PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Quality of clinical practice guidelines and recommendations for the management of pain, sedation, delirium, and iatrogenic withdrawal in pediatric intensive care: A systematic review protocol
AUTHORS	Perez, Marie-Hélène Amiet, Vivianne Trombert, Alexia Ramelet, Anne-Sylvie MacDonald, Ibo

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Erwin Ista Institution and Country: Erasmus Medical Center United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	12-Oct-2021

GENERAL COMMENTS	The authors aimed to perform a systematic review of CPG for pain, sedation, withdrawal and delirium in critically ill children, and appraise the quality of these CPG based on the AGREE II instrument. This protocol paper was clearly written. However, I have a few concerns. First, the authors described pain, sedation, iatrogenic withdrawal syndrome and delirium as symptoms. I disagree with this. For example, according the DSM-V delirium is a neurocognitive disorder. The same for withdrawal syndrome, it's defined as disorder or syndrome. Both could be observed based on different signs and symptoms. Therefore, the authors should redefine it as e.g. 'condition'. Next, the discussion was very short and strengths and limitations were obviously not surprising.

REVIEWER	Reviewer name: Dr. Kaitlin Best Institution and Country: University of Pennsylvania Perelman School of Medicine, United States Competing interests: None
REVIEW RETURNED	28-Oct-202

GENERAL COMMENTS	Thank you for the opportunity to review this comprehensive and well-described systematic review protocol. The authors propose to review clinical practice guidelines (CPGs) and recommendations for the management of four interrelated symptoms common to the PICU: pain, sedation, agitation, delirium, and withdrawal. This work is important as CPG development is heterogenous across organizations, and few systematic reviews exist that compile evidence across CPGs. Overall, I found this protocol to be thorough and appropriately based on rigorous methodologies, including PRISMA and AGREE guidelines, and I have very few, minor comments for strengthening the presentation of this manuscript.

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	1. In the Introduction, the authors reference a few of the available instruments for assessing pain, sedation, delirium and withdrawal. However, references to other commonly used instruments, such as the CAP-D and WAT-1 scales, should also be included. 2. It is unclear why the 'condition' part of the PICAR statement is focused particularly on non-communicative children, as all children in the PICU are vulnerable to experiencing pain, agitation, delirium and/or withdrawal. Please provide a rationale for this criterion. 3. Please justify the decision to restrict the search to 2010 onward. 4. Minor grammatical errors were noted throughout the manuscript. Please pay particular attention to use of parentheses, as they were not always closed.

VERSION 1 – AUTHOR RESPONSE

Revision Comments

Editor in Chief	
Comments of Author	*Change made to Manuscript*
Why restrict your search to English & French only. Better to include all languages and then state the number that you could not translate. This also helps identify the languages and countries where there is work on the subject.	**The language restriction was removed and the search strategy has been updated**
What this study hopes to add - avoid abbreviations (CPGs)	**Abbreviations were removed**
Associate Editor	
Dear authors, Thank you for submitting this protocol. The reviewers have provided guidance for improvement. In addition, please add the final search string. Without this search string, we can not properly evaluate the value of the protocol.	**We have added the below final search string into table 1C of the supplemental material:** **Embase.org -** 9849 references (17 November 2021) ('pain'/de OR 'postoperative pain'/de OR 'analgesia'/exp OR 'conscious sedation'/de OR 'hypnotic sedative agent'/de OR 'delirium'/de OR 'hyperactive delirium'/de OR 'hypoactive delirium'/de OR 'withdrawal syndrome'/de OR (pain OR discomfort OR analgesia OR sedation OR sedative* OR delirium OR delirious* OR withdrawal*):ti,kw) AND ('practice guideline'/de OR 'consensus development'/de OR ((expert* NEAR/3 opinion*) OR guideline* OR cpg* OR guidance OR ((position OR policy) NEAR/3 (paper* OR development)) OR ((practice OR clinical) NEAR/3 development) OR (practice NEAR/2 guide$) OR recommendation* OR consensus OR standards OR statement*):ti,kw) NOT ('adult'/exp NOT 'juvenile'/exp) AND [2010-3000]/py NOT ('conference abstract'/it OR

