Author's response to reviews

Title: Drug related problems in Neonatal Intensive Care Unit: incidence, characterization and clinical relevance

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Response to reviewers' comments (second review)

The authors are grateful to the reviewers for their comments that helped us to improve our paper. Below are the responses to the two reviewers.

Luke Grzeskowiak (Reviewer 1): The authors have done a reasonable job in responding to previous reviewer comments. I have only a few more additional comments below. A couple have arisen as a result of the new supplemental files attached, while a couple relate to appropriately addressing previously reviewer comments. The additional of the supplemental files is useful in providing the reader with additional information to interpret and determine the clinical relevance of this paper to their own clinical practice. I do, however, have some concerns regarding the interpretation/reporting of some of the classifications.

1. No clinical example has been provided for C1.3. "inappropriate combination of drugs, or drugs and food" - yet under C5.5 the example provided for "Wrong drug administered" is "intravenous drug administered concurrently with another incompatible drug". Wrong drug accounts for 164 DRPs but this example does not fit with the definition. C5.5 would be situations where the completely wrong drug was administered. The example of incompatible drugs being given together actually fits with C1.3. Please amend these.
R: We included the C1.3 example ("patient is receiving ciprofloxacin and fluconazole, medicines that may increase the risk of QT interval prolongation and, consequently, ventricular arrhythmias") and changed C5.5 example to "norepinephrine was administered in the wrong route".

2. C3.7 - it is interesting that "pharmacokinetic problems requiring dose adjustment" was considered not applicable for the study, yet a number of medications used in neonatal unit require pharmacokinetic assessment. Does this mean pharmacokinetic evaluation and dosage adjustments of vancomycin, amikacin, gentamicin, theophylline were not taken into consideration?

R: As most newborns are very premature, the therapeutic drug monitoring is not a usual practice in the institution. We understand this as a limitation of the study, so we add the sentence: "Lastly, the therapeutic drug monitoring service is not a usual practice in our NICU, so it is possible that some DRPs have been underestimated" (Discussion – page 11).

3. C6.2 example provided is "vancomycin is prescribed without the infusion time" - presume this is meant to mean that vancomycin was prescribed without a specified administration time - the infusion time would not be something to be expected to be specified on the medication prescription as it would be standardised as part of the medication administration procedure. Please clarify.

R: We changed the sentence of C6.2 example for "vancomycin is prescribed, but there is no information on the minimum recommended time for administration".

4. C8.2 "No obvious cause" - no example is listed of DRPs that were classified in this section. Given this accounts for 76 DRPs it would be useful to know what types of things this included as it is completely unclear at this stage what it would include.

R: All the causes of DRP classified in the "C8 – Other" domain have been specified ("C8.1 – Others specific causes" subdomain), so we changed the "C8.2 – No obvious cause" subdomain from "There is a DRP with no obvious cause" to "Not applicable for the study". We could not identify a possible cause in this classification. However, we detail in Table 3 the DRP types related to the C8 - other domain.

5. I completely disagree with the statement that results can be safely generalised to other NICUs. The reality is that this cannot be assured and therefore a limitation of this study is whether results
are generalizable to other units. It is already mentioned that certain medication error prevention strategies are not implemented in this specific neonatal unit, so that factor alone means the distribution and type of DRPs in neonatal units is likely to be different based on support strategies in place. Please amend this as a limitation.

R: This limitation is highlighted in the sentence: “Firstly, the study was conducted in a single NICU, which may limit generalization of the results” (Discussion – page 11).

6. Reference 27 is not adequate as evidence of error prevention strategies - please cite a systematic review on medication safety error prevention strategies specific to the neonatal unit setting. E.g. Nguyen et al (2018). Interventions to Reduce Medication Errors in Neonatal Care: A Systematic Review. Therapeutic Advances in Drug Safety. 9 (2): 123-155. There are also others that could be cited.


7. It should be noticed that in our study the DRPs occurred even though the NICU has an institutional clinical practice guideline” - this statement does not make complete sense and does not specifically address the reviewer comment. Please specify whether or not specific dosing guidelines are available for all medications where dosing errors were present.

R: This sentence was changed to “It should be noticed that in our study the DRPs occurred even though the NICU has an institutional clinical practice guideline that includes dosing guidelines for all drugs” (Discussion – page 9).

8. I agree with the other reviewer regarding the questionable validity of the safety-relevance assessment. This really needs examples around things classified as being minor, significant or high relevance. The additional description provided in the text regarding the limitations associated with this specific part of the method is not adequate. This needs a statement highlighting the limitation that it was only the pharmacist evaluating severity, had clinicians been involved the severity assessments may have been different. There does not appear to be inter-rater agreement evaluated between assessors to see what level of agreement there actually was either in terms of severity assessment. Please amend wording in discussion accordingly.

R: We include in the limitations (Discussion – page 11) the following sentence: “Thirdly, the evaluation of the safety-relevance of the DRPs was made only by pharmacists with an unvalidated tool and supported by Neofax® 2011, which in part may have compromised this
analysis. However, in the context of DRPs, we consider the relevance-safety analysis more adequate than just severity, because it combines the severity of a potential adverse event with its likelihood, offering a better measure of the potential risk to which the patient was exposed”.

Reviewer 2: "REVISION ASSESSMENT FROM THE ACADEMIC PEER REVIEWER.

1. I only have two specific, minor suggestions

firstly, the use of neofax 2011 is another limitations that should be mentioned in the discussion part.

R: We include in the limitations (Discussion – page 11) the following sentence: “Thirdly, the evaluation of the safety-relevance of the DRPs was made only by pharmacists with an unvalidated tool and supported by Neofax® 2011, which in part may have compromised this analysis. However, in the context of DRPs, we consider the relevance-safety analysis more adequate than just severity, because it combines the severity of a potential adverse event with its likelihood, offering a better measure of the potential risk to which the patient was exposed”.

2. Secondly, I suggest to further stress at the end of the introduction that the most relevant DRP the unlicensed and off label use of drugs is in neonates, perhaps with adding a reference (like Ward et al, Pediatr Research 2017): studies have not yet adequately addressed the therapeutic needs of neonates.

R: We added in the third paragraph of the introduction (page 3) the following sentence: “The latter condition is even more worrying due to the lack of studies adequately addressing the therapeutic needs of neonates (Ward et al., 2017)”.