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Correction (11/4/14): On page 2, last paragraph, last sentence, "(93% to 100%)" should have been "(92% to 98%)"

Testimony Before the Secretary's Advisory Committee on Human Research Protections Regarding the Office for Human Research Protections' Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care and the SUPPORT Trial

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I am Dr. Michael Carome, Director of Public Citizen's Health Research Group, testifying on behalf of myself; Dr. Sidney Wolfe, the founder of our group; and Public Citizen. We have no financial conflicts of interest.

Public Citizen applauds the Office for Human Research Protections (OHRP) for strongly reaffirming in its October 24 *Federal Register* notice announcing the release of its draft guidance on risks in research evaluating standard of care that the parents of premature infants enrolled in the National Institutes of Health (NIH)-funded Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPPORT) were not informed of the trial's reasonably foreseeable risks, including risks of blindness and death.[1]

OHRP's draft guidance

While the draft guidance lacks clarity on some important points, Public Citizen endorses OHRP's fundamental conclusion that:[2]

> With regard to which risks should be considered "reasonably foreseeable," …at a minimum, identified risks associated with a standard of care that are being evaluated as a purpose of the research, should certainly be considered 'reasonably foreseeable.'

SUPPORT: Not "standard of care"

Many have argued that SUPPORT — a complex experiment in which premature infants were randomly assigned to a low (85-89%) or high (91-95%) oxygen saturation (SpO_2) target and to one of two ventilation strategies — exemplifies oxygen-management research that involved standard of care interventions. As Public Citizen's prior analyses of the SUPPORT protocol have shown, it was not. For example, the use of the falsely reading pulse oximeters represented an extraordinary deviation from "standard of care" in the non-research setting, particularly since oxygen saturation levels played a role in many important clinical decisions related to adjustment in the oxygen therapy and whether to intubate or extubate an infant.

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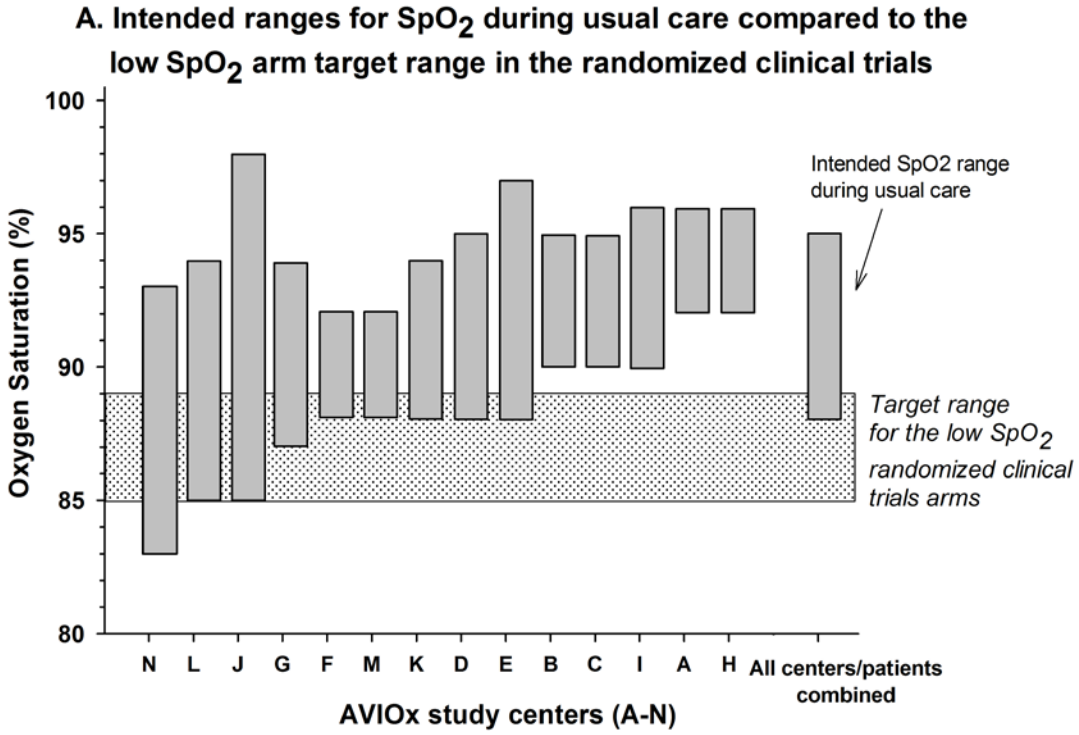
[1] 79 FR 63629-63634.
[2] *Ibid.*

To further demonstrate this point, in collaboration with researchers at the NIH Clinical Center, we conducted a systematic literature search to identify all publications describing intended and achieved SpO_2 levels in usual care NICU settings back to 1990. We then compared protocol-specified interventions in SUPPORT and four other very similar trials run concurrently — the Benefits of Oxygen Saturation Targeting trials (BOOST II) in Australia, New Zealand, and the U.K. and the Canadian Oxygen Trial (COT) — to those employed in NICUs reporting on usual care.

One study, the AVIOx study,[3] provided robust data on usual care oxygen therapy for premature infants. From 2003 to 2004, the AVIOx study documented target and achieved SpO_2 levels in premature infants at 14 NICUs in the U.S., U.K., and New Zealand (including several NICUs that participated in the five trials). We conducted a series of detailed analyses comparing the five trials to corresponding data from the AVIOx study.

