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January 22, 2015

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Director
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Submitted electronically at www.regulations.gov

RE: Docket HHS-OPHS-2014-0005, Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care (79 FR 63629), October 24, 2014

Dear Dr. Menikoff:

Public Citizen, a consumer advocacy organization with more than 350,000 members and supporters nationwide, is writing in response to the request for comments on the Office for Human Research Protections' (OHRP's) above-referenced draft guidance. These written comments are intended to supplement the testimony we provided at the October 29 meeting of the Secretary's Advisory Committee on Human Research Protections (SACHRP) (copy enclosed).

We applaud OHRP for strongly reaffirming in the Federal Register notice announcing the draft guidance[1] the agency's previously stated position that the parents of premature infants enrolled in the National Institutes of Health (NIH)-funded Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT study) were not appropriately informed of the reasonably foreseeable risks of the research. These risks included risk of death, brain damage, and retinopathy of prematurity.

We generally support the positions expressed by OHRP in the draft guidance regarding the disclosure of reasonably foreseeable risks in research evaluating "standard of care" or usual care interventions.[2] However, the draft guidance is too narrowly constrained in its scope and fundamental position statement and lacks clarity with respect to several important points. Of note, your presentation at the October 29, 2014, SACHRP meeting appeared to provide a much clearer description of OHRP's position and the underlying ethical rationale for that position than what was described in the draft guidance document itself.

[1] 79 FR 63629, 63631 (October 24, 2014).
[2] We prefer the term "usual care" over "standard of care" and will use our preferred terminology in the remainder of our comments.

Major general comment

The language describing the scope of the draft guidance and OHRP's fundamental position statement, found in the following excerpts for the **Scope** section of the draft guidance, is difficult to understand and overly narrow in scope:[3]

> [The draft guidance] discusses whether risks are considered *risks of research* when one of the purposes of the research is the evaluation or comparison of risks associated with standards of care. It also discusses disclosing certain *reasonably foreseeable risks* to prospective subjects when seeking their informed consent to participate in such research activities. It explains OHRP's position that in general the *reasonably foreseeable risks of research* in a study include the already identified risks of the standards of care being evaluated as a purpose of the research when the risks being evaluated are different from the risks some of the subjects would be exposed to outside of the study. … [Emphasis in original]
>
> This draft guidance focuses on reasonably foreseeable risks of research in studies whose purposes include evaluating risks of treatments or procedures that are medically recognized standards of care. The draft guidance does not address the broader topic of identifying *all* of the risks in studies designed to evaluate treatments or procedures that are medically recognized standards of care. Moreover, it does not provide a comprehensive review of which of such risks will be reasonably foreseeable.

This language is tortured and difficult to understand. In particular, it is unclear whether investigators obtaining informed consent for research must disclose to subjects risks associated with the standards of care interventions under study, risks being evaluated as a purpose of the research, risks that differ from the risks to which subjects would be exposed outside the study, or some combination of these factors.

Furthermore, the scope of the guidance is too narrowly constrained. Reasonably foreseeable risks that must be disclosed to prospective subjects considering enrollment in a randomized trial comparing alternative usual care interventions should certainly include those risks being assessed as a purpose of the research, but the disclosure should not be limited to only those risks. Instead, the disclosure must include all reasonably foreseeable risks of each alternative to which subjects may be randomly assigned. The description of the reasonably foreseeable risks should highlight the major differences in the known or suspected risks of the alternative usual care treatments or procedures being compared in the trial, including any risks being evaluated as a purpose of the research. Such risks must be disclosed even if they are already identified as risks associated with usual care treatments or procedures to which patients might reasonably be exposed in clinical practice.

