

Refining the Declaration of Helsinki's additional protections for research in children

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ANNA WESTRA, MA, MD, PHD

**JULIANA CHILDREN'S HOSPITAL, THE HAGUE/
DEP. OF MEDICAL ETHICS, ERASMUS MC, ROTTERDAM**

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Helsinki's Paragraph 27

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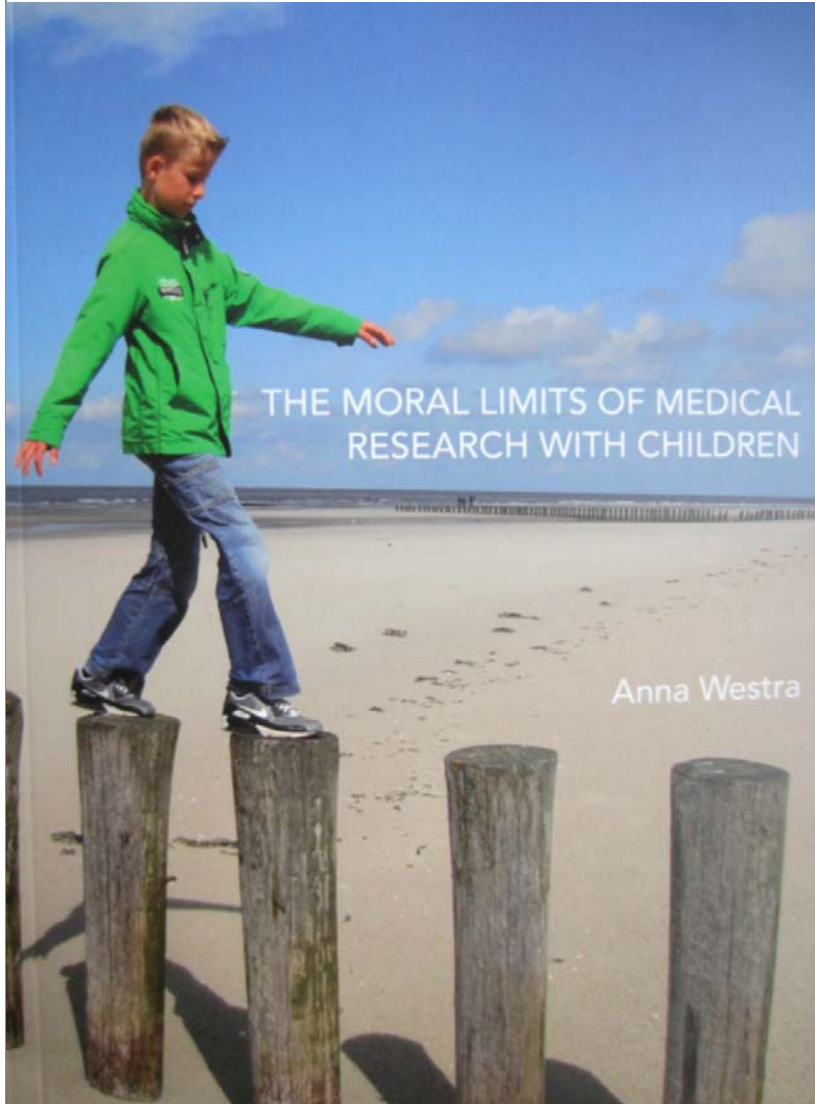
- For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative.
- These individuals must not be included in a research study that has **no likelihood of benefit** for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only **minimal risk and minimal burden**.

Presentation

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I will argue

1. Why I endorse the focus on protection of this group of subjects, as well as the central role of the requirement of minimal risk and burden
2. That Paragraph 27 however is not very subtle, and how the two issues that deserve most attention could be dealt with
3. Why now, time has come for refinement



THE MORAL LIMITS OF MEDICAL
RESEARCH WITH CHILDREN

Anna Westra



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Background: the ethical dilemma

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- Research with children is necessary to improve prevention and medical care for children as a group
- Not all necessary data can be provided by studies that are likely to benefit the subjects themselves
- Risks and burdens that are not compensated for by potential benefits are faced purely for research reasons: the so called 'net' research risks and burdens
- Children cannot consent to facing these risks/burdens

Ways of dealing with this dilemma

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Focus on the importance of the research

