

# **Biopsy of Diffuse Intrinsic Pontine Glioma for Research: Ethical Issues**

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## **Preface**

- Although I will allude to regulatory context, we are not asked to make a regulatory determination
- My comments imply no final judgment about whether biopsies of diffuse intrinsic pontine gliomas (DIPGs) for research are ethical
- I am not a neuro-oncologist

**Question:**

**Is biopsy of DIPG in children for  
research purposes ethical?**

**But first:**

**Would biopsy of DIPG  
for research purposes  
be ethical in consenting adults?**

## Criteria for Ethical Research

1. Social value
2. Scientific validity
3. Fair subject selection
4. Favorable risk-benefit balance
5. Independent review
6. Informed consent
7. Respect for enrolled participants

JAMA 283:2701, 2000

## Favorable Risk-Benefit Balance

- “...additional evaluation is necessary for any clinical research that presents no potential benefits to individual subjects...or when the risks outweigh the potential benefits to individual subjects. This determination...assesses whether the societal benefits in terms of knowledge justify the excess risks to individual subjects.”

JAMA 283:2701, 2000

## **Favorable Risk-Benefit Balance**

- “In order to approve research covered by these regulations the IRB shall determine that ...risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, *and the importance of the knowledge that may be expected to result*”

21 CFR 56.111(a)(2)

## **How Much Net Risk is Permissible in Research with Consenting Adults?**

- According to the Declaration of Helsinki:
  - “In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests” (Paragraph 6)
  - “The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects” (Paragraph 31)

Declaration of Helsinki, 6<sup>th</sup> Revision, 2008

## **How Much Net Risk is Permissible in Research with Consenting Adults?**

- Belmont: “When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation)”
- Nuremberg: “No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects” (Article 5)

## **What Do We Need to Know to Make This Risk-Benefit Determination?**

- Nature, probability & magnitude of:
  - Risks of biopsy to study participants
  - Benefits of biopsy to study participants
  - Knowledge benefits of proposed study
    - Social value of research question
    - Likelihood that proposed research will realize that social value
- But: integrating these data inevitably requires judgment

## **Special Considerations in Pediatric Research**

- Children's participation in research requires proxy (typically parent) permission, not autonomous consent
- Two especially difficult questions follow:
  - How much risk, not justified by a prospect of benefit, can parents agree to on behalf of their child?
  - What role should children play in decisions about their research participation?

## **How Much Net Risk is Permissible in Research with Children?**

- Parents' authority to agree to risks on behalf of their children is more constrained than that of adults to consent for themselves
  - Parents are fiduciaries for their children and must put their children's best interests first when making decisions for them
  - Altruism (the presumed basis for adults' consent to risky, nonbeneficial research) is something one can give of oneself, but not something one can give of another

## **How Much Net Risk is Permissible in Research with Children?**

- Possible thresholds of permissible risk, not justified by prospect of benefit, in pediatric research include:
  - Always impermissible
  - No-discernible-risk/minimal risk
  - Minor increment over minimal risk
  - More than a minor increment over minimal risk

## **Pediatric Research not Justified by Benefit to Child is Impermissible**

- Paul Ramsey
  - A parent owes “the individual child the highest fiduciary loyalty we know how to perform. [It would contradict this loyalty] to consent to submit a child to procedures believed not to be in the child’s behalf. Parenthood was not made for this.”
  - Objection grounded in central role of autonomous consent in legitimizing entry into activity that involves risk for the sake of others

The Patient as Person, Yale U. Press, 1970, p. 40

## No-Discernible-Risk Position

- Richard McCormick
  - “when a particular experiment would involve no discernible risks, no notable pain, no notable inconvenience, and yet hold promise of considerable benefit, should not the child be constructed to wish this...because he ought to?”
  - McCormick notes, as an example, that venipuncture *might* be judged to satisfy these conditions
  - Analogous, but not identical, to minimal-risk threshold

