June 14, 2017

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Kristina Borror, Ph.D.
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Re: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (also known as the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial or SUPPORT trial)
Sponsor: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network
ClinicalTrials.gov Identifier: NCT00233324

Dear Drs. Menikoff and Borror:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, hereby requests that the Office for Human Research Protections (OHRP) immediately expand its ongoing compliance oversight investigation of the SUPPORT trial to evaluate newly uncovered information — recently obtained by Public Citizen under the Freedom of Information Act (FOIA) — that reveals additional major ethical lapses and failures to materially comply with key requirements of the Department of Health and Human Services (HHS) regulations for the protection of human subjects at 45 C.F.R. Part 46 during the investigators’ conduct of the trial.

On March 3, 2017, Public Citizen obtained key SUPPORT trial-related documents that we originally sought from the National Institutes of Health (NIH) under FOIA in April 2013 and that the NIH finally released during the course of litigation brought by our organization against the HHS. These documents reveal that in June 2008 — while enrollment in the SUPPORT trial was still ongoing — the lead SUPPORT trial investigators were informed about serious problems with the experimentally masked pulse oximeters (oxygen monitors) that were being used in the trial. These problems with the pulse oximeters — which were first uncovered by researchers in the U.K. who were conducting a trial that was nearly identical to the SUPPORT trial’s oxygen
experiment and which were eventually linked to a defect in the devices’ underlying calibration software — raised additional troubling concerns about the following:

(1) The safety of subjects enrolled in the trial (particularly those randomly assigned to the low-oxygen group, because the oxygen monitor problems were unexpectedly causing babies in this group to have excessive exposure to blood oxygen levels below the range considered to be safe);

(2) The truthfulness of key statements in the institutional review board (IRB)-approved consent forms signed by the parents of premature babies enrolled in the trial; and

(3) The soundness of the trial’s design.

For these reasons, the information about the problems with the pulse oximeters clearly represented an unanticipated problem involving risks to subjects that should have been promptly reported to the IRBs that reviewed and approved the trial, appropriate institutional officials at each participating institution, the NIH or NICHD Director, and the OHRP, as required by HHS regulations at 45 C.F.R. §§ 46.103(a) and (b)(5).

Moreover, the information about the problems with the pulse oximeters would have been directly relevant to the IRBs’ determinations, which are required for approval of research involving human subjects, regarding whether:

(1) The risks to the subjects were minimized by using procedures that were consistent with sound research design and that did not unnecessarily expose subjects to risk, as required by HHS regulations at 45 C.F.R. § 46.111(a)(1);

(2) The risks to subjects were reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result, as required by HHS regulations at 45 C.F.R. § 46.111(a)(2); and

(3) The information that was being provided to subjects’ parents when their consent was sought included an adequate description of the trial’s research procedures and reasonably foreseeable risks, as required by HHS regulations at 45 C.F.R. §§ 46.116(a)(1) and (2).

Upon learning about the serious problems with the pulse oximeters, the ethically appropriate course of action for the investigators to take would have been to immediately suspend subject enrollment in the trial, terminate further use of the experimental pulse oximeters in already enrolled subjects, promptly report the problems to the responsible IRBs, and wait for the outcome of the IRBs’ review of the oxygen monitor problems and reassessment as to whether the trial still satisfied the ethical and regulatory requirements for approval and therefore should be allowed to continue and, if so, under what conditions.
Disturbingly, the SUPPORT trial investigators — apparently reluctant to delay the progress of their research — continued to enroll more than 200 additional subjects in the trial and to use the defective pulse oximeters after learning about the devices’ serious, potentially life-threatening problems. In addition, our review of internal documents that we obtained from the NIH and OHRP provided no evidence that the problems with the pulse oximeters and their adverse effects on the safety of the subjects and the soundness of the trial’s design were ever reported to the IRBs responsible for reviewing and approving the trial or to the OHRP. The apparent course of action taken by the investigators, if confirmed, represents a reckless disregard for the safety of the trial subjects and major breaches of fundamental ethical principles and regulatory requirements governing research involving human subjects.

Below is a more detailed discussion of the newly discovered information regarding the SUPPORT trial and the apparent additional major ethical and regulatory lapses that Public Citizen has uncovered.

Overview of the SUPPORT trial design

As the OHRP is well aware, the SUPPORT trial involved 1,316 extremely premature infants enrolled between February 2005 and February 2009 at approximately two dozen medical centers across the U.S. 1 The infants in the trial were born at approximately 24 to 28 weeks of gestation. 2 The trial is ongoing as the investigators collect data on long-term outcomes in the surviving subjects. 3

The SUPPORT trial involved two simultaneous experiments. In one experiment (the ventilation experiment), the babies were randomly divided into two groups, and each group received a different treatment to assist their breathing following delivery. 4 Babies in one group were treated with a face mask, called a continuous positive airway pressure (CPAP) mask, to deliver pressurized air supplemented with oxygen (CPAP group). Babies in the other group were intubated (underwent an invasive procedure involving insertion of a tube into the trachea, the main airway leading to the lungs); given the life-saving drug surfactant, which prevents the lungs from collapsing; and then treated with mechanical ventilation (an artificial breathing machine; mechanical-ventilation group).

For the other, simultaneous experiment, babies assigned to both the CPAP and mechanical-ventilation groups were further randomly divided between a high-oxygen group and a low-

2 Ibid.
oxygen group.\textsuperscript{5} For the high-oxygen group, the SUPPORT trial investigators tried to maintain the babies’ blood oxygen levels in a high target range (oxygen saturation level of 91% to 95%), and for the low-oxygen group in a low target range (oxygen saturation level of 85% to 89%). While the high oxygen target range was consistent with usual care, the low range was not used outside of the SUPPORT trial according to surveys and clinical studies of usual care.\textsuperscript{6} The researchers then measured the effect of the two target ranges of oxygen levels on the premature babies – specifically, whether infants in one group were more likely than those in the other group to die, suffer brain damage, or develop an eye disease called retinopathy of prematurity, which can cause blindness.\textsuperscript{7}

For the SUPPPORT trial, the investigators used commercially available pulse oximeters that were manufactured by Masimo — one of several companies that make such devices — to monitor the babies’ oxygen levels. For the purposes of the SUPPORT trial’s oxygen experiment, the pulse oximeters were modified by Masimo: A masking algorithm was programmed into the pulse oximeters so that the caregivers for the babies enrolled in the trial would not know to which oxygen group the subjects had been assigned.\textsuperscript{8} Across the range of oxygen saturations measured by the pulse oximeter between 85% and 95%, the displayed values were as much as 3% lower in the high-oxygen group and 3% higher in the low-oxygen group than the actual measured oxygen levels. Caregivers were instructed to try to maintain all babies enrolled in the trial at a displayed oxygen level of 88% to 92%, which was supposed to correspond to an actual measured level of 91% to 95% in the high-oxygen group babies and 85% to 89% in the low-oxygen group babies.

During the course of the SUPPORT trial, a problem was detected with the underlying calibration software of commercially available Masimo pulse oximeters that was unrelated to the trial. This calibration problem resulted in a 1% to 2% overestimation of oxygen saturation measurements, especially between values of 87% and 90%,\textsuperscript{9} which overlapped with the upper range of the low-oxygen group’s target range. Importantly, when the SUPPORT trial began, the investigators had no idea how their experimental masking algorithm would interact with the underlying calibration software of the Masimo pulse oximeters and affect the actual levels of oxygen to which the babies would be exposed over the course of their participation in the experiment, which could have lasted for as long as approximately 12 weeks.

