Ethical issues in comparative effectiveness research

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Feds Fault Preemie Researchers For Ethical Lapses

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ETHICS DEBATE FOR MEDICAL RESEARCH ON PREEMIES: HOW MUCH SHOULD PARENTS BE WARNED OF RISKS?

Health & Science

Watchdog agency criticizes ethics of study of premature infants
Comments of Shawn Pratt

• Daughter, Degan, born at 25 weeks, enrolled in SUPPORT trial.

• “The SUPPORT trial looked good on paper. We were guaranteed that the study wouldn’t hurt Degan in any way.”

• “We were shocked to learn that the care she received was based not on what she needed but on some protocol.”
A guinea pig?

- “They turned her into a subject of an experiment instead of a participant in a study.”
- “They said that she was going to be cared for.”
“Tell me that the SUPPORT study did not hurt Degen in any way,” her father, Shawn Pratt, challenged a government panel on Wednesday as his daughter, dressed in a bright sundress, stood quietly by.”
-AP report,
Can we honestly tell Mr. Pratt that his daughter was not harmed by being in the study?
Degan’s outcomes

• She survived
• She has neurologic damage (cerebral palsy)
• She has severe retinopathy of prematurity (but is not blind)
• She had some bad outcomes. Were these a result of being in the study?
OHRP says “yes.”

• “The SUPPORT study involved changing the treatment of enrolled infants from the treatment of infants according to standard care, with attendant changes in the risks and potential benefits.”

• “...reasonably foreseeable risks of blindness, neurological damage and death.”

Public Citizen says, “Absolutely!”

• April 10, Public Citizen to Sebelius:
  – “Any study comparing the two experimental target levels of oxygen saturation would be both unethical and not compliant with requirements of HHS regulations at 45 C.F.R. 46.11(a)(1) and (2).”
  – SUPPORT study “highly unethical” because it “exposed 1,316 extremely premature infants to increased risks of either death or retinal damage.”
Public Citizen’s concerns

• Enrolling babies in the study would expose them to
  – an increased risk of brain injury.
  – an increased risk of retinopathy and/or blindness.
  – an increased risk of death.
• Doctors, using clinical judgment, would have made clinical decisions that would have resulted in better outcomes than doctors following the study protocol.

  • http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6357&blogid=140#ixzz2pMzHA1uZ
New York Times agreed

A lead editorial in the *New York Times* echoed Public Citizen’s concerns and called the failure to disclose risks “startling and deplorable.”

New England Journal disagreed

• Informed consent document – stating that there was no increased risk by being in the study - spelled out the risks and benefits “clearly and succinctly.”

• Consent form “addressed the prevalent knowledge fairly and reasonably.”

• “…OHRP investigation has…cast a pall over the conduct of clinical research to answer important questions in daily practice.”
  • April 18, 2013; NEJM
NIH also disagreed

• “The babies included in SUPPORT were, of course, facing substantial risks because of prematurity... but their care was never compromised for the sake of the study.”

So which was it?

• An important and well-designed study conducted with the highest ethical standards?

OR

• An egregious violation of ethics and federal regulations?
Background
Background: significant uncertainty

• “Oxygen must have been given to more infants than any other medicinal product in the last 60 years. Despite that, we still know very little about how much infants actually need, or how much it is wise to give. The depth of our ignorance is really quite embarrassing.”

Equipoise – what was known in 2005?

• Mortality of high-risk infants can be increased by administering too much or too little oxygen.
• Preemies harmed by exposure to high oxygen.
• Some advocated sats of 85-90%, some 88-95%, some 85-95%. Neonatal textbooks and the AAP recommended 85-95%.
  • Saugstad OD, Neonatology, 2007
What oxygen therapy was recommended in 2005?

• 2007 *Guidelines for Perinatal Care* recommended oxygen targets of 85-95%.
• A leading 2005 textbook: “Neonatologists are now considering goal O2 saturation ranges to be approximately 85% to 92%.”

