The SUPPORT Trial and Beyond

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- SUPPORT Trial Case History
- OHRP Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care
- The Controversy over the impact of the draft guidance on Informed Consent in Comparative Effectiveness Research (CER)

SUPPORT Trial Case History

- The SUPPORT Trial (2005-2009)
- Complaint: May, 2011
- OHRP Compliance Determination Letter (3/7/13)
- OHRP Compliance Suspension of Action Letter (6/4/13)
- HHS Public Meeting (8/28/13)
- OHRP Draft Guidance Published for Public Comment (10/24/14)
- Public Comment Period Closed (1/22/15)

SUPPORT Trial Descriptions

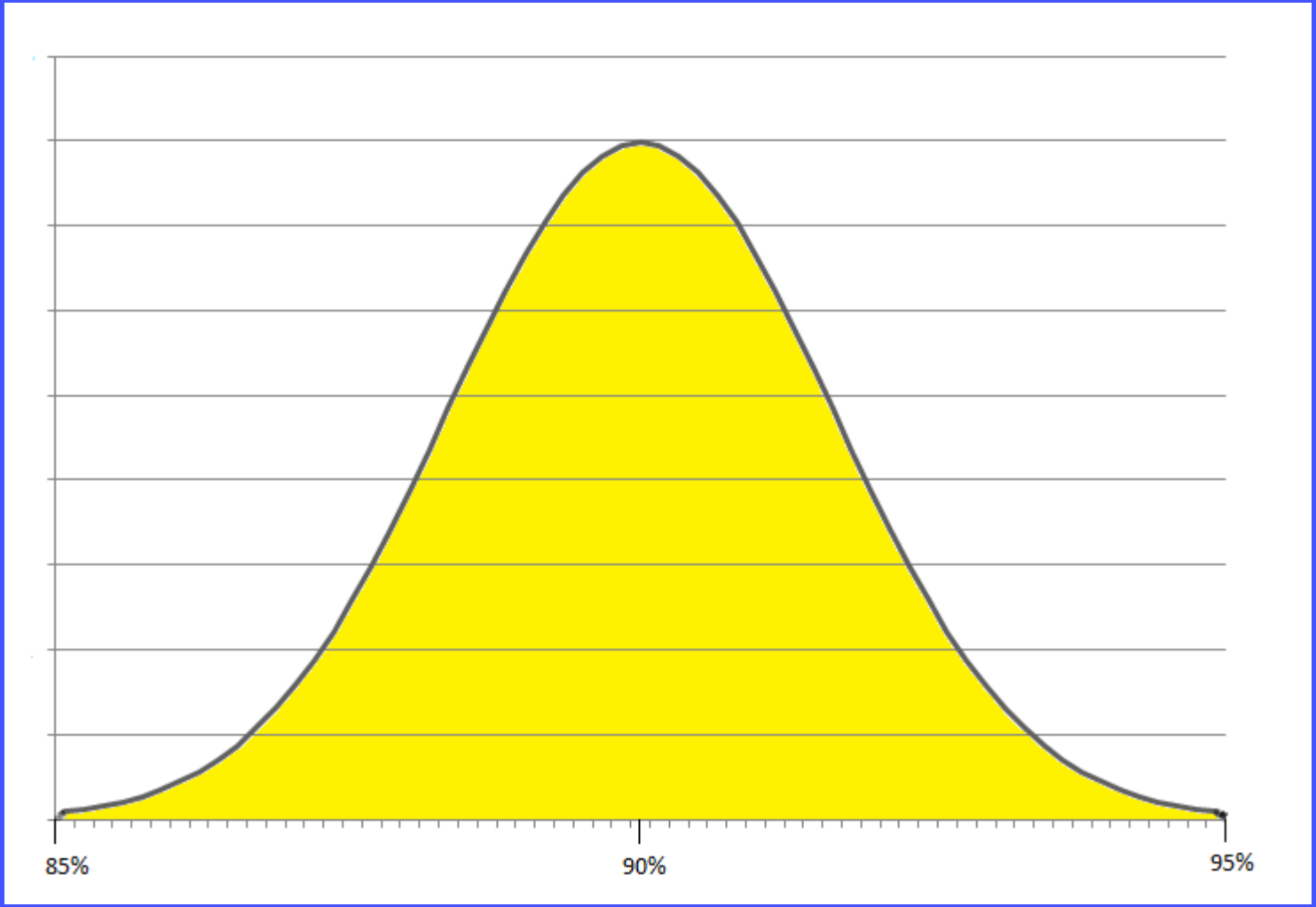
"…relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention."(Protocol hypothesis, 2004)

