The Ethics and Regulatory Aspects of Clinical Research Course

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Ethical Issues in Research Involving Children

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The Ethics and Regulatory Aspects of Clinical Research Course

Disclosure:

I have no financial conflicts of interest to disclose, but…

The opinions in this presentation are not unbiased. They are solely those of the speaker and may not reflect the views, policy, or position of any other organization or person with whom the speaker is, or has been, affiliated.

Alan R. Fleischman, M.D.

Ethical Issues in Research Involving Children

Can we justify research involving children?

Children are Unique

- **Diseases**
- **Development**
- **Growth**
- **Metabolism**
- **Toxicity**

Ethical Issues in Research Involving Children

Is it ethical to do research involving children?

- **Are we willing to place a child at any risk or discomfort today for the sake of other children who might benefit in the future?**

- **If so, how do we protect the children to assure they are not placed at undue risk?**

Ethical Issues in Research Involving Children

A century of research "abuses" involving children

Pre World War II

- Spinal taps on healthy children to define normal values
- Xrays and Flouroscopy to define normal stomach emptying time
- Restraint of infants in "metabolic beds" to collect stool and urine for analysis for metabolic balance studies

The Nazi Experiments

- Twin studies of infection, cross transfusion, transplantation…

Ethical Issues in Research Involving Children

The Nuremberg Code (1947)


Children victims of Nazi medical experiments

- **The voluntary consent of the human subject is absolutely essential.**
- **The experiment should be such as to yield fruitful results for the good of society.**
- **The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.**
- **During the course of the experiment the human subject should be at liberty to bring the experiment to an end.**

Ethical Issues in Research Involving Children

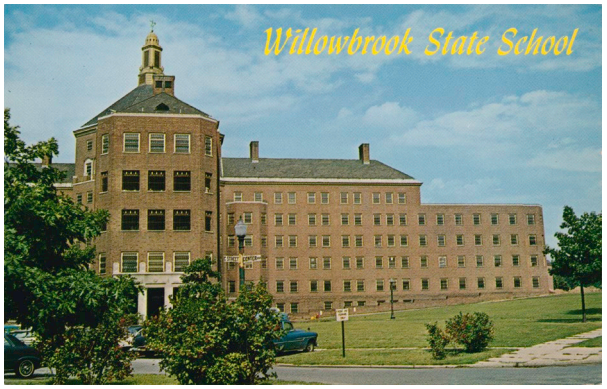
A century of research "abuses" involving children

Post World War II

- Willowbrook – Natural history of infectious hepatitis
- Andrew Wakefield -- Measles Vaccine and Autism
- Kennedy Krieger -- Lead ExposureStudy
- CHEERS Study – Natural history of infant pesticide exposure
- Jesse Gelsinger -- Gene Transfer Study
- SUPPORT Study -- Oxygen Trial in Preterm Babies

Ethical Issues in Research Involving Children

Willowbrook State School (1963-1966)



Research questions: What is the natural history of infectious hepatitis?

Can gamma globulin prevent transmission and ameliorate disease?

- **Having just completed a brand new wing to the facility, admission was based on agreement to be in this study;**
- **Children were deliberately infected with hepatitis virus by feeding extracts of infected patients stool;**
- **Investigators justified the study because most children at Willowbrook became infected with hepatitis anyway, and it might be better if it were done in a controlled environment.**

Ethical Issues in Research Involving Children

Andrew Wakefield M.D.

There seems to be an association between MMR vaccination at about 14 months of age and the development of bowel disease and a pervasive developmental disorder resembling autism.

Lancet; Feb, 1998

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associated, by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12 children had intestinal abnormalities, ranging from lymphoid nodular hyperplasia to aphthoid ulceration. Histology showed patchy chronic inflammation in the colon in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (two). There were no focal neurological abnormalities and MRI and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls ($p=0.003$), low haemoglobin in four children, and a low serum IgA in four children.

Interpretation We identified associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers.

