Author’s response to reviews

Title: MAPPING THE PREVALENCE AND NATURE OF DRUG RELATED PROBLEMS AMONG HOSPITALISED CHILDREN IN THE UNITED KINGDOM: A Systematic Review

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Author’s response to reviews:

Dear Dr Zyoud;

We were delighted to receive your peer review assessment for this manuscript on October 15th. We thank you for your time, and are deeply grateful to your reviewers for their time and contribution. We welcome all the reviewers’ comments and are pleased to respond to each point in the table below.

Reviewer 1 - Rand Randall Martins

“…the work was restricted to the safety aspects of drug use. As known, DRPs may also describe ineffectiveness and unnecessary drug use, aspects not addressed in the study. In fact, it is a review of adverse events. I believe that readjustment would be more appropriate for this purpose.”

Many thanks for this comment. We would respectfully argue that this review set out to identify all studies of DRPs in the UK context, but that the existing UK literature has been restricted to the safety aspects. Through our search we found no studies specifically studying the necessity of prescribing in CYP in-patient settings. There were actually two papers included in the narrative synthesis (Ibrahim et al. 2014; Rashed et al 2016) which do explore necessity and effectiveness and we have presented the data from these studies on page 19 para 2 (DRPs as a specific outcome).

To clarify their place in this review we have included some critique of the assessment method used in comparison to the rest of the literature, but they serve to provide an interesting insight into the complexities of medication use in this population (Page 19, line 447-451)
“I suggest that the introduction starts with the definition of DRPs and what their main categories are (effectiveness, safety and necessity). Then highlight the interface between the term adverse events and DRPs.”

This is a very useful suggestion and we have brought forward and adapted our discussion around definitions into the introduction (on page 3 para 2) per your suggestion.

Reviewer 2 - A Gouveia Oliveira

“Given the heterogeneity of the pediatric population and of the study designs, I think it would be most useful to provide more information in Supplementary File 3 on those aspects of the studies … , it would be important to know for each study whether it was conducted in a general pediatric wards or in a specialized pediatrics department; what was the age range of the study populations; the number of patients providing data; in observational studies whether they were cross-sectional or cohort and, in the latter case, whether patients were observed throughout the entire hospitalization; in multi-centre studies how many centers collaborated; how and by whom were DRPs detected; whether there was an CPOE system with or without a coupled medication alert system.”

Thanks for this very helpful direction. We have included this information in Supplementary File 2. We appreciate that you have suggested that we include this information in Supplementary File 3, but this serves as a summary only of the assessments of quality. Supplementary Table 2 outlines the information that we have used to assess this and thus makes for a better home for this data. It will still provide readers with an opportunity to assess the generalisability of the study data.

“So in a way this may be seen as a meta-analysis that is not using the adequate meta-analytical methodology. In my opinion, presenting the median estimate is rather confusing as this statistic ignores the precision of the several studies, giving equal weight to studies with 20 and with 200 observations. I understand the authors' argument that the large heterogeneity across studies, along with the small number of studies, may make meta-analytical estimates unreliable. Still, in my opinion they are more meaningful than the median estimate.”

This is a very interesting point and we welcome the opportunity to review and discuss, having considered this at length during analysis.

The majority of the included studies were cross-sectional studies and there were marked differences in how outcomes were operationalised between studies. This was demonstrated in the very different rates reported in studies purporting to measure similar outcomes. This, in our opinion, would have made pooled estimates using the mean less reliable. The use of median and IQR give readers an idea of the prevalence of these events, and the variation in the prevalence between studies. We have clarified this decision in the methods section (Page 9, Line 221)

Reviewer 3 - Ali Mohammed Sabzghabee
"It deserves for publication in BMC Pediatrics because the message of it should be repeatedly advised to clinicians for the sake of pediatric patients safety".

We are grateful for your encouragement.

We have made the following small changes as well:

<table>
<thead>
<tr>
<th>Page</th>
<th>Line</th>
<th>Change</th>
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<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>Insertion of middle initial for author</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>Deleted erroneous spacing</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>Corrected the search period</td>
</tr>
<tr>
<td>4</td>
<td>114</td>
<td>Capitalisation of C in “children”</td>
</tr>
<tr>
<td>6</td>
<td>144</td>
<td>Clarification of definitions used in the review</td>
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<tr>
<td>8</td>
<td>200</td>
<td>Correction of number of intensive care studies identified (7)</td>
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</table>

We trust that all is in order and that we have dealt with your reviewers comments adequately. In the spirit of open discussion and debate, we welcome further comments and feedback.

We look forward to hearing from you

Yours sincerely

Adam Sutherland