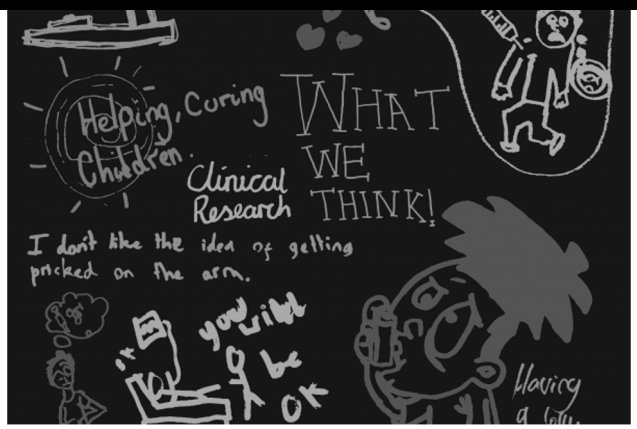
PICU Research in LMICs – ethical considerations



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Why research ethics is important…

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Ethical lapses

"*Ethical lapses are almost never a case of bad people, doing bad things, for no good reason. More often they are good people, doing bad things, for good reasons*"

– M. Angell

3

Why is PICU research necessary?

- Inform practice ["evidence based care"]
- Improve care
  - Ensure treatment is effective and safe
  - Optimise patient outcomes
- Burden of critical illness growing globally
  - Human and financial cost
- Medical care should be based on best available evidence.
  - Balance between discovering new knowledge and protecting patients

Weijer (2004) *Critical Care* 8: 85 – 86
ATS Statement *Am J Respir Crit Care Med* 170: 1375 - 1384

4

In PICU….

- Medical management still largely based on experience, anecdote and adult/animal studies.
- … "therapeutic orphans"
  - Dr. Harry Shirkey, the "father of pediatric therapeutics in the U.S", 1960s

5

… sickest, most vulnerable children are subjected to the most anecdotally based medical practice

- Brierley, Larcher (2011) J Med Ethics 2011, **37**(7):429-432.
- Knox; Burkhart (2007) J Pediatr Nurs 2007, **22**(4):310-318.
- Brierley; Larcher (2010) Arch Dis Child, **95**(11):863-866.

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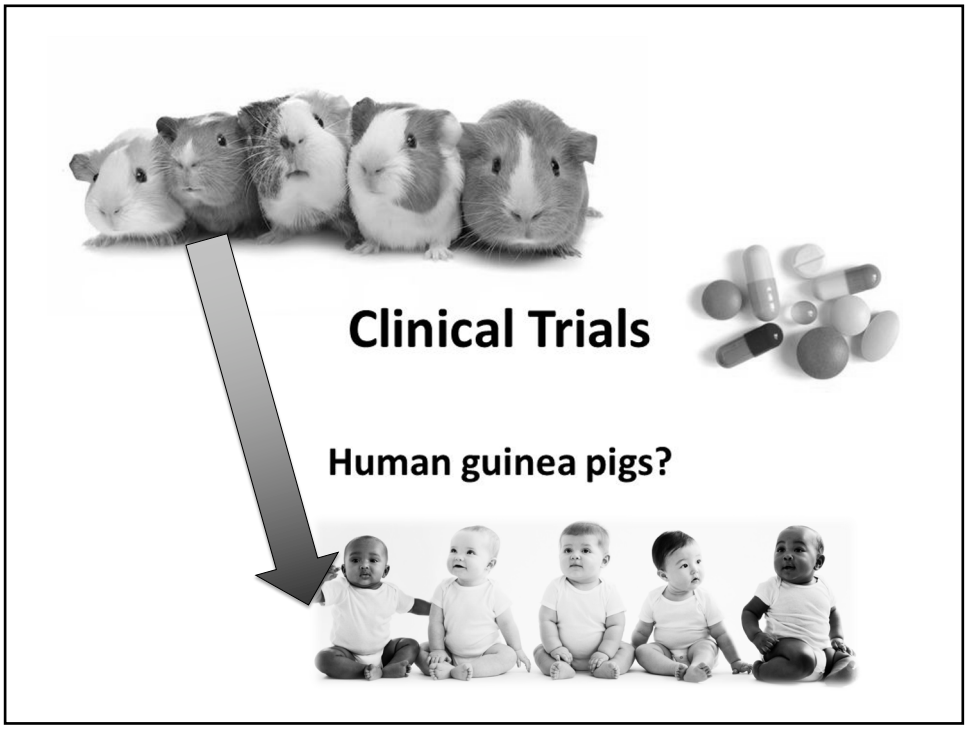

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- Extrapolating results from adult trials is not appropriate
- Research must be done *in the PICU population*

- Knox; Burkhart (2007) J Pediatr Nurs 2007, **22**(4):310-318.

