Informed Consent for “Standard of Care” Research Interventions

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A case

- Two FDA approved drugs are commonly used for the treatment of hypertension. The drugs represent different classes of agents.

- Investigators plan a head-to-head comparison of the relative safety and efficacy of the drugs in patients with hypertension. Both drugs are on the University Hospital formulary and are commonly used by our clinicians.
A case

- Patients with new onset, moderate hypertension will be randomized to one agent or the other and followed for 6 months to assess side effects and efficacy.

- Is the informed consent of the patients necessary?
A case

- Are there incremental risks of research participation above what participants would experience as part of their clinical care?

- How should the risks of the research be described?
Another Case

- Research has shown that bronchodilator Drug A is superior to other commonly used bronchodilators for patients with acute asthma exacerbations. The pulmonary service has recommended that outpatients with asthma be provided Drug A as first line therapy.

- Clinicians propose conducting chart reviews for patients with asthma treated over the past year to assess baseline bronchodilator drug use.

- An educational intervention will be initiated to promote the use of Drug A in the University of Utah clinics.

- Data on use of bronchodilators will be prospectively collected over the next year.
Another Case

- Is the informed consent necessary of asthma patients being offered bronchodilator Drug A?
SUPP OR T Study

- “Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial”
- NICHD funded study through the Neonatal Research Network from 2005 – 2009
- 1316 infants enrolled born between 24 and 27⁶/₇ weeks gestation at 22 centers around the country
- Infants randomized in 2x2 design to evaluate impacts of oxygen saturations at two levels and two ventilation approaches (CPAP vs intratracheal intubation/surfactant)
- Controversy involved the oxygen saturation groups
Background

- Infants born at 24 – 28 weeks gestation are at high risk for retinopathy of prematurity, developmental delay, chronic lung disease, and death

- Experience in the 1950’s showed that high levels of oxygen administration are associated with retinopathy leading to blindness

- Low levels of oxygen are associated with neurological complications and death

- Clinical practice evolved to a general consensus that oxygen saturations between about 85% and 95% was appropriate
Background

- Uncertainty remained about the most appropriate level of oxygen saturation. Some clinicians preferred the lower end of the range, some preferred the upper end of the range.

- The SUPPORT Study randomized infants to lower part of the range (85\% - 89\%) or higher end of the range (91\% - 95\%)

- Hypothesis: “The oxygen saturation component of the trial tested the hypothesis that a lower target range of oxygen saturation (85 to 89\%), as compared with a higher target range (91 to 95\%), would reduce the incidence of the composite outcome of severe retinopathy of prematurity or death among infants who were born between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation.”
### Results

**Table 2. Major Outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lower Oxygen Saturation (N = 654)</th>
<th>Higher Oxygen Saturation (N = 662)</th>
<th>Adjusted Relative Risk (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Severe retinopathy of prematurity or death before discharge</td>
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<td>198/616 (32.1)</td>
<td>0.90 (0.76–1.06)</td>
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<td>By 36 wk postmenstrual age</td>
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<td>BPD, defined by use of supplemental oxygen, at 36 wk</td>
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Retinopathy: 8.6% in low O2 vs 17.9% in higher O2

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Death: 19.9% in lower O2 vs 16.2% in higher O2

Results

Figure 2. Kaplan–Meier Estimate of Survival to Hospital Discharge, Transfer, or 1 Year of Life.

Cox proportional-hazards analysis indicated that there was an increased hazard of death in the lower-oxygen-saturation group as compared with the higher-oxygen-saturation group (hazard ratio, 1.28; 95% CI, 0.98 to 1.68; P=0.07). The analysis assumed that infants who were discharged or transferred from the hospital survived to 1 year of age.
Results

“In summary, a target range of oxygen saturation of 85 to 89%, as compared with a range of 91 to 95%, did not affect the combined outcome of severe retinopathy or death, but it increased mortality while substantially decreasing severe retinopathy among survivors. At the present time, caution should be exercised regarding a strategy of targeting levels of oxygen saturation in the low range for preterm infants, since it may lead to increased mortality.”

OHRP Determination

- In response to a complaint, OHRP reviewed the study.
- Issued a finding in March 2013 for the University of Alabama at Birmingham (lead study site)
- OHRP: “...[W]e determine that the informed consent document for this trial failed to adequately inform parents of the reasonably foreseeable risks and discomforts of research participation.”
UAB Consent Form

- From the section labeled “Possible Benefits”:

  “It is possible that using lower pulse oximeter ranges will result in fewer babies with severe Retinopathy of Prematurity (ROP).”

- From the Section labeled “Possible Risks”:

  “There is no known risk to your baby from monitoring with the pulse oximeters used for this study. The possible risk of skin breakdown at the site will be minimized by your baby’s nurse moving the oximeter to another arm or leg a couple of times a day.”
Risks
All treatments proposed in this study are currently accepted standard of care. All of these treatment options may have risks but there is no known predictable increase in risk to your baby from any one approach. We don’t know which approach to treatment is better or safer – that is why we are doing this study. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted ventilation. If the attending physician deems necessary, participating in this study will not affect this decision. Some unknown risks may be learned during the study. If this occurs, you will be informed by the study personnel. The only other risk in this study is the risk to confidentiality. Every effort will be made to keep your child’s medical
record confidential. There will be no names or other patient identification in any study report that may be published after the study is complete. Measures taken to protect you and your baby’s identity are described in the confidentiality.

**Benefits**
There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen at discharge) and decrease in the need for eye surgery as a result as exposure to oxygen. However, we cannot promise any benefits to your baby from being in this study. The knowledge learned from this study may help us treat babies in the future.
45C FR46.116

- ...[l]n seeking informed consent the following information shall be provided to each subject:

- 46.116a(2): “A description of any reasonably foreseeable risks or discomforts to the subject.”
"When the study was planned, the best evidence showed that lower oxygen targets - even lower than used in the study - resulted in less eye disease without a higher death rate. The finding of a higher death rate in one study group was not anticipated. Thus, the consent forms, rigorously developed at twenty-three leading medical institutions in concert with their Institutional Review Boards (IRBs), did not list an increased risk of death among participation risks.”

- Death was included as an outcome because it could confound other outcome measures
- Death rate for infants not in the study was greater than for those in the study
What are the Issues?

- When is consent required when randomizing participants to different “standard of care” interventions?
  - Consent required if patient management is altered by participation in research

- Risk language: Why are the investigators doing the research?
  - If they are looking for different outcomes in the different groups, state that those outcomes might differ
  - If they think other outcomes might reasonably differ between groups, state that those outcomes might differ
  - The challenge will remain to determine what risks are “reasonably foreseeable”
Literature on IC for CER

- Feudtner C et al: Risks (and Benefits) in Comparative effectiveness research. NEJM 2013;369:892

... consider, manage and communicate nine different types of potential risk - some unique to CER, some common to all RCTs.

1. Risk associated with standard care
2. Risks (and benefits) of intervention A as compared to intervention B
3. Risks due to randomization
4. Risks due to experimental assignment versus practice variation
5. Risks due to making of “standard” interventions
6. Risks due to protocol fidelity
7. Risks of being assigned to the study group that receives less benefit
8. Risks due to acknowledgement of uncertainty
9. Risks associated with being in the trial compared with not being in it