"[A large sample will be needed to] …exclude smaller, important differences in outcomes such as mortality and disability to address real concerns about the safety of lower oxygen tensions" (NeOPromM Collaboration, 2004).

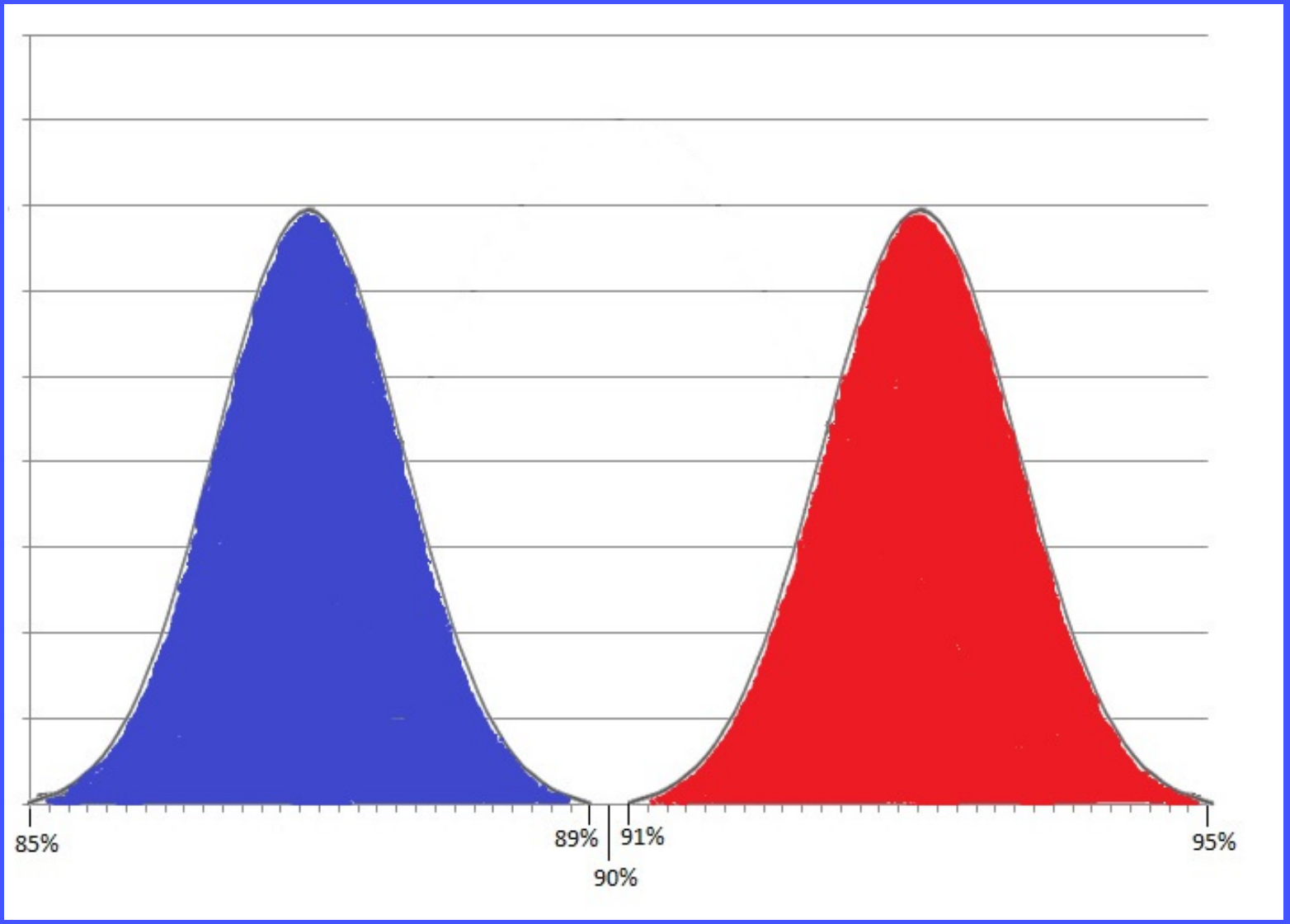
SUPPORT Trial Arms

- A Comparative Effectiveness Research (CER) trial