

### Viewing Time

The program will take up to one hour to complete.

### Target Audience

This program is designed for primary care physicians.

Other health care professionals working with patients and their families may also find this program of interest.

### Faculty Disclosure

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### Faculty Disclosure

**Julia Steinberger, MD, and Joseph Neglia, MD** have disclosed no actual or potential conflict of interest in relation to this educational activity.

During this educational activity **Dr. Steinberger** and **Dr. Neglia** will not be discussing the use of any commercial or investigational product not approved for any purpose by the FDA.

### No More Hand Me Downs: Research Designed for Children

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### No More Hand Me Downs: Research Designed for Children

*A lecture about the importance of and  
the issues involved in clinical research  
in children*

## Program Objectives

*Upon completion of this program, participants should be able to:*

- Discuss consideration of “Risk” an IRB must make
- Understand the importance of assent
- Recognize common failures in clinical research

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## Receiving CME Credit

To receive CME credit you must view the entire program and complete the evaluation form at the end.

## No More Hand-Me-Downs: Research Designed for Children

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Department of Pediatrics  
University of Minnesota Medical School



## Scope

Discuss the importance of clinical research in children, some of the issues related to involving minors in research, and the comprehensive framework in place for protecting research participants.

# Julia Steinberger, MD and Joseph Neglia, MD No More Hand Me Downs: Research Designed for Children

## Historical Overview of Children in Research

In the 18th and 19th centuries children recruited as research subjects to observe the effects of infectious diseases (e.g., syphilis, gonorrhea, tuberculosis, and yellow fever) on humans. Procedures protecting children from such exploitation were not put into effect until after the Nazi war crimes of WW II.

In the aftermath of the Nazi experiments and a series of research scandals in the US and the UK minors were excluded from clinical trials. This was thought to be an efficient way to protect minors, but this strategy was eventually judged untenable.

## Historical Overview of Children in Research

Denying minors access to clinical studies makes children "therapeutic orphans" and results in a high rate of off-label prescriptions (the prescribing of drugs not tested in children and not labeled for pediatric use). Currently only 20% of drugs approved by the FDA are labeled for pediatric use.

In the absence of tested drugs every treatment in a child becomes an experiment.

## Historical Overview of Children in Research

In the course of the 20th century, it became increasingly clear that results from laboratory research, animal experimentation and research in adults could not offer proper data to develop safe and effective drugs for use in pediatric practice.

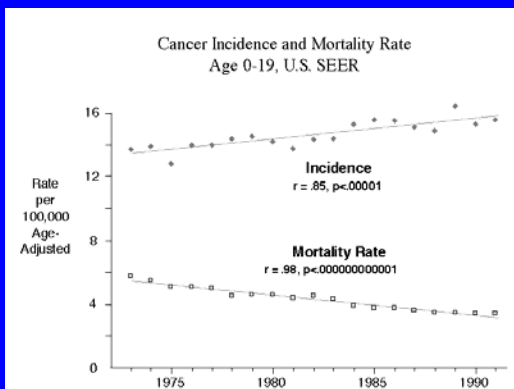
Adults and children differ in pharmacodynamics and pharmacokinetics, results obtained in adults cannot easily be transposed to children. A mere recalculation of drug dosages based on a child's weight or BSA is not reliable.

As a consequence, there are no viable alternatives to enrolling children in clinical trials.

## Current State of Research in Children

In 1998, the NIH released a statement encouraging investigators to include children in clinical trials or to provide substantive rationale for their exclusion.

A remarkable proportion of children with cancer - about 70% - participate in a trial during their illness. This unprecedented and unequalled integration of research and care means that pediatric oncology professionals took a leadership role the conduct of clinical research in children.