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	'conference review'/it) NOT ([animals]/lim NOT [humans]/lim)
also, how will you search for pain, and will be inclusion and exclusion criteria for CPGs? as postoperative pain is a major reason for analgesics in the PICU, but how will you handle these guidelines? Similarly, for procedural sedation?	**In the PICAR table we identified that our search will be for guidelines that are general and applicable to the entire PICU population for all four conditions. We combined free text words and index terms to search for pain as a general concept. In Embase.com, 'pain'/de (narrower terms were not included), 'analgesia'/exp (term used for pain management), 'postoperative pain'/de were combined with the words pain, discomfort or analgesia searched in title and keywords fields.** **The PICAR table was updated and we added the following sentence for clarity into the text** (lines 124-128): This review will include broad CPGs for the assessment and management of any of the four conditions, including postoperative pain. However, CPGs will be excluded if focused on specific patient groups (e.g. cardiac). CPGs on diagnostic procedures (e.g. endoscopy) or procedures of limited temporal duration (e.g. venipuncture) will be excluded. Procedures that require prolonged use in the PICU setting (e.g. respiratory support), will be included.
The introduction could benefit from reducing the part on the interrelation between sedation, pain, delirium and withdrawal. This distracts from the goal of your review. We all know that there is overlap, at the same time, a large body of effort has been put in developing psychometric tools to make the distinction between these different symptoms/diagnoses. Just to help individualize treatment. Many CPGs in the PICU are based on this premise, and you should acknowledge this in the discussion.	**We have revised the entire second paragraph in the introduction on measurement instruments and the overlap of the four conditions** (lines 51 – 72). **We have revised the discussion and acknowledged the need for individualized treatment in the discussion. We added the following paragraph** (lines 246-251): Research on pain, sedation, delirium and iatrogenic withdrawal practices across an international sample of 161 PICUs continues to demonstrate variation.[9] Although HCPs use measurement instruments to identify patient changes based on behavioural cues, HCPs may find it challenging to interpret and use scores and determine which multi-modal interventions to use. Using measurement instruments is the first step towards goal-directed care, and this review will give HCPs strategies to inform clinical practice.

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Reviewer: 1 Erwin Ista, Erasmus Medical Center	
The authors aimed to perform a systematic review of CPG for pain, sedation, withdrawal and delirium in critically ill children, and appraise the quality of these CPG based on the AGREE II instrument. This protocol paper was clearly written. However, I have a few concerns. First, the authors described pain, sedation, iatrogenic withdrawal syndrome and delirium as symptoms. I disagree with this. For example, according the DSM-V delirium is a neurocognitive disorder. The same for withdrawal syndrome, it's defined as disorder or syndrome. Both could be observed based on different signs and symptoms. Therefore, the authors should redefine it as e.g. 'condition'.	**Thank-you for the comment, we fully agree and have changed the word "symptom" to "condition" throughout the manuscript.**
Next, the discussion was very short and strengths and limitations were obviously not surprising.	**We have reformulated the discussion to include more strengths and limitations.** (Lines 271-276)
Reviewer: 2 Dr. Kaitlin Best, University of Pennsylvania Perelman School of Medicine, The Children's Hospital of Philadelphia	
Thank you for the opportunity to review this comprehensive and well-described systematic review protocol. The authors propose to review clinical practice guidelines (CPGs) and recommendations for the management of four interrelated symptoms common to the PICU: pain, sedation, agitation, delirium, and withdrawal. This work is important as CPG development is heterogenous across organizations, and few systematic reviews exist that compile evidence across CPGs. Overall, I found this protocol to be thorough and appropriately based on rigorous methodologies, including PRISMA and AGREE guidelines, and I have very few, minor comments for strengthening the presentation of this manuscript.	**Thank-you.**
1. In the Introduction, the authors reference a few of the available instruments for assessing pain, sedation, delirium and withdrawal. However, references to other commonly used instruments, such as the CAP-D and WAT-1 scales, should also be included.	**Thank-you for this comment, we intended to include more references for delirium and withdrawal measurement instruments (including those mentioned by the reviewer) in our original draft but due to limits on the number of references, some were removed. To accommodate the need for mentioning more measurement instruments we have changed the references to that of a systematic**

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	review of measurement instruments in the same manner as the reference for pain and sedation.
2. It is unclear why the 'condition' part of the PICAR statement is focused particularly on non-communicative children, as all children in the PICU are vulnerable to experiencing pain, agitation, delirium and/or withdrawal. Please provide a rationale for this criterion.	**Thank-you for your comment, this was an oversight from an earlier version on the PICAR table. We have removed it from the table.**
3. Please justify the decision to restrict the search to 2010 onward.	**We have added the following sentence to justify our restriction to publication from 2010 and onward** (lines 120 -123)**:** Publication year will be limited to 2010 to present for two reasons. Firstly, this timeframe corresponds with a paradigmatic shift in intensive care unit sedation practice.[36] Secondly, the first consensus guideline for critically ill children was published in 2006.[22] If updated within 5 years, as recommended,[37] it would be captured within the search strategy.
4. Minor grammatical errors were noted throughout the manuscript. Please pay particular attention to use of parentheses, as they were not always closed.	**We have thoroughly reviewed the manuscript for grammatical errors, made changes and closed all parentheses.**
Other changes we would like to note	
We added to our methods for using the AGREE-REX instrument and how training of the review team will be conducted.	