Lancet 1998; **351:** 637–41
See Commentary page 611

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield FRCS, A Anthony MB, J Linnell PhD, A P Dhillon MRCPath, S E Davies MRCPath) **and the University Departments of Paediatric Gastroenterology** (S H Murch MB, D M Casson MRCP, M Malik MRCP, M A Thomson FRCP, J A Walker-Smith FRCP.), **Child and Adolescent Psychiatry** (M Berelowitz FRCPsych), **Neurology** (P Harvey FRCP), **and Radiology** (A Valentine FRCR), **Royal Free Hospital and School of Medicine, London NW3 2QG, UK**

Correspondence to: Dr A J Wakefield

Introduction

We saw several children who, after a period of apparent normality, lost acquired skills, including communication. They all had gastrointestinal symptoms, including abdominal pain, diarrhoea, and bloating and, in some cases, food intolerance. We describe the clinical findings, and gastrointestinal features of these children.

Patients and methods

12 children, consecutively referred to the department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms (diarrhoea, abdominal pain, bloating and food intolerance), were investigated. All children were admitted to the ward for 1 week, accompanied by their parents.

Clinical investigations

We took histories, including details of immunisations and exposure to infectious diseases, and assessed the children. In 11 cases the history was obtained by the senior clinician (JW-S). Neurological and psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.[1] Developmental histories included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.[2] Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid zones from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample t test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for antiendomyseal antibodies and boys were screened for fragile-X if this had not been done

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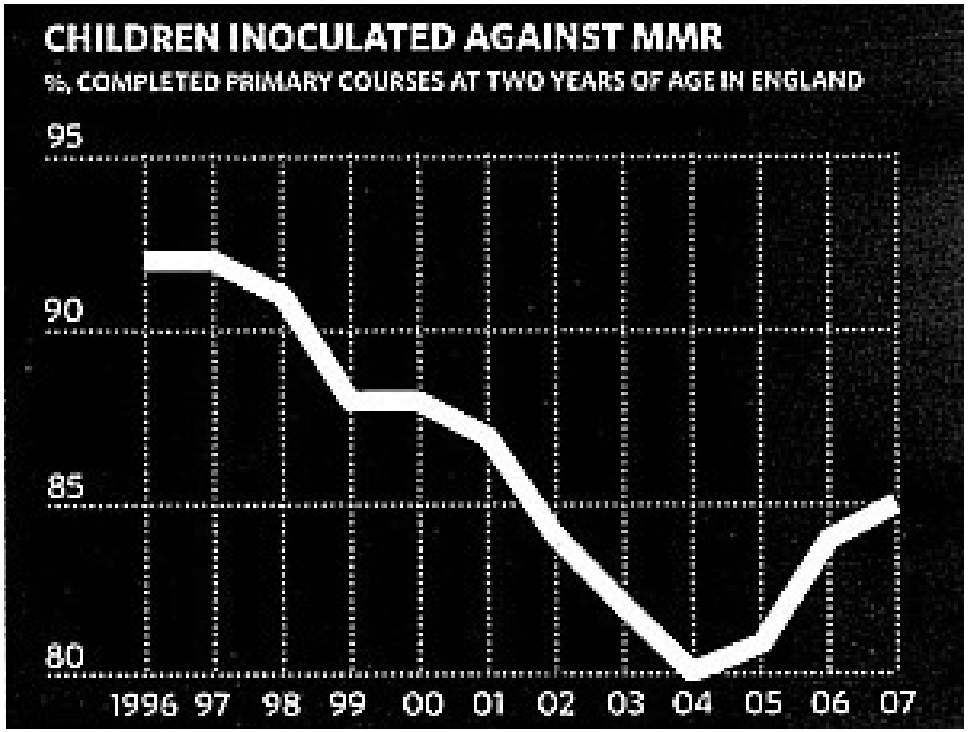
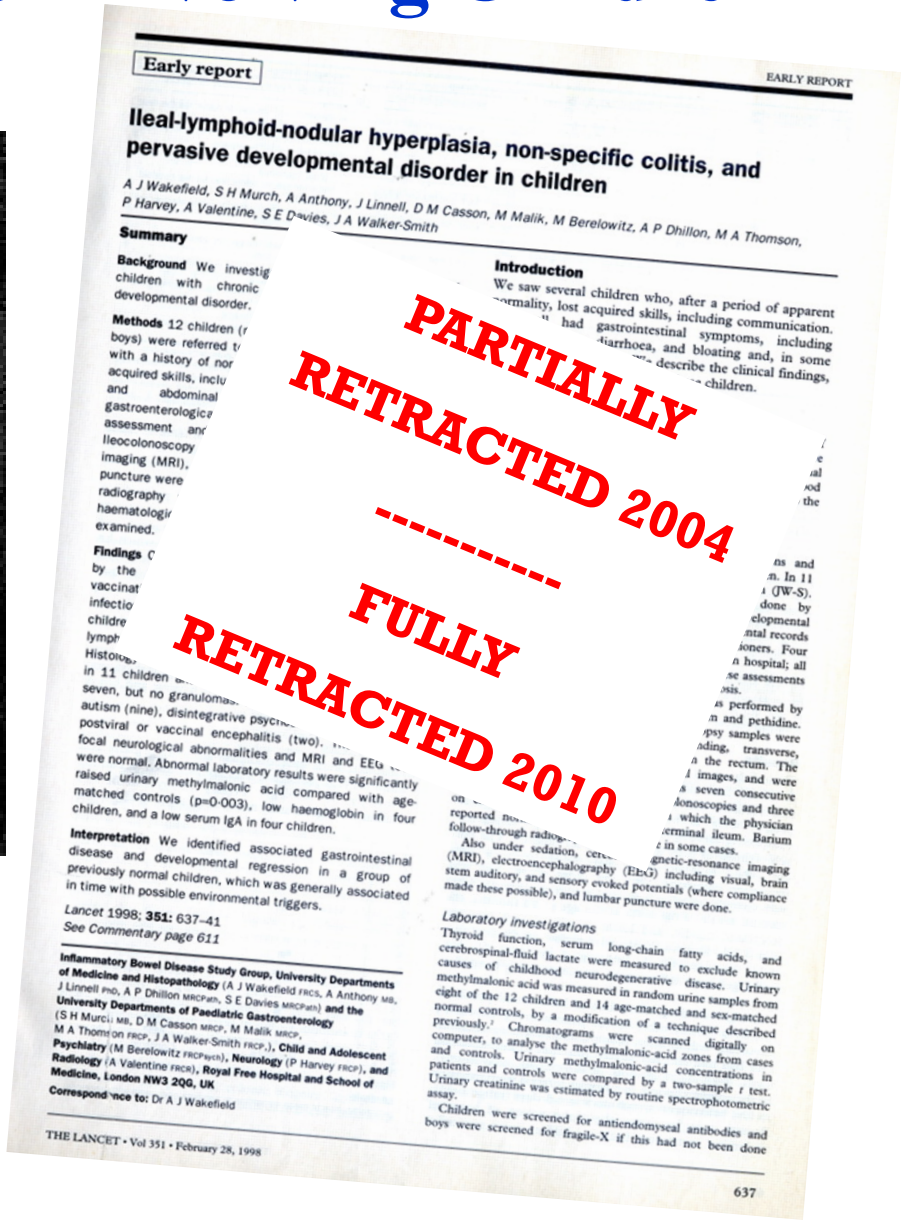




