



UNIVERSITY *of* MARYLAND  
THE FOUNDING CAMPUS

# Pediatric Research

## *Ethical and Regulatory Considerations*

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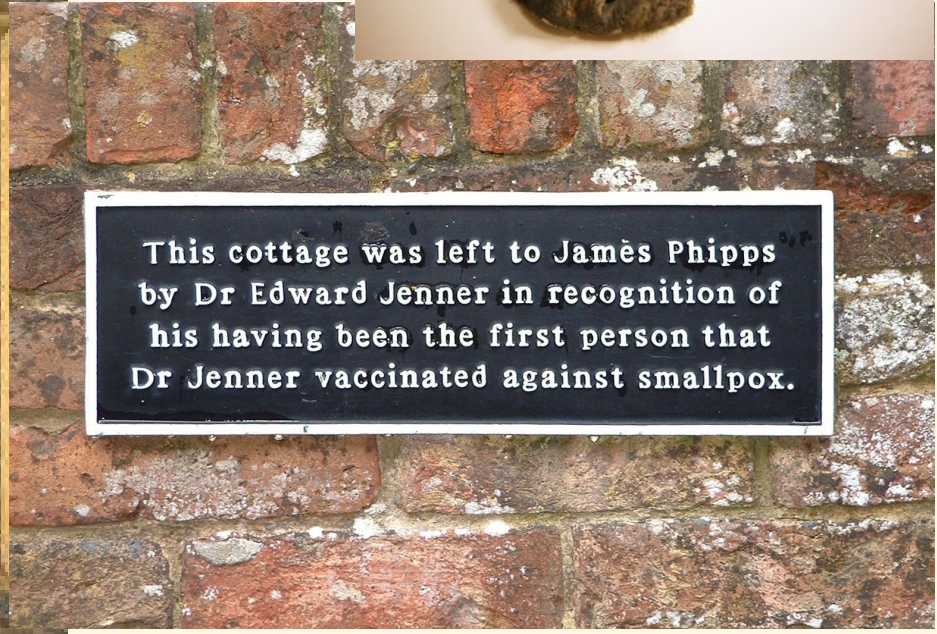
*University of Maryland School of Nursing*