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Erwin Ista Institution and Country: Erasmus Medical Center United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	23-Dec-2021

GENERAL COMMENTS	I thank the authors for addressing the comments in the revised version. I have no further comments.

REVIEWER	Reviewer name: Dr. Kaitlin Best Institution and Country: University of Pennsylvania Perelman School of Medicine, United States Competing interests: None
REVIEW RETURNED	24-Dec-2021

GENERAL COMMENTS	Thank you for the opportunity to review the revisions to this well-written manuscript. As in my previous review, my overall impression is that this protocol is comprehensive, rigorously designed, and will add to the literature. I have a few very minor comments for strengthening its presentation, as follows:

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	1. My first comment from my original review still has not been addressed. The authors are Eurocentric in their citation of the available instruments for assessing pain, sedation, delirium, and withdrawal, and in the interests of a balanced presentation of the evidence, they should also reference instruments commonly used in the US, such as the CAP-D and WAT-1. 2. While I appreciate the authors' discussion of the challenges of measuring these four overlapping symptoms/conditions in critically ill children, paragraph two of the Introduction is long and somewhat detracts from the focus of the protocol, which is principally symptom management and not measurement. Similarly, paragraph two of the Discussion is cursory, repeats the same information from the Introduction, and does not explain how this CPG review will improve symptom assessment in clinical practice. I recommend streamlining the discussion of measurement tools and/or better incorporating this information into the whole manuscript if the intention of the review is to evaluate assessment as well as management.

VERSION 2 – AUTHOR RESPONSE

Revision Comments

One change we would like to address

We revised the total number of repositories and websites to be searched by:

1. Moving the BIGG International database of GRADE guidelines up into the repositories section from websites, and
2. Adding the NICE evidence search into repositories.

These changes altered the number of repositories and websites indicated in the manuscript. Lines 141 - 142.
The supplement has been revised to show these changes.

Reviewer: 2 Dr. Kaitlin Best, University of Pennsylvania Perelman School of Medicine, The Children's Hospital of Philadelphia

1. My first comment from my original review still has not been addressed. The authors are Eurocentric in their citation of the available instruments for assessing pain, sedation, delirium, and withdrawal, and in the interests of a balanced presentation of the evidence, they should also reference instruments commonly used in the US, such as the CAP-D and WAT-1.	**Thank-you for your review of our revised manuscript and for helping to strengthen its presentation. You are correct that we did not address your original comment as the wrong citation was included. Reference 9 and 10 were unintentionally reversed. We have changed the citation to the intended review article of delirium and withdrawal assessment instruments:** (line 51) Madden K, Burns MM, Tasker RC. Differentiating Delirium From Sedative/Hypnotic-Related Iatrogenic Withdrawal Syndrome: Lack of Specificity in Pediatric Critical Care Assessment Tools. *Pediatr Crit Care Med* 2017;18(6):580-88. doi: 10.1097/PCC.0000000000001153 [published Online First: 2017/04/22]

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	This review includes the following measurement instruments: **a. Withdrawal: WAT-1, SOS, NAS/Finnegan** **b. Delirium: CAPD, PCAM-ICU, psCAM-ICU** **We have carefully reviewed the entire manuscript to ensure all references and citations align and apologize for the oversight.**
2. While I appreciate the authors' discussion of the challenges of measuring these four overlapping symptoms/conditions in critically ill children, paragraph two of the Introduction is long and somewhat detracts from the focus of the protocol, which is principally symptom management and not measurement. Similarly, paragraph two of the Discussion is cursory, repeats the same information from the Introduction, and does not explain how this CPG review will improve symptom assessment in clinical practice. I recommend streamlining the discussion of measurement tools and/or better incorporating this information into the whole manuscript if the intention of the review is to evaluate assessment as well as management.	**We have reformatted paragraph two in the introduction to remove some of the focus on measurement instruments but wanted to still highlight the importance of assessment in management and the confusion which may exists for healthcare professionals with assessment items and instruments.** Lines 48 – 68. **We made some changes in the discussion to address your comment. We hope it is clearer now.** Lines 241 - 254.

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