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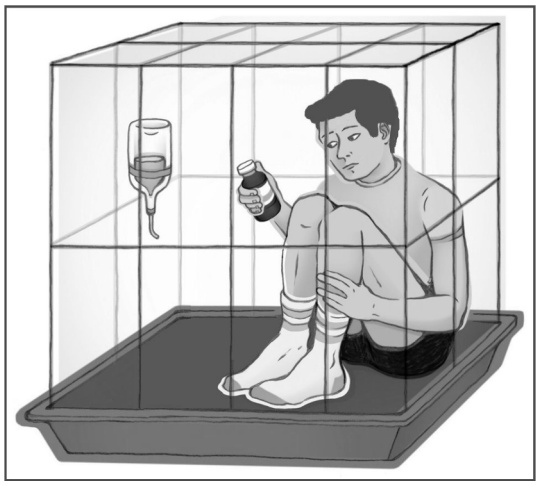
Ethical challenges in PICU research



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Ethically acceptable research can be conducted in vulnerable populations

Additional safeguards needed

Silverman (2011) *Annals of Intensive Care* 1:8

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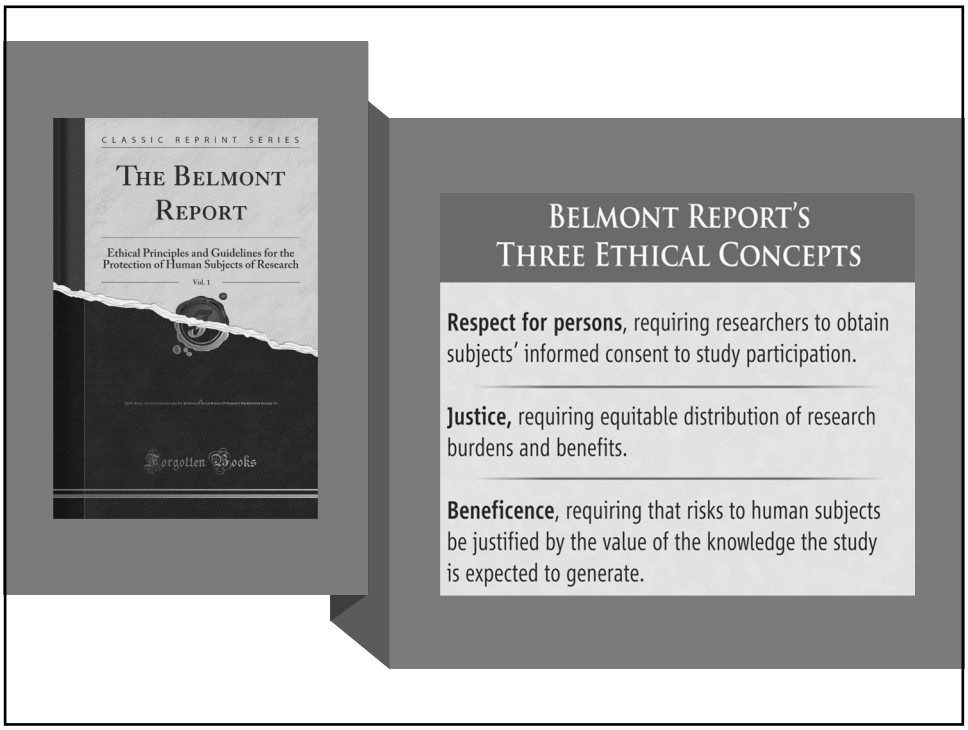
CLASSIC REPRINT SERIES
THE BELMONT REPORT
Ethical Principles and Guidelines for the Protection of Human Subjects of Research
Vol. 1
Forgotten Books
BELMONT REPORT'S THREE ETHICAL CONCEPTS
Respect for persons, requiring researchers to obtain subjects' informed consent to study participation.
Justice, requiring equitable distribution of research burdens and benefits.
Beneficence, requiring that risks to human subjects be justified by the value of the knowledge the study is expected to generate.