regarding the standard of care (SOC) for oxygen saturation levels for premature infants.
- The normal treatment oxygen range was between 85% and 95%.
- Infants were randomly assigned to one of two treatment ranges, 85%-89%, and 91%-95%.

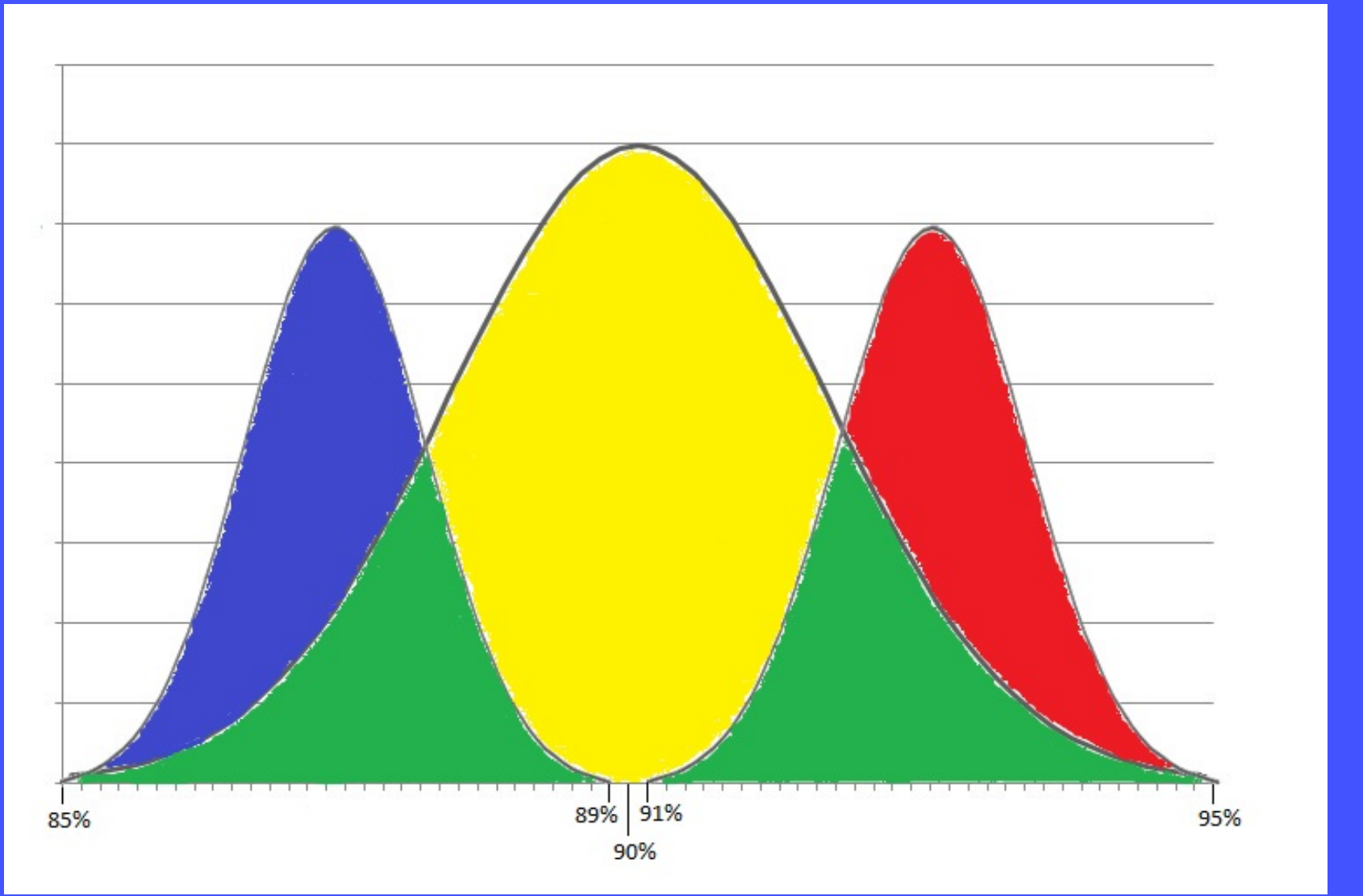
Normal Distribution Curve for SOC Oxygen Level Treatment