JOHNS HOPKINS
CHILDREN'S CENTER

The Lead-Based Paint Abatement and Repair and Maintenance Study in Baltimore

Background:

- **In the 1990's, 95% of children living in low-income housing in Baltimore were at risk for toxic levels of lead exposure**
- **40-50% of children in low-income areas had elevated blood lead levels**
- **Lead abatement of an individual apartment may cost up to $10,000.**
- **Owners are likely to abandon buildings rather than do abatements.**

Research question:

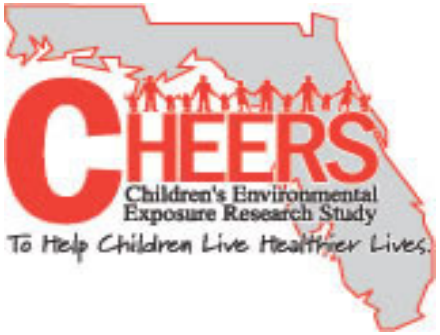
Can partial (less costly) lead abatement of affected apartments sufficiently prevent young children from exposure to toxic levels of lead?

The Lead-Based Paint Abatement and Repair and Maintenance Study in Baltimore

Design:

- **Compare three different levels of abatement with two control groups.**
- **Follow children longitudinally; Measure blood and dust lead levels and refer to the Johns Hopkins Kennedy-Krieger Lead Program for any elevated lead levels.**

Group	Occupied at recruitment	Intervention
I	Yes	$1650 —cleaning and education
IIa	Yes	$3500 — "I" plus floor window and door treatments
IIb	No	$3500 --Same as IIa
III	Yes	$7500 — "II" plus replace windows door trim and flooring
Control Group 1 Previously abated	Yes	No cap —III plus enclose all lead painted surfaces
Control Group 2 Modern Apartment	Yes	Presumed lead free



Children's Environmental Exposure Research Study (CHEERS)

Study conducted by the EPA in Florida in 2004, designed to understand how young infants may be exposed to pesticides and other common household chemicals

•Design:

- **Observational, 2-year, "minimal risk" study;**
- **Enroll two groups of infants: <3 months old and 9-12 months old;**
- **Eligibility—homes where parents routinely spray pesticides;**
- **Samples of food the children eat, urine, and hand wipes will be obtained during six multi-day periods over two years;**
- **Names of all chemicals in the home and history of spraying for pesticides during the interval will be obtained;**
- **Parents will video tape the child for several hours while playing during the same six periods.**

Children's Environmental Exposure Research Study (CHEERS)

Compensation:

- ***You will receive compensation for each phase of the study, up to $970 over the two year period if you complete all of the study activities;***

- ***Your family will also receive an official Certificate of Appreciation, a CHEERS bib, a t-shirt, a calendar, a study newsletter and you will be allowed to keep the video camcorder at the end of the study.***

Ethical Issues in Research Involving Children

The case of Jesse Gelsinger at Univ. of Pennsylvania

Jesse was an 18 year old boy with a mild version of OTCD (ornithine transcarbamylase deficiency) -- a rare genetic disease of ammonia metabolism, generally fatal in infancy.

He volunteered for a phase 1 trial to determine if normal genes for the OTC enzyme carried by an adenovirus could be injected directly into the arterial circulation of the liver, enter liver cells, and result in active production of the enzyme.

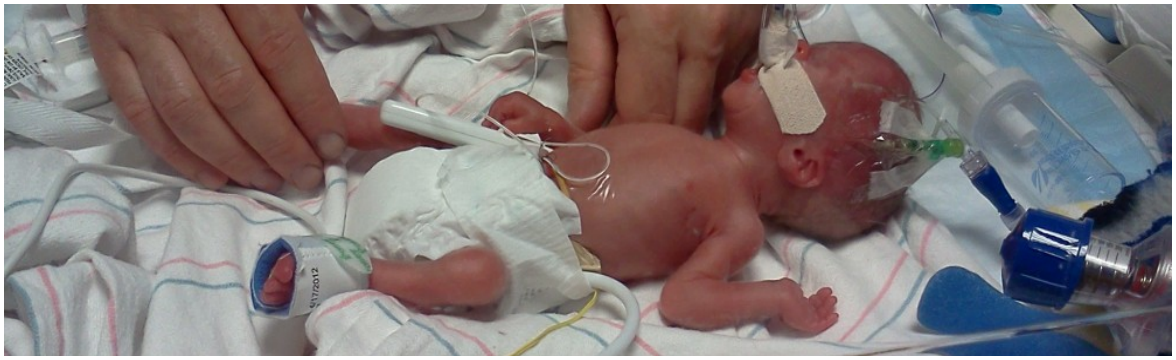
- **Shortly after the injection, Jesse's ammonia level rose dramatically resulting in coma, multi-organ failure, and ultimately death.**
- **Jesse's family grieved his loss but took it as an unfortunate but unforeseeable consequence of his altruistic attempt to help other children.**

Ethical Issues in Research Involving Children

What Jesse and his Family Didn't Know

- During the animal phase of these studies, two monkeys had died suddenly from liver failure. This fact had appeared on the informed consent forms approved by the NIH for this trial, but was not on the form Jesse and his father signed.
- Jesse's ammonia level on the day of the study was above the acceptable level for eligibility in the trial.
- The Principal Investigator (Director of the Genetics Program) and the Univ. of Penn each had an equity stake in the company that was funding the trial as a model for administering gene therapy more broadly.
- The Director of the Bioethics Center at Univ of Penn was being paid by the study funder to consult on the ethical aspects of the research studies for the Genetics Program.

