Ethical Complexities in Randomized Trials: Compared to what?

Benjamin S. Wilfond MD

Seattle Children’s Hospital
Treuman Katz Center for Pediatric Bioethics
Center for Clinical and Translational Research

University of Washington
Division of Bioethics, Department of Pediatrics
Department of Bioethics and Humanities
Institute of Translational Health Sciences
Does a novel drug help adults with a fatal neurological condition?

- Progressive supranuclear palsy causes motor, cognitive, and communication deficits and no effective intervention

- Glial Derived Neurotrophic Factor (GDNF) is a novel intervention that would be delivered via an intraventricular catheter with an abdominal reservoir

- Questions
  
  A. Do we need a study or should we just do it?
  B. Should we use a control group of some sort?
  C. Should we use a placebo or other blinding mechanism?
Does newborn screening for cystic fibrosis improve health?

• Child are typically diagnosed clinically after symptoms of failure to thrive and lung disease is present.

• A screening test has been developed that can identify newborns at high risk of having cystic fibrosis.

• Questions
  
  A. Do we need a study or should we just do it?
  B. Should we use a control group of some sort?
  C. Should we use a placebo or other blinding mechanism?
Does lowering target oxygen saturations reduce retinopathy of prematurity (ROP)?

• Clinical guidelines recommend target oxygen saturations in premature infants be set between 85% -95%.

• Observational research suggests lower saturation targets are associated with reduced ROP.

• Questions
  A. Do we need a study or should we just do it?
  B. Should we use a control group of some sort?
  C. Should we use a placebo or other blinding mechanism?
Why Randomization and Comparative Research are necessary

• We don’t know that what we think we know is wrong

• Observations in science and medicine often lead to wrong conclusions

• Randomization often proves that well accepted therapies are harmful

• Randomization often proves that promising new therapies are useless
The contexts of RCTs

• Human Context
  • Equipoise: Evaluation of professional opinions about treatment
  • Therapeutic misconception: managing patient expectations from research

• Social context
  • Overall social and community resources
  • Access to health care
  • Community involvement and attitudes about research

• Research Context
  • Early stage drug development?
  • New biological concept or new class of drugs?
  • Expectations for adverse effects?

• Clinical Context
  • Life-threatening
  • Emergency
  • Effective clinical options
Why Ethical Guidelines for Research are necessary

• Clinical research develops generalizable knowledge that improves health or increases understanding

• People who participate in clinical research are a means to securing that generalizable knowledge

• As a means, these people can be exploited (taken unfair advantage of for the benefits of others)

• Ethical benchmarks for clinical research are meant to minimize the possibility of exploitation
8 Ethical Benchmarks

1. Collaborative Partnership
2. Social Value
3. Scientific Validity
4. Fair Subject Selection
5. Favorable Risk-Benefit Ratio
6. Independent Review
7. Informed Consent
8. Respect for Human Subjects

Improving Clinical Care

“If we knew what it was we were doing, it would not be called research”

-Albert Einstein

Clinical Innovation:
New use for approved drug

Clinical Care:
Implement standard approach

Clinical Research:
New drug or new indication

Quality Improvement:
Ensure agreed upon approaches are followed
GDNF in PSP

- Patient demand for access to drug was a challenge for research
- Not clear it would be useful or harmful
- Study design:
  - Each person had two reservoirs implanted
  - “Assessment committee” to determine eligibility
  - “Consent monitoring of participants
- Outcome
  - First participant had reservoir malfunction and received 10 fold dose
Issues with Placebos

- Placebos can be overused and underused comparators

- Placebos may be helpful to avoid harming people by using non validated interventions clinically

- How do we account for the placebo effect?
  - Benefit or risk?

- Placebos generally do not offer a prospect of direct benefit
  - The risks of additional research interventions can be harder to justify in placebo arms
  - Risks of forgoing or delaying effective interventions can be problematic from a patient or community perspective
Criteria for Placebo Research in Children

- No commonly accepted therapy for the condition

- Commonly used therapy is of questionable efficacy

- Commonly used therapy for the condition carries with it a high frequency of undesirable adverse effects and the risks may be significantly greater than the benefits

- Placebo is used to identify incidence and severity of adverse effects produced by adding a new treatment to an established regimen

- Disease process is characterized by frequent, spontaneous exacerbations and remissions and the efficacy of the therapy has not been demonstrated

AAP 1995/2010
NHLBI asthma guideline adherence in clinical asthma trials including children (n = 70)

Were all subjects with more than mild asthma on anti-inflammatory medications prior to the study?
- Yes: 18(4)
- No: 52(14)

Were all subjects kept on anti-inflammatory medications throughout the study?
- Yes: 12(1)
- No: 6(3)

Were all subjects begun on anti-inflammatory medications upon enrollment?
- Yes: 10(1)
- No: 42(13)

Total number of trials (number of trials including only children)

Coffey, Wilfond, Ross. Paediatrics 2004;113:87-94
Wisconsin Cystic Fibrosis Newborn Screening Study

• 1985-1994: 650,000 infants enrolled in a randomized clinical trial of cystic fibrosis newborn screening
  • Results returned in 6 weeks or in 4 years
  • All infants with CF were treated using standard care approaches

• NIH, IRBs, Cystic Fibrosis Foundation, community review:
  • Waiver of informed consent was appropriate
  • Efforts made to disclose screening and allow parents access to results