## Challenges

The involvement of children in clinical studies, however, is a problematic enterprise. There are at least 3 reasons for this:

- 1) Children are a vulnerable population because
  - limited developmental capabilities
  - reliance on adults for protection
- 2) The small number of pediatric patients makes research on the diseases of children commercially less appealing (and hence less likely) than research on adult diseases.
- 3) Clinical trials in children are practically difficult. The limited pool of children eligible and willing to participate in a clinical trial makes it difficult for physicians to recruit a sufficient number of research subjects

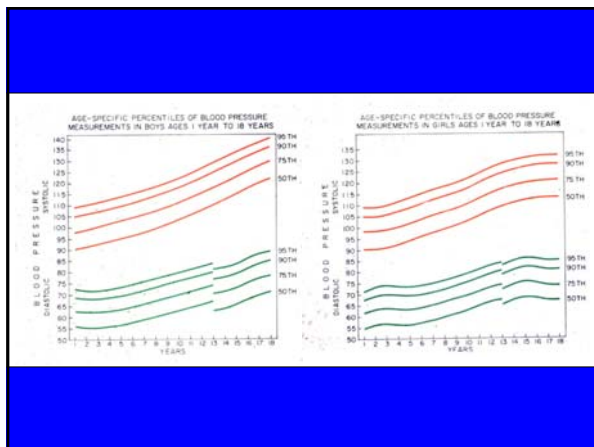
### Legal and Ethical Issues

Research with this vulnerable population involves many unique ethical and legal considerations. In order to enroll minors in clinical research, researchers must comply with a series of federal codes, including the full approval of a research ethics committee (IRB) and obtain valid permission including consent from parents and, when possible, assent from their child to participate in a study.

### Rationale for Studies in Children

#### LEARN

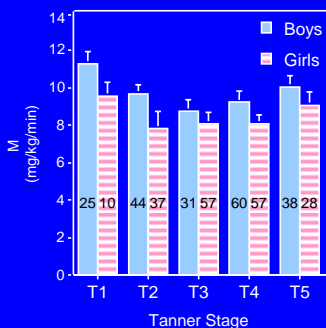
- [Changes during aging and maturity](#)
- Changes during puberty
- Population changes
- Changes beginning at birth or during gestation
- Natural history of development or disease
- Tracking effects
- Interventional studies



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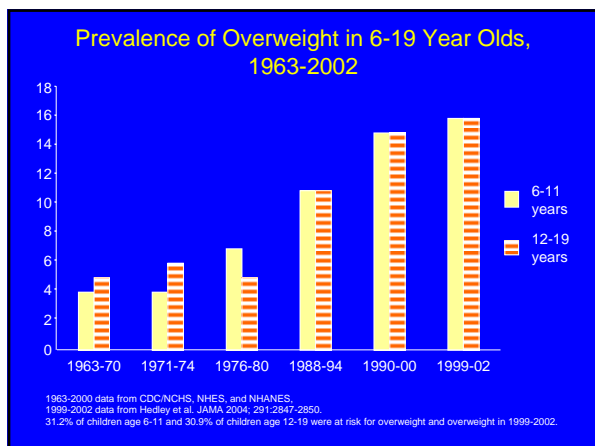
### Insulin Sensitivity by Tanner Stage in Boys and Girls



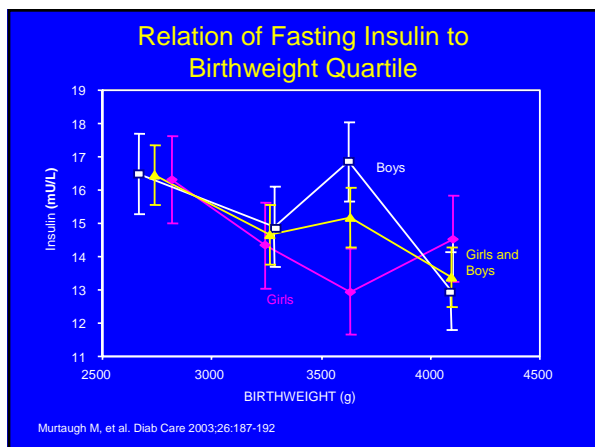
Moran A, et al. Diabetes 1999;48:2039-2044