By limiting the scope of the guidance — and its fundamental position statement — to the reasonably foreseeable risks of research where one of the purposes of the research is the

[3] Office for Human Research Protections. Guidance on disclosing reasonably foreseeable risks in research evaluating standards of care (Draft). October 20, 2014. http://www.hhs.gov/ohrp/newsroom/rfc/comstdofcare.html. Accessed January 22, 2015.

evaluation of risks of standard of care treatments or procedures being studied, OHRP appears to be causing confusion and providing a basis for some critics to attack OHRP's fundamental position. Moreover, such guidance, if finalized as written, could be misused by investigators to avoid disclosing reasonably foreseeable risks of research evaluating usual care interventions if they simply avoid any mention of the evaluation of risks of the research interventions in the purpose section of research protocols.

During your discussion of the underlying ethical rationale for the draft guidance at the October 29, 2014, SACHRP meeting, you made several important statements indicating that the risks that must be disclosed to subjects when their consent is sought for research evaluating usual care interventions are *not* limited to risks being evaluated as a purpose of the research. For example, you stated in your slide presentation the following:[4]

> Slide 4:
> An (old) core concept [Emphasis in original]
>
> If a study involves possibly exposing a person to *different* non-minimal risks from those to which they would otherwise be exposed – risks that *have already been identified* (no gotchas) – they should be told these risks, and allowed to decide if they want to be exposed to them." [Emphasis in original]
>
> Slide 5:
> An important point [Emphasis in original]
>
> Note: nothing in this core concept refers to whether or not the new risks are part of a standard of care. That doesn't matter – we generally don't expose people to substantial risks for research purposes without their consent.
>
> Slide 8:
> An assumption [Emphasis in original]
>
> The discussion that follows is about studies in which participation may *change* the treatment given to a patient -- and thus *change the risks* to which they are exposed. [Emphasis in original]
>
> Slide 10
> Another assumption [Emphasis in original]
>
> The discussion that follows is about studies in which there is concern that the risk differences between the two treatments may be more than minimal – and we have already identified specific differences. [Emphasis in original]

[4] Menikoff J. Disclosing risks in research evaluating standards of care. PowerPoint slide presentation presented at the Secretary's Advisory Committee on Human Research Protections. October 29, 2014.

> Slide 19
> The Truth [Emphasis in original]
>
> ● There are often substantially different risks from different versions of standard care.
> ● Choosing which version of standard care to receive can often be one of the most important decisions a patient makes.

While we do not agree with every point made in your presentation — such as the unhelpful use of the term "non-minimal" when characterizing risks that should be disclosed — the above statements do clearly acknowledge that (a) interventions used in usual care routinely have known reasonably foreseeable risks; (b) the risks of various alternative usual care interventions for a particular disease or disorder often differ — in many cases substantially — in terms of their type, magnitude, and probability of harm; and (c) such differences would be material to a prospective subject's decision about whether to enroll in a randomized trial comparing such alternatives. It follows, therefore, that the reasonably foreseeable risks of each alternative usual care intervention in such a trial obviously must be disclosed to prospective subjects, regardless of whether an assessment of those risks is a stated purpose of the research.

Indeed, in the October 24, 2104, *Federal Register* notice announcing the availability of the draft guidance, OHRP stated the following:[5]

> Certain treatments and procedures that are commonly used in health care for a given type of disease or condition have come to be known as "standards of care." Multiple "standards of care" involving widely differing treatments and risks may be available for the same disease or medical condition. Where multiple "standard of care" options are available for a given disease or condition, the use of the term does not imply that the options will produce similar benefits or incur similar risks. Furthermore, **patients may not find those options equally acceptable**, nor do physicians always use them interchangeably. Importantly there is not necessarily a limit on how different the risks from two versions of a standard of care might be. **For example, it may already be known that one of those versions imposes a significantly higher risk of death than the other**. …
>
> **Patients randomized to different standards of care in a comparative effectiveness trial should accordingly be made aware of the risks of the standards of care that are being compared**.
>
> [Emphasis added]

We therefore urge OHRP to widen the scope of the guidance and provide a more expansive and clearer position statement that incorporates the rationale detailed in your presentation to SACHRP and the above statements made by OHRP in the *Federal Register* notice announcing the availability of the draft guidance. This could be accomplished most simply by revising the