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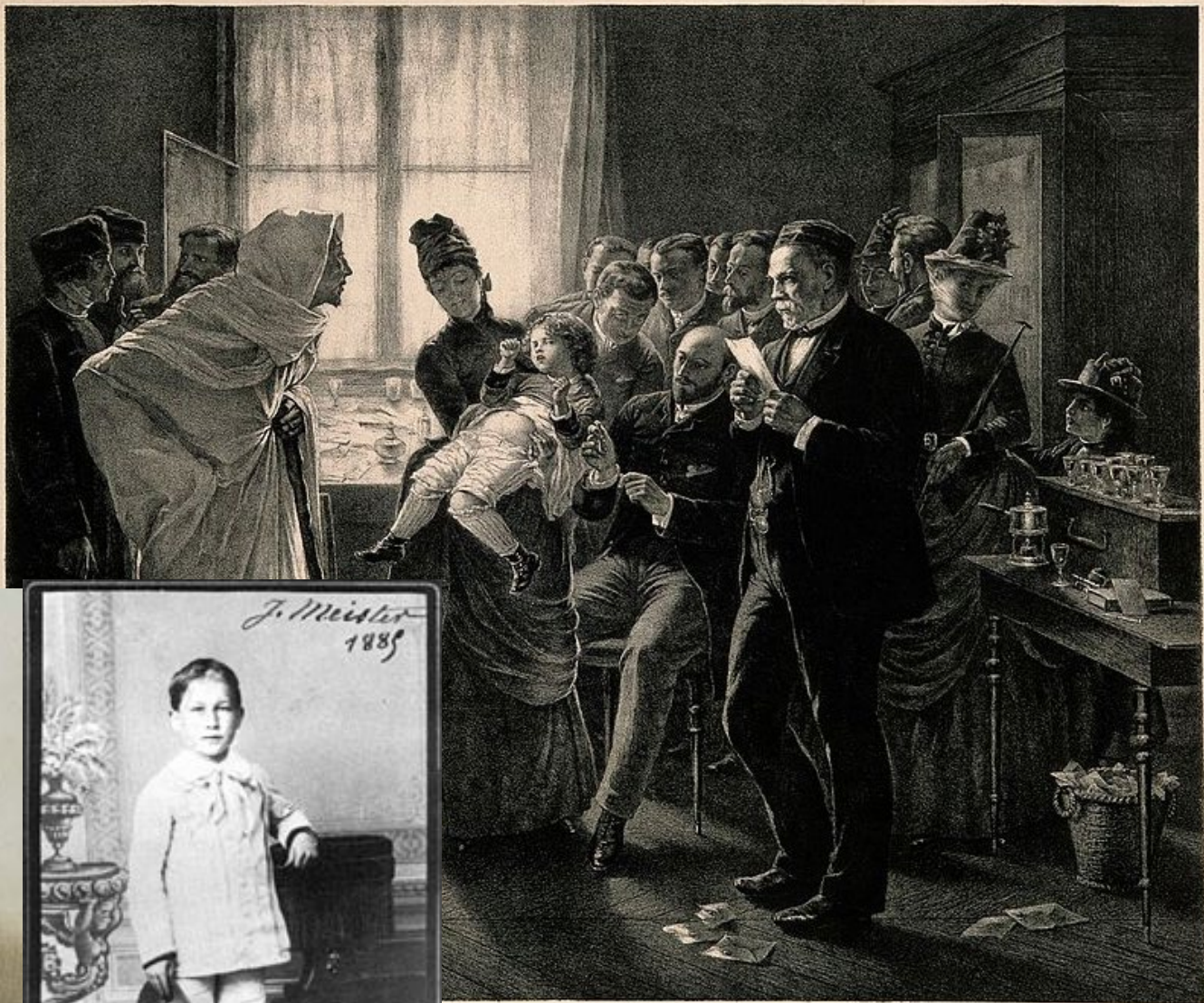
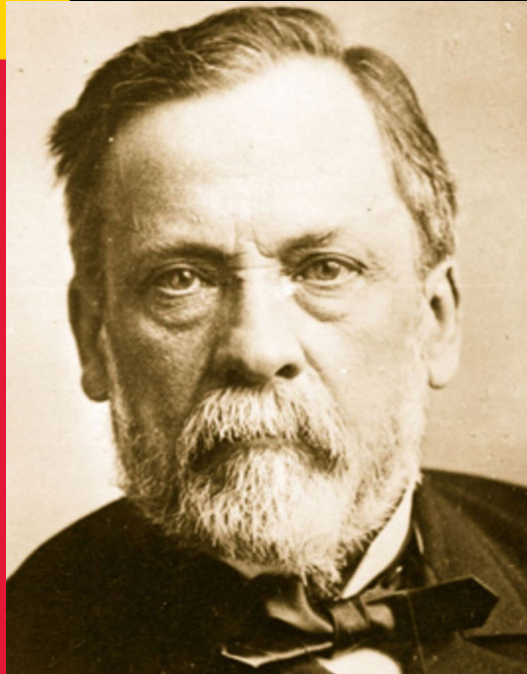


© Edward Jenner Museum, Berkeley, UK



This cottage was left to James Phipps by Dr Edward Jenner in recognition of his having been the first person that Dr Jenner vaccinated against smallpox.





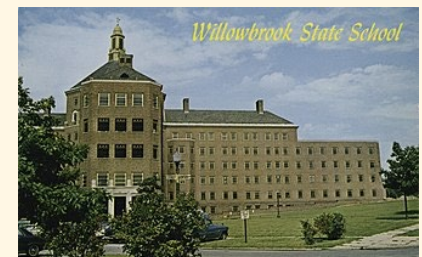
RAGE AU LABORATOIRE DE M. PASTEUR

# History

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- **Human Radiation Experiments (1944-74)**
  - MIT and Harvard enroll 74 boys at Fernald School (residential institution for kids with MR) in Waltham, MA
  - “science club”, in part sponsored by Quaker Oats
  - radioactive Ca and Fe in their cereal
  - parents notified of “special diet” for brighter children
  - (may have actually been quite low doses)
- **Willowbrook State School Studies (1950s-60s, Staten Island NY)**
  - institutionalized children with MR
  - infected children with hepatitis A to study natural history
  - special unit for those in studies- more hygienic, better nutrition, expedited entry if parents allow study