As we explained in detail in our May 8, 2013 report to Secretary Sebelius, the use of the experimental masked pulse oximeters, which provided inaccurate information to caregivers about the babies’ actual oxygen levels, could have adversely affected critically important clinical decisions about whether to start or stop mechanical ventilation treatment in the babies enrolled in the trial under protocol-stipulated experimental criteria for starting or stopping such treatment under the ventilation experiment.10

New evidence of major ethical and regulatory lapses

Emails and other documents that Public Citizen recently obtained from the NIH under FOIA reveal (a) when and how the SUPPORT trial lead investigators learned about serious problems related to the experimentally masked Masimo pulse oximeters that were being used in the trial and (b) the actions (or lack thereof) that the investigators subsequently took in response. The following are important excerpts from those emails and pertinent attachments, followed by key observations regarding each (excerpts below are marked with italics; copies of the complete emails and attachments are enclosed):

(1) June 12, 2008, 7:43 AM email from Peter Brocklehurst, Professor of Perinatal Epidemiology; Director, National Perinatal Epidemiology Unit, University of Oxford; and a lead investigator for the Benefits of Oxygen Saturation Targeting (BOOST) II UK trial, one of several other clinical trials that was nearly identical to the SUPPORT trial’s oxygen experiment and that used the same experimentally masked Masimo pulse oximeters (Enclosure A):

- Sent to: Neil Finer, M.D., Professor of Pediatrics and Director, Division of Neonatal-Perinatal Medicine, University of California, San Diego School of Medicine; and a lead investigator for the SUPPORT trial
- Subject: BOOST II UK
- Cc: Edmund Hey, a lead investigator for the BOOST II UK trial; Ben Stenson, a lead investigator for the BOOST II UK trial; and Ed Juszczak, statistician for the BOOST II UK trial
- Message excerpts:

  Dear Neil

  I know that you have been having some email correspondence with Ben Stenson about the Masimo oximeters being used in the oxygen targeting trials and the potential issues we are finding with the ‘gap’ in saturations between 85 and 90%.

We have done some more work on this and Ben has pulled together the attached discussion document about the issues which we would be grateful for your views on. It would be fair to say that Ben is so anxious about these issues that he has suggested that the UK trial consider stopping recruitment until such time as the issue with the oximeters can be resolved. Clearly stopping the trial will send out a message that we have a problem and I am loath to consider doing this without confirmation that others are finding the same problem (we are currently the smallest trial!) and I am also anxious that we do nothing which calls into question the reliability of the oximeters at these saturation levels until we have very clear evidence that this is the case.

Although you will be familiar with most of the data contained in the attached [discussion] document, it is Figure 9 (from our own data) which is causing us the greatest concern and where the possibility of greater levels of hypoxia [low oxygen levels] has the potential to lead to harm. Have you done anything similar with data from SUPPORT and is this pattern something that you are finding? If you haven’t looked at the data in this way, would it be possible for you to do so?

[Emphasis added]

(2) A document titled “CONFIDENTIAL Discussion document[:] Oxygen saturation monitoring in the BOOST-II UK Trial,” that was dated “11.06.08” (i.e., June 11, 2008) and authored by Ben Stenson (Enclosure B); this document was attached to the June 12, 2008, 7:43 AM email from Professor Brocklehurst to Dr. Finer described in item (1) above:

Discussion document excerpts:

When we monitor [oxygen] saturation, the value fluctuates over time as there are variations in breathing, Fi02 [the amount of oxygen in the air a patient is inhaling] and disease severity. If all of a baby’s values are stored over time it is possible to plot them in the form of a frequency distribution with the percentage of all values on the y-axis against a given saturation on the x-axis. This would usually be expected to be roughly bell-shaped,...

[I]t appears that at least with Nellcor, Ohmeda and Seimens oximeters [oximeters made by three other companies] the usual pattern for frequency plots is a fairly even bell-shaped distribution...

When we started with BOOST II UK[,] we expected to get the same sort of thing. Downloads were obtained from a large number of babies before recruitment began using non-offset [pulse oximeters (i.e., those without the masking algorithm)] as part of the pre-trial audits. It appears that the downloads from the Masimo [pulse] oximeters produce a different distribution of values to that
seen with the other [pulse oximeters]… I have been trying to get to the bottom of this and I am worried that we have a major problem with the trial.

Figure 4 shows a download from a single patient during the pre-[BOOST II UK] trial audit. You will see that this follows a familiar shape except that there is a dip in the frequencies in the saturation range 87-90%. The monitor was not offset...

Briedge has 150 or so pre-trial audit downloads and I understand that they all have this big dip in them. It is difficult to think of a physiological explanation for this dip. It will affect a lot of the values, far more if the baby is expected to saturate in the range 85-90% than in the range 90-95%. I don’t think that we have any downloads that don’t show it. It is not apparent with the other 3 brands of oximeter…

There are a number of ways that this information gives us a problem.

The study design was based on a clear separation of profiles along the lines seen in the first BOOST study and that included assumptions about the profile shape, but the shape of the Masimo profile is very different in the target range for the low [oxygen] (high offset) group than in the target range for the high [oxygen] (low offset) group. This is going to complicate statistical comparisons[.]

If the saturation monitor is relatively unable to assign saturations in the 87-90% range and pushes some values up or down from this range in some way, then a group of babies targeted to achieve saturations of 85-90% are going to have their saturations pushed above and below target range more often. They will be expected to spend more time out of range. This may cause them to alarm more frequently, get more frequent adjustments to their oxygen and fluctuate more widely still. They are going to be systematically disadvantaged in terms of compliance with protocol in comparison with a group targeted to achieve saturations of 90-95%.

I asked Andy King to produce some data from the BOOST II UK trial infants. He has supplied data from the first 50 infants enrolled…

There is a big dip in values in the middle of the range of the high offset (low [oxygen]) group.

The high offset (low [oxygen] group) spend about twice as much time as the other group at any low [oxygen] saturation that you might choose.
As a result of spending more time out of range, the high offset (low [oxygen]) group have a lot more [oxygen] saturation variability (SD [standard deviation] 7.7% vs 6.4%)...

So, to summarise all of [the above]

- We have a significant concern about the distribution of [oxygen] saturation data in a central region of one of our target ranges. Its profile is different to that of any other [pulse oximeters] that we have looked at and we don’t have a physiological explanation.
- We need to investigate this further to make sure that the Masimo oximeter is suitable for targeting saturations in the 85-90% [oxygen] range[.]
- We are only achieving 2% separation in the middle of the range.
- We are not avoiding hyperoxia [excessive oxygen levels] at all.
- We are exposing our low[-oxygen] group to more “hypoxia” [low oxygen levels] than we expected.
- We are exposing our low[-oxygen] group to more [oxygen] saturation variability than the high[-oxygen] group.

[Emphasis added]

Key observations: The above email and discussion document demonstrate that by as early as June 12, 2008, Dr. Finer was aware that (a) the commercially available Masimo pulse oximeters had an unexplained but reproducible data output problem and (b) the experimentally masked Masimo pulse oximeters that were being used in the SUPPORT trial and other similar trials that were ongoing around the world at the time were causing serious problems with the management of the oxygen therapy in babies enrolled in the trial, particularly for those randomly assigned to the low-oxygen group. From a subject safety standpoint, these problems, at a minimum, were apparently causing babies in the low-oxygen groups to be exposed unexpectedly to more hypoxia (i.e., more time at oxygen levels below the range considered to be safe). The BOOST II UK trial investigators rightly recognized that the greater exposure to low oxygen levels had “the potential to lead to harm.”

With respect to the soundness of the trial’s design, the problems with the pulse oximeters were causing unexpected differences between the high-oxygen and low-oxygen groups beyond the intended difference in the assigned oxygen target ranges. In particular, the investigators were concerned that the pulse oximeter problems were causing babies in the low-oxygen groups to spend more time both below and above their assigned target ranges than babies in the high-oxygen groups. This in turn could have been causing more frequent alarming of the pulse oximeters, which could have caused more frequent adjustments to the babies’ oxygen and greater fluctuations in oxygen exposure. Consistent with these concerns, the BOOST II UK trial investigators had found that the babies in the low-oxygen group had greater variability in oxygen levels than those in the
high-oxygen group. Taken together, these findings raised substantial concerns about the soundness of the trial’s design.

Remarkably, the data that revealed the serious problems with experimentally masked Masimo pulse oximeters had been collected by the BOOST II UK trial investigators as part of a pre-trial audit before the trial began, but enrollment in the trial was initiated before that data were analyzed.