Perspect Biol Med 18:2, 1974, p. 14

## 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 50.3(k)

## Minor Increment Over Minimal Risk Position

- Council of International Organizations of Medical Science
  - “...the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. *Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them.*”

CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2002 ([http://www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm))

## Minor Increment Over Minimal Risk Position

- CIOMS (cont'd)
  - “There is no internationally agreed, precise definition of a ‘slight or minor increase’ above the risks associated with routine medical or psychological examination of such persons. Its meaning is inferred from what various ethical review committees have reported as having met the standard. Examples include additional lumbar punctures or bone-marrow aspirations in children with conditions for which such examinations are regularly indicated in clinical practice.”

CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2002 ([http://www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm))

## Minor Increment Over Minimal Risk Position

- National Commission:
  - “a minor increase in risk would be permissible in order to attain substantial future benefits to children other than the subject. ‘Minor increase’ refers to a risk which, while it goes beyond the narrow boundaries of minimal risk...*poses no significant threat to the child’s health or well-being.*”
  - But note: Two of eleven Commissioners dissented from this position

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, “Research Involving Children,” 1977, p. 139

## More than a Minor Increment over Minimal Risk Position

- National Commission
  - Research exceeding the minor increment threshold may be approved under limited circumstances
    - IRB determines “that the research presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children”
    - The research is approved by a national ethical advisory board and the Secretary of the responsible federal department

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, “Research Involving Children,” 1977, p. 10

## **Justification for this Exception**

“the Commission acknowledged that exceptional situations may arise in which considerable dangers to children or to the community at large might be avoided or prevented by exposing children to research attended by more than minimal risk”

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, “Research Involving Children,” 1977, p. 140

## **Justification for this Exception**

“The ethical principles at stake are the moral obligation to protect the community or to come to the aid of certain sufferers within it and the moral prohibition against using unconsenting persons, at considerable risk to their well-being, for the promotion of the common good. These principles are of such moment and their observance so basic to a just and humane society that any debate about their application should be held at the most public level of discourse”

- i.e., procedural, not substantive, approach

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, “Research Involving Children,” 1977, p. 140-1

## Regulatory Framework

- 21 CFR § 50.51: Clinical investigations not involving greater than minimal risk
- § 50.52: Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects

## Regulatory Framework

- § 50.53: Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition
  - Minor increase over minimal risk
  - Experiences reasonably commensurate with those inherent in subjects' actual or expected situations
  - Generalizable knowledge “of vital importance for the understanding or amelioration of the subjects' disorder or condition”

## Regulatory Framework

- § 50.54: IRBs can refer protocols that they believe are not approvable under § 50.51-3 for federal review
  - FDA Commissioner must determine, after consultation with panel of experts and opportunity for public review, either that the research is approvable under § 50.51-3, or that it:
    - presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
    - will be conducted in accordance with sound ethical principles; and
    - includes adequate provisions for soliciting assent & parental permission

## Ethical Arguments for Permitting Research Involving Significant Risk

- Value of knowledge: “We owe it to current and future patients to biopsy brain stem tumours, not only to help optimize their own treatment, but also to help understand these tumours for the future”
- Affected children’s interests, broadly conceived: “it must be in a child’s social interests to have suitable medical treatments for herself and her fellows” (Harris and Wilkinson)
  - A regime that permits such procedures for research is in the interests of children, compared with one that does not

## **Other Considerations, if Approved**

- How will optimal parental understanding & decision-making be ensured?
- What role will children play in decisions about participation?
- Who will pay for biopsies & associated care?
- What compensation will be available if a research-related injury occurs?

## **Summary**

- Contemporary ethics and regulation accept inclusion of children in research that imposes a minor increment over minimal risk, not justified by prospect of direct benefit, for studies related to child's condition
  - National Commission and federal regulations recognize possibility of exceptions for higher-risk research
  - But offer no substantive guidance for deciding when such exceptions are appropriate
  - So...we are in new territory here