number of irrelevant articles are found and it seems that the search strategy may be too broad. Indeed, there are 15,531 hits in the PubMed search presented in Table 2. Will the research team go through this large number of hits manually? This appears to not be the best use of resources and may not utilize the strength of the search tools effectively. It will also be more difficult for other research groups to do a new review for a similar topic some years ahead. I recommend the authors to consider developing shorter and more effective search strategies, substantially reducing the complexity of the current search strategy. It may be valuable to do several tests comparing different strategies and their effectiveness in finding relevant papers and exclude irrelevant articles.

Thank you for your comment. This protocol was guided by our research librarian team member who supported the crafting of our search strategy for each database, as is typical for literature reviews [1]. This included testing and refining our search strings across each identified database to ensure the results produced relevant articles. In the context of this review, we found that our large search string ensured that the results were comprehensive, where 15,000 – 20,000 articles are not unusual for abstract screening in scoping reviews, but supports a rigorous search [2,3].

[1] Kako, J., Kobayashi, M., Kanno, Y., Kajiwar, K., Nakano, K., Morikawa, M., Matsuda, Y., Shimizu, Y., Hori, M., Niino, M., Suzuki, M., & Shimazu, T. (2022). Nursing support for symptoms in patients with cancer and caregiver burdens: a scoping review protocol. *BMJ Open*, 12(9), e061866. <https://doi.org/10.1136/bmjopen-2022-061866>

[2] Brazeau BW, Hodgins DC. User engagement with technology-mediated self-guided interventions for addictions: scoping review protocol. *BMJ Open* 2022;12:e064324. doi: 10.1136/bmjopen-2022-064324.

[3] Ogunlana, M. O., Govender, P., Oyewole, O. O., & Nwosu, I. B. (2021). Adult stroke survivor's reintegration to normal living: a scoping review protocol. *Systematic Reviews*, 10(1), 300. <https://doi.org/10.1186/s13643-021-01851-x>

- In step 3, please provide a rationale for including patients up to 20 years of age (in some countries paediatric care do not include adults, e.g. patients ≥ 18 years of age). There are some relatively broad criteria that may be difficult to judge, e.g. "The article describes how the digital technology was designed, validated for its effectiveness, or evaluated for its usability in the context of a healthcare facility". If strictly applied this may exclude a lot of papers that may have bearing on some or all of the research questions. I recommend the authors to perform some tests to see if the eligibility criteria are suitable and appropriately detailed. If several authors come to different decisions based on disagreement concerning a specific criteria, it may be too inexact / unspecific. This is an important aspect when performing the review. For the exclusion criteria, some criteria may exclude relevant papers, please provide rationales for the three last criteria in the bullet list.

Thank you for your comment. We have included patients up to 21 years of age in our study to be inclusive of countries that have the widest paediatric age definition. In this case, we have found that the United States has the broadest definition where the Department of Health and the Food and Drug Administration reference approximate age ranges for late adolescence of 18-21 years, and where the American Academy of Pediatrics identified the upper age limit as 21 years. We have therefore included up to 21 years of age to ensure the review of studies with age groups where paediatric services are provided in a professional, licensed setting, focusing on studies where most patients included are < 21 years old. In other words, we would not include studies where more than half of the participants are adults, but which may have a lower value of 18 or 20 years of age.

Since this protocol was submitted, we have refined our inclusion criteria to achieve greater consistency in article selection. Our updated inclusion criteria are now the following:

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

- The article is written in English.
- The article is a peer-reviewed journal article, full conference proceeding, or research published on a commercially available digital technology which may be approved by a medical device regulatory body.
- Following the American Academy of Pediatrics' definition for late adolescence, more than the majority of data reported will include children aged > 90 days post-natal to < 21 years old (49).
- The article is about an automated data-driven or knowledge-based approach toward paediatric sepsis recognition in a healthcare facility.
- The digital technology is evaluated for its performance through validation testing, experiments, or an observational study.
- There is no specification for publication years."

For two of the three last exclusion criteria, we have provided further justifications. Upon further review of the literature and conducting our abstract screening, we have decided to include articles that predict paediatric sepsis mortality to broaden the review of prediction technologies, as there is evidence that they could be used as a recognition support tool.