# History

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- **Institutionalized children**
  - Frequently used as subjects
- **Nuremberg Code (1947)**
  - emphasis on consent and individual autonomy
- **Declaration of Helsinki (1964)**
  - allows research with children if permission from responsible relative



# History

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- **National Commission for Protection of Human Subjects (Belmont Report)**
  - Respect for Persons- autonomy
    - Extra protections for those with diminished autonomy
  - Beneficence
    - Minimize harm/maximize benefit
  - Justice
    - Fair distribution of benefits and burdens
- **Focus on this “tension”**
  - unfairly excluded vs. protection from risks
- **National Commission’s report guided the current US regulations**

# History

## *Grimes v KKI*



- **Lead paint** abatement study 1993
  - 5 groups of 25 houses each, 2 years, EPA and state of MD sponsored
- **Ericka Grimes:** infant, full abatement, EBL
- **Myron Higgins:** 4 yo, intervention gp, EBL
- Claimed **negligence** -- need duty, breach, harm
- **Summary judgment**, 2000-- no duty
- **Court of Appeals**—reverses the summary judgment
  - not in the best interest of child, no parental authority to give permission, research and IRB unethical
  - compared to Tuskegee and Nazi experiments



# History

## *Grimes v KKI*

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- **Ways to avoid (*my opinion*)**
  - better consent with full explanation and maybe a quiz or witness
  - proactively contacting parents and providers (benefit)
  - treating all EBL (benefit)
  - DSMB
- **No specific new restrictions in Maryland**
  - but does make us look even more closely at all pediatric research that is GTMR
- In protocol design: **maximize benefit and minimize risks**

# Code Federal Regulations

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- **45 CFR 46-** human research
- **Subpart D** added in 1983-  
additional protections for children
- **Children:** “persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted”



# Code Federal Regulations

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- **Is it human subject research? Or NHR?**
  - Not practice
- **Research:** “systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge”
- **Human subject:** “living individual about whom an investigator (whether professional or student) conducting research:
  - (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
  - (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.”



# Why have an IRB review?

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- Minimize risks
- Optimize benefit-to-risk ratio
- Assure valid informed consent
- Assure respectful, ethical treatment
- Regulatory requirements met



# Types of Risk

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- Physical injury
- Pain
- Distress
- Psychological harm
  - anxiety, guilt, sadness
- Social
- Economic
- Legal



# Categories of Research Involving Children

**Table. Allowable categories of research involving children and basic consent/assent requirements**

Category (CFR)	Level of risk	Prospect of direct benefit?	Parental permission	Assent from child*
46.404	No greater than minimal	Not necessary	One parent	Yes
46.405	Justified by anticipated benefit At least as favorable as any available alternatives	Necessary Must justify risks	One parent	Yes
46.406	Minor increase over minimal	Not necessary	Two parents	Yes
46.407	Not defined	Not necessary	Two parents	Yes

\*An IRB may waive assent for certain ages of children if it determines that the capability of the child is so limited that he or she cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health and well-being of the child and is available only in the context of the research.

- The **regulations dictate** what elements the IRB reviews to determine category
  - Risk: MR, GTMR, GTMR minor increase
  - Prospect of Direct Benefit: yes or no
  - Parent permission: one or two
  - Assent: based on age, maturity
- **It's all about definitions** and the regulations leave much open to interpretation
  - So state your case to the IRB- "an educated consumer is our best customer"



# Why vulnerable?

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- **Without full autonomy**
  - cannot consider risks and benefits of participation for themselves, so cannot provide true informed consent
  - higher burden of **protection** placed on investigator
- **Federal categories**
  - Pregnant women, fetus, newborn (Part B),
  - Prisoners (Part C),
  - Children (Part D)
- **Others**
  - poor, homeless, illiterate, students, employees, stigmatized, mentally ill