### Rationale for Studies in Children

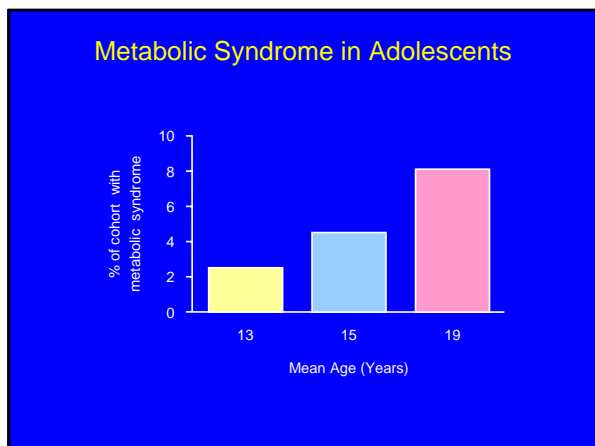
- Changes during aging and maturity
- Changes during puberty
- [Population changes - secular trends](#)
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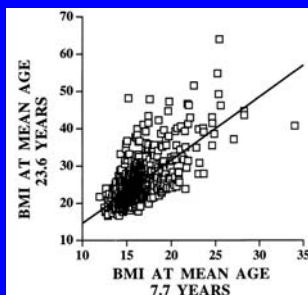
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Julia Steinberger, MD and Joseph Neglia, MD No More Hand Me Downs: Research Designed for Children

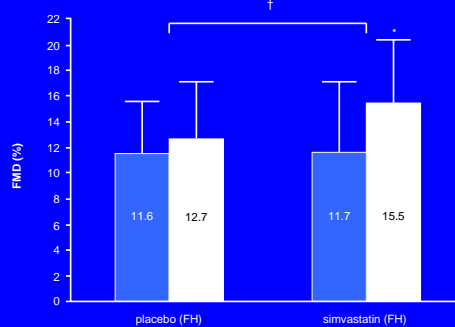
Relation of Childhood BMI to Adult BMI



Sinaiko A, et al. Circulation 1999;99:1471-1476.

Rationale for Studies in Children

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Changes from baseline (colored bar) to 28 weeks (white bar) in flow-mediated dilation (FMD) in the placebo and simvastatin groups of children with familial hypercholesterolemia (FH). \*P<0.0001 vs baseline; †P<0.05 for change in placebo vs change in simvastatin groups. Reproduced from de Jongh et al, with permission from the American College of Cardiology Foundation. Copyright 2002 American College of Cardiology Foundation.

What Motivates Parents to Consent for Research?

Benefit to their own child (91%) and benefit to all children (89%).

What factors helped them to decide to allow their children to participate in research:

- initial meeting, the researcher outlined the direct and immediate advantages that the child would gain by participating in the study
- the opportunity to ask questions and discuss potential problems with the researcher
- were allowed time to think over the child's participation and discuss how participation would affect the family. Older children require specifics of time, location, and frequency of the procedures to be performed.

[www.childrenandclinicalstudies.nhlbi.nih.gov](http://www.childrenandclinicalstudies.nhlbi.nih.gov)

