## PEER REVIEW HISTORY

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## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | STANDARDISING NEONATAL AND PAEDIATRIC ANTIBIOTIC CLINICAL TRIAL DESIGN AND CONDUCT: THE PENTA-ID NETWORK VIEW |
| **AUTHORS** | Folgori, Laura; Lutsar, Irja; Standing, Joseph; Walker, Sarah; Roilides, E; Zaoutis, Theoklis; Jafri, Hasan; Giaquinto, Carlo; Turner, Mark; Sharland, Mike |

## VERSION 1 – REVIEW

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| **REVIEWER** | Catherine Sherwin<br>Department of Pediatrics,<br>Wright State University Boonshoft School of Medicine<br>Dayton Children's Hospital<br>Dayton, Ohio, USA |
| **REVIEW RETURNED** | 15-Sep-2019 |

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| **GENERAL COMMENTS** | This commentary outlines a pathway to trying to improve how neonatal and pediatric antibiotic trials clinical trials can be undertaken. The authors have done a good job in outlining the direction the network wants to go in.<br>Minor comments<br>Abstract<br>Pg 4, line 8, it is discussed here that the suggestion is to use adult EMA guidance be adapted for neonates and children. Is there any plan to develop a specific plan that provides guidance for children that is not an adaptation from an adult one?<br>What is the problem<br>Pg 6, under the general principles there is a reasonable list of what is provided in the suggested guidance. Have you considered the barriers that will be faced to implement something like this and how those will be addressed? The other question, who will oversee the setting of “harmonization” between regulatory and strategic trails.<br>General Principals<br>Pg 6, line 10 with the proposal to develop similar standards across different studies. Who has the responsibility for this, the sponsor, or regulatory authorities?<br>Pg 7, line 10 In general, I think this proposal for antimicrobials is a reasonable goal to set up something along these lines. Would this process work for other drugs, other diseases that are studied? Why limit to “well-established” drug classes? Is this then a limitation for what is being proposed here?<br>Pg 7, there is mention of the structure that has been set up I paediatirc HIV, so are there lessons that have been learned from the developmental of that structure that can be applied here to antimicrobials? |

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| **REVIEWER** | Elise LAUNAY<br>Pediatrics department, CHU Nantes, France<br>INSERM U1153, Paris, France |
| **REVIEW RETURNED** | 01-Oct-2019 |

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| **GENERAL COMMENTS** | Here are the specific points to address for communications articles<br>- Are the issues raised by the article important to BMJ Open's broad and international<br>readership that includes patients, researchers, policy makers, health professionals, and<br>doctors of all disciplines ?<br>Certainly, it of major importance for all the people interested in children health to get specific recommandations to study medication in children and neonate ans particularly antibiotics. "Children are not just small adults"<br><br>- Is the article interesting and offering novel insights that have not been sufficiently<br>considered in the existing published literature?<br>Yes, this article raises and important ans so far somehow neglected issue. It reports and multidisciplinary and original work to improve quality and avoid waste in medical research<br><br>-Is the article well written and is the content clearly presented? Does it have a clear<br>message?<br>Yes, I just have a comment concerning a sentence that may be ambiguous. Page 8 " First, the rates of Aes/serious Aes in children are generally low". The "/" may be interpreted as division (rate) meaning that the number serious Aes are higher that Aes and then that the rate is low....authors might replace the "/" by and : "the rates of Aes and serious Aes are generally low"<br>my second comment concern the choice of 1/20 (5%) for Aes which may seem to high for serious events. It may be useful to precise how the experts chose this cut-off (the reference 13 does not refer to this choice)<br><br>- Will the article help medical researchers, patients or related groups of readers to make better decisions?<br>Yes, the aim of the article is to provide guidance to researcher to conduct appropriate antibiotic clinical trials. This guidance would also be useful for the policy makers by giving them critical point when analyzing antibiotic clinical trials for children and neonate<br><br>- Does the article demonstrate one or more of the following values: transparency, openness, collaboration, innovation, reproducibility, patient/ public involvement, improving peer review and journal best practice, and reducing research waste<br>This article demonstrate several of these values: collaboration, patient and public involvement (children and neonate deserve good quality trials and have specificity that should absolutely be taken into account), improving peer review (this guidance should serve for the reviewing of study), and it would definitely contribute to reduce research waste.<br><br>Thank you for giving me the opportunity to review this paper. It is of major importance to raise awareness about the children and neonates specificity in clinical trials. Did the authors consider to complete this guidance by proposing a specific reporting guideline as a variant of CONSORT ? |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Catherine Sherwin
This commentary outlines a pathway to trying to improve how neonatal and pediatric antibiotic trials clinical trials can be undertaken. The authors have done a good job in outlining the direction the network wants to go in.
Minor comments
Abstract
(2) Pg 4, line 8, it is discussed here that the suggestion is to use adult EMA guidance be adapted for neonates and children. Is there any plan to develop a specific plan that provides guidance for children that is not an adaptation from an adult one?
(2) Thank you for this comment. The WG decided to adapt the adult EMA criteria for children and neonates in all those CIS in which a similar pathophysiology and a similar spectrum of pathogens across the target age groups could be supposed. This has been also the principle that has be adopted in the Paediatric Addendum for the extrapolation of efficacy against an infectious disease from adults to paediatric patients. This situation applies to the majority of infectious diseases that occur both in adults and in one or more paediatric age sub-groups. However, there are some cases in which the pathophysiology and the spectrum of pathogens differ substantially between children/neonates and adults. This is the case of neonatal sepsis (neonatal Severe Bacterial Infection). In this case, age-specific criteria have been adopted specifically designed for the neonatal age. Other examples of differences from adults are when drugs have specific age-dependent toxicities or there is absence of valid diagnostic biomarkers in neonates and children for specific infectious syndromes therefore hampering the extrapolation process.
What is the problem
(3) Pg 6, under the general principles there is a reasonable list of what is provided in the suggested guidance. Have you considered the barriers that will be faced to implement something like this and how those will be addressed? The other question, who will oversee the setting of “harmonization” between regulatory and strategic trails.
(3) We are well aware of the difficulties in the attempt to harmonise the design and conduct of paediatric clinical trials. However, as stated in the manuscript, the collaboration between clinical academic clinical trial networks and pharma is improving. In our experience, one of the major barriers in conducting CTs in children is the complexity of the inclusion/exclusion criteria often limiting significantly the enrolment process. The group therefore attempted to draft criteria for each CIS that would be as simple and inclusive as possible, to try and encourage as wide an adoption as possible of this guidance by both clinicians and industry. The next step will be a further discussion of this guidance internationally with investigators, paediatric clinical trials networks and regulators. Our experience is that investigators are keen to use widely recognised criteria when available. Regarding the other question, this WG has been developed by the board of the EnprEMA in collaboration with academic, regulatory and industry representatives of both the US and Europe. The main regulatory agencies (including the EMA, the FDA and the Japanese PMDA), paediatric clinical trial networks and industry have been involved, with the aim to reach a broader audience as possible.
General Principals
(4) Pg 6, line 10 with the proposal to develop similar standards across different studies. Who has the responsibility for this, the sponsor, or regulatory authorities?
(4) The regulatory agency has the responsibility for the approval of clinical trials designed for obtaining a marketing authorisation for a new molecular entity. The sponsor has the responsibility to ensure that the protocol is designed to be as efficient as possible and reflects the relevant current guidance documents for that specific clinical infection.
(5) Pg 7, line 10 In general, I think this proposal for antimicrobials is a reasonable goal to set up something along these lines. Would this process work for other drugs, other diseases that are studied? Why limit to “well-established” drug classes? Is this then a limitation for what is being