1. No additional protective measures at all
2. Only some basic additional safeguards: benefit for the group; not possible with competent adults; risks and burdens as low as possible (European CTD)

Focus on protection: such research only acceptable if

1. No risks or burdens at all
2. Minimal risk and burden (**Helsinki**; European Convention)
3. Subjects that are healthy: Minimal risk and burden;
Subjects with the disease: A minor increase over minimal (US)

Helsinki's choice seems best

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- Focus on protection seems valid:
 - Proxy consent does not have the same moral value as informed consent (altruism seems to be rather personal)
 - Risk of using children merely as a means
- Minimal risk and burden requirement seems valid:
 - No risk and burden at all, is not necessary¹
 - No valid grounds for allowing a minor increase over minimal risk for all subjects with the disease under study²

1. Wendler D. The ethics of pediatric research, 2010; 2. Westra AE et al. Regulating “Higher Risk, No Direct Benefit” Studies with Children: Challenging the US Federal Regulations. In: Schildmann J et al, eds. Human Medical Research, 2012

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Paragraph 27: not very subtle

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- Issue 1:
When distinguishing between *studies* with and without potential benefit, the 'net' research risks and burdens often cannot accurately be identified
- Issue 2:
Not all children need the same level of protection

Research in children versus in adults

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- More complex ethical review process:
The net research risks and burdens should be minimal
 - More need to identify the net research risks and burdens
- More complex study designs:
 - More often combined with medical care
 - More often a mixture of components
 - More difficult to identify the net risks and burdens

Example study (ADHD)

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1. Visits to hospital (30x)
2. Medication washout
3. Treatment with the new drug (initial 12 wks)
4. Treatment with the new drug after good response, or placebo treatment (6 or 9 months)
5. Blood draw (6x); ECG (6x); physical examination including pubertal staging (5x)



Study-level approach is inadequate

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- Paragraph 27 distinguishes between **studies** with/without potential benefit
- To adequately identify the net research risks/burdens, **study components** require separate moral evaluation
 - Procedures that are performed pure for research reasons:
 - risks and burdens should be minimal
 - Procedures that have potential benefits for the subjects (i.e., those that are combined with medical care):
 - risk/benefit profile should be acceptable

Recommendation 1

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- To stimulate research ethics committees to more accurately identify those risks and burdens that the research subjects have to undergo purely for research reasons and that thus have to be minimal,
- by distinguishing between research **procedures** with and without potential benefit instead of between **studies** with and without potential benefit

Westra AE et al. The merits of procedure-level risk-benefit assessment. IRB 2011;33(5):7-13.

Paragraph 27: not very subtle

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- Issue 1:

When distinguishing between *studies* with and without potential benefit, the 'net' research risks and burdens often cannot accurately be identified

- Issue 2:

Not all children need the same level of protection

Not all children need equal level of protection

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- With increasing age, children are increasingly capable
 - of understanding the proposed study
 - of making their own informed decisions
- If a child is generally capable of doing so, it can be asked for its assent
- If a child can give assent: less need for protection (although still extra protection as compared to adults)

Helsinki's Paragraph 28

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- When a potential research subject who is deemed incompetent is able to give **assent** to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative.
- The potential subject's dissent should be respected

Recommendation 2

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To allow for **exceptions** to the minimal risk and burden requirement in cases of studies that involve children who can give their **assent** to participate in the study; and that involve at most **a minor increase over minimal risk**

Paragraph 27 with revisions (1)

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- For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative.
- These individuals must not be included **in research procedures that have no likelihood of direct benefit** for them unless **these procedures are essential parts of a research study that is** intended to promote the health of the population represented by the potential subject and that cannot instead be performed with competent persons, **and all together, these procedures entail only minimal risk and burden.**

Paragraph 27 with revisions (2)

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- The minimal risk and burden requirement does not apply to studies involving subjects who are able to give assent and involving at most a minor increase over minimal risk and/or burden.

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Refining paragraph 27: why now?

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- Currently, many drugs prescribed for children have not been proven safe and effective for them
- Extrapolation from adult studies: often inappropriate
- Need for trials has been increasingly recognised: US and EU have taken stimulative measures (financially)
- These measures have made optimizing the system that protects the subjects all the more pressing

