Citizens for Responsible Care and Research, Inc. (CIRCARE)
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incorporated under the laws of the State of New York)
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In re: U.S. Department of Health and Human Services Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions Docket HHS-OPHS-2013-0004 78 FR 38343

CIRCARE is a nonprofit independent organization dedicated to equitable protections for human subjects of research. Via our website of more than 1900 pages and personal communication, we provide information and support to research subjects and their families, members of the media, and other interested parties. We appreciate the opportunity to comment on the important issues arising from OHRP's determination letter to UAB regarding noncompliance in obtaining informed consent in the SUPPORT study. (1)

OHRP should not issue guidance on application of the Common Rule to research studying one or more so-called standard of care interventions at this time because the controversies arising from OHRP's determinations in the SUPPORT trial do not indicate a need for such guidance.

The National Research Act requires entities receiving federal funding for human research to submit an assurance to the Secretary attesting that it has established an Institutional Review Board to review proposed research conducted by or sponsored by the entity in order to protect the rights of subjects of such research. (2) The purpose of IRB review is to protect the rights and welfare of research subjects. 45 CFR 46 aims to instantiate the ethical principles so eloquently adduced in the Belmont Report.

For the sake of brevity we agree with the findings in OHRP's determination letter to UAB, as well as the conclusions regarding the SUPPORT study protocol and consent form in Public Citizen's report by Carome *et al*. (3) In addition to these issues, we note the UAB consent form states in two places FDA may examine subjects' medical records. (4) There is no indication in the SUPPORT protocol that the study was conducted under an Investigational New Drug application or an Investigational Device Exemption. (5) Accordingly these statements may mislead parents to believe SUPPORT was sanctioned by FDA and so affect their decision about whether it would be in their baby's best interest to grant permission for enrollment.

Public dismay over informed consent and study design in the SUPPORT study unsurprisingly prompted investigators, institutions, and NIH to defend themselves. The spectre of vulnerable premature infants unjustifiably exposed to risk of harm or death in research contributed to inapposite defensive arguments, chief of which is the contention that because these babies were allegedly randomized to interventions that variously met "the standard of care", were "routine", or "acceptable", babies were exposed to no greater risk of harm in research than they would have been if they were treated outside the study. Further, on this basis, disclosure of risks in the consent form was appropriate. For the reasons discussed in Public Citizen's report as well as OHRP's determination letter to UAB, we reject the argument that "standard of care" *vel sim* includes: randomization of premature infants to one of two target ranges of oxygen saturation levels, one of which is more conventional and another less conventional; use of pulse oximeters altered to provide inaccurate information to caregivers, or

randomization to ventilator or CPAP, recommendations for the use of which latter following delivery of premature infants did not exist according to the SUPPORT consent form. Even if it were true that these and other interventions in SUPPORT were standard treatments, established rights of research subjects or their representatives to determination and bodily integrity obligate investigators to obtain valid legally effective informed consent. To meet this obligation foreseeable harms must be disclosed in a way that's understandable to subjects or their representatives. Indeed SUPPORT investigators identified a list of noxious primary and secondary outcomes designated as safety issues in the study registration. (6) Excluding these from the consent form is baffling.

Standard of care is applicable to the practice of medicine in evaluation of professional conduct and as such is a legal and professional determination of what an adequately trained physician would recommend to her individual patient based on her unique circumstances. Given that research and medical treatment are not equivalent, and that institutions, IRBs, and investigators have an obligation to clarify the distinction between research and medical practice so as not to foster the therapeutic misconception, it seems wise to avoid the term in research.

By conceptualizing proposed research interventions as standard of care IRBs and investigators may lose sight of their obligations to protect research subjects. So too potential research subjects may not scrutinize consent forms as they otherwise might have done if they suppose there is little or no risk of harm to them *simply* because they believe research interventions are the same as medical treatment. There is nothing inherently unique about studies that randomize subjects to one or more interventions involving use of available first-line treatments. From our viewpoint, rather than detailed guidance on hypothetical cases and purported grey areas, the SUPPORT study indicates the need for consistent consideration of basic ethical principles to ensure potential research subjects are provided with sufficient information during the process of informed consent, as documented in a consent form that complies with the current regulations at 45 CFR 46.116. Respect for persons obligates SUPPORT investigators to disclose the purpose of their research, their thinking about the study hypothesis if you will, in sufficient detail and in terms understandable to potential subjects. OHRP correctly determined that the SUPPORT consent form (UAB version) failed to provide important information that parents needed to consider in order to provide valid legally effective informed consent (correctly, permission in this case). We do not suggest SUPPORT investigators deliberately concealed reasonably foreseeable risk of death or neurological impairment to infants randomized to the lower oxygen arm of the trial yet it is not credible that SUPPORT investigators did not believe lower oxygen saturation levels posed no foreseeable risk of harm to infants: oxygen saturation is clearly a crucial parameter of human physiology. While we understand that mortality is but one component of the composite outcome in the SUPPORT trial we nevertheless insist the possibility of death or neurological injury should have been disclosed in the consent process.

