Challenges with Consenting Vulnerable Populations

Jonathan Davis, MD
Vice-Chair of Pediatrics,
Floating Hospital for Children at Tufts Medical Center,
Boston, MA
Chair, Neonatal Advisory Committee,
Office of the Commissioner, FDA
Informed Consent

- Consent has two major goals:
  - Respect for autonomy, Protection from harm
- The most crucial aspect of informed consent is the ability to understand what is being consented to
- Research subjects actually understand very little of the information in informed consent forms
- The Common Rule is a set of federal regulations for the ethical treatment of human research subjects
  - “Consent forms would no longer be able to be unduly long documents, with the most important information often buried and hard to find…”
Informed Consent

• Increased wording is devoted to legal, ethical, financial, and data and sample storage
  • Longer forms do not help with understanding
  • Increased wording actually hinders understanding
  • Protects the institution and not the participants

• The average Flesch Kincaid Reading Level of consent forms ranges from the 9th-12th grade level
  • Fifty-percent of adults cannot read at an 8th grade level
  • 45 million Americans are functionally illiterate
  • Pediatric forms are more complex than adult forms
I, , give authorization to participate in the Project: Effect of Thermal Environment on Insensible Water Loss in Low-Birth-Weight Infants.

Study involves:

A. The nature, duration, and purpose of the study:

The purpose of the study is to see whether a change of two degrees in the incubator temperature will have any effect on the very small amount of weight loss which normally occurs between feedings. The study will last 5 to 6 hours.

B. The means by which it is to be conducted:

The baby will be placed on a special scale inside the incubator, which continuously measures the very small minute-to-minute changes in weight. Two small thermometer discs will be taped to his/her skin. The weight changes will be measured at two different temperatures, two degrees apart.

C. The possible benefit or lack of benefit to myself and/or my child:

The information learned from the study might help to determine more exactly what the baby's water requirements are. We will also learn which of the two temperatures is better for your baby.

D. The risks and hazards of the study:

There are no known risks from a two degree change in incubator temperature. No blood samples will be collected. The baby will be continuously observed during the study. The study will be stopped if the body temperature falls to one degree below normal. Nursing and treatment routines will carry on as usual.

E. The possible alternative procedures:

The standard method of heat control involves adjusting the incubator temperature by hand or with a special thermostat to keep the baby's body temperature near normal. With this method, the incubator temperature often changes by two degrees or more.

I CERTIFY (a) that I understand this written/oral explanation; and an offer was made to answer any questions;

(b) that any dissemination of statistical data may be for professional, education and research purposes; in no instance would patient identification be made. Specific patient conditions may be discussed at a personal conference with physician and family;

(c) that I will be informed of any changes in the status of risks or benefits during the course of this project;

(d) that I am free to withdraw consent and discontinue participation at anytime without prejudice.

Patient or Parent/Guardian ________________________________ __________________________ (Date)

Witness ________________________________ __________________________ (Date)
Prior Attempts to Improve Informed Consent

• Forms were made longer to provide more information
  • Length has nearly tripled over the past 20 years, forms in the US are nearly 10 pages longer than other countries for multinational trials
  • This did not enhance understanding

• Video and enhanced computer consent forms
  • Majority of studies did not show improved understanding when compared to traditional consent forms
  • Only two studies showed a significant difference when a video enhanced form was used in a non-simulated study

Unique Pediatric Concerns

• Few drugs used in neonates and older children have been adequately studied and approved for use in children by FDA or other regulatory bodies
• Legislation to improve pediatric research efforts have increased in the US and Europe
• Increased numbers of children that need to be enrolled in clinical trials - need for efficient and understandable informed consent forms
• Overly complex ICFs are impairing participant recruitment for clinical trials – need to balance safety with recruitment (NAS trials)
History of Pediatric Initiatives

...but 55% of Medicines Still Do Not Have Data in Labels to Guide Appropriate Use in Children

Proportion of medicines in PDR with information on children

- 78% Yes
- 22% No
Sources, previous slide


1994: PPRU Launch: The NICHD established the PPRU Network in 1994 to facilitate and promote pediatric labeling of new drugs or drugs already on the market by fostering cooperative and complementary research efforts among academia, industry, and health care providers. The PPRU Network sunsetted in 2010 and is no longer active. Visit this site to learn more: https://www.nichd.nih.gov/research/supported/Pages/ppru.aspx

1997: US FDAMA: Food and Drug Administration Modernization Act (FDAMA) - Created incentives for new drug testing in pediatric patients including 6-month patent extension.