Prevailing standard of care

• In ELBW infants, oxygen saturation levels should be kept between 85 and 93% or possibly between 88 and 95%.
  – Saugsted, Neonatology, 2007
What was known in 2005

- During the early neonatal period, restricted compared with liberal oxygen administration had no significant independent effects on death rates in preemies.

- Restricted compared with liberal oxygen administration did not significantly reduce a combined measure of adverse outcome, death or retinopathy.
  - http://www.nichd.nih.gov/cochrane_data/askiel_03/askiel_03.html
What were actual practices with regard to oxygen levels for preemies?

• We don’t know....
Equipoise

• “When we were planning the O2 trials, and I was asked to present the rationale for the COT, Canadian Oxygen Trial. In that presentation were two slides, one was the claims of the doctors who were happy using higher saturations, the other included the claims and rationale of those of us who were advocating lower saturations. Both groups claimed that their favorite range would reduce death, reduce BPD, and reduce morbidity in the long term.” (italics added)

• Barrington K. www.neonatalresearch.org
International collaboration

• The most expedient, ethical, scientifically rigorous way to resolve the uncertainty of oxygen therapy is to conduct a large, multicenter, randomized, masked trial.

• Timely recruitment of sufficient numbers and will permit more robust generalizability of the results.

• Unlikely to find funding agencies for repeated trials of the necessary magnitude. Any study must be rigorous and as complete as possible the first time.

Three multicenter studies, many countries

- SUPPORT (USA, 23 sites, 1316 babies)
- BOOST (UK (34 sites), AUS (15 sites), NZ (5 sites, 2448 babies)
- COT (Canada, US, Argentina, Israel, Europe, 25 sites, 1201 babies)
- Total – 82 sites, 4955 babies
Study design

• Prospective randomization to different target saturations – 85-89% and 91-95%
• Feb 2005-Feb 2009
• Masking by “altered oximeters”
• Primary outcome: composite variable of severe retinopathy or death.
Altered oximeters

• One type reads 88%-92% when the oxygen saturation is actually 3% lower at 85-88%.
• The other type reads 88-92% when the saturation is actually 3% higher at 91-95%.
• Both read correctly below 85% and above 95%.

– This information was in the parent information sheet in NZ but not in the US.
Key question

• Does randomization and treatment by protocol, within the range of widely used and recommended treatments, add risk?

• This is the key question for the ethics of “comparative effectiveness research.”
CER vs. “traditional” research

• Traditional: standard vs. innovative treatment.
  – Innovative treatment usually hasn’t been used before in humans.
  – “default” is the standard treatment

• CER: both approved and in widespread use.
  – Retrospective data doesn’t resolve questions of safety and efficacy
  – No default
No facts, many opinions

• The main source of conflict precipitating this meeting are contrasting views of whether interventions in SUPPORT and similar studies are more like experiments or more like existing standards of care.

— Sidney Wolfe, Public Citizen, at HHS meeting re SUPPORT
Does “protocolized” care alter risk?

- As part of routine care for such infants outside the research context, oxygen therapy would have been individually titrated...
- Determining which level of oxygen to administer as part of routine care is based on what is in the best interests of that infant.

— Public Citizen letter to Secretary Sebelius,
Individualized care

• It may be the case that the individual care is not very evidence-based, but in the cases when you are not in research your physician is attempting to individualize your care; as soon as you go into a randomized system that ceases.
  • Dreger, HHS meeting
• Infants assigned to lower oxygen level had a possibly increased risk of death compared to infants assigned to higher level. If these infants were cared for in a NICU that usually targeted the higher oxygen level they did in fact through enrollment in the study face an increased risk of death from that aspect of the study. Even if they may have benefited from other aspects.

  — Lois Shepherd
What did experts in neonatology say?

When I institute treatment according to a protocol, it is because that protocol is consistent with my fiduciary obligation to provide optimal treatment.

Treatment under another different protocol could also be consistent with those obligations.

If I am unsure which is better, then using either protocol, even if they are substantially different, is consistent with my obligations to my patients.