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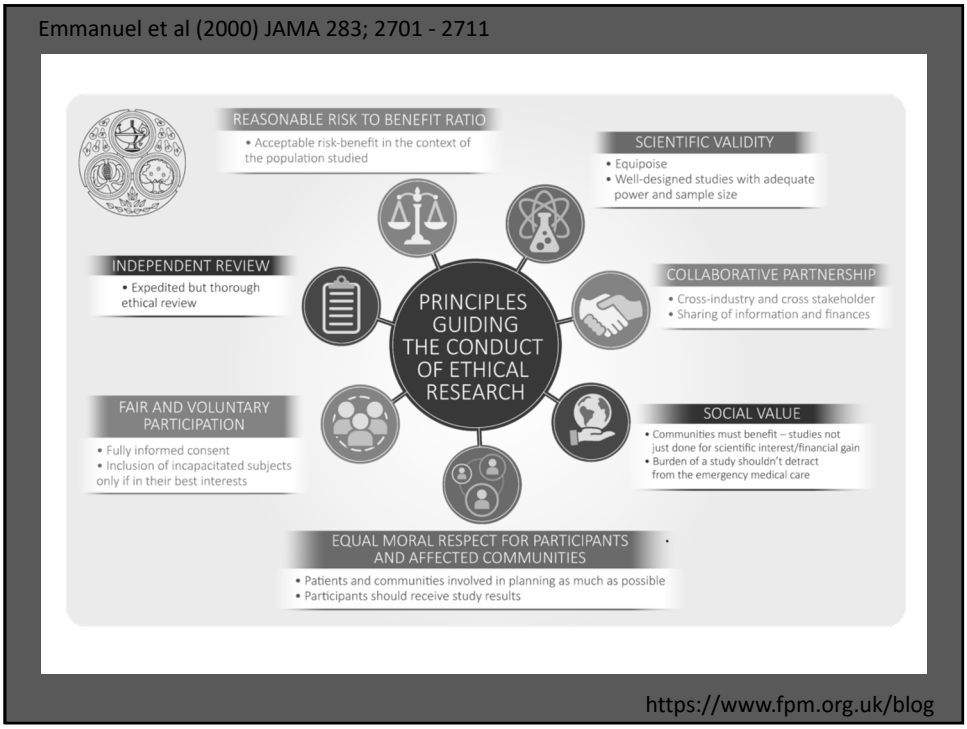
Emmanuel et al (2000) JAMA 283; 2701 - 2711
REASONABLE RISK TO BENEFIT RATIO
• Acceptable risk-benefit in the context of the population studied
SCIENTIFIC VALIDITY
• Equipoise
• Well-designed studies with adequate power and sample size
INDEPENDENT REVIEW
• Expedited but thorough ethical review
PRINCIPLES GUIDING THE CONDUCT OF ETHICAL RESEARCH
COLLABORATIVE PARTNERSHIP
• Cross-industry and cross stakeholder
• Sharing of information and finances
FAIR AND VOLUNTARY PARTICIPATION
• Fully informed consent
• Inclusion of incapacitated subjects only if in their best interests
SOCIAL VALUE
• Communities must benefit – studies not just done for scientific interest/financial gain
• Burden of a study shouldn't detract from the emergency medical care
EQUAL MORAL RESPECT FOR PARTICIPANTS AND AFFECTED COMMUNITIES
• Patients and communities involved in planning as much as possible
• Participants should receive study results
https://www.fpm.org.uk/blog

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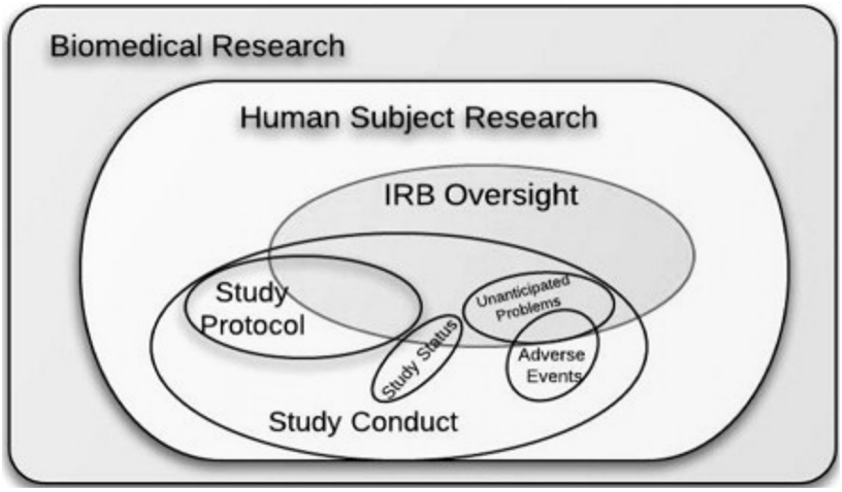
Independent ethics review