Normal Distribution Curves for SUPPORT Trial Arm Oxygen Level Treatments



Normal Distribution Curves for SOC and SUPPORT Trial Arms Oxygen Levels



Informed Consent Form Descriptions of risks of ROP

In the “Possible Benefits” section:

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

In the “Possible Risks” section: [Nothing comparable]

OR….

“Because all treatments proposed in this study are currently accepted standards of care, there is no predictable increase in risk to your baby.”

Informed Consent Form Descriptions of Risk of Death/Neurological Development Impairment

[Nothing.]

SUPPORT Trial Results

- 8.6% of infants in the low oxygen group developed retinopathy of prematurity (ROP), while 17.9% of infants in the high oxygen group developed ROP.

- 19.9% of infants in the low oxygen group died before discharge, while 16.2% of infants in the high oxygen group died before discharge.

OHRP Compliance Letter:

"…the level of oxygen an infant receives would in many instances be changed from what they would have otherwise received…"

"…the IRB approved informed consent documents for this study failed to include or adequately address:

…section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts."(3/7/13)

OHRP Draft Guidance: Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care

1. What are "standards of care"?
2. What are "risks of research" in studies evaluating risks associated with standards of care?
3. When is evaluating a risk in a research study considered a "purpose" of the research?
4. Are the risks of research associated with the purposes of studies of standards of care "reasonably foreseeable risks" that must be disclosed to prospective subjects in the informed consent process?

1. What are "standards of care"?

- Medically recognized standards of care (SOC): treatments or procedures that have been accepted by medical experts as appropriate treatments or procedures for a given type of disease or condition and are commonly used by healthcare professionals.
- [Note: There can be significant variation in the amount and quality of evidence on risks of standards of care being evaluated.]

2. What are the "risks of research" in studies evaluating risks of standards of care? The regulatory provision:

"In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research) …"

(45 CFR 46.111(a)(2))

2. What are the "risks of research" in studies evaluating risks of standards of care? Draft Guidance

- OHRP generally considers the risks of a specific standard of care being evaluated to be risks of research if:
  1. At least some of the subjects will be assigned to receive a standard of care different from what they would have received outside of the study; AND
  2. There might be different risks associated with those standards of care.

3. When is evaluating a risk in research considered to be a "purpose"? Draft Guidance

- When a study is designed and conducted to ascertain the existence, extent or nature of a particular harm, *and* the evaluation of those risks is sufficiently important to justify conducting the study.