The SUPPORT Trial



SUrfactant Positive Pressure and Oxygenation Randomized Trial

An NICHD Neonatal Network Research Study to Compare Two Different Standard Approaches to Care (2004-2009)

- **Eligible Infants: Very Preterm (24 wks 0 days -- 27 wks 6 days)**

- **Standard practice: Oxygen is administered to keep the blood saturation between 85-95%. Oxygen level and prematurity are associated with retinal damage**

- **Research Question: Within the standard range, can you decrease the incidence of retinopathy (retinal damage and blindness) and bronchopulmonary dysplasia (chronic lung disease) if you decrease the level of oxygen saturation to 85-89%?**

- **Randomized Clinical Trial: Compare Target Oxygen Saturation of 85-89% vs 91-95%**

The SUPPORT Trial –Results*

	O_2 85-89%	O_2 91-95%
Died	130	107
Survived	524	555
Had ROP	41	91
No ROP	434	418
ROP undet	49	46

*N Engl J Med, 2010;362:21,1959-1967.

The New York Times

April 16, 2013

Editorial: *An Ethical Breakdown*

"Leading medical centers failed to inform parents of a study's real risks to their babies

…23 academic institutions authorized a research project that failed to meet the most basic standard: providing an informed consent document to parents that accurately described the risks and benefits of the research to be conducted on extremely premature babies. This failure was startling and deplorable."

Ethical Issues in Research Involving Children

Henry K. Beecher, M.D. (NEJM, 1966)

- **22 examples of published clinical research (many involved children)**
- **Many of the patients or parents never had the risks explained**
- **Hundreds never knew they were subjects of research**

Ethical Issues in Research Involving Children

Is it ethical to do research involving children?

- **Paul Ramsey—Protestant theologian:**

  only if the research furthers the medical interests of the child

- **Richard McCormick—Catholic theologian:**

  parents may consent even if there is no therapeutic benefit

Ethical Issues in Research Involving Children

The Tuskegee Study (1932-1972)

"Syphilis victims get no therapy" -- NY Times, July 26, 1972

U.S. Public Health Service Study

Research Question: What is the natural history of untreated syphilis?

- **Enrolled 400 black men in Alabama with syphilis and provided health care and regular examinations;**
- **By 1950, penicillin was available to treat syphilis, but it was not offered to the men;**
- **The CDC affirmed the need to continue the study until all subjects had died and could be autopsied;**

Ethical Issues in Research Involving Children

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978)

- **The Belmont Report**
- **Research Involving Children**
- **Institutional Review Boards**
- **Research Involving those Institutionalized as Mentally Infirm**

Ethical Issues in Research Involving Children

Belmont Report (1978)

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

- **Beneficence**
- **Respect for Persons**
- **Justice**

Ethical Issues in Research Involving Children

Belmont Report (1978)

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

- **Beneficence**:

"effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children"

"research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices…that may turn out to be dangerous"

Ethical Issues in Research Involving Children

Belmont Report (1978)

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

- **Respect for Persons:**

  Individuals with capacity…
  treated as autonomous

  Persons with diminished autonomy…
  entitled to protection

Ethical Issues in Research Involving Children

Belmont Report (1978)

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

- **Justice:**

"Historically the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients."

Federal Policy for the Protection of Human Subjects (45 CFR46)

- **Subpart A: Basic Policies**
  Institutional Review Boards
  Informed consent

- **Subpart B: Pregnant women, fetuses, and neonates**

- **Subpart C: Prisoners**

- **Subpart D: Children**

Ethical Issues in Research Involving Children

Belmont Report

Respect for Persons Principle:

Individuals with capacity, should be treated as autonomous; Persons with diminished autonomy are entitled to protection

Federal Policy for the Protection of Human Subjects

45CFR46.111(a) Criteria for IRB Approval of Research

(2)Risks to subjects are reasonable in relationship to anticipated benefits, if any, to subjects

Adult Standard: "Reasonable Risk" and patient consent

Child Standard: "Minimal Risk" unless there is a prospect of direct benefit (accept in very specific circumstances) and parental permission

Federal Policy for the Protection of Human Subjects (45CFR46)

"Children"

"Children are persons who have not attained the legal age for consent to treatment or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."