• Outcome:
  • Early detection improved nutritional status
  • Early detection increased chance of early *Pseudomonas* acquisition
  • A 2004 CDC Workshop concluded that CF NBS was justified
ETHICAL ISSUES IN NEWBORN SCREENING RESEARCH: LESSONS FROM THE WISCONSIN CYSTIC FIBROSIS TRIAL

HOLLY A. TAYLOR, MPH, PHD, AND BENJAMIN S. WILFOND, MD

Newborn screening (NBS) is a well-established approach to genetic testing, with a 40-year history of improving public health.\textsuperscript{1} With advances in technology, the number of diseases that are included in NBS programs is anticipated to expand over the next decade.\textsuperscript{2} With the technological advances, a consensus, supported by a number of national expert groups, has been emerging that clinical trials to assess clinical validity and utility are important before the introduction of new genetic tests (including NBS tests) into clinical practice.\textsuperscript{3–8} In fact, randomized trials of early interventions for sickle cell anemia and cystic fibrosis (CF) commenced in the 1980s influenced the rapid introduction of NBS in the former case\textsuperscript{9} and a more conservative approach in the latter case.\textsuperscript{10} Thus, proposals for randomized, clinical trials may be anticipated for conditions for which NBS has been suggested, including Duchenne muscular dystrophy,\textsuperscript{11} fragile X syndrome,\textsuperscript{12} severe combined immune deficiency,\textsuperscript{13} and organic acidemias.\textsuperscript{14} Newborn screening research raises complicated ethical issues related to risk/benefit assessment, use of control groups, withholding of information, and informed consent.\textsuperscript{15} Although the design of future NBS trials will depend on the specific disorder under study and the outcome of interest, we believe that the randomized, controlled trial, despite the large sample and time investment required when studying relatively rare disorders, can be scientifically and ethically justified to determine the utility of NBS tests before their introduction into clinical practice.
The SUPPORT Study

- To determine impact or target oxygen saturations levels on retinopathy of prematurity
  - 23 sites and 1300 infants between 2005-2009
- Infants randomized to saturation range of 85-89% or 91-95% using “offset” pulse oximetry that would display 88-92%, using a 3% correction
- In 2013, OHRP (US regulatory agency) issued finding for lack of consent about foreseeable risk of death from study interventions
- OHRP subsequently suspended finding pending further examination of how to understand “standard of care” research
“The parental consent dilemma: Saving extremely premature babies by signing forms” - Kelly Benham, Oct 18, 2013, Tampa Bay Times

“All babies born so young are experiments. The rest is just paperwork”

“Had I been asked, I probably would have signed her up for a research study. If things had gone well, I might have believed the study had helped. If things had gone poorly, I might have blamed the study and feared I'd been duped.”
The OHRP and SUPPORT

“Furthermore, the conclusion of OHRP ...overreaches. Although we acknowledge that the permission forms could have been improved, we disagree that the random assignment of infants ...imposed additional risks that the investigators failed to disclose.”

Wilfond BS, Magnus D, et al., June 20, 2013 (with 46 signatories)

The OHRP and SUPPORT—Another View

“Given the seriously deficient nature of the consent documents, the determination of the OHRP on March 7, 2013, was justified and did not overreach.”

Goals are different and constrained by different ethical obligations but the activities and issues are overlapping.

**Clinical Practice:**
- Clinical decision to benefit a patient

**Clinical Research:**
- Designed to contribute to scientific knowledge

**Learning Health Systems:**
- Implements knowledge to benefit future patients in an organizational setting

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Joffe and Miller. Hastings Center Report 2008

Kass, Faden Hastings Center Report 2012
Research on Medical Practices

• The risks of usual treatments are NOT risks of research
  • Research comparing two standard treatments is the best way to identify the risks of the clinical interventions
  • Randomization itself is not a risk

• We need better approaches for informed consent processes
  • Focused on helping prospective participants truly understand the most crucial elements of research and clinical practice

• Sometimes consent can be waived for research
  • Requires active and innovative community engagement and alternative ways to reach patients
“Personalized” Medicine for Cancer: Promise or Peril?

- Convergence of diagnostics and therapeutics
- Conceptually challenges the use of comparators
- High expectations of clinicians and researchers
- Desperation of families
- Commercial availability
- Very expensive and limited evidence

- Requires a deliberative and measured professional and public approach to research and policy
Research Bioethics Consultations

ITHS.org/RSB  |  (206) 598-6477  |  rsbcore@uw.edu

The ITHS Research Bioethics program provides a forum for discussion and analysis of ethical issues in clinical and translational research. Our team can help address ethical questions in areas such as:

Study Development
- What if informed consent is not practical for my study?
- When is a placebo-controlled study design ethically appropriate?

Study Implementation
- Can I withdraw participants against their wishes?
- What must I do if my participants need medical care or other help?

The Consultation Process

ITHS offers research bioethics consultations to researchers, trainees, research staff, and personnel involved in the protection of human subjects. Discussions with consultants can take place by telephone or in person. There is generally no charge.

Bioethics consults are advisory and provide a forum for in-depth conversation and analysis of ethical issues in clinical and translational research. Recommendations are supplemental to the authority and oversight of review groups such as an Institutional Review Board or Data Monitoring Committee.

To ensure a balanced understanding of the facts or to facilitate resolution of a conflict, the consultant is available to talk with others involved in the issue if the requestor so desires.

In some cases, the issue may warrant referral to offices such as the institutional ombudsperson, human resources, or legal counsel.

In rare cases, consultants have obligations to share consult information with others. Examples include significant concerns about safety, sexual harassment, research misconduct, or research non-