



# Risks in Pediatric and Obstetrics Research

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Ethical Considerations in Research

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## Note

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- The views expressed by the speaker are his own and do not represent official policy of the University of Manitoba Board of Governors, Senate, Senate Committee on Ethics and Human Research Integrity, the office of the Vice President—Research, or the five University of Manitoba Research Ethics Boards and their offices



# Objectives

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- After this session, participants should
  - Be aware of the existence, role, and risk-benefit guidance of TCPS 2 for researcher and REB evaluation of pediatric research
  - Have operational definitions for
    - Minimal Risk
    - Direct Benefits
    - Component Analysis



# TCPS 2 (2010)

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- Governing statement on protections for human research participant in Canada
- Authority derives from legal agreements (MOU) signed by institutions in order to receive funding from the three federal government research councils
- Principlism-based
  - Origins: Nuremberg Code 1947 (American Military Tribunal “Doctors’ Trial”, n=23: war crimes and crimes against humanity 7/9/7), Declaration of Helsinki, Belmont Report, TCPS 1 (1998)



# Belmont Report, 1979

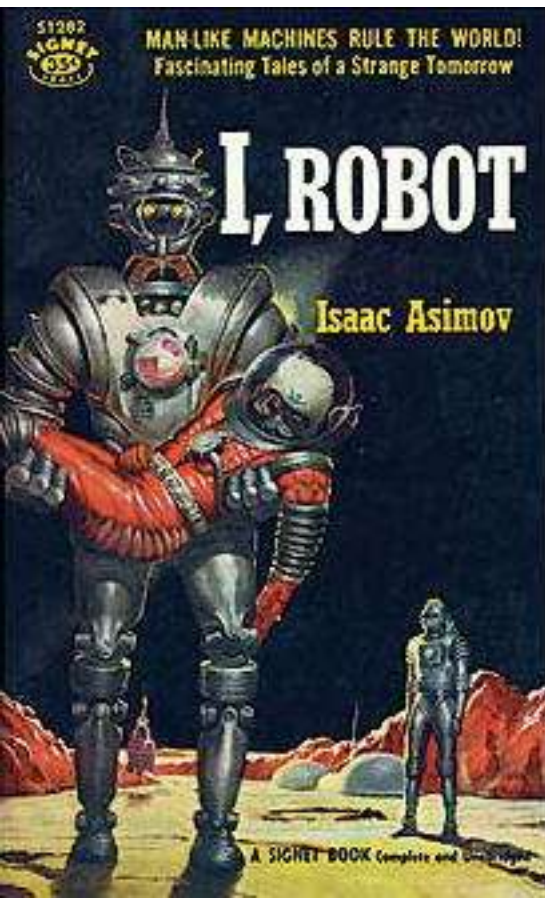
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- US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- 3 ethical principles (Principlism)
  - Respect for persons, Beneficence, Justice
- AKA (the mantra)
  - Non-maleficence, Beneficence, Autonomy, Justice

# Principles compete

- **The Three Laws of Robotics** are a set of three rules written by Isaac Asimov and later expanded upon. The rules are introduced in his 1942 short story “Runaround” although they were foreshadowed in a few earlier stories (ref Wikipedia) The Laws are:

- 1. A robot may not injure a human being or, through inaction, allow a human being to come to harm.
- 2. A robot must obey any orders given to it by human beings, except where such orders would conflict with the First Law.
- 3. A robot must protect its own existence as long as such protection does not conflict with the First or Second Law.





# TCPS 2 Ethical Principles

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- Respect for persons
  - Respect for autonomy
    - Free informed and ongoing consent
  - Protection for those with less autonomy
- Concern for welfare
  - Individuals: balance of risks and benefits
  - Communities
- Justice
  - Treat people fairly and equitably
    - Benefits and burdens
    - Inclusion criteria



# TCPS 2 Chapter 4: Fairness and equity in research ...

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- “Women have historically been inappropriately excluded from participating in some research. This exclusion of women, where unwarranted, has delayed the advancement of knowledge, denied potential benefits to women, and exposed women to harm when research findings from male-only research projects were generalized inappropriately to women, as has often been the case in clinical drug trials...”