(3) 12/06/08 [June 12, 2008] 17:01 email from Dr. Finer responding to Professor Brocklehurst (Enclosure A):

Message excerpts:

Hello Peter

This is very worrisome[.]

Our own data sent to Ben confirms his observations...
I have asked RTI [Research Triangle Institute], the data center [for the SUPPORT trial] to look at some of our altered data and see if there is a systematic dropout in any area...

I think that the gap has the potential to systematically reduce or increase the difference between the groups. We are not privy to the ongoing differences from RTI - we only see grouped data as a feedback to encourage compliance with the targets.

We are already 3/4 complete and approaching 1100 infants. If needed, we may be able to mathematically adjust the results if this should prove necessary, but this is not ideal. I also fear that if Masimo is unresponsive etc, we may not be able to find another device that can be altered for the trials.

I will get back to you as soon as I have additional information – I expect that the first piece will be the look at RTI downloads to see if there is any obvious skew.

[Emphasis added]

Key observations: In the above email, Dr. Finer confirms that the same problems with the pulse oximeters that had been documented by the BOOST II UK trial investigators were found in the SUPPORT trial, and he characterizes these problems as “very worrisome.”

He also indicates that at the time, a substantial number of subjects still needed to be enrolled in the SUPPORT trial in order to reach the planned total subject enrollment of 1,310. Although his email made no mention of concerns about possible harm to the
subjects, he did note the possibility of needing to “mathematically adjust the results” of the trial, indicating an apparent awareness that the problems with the pulse oximeters may have undermined the soundness of the trial’s design.

(4) June 18, 2008, 17:13:37 email from Ms. Meg Cunningham at RTI (Enclosure C):

- Sent to: Dr. Finer; Rosemary D. Higgins, M.D., Program Scientist for the Neonatal Research Network, NICHD, who helped oversee the development and conduct of the SUPPORT trial; and multiple other SUPPORT trial investigators
- Subject: Urgent Support Call Needed
- Message excerpts:

All-

We need an urgent SUPPORT conference call to discuss oximeter skew this coming Tuesday. Please send your availability for Tuesday, June 24th, [2008,] ... Rose will email around handouts prior to the call.

[Emphasis added]

Key observations: The above email documents that by June 18, 2008, Dr. Higgins at NICHD and multiple other SUPPORT investigators at other institutions participating in the trial had been alerted that there were problems with the Masimo pulse oximeters.

(5) 20/06/08 [June 20, 2008] 15:54 email from Dr. Finer (Enclosure D):

- Sent to: Professor Brocklehurst
- Cc: Edmund Hey and Ben Stenson
- Subject: RE: BOOST II UK
- Message excerpts:

Hi Peter

We had a rather lengthy and somewhat difficult discussion with the Masimo Engineers etc. They finally acknowledged that there is an issue and it is apparently related to the calibration that they use to convert the wavelength ratios to an SpO2 [arterial blood oxygen saturation] value. They decided a number of years ago for a variety of reasons to mate 2 curves as opposed to using a single curve, and - you guessed it - where the 2 curves meet is where we are all seeing the alteration and decreased time at SpO2 between 87-90%.

I had asked Masimo to provide a written explanation as quickly as possible, and I heard yesterday from one of their VPs that they were all concerned. Their opinion is that it won’t affect the studies. Our own initial take is that the skew in
their algorithms is a problem, but probably will not affect the separation between the 2 groups.

Our DSMC [Data and Safety Monitoring Committee] I believe - I do not [know] for sure as I am not privy to their detailed deliberations - is probably looking at separation and we have been given green lights to proceed. We are now well over 1100 infants on our way to 1310 so we will no doubt continue as we are. There may be a way to mathematically adjust if needed, but if we have achieved separation in SUPPORT, then we have accomplished what we set out to do for this arm of SUPPORT.

Masimo says that they can install software to replace the 2 curve algorithm with a single curve. This may be an option for the studies that have few infants. I can only encourage them to share their findings with every PI and I have asked that this be done ASAP...

I think that Ben and you should take the lead, and others and we would also participate to publish these observations so that all users are aware of this anomaly.

[Emphasis added]

Key observations: The above email documents that by June 20, 2008, Dr. Finer and other unidentified individuals had learned from Masimo that the problems that had been observed with the company’s commercially available pulse oximeters were due to a defect in the calibration software used in the devices.

Dr. Finer’s comments discussing the calibration software problem are troubling in several respects. First, he appears to have relied, in part, on the opinion of Masimo company employees that the problem with the pulse oximeters calibration software would not “affect the studies,” despite clear evidence from the BOOST II UK trial investigators that the problems with the pulse oximeters indeed were causing unexpected differences between the high-oxygen and low-oxygen groups and adversely affecting the oxygen therapy management in subjects in the low-oxygen group.

Second, he seemed to only have been focused on the separation between the low- and high-oxygen groups in overall oxygen exposure; he made no mention of the other ways in which the pulse oximeters were adversely affecting the oxygen therapy management of the low-oxygen group babies, as described originally by the BOOST II UK investigators, or the concerns about possible harm that could have occurred in these babies.

Finally, he signaled that the SUPPORT trial investigators would “no doubt” continue to enroll subjects and to use the defective Masimo pulse oximeters with the experimental masking algorithm, despite the fact that internal deliberations among SUPPORT trial
investigators had not yet been completed and the fact that there had been no report of the serious pulse oximeter problems to the DSMC for the trial or to the IRBs that reviewed and approved the trial.

(6) June 22, 2008, 7:06:00 PM email from Dr. Finer (Enclosure E):

- Sent to: Ms. Cunningham, Dr. Higgins, and multiple other SUPPORT trial investigators
- Cc: Multiple other SUPPORT trial investigators and others
- Subject: FW: URGENT and CONFIDENTIAL
- Message excerpts:

  Hello Again
  This is probably all that we will need to know or actually have to discuss this issue.

Included with Dr. Finer’s email were (a) the document titled “CONFIDENTIAL Discussion document[:] Oxygen saturation monitoring in the BOOST-II UK Trial” (Enclosure B) that was initially sent to Dr. Finer by Professor Brocklehurst by email on June 12, 2008 (Enclosure A) and that discussed the serious problems related to the Masimo pulse oximeters (see items (1) and (2) above) and (b) a document provided by Masimo with graphs that explained the underlying problem with the oximeters’ calibration software.

Dr. Finer’s email also forwarded a June 20, 2008, email from Professor Brocklehurst to Dr. Finer and to lead investigators for the BOOST II Australia trial, BOOST II New Zealand trial, and the Canadian Oxygen Trial, all of which were nearly identical to the SUPPORT trial’s oxygen experiment (Enclosure E). The following are excerpts from that forwarded email:

I have attached a number of documents to this email which highlight a potentially very important problem with all of our oxygen targeting trials. Rather than repeat all of this issues again, I would refer you to the document written by Ben Stenson entitled 'Discussion paper2’...

I am also keen that we limit the ‘fall-out’ from this until we have had an opportunity to talk to each other and agree what we are each going to do about it.

[Emphasis added]

Key observations: The above email documents that by June 22, 2008, Dr. Higgins at NICHD and multiple other SUPPORT trial investigators were made aware of the details of (a) the serious problems with the Masimo pulse oximeters that had been detected
originally by the BOOST II UK trial investigators and (b) the underlying calibration software defect identified by Masimo.