4. Are risks of research associated with the purposes of studies of standards of care "reasonably foreseeable risks" requiring disclosure in consent?
The Regulatory Provision

Basic elements of Informed Consent:

"(2) A description of any reasonably foreseeable risks or discomforts to the subject;" (45 CFR 46.46.116(a)(2))

Draft Guidance: The Conclusion

In general, if evaluating a particular risk of research associated with a standard of care is a purpose of the research, then the research risk being evaluated has been recognized as a sufficiently possible outcome to make it a "reasonably foreseeable" risk that should be disclosed.

Public Comments

- 93 comments
- 1 thought the guidance was clear

Critical Public Comment Themes: The Guidance will:

- Hinder research
- Inflate the perception of risk
- Lead to lengthy informed consent forms
- Include treatment risks as risks of research
- Require disclosure of options to subjects that clinicians frequently do not provide to their patients when delivering clinical care

“Comparative Effectiveness Research” (IOM)

- “…is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels." (Institute of Medicine)

Some Randomly Selected Activities

1. Addressing Bioburden While Admitted to Eliminate Infection
2. Quality Improvement Strategies for Type 2 diabetes on Glycemic Control
3. Implementation/Use of Computerized Physician Order Entry Systems
4. An Intervention to Decrease Catheter-Related Bloodstream Infections in the ICU
5. A Resident Handoff-Improvement Program
6. Nighttime Dosing of Anti-Hypertensive Medications: A Pragmatic Clinical Trial

CER trials

- CER trials compare SOC treatments
- CER trials sometimes assign the SOC treatment to subjects (via randomized assignment in clinical trials, or cohort studies).
- In CER trials with SOC treatment assignment, some subjects will receive standard of care treatment other than what they would have received outside the trial.

SOC treatments compared in CER trials vary, for example:

- Difference in dose of the same treatment
- Two different drug treatments
- Chemotherapy vs. chemotherapy plus radiation
- Surgery vs. drug treatment
- Treatment for condition vs. treating symptoms
- Intervention vs. monitoring

A Learning Health Systems Take

- All X's will receive a treatment they might (or might not) have received anyway.
- The risks of compared treatments seem equivalent (or else there is 'equipoise').
- There are no additional risks associated with X's being in the activity compared to not being in the activity.

A Learning Health Systems Take: To Achieve the Optimal Results, Eliminate Informed Consent

- These activities involve no added risk, and are *minimal risk*.
- People who benefit from learning healthcare systems are obliged to contribute to them.
- Eliminating Informed Consent cuts costs, and speeds learning and improvement.
- Eliminating Informed Consent eliminates a potential bias, and strengthens generalizability.

Respect for Persons (1785)

Immanuel Kant, leading philosopher of *Deontology* and the *categorical imperative* of treating every rational being (person) as a free rational agent, and as ends in themselves.

Respect for Persons

Principle:

- Subjects as Autonomous Beings
- Protection of Subjects with Limited Autonomy

Applications:

- Informed Consent as Informed, Competent, and Voluntary
- Subjects' Assent and Third Party Consent

Beneficence (1789)

Jeremy Bentham,

leading philosopher of *Utilitarianism* and the *Principle of Utility of the Greatest Happiness of the Greatest Number*

Beneficence

Principle:

- Do No Harm
- Maximize Benefits and Minimize Possible Harms

Applications:

- Favorable Risk/ Benefit Assessment
- Systematic Analysis and Minimization of Acceptable Risks of Harm

Justice (350 BCE)

Aristotle,

leading philosopher of *Aristotelian Philosophy* and of the principle of *distributive justice,* distributing goods, rights, , burdens, etc., according to what people deserve.

Justice

Principle:

- Distribute Burdens and Benefits Equitably
- Don’t Exploit Vulnerable Populations

Applications:

- Select Individuals and Classes of Subjects Equitably
- Link Burdens to Benefits

Questions or Comments?