# Research Involving Children

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- Children have varying degrees of maturity – metabolically, immunologically and cognitively – that may present important challenges for research design and the consent process, depending on the nature and complexity of the research. In addition to the vulnerability that arises from their developmental stage, children may also lack capacity to consent to participate in research (see Article 4.6). As well, physical or psychological harms a child may experience in a research setting may have long-lasting consequences.



# Research Involving Children 2

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- As a result, researchers have often avoided the inclusion of children in some research, especially in clinical trials testing new treatments, so as to eliminate any risks. Clinical trials conducted only with adults yield a generally poor understanding of the results that apply to children. As is the case with women, the inclusion of children in research advances the commitment to justice in research by improving our knowledge of, and ability to respond to, the unique needs of children throughout their development.



# TCPS 2 Chapter 4: Fairness and equity in research ...

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- Article 4.1 Taking into account the scope and objectives of their research, researchers should be inclusive in selecting participants. Researchers shall not exclude individuals from the opportunity to participate in research on the basis of attributes such as culture, language, religion, race, disability, sexual orientation, ethnicity, linguistic proficiency, gender or age, unless there is a valid reason for the exclusion.



# TCPS 2 Chapter 4: Fairness and equity in research ...

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- Article 4.2 Women shall not be inappropriately excluded from research solely on the basis of gender or sex



# TCPS 2 Chapter 4: Fairness and equity in research ...

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- Article 4.3 Women shall not be inappropriately excluded from research solely on the basis of their reproductive capacity, or because they are pregnant or breastfeeding.



## Article 4.4

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- Children shall not be inappropriately excluded from research solely on the basis of their age or developmental stage. The inclusion of children in research is subject to Article 4.6.



# Article 4.4 Application

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- Researchers should not exclude children from research unless there is a valid reason for doing so. **Participation of children in research is justifiable when the research objective cannot be achieved with adult participants only.** When considering the inclusion of children in research, researchers and REBs shall consider a child's stage of physical, physiological, psychological, and social development to ensure adequate protections for the child's welfare. Where children have not yet attained the capacity to consent for themselves to participate in research, researchers shall seek consent from an authorized third party while ascertaining the child's assent or dissent, as outlined in Chapter 3. Note that Article 4.6 equally applies to children



## Article 4.6

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- Subject to applicable legal requirements, individuals who lack capacity to consent to participate in research shall not be inappropriately excluded from research.
- Where a researcher seeks to involve individuals in research who do not have capacity to consent for themselves, the researcher shall, in addition to fulfilling the conditions in Articles 3.9 and 3.10, satisfy the REB that:





## Article 4.6, continued

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- (a) the research question can be addressed only with participants within the identified group; and
- (b) the research does not expose the participants to more than minimal risk without the prospect of direct benefits for them; or
- (c) where the research entails only minimal risk, it should at least have the prospect of providing benefits to participants or to a group



# Protecting Participants From Unethical Research

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- A series of defenses
  - PI, the first line of defense
  - REB, the second line
  - Autonomy, the last line of defense
    - free, informed (and advised) ongoing consent
- Without autonomy
  - PI, the first line of defense
  - REB, the second line
  - Authorized third party consent ± assent, the last line of defense, is not as powerful a protection as autonomy



# Is it ethical to

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- expose children to greater than minimal risk if the knowledge gained would be extremely beneficial to others?
  - of major medical or scientific significance



## Article 4.6, continued

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- (a) the research question can be addressed only with participants within the identified group; and
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# About Risk (TCPS 2 Ch. 2)

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- Risk is a function of the **magnitude** or seriousness of the harm, **and** the **probability** that it will occur, whether to participants or to third parties (as outlined below).