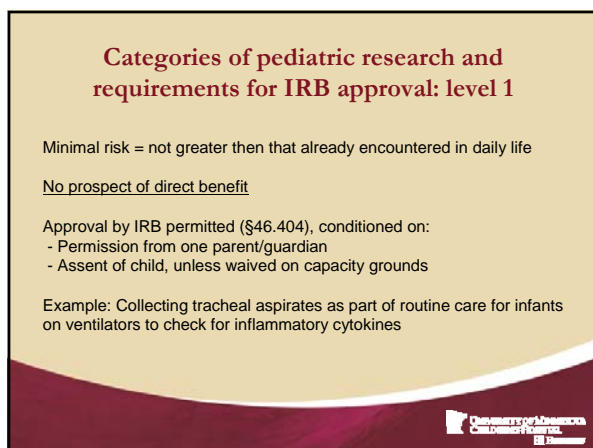
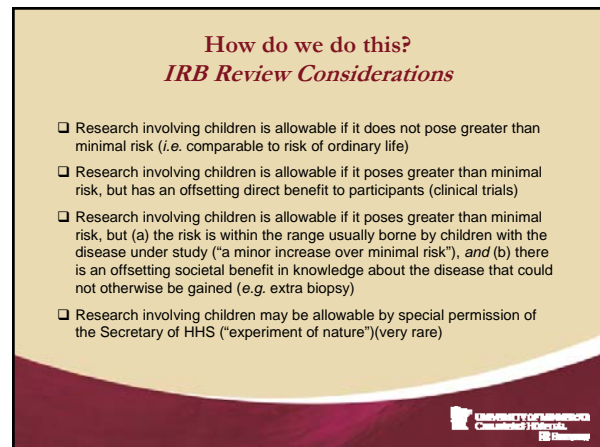
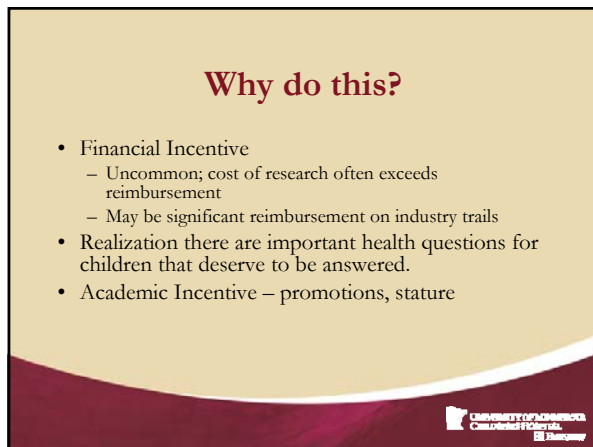
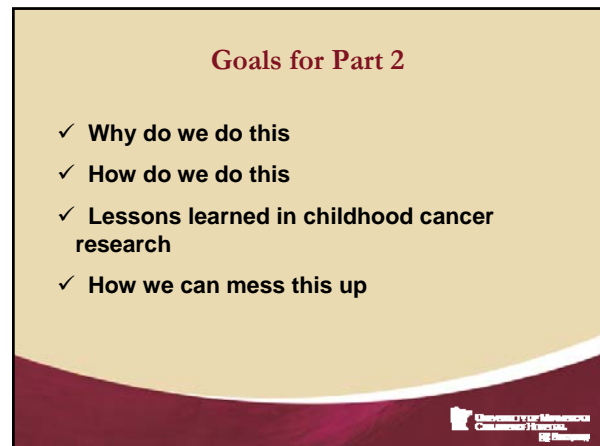
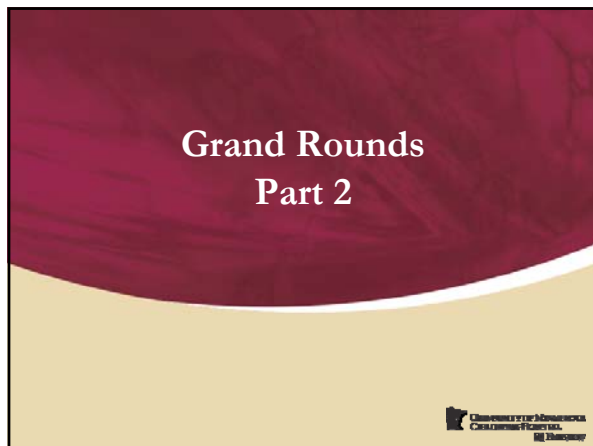
Oct '08 NHLBI launched a website for parents and children on medical research studies for children.

Offers parents and health care providers an insider's guide to medical research, combines information on how clinical studies are conducted, what measures are taken to protect participants safety and privacy, rewards and challenges of participating in research.

Interviews with children who participated in studies and their parents.



From <http://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php>



### Categories of pediatric research and requirements for IRB approval: level 3

Greater than minimal risk and no prospect of direct benefit (§46.406)

Allows the IRB to consider "societal benefit" that is specifically targeted toward children.

Can apply to children who do not have a diagnosed illness, but risk of an illness


Can apply to social science and behavioral studies

Risk can only be minor increment over "minimal risk" and the study must yield important information

The less risky the condition under study is, the less risk is acceptable

Examples:

- Additional diagnostic tests: more bone marrows for research
- Testing done outside of therapy: measuring leptin and cytokines in children with DM after fatty meal




### Categories of pediatric research and requirements for IRB approval: level 4

Not otherwise approvable, but presents opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

No prospect of direct benefit

Approval requires Department of Health and Human Services approval after consultation with an expert panel and opportunity for public review and comments (§46.407), conditioned on:

- Research presents reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children
- Permission from both parents if reasonably available
- Assent of child, unless waived on capacity grounds




### Parent Permission and Child Assent

Informed consent - Is a process and not an event. Parents give the researcher permission for research and to approach the child about participating in the research.