(7) July 3, 2008, 3:06 PM email from Dr. Higgins (Enclosure F):

- Sent to: Gordon Avery, M.D., Ph.D., Chair, Neonatal Research Network DSMC, a committee that was charged with monitoring the safety of the SUPPORT trial
- Message excerpts:

  *It has come to the SUPPORT investigators’ attention that the Massimo oximeters have an inherent software issue whereby the calibration used to convert the wavelength ratios to an SpO2 value via the sensor placed on the baby results in a decreased time at SpO2 between 87-90%. This was identified by investigators performing the other trials around the world including BOOST II, Canadian oxygenation trial and the UK oximetry trial. This results in a slight dip in the calibration curve as shown in the first figure on 7.3.08 [conference] call slide. This is inherent to all Massimo oximeters (not just study oximeters) but is in the area of target for the low [oxygen] saturation group.*

*The Massimo Company had a conference call with the investigators of the various trials around the world today and sent the attached pdf. In retrospect, this was visible in our low target group (see slide 19 on the attached PowerPoint presentation that Neil Finer presented to the DSMC in January 2006). It is our understanding that the DSMC has evaluated separation of the two groups and time in oxygen and we are to concentrate on obtaining target saturations.*

*The Massimo company is going to send all of the investigators of the trials a document next week outlining this issue. The SUPPORT subcommittee has discussed the issue as well as the NRN steering committee. Since we have already enrolled almost 1100 children and there have been two looks by the DSMC so far, we think it prudent to continue, unless you see otherwise. ...*

*Let me know if you agree.*

[Emphasis added]

**Key observations:** The above email from Dr. Higgins appears to be the only communication that was sent to Dr. Avery, the chair of the DSMC monitoring the SUPPORT trial, (or to any other DSMC member) regarding the serious problems related to the defective pulse oximeters that had been detected originally by the BOOST II UK trial investigators and confirmed by the SUPPORT trial investigators. The text of Dr. Higgins’ email focused on the separation between the low- and high-oxygen groups in the overall oxygen exposure. Strikingly absent from text of her email was any mention of the other ways in which the pulse oximeters were adversely affecting the oxygen therapy
management for the low-oxygen group babies, as described originally by the BOOST II UK investigators, or the concerns about possible harm that could have occurred in these babies. For example, there was no mention that (a) the pulse oximeter problems apparently were causing babies randomly assigned to the low-oxygen groups to be exposed unexpectedly to more time at oxygen levels below the range considered to be safe and the potential serious harm that could result or (b) babies in the low-oxygen group may have had greater fluctuations in oxygen exposure. Such problems had never previously been brought to the attention of the DSMC.

The email also indicated that the SUPPORT trial investigators had decided it was “prudent” to continue to enroll subjects and to use the defective Masimo pulse oximeters with the experimental masking algorithm. Dr. Higgins seeks confirmation from Dr. Avery that this plan is acceptable.

(8) July 18, 2008, 8:42:40 AM email from Dr. Avery (Enclosure F):

- Sent to: Dr. Higgins
- Subject: Re: Massimo oximeters
- Message excerpts:

I agree with continuing. The DSMC felt the study has not achieved the goal of administering oxygen, in the protocol-specified range, to the two groups. Thus a negative final result might be in error. However, if there is a positive result, then a strong enough signal is there to adduce an advantage based on intent to treat. In the real world, intent to treat is what we have. The fact that oxygen saturations wander a lot in very sick [preemies] is part of that real world.

[Emphasis added]

Key observations: The above email appears to indicate that the DSMC chair made a decision — based on incomplete information about the serious problems related to the pulse oximeters that had been detected originally by the BOOST II UK trial investigators — to allow the SUPPORT trial investigators to continue to enroll subjects and to use the defective Masimo pulse oximeters with the experimental masking algorithm, and we found no evidence in the records provided to us by the NIH that this matter was ever referred to the full DSMC for consideration.

(9) PowerPoint presentation, Steering Committee Report, SUPPORT, July 22, 2008, presented by Dr. Finer (attached to a July 22, 2008, 10:45:30 AM email from Dr. Finer to Ms. Cunningham and others)(Enclosure G):

Excerpts:

Enrollment- Completion

• Enrollment = 1,109
• 200 infants to go
• At 30/month, we have 7 months to go-
  • Should complete by Feb 09, and have final data apart from follow-up about 4 - 6 months later…
  • I would aim to get manuscript(s) out Oct – Nov 2009

Oximeter Issues
  • Does the Masimo anomaly - standard in all Masimos for Neonates - effect separation?
  • Impossible to know
  • May actually increase by compensating for decreased low SpO2 at 87-90% by increasing SpO2 at 91-94%
  • This could lead in 85-89% group to having more time at Higher SpO2 values than target and caretakers reducing FiO2 more.

Oximeter Issues
  • Reverse could happen in 91-95% group but I think it would be a lesser effect.
  • We will probably have an idea at the end of the trial
  • SUPPORT SubCommittee after much discussion agreed to continue without any oximeter change

Oximeter Issues - Why
  • We did not think to check an unaltered Masimo as this was the state of the art oximeter and we had no reason to believe that there was any distribution problem
  • At first DSMC, the trend was there, but we did not pay enough attention to it- We were trying to defend the study and were concentrating on the time> 95%o -not a result of this problem (we think)

[Emphasis added]

Key observations: In his presentation on July 22, 2008, Dr. Finer indicated that at the time, approximately 200 subjects still needed to be enrolled in the SUPPORT trial in order to reach the planned total subject enrollment of 1,310.

His comments also indicated that the SUPPORT trial investigators had no idea how the defect in the calibration software for the Masimo pulse oximeters was affecting oxygen delivery to the two oxygen groups, but nevertheless, the SUPPORT trial investigators decided to continue to enroll subjects and to use the defective Masimo pulse oximeters with the experimental masking algorithm. Finally, his presentation confirms that when the SUPPORT trial began, the investigators had no idea how their experimental masking algorithm would interact with the underlying calibration software of the Masimo pulse oximeters and affect the actual levels of oxygen to
which the babies would be exposed over the course of their participation in the experiment, which could have lasted for up to approximately 12 weeks.

Identification of major ethical and regulatory lapses

Failure to meet regulatory requirements for reporting unanticipated problems involving risks to subjects

HHS regulations at 45 C.F.R. §§ 46.103(a) and (b)(5) require that any unanticipated problems involving risks to subjects be promptly reported to the IRB, appropriate institutional officials, the head of the department or agency funding the research, and the OHRP. Typically, these reports are made initially by investigators to the IRBs, and the IRBs then forward them to appropriate institutional officials, the head of the department or agency funding the research, and the OHRP.

The serious problems related to the defects in the experimentally masked Masimo pulse oximeters that were brought to the attention of the SUPPORT trial lead investigators in June 2008 clearly represented serious unanticipated problems involving risks to the subjects. As discussed above, the investigators had evidence that these unanticipated problems were adversely affecting the management of the oxygen therapy in babies enrolled in the trial. Of particular concern was the fact that these problems, at a minimum, were apparently causing babies randomly assigned to the low-oxygen groups to be exposed unexpectedly to more time at oxygen levels below the range considered to be safe, which had the potential to cause serious harm to the babies.

Nevertheless, we find no evidence that these unanticipated problems involving risks to the babies enrolled in the SUPPORT trial were ever reported to the IRBs that reviewed and approved the trial, appropriate institutional officials at each participating institution, the NIH Director or the NICHD Director, or the OHRP. In particular, we note the following:

(1) Among the tens of thousands of pages of documents regarding the SUPPORT trial that we obtained from the NIH under FOIA, we found no documents indicating that the problems with the experimentally masked Masimo pulse oximeters were reported to the NIH Director or the NICHD Director. Moreover, there were no email communications or other documents discussing the reporting of these problems to the IRBs that reviewed and approved the trial, appropriate institutional officials at each participating institution, or the OHRP.