[5] 79 FR at 63630, 63632.

scope section of the guidance as follows and making conforming edits throughout the subsequent sections of the document:

> **Scope:** This guidance pertains to nonexempt research involving human subjects that is designed to evaluate alternative treatments or procedures that are used in usual care. The guidance applies to such research that is conducted or supported by the Department of Health and Human Services (HHS).
>
> This guidance explains how to apply the HHS Regulations at 45 CFR 46.116(a)(2) to studies that are designed to evaluate one or more alternative usual care treatments or procedures. It explains OHRP's position that for a trial involving random assignment of subjects to one of two or more alternative usual care treatments or procedures, the *reasonably foreseeable risks of each alternative* must be disclosed to subjects. It further explains that this description of the reasonably foreseeable risks should highlight the major differences in the known or suspected risks of the alternative usual care treatments or procedures being compared in the trial, including any risks being evaluated as a purpose of the research. Such risks must be disclosed even if they are already identified as risks associated with usual care treatments or procedures to which some patients might reasonably be exposed in clinical practice.

Additional comments

(1) In the **Supplementary Background** section, OHRP included a limited discussion of the SUPPORT study and OHRP's compliance oversight findings regarding the failure of the investigators to disclose important reasonably foreseeable risks of the research. We recognize that the controversy surrounding the SUPPORT study was the impetus for the August 28, 2013, public meeting convened by HHS and for OHRP's draft guidance. **However, the continued inclusion of the SUPPORT study in discussions of research evaluating alternative usual care interventions perpetuates the misunderstanding that the SUPPPORT study was an example of such research, which it clearly was not.**

The SUPPORT study was 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 (the continuous positive airway pressure [CPAP] experiment). As we have extensively documented, the infants enrolled in the study were exposed to multiple interventions that were not representative of usual oxygen and ventilatory care for extremely premature infants.[6] For example:

- For the low oxygen saturation target group, the oxygen saturation target was lower and narrower than the ranges used in usual care.

[6] Carome M, Wolfe S, Macklin R. *Report Prepared for Secretary of Health and Human Services Kathleen Sebelius: Analysis of the Complete Protocol and Consent Form for the SUPPORT Study: Lack of Informed Consent and a Failure to Ensure That Risks Were Minimized*. May 8, 2013. http://www.citizen.org/documents/2124.pdf. Accessed January 22, 2015.

- The use of the falsely reading pulse oximeters represented an extraordinary deviation from usual care, 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.
- The study's CPAP experiment included an experimental group that did not receive usual care ventilation management. The experimental group received early CPAP with strict criteria for intubation and extubation designed to force babies off ventilation, whereas the control group received what the investigators described as standard of care interventions, with early intubation, surfactant — which had been shown to be life-saving when given early to extremely premature infants, especially those at 24-25 weeks gestation — and conventional ventilation, plus criteria for intubation that the investigators described as unit standard of care. The drafters of the SUPPORT study protocol noted that the CPAP-group intubation criteria were "*more severe* than have been used in *any* trial, and as far as we can tell, are more severe than used in most Network centers…"[7] [Emphasis added]

We therefore urge OHRP to exclude reference to the SUPPORT study from any final guidance document addressing the disclosure of risks in research involving usual care interventions, *unless* OHRP explicitly notes in any such reference that the SUPPORT study was not a representative example of such research.

(2) Some commentators have criticized the draft guidance as violating "both the spirit and letter of the Belmont Report principles."[8] We believe such criticism is unfounded and should be countered by adding a discussion of the Belmont Reports' principle of respect for persons, as well as the key points from your description of the underling ethical rationale for OHRP's position in your presentation to SACHRP, to the background section of the guidance. The draft guidance only makes a passing reference to the principle of respect for persons in the final sentence of the **Conclusion** section.

