**Reviewer’s report**

**Title:** Practice variation in anti-epileptic drug use for neonatal hypoxic-ischemic encephalopathy among regional NICUs

**Version:** 0  **Date:** 23 Oct 2018

**Reviewer:** Sonia Bonifacio

**Reviewer's report:**

This is a well designed and well written manuscript. It is important information that is needed to improve the quality of care provided to this group of patients.

I think there is an opportunity within this data set to also evaluate if over the course of time there has been change in practice across centers. Specifically related to the question of use of AEDs without EEG seizures, especially in the several centers that expose patients to AEDS who do not have EEG seizures > 40% of the time. These centers may have changed practice between 2010 and 2016 (hopefully). In addition figure 1a could also be done by removing patients with 'clinical seizures only' and then we can see if the variation by center is related to clinical only vs EEG confirmed seizures. Only by looking at the data over time can we then take the data to inform a CHND QI project because what is happening now or in the last year of data that you have may be very different from what was happening in 2010.

A few other areas that I suggest you evaluate and present in this manuscript:

1. Can you present the size of each center in terms of number of critical care beds?

2. What is the average number of babies per center that is treated with TH per year? Is this changing over time? Is the number of babies with diagnosis of seizures changing over time? As we educate and improve our use of EEG or aEEG are there fewer babies being diagnosed with clinical seizures only?

3. Of the 20 centers reported included how many actually have some sort of a NEURONICU or a team dedicated to providing neurocritical care? Is the presence of a NeuroNICU team or daily involvement of a neurologist associated with decreased variation in care? Surely you can also survey the centers as ask if it was usual practice to provide prophylactic phenobarbital.

4. In the background I am not sure that you can say there is a lack of consensus about the order of AEDS - from your data and from others it appears that most places still use PHB
as first line agent. When we write in manuscripts that there is a 'lack of consensus' then it encourages others to try Lev as a first line agent when we don't actually know that it is any better than PHB and it is as you have shown far more costly.

5. On page 6 line 51 Data Analysis section - there is an 'in' or 'in AED' missing after you write "ICV (should insert either in or in AED) duration was evaluated..."

6. In section labeled AED selection - there were only 757 patients who received any AED - therefore it is not possible to say that 452 received only 1, 317 received 2, and 483 received 3 or more AEDs.

7. In the discussion you mention trends over time - should also evaluate if there was a trend over time in Exposure to AEDs without EEG seizures.

8. In the discussion - should also mention staggering cost of Lev when there is no evidence that it is any better than PHB, especially as first line and also in general. One way to drill down on LEV use would be to see how many patients of those that only received 1 AED received LEV - this way you know if it is being used as first line in which case this is another opportunity for QI.

9. Discussion - since you are proposing this as data to be used in a QI project one would wonder and should postulate - do we have an idea about what amount of AED exposure without EEG seizures we should accept - clearly 81% in center 18 is too high - but should the goal be 20%?

10. You could also mention that the AAP has made recommendations for what services should be available at centers that provide TH. In California, the governing body that certifies NICUs has mandated which services must be available in order to be a TH center. Those centers that can not comply with the requirements must close their programs until they can provide the services, education, training that is needed to be a TH center. Can google - CCS numbered letter therapeutic hypothermia. This set of requirements was developed by key stakeholders and providers at regional NICUs.


11. Please review numbers in table 1. In particular row "treated with AED" the % listed under column of EEG seizure can not be 59%. 447/472 is 95%, 310/1186 is 26% not 40.9%
12. Another possible analysis - how many of the 'mild HIE' patients received AEDs and then broken down by EEG seizures or not. This is another important QI topic - why are we cooling so many milds - clearly part of this is a definitional problem using the VON definition is probably not accurate - and are we causing them harm.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
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