"Screened articles that fit within the following categories will be excluded from this review: Commentaries, dissertations, editorials, books and book chapters, lectures and addresses, study protocols, review articles, and articles inaccessible for full-text review after utilizing library resources.

Articles that describe digital technologies informing sepsis treatment strategy selection such as antibiotic type or fluid bolus volume are outside the scope of this review, because this study is focused on the first step of sepsis recognition. Also, digital technologies developed for at-home use are also outside the scope of this review, as the context of protocol is to review the evidence on automated sepsis recognition technologies in regulated healthcare settings.”

- In step 4, a large number of data points are presented. I deem that it is unlikely that included papers provide all this information, and some of the points may suffer from low quantity due to not being reported by many studies. It will also be challenging to present a meaningful summary of all these points in a clear way to the readers that brings much knowledge to the community. I recommend the authors to condense this list into the most important points that are commonly reported in the literature.

Thank you for your suggestion. After conducting the abstract screening, we agree that that the extracted items can be further refined to provide a more meaningful summary while still scoping the important and relevant aspects of digital sepsis prediction technologies. We have reduced the listed data points to the following, which adjacently aligns with similar protocols [1,2].

- Article information: author(s), year published, city, country, discipline(s).
- Prediction task: the definition of sepsis being identified and the use context for recognition in paediatrics.
- Prediction task type:
 - o Alerting automation that provides a notification that a patient has met the objective sepsis prediction criteria.
 - o Decision support automation that provides assistance in the diagnosis of sepsis.
 - o Data automation that collects clinically relevant cues and information on behalf of the user(s), which may be used in combination with alerting and decision support.
- Prediction method:
 - o Data-driven methods that use retrospective datasets to build a statistical or machine learning-based prediction model.
 - o Knowledge-based methods that use consensus criteria to build a prediction algorithm with threshold-based criteria.
- Participant demographics: age cohort, sepsis prevalence, validation dataset size.
- Prediction indicators: vital signs, biomarkers, socio-demographics, treatment, medical history.
- Prediction interface: audible alert, dialog box, provided information
- Validation measures:
 - o Reported number of true positives, false positives, and false negatives.
 - o Reported sensitivity and specificity.
 - o Time to accurate sepsis recognition by the technology and/or the clinician.
 - o Measured or expected impact on patient outcomes.
 - o Generalizability of the digital technology in the context of bias, fairness, and appropriateness (49,50)

[1] Neal, S. R., Musorowegomo, D., Gannon, H., Cortina Borja, M., Heys, M., Chimhini, G., & Fitzgerald, F. (2020). Clinical prediction models to diagnose neonatal sepsis: a scoping review protocol. *BMJ Open*, 10(8), e039712. <https://doi.org/10.1136/bmjopen-2020-039712>

[2] Pepic, I., Feldt, R., Ljungström, L., Torkar, R., Dalevi, D., Maurin Söderholm, H., Andersson, L.-M., Axelsson-Fisk, M., Bohm, K., Sjöqvist, B. A., & Candefjord, S. (2021). Early detection of sepsis using artificial intelligence: a scoping review protocol. *Systematic Reviews*, 10(1), 28. <https://doi.org/10.1186/s13643-020-01561-w>

Reviewer: 2

Dr. Sandeep Reddy, Deakin University

Comments to the Author:

- Thanks for presenting a compelling case to undertake a literature review of a pertinent topic that lacks enough evidence. The protocol is well written, but I am concerned if a protocol by itself, no matter how sound, is enough to justify publication in this journal. As the review methods are not novel, it is unlikely to inform the readership aside from the need for a review of the topic. A more appropriate process would be to publish when you have completed your review.

We appreciate your concerns, however, publishing protocols for literature reviews in health-related fields is a standard practice to allow for peer review of the methods prior to completing the full review, with an increasing number of journals requiring it as a matter of course. Additionally, it is required as part of the PRISMA checklist. We have chosen BMJ Open for manuscript submission as scoping review protocols are regularly published in this journal [1-3]. Thank you for your comment.