Assent from the child (age 8+) can only be sought after obtaining parental permission and must be obtained before the child's enrollment into the study.


So, can the child refuse?

- Yes and no
  - Yes - in the context of a no benefit study or a study with a standard care arm
  - No - in the context of not receiving a therapy that is unavailable outside of the study

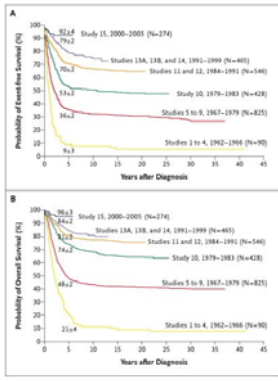




### Lessons Learned - 1

- Clinical research in children works.
  - Childhood ALL has been changed from a fatal disease to a curable disease in over 80% of children.



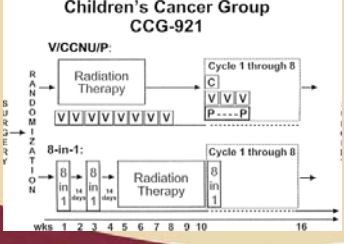
Pui et al – Outcomes of 2628 children with ALL at SJCRH from 1962 to 2005

### Lessons Learned - 2

- We are not as smart as we think we are.


**Children's Cancer Group CCG-921**

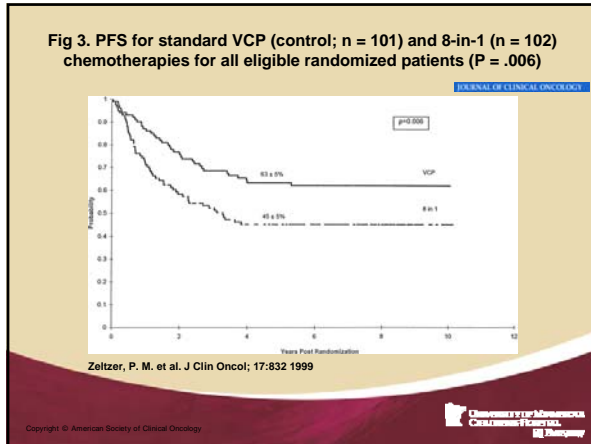


VCR/CCNU/Pred

Or

VCR/CCNU/Pred/  
Procabazine/Hydra/  
Cisplatinum/Cytosan/  
AraC





### Lessons Learned - 3

- We do better thinking together
  - UK Study, 2 year period review of Wilms' Tumor..... 20 children not on study
  - 10/20 received more therapy than UKCCSG would have recommended
    - 3 with not indicated XRT
    - 4 with additional chemo
  - Overall inferior survival (65% vs 82%)

### Lessons Learned - 4

- Children can benefit from Phase I trials
  - 16 NCI Phase I trials conducted 1992 to 2005; 262 patients
  - 5% discontinued due to toxicity
  - 1 drug related death (0.4%)
  - 4% with either CR or PR (>50% dec in dz)
  - 17% with stable disease for 3 or more months

Kim et al; The Oncologist 2008

### Lessons Learned - 5

- Why do families agree to experimental trials
  - Hope
  - Prolongation of life
  - Continuation of Care
- What do families value at end of life?
  - Control
  - Some sense of normal life and activity

Barrera et al; Palliative and Supportive Care 2005

### How to mess up (a partial listing)

- Ask a bad question
  - Unimportant (doesn't lead anywhere)
  - Uninformed (several beat you to it)
- Design a poor study
  - Lack of a detailed protocol
  - Study not powered to answer the question
- Execute it poorly
  - Poor study coordinators
  - Don't adhere to your own protocol

### How to mess up (a partial listing (continued))

- Fail at getting informed consent
  - Poor process
  - Investigator bias
  - Failure to consider or disclose conflict of interest
- Don't share your results
  - No abstracts
  - No publications

### Acknowledgements / Discussion

- U of M IRB: Patrice Webster, Moira Keane
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  - Juli Tidwell & Jenilyn Gunn
  - Stephannie Walczak, Angela Cho, Christine Jacox
- Heme/Onc/BMT NPs, Nurses, Faculty and Fellows



### Comments and Questions

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this presentation!*



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