# What is Minimal Risk?

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- “For the purposes of this Policy, ‘minimal risk’ research is defined as research in which the **probability and magnitude** of possible harms implied by participation in the research is no greater than those encountered by participants in those aspects of their everyday life that relate to the research.”
- Eligible for REB delegated review (Article 2.9)



# Allowable Risks of Research

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- USA

- 21 CFR 50, Subpart D—Additional Safeguards for Children in Clinical Investigations
  - Minimal risk (21 CFR 50.51)
  - Minor increase over minimal risk (21 CFR 50.53)
  - Risks justified by anticipated direct benefits to the child and are as favorable as any available alternatives
- Definition of minimal risk
  - “the **probability and magnitude** of harm or discomfort anticipated in the 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.” (21 CFR 56.102i)



# Allowable Risks of Research 2

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- Council for International Organizations of Medical Sciences (CIOMS)
  - Where there is an overriding scientific or medical rationale for such an increase and
  - Where an REB has provided its approval
    - 4 criteria
- Council of Europe
  - “any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk”





# Framework for Systematic Evaluation of Research Risks

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- Developed by group of Dr. David Wendler, Department of Bioethics, NIH Clinical Centre (Head of the Unit on Vulnerable Populations)
- See Rid et al, JAMA 2010 for explanation of SERR



# Issues with probability and magnitude

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- Comparing likelihoods
  - Judgment of quality of data
  - Judgment of equivalence
    - Is 25 per 100,000 equivalent to 20 per 100,000
    - 1/4,000 versus 1/5,000
- Comparing magnitudes
  - 7 category scale eventually developed
  - Classification influenced by 7 factors

