[SLIDE 1] Good morning. The most important take-home message for OHRP today is that the *obvious, serious deficiencies* in the SUPPORT study consent process signal an *urgent need* to strengthen informed consent for human subjects research, not to *weaken it* as many in the research community are advocating.

[SLIDE 2] It is *remarkable and disturbing* that the pretext for this meeting is based on *two major fallacies*. The first is that the SUPPORT study is a representative example of research involving interventions used as "standard of care" treatment in the non-research context. It is not, as a review the protocol and related documents shows.

[SLIDE 3] Let me highlight just a few of the SUPPORT study's many complex experimental interventions that *cannot be considered* "standard of care" treatment in the non-research context.

- Relying on a flip of a coin to make *life-and-death* medical decisions *independent* of subjects' clinical status or need is not "standard of care."

- Attempting to maintain oxygen saturations within a narrow high or low range, combined with a masking procedure using pulse oximeters that displayed either falsely high or falsely low oxygen readings depending on experimental group assignment, was not standard of care.

  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.

  [SLIDE 4] The stated purpose for using the altered pulse oximeters was to have a blinding procedure to avoid bias. However, the *unstated — and more important — purpose* was to *force* the medical teams caring for the premature infants to consistently target the assigned experimental oxygen levels and achieve separation between the two groups. This masking was considered "*essential* to minimize *co-intervention* and contamination by bias of neonatal care providers."

  Cole et al's comment in a paper discussing the rationale behind the design of the SUPPORT, BOOST II and COT studies reflected an awareness that if medical teams caring for the study infants were given *accurate* oxygen data, they would *not* maintain oxygen levels within the ranges stipulated by the research protocol. This is a clear acknowledgement that the *experimental target ranges* were not consistent with "*standard of care*" interventions in the non-research setting.

- [**SLIDE 5]** The study's CPAP experiment included an experimental group that did not receive "standard of care." The "Treatment" (i.e., experimental) group: received early CPAP with strict criteria for intubation and extubation designed to "f*orce*" babies off ventilation; versus the "control" group: received similar to "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 were "unit standard of care."

[SLIDE 6] In a 2004 presentation describing the SUPPORT study's CPAP interventions, the investigators noted the following:

-"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…"

The CPAP group intubation criteria clearly did *not* represent "standard of care" treatment.

- **[SLIDE 7]** Finally, there was a complex interaction between the oxygen experiment's use of falsely reading pulse oximeters and the experimental criteria for deciding when to intubate or extubate an infant in the experimental CPAP group, as shown in these protocol excerpts.

  It is notable that these criteria are based, in part, on a f*alse* pulse oximetry readings.

[SLIDE 8] The investigators recognized that these criteria were *not* consistent with "standard of care as they stated in the protocol that "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*."

[SLIDE 9] Thus, the SUPPORT study clearly involved many interventions that deviated from "standard of care" treatment in the non-research context. *Every infant* in the study received experimental 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.

[SLIDE 10] The second fallacy on which the pretext of this meeting is based is that 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. This fallacy *must be rejected*. Randomized clinical trials comparing different interventions that have been used as treatments in the non-research context have been conducted for many decades, and claims of ignorance regarding how to apply the regulations to such research ring hollow.

[SLIDE 11] The history of human experimentation over the past century is filled with victims of unethical research conducted without adequate informed consent. When outrage over revelations of unethical research reached a crescendo in the early 1970s, Congress finally passed a law requiring HHS to ensure the protection of human research subjects. The resulting regulations were implemented nearly four decades ago.

Now, in the wake of disclosures of about the unethical conduct of the SUPPORT study, there appears to be a real possibility that these disclosures will result in a weakening of human subjects protections, particularly with respect to the implementation of the ethical principle of respect for persons through informed consent.

[SLIDE 12]

Soon after OHRP's findings regarding the SUPPORT came to public attention, a group of individuals within the medical research establishment launched a well-orchestrated attack against OHRP and a defense of the SUPPORT study. Leading this effort have been the editors of the New England Journal of Medicine, the NIH director, and many researchers and bioethicists with close ties to the SUPPORT study researchers or NIH.

Many critics of OHRP's actions have sought to blur the line between human subjects research and clinical care and appear to view the process for obtaining informed consent as an unnecessary impediment to conducting clinical trials and advancing medical knowledge. They want to change the rules to satisfy their research needs at the expense of subjects' rights.

The fact that this meeting is occurring reflects the tremendous influence that NIH, which approved the SUPPORT study and spent more than $20 million for it, has wielded in an effort to undermine OHRP's authority and reverse OHRP's findings.

[SLIDE 13]

In conclusion, these efforts to weaken human subjects protections must not succeed. Many in the bioethics and research community agree that the deficiencies in the SUPPORT study's consent forms were obvious and that OHRP was correct in its finding. In the interests of protecting vulnerable human subjects, OHRP must stand its ground.

As the *Nature* editorial said last week: "No matter the thorniness of the issues raised [here] research is still research in whatever context, and the duty to protect human subjects must remain paramount.

In closing, per the words of Dr. Menikoff, commenting on the SUPPORT study consent failures, "this should never happen again." Unfortunately, even now, it is happening again.