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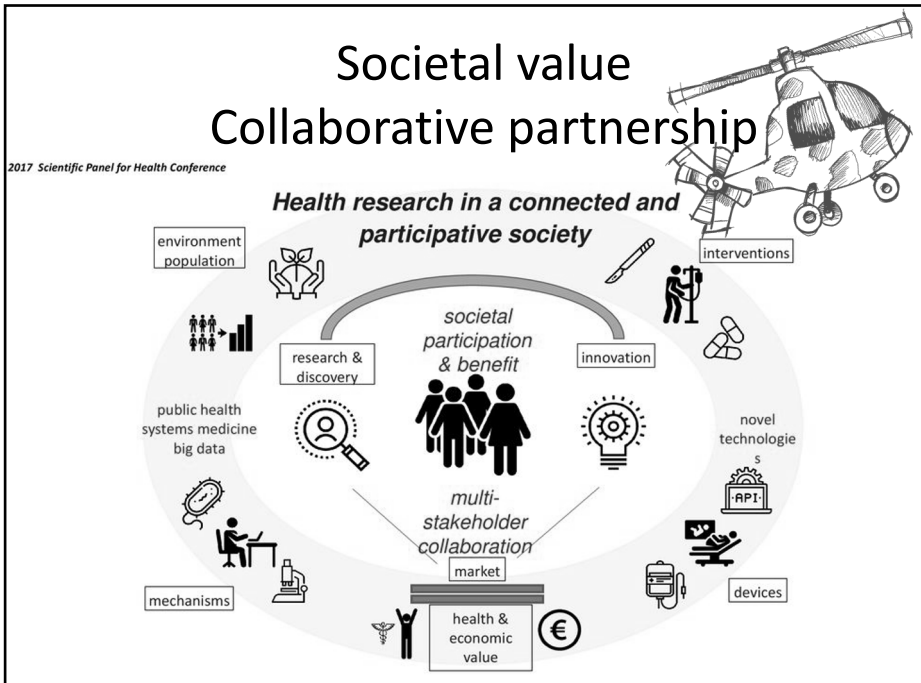
Societal value
Collaborative partnership



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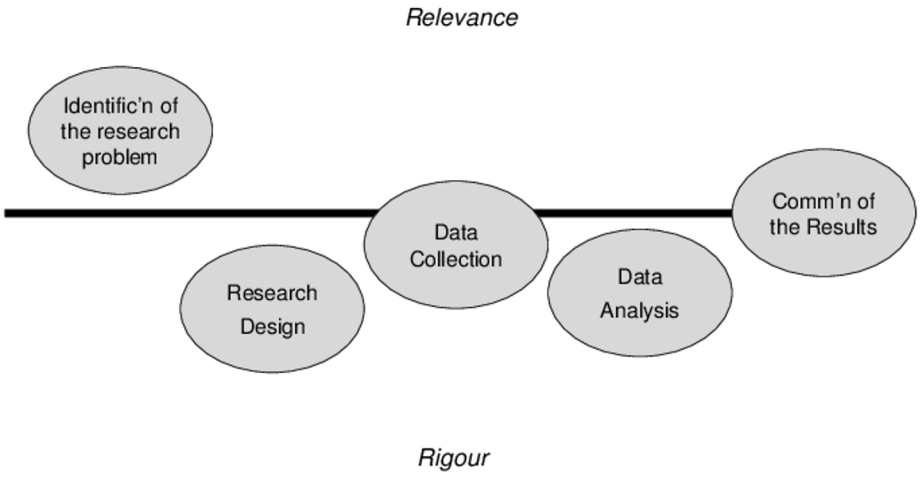
Scientific validity