Public meeting testimony by parents of infants enrolled in SUPPORT couldn't have been more clear: they did not have sufficient information that they could understand so as to be able to decide whether it was in their infants' best interest to join the SUPPORT study. It may be helpful for OHRP to know that CIRCARE officers and board members, all of whom have graduate or professional degrees and experience in reading consent forms, had difficulty understanding the SUPPORT consent form. While it's true some of our questions would have been addressed by the study nurse or investigator, there were sections in the consent form, notably regarding randomization to CPAP or ventilator, where we were at a loss to know what to ask. With respect to this section and elsewhere in the consent it would have been helpful to use "continuous positive airway pressure" consistently rather than "CPAP". This would not add appreciably to the length of the consent and repetition is a tried and true learning strategy. A colleague, an attorney with an LL.M., drew attention to the use of the term "routine" where the consent form stated if parents declined to have their infants participate, "routine" care would be provided in the delivery room. She wondered if parents

would understand what was meant or be confused as to whether there was a difference between the life-saving interventions described in the research context and "routine" care. This insightful comment makes us wonder if confusion may have led parents to agree to let their infants participate so they would receive the best possible care. (7) It's been our consistent experience that research subjects do not understand the difference between research and medical treatment and that consent forms do little to explain the difference. We believe when proposed research involves one or more first-line interventions, IRBs must make extra effort to ensure that subjects understand the difference between research and medical treatment.

Another argument offered to defend SUPPORT (apparently) asserts that physicians lack good evidence for most of their treatment recommendations and so the urgent need to conduct research to obtain allegedly lacking evidence is somehow impeded by burdensome requirements for informed consent. This comes perilously close to the familiar refrain of quacks and purveyors of purported cures and nostrums and has the capacity to undermine public confidence in medicine, something that can harm individuals and society. While it's true that there is room for refinement and improvement in medical treatment, it's demeaning to highly trained physicians to suggest the medical care they provide is haphazard, random, or unsupported by evidence; it's also incorrect. (8) The need to conduct medical research does not overcome individuals' basic rights and in particular the right to consent or decline to consent to medical treatment or research participation. This is not a new argument and in fact in 1967 FDA felt the need to refer to rights of individuals in the U.S. Constitution to support newly promulgated regulation requiring investigators to obtain informed consent from patients in IND drug trials. (9) FDA asserted the requirement would not impede research, apparently in response to claims to the contrary, and history proved FDA correct.

Our experience indicates the greatest threat to medical research is loss of public confidence; egregious instances of noncompliance in research coupled with enforcement responses that are feeble at best undermine public confidence in research, as well as in medicine and science generally. To be sure, disaffected people vote. (10)

Additional Comments

Earlier this year we learned that NICDH does not require its awardees to provide consent form templates or IRB approved consent forms. (11) If this policy has not been modified since 2011, we urge NICDH to consider revising their policies to require awardees to submit informed consents. We realize that consent templates are subject to revision by IRBs and we are not suggesting that NICDH should "word-smith" these documents. Rather we believe that NICDH program officers should review consent forms and recommend revisions as needed based on their expertise. We believe this is generally consistent with NIH's stewardship obligations. (12)

NIH's forceful response to OHRP's determination letter to UAB detracts from the authority and credibility of agency and tends to undermine public confidence in research. NIH has much to be proud of and also has the right to express opinions. At the same time NIH is, in fact, a regulated party, and OHRP is the legally authorized regulator. NIH is also staffed by human beings and humans make mistakes from time to time. We respectfully suggest NIH consider the way in which they disagree or otherwise express opinions because not only does this impact public confidence in research, particularly vehement disagreement may undermine OHRP authority and send the wrong message to NIH-funded investigators. In the worst case this may set the stage for future noncompliance.

We urge OHRP to investigate the circumstances in the SUPPORT study wherein eleven attempts (each) were made to obtain consent from two mothers or legally authorized representatives. (13) 45 CFR 46.116 General requirements for informed consent state, in part, that:

> "An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence."

Eleven attempts to obtain consent, on two separate occasions no less, is inconsistent with the requirement to minimize the possibility of undue influence. It is crucial this matter be resolved promptly to prevent repeats in trials currently being conducted by members of the NICHD Neonatal Research Network.