proposed here?
(5) Yes, we think this could be an example for other drugs and other disease areas. This process would be relevant to other antimicrobials such as antivirals and antifungals, where the heterogeneity of published studies limits the wider use of the available data. We limited this guidance to “well-established” drug classes because this pathway is largely based on the extrapolation process. Given this, it is more difficult to extrapolate efficacy or safety data when the pathophysiology of the disease is expected to differ significantly across different age groups or for new drugs that do not have a very well described safety profile. There are many limitations to the approach that is being described here, including the lack of evidence base for some of the recommendations, but these are clearly laid out in the text.
(6) Pg 7, there is mention of the structure that has been set up I paediatirc HIV, so are there lessons that have been learned from the developmental of that structure that can be applied here to antimicrobials?
(6) Although not the focus of this paper, the main lessons learnt are around pharmacovigilance for new drugs as part of post marketing surveillance. This is an increasingly important area for all medicines as key regulatory trials have smaller sample sizes related to cost considerations. We have recently published an example of how data can be obtained from different sources to enhance this type of surveillance activity and have added a short section to the text (Sharland M, Pediatr Infect Dis J. 2019 Jul;38(7):710-715). We revised the paper on page 7.

Reviewer: 2
Reviewer Name: Elise LAUNAY
(7) I just have a comment concerning a sentence that may be ambiguous. Page 8 " First, the rates of Aes/serious Aes in children are generally low". The "/" may be interpreted as division (rate) meaning that the number serious Aes are higher that Aes and then that the rate is low....authors might replace the "/" by and : "the rates of Aes and serious Aes are generally low"
(7) Thank you for this comment. The text have been changed accordingly on page 8.
(8) My second comment concern the choice of 1/20 (5%) for Aes which may seem to high for serious events. It may be useful to precise how the experts chose this cut-off (the reference 13 does not refer to this choice)
(8) Thank you for this question. The 5% threshold, as the majority of thresholds, is arbitrary. However, 5% is an accepted level for Type I error (false-positive). Further, we would note that operationally we have implemented this in Table 1 as sufficient numbers such that an observation of 0 events (i.e. 0% event rate) has an upper limit of the 97.5% CI that is below 5% (lower limit is 0% by definition). We revised the manuscript on page 8.
(9) Thank you for giving me the opportunity to review this paper. It is of major importance to raise awareness about the children and neonates specificity in clinical trials. Did the authors consider to complete this guidance by proposing a specific reporting guideline as a variant of CONSORT ?
(9) Thank you for this comment, this is a very important topic. Considering the limited data currently available on paediatric pharmacology, it is clear that robust evidence of efficacy and safety of different drugs in children can only be gained if CTs are properly conducted and reported. This issue was raised by Agnès Saint-Raymond et al. (Lancet 2010; 376(9737): 229-30) who suggested additional reporting requirements to the 2010 CONSORT Statement specifically for trials in children. Data on neonates are even more limited. To improve the quality of reporting and strengthen research in this age group, an extension of the STROBE statement for neonatal infection research has been published recently – STROBE-Neonatal Infection (Fitchett EJ et al, Lancet Infect Dis 2016; 16(10): e202-13). This would help the process of harmonisation in data collection and reporting, therefore increasing translation of results into clinical practice.