(2) In a separate FOIA request submitted to the OHRP, we obtained copies of all entries for incident reports from 1999 to early 2014 in the OHRP’s compliance activities tracking system database, which contained descriptions of unanticipated problems involving risks to subjects or others that had been reported to the agency. Our search of these documents revealed no entries for reports to the OHRP of unanticipated problems involving risks to subjects related to the SUPPORT trial for 2008 or later.
Subverting the IRBs’ roles in protecting the babies who were enrolled in the SUPPORT trial

Reporting to IRBs unanticipated problems involving risk to subjects or others is particularly important because such problems may alter the IRBs’ determinations that are required for approval under HHS regulations for the protection of human subjects at 45 C.F.R. § 46.111. In this case, the information about the serious problems related to the experimentally masked Masimo pulse oximeters, at a minimum, would have been directly relevant to the IRBs’ required determinations regarding whether:

(1) The risks to the subjects were being minimized by using procedures that were consistent with sound research design and that did not unnecessarily expose subjects to risk, as required by HHS regulations at 45 C.F.R. § 46.111(a)(1);

(2) The risks to subjects were reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result, as required by HHS regulations at 45 C.F.R. § 46.111(a)(2); and

(3) The information that was being provided to subjects’ parents when their consent was sought included an adequate description of the trial’s research procedures and reasonably foreseeable risks, as required by HHS regulations at 45 C.F.R. §§ 46.116(a)(1) and (2).

From an ethical and regulatory standpoint, the SUPPORT trial investigators should have immediately suspended their trial, promptly notified all the IRBs that reviewed and approved the trial of the unanticipated problems, and awaited the IRBs’ review of the problems and determinations as to whether the trial should be allowed to proceed and, if so, under what conditions (for example, the IRBs reasonably might have required that the defect in the calibration software of the Masimo pulse oximeters be corrected before the trial resumed, or they might have concluded that the trial should be terminated because the problems had undermined the soundness of the trial’s design).

Disturbingly, the SUPPORT trial investigators decided — independently — to continue to enroll more than 200 additional subjects in the trial and to use the defective Masimo pulse oximeters without seeking the input of the IRBs that reviewed and approved the trial. The documents that we obtained from the NIH appear to suggest that the investigators placed a higher priority on quickly completing their trial and publishing the trial’s results than on ensuring the safety of the babies who were enrolled in the trial.

By not suspending their research and promptly informing the IRBs of the unanticipated problems involving risks to the subjects, the SUPPORT trial investigators subverted the IRBs’ central role in protecting the babies who were still to be enrolled in the trial. Uninformed of the serious problems related to the defective Masimo pulse oximeters with the experimental masking algorithm, the IRBs had no opportunity to reassess whether the trial still satisfied key requirements needed for approval and to make a determination as to whether the trial should be allowed to continue.
Further evidence of inadequate informed consent

As the OHRP is well aware, Public Citizen has highlighted in prior publications serious deficiencies in the descriptions of the purpose, nature, and risks of the research that were presented in the consent forms signed by the parents of babies who were enrolled in the SUPPORT trial.¹¹,¹² However, even if one assumes that the consent forms had been adequate at the start of the trial, they certainly should have been recognized as no longer being adequate following the discovery of the serious problems related to the defective Masimo pulse oximeters with the experimental masking algorithm and, accordingly, should have been changed.

For example, most of the IRB-approved consent forms for the SUPPORT trial explicitly or implicitly indicated that all procedures being used in the trial were consistent with standard or usual care and that the research involved no risks to the babies. However, such representations could no longer have been considered true given that the serious problems related to the defective Masimo pulse oximeters, at a minimum, were apparently causing babies randomly assigned to the low-oxygen groups to be exposed unexpectedly to more time at oxygen levels below the range considered to be safe, which was recognized as having the potential to lead to harm. Such harms could have included increased risks of brain injury and death. There was also concern that the defective pulse oximeters used in the trial may have been causing greater variability in oxygen levels in babies enrolled in the low-oxygen group, which would have represented a further deviation from usual care.

Additional notable lapses

The serious problems related to the defective Masimo pulse oximeters with the experimental masking algorithm should have been evaluated by the full DSMC for the SUPPORT trial. However, we found no evidence that these problems were ever communicated to the full DSMC membership. Instead, the DSMC chair apparently made a decision on his own — based on incomplete information about the serious problems with the pulse oximeters that had been detected originally by the BOOST II UK trial investigators — to allow the SUPPORT trial investigators to continue to enroll subjects and to use the defective Masimo pulse oximeters with the experimental masking algorithm. Such actions short-circuited the full DSMC’s important role in monitoring the safety of the trial.

Finally, although the following issue is outside the purview of the OHRP, it is troubling that the SUPPORT trial investigators failed to disclose the serious problems related to the defective

Masimo pulse oximeters in their published scientific journal articles about the trial.\textsuperscript{13,14} Such information would have been important to readers’ assessments of the design and conduct of the study and their interpretation of the data, particularly given the fact that these problems may have undermined the soundness of the trial’s design.

**Conclusions and requested actions**

In closing, the newly uncovered information summarized above appears to reveal additional major ethical lapses during the conduct of the SUPPORT trial. Public Citizen therefore urges the OHRP to immediately expand its ongoing compliance oversight investigation of the trial to examine these matters.

If the OHRP confirms that these lapses occurred, the agency should sanction the responsible investigators and institutions that participated in the trial for failing to adequately protect the human subjects who were enrolled in the trial. The OHRP also should require that the parents of all subjects enrolled in the trial be informed of the serious problems related to the defective Masimo pulse oximeters with the experimental masking algorithm. In addition, the parents of the more than 200 subjects enrolled after the investigators became aware of the problems related to the defective pulse oximeters should be told that these problems were known to the investigators, yet not shared with those parents, at the time their babies were enrolled in the trial.

Please note that the OHRP may share our complaint letter, with identifiers, with anyone. We will be posting a copy on Public Citizen’s website as well.

Thank you for your prompt attention to this important matter regarding the protection of human subjects. We look forward to the OHRP’s thorough and careful investigation into these new concerns about this unethical trial.

Please contact us if you have any questions or need additional information.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen’s Health Research Group


June 14, 2017, Letter to OHRP
Regarding the SUPPORT Trial

Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen’s Health Research Group

Ruth Macklin, Ph.D.
Distinguished University Professor Emerita
Albert Einstein College of Medicine
Bronx, NY

Board of Directors and Past President, International Association of Bioethics

Lois Shepherd, J.D.
Peter A. Wallenborn, Jr. and Dolly F. Wallenborn Professor of Biomedical Ethics
Professor of Public Health Sciences
Professor of Law
University of Virginia
Center for Biomedical Ethics and Humanities
Charlottesville, Virginia

Enclosures

cc: The Honorable Thomas E. Price, Secretary of Health and Human Services
The Honorable Don Wright, Acting Assistant Secretary for Health, HHS
Enclosure A

June 12, 2008, email exchange between:

(a) Peter Brocklehurst, Professor of Perinatal Epidemiology; Director, National Perinatal Epidemiology Unit, University of Oxford; and a lead investigator for the BOOST II UK trial, one of several other clinical trials that was nearly identical to the SUPPORT trial’s oxygen experiment and that used the same experimentally masked Masimo pulse oximeters; and

(b) Neil Finer, M.D., Professor of Pediatrics and Director, Division of Neonatal-Perinatal Medicine, University of California, San Diego School of Medicine; and a lead investigator for the SUPPORT trial

The emails discuss the BOOST II UK trial investigators’ discovery of serious problems with the experimentally masked Masimo pulse oximeters that were being used in both the SUPPORT and BOOST II UK trials.
Hi Peter

Hello Peter

This is very worrisome

Our own data sent to Ben confirms his observations. We have not heard back from Masimo, but I am going to once again make the call. I have asked RTI, the data center to look at some of our altered data and see if there is a systematic dropout in any area.

Our choice of oximeter for this trial was based on the fact that Masimo was willing to work with us whereas no other large manufacturer showed any interest.

I think that the gap has the potential to systematically reduce or increase the difference between the groups. We are not privy to the ongoing differences from RTI - we only see grouped data as a feedback to encourage compliance with the targets.

We are already 3/4 complete and approaching 1100 infants. If needed, we may be able to mathematically adjust the results if this should prove necessary, but this is not ideal. I also fear that if Masimo is unresponsive etc, we may not be able to find another device that can be altered for the trials.

I will get back to you as soon as I have additional information - I expect that the first piece will be the look at RTI downloads to see if there is any obvious skew.

Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

-----Original Message-----
From: Peter Brocklehurst [mailto:Peter.Brocklehurst@npeu.ox.ac.uk]
Sent: Thursday, June 12, 2008 7:43 AM
To: Finer, Neil
Cc: Edmund Hey; Ben Stenson; Ed Juszczak
Subject: BOOST II UK

Dear Neil

I know that you have been having some email correspondence with Ben Stenson about the Masimo oximeters being used in the oxygen targeting trials and the potential issues we are finding with the 'gap' in saturations between 85 and 90%.

We have done some more work on this and Ben has pulled together the attached discussion document about the issues which we would be grateful for your views on. It would be fair to say that Ben is so anxious about...
these issues that he has suggested that the UK trial consider stopping recruitment until such time as the issue with the oximeters can be resolved. Clearly stopping the trial will send out a message that we have a problem and I am loath to consider doing this without confirmation that others are finding the same problem (we are currently the smallest trial!) and I am also anxious that we do nothing which calls into question the reliability of the oximeters at these saturation levels until we have very clear evidence that this is the case.

Although you will be familiar with most of the data contained in the attached document, it is Figure 9 (from our own data) which is causing us the greatest concern and where the possibility of greater levels of hypoxia has the potential to lead to harm. Have you done anything similar with data from SUPPORT and is this pattern something that you are finding? If you haven't looked at the data in this way, would it be possible for you to do so?

Our current thoughts are to ask you for your views about what we are finding and whether you are finding it as well - and if you are, to consider (fairly promptly) sharing these data with the other CIs around the world (Barbara, William and Brian) to then discuss a strategy for moving forward.

I would be very happy to discuss any of these issues over the phone if this would be helpful.

Many thanks.

Best wishes

Peter

Peter Brocklehurst
Professor of Perinatal Epidemiology
Director
National Perinatal Epidemiology Unit
University of Oxford
Old Road Campus
Headington
Oxford
OX3 7LF
Tel: 01865 289719
Fax: 01865 289720

Visit our website at: www.npeu.ox.ac.uk
Enclosure B

Document titled “CONFIDENTIAL Discussion document[:] Oxygen saturation monitoring in the BOOST-II UK Trial,” that was dated “11.06.08” (i.e., June 11, 2008) and authored by Ben Stenson, a lead investigator for the BOOST II UK trial.

This document was sent by email on June 12, 2008, by Professor Brocklehurst, a lead investigator for the BOOST II UK trial, to Dr. Finer, a lead investigator for the SUPPORT trial.

The document explains in detail the serious problems with the experimentally masked Masimo pulse oximeters that were being used in both the SUPPORT and BOOST II UK trials.
Oxygen saturation monitoring in the BOOST-II UK Trial

When we monitor saturation, the value fluctuates over time as there are variations in breathing, FiO₂ and disease severity. If all of a baby’s values are stored over time it is possible to plot them in the form of a frequency distribution with the percentage of all values on the y-axis against a given saturation on the x-axis. This would usually be expected to be roughly bell-shaped, although if the baby is maintained at high sats the upper end of the distribution can be cut off because saturation cannot go over 100%.

Figure 1 shows the cumulative saturation profiles that were obtained by downloading data from the Nellcor saturation monitors that were used in the original BOOST study.

![Cumulative Saturation Profiles](image)

The data used to plot the above figure were sampled every 10 seconds during twice weekly downloads from the study patients that lasted 8-24 hours each. They appear to have achieved impressive separation of the saturation profiles between groups but perhaps this can be explained because the very high saturations are more stable and would require significant extra oxygen to achieve them. The high sats group were in oxygen twice as long after randomization as the low sats group.
A similar plot was provided in the STOP ROP study (fig 2). In this study the data were obtained from Ohmeda 3740 oximeters. Again the saturation profiles were bell shaped and were well separated. Again this may have been helped by the target sats in one group being high and a big step up in FiO₂ was required to achieve them. The data were sampled once every 40 seconds for the duration of the intervention.

Figure 2.

We have done a lot of similar downloading and charting of saturation profiles over the years in Edinburgh and our observations have been similar. Figure 3 shows an example of some of our downloads. These data are pooled plots from 30 babies, each studied for two 3-hour downloads. As in the BOOST II UK study the data here were only recorded
when the baby was receiving supplemental oxygen. The oximeter for this study was a Seimens SC7000 and the data were sampled every second.

Narrow refers to the saturation distribution when the alarm limits were 86-94% and wide when they were 80-94%. These curves are smooth and bell shaped.

Figure 3.

So it appears that at least with Nellcor, Ohmeda and Seimens oximeters the usual pattern for frequency plots is a fairly even bell-shaped distribution, chopped off on the right if the baby has very high sats.

When we started with BOOST II UK we expected to get the same sort of thing. Downloads were obtained from a large number of babies before recruitment began using non-offset monitors as part of the pre-trial audits. It appears that the downloads from the Masimo oximeters produce a different distribution of values to that seen with the other monitors. Bridged Boyle noticed this and asked me to try and explain it. I have been
trying to get to the bottom of this and I am worried that we have a major problem with the trial.

Figure 4 shows a download from a single patient during the pre-trial audit. You will see that this follows a familiar shape except that there is a dip in the frequencies in the saturation range 87-90%. The monitor was not offset.

Fig 4.

![Oxygen saturation graph](image)

In this case the highest frequencies were seen at around 93% and the dip at 87 to 90% looks small. However in figure 5, where the peak frequency was closer to 90% the dip looks a great deal bigger.

Figure 5

![Oxygen saturation graph](image)
Briedge has 150 or so pre-trial audit downloads and I understand that they all have this big dip in them. It is difficult to think of a physiological explanation for this dip. It will affect a lot of the values, far more if the baby is expected to saturate in the range 85-90% than in the range 90-95%. I don’t think that we have any downloads that don’t show it. It is not apparent with the other 3 brands of oximeter.

I have sought information from colleagues around the World who are interested in this area. A neonatologist from the US looked at some stored data from non-offset babies, monitored with Masimo’s and plotted the graphs. He found a similar large dip in all cases. Two of his plots are in figures 6 and 7. His software plots them differently but you can see the same message, that there is a big dip at 87-90% and it is bigger when the general distribution is expected to put more values in that range.

Fig 6
The same team also monitored a baby simultaneously with both a Masimo and a Nellcor and downloaded the saturations. I have plotted them as fig 8. I only included the values for sats above 80% as they were very similar below this.
So the large dip was again present with the Masimo but not with the Nellcor. The paucity of values 87-90% on the Masimo was matched by an apparent excess of higher values, although in this single one-to-one comparison it cannot be assumed which is more reliable in this upper range.

I have Masimo downloads from 2 further independent sources and they both show the same “bite” out of the data.

So, there is a fundamentally different shape in the distribution of the saturation profile that you get from a Masimo in comparison with at least 3 other brands of oximeter. The Masimo shows an unexpected paucity of values in the range 87-90%. I have yet to encounter anyone else who had noticed this. But once looked for it looks as though it is always there. Most patient groups have saturations that are mostly in the mid to upper 90’s and before now that is where most preterm babies have been targeted so it may not be surprising that it has not been noted until we have started trying to target these babies at lower saturations.

I have contacted the scientific people at Masimo to see if they can give an explanation. They have not yet come up with anything. At the third prompt they replied that they consider it to be genuine physiology. They tell me that they have started working with Wade Rich from Neil Finer’s group to get to the explanation. I have e-mailed Wade and asked for more details.

There is a lot more signal analysis going on inside a Masimo, particularly aimed at giving values when the pulse signal is complicated by motion. Various assumptions are used to subtract different frequencies and help to separate venous from arterial signal. It therefore seems possible that some of this signal processing may be excluding some of the information that would otherwise yield saturation values in the range 87-90% and that this has not been apparent before now because most patients spend little time in this range.

There are a number of ways that this information gives us a problem.

The study design was based on a clear separation of profiles along the lines seen in the first BOOST study and that included assumptions about the profile shape, but the shape of the Masimo profile is very different in the target range for the low sat (high offset) group than in the target range for the high sat (low offset) group. This is going to complicate statistical comparisons.