(3) Section 3, **When is evaluating a risk in a research study considered to be a "purpose" of the research study?**, includes the following statements:

> If a study is designed to discover the degree to which that particular harm will or will not occur, the possibility of that harm occurring is clearly foreseen by those responsible for the design and conduct of the study. The risks should accordingly be disclosed to the people who are being asked to be exposed to that risk as subjects in the study. …
>
> In the context of research evaluating standards of care, the evaluation of the risks in studies comparing standards of care that OHRP generally considers to be

[7] SUPPORT TRIAL: Rationale, Evidence, Protocol. PowerPoint presentation prepared by the SUPPORT study investigators. Obtained by Public Citizen in response to a Freedom of Information Act request to the National Institutes of Health. Slide 78.

[8] Lantos JD, Spertus JA. The concept of risk in comparative-effectiveness research. *N Engl J Med*. 2014;371(22):21292130.

> identified as "purposes" of the research should be limited to evaluating those risks that are sufficiently important to justify the conduct of the study.

Section 4, **Are the risks of research associated with the purposes of studies of standards of care "reasonably foreseeable risks" that must be disclosed to prospective subjects in the informed consent process?**, also includes the following statements:

> If evaluating a particular risk of research associated with a standard of care is a purpose of the research, then in general OHRP considers that particular risk to be "reasonably foreseeable." Such reasonably foreseeable risks must be disclosed as risks in the informed consent process in accordance with the regulatory requirements of 45 CFR 46.116(a)(2).

We generally agree with these statements. However, as we discussed in our major general comment above, the reasonably foreseeable risks that must be disclosed to prospective subjects considering enrollment in a randomized trial comparing alternative usual care interventions should not be limited to those risks being assessed as a purpose of the research.

In the hypothetical example described in section 4, there may be known differences in the risk profile of the two doses of radiation therapy — in terms of probability and magnitude of harm — that must be described to the parents when obtained permission for the children to enroll in the trial. For example, the higher radiation dose may be more likely to cause short term adverse effects such as radiation burns to the skin or radiation-induced colitis. The guidance should indicate that such differences must be described when seeking parental permission for the research and disclosing the reasonably foreseeable of the research, regardless of whether a purpose of the research is to evaluate these risks.

(4) In the October 24, 2104, *Federal Register* notice announcing the availability of the draft guidance, OHRP stated the following in the discussion of public comments responding to the question of how an institutional review board (IRB) should assess the risks of standard of care interventions provided to subjects in the research context:[9]

> The key issue is not whether an intervention provided to subjects is within a standard of care…

Likewise, during your presentation of the guidance at the October 29, 2014, SACHRP meeting, you stated the following:

> The concept is broad enough that it actually doesn't matter that much whether or not what you're randomizing somebody to is standard of care or not…

[9] 79 FR at 63632.

We agree that for the purposes of determining what the reasonably foreseeable risks of the interventions in a randomized clinical trial are, it does not matter whether the trial interventions being compared are within the scope of usual care. However, accurately communicating whether the interventions in the research are within the scope of usual care or fall outside the scope of usual care (i.e., are experimental) is required from both an ethical and regulatory standpoint. The distinction also is clearly material to a prospective subject's decision about whether to enroll in a randomize trial. One of the key deficiencies in most of the SUPPORT study consent forms was the misrepresentation of all of the research procedures as being with the scope of standard or usual care. We recommend that the guidance briefly address the importance of this distinction.

The guidance should also advise that for trials purportedly studying usual care or standard of care interventions, researchers must provide IRBs with evidence for this assertion. This is especially important for studies of life-threatening or rapidly lethal conditions, 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.

Response to criticism of the draft guidance by others

A number of commenters have asserted that OHRP's guidance, if finalized as written, would stifle comparative effectiveness research by imposing enormous burdens and by alarming prospective subjects, causing them to decline enrollment in such research. Such assertions have no merit. Over the past several decades, many randomized clinical trials involving thousands, in some cases tens of thousands, of subjects have been conducted using consent procedures that included appropriate disclosure of the reasonably foreseeable risks of the research interventions being tested. There is no reason to believe that people would be unwilling to enroll in clinical trials involving comparisons of alternative usual care interventions if the reasonably foreseeable risks of those study interventions were described.