In Figure A, the usual care intended SpO_2 target ranges from 14 NICUs in the AVIOx study are plotted as vertical solid bars. The grey-shaded area represents the low target range studied in the five trials. The upper 89% limit of the low SpO_2 target range studied in the five trials was far lower than the upper limit of intended ranges (93% to 100%) used during usual care at all 14 AVIOx NICUs.

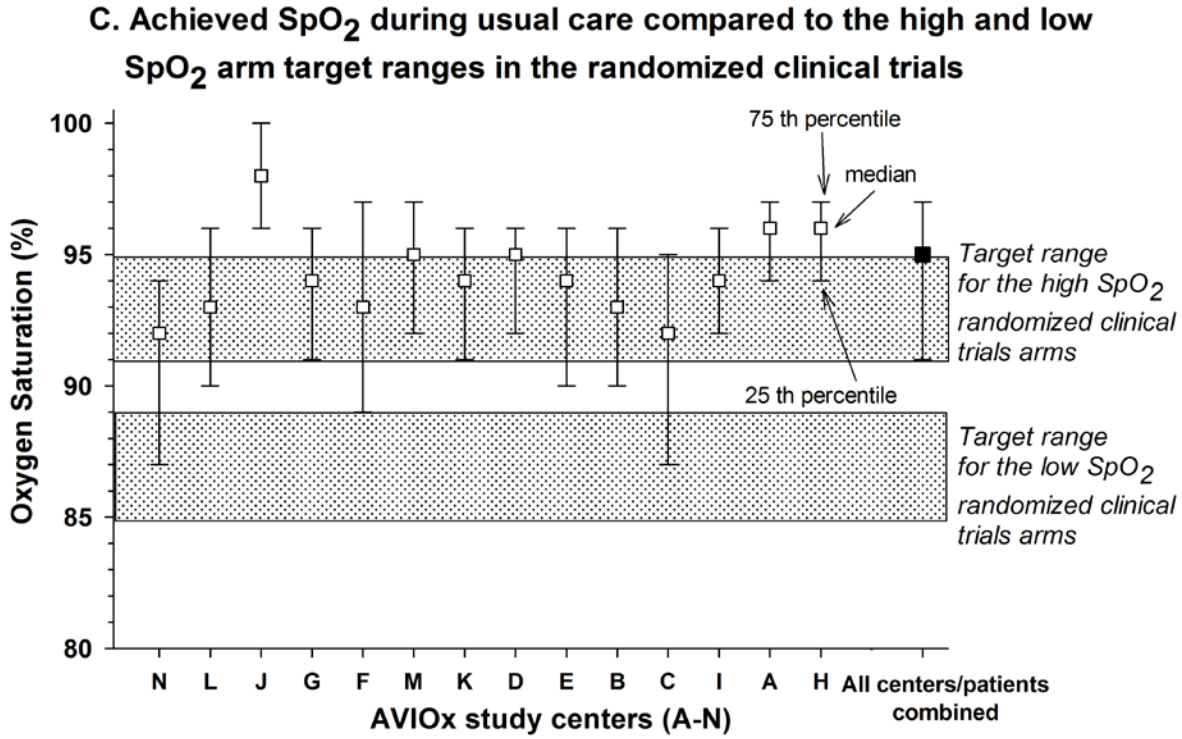


[3] Hagadorn JI, Furey AM, Nghiem TH, et al. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. *Pediatrics.* Oct 2006;118(4):1574-1582.

Our literature search showed that intended SpO_2 ranges used in usual clinical care at more than 100 other NICUs are remarkably consistent with the AVIOx study ranges.

Importantly, the median achieved SpO_2 values at the 14 usual care AVIOx NICUs during usual care were skewed toward or above the upper limit of intended ranges at all centers but one (data now shown).

The figure below compares median achieved SpO_2 values and interquartile range from the 14 AVIOx NICUs to the target ranges of the low (lower grey-shaded area) and high (upper grey-shaded area) SpO_2 arms of the five trials. The achieved SpO_2 values in clinical practice extensively overlapped with those targeted by the high, but not the low SpO_2 arms of the clinical trials. Achieved SpO_2 ranges during usual care at all AVIOx NICUs were well above the low SpO_2 target range of the five randomized trials.



Additional analyses revealed other important differences between usual care at the AVIOx study centers and the oxygen interventions in the five trials. We also have data showing how use of pulse oximeters displaying false values altered care of infants in different ways for the high and low oxygen groups in comparison to usual care.

Conclusions

(1) The oxygen interventions in the five trials, especially the low oxygen target range, resulted in substantial deviations from routine clinical practices and differentially altered risks in the two study arms.

(2) For trials purportedly studying usual care or standard of care interventions, researchers must provide institutional review boards (IRBs) with evidence for this assertion. This is critically important for studies of rapidly lethal conditions with high mortality rates, where basic interventions such as oxygen therapy may be lifesaving and protocol-driven changes in their administration can have serious consequences. A thorough review of available literature, combined with detailed surveys of usual practice and appropriately designed pilot studies, can provide such information. These easily achievable steps would have shown investigators and IRBs that the interventions in the five oxygen trials, as designed, markedly differed from usual care. OHRP's final guidance should be expanded to address this issue.

(3) Public Citizen urges OHRP to immediately:

- Rescind its 16-month suspension of compliance actions against the SUPPORT institutions.
- Require these institutions to write letters to the parents of all SUPPORT subjects divulging the information about the risks of the research and the experimental nature of the study procedures that was missing from the consent forms, as the agency has done in the past when similar serious ethical lapses have occurred during the conduct of research.

Such actions are long overdue.