- Barrington, AJOB, 2013
What did experts in neonatology say?

Some centers do not have a protocol. In these there may be great variability between doctors. You could call this “individualized care” but, in reality, it is haphazard variation in practice, which is due to a lack of good data.

- Barrington, AJOB 2013
What do we know about haphazard practice variation?
What do we know about haphazard practice variation?

It is rampant!
Tonsillectomies per 1000 children/year, 2007-2010

Littleton, NH – 10.9
Burlington, VT – 2.9
St. Johnsbury, VT – 5.7

http://www.dartmouthatlas.org
Chest X-rays per 1000 children/year – 2007-2010

Townshend - 41.5
Brattleboro – 51.6
Springfield – 92.0
Bennington – 76.5

http://www.dartmouthatlas.org
Antibiotic prescriptions/1000 children/year – 2007-10

Norway 58.5
Lewiston 75.5
Brunswick 84.6

http://www.dartmouthatlas.org
Minimal risk

• The consent form did not mention any risks relating to the randomization between the higher and lower levels of oxygen, instead suggesting that this was a low risk study, noting that all of the treatments in the study were “standard of care,” and that there was “no predictable increase in risk for your baby.”

– OHRP letter to UAB
Patients want individualized decisions.....

• “How worried are we about the loss of the physician’s individual decision when nobody really knows what the right answer is? We're really worried about it...(A) doctor's judgment matters. We have trained them, we think medical education means something. We put them through residency and fellowships. We want their judgment over our own. We value that very highly.”

• George Annas at OHRP Open Meeting
Even if there is no evidence....

- It may be the case that the individual care is not very evidence-based, but in the cases when you are not in research your physician is attempting to individualize your care; as soon as you go into a randomized system that ceases.
  - Alice Dreger, HHS meeting
So, were babies harmed?
### Mortality for babies in 3 oxygen studies

<table>
<thead>
<tr>
<th>Study</th>
<th>85-89% O2 sat</th>
<th>91-95% O2 sat</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>COT (23-27)[i]</td>
<td>16.6%</td>
<td>15.3%</td>
<td>15.9</td>
</tr>
<tr>
<td>SUPPORT (24-27)[ii]</td>
<td>19.9%</td>
<td>16.2%</td>
<td>18%</td>
</tr>
<tr>
<td>BOOST II (24-27)[iii]</td>
<td>23.1</td>
<td>15.2</td>
<td>19.5%</td>
</tr>
</tbody>
</table>

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Mortality for comparable babies in national databases during the same time period (with gestational age of babies in the database)

- Canadian neonatal network (23-27)\[i\] 21.4%
- Canadian neo network (24-26) 25.5%
- Babies eligible for but not enrolled in SUPPORT (24-27)\[iii\] 24%
- NICHD neonatal research network\[iii\] (24-27) 23.9%
- Swedish Neonatal Network (24-26)\[iv\] 29.8%
- Israel Neonatal Network (24-26)\[v\] 50%
- Victorian Infant Collaborative (24-27)\[vi\] 25.5%
- UK – Epicure study (24-26)\[vii\] 34%


• Overall mortality in randomized trials: <20%
• Overall mortality in databases: 21-50%

• Babies in the three studies had lower rates or mortality and retinopathy than any comparable cohort of babies ever reported.
Was Degan Pratt harmed?
Degan Pratt’s outcomes

• She survived.
Degan Pratt’s outcomes

• She survived.

• The main critique of the consent forms was that they didn’t mention the possibility of an increased risk of death.
Degan Pratt’s outcomes

• She had cerebral palsy.
Degan Pratt’s outcomes

• She had cerebral palsy.
• There was no difference in cerebral palsy between the two arms of the trial. Babies in the trial had lower rates of CP than babies who were not in the trial.
SUPPORT – 2 year follow-up

• Primary outcome: death or neurodevelopmental impairment.

• No differences on this composite outcome: 30.2% v. 27.5% (p value = 0.21).