If the saturation monitor is relatively unable to assign saturations in the 87-90% range and pushes some values up or down from this range in some way, then a group of babies targeted to achieve saturations of 85-90% are going to have their saturations pushed above and below target range more often. They will be expected to spend more time out of range. This may cause them to alarm more frequently, get more frequent adjustments to their oxygen and fluctuate more widely still. They are going to be systematically
disadvantaged in terms of compliance with protocol in comparison with a group targeted to achieve saturations of 90-95%.

I asked Andy King to produce some data from the BOOST II UK trial infants. He has supplied data from the first 50 infants enrolled. There are 102 downloads covering about 1000 patient days of data. Data are only charted when the babies are receiving supplemental oxygen. The plot from this analysis is below as figure 9.

Fig 9

There are various ways that you can look at these data.

There is no difference between the groups in the proportion of time spent at the highest saturation range of 97-100%. We hoped to avoid this more in the low sat (high offset) group. The 75th centile for saturation is 94% in both groups. We are not therefore reducing exposure to hyperoxia at all

The median saturations of the 2 groups are 92% and 90% (ie 2% separation in the middle of the range and not 6% as we are aiming for).

The comparison of the 2 groups is complicated by the flat portion of the curve at saturations 93-96% (red values) and 84-87% (blue values) where the offset reads the same value whichever the saturation. In the above figure these readings have been shared out evenly between the 4 values but this is unlikely to be their true distribution. They are more likely to be shared out in similar proportions to the values in the same range with
the other offset oximeter. Adjusting the values in this way would make the profiles look more similar than at present.

There is a big dip in values in the middle of the range of the high offset (low sat) group.

The high offset (low sat group) spend about twice as much time as the other group at any low saturation that you might choose.

As a result of spending more time out of range, the high offset (low sat) group have a lot more saturation variability (SD 7.7% vs 6.4%)

The high sat (low offset) group spend more time with saturations in the 90-95% range than the low offset group although the difference would be lessened by adjusting the flat part of the other curve as discussed above.

So, to summarise all of that

- We have a significant concern about the distribution of saturation data in a central region of one of our target ranges. Its profile is different to that of any other monitors that we have looked at and we don’t have a physiological explanation.
- We need to investigate this further to make sure that the Masimo oximeter is suitable for targeting saturations in the 85-90% range
- We are only achieving 2% separation in the middle of the range.
- We are not avoiding hyperoxia at all.
- We are exposing our low sat group to more “hypoxia” than we expected.
- We are exposing our low sat group to more saturation variability than the high sat group.

Ben Stenson 11.06.08
Enclosure C

June 18, 2008, email from Ms. Meg Cunningham at the Research Triangle Institute, the data center for the SUPPORT trial, requesting an urgent conference call to discuss the serious problems with the experimentally masked Masimo pulse oximeters. The email was sent to:

(a) Dr. Finer, a lead investigator for the SUPPORT trial;

(b) Rosemary D. Higgins, M.D., Program Scientist for the Neonatal Research Network, NICHD, who helped oversee the development and conduct of the SUPPORT trial; and

(c) Multiple other SUPPORT trial investigators
I should have thought of this earlier, but would it have made more sense to have this call after Masimo made their writeup (on an explanation of what happened) available?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto] 
Sent: Wednesday, June 18, 2008 5:25 PM
To: Cunningham, Meg; nfiner@ucsd.edu; Das, Abhik; Gantz, Marie; wrich@ucsd.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Archer, Stephanie (NIH/NICHD); Zaterka-Baxter, Kristin; fmartinez@ucsd.edu; msumner@peds.uab.edu; sharon.gough@hsc.utah.edu; BVecchio@WIHRI.org; Huitema, Carolyn
Subject: Re: Urgent Support Call Needed

All availability prior to and including tuesday is welcome.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message ----- 
From: Cunningham, Meg <mcunningham@rti.org>
To: nfiner@ucsd.edu <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [mailto]; Das, Abhik <adas@rti.org>; Gantz, Marie <mgantz@rti.org>; wrich@ucsd.edu <wrich@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; mcw3@cwru.edu <mcw3@cwru.edu>; Bradley Yoder <Bradley.Yoder@hsc.utah.edu>; Roger.Faix@hsc.utah.edu <Roger.Faix@hsc.utah.edu>
Cc: Archer, Stephanie (NIH/NICHD); Zaterka-Baxter, Kristin <kzaterka@rti.org>; Martinez, Fernando <fmartinez@ucsd.edu>; msumner@peds.uab.edu <msumner@peds.uab.edu>; sharon.gough@hsc.utah.edu <sharon.gough@hsc.utah.edu>; Brenda Vecchio <BVecchio@WIHRI.org>; Huitema, Carolyn <petrie@rti.org>
Subject: Urgent Support Call Needed

All-

We need an urgent SUPPORT conference call to discuss oximeter skew this coming Tuesday. Please send your availability for Tuesday, June 24th, indicating time zone if other than ET as soon as possible. Rose will email around handouts prior to the call.
Enclosure D

June 20, 2008, email from Dr. Finer, a lead investigator for the SUPPORT trial to Professor Brocklehurst, a lead investigator for the BOOST II UK trial.

The email explains that the serious problems with the experimentally masked Masimo pulse oximeters were due to a defect in the calibration software used in Masimo’s commercially available pulse oximeters.
Hi Peter

We had a rather lengthy and somewhat difficult discussion with the Masimo Engineers etc. They finally acknowledged that there is an issue and it is apparently related to the calibration that they use to convert the wavelength ratios to an Sp02 value. They decided a number of years ago for a variety of reasons to mate 2 curves as opposed to using a single curve, and - you guessed it - where the 2 curves meet is where we are all seeing the alteration and decreased time at Sp02 between 87-90%.

I had asked Masimo to provide a written explanation as quickly as possible, and I heard yesterday from one of their VPs that they were all concerned. Their opinion is that it won't affect the studies. Our own initial take is that the skew in their algorithms is a problem, but probably will not affect the separation between the 2 groups.

Our DSMC I believe - I do not for sure as I am not privy to their detailed deliberations - is probably looking at separation and we have been given green lights to proceed. We are now well over 1100 infants on our way to 1310 so we will no doubt continue as we are. There may be a way to mathematically adjust if needed, but if we have achieved separation in SUPPORT, then we have accomplished what we set out to do for this arm of SUPPORT.

Masimo says that they can install software to replace the 2 curve algorithm with a single curve. This may be an option for the studies that have few infants.

I can only encourage them to share their findings with every PI and I have asked that this be done ASAP.

I am going to append the graphs that they sent to explain this issue, and I hope that these make some sense to you. The Network wants a written explanation from Masimo ASAP and they heard this from Rose Higgins on our call.

I think that Ben and you should take the lead, and others and we would also participate to publish these observations so that all users are aware of this anomaly.

Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

-----Original Message-----
From: Peter Brocklehurst [mailto:Peter.Brocklehurst@npeu.ox.ac.uk]
Sent: Friday, June 20, 2008 5:59 AM
To: Finer, Neil
Subject: RE: BOOST II UK

Dear Neil

Sorry to hassle you, but have you heard anything more from Masimo yet? And do you know whether your RTI is able to do something similar with your saturation data?

Andy King, our programmer on the BOOST study, has done some further work with the data we have, but it is still only on 57 babies - please see attachment.

Best wishes

Peter
Enclosure E

June 22, 2008, email from Dr. Finer, a lead investigator for the SUPPORT trial to:

(a) Ms. Cunningham at the Research Triangle Institute, the data center for the SUPPORT trial;

(b) Dr. Higgins, Program Scientist for the Neonatal Research Network, NICHD, who helped oversee the development and conduct of the SUPPORT trial; and

(c) Multiple other SUPPORT trial investigators and others

The email provided documents explaining in detail the serious problems with the experimentally masked Masimo pulse oximeters that were being used in the SUPPORT trial.
Hello Again
This is probably all that we will need to know or actually have to
discuss this issue.
Regards
Neil

-----Original Message-----
From: Peter Brocklehurst
Sent: Friday, June 20, 2008 9:09 AM
To: Brian Darlow; William Tarnow-Mordi;
Finer, Neil; barbara.schmidt@uphs.upenn.edu
Cc: Ben Stenson; Michelle Gabriel
Subject: URGENT and CONFIDENTIAL

Dear Barbara, Brian and William

I have attached a number of documents to this email which highlight a
potentially very important problem with all of our oxygen targeting
trials. Rather than repeat all of this issues again, I would refer you
to the document written by Ben Stenson entitled 'Discussion paper2'.