# 45 CFR 46.404 (21CFR50.51)

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- **Not greater than minimal risk**
- **Minimal risk** does not mean low risk
  - “where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”
- **Average healthy child**
  - absolute, not relative to situation
- **Examples?**

# 45CFR46.404 (21CFR50.51)

**TABLE 4.1** Common Research Procedures by Category of Risk

Procedure	Category of Risk		
	Minimal	Minor Increase over Minimal	More Than a Minor Increase over Minimal
Routine history taking	X		
Venipuncture/fingerstick/heelstick	X		
Urine collection via bag	X		
Urine collection via catheter		X	
Urine collection via suprapubic tap			X
Chest X-ray	X		
Bone density test	X		
Wrist X-ray for bone age	X		
Lumbar puncture		X	
Collection of saliva	X		
Collection of small sample of hair	X		
Vision testing	X		
Hearing testing	X		
Complete neurological exam	X		
Oral glucose tolerance test	X		
Skin punch biopsy with topical pain relief		X	
Bone marrow aspirate with topical pain relief		X	
Organ biopsy			X
Standard psychological tests	X		
Classroom observation	X		

NOTE: The category of risk is for a single procedure. Multiple or repetitive procedures are likely to affect the level of risk.

SOURCE: NHRPAC, 2002.

- Each IRB decides on a case by case basis the risk level
- There have been recommendations to formalize a list, but none are set in stone
- Make your argument when you apply



# 45 CFR 46.405 (21CFR50.52)

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- **Greater than minimal risk**
- **Prospect of direct benefit to the individual child**
  - **Prospect** means not a sure thing, reasonable expectation
  - **Direct** means due to the intervention or participation
    - FDA guidance not in favor of the “inclusion” benefit- that you might get allocated to the active arm and therefore have prospect of benefit (the chance of entering a beneficial arm)
    - Placebo recipients– minimal or minor increase over minimal
  - **Individual**
  - **Compensation** is not a benefit (in regulatory-land)
- **Risk must be justified** by the anticipated benefit to the participant
- Anticipated **benefit to risk ratio** as least as favorable as presented by available alternative (non-research) approaches
- **Component analysis** is encouraged
- **Examples?**

# 45 CFR 46.406 (21CFR50.53)

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- **Greater than minimal risk**
- **No prospect of direct benefit** to the individual child
- Risk is **minor increase** over minimal
- **Likely to yield generalizable knowledge** about the subject's **disorder or condition**
- Research **procedures commensurate** with those inherent in the subject's actual or expected medical, dental, psychological, social, or educational situations
- At UMB, IRB approves, but is **also reviewed by Institutional Official** (the IO, in regulatory-land)
- **Examples ?**

# 45 CFR 46.407 (21CFR50.54)

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- **Greater than minimal risk**
- **No prospect of direct benefit** to the individual child
- Risk is **more than minor increase** over minimal
- **Cannot be approved** by an IRB, if HHS funded
- **IRB** determines if research provides a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children.
- If yes, the protocol may be **submitted to OHRP** and may be approved by the Secretary HHS after soliciting **opinions of an expert** panel and providing for a period of **public comment**.
- If involves a product that is FDA-regulated, must meet FDA requirements in **21CFR50.54** - outside panel convened by FDA commissioner.
- **Examples?**



# Parental Permission

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- **Parents**
  - assumed to act in the **best interests of the child**.
- Research involving children **requires** parental permission
  - Very few exceptions
- Process and **documentation**
  - mirrors consent, except refer to the child - same elements
- Written and delivered at an **understandable** level
  - Native language, simple as possible
- **Tension** between voluntariness/lack of undue influence vs. physician patient relationship
  - Difficult for parent to refuse child's enrollment when the one asking is the one doing surgery, tending to injury, etc.

