The Informed Consent Process for Human Research Must be Strengthened, Not Weakened

HHS Meeting on Human Subjects Research Studying "Standard of Care" Interventions
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Pretext for the HHS Meeting: Based on Two Major Fallacies

- **<u>Fallacy #1</u>:**

  The SUPPORT study is a representative example of research involving interventions used as "standard of care" treatment in the non-research context.

SUPPORT Study Interventions ≠ "Standard of Care" Treatments

- Randomization (relying on a flip of a coin) to make life-and-death medical decisions independent of infants' clinical status or need.
- Attempting to maintain oxygen saturation levels within a more narrow high or low range in comparison to the broader range used for titrating oxygen therapy in the non-research setting, combined with a masking procedure using pulse oximeters that provided to the NICU medical teams either falsely high or falsely low oxygen readings.

Electronically Altered Pulse Oximeters

- **Stated purpose: blinding procedure to avoid bias**

- **Unstated, and more important purpose: force medical teams caring for the premature infants to consistently target the desired experimental oxygen levels and achieve separation between the two experimental groups (this masking was considered "essential to minimize co-intervention and contamination by bias of neonatal care providers"; *Cole et al, Pediatrics 2003;112:1415-18*)**

SUPPORT Study Interventions ≠ "Standard of Care" Treatments

- CPAP Experiment: "Treatment" (i.e., experimental) group: early CPAP with strict criteria for intubation and extubation designed to "force" babies off ventilation; versus the "control" group: similar to "standard of care," received 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; criteria for intubation were "unit standard of care."

CPAP Experiment – Investigators' Characterization of the Interventions

***Fall 2004 PowerPoint presentation prepared by SUPPORT study investigators*:**

- **"These [CPAP-group intubation] criteria are 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…"**

CPAP Experiment: CPAP Group Intubation/Reintubation Criteria

"…*MAY* be intubated if they meet *ANY of* [these] criteria…:

- "An FiO_2 >.50 to maintain an indicated SpO2 ≥ 88% (using altered Pulse Oximeters) for one hour"

"…*MUST have extubation attempted within 24 if all of the following criteria are met*…:

- An indicated SpO2 ≥ 88% with an FiO2 ≤ 50%..."

[*SUPPORT protocol, Final, Updated March 28, 2005*]

CPAP Experiment – Investigators' Characterization of the Interventions

"CPAP infants who require intubation three times, for any criteria, will have all subsequent treatment including subsequent extubations and any further re-intubations performed using unit Standard of Care. This addition is to prevent such infants from being exposed to further protocol driven intubations and extubations."

[*SUPPORT protocol, Final, Updated March 28, 2005*]

SUPPORT Study Experimental Procedures ≠ "Standard of Care"

- **Every infant in the study received multiple interventions that were not "standard of care"**
- **The Low-Oxygen-CPAP group received the most extreme combination of experimental interventions: low O_2 target range, management with miscalibrated pulse oximeters, CPAP, and severe criteria for intubation and extubation designed to force infants off mechanical ventilation.**

Pretext for the HHS Meeting: Based on Two Major Fallacies

- **<u>Fallacy #2</u>: We have entered a new era of human subjects research that involves studies comparing different treatments that are used as part of "standard of care" or usual clinical care treatment in the non-research context, and as a result, investigators and IRBs that conducted and reviewed the SUPPORT study (and similar studies) are justifiably unsure how to apply the requirements of the human subjects regulations regarding informed consent.**

Human Subjects Protections at a Crossroads

- The history of human experimentation over the past century is filled with victims of unethical research conducted without adequate informed consent.
- Prior revelations of unethical research ultimately led to strengthening of human subjects protections. The opposite may occur in the wake of the SUPPORT study disclosures.

Human Subjects Protections at a Crossroads

- **OHRP's finding regarding SUPPORT triggered a well-orchestrated attack against the office.**
- **OHRP's critics seek to blur the line between human research and clinical care.**
- **The fact that this meeting is occurring reflects the tremendous pressure that the leadership of NIH, who have a serious conflict of interest in the matter, has wielded.**

Conclusions

- **The efforts of OHRP's critics to weaken human subjects protections must not be allowed to succeed.**
- **Aug. 22 *Nature* editorial: "No matter the thorniness of the issues raised [at this meeting], research is still research in whatever context, and the duty to protect human subjects must remain paramount.**
- **Per the words of OHRP Director Dr. Jerry Menikoff, to the *Iowa City Press-Citizen* on Apr. 12, commenting on the SUPPORT study consent failures, "this should never happen again."**

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