• Difference in mortality (22.1% v. 18.2%, p=0.046).

• No differences in cognitive impairment, moderate or severe cerebral palsy, blindness, or hearing impairment.

   – NEJM 2012
Degan Pratt’s outcomes

• She had severe retinopathy
Degan Pratt’s outcomes

• She had severe retinopathy.
• Babies in the trial had lower rates of retinopathy than babies who were not in the trial.
Severe retinopathy

Babies in SUPPORT study

- Severe ROP: 8.6% 17.9%*
  - *p<0.001

Babies not in SUPPORT study

- Severe ROP: 24.1%
Degan Pratt’s outcomes

• By enrolling in the trial and being treated by protocol, rather than doctors exercising their clinical judgment, Degan had better outcomes than she otherwise would have had.
So what happened?

- OHRP withdrew its “determination” that the SUPPORT investigators violated federal regs.
- Open meeting held Aug 28 at HHS
- Testimony and comments are on-line:
  - http://www.youtube.com/playlist?list=PLrl7E8KABz1Gc_ndt9grGg8O_jE5G1RNC
- Public Citizen has called for halting all NICHD neonatal research.
Who was there

- Michael Carome, MD   Public Citizen (Washington, DC)
- Sidney Wolfe, MD   Public Citizen (Washington, DC)
- Alice Dreger, PhD   Northwestern University (Evanston, IL)
- Lois Shepherd, JD   University of Virginia Health System
- George Annas, JD, MPH Boston University
- Charles Natanson, MD   NIH
- Vera Sharav   Alliance for Human Research Protection (New York, NY)
- Elisa Hurley, PhD   Public Responsibility in Med & Research (Boston)
- John Lantos, MD   Children's Mercy Hospital (Kansas City, MO)
- Benjamin Wilfond, MD   Seattle Children's Research Institute
- Robert Danner, MD
- Nancy Kass, ScD   JH/Bloomberg School of Public Health (Baltimore)
- Jeffrey Drazen, MD   NEJM & Harvard Medical School
Who was there

• Peter Vasilenko, PhD   Alion HRPP Accreditation Services, DC
• Steven Joffe, MD, MP  University of Pennsylvania
• David Forster, JD, MA, CIP  WIRB-Copernicus Group (Olympia, WA)
• David Magnus, PhD  Stanford University (CA)
• Carl D'Angio, MD  University of Rochester (NY)
• Jon Tyson, MD, MPH  University of Texas Health Medical School
• Michele Walsh, MD, MS  Case Western (Cleveland, OH)
• Shawn Pratt  Private Citizen (WV)
• Sharissa Cook  Private Citizen (AL)
• Edward Campion, MD  New England Journal of Medicine
• Richard Platt, MD, MSc  Harvard Medical School
• Ann Bonham, PhD   AAMC (Washington, DC)
• Robert Califf, MD  Duke University (Durham, NC)
Format of the meeting

- Anybody could submit written comments or request to speak at the meeting.
- Speakers had 7 minutes.
- Panel of 3 representing NIH, FDA and OHRP questioned speakers.
- No audience questions or discussion
- Comments posted, speeches available on YouTube. (http://tinyurl.com/qymtpnq)
OHRP’s concerns

Consent forms should have said that:

(1) the study involves substantial risks;

(2) by participating in this study, the level of oxygen an infant receives would in many instances be changed from what he or she would have otherwise received, although it is not possible to predict what that change will be;

(3) some infants would receive more oxygen than they otherwise would have, in which case, if the researchers are correct in how they suppose oxygen affects eye development, those infants have a greater risk of going blind;

(4) the level of oxygen being provided to some infants, compared with the level they would have received had they not participated, could increase the risk of brain injury or death.
In the United States people have a legal right to choose whether to participate in clinical research or receive clinical care from physicians who have a duty to put medical interests first.

Unless they're told the differences between the care they would receive outside the study and the care they would receive in it, they cannot exercise that right by making an informed choice.