# Table. Magnitude of Harms Scale With Illustrative Examples<sup>a</sup>.

**Table. Magnitude of Harms Scale With Illustrative Examples<sup>a</sup>**

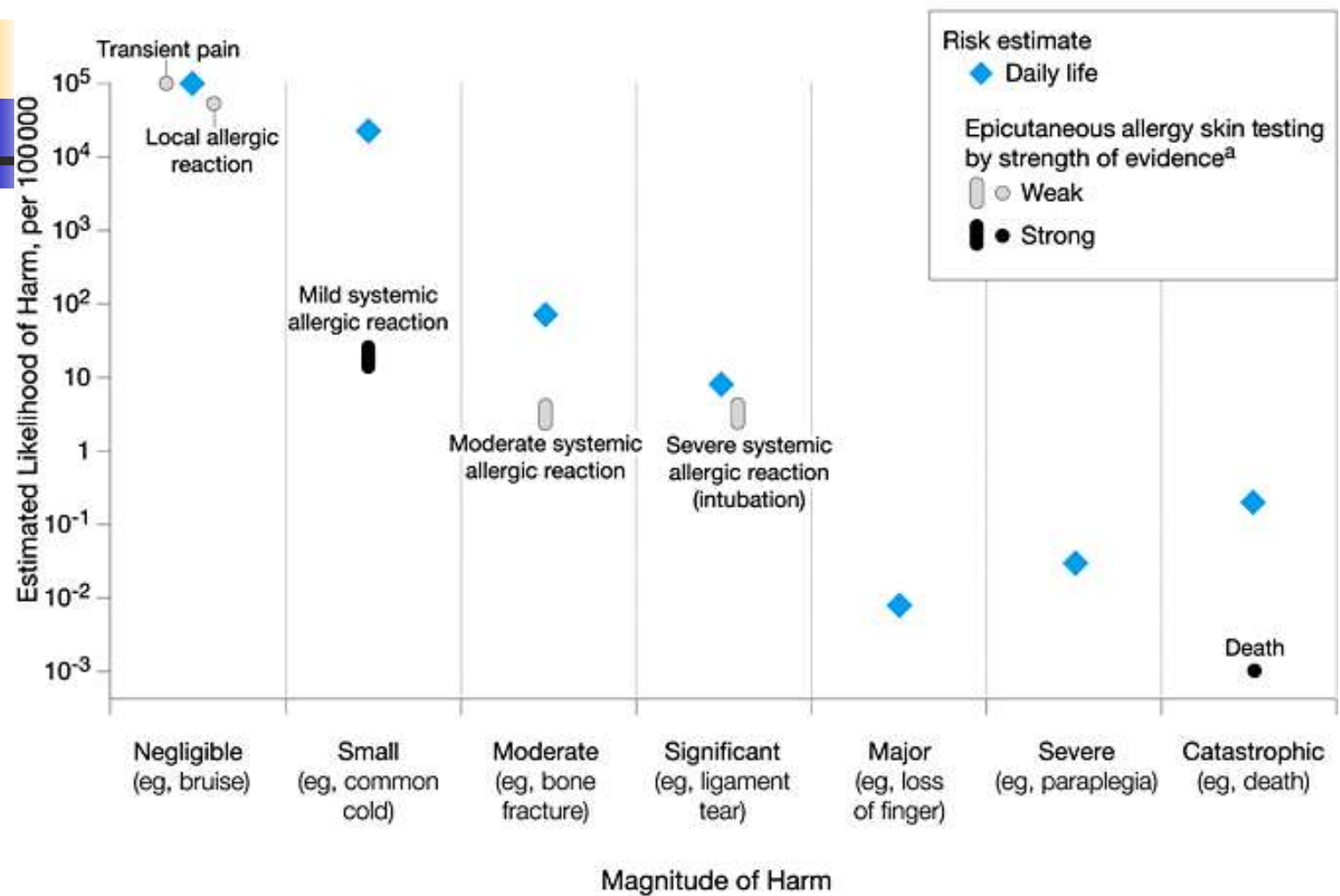
Examples of Harms by Magnitude	Examples and Details of Harms		
	Effect/Disability	Treatment	Duration
<b>Negligible</b>			
Mid nausea	Discomfort, can interfere with ability to pursue some minor life goals (eg, eat)	May require medication	Minutes to several hours
Skin bruise or abrasion	Mild pain	Can require cleaning and coverage	Bruise or abrasion pain, minutes to several hours; healing, <10 days
<b>Small</b>			
Headache	Moderate pain, inability to pursue some minor (eg, 1 day hiking) and some major (eg, attend school) life goals	May require medication, rest, or both	Hours
Common cold	Discomfort, inability to pursue some minor (eg, visit museum) and some major (eg, work) life goals	May require medication, rest, or both	Several days
<b>Moderate</b>			
Uncomplicated bone fracture	Moderate pain, inability to pursue some minor life goals (eg, play sports)	Requires some medication and wearing a cast	Fracture pain, hours; recovery, weeks to months
Moderate insomnia for 1 month	Annoying experience, inability to pursue some minor (eg, meet friends) and some major (eg, work) life goals	Can require lifestyle changes and medication	Weeks intermittently
<b>Significant</b>			
Ligament tear of knee with permanent instability	Moderate pain that interferes with pursuing some minor life goals (eg, exercise); permanent instability precludes vigorous exercise and requires adaptation (eg, seek new types of exercise)	Requires surgery and rehabilitation	Tear, hours to days; rehabilitation time following surgery, weeks to months