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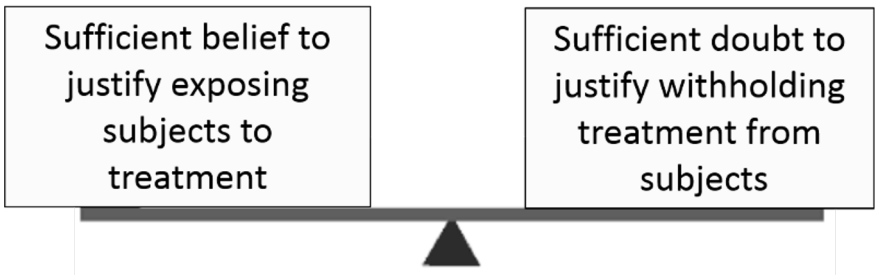
Acceptable risk : benefit



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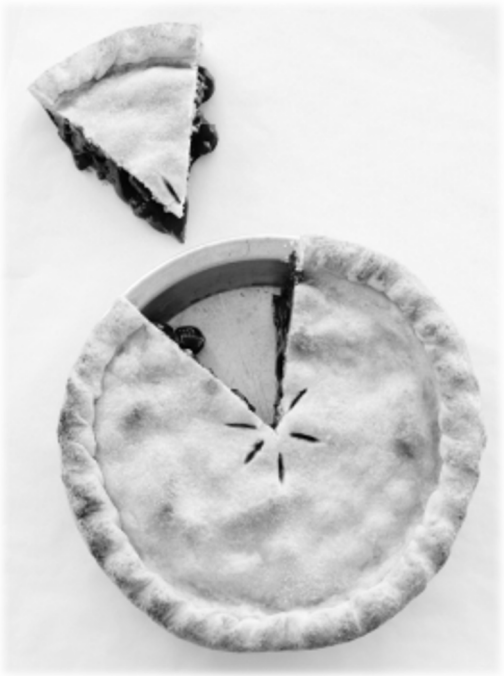
Fair selection (Justice)



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Informed Consent Process

- Having full knowledge and understanding
- Decision to Voluntarily accept/ provide permission
- Continuous/ ongoing consent

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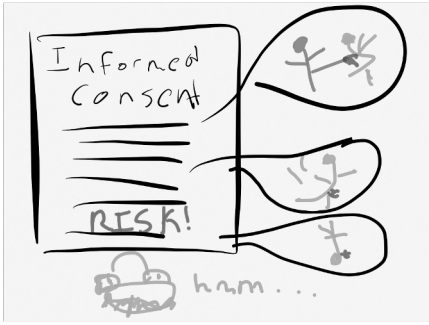
- Obtaining informed consent is particularly difficult in
  - emergency situations
  - research involving children



- Brierley; Larcher (2010) Arch Dis Child, **95**(11):863-866.

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- "When the two sets of circumstances combine, **as they do when research involves the care and treatment of critically ill infants and children**, there may by particular difficulties in satisfying the requirement to obtain voluntary informed consent"

- Brierley; Larcher (2010) Arch Dis Child, **95**(11):863-866.

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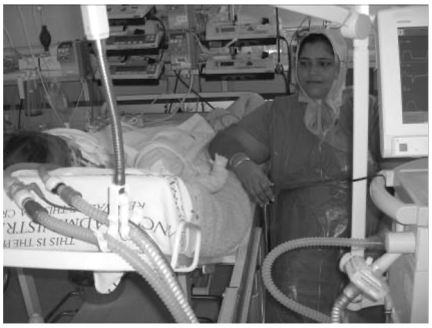
Informed consent…issues and options

- Children have no legal authority to make decisions for themselves
- Parent/s or legal guardian make the decision for the child



Zawistowski CA, Frader JE (2003). Crit Care Med, **31**(5 Suppl):S407-10.

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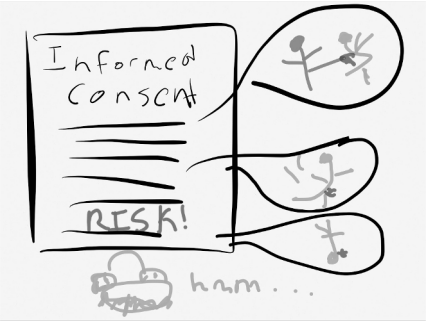
Parental consent for child participation

- Requirements for valid consent:
  - Intact decisional capacity
  - Legally competent
  - Fully informed (and understandable)
  - Voluntary – no coercion or undue influence



http://www.medicalprotection.org/southafrica/booklets/consent/introduction

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Parental consent for child participation

- Requirements for valid consent:
  - Intact decisional capacity
  - Legally competent
  - Fully informed (and understandable)
  - Voluntary – no coercion or undue influence

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Parental incapacity

- if at the time a decision needs to be made he or she is unable, temporarily or permanently and irrespective of the cause –
  - to make the decision for him or herself on the matter in question; or
  - to communicate his or her decision on that matter.
- if he or she is unable
  - to understand or retain the information relevant to the decision; or
  - to make an informed, rational decision based on that information.