It may be useful for OHRP to consider what impact, if any, NIH sponsorship may have on IRB review. Does the fact that NIH approved (broadly defined) the proposed research lead IRB members to consider such research, perhaps subconsciously, in a different way than they might, for example, approach a study testing an investigational drug submitted by a commercial sponsor with whom there is no prior history? The fact that SUPPORT consent forms from participating institutions were defective to varying extents might indicate this is possible. It's not unreasonable to expect a certain level of excellence in NIH-supported research, yet expectations should not make review of proposed research less rigorous. We note that IRBs at more than 30 institutions approved the consent form in the NIH-sponsored Trial to Assess Chelation Therapy (TACT). (14) In 2009 OHRP determined the informed consent falsely implied that the drug being used in the TACT study was approved for treatment of lead toxicity, which suggests IRB members somehow overlooked the investigator's brochure and the FDA approved drug label. (15)

We commend HHS, OHRP, FDA, and NIH for their hard work in organizing and participating in the public meeting held on 2013-08-28, and we especially appreciate timely availability of video rebroadcasts on YouTube.

Sincerely,

Elizabeth Woeckner, M.A., President
Citizens for Responsible Care & Research, Inc.

Bruce A. Middleton, J.D., Board of Directors
Citizens for Responsible Care & Research, Inc.

Notes

1. OHRP Determination Letter to UAB 2013-04-07
http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf Accessed on 2013-09-08.

2. National Research Act Public Law 93-348 1974-07-12
http://history.nih.gov/research/downloads/PL93-348.pdf Accessed on 2013-09-08.

3. Carome M, Wolfe S, Macklin R. Analysis of the Complete Protocol and Consent Form for the SUPPORT Study: Lack of Informed Consent and a Failure to Ensure Risks Were Minimized. 2013-05-13. http://www.citizen.org/documents/2124.pdf Accessed on 2013-09-08.

4. SUPPORT Study Consent Form (UAB), pp. 5, 7.
http://www.nejm.org/doi/suppl/10.1056/NEJMe1304996/suppl_file/nejme1304996_appendix.pdf Accessed on 2013-09-08.

5. SUPPORT Study Protocol. http://www.nih.gov/icd/od/foia/library/Protocol.pdf Accessed on 2013-09-08.

6. SUPPORT Study NCT00233324 http://clinicaltrials.gov/ct2/show/study/NCT00233324 Accessed on 2013-09-08.

7. SUPPORT Study Consent Form (UAB), Alternative Procedures, p. 4. http://www.nejm.org/doi/suppl/10.1056/NEJMe1304996/suppl_file/nejme1304996_appendix.pdf Accessed on 2013-09-08.

8. Imrie RH, Ramey DW. The Evidence for Evidence-based Medicine. *Scientific Review of Alternative Medicine* 2001(5) 2: 104-108. http://www.sram.org/media/documents/uploads/article_pdfs/5-2-06.Imrie-Ramey.pdf Accessed on 2013-09-08.

9. Minchew BH, Gallogly C. Informed Consent. *FDA Papers* October 1967:8-11. http://www.circare.org/fda/informedconsent_fdapapers_101967.pdf Accessed on 2013-09-08.

10. Emanuel EJ. The Future of Biomedical Research. *JAMA*. 2013;309(15):1589-1590. (Abstract) http://jama.jamanetwork.com/article.aspx?articleid=1675581 Accessed on 2013-09-08.

11. PHS Appeal No.: 11-0303, Response 2011-08-17. http://www.circare.org/info/phs-appeal_11-0303_20110817.pdf Accessed on 2013-09-08.

12. See for example NIH Director Collins opining that program staff are responsible for the stewardship of the research within their portfolios, Appendix A, p. 15, agency response, in: Data Safety and Monitoring Boards in NIH Clinical Trials OEI 12-11-00070 Department of Health and Human Services Office of Inspector General, June 2013. https://oig.hhs.gov/oei/reports/oei-12-11-00070.pdf Accessed on 2013-09-08.

13. Wade RD et al. Antenatal Consent in the SUPPORT Trial: Challenges, Costs, and Representative Enrollment *Pediatrics*. 2010 July; 126(1): e215—e221. http://dx.doi.org/10.1542/peds.2009-3353 Accessed on 2013-09-08.

14. Lamas GA, Chandra R. Response to Form FDA 483. 2010-06-04. p. 2. http://www.circare.org/tact/tactsite_responsetofdainspection.pdf See also Bauchner H, Fontanarosa PB, Golub RM. Evaluation of the Trial to Assess Chelation Therapy: the scientific process, peer review, and editorial scrutiny. Supplemental Content eAppendix. Editors' Comments and Author Responses. *JAMA*. 2013;309(12):1291-1292. (eAppendix, p.5) http://jama.jamanetwork.com/data/Journals/JAMA/926663/JED130031_supp.pdf Accessed on 2013-09-08.

15. OHRP Determination Letter to Mount Sinai Medical Center. 2009-10-30. http://www.hhs.gov/ohrp/detrm_letrs/YR09/oct09a.pdf ; OHRP Determination Letter to Mount Sinai Medical Center, University of Miami, and Duke University Health System. 2009-05-27. http://www.hhs.gov/ohrp/detrm_letrs/YR09/may09b.pdf Accessed on 2013-09-08.