2002: Best Pharmaceuticals for Children Act (BPCA) - Extends the 6-month exclusivity extension provision through 2007 (renewable every 5 years). “Carrot”

2003: Pediatric Research Equity Act (PREA) - Congress reinstated and expanded the Pediatric Final Rule. (renewable every 5 years) “stick”

2006: EU Pediatric Legislation - The Pediatric Regulation came into force in the European Union (EU) on 26 January 2007. Its objective is to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0 to 17 years, ensuring that medicines for use in children are of high quality, ethically researched and authorized appropriately and improving the availability of information on the use of medicines for children. It includes authority to grant incentives “carrots” and require mandated studies “sticks”

2007: FDA Amendments Act (FDAAA) - Congress reinstated BPCA and PREA; and the Pediatric Medical Device Safety and Improvement Act.

2012: Food and Drug Administration Safety and Innovation Act (FDASIA) - The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) are made permanent parts of the law (reauthorized every 5 years is no longer required).

PEDIATRIC RESEARCH IS A PERMANENT PART OF DRUG DEVELOPMENT NOW.
Shortened Informed Consent Forms

• Many attempts at improving ICFs have been made
• A shortened ICF adapted from an existing ICF for a novel neonatal respiratory drug that was completed
• Two page document that described the purpose of the study, study procedures, and risks and benefits; everything else placed in an Appendix
• Appendix written in question and answer format as a reference for parents
• The shortened or conventional ICF was randomly distributed to two parental advocacy groups
• Participants answered survey questions about the form they received

Subjective Questions

• The information was short and to the point
• There were some parts of the consent that were difficult to understand
• Overall, this form was hard to understand
• Overall, I understood what I read
• Overall, I found the form was too simple
• Overall, I did not think the form had enough information

Murray P, Pediatric Research, in press
Objective Questions

• Can you tell me why this study is being done?
• How would you explain the study to another person?
• Will all babies receive the active study drug?
• What samples will be taken from babies in the study?
• What will be done to a baby in this study?
• Please select any risk(s) associated with the study
• Are there any possible benefits being in the research study?
• Where will information be kept and who will have access to it?
• Does a parent have a choice to enter their baby in this study?

Shortened Informed Consent Forms

• 31/41 (76%) parents in the shortened ICF and 28/41 (68%) in the conventional ICF group responded
• Objective questions correct in 87% shortened ICF group and 89% in the conventional form group
• Significantly more parents in the shortened ICF group found their form “short and to the point” (87% vs. 61%)
• Significantly more parents felt that the shortened ICF did not provide enough information (35% vs. 4%)
• There were no significant differences between groups measuring understanding of key study components

Murray P et al, Pediatr Res, in press
• If you decide to participate in the study, the following groups may share your data and samples to improve new treatments or other clinical trials:

• Health authorities throughout the world (e.g., Food and Drug Administration, European Medicines Agency, etc.)

• Institutional Review Boards

• The study sponsor and affiliates of the sponsor

• Other groups such as: academic, government, or industry researchers; public-private partnerships; and/or external research collaborations. These entities will have oversight committees that will supervise the ethical use of the data and samples
Co-Enrollment in Clinical Trials

- Populations are limited (especially premature infants)
- Access to trials is smaller (rare diseases)
  - Many neonates are treated at non-academic centers
  - NICUs conducting one trial usually have multiple trials
  - Neonates are already being exposed to multiple agents
- Co-enrollment is happening in real life
- Is it ethical and scientifically valid to enroll a neonate in more than one clinical trial?
- There is limited input - regulatory agencies and industry are generally against it (increased risk)
- What should the ICF indicate about co-enrollment?
Ethical/Scientific Considerations

- IF it is reasonable to assume that:
  1. Randomized treatment in Trial A has not influenced enrollment in Trial B
  2. Neither treatment influences the natural course of disease of the other condition being studied
  3. There is unlikely to be a drug-drug interaction
- THEN the scientific validity of the individual trials should not be compromised by co-enrollment
- Violating any of the above conditions, means that careful consideration of bias, interaction, sample size/power will require careful consideration

# Co-Enrollment in Clinical Trials

**Avoid Co-enrollment**

- Early-phase PK studies
- Randomized trials studying ≥2 drugs or interventions with known interactions
- Trials with similar primary outcome measures
- Specifically targeting the same organ system

**May be Permissible**

- Brief PK and or safety/studies
- Device validation studies
- Factorial study designs with adequate sample sizes
- Drugs used routinely in the NICU - considered standard
Conclusions

• Most infants and children are treated with drugs that have not been adequately studied for safety/efficacy

• Legislation and interest have increased the need for pediatric clinical trials – focusing on the need to enroll children in more than one clinical trial at the same time

• Current approaches to Informed Consent are impeding recruitment and are not necessarily improving safety

• A concise, shortened consent for with an Appendix may help improve the consent process

• Alternative approaches are urgently needed
That’s All Folks!