  - South African Law Reform Commission, Discussion Paper 105, *Assisted Decision-making: Adults with Impaired Decision-making Capacity* (January 2004).

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- In order to make decisions for their children, the parent would need to display:
  - commitment to the child's best interests
  - adequate knowledge and information
  - emotional stability
  - the ability to make reasoned judgements
    - (Childress 1985)
- **Only a parent with decisional capacity can give truly informed consent**

- Zawistowski CA, Frader JE (2003). Crit Care Med, **31**(5 Suppl):S407-10.
- Childress (1985) **Protecting handicapped newborns.** In *Genetics and the Law: III.* Edited by Milunsky A, Annas GJ. New York: Plenum Press.

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- Problems with obtaining consent from a parent with a critically ill child
  - Impracticability (parent absent or urgent action needs to be taken, e.g. resuscitation)
  - Concern about validity of consent:
    - Severe illness of a child has significant emotional and psychological effects on parents which may **impair capacity for rational informed decision making**, including decisions relating to research
    - Levels of stress **approach panic** at times
    - May be **completely unable to assimilate study information** under the circumstances

- Brierley, Larcher (2011) J Med Ethics 2011, **37**(7):429-432.
- Shudy et al (2006)**.** Pediatrics, **118 Suppl 3**:S203-18.
- Molyneux et al (2013). PLoS One, **8**(2):e54894.

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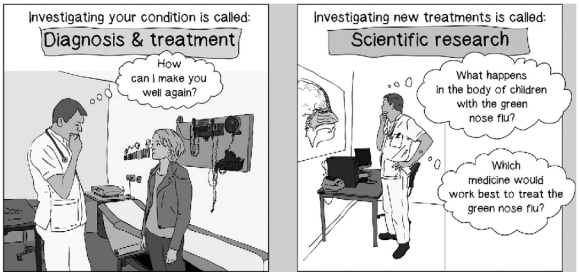
Clinical Research vs Clinical care

Clinical Research

- Generate generaliseable knowledge for future patients

Clinical care

- Provide benefit to individual patient (now)



Silverman et al 2005 Crit Care Med 33(4) 867 - 882

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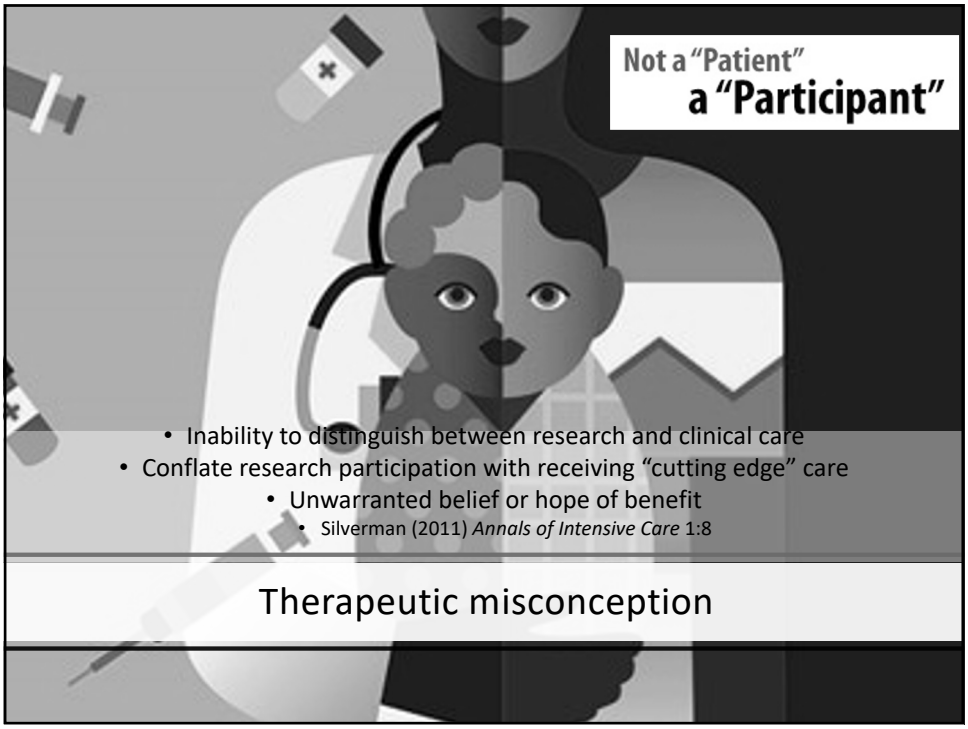