Intensive care for several weeks (assuming no sequelae)	Often intense pain and physical exhaustion, inability to perform activities of daily life and to pursue essentially all minor and major life goals		Weeks
<b>Major</b>			
Psychotic episode	Terrifying distortions of reality, changes in personality that undermine relationships, precludes performance of daily life activities and many minor and major life goals	Requires medication, can require adaptation of some major life goals (eg, work)	Weeks to a month
Rheumatoid arthritis	Daily episodes of serious pain and permanent stiffness, unable to pursue some minor (eg, vacation) and some major (eg, work) life goals, sometimes unable to perform some activities of daily life	Requires aggressive medication, physiotherapy, requires major adaptation	Years
Loss of finger	Destabilizes hand, interferes with many activities of daily life, interferes with some minor and major life goals, requires adaptation, distressing transition period	None	Permanent
<b>Severe</b>			
Major depression	Depressive episodes with hopelessness/worthlessness, loss of interest in usual activities, insomnia, and eating, can preclude performance of some daily life activities and some minor and major life goals, often baseline anxiety and low mood	Requires medication; requires adaptation of some major life goals (eg, relationships)	Decades
Paraplegia	Inability to perform some activities of daily life, inability to pursue many minor (eg, hiking) and some major (eg, having children) life goals, often distressing transition period	Requires daily support and close clinical observation, requires major adaptation	Permanent
<b>Catastrophic</b>			
Severe dementia	Precludes performance of daily life activities and essentially all minor and major life goals, adaptation impossible, distressing	Requires full-time care	Permanent
<b>Death</b>			