We initially discussed this problem with Neil Finer, as he was aware of
this issue and SUPPORT has recruited the largest number of babies so far
- his response is attached (RE BOOST II UK.rtf), including some data
provided by Masimo in relation to this (USCD_2_.pdf). We have also done
some more work looking at babies recruited in the UK (based on the first
57 babies with complete data - SaturationAnalysis_19Jun08.pdf).

Once you have time to digest this information - and potentially been
able to look at the degree of separation you have been able to achieve
in your own trials, can I suggest we arrange an urgent teleconference to
discuss these issues? As there are a few of us, I would like to suggest
just 2 of us from each of the trials get together to discuss what we do
about this information - this will (a) limit the number of people on the
teleconference but (b) I am also keen that we limit the 'fall-out' from
this until we have had an opportunity to talk to each other and agree
what we are each going to do about it. I hope you agree this sounds a
reasonable first step.

I am aware that we all have widely different time zones but if you could
email Michelle Garbriel (this email is copied to her) she will sort out
a data and time. Hopefully we can do this early next week.

Many thanks.
Enclosure F

July 3 and 18, 2008, email exchange between:

(a) Dr. Higgins, Program Scientist for the Neonatal Research Network, NICHD, who helped oversee the development and conduct of the SUPPORT trial; and

(b) Gordon Avery, M.D., Ph.D., Chair, Neonatal Research Network Data and Safety Monitoring Committee, a committee that was charged with monitoring the safety of the SUPPORT trial.
From: Gordon Avery
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Massimo oximeters
Date: Friday, July 18, 2008 8:42:40 AM

I agree with continuing. The DSMC felt the study has not achieved the goal of administering oxygen, in the protocol-specified range, to the two groups. Thus a negative final result might be in error. However, if there is a positive result, then a strong enough signal is there to adduce an advantage based on intent to treat. In the real world, intent to treat is what we have. The fact that oxygen sats wander a lot in very sick premies is part of that real world. Best, Gordon

On Thu, Jul 3, 2008 at 3:06 PM, Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov> wrote:

Dr. Avery,

It has come to the SUPPORT investigators attention that the Massimo oximeters have an inherent software issue whereby the calibration used to convert the wavelength ratios to an SpO2 value via the sensor placed on the baby results in a decreased time at SpO2 between 87-90%. This was identified by investigators performing the other trials around the world including BOOST II, Canadian oxygenation trial and the UK oximetry trial. This results in a slight dip in the calibration curve as shown in the first figure on 7.3.08 conf call slide. This is inherent to all Massimo oximeters (not just study oximeters) but is in the area of target for the low saturation group.

The Massimo Company had a conference call with the investigators of the various trials around the world today and sent the attached pdf. In retrospect, this was visible in our low target group (see slide 19 on the attached PowerPoint presentation that Neil Finer presented to the DSMC in January 2006). It is our understanding that the DSMC has evaluated separation of the two groups and time in oxygen and we are to concentrate on obtaining target saturations.

The Massimo company is going to send all of the investigators of the trials a document next week outlining this issue. The SUPPORT subcommittee has discussed the issue as well as the NRN steering committee. Since we have already enrolled almost 1100 children and there have been two looks by the DSMC so far, we think it prudent to continue, unless you see otherwise.

I will forward you additional information as I receive it from Massimo.

Let me know if you agree.

Regards,
Enclosure G

July 22, 2008, PowerPoint presentation by Dr. Finer, a lead investigator for the SUPPORT trial, that provided a status report on the SUPPORT trial.
From: Finer, Neil  
To: Cunningham, Meg; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: Steering Comm newest version  
Date: Tuesday, July 22, 2008 10:45:30 AM  
Attachments: Steering Committee Report July 22 revised 2008.ppt  

Meg  
If you have time can you load this version for me?  
I will be on the phone in 5 minutes waiting  
Thanks  
Neil
Subcommittee
Neil Finer - PI for the Support
Support Committee Report
Steering Committee Report
July 22, 2008
Enrollment - Completion

• Enrollment = 1109
• 200 infants to go
• At 30/month, we have 7 months to go –
• Should complete by Feb 09, and have final data apart from follow-up about 4 - 6 months later
• Will be too late for PAS –
• Can think about HOT Topics –
• I would aim to get manuscript(s) out Oct - Nov 2009
Nothing new to report • Continuing as expected • Protocol Deviations
Adverse Events

• Only Air Leaks higher than baseline
• 9.6% vs 8.2% overall
• 12.6% vs 11.% for 24-25 wks
• 7.3% vs 6.1% for 26-27 wks
• This could be a problem between randomized groups
• All others lower than baseline occurrence
• We have not been stopped nor should we as the overall event rate is within Network expectations
Masimo Oximeters: Will it ever end??

• B Stenson found reduced histograms at 87% - 90% SpO2 when compared with other oximeters

• We ran a baby on Masimo and Nellcor simultaneously – both legs

• Next Pages tell the story
Here less time spent at 87% - 90%
Here – more time spent at 87%-90%
Plot of Cumulative SpO2 from Nellcor (Blue) vs Masimo (Pink) from single baby

Paired study of Masimo and nellcor in same baby

Simultaneous recordings – UCSD 2008

% of values

Saturation

Overestimates

Underestimates
Explanation – 2 Curves spliced into one
Answer – Smoothed Curve
Won’t help SUPPORT, may not help anyone
Oximeter Issues

• Does the Masimo anomaly – standard in all Masimos for Neonates - effect separation?

• Impossible to know

• May actually increase by compensating for decreased low SpO2 at 87-90% by increasing SpO2 at 91-94%

• This could lead in 85-89% group to having more time at Higher SpO2 values than target and caretakers reducing FiO2 more.
Oximeter Issues

• Reverse could happen in 91-95% group but I think it would be a lesser effect.
• We will probably have an idea at the end of the trial
• SUPPORT SubCommittee after much discussion agreed to continue without any oximeter change
Oximeter Issues - Why

• We did not think to check an unaltered Masimo as this was the state of the art oximeter and we had no reason to believe that there was any distribution problem

• At first DSMC, the trend was there, but we did not pay enough attention to it – We were trying to defend the study and were concentrating on the time > 95% - not a result of this problem (we think)

• I think Marie mentioned – She should be the PI!!!
Unblinded Data for DSMC Jan 2005

Percent of time at each SpO2 value (smoothed data)

- Distribution of smoothed data
- Target groups: Low target (85-89), High target (91-95)
Response of Dr Avery to Masimo issue

- I agree with continuing. The DSMC felt the study has not achieved the goal of administering oxygen, in the protocol-specified range, to the two groups. Thus a negative final result might be in error. However, if there is a positive result, then a strong enough signal is there to adduce an advantage based on intent to treat. In the real world, intent to treat is what we have. The fact that oxygen sats wander a lot in very sick premies is part of that real world. Best. Gordon
Oximeter Problems

• I believe that if there is any fault attributable to any investigator – it can only be assigned to me.
• No other investigator knew enough of the oximeter function and skew.
• At least I now know why I am not in the Network
• No fault should be ascribed to any Network PI or Rose
Oximeter Problems

• I did try to get Nellcor to work with us to develop a study oximeter – no interest – ( Oh yes, they were being sued by Masimo )
• Here is your chuckle for the day
• The merged 2 curves was so that the Masimo would better resemble the values in the higher SpO2 ranges as reported by the Nellcor!!
• Safe travels!

• Get this study done.

• Thanks to everyone for all the great efforts to