- Inability to distinguish between research and clinical care
- Conflate research participation with receiving "cutting edge" care
- Unwarranted belief or hope of benefit
- Silverman (2011) *Annals of Intensive Care* 1:8

Therapeutic misconception

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Do you ALWAYS need informed consent?

- Research in critically ill or injured children may be ethically justifiable **without full voluntary informed consent** if
  - potential to **benefit the population** by producing evidence or a better understanding of best treatment,
  - **and** where the intervention has only **minimally increased risk** in the context of the child's underlying condition.

- Brierley, Larcher (2011) J Med Ethics 2011, **37**(7):429-432.

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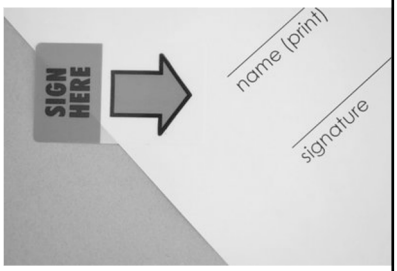
Informed consent models

- Prospective IC (>minimal risk)
  - E.g. Drug trials
- Deferred (low risk/emergency Rx)
  - E.g. paed CPR
- Waived (very low risk)
  - E.g folder reviews/audits



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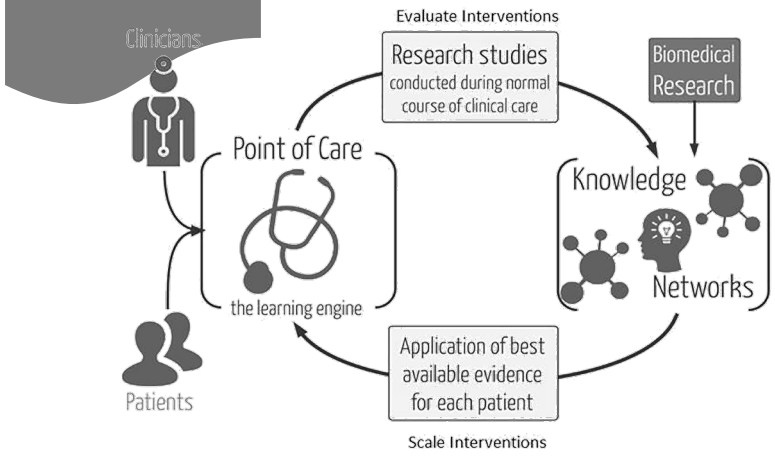
"Learning health systems"

Deans et al. Semin Pediatr Surg. 2018 Dec;27(6):375-378



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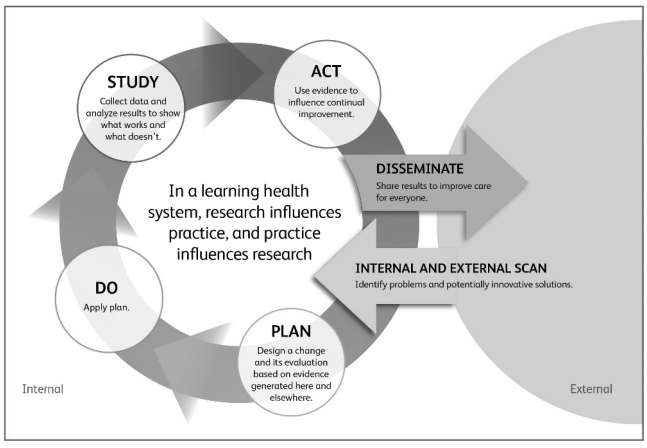

"Research needs to be woven into the fabric of our work, so we can understand the issues, move quickly to address them, and continue to deliver an exceptional care experience for our…patients.'"

https://medium.com/@KPWaResearch/learning-health-system-initiative-weaves-research-into-kaiser-permanente-washington-health-care-9afe1d4ed009

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