<sup>a</sup>Important factors that influence the magnitude of a harm include associated experience (ie, sensory impact, nuisance, uncomfortable, distressing, suffering), burden of efforts to mitigate condition (low/moderate/high, weeks/months/years/permanent), inability to perform activities of daily life (partial/complete), inability to realize life goals (minor/major life goals, some goals in one category/some goals in both categories/all goals in one or both categories), duration (minutes/hours/days/weeks to months/years/permanent, intermittent/continuous), potential to adapt to new (realist) condition (minor/moderate/major adaptation, impossible to adapt), and burden of adaptation period (low/moderate/high). The examples were chosen based on input from 43 international experts in clinical research, research ethics, and risk assessment. The examples have an illustrative function to show how the harm scale might be applied. Factors not mentioned in the description of an example are considered not relevant. It is assumed that the given harms occur in otherwise healthy, normal, average individuals (adults), which implies that the selected examples might fall into a different category on the harm scale in individuals who are not healthy, normal, or adults. No examples of economic or social harms are given due to their strong context dependence.

Rid, A. et al. JAMA 2010;304:1472-1479

**JAMA**

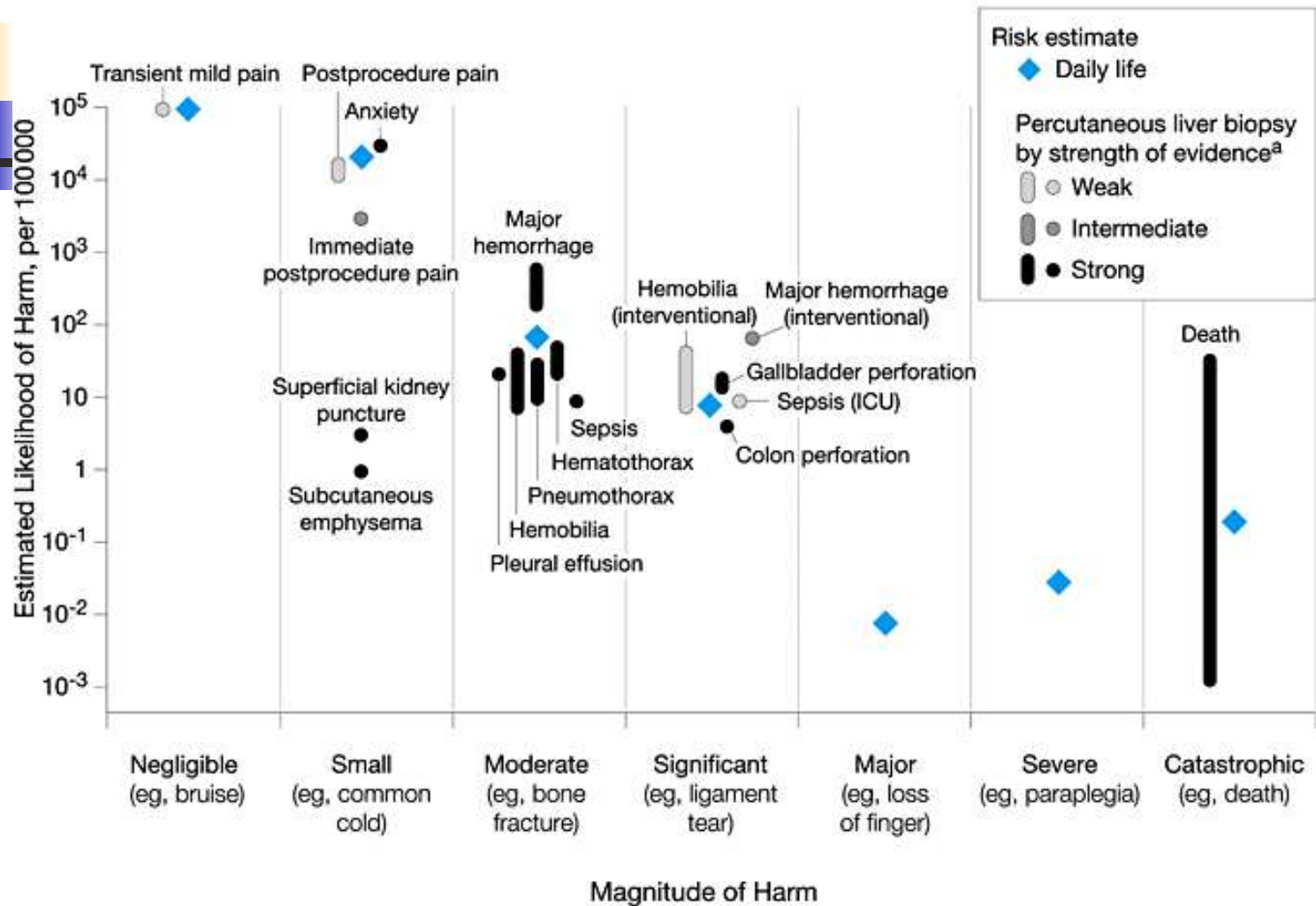
**Figure 1. Comparison of the Risks of Daily Life With the Risks of Epicutaneous Allergy Skin Testing**