Furthermore, if it is assumed — as some critics of OHRP's draft guidance contend — that people would not enroll in clinical trials when the reasonably foreseeable risks of usual care are disclosed, then it would seem to logically follow that people would also refuse to consent to some usual care interventions when health care providers disclose risks to patients when obtaining informed consent for treatment. The critics thus seem to be implying that risks also should not be disclosed by physicians in the clinical context because patients might refuse potentially beneficial interventions.

Some critics of OHRP's draft guidance and its findings regarding the SUPPORT study also have argued that patients will already know the risks of usual care and, therefore, those risks need not be disclosed during the consent process for clinical trials comparing different usual care interventions. Such arguments are flawed for three reasons. First, patients often remain uninformed of important reasonably foreseeable risks of usual care interventions during clinical care, because their treating health care providers have inappropriately neglected to inform them of these risks. Second, clinical trials may involve usual care interventions that some prospective subjects have never previously heard about or discussed with their health care providers. And

third, the requirements of the HHS regulations do not exclude from disclosure reasonably foreseeable risks of which prospective subjects may already be aware.

Most importantly, the ethical imperative to satisfy the requirements of the Belmont Report's principle of respect for persons far outweighs any burden that may result from appropriately disclosing reasonably foreseeable risks when the informed consent of prospective subjects is sought for usual care research. The real threat to the comparative effectiveness research enterprise is in conducting such research in an unethical manner, which understandably will undermine the public's trust in the motives and behavior of researchers. Conformance with the fundamental ethical principles for conducting human subjects research must never be sacrificed in the quest to advance medical knowledge.

Thank you for the opportunity to comment on these important issues.

Sincerely,

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Enclosure

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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

Michael A. Carome, M.D., and Sidney M. Wolfe, M.D.
Public Citizen's Health Research Group
October 29, 2014

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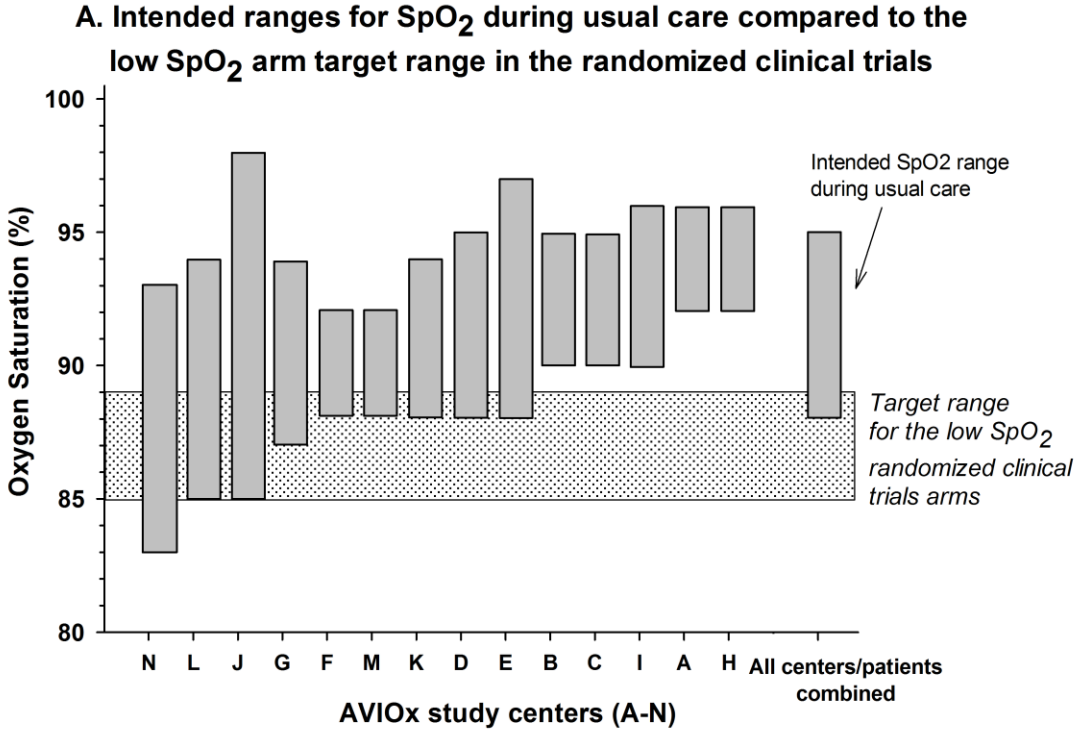
[1] 79 FR 63629-63634.
[2] *Ibid.*