— Lois Shepherd - HHS meeting
Two implicit claims

• Physicians put the patient’s medical interests first. (Researchers do not.)

• Patients know (and choose) the treatments that they receive. Research subjects do not.

• Both claims are wrong.
Comparative effectiveness research

• Designed evaluate treatments that are in widespread clinical use but have not been rigorously compared with one another.

• Must be distinguished from studies in the prevailing standard of care is with a new, previously untested, agent.
Differences between traditional research and CER

• In studies of new treatments, it is clear what the default will be for patients who don’t enroll in the study – the existing standard.

• In CER, both therapies are “standard.” Patients who don’t enroll may get one or the other.
  – With SUPPORT, we don’t know what non-enrolled babies got or would have gotten.
Two separate risks in CER

• Comparative risks between arms of the trial
  – Presumably, one of the therapies will prove better or worse than the other. But, presumably, experts disagree about which therapy will be better. If they did not, then there would be no reason to do the study.

• Comparative risks of being in the study vs. not being in the study.
  – It is unclear, in CER, whether it is more risky to be in the study than to receive the same therapies off protocol.
• In standard care the doctor’s fiduciary responsibility is to prescribe treatments that serve each patient’s best interest, adjusted in response to each patient’s individual, fluctuating need.

• In research, treatment is predetermined by protocol that seeks to resolve uncertainty and contribute generalizable knowledge.

  — Vera Sharav
• When critically ill patients are receiving a therapy titrated to individual need, randomization to dosage extremes has foreseeable risks.
• Therapy is changed independent of need.
• Such trial designs may harm patients
  • Charles Natanson – HHS meeting
Different kinds of risk

• Lack of “conventional treatment arm.”
• Protocols vs. clinical judgment
• Randomization vs. clinical judgment.
• Different outcomes between arms
• Different outcomes in or out of study.
Do doctors individualize oxygen therapy?

• One critique of the studies is that patients were denied individualized therapy by being randomized and treated by protocol.
Were some babies harmed?

• “While it would have been unwarranted to predict, ahead of time, specific outcomes (i.e., which infants developed which outcomes), the researchers had sufficient available information to know, before conducting the study, that participation might lead to differences in whether an infant survived, or developed blindness, in comparison to what might have happened to a child had that child not been enrolled in the study.”

• OHRP letter to UAB
Individuals v. population

• If the population of babies in the study had, on average, better outcomes than the population of babies not in the study, then can we say that individual babies in the study were harmed by being in the study?
Psychological risks

• Participation in a randomized trial “confronts research participants and/or their families with the inadequacy of current medical knowledge, which may be upsetting in the context of a critical illness.”

• “Half of (RCT) participants denied that a doctor could be completely unsure about the best treatment. A majority of participants judged it unacceptable for a doctor to suggest letting chance decide when uncertain of the best treatment.”


Was there increased risk?

- Babies in the “low oxygen” arm had a mortality rate of 19.9%; babies in the “high oxygen” arm had a mortality rate of 16.2%; babies in the network overall had a mortality rate of 24%.
- For severe retinopathy, the numbers are 8.6% (low oxygen group), 17.9% (high oxygen group), and 24.1% (overall group).
- Babies in both arms had lower mortality and less ROP than babies who were not in the study.
Take home lessons

• Research regulation is complicated and ambiguous.
• The public doesn’t understand research or neonatology and so really doesn’t understand neonatal research.
• Need to be able to speak clearly about ethical issues and be prepared for scrutiny of study design, consent, and safety monitoring.
THANKS!
Psychological risks

• If many patients do not believe, or do not want to acknowledge, that their own physicians are genuinely uncertain about which treatment is best, and if patients must be informed of this in order to be enrolled in a clinical trial, then any enrollment in a clinical trial will cause harm to some subset of potential study subjects.
  • Lantos, Bioethics Forum of The Hastings Center
Psychological risks

• The obligation to protect research subjects from harm is in tension with the obligation to disclose the truth.
  – Lantos, Bioethics Forum of The Hastings Center