45 CFR § 46.402

Federal Policy for the Protection of Human Subjects (45CFR46)

Permissible Research in Children

- Minimal risk (§ 46.404)
- Greater than minimal risk and with the prospect of direct benefit (§ 46.405)
- Minor increase over minimal risk and no prospect of direct benefit (§ 46.406)
- Significant risk and special opportunity (Secretary HHS review) (§ 46.407)

Federal Policy for the Protection of Human Subjects (45CFR46)

Permissible Research in Children

- **Minimal risk (§ 46.404)**
- **Greater than minimal risk and with the prospect of direct benefit (§ 46.405)**
- **Minor increase over minimal risk and no prospect of direct benefit (§ 46.406)**
- **Significant risk and special opportunity (Secretary HHS review) (§ 46.407)**

Federal Policy for the Protection of Human Subjects (45CFR46)

Minimal Risk

"That the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

45 CFR § 46.102(i)

"Ethical Conduct of Clinical Research Involving Children"
Institute of Medicine of the National Academies -- 2004

Minimal risk:

- **Interpret minimal risk in relation to the normal experiences of average, healthy, normal children**
- **Minimal risk may vary with age but not social status, illness, or circumstances**
- **Focus on "equivalence of risk" in daily lives or experiences in routine physical or psychological exams or tests**
- **Minimize risks even when risks are minimal**

Federal Policy for the Protection of Human Subjects (45CFR46)

Permissible Research in Children

- **Minimal risk (§ 46.404)**
- **Greater than minimal risk and with the prospect of direct benefit (§ 46.405)**
- **Minor increase over minimal risk and no prospect of direct benefit (§ 46.406)**
- **Significant risk and special opportunity (Secretary HHS review) (§ 46.407)**

"Ethical Conduct of Clinical Research Involving Children"
Institute of Medicine of the National Academies -- 2004

Prospect of direct benefit:

- **Tangible positive outcome (e.g. cure of disease, relief of pain, increased mobility)**
- **Level of risk may be greater than minimal but balanced by the compensating benefit**
- **Collateral or indirect benefits are not considered prospect of direct benefit**
- **Gifts, payments, compensation are not considered prospect of direct benefit**

Federal Policy for the Protection of Human Subjects (45CFR46)

Permissible Research in Children

- Minimal risk (§ 46.404)
- Greater than minimal risk and with the prospect of direct benefit (§ 46.405)
- Minor increase over minimal risk and no prospect of direct benefit (§ 46.406)
- Significant risk and special opportunity (Secretary HHS review) (§ 46.407)

Federal Policy for the Protection of Human Subjects (45CFR46)

§ 46.406: Greater than minimal risk with no prospect of direct benefit: (*these are children with a disorder or condition*)

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

Federal Policy for the Protection of Human Subjects (45CFR46)

Permissible Research in Children

- Minimal risk (§ 46.404)
- Greater than minimal risk and with the prospect of direct benefit (§ 46.405)
- Minor increase over minimal risk and no prospect of direct benefit (§ 46.406)
- Significant risk and special opportunity (Secretary HHS review) (§ 46.407)

§ 45CFR 46.407: Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of § 46.404, § 46.405, or § 46.406 only if:

(a)the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children; and

§ 45CFR 46.407:

(b)the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1)that the research in fact satisfies the conditions of § 46.404, § 46.405, or § 46.406, as applicable, or

(2) the following:

(i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) the research will be conducted in accordance with sound ethical principles;

(iii) adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

Ethical Issues in Research Involving Children

Three Levels of Protection:

- Ethical Researchers
- Peer Review
  - Division/Department
  - Institutional Review Board(s)
- Informed Consent Process
  - Parental Permission
  - Child Assent

Comments??? Questions???

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The New York Times

September 25, 2018

Science Times: *Critics Demand Halt of a Sepsis Trial*

"Complaints that it's like an experiment on lab animals"

"The goal of the trial is to determine whether it is better to limit fluids and start vasopressors – drugs that constrict blood vessels – quickly, or to use more intravenous fluids and postpone giving the drugs to patients."

"Critics say…Patients in both treatment arms potentially could go without lifesaving therapy and are not being properly informed of the risks."