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.

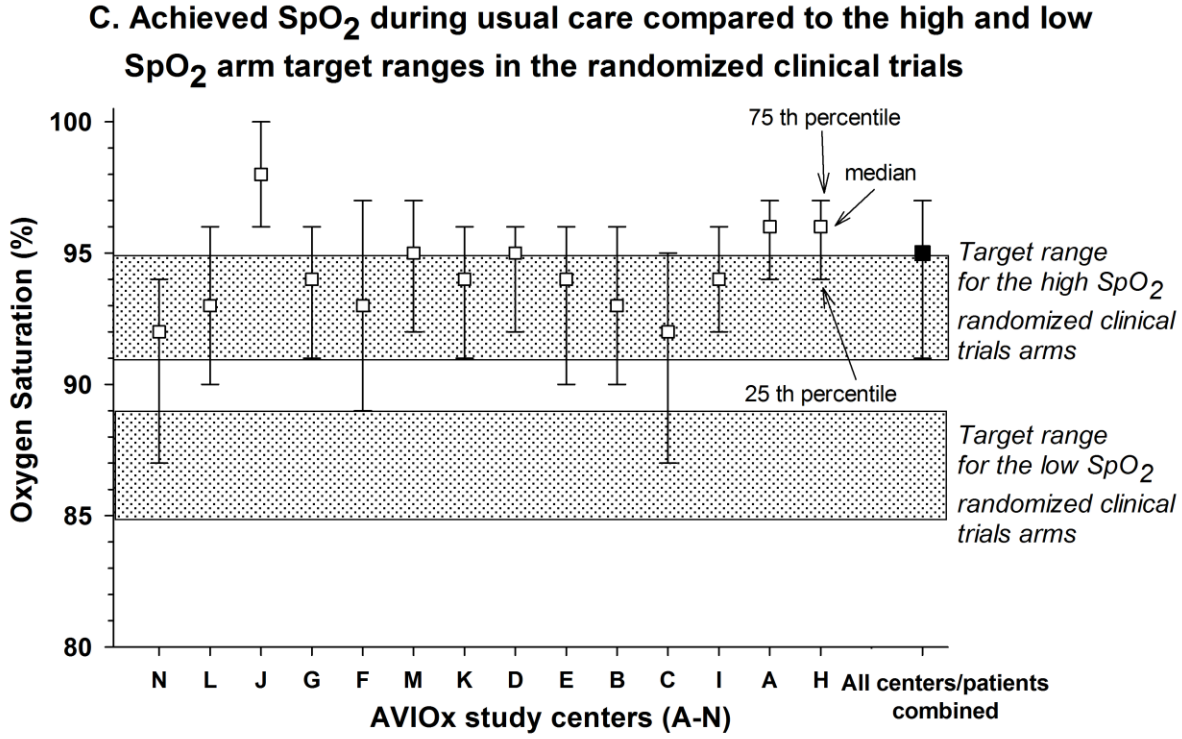


[3] Hagadorn JI, Furey AM, Nghiem TH, et al. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. *Pediatrics.* Oct 2006;118(4):1574-1582.

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.