Rid, A. et al. JAMA 2010;304:1472-1479

**JAMA**

**Figure 2. Comparison of the Risks of Daily Life With the Risks of Percutaneous Liver Biopsy**



Rid, A. et al. JAMA 2010;304:1472-1479

**JAMA**



# Direct! Benefits

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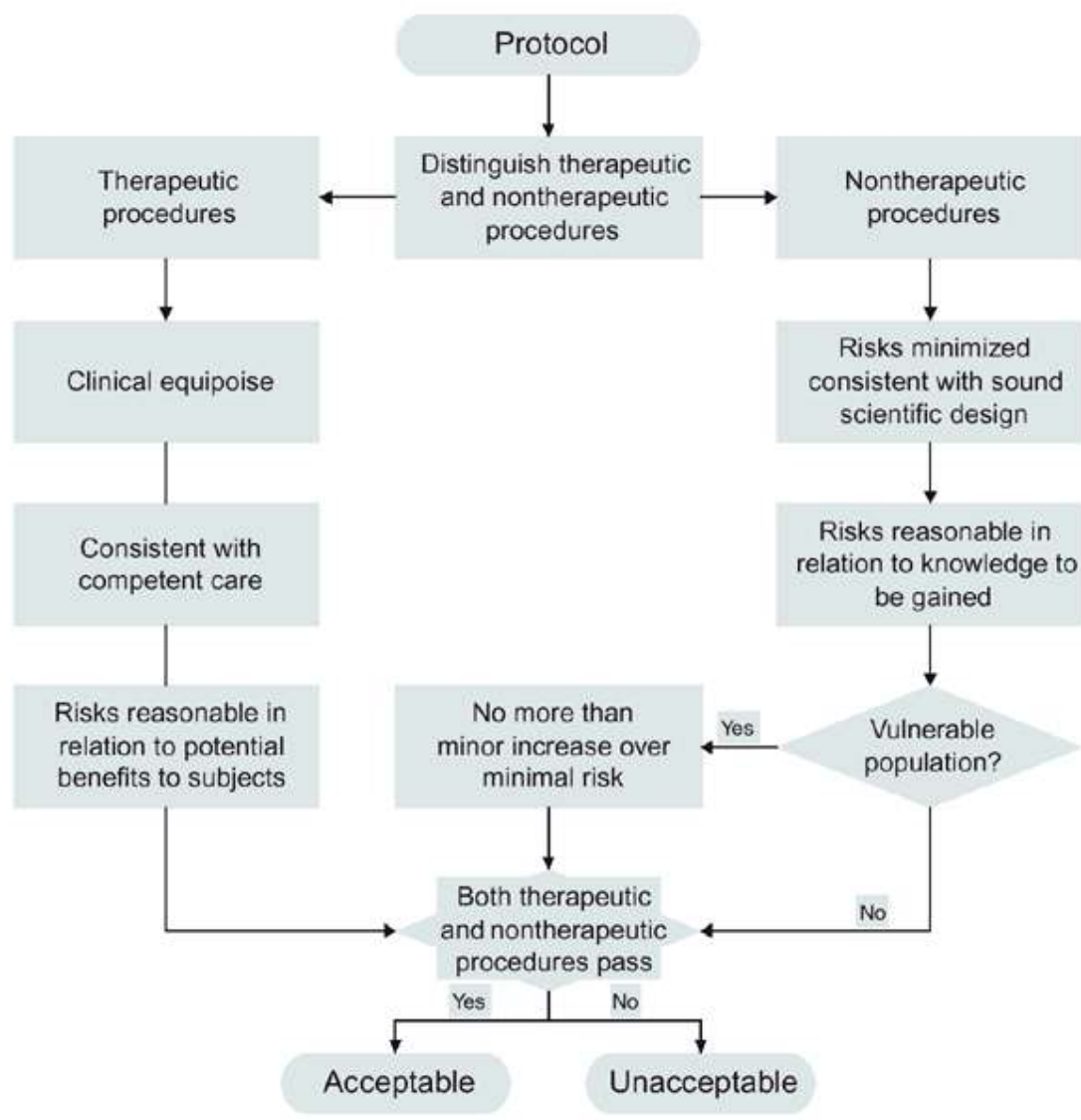
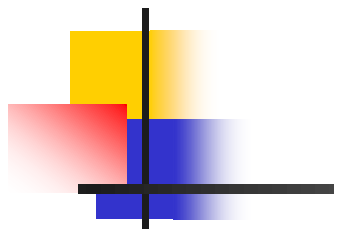
- As in the definition of minimal risk, benefit assessment should include **probability** and **magnitude**
- The Belmont Report, 1979
  - US National Commission concerned that potential benefits in the distant future are too speculative to justify exposing vulnerable subjects
- King, J Law Med Ethics, 2000
  - “Benefits arising from receiving the intervention being studied”
  - Avoids the “fallacy of the package deal”
  - But what about a biopsy?



# Component Analysis (Weijer, 2004)

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- US Institute of Medicine 2004
  - The potential benefits from one component of the research should not be held to offset or justify the risks presented by another







# Wendler's modification of Direct Benefits

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- Friedman et al, Bioethics 2010
- Define direct benefits as: the clinical benefits that result from the interventions that are needed for scientific reasons to test the experimental intervention
- Then REB can do its risk-benefit assessment of this restricted package



# Implementing Wendler's modification of Direct Benefits

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- REBs can choose to do so, unless under regulatory rules that literally specifies component analysis for minimal risk for each interventional procedure
- No such specification limiting REB definition of direct benefits in TCPS 2
  - “the **research** does not expose the participants to more than minimal risk without the prospect of direct benefits for them”



Thank you

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