Author's response to reviews

Title: Preliminary Evaluation of Near Infrared Spectroscopy as a Method to Detect Plasma Leakage in Children with Dengue Hemorrhagic Fever

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Author's response to reviews: see over
We thank the reviewers for the time they took to review our manuscript and the helpful comments that were provided. We have addressed their comments in this revision of the manuscript with clarification below for each comment.

**Reviewer 1**

**Question 1: Was the assignment of fever day 0 done prospectively or retrospectively, and if so, was this done independently?**

The initial assignment of fever day was done prospectively as chest x-rays for PEI were to be done on fever day +1. However, in a few instances, fever recurred (‘saddleback fever’) and the fever day was reassigned retrospectively.

**Question 2: Since temperatures were measured 6 hourly, and day 0 was when temperature <38 Celsius, there would be a lag phase of 6 hours in day 0. How would this affect the interpretation of the NIRS data? A shift in the time frame may have an impact on the presentation of results as shown in Fig. 4.**

Fever time zero was done to normalize all data to the same time period for statistical analysis as this timing is more precise than the determination of fever day 0. We agree that the assignment may be somewhat artificial, but we showed in Figures 2 and 5 that any day that NIRS-determined SmO2 was less than 48% there was a strong likelihood that there was plasma leakage. With this information, you don’t need to know what the fever day is, just that SmO2 is low.

**Question 3: Although NIRS data was collected almost continuously, ultrasound exam of plasma leakage was done at intervals. So does the time of decrease of NIRS simultaneous with maximum plasma leakage by ultrasound?**

We only used qualitative ultrasound analysis, either plasma leakage was present or not, so we have not examined whether the lowest SmO2 corresponded to the maximum amount of plasma leakage on a given day. However, in Figure 4 we show that there is a correlation between the amount of fluid (as measured by pleural effusion index) and SmO2.

**Question 4: How do you interpret the decrease in SmO2 – was this due to increase interstitial fluid from plasma leakage or due to hypovolemia? Whichever way the NIRS data is interpreted, may lead to conflicting treatment strategies.**

At this time we do not know if the decrease in SmO2 is a result of hypovolemia or increased interstitial fluid. We do not suggest that SmO2 alone would be used to make treatment decisions. The clinician would know if the patient has been given fluid or not and could use this information, along with other clinical data to decide on treatment strategy.
Reviewer 2

Specific comments: The introduction should end with the research objectives of this study, not with the end result. Delete that sentence.
We have deleted the sentences that described the results from the introduction.

Methods: It would be nice to add a picture of the instrument so that the reader can have an idea about the size and appearance of NIRS. It would also be nice to find out whether the patients or nursing staff found this device as a nuisance or whether it was well tolerated and acceptable on a daily basis. Information whether the patients have to lie in bed throughout the monitoring would be important for the reader to know. Most importantly, what is the cost of NIRS? IF we are looking for alternative point of care diagnostic tools to chest x ray or ultrasound, we need to know whether NIRS would be more cost effective and also practically feasible on a routine basis in resource limited countries.
The NIRS sensor used in the study is shown in Figure 1. We’ve added text in the methods section to describe the 10” touch screen computer that runs the software for the CareGuide 1100 product (lines 131-132). The CareGuide 3100 product runs on an Android tablet. The interface is simple and was easily managed by nurses in our study. The question of cost was commented on in the rewritten discussion (lines 223-225).

Results: please add the mean day of admission after onset of fever.
Table 1 captures the “Days ill prior to enrollment”.

Discussion: discuss the true value of a possibly expensive device with continuous monitoring in all dengue patients given that only a small proportion proceeds to more severe disease? How can nurses or doctors obtain the results and values in real-time, or are complex methods needed to calculate real-time results for cut-off values? Can a cutoff value be applied in routine settings? What are your suggestions for next studies to enhance our knowledge of the applicability of this method?
The prototype sensor used in the study had mobility limitations that the current CareGuide products do not. The CareGuide product has a removable sensor, attached to a foam pad that adheres to the patient’s skin. If the patient needs to leave the bed monitoring can be paused and the sensor removed from the foam pad. When the patient returns, the sensor is reattached and monitoring resumes. The battery powered CareGuide 3100 is totally portable with an Android tablet and can continue to monitor the patient when they are not in bed.
The CareGuide sensor provides real-time output of SmO2; this was clarified in lines 218-219 of the manuscript. Once the cut-off value is validated in studies of children and adults, our next study (lines 221-222) one would look at real-time trends to determine if the patient is at risk. Figure 2 provides an indication of what a real-
time trend would look like. The CareGuide product displays each SmO2 reading on a trend screen, though currently there is no opportunity to set an alarm or cutoff value.

The CareGuide product is significantly less expensive than chest x-ray or ultrasound, which are not routinely used in resource limited countries. We do not feel it is appropriate to list the cost or the product details in the manuscript, as we do not want to appear to be promoting a product. While the cost is modest, we recognize that in its current state is may still be too expensive for many places (noted in lines 223-225 of the manuscript). As we continue to study the clinical utility we are also investigating methods to reduce the cost so it could become available on a routine basis in most locales.

Conclusion: Add the cut-off value.

The cut-off value was added (line 230)