# How many parents?

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- **One parent:** 404, 405
- **Two parent:** 406, 407
  - Unless only one parent has legal custody and medical decision making rights
  - Or other parent is dead, unknown, incompetent, or not reasonably available
- IRB can decide to be more, but not less strict
  - For some 405s, may go with 2 parents



# Can you waive parental permission?

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- Requires **serious consideration** because means studying people or their data without their permission
- **Waiver type 1**
  - Minimal risk, rights and welfare not adversely affected, not practicable otherwise, participants provided additional pertinent info after (often retrospective chart reviews)
- **Waiver type 2**
  - Conditions or subject population for which parental permission is not a reasonable requirement to protect the participant
  - Examples: abuse, pregnancy, STI
  - Parental permission replaced by appropriate mechanism, such as assent or advocate
- **Waiver type 3**
  - Emergency protocols
  - Many requirements: unconscious or incapacitated, life-threatening/disabling and only known therapy is investigational, unproven, unsatisfactory; parents not available, no accepted superior therapy
  - IRB review- realistic probability of benefit that is at least as good as standard, risks reasonable, no possibility of getting consent prior, info to parents ASAP, community input, public disclosure before and once results found

# Mature minors- an oxymoron?

## *Maryland*

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- **Mature minor** = adolescent legal authority to consent to care
- Minor can **consent as an adult** to all medical and dental treatment if
  - Married, parent, living separate from parent and self-supporting
  - Emancipation before reaching majority (18 yo in MD) can occur, by court decree, but it is not what determines if consent can be given; overlap
- **Minor can consent to treatment and advice** about
  - Pregnancy
  - Contraception other than sterilization
  - STDs (includes HIV)
  - Emergency treatment- if life/health adversely affected by delay to find parents
  - Drug/alcohol
  - Outpatient mental health services : ages 16 and up
  - Sexual assault and rape
  - Physical Exam at detention center



# Mature minors- an oxymoron?

## *Research*

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- **Children**
  - “persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted”
- **Mature minors**
  - if they are potential subjects in a study in which the research involves only **activities for which they could normally themselves consent**,
  - then **they are not “children”** and the Part D regulations may not apply
- **However**, must be very careful in this zone and give careful scrutiny to the risks, procedures, etc.

# Assent v. Consent v. Permission?

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- **Assent:** child's voluntary affirmative agreement to participate in research
  - Not merely failing to object
- Not the same as **consent**
  - We treat children with dignity and respect;
  - We teach children to ask for permission before “doing something to others”
- **Typical scenario** is parental permission plus child assent
  - for all other permutations, need special review and protections

# Assent v. Consent v. Permission?

- IRB determines appropriate **documentation of assent**
- **Who assents?**
  - Based on age, maturity, psychological state; no age specified
  - **One approach:** birth to 6: none; 7-11:verbal; 12-17: written
  - Tailored
- **Waivers**
  - **Type 1:** prospect of direct benefit, important to health or well being, and only available in research
  - **Type 2:** such limited capacity as to be unable to give meaningful assent

# What about compensation?

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- Careful not to lead to **undue influence** on child or parent
- Consider out-of-pocket costs and inconvenience, lost work, travel, appreciation
- Some worry \$ can **distort parent's ability to choose** in the best interest of child
  - others find that paternalistic and demeaning
- **Directed towards whom?**
  - Compensation for out of pocket costs- to parents;
  - Compensation for appreciation- direct to the person bearing burden- the child
    - should also go to those who withdraw
    - be creative: book, toy, movie pass, etc.



# **Encourage Pediatric Studies**

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- **FDAMA is the FDA Modernization Act 1997**
  - Economic incentives for manufacturers to conduct pediatric studies of drugs- 6 added months of marketing exclusivity
  - Authorized under BPCA or Best Pharmaceuticals for Children Act of 2002 and 2007
- **FDA Pediatric Rule 1998**
  - Product approvals from 1999 on must include pediatric assessments, unless waived
  - Suspended but elements codified in PREA
- **Pediatric Research Equity Act 2003 and 2007**

# Top Quote

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- “The history of research in the US should invest all who perform research involving children with a strong sense of humility, serving to remind us how easily the frail balance between the social value of involving children in research and the protection of children from unnecessary harms can be tipped by utilitarian thinking. Although the future health of children is dependent on the performance of clinical research in which children participate, research must be carefully designed to assure that the participants are not placed at excessive risk or denied potential benefits unfairly.” *Diekema J Peds 2006, p. S3-11*
- Although the regulations and IRBs exist to protect children, ultimately both the science and the well being of the children depend on knowledgeable, caring, responsible investigators and coordinators-you.

# Thank you.

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