Is there a prospect of direct benefit in first-in-human paediatric gene therapy trials? An ethical analysis.

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Recent developments in gene transfer and gene editing provide promising avenues for the treatment of monogenetic paediatric diseases. Some of these therapies might soon be tested in first-in-human (FIH) trials. Review of FIH paediatric gene therapy trials is complex and involves many steps in which research ethics committees (RECs) need to make choices and (value) judgements. In **research involving minors**, many regulations stipulate the need to provide a **prospect of direct** benefit if research poses more than minimal risk. However, it is not clearcut what the risks and benefits of FIH paediatric gene therapy trials are and how these should be evaluated. Here we offer an analysis of different steps necessary in review of paediatric trials to clarify decisions and aid RECs in review.

Evaluation of paediatric first in human gene therapy trials

1. Do first-in-human paediatric gene therapy trials pose more than minimal risk?

Relative interpretation	Absolute interpretation
Risks are compared to risks encountered in the daily life or normal clinical practice of *proposed research subjects*	Risks are compared to risks encountered in daily life during routine examinations by an *average, healthy child*

2. Which benefits can justify research risks in minors?

Direct benefits

A direct benefit is considered the (potential) response of or in the patient to the intervention itself

- What is a beneficial and relevant outcome?
- What are suitable outcome measures?

Collateral benefits

Another benefit gained from participation in a trial, not resulting from administration of the intervention such as increased medical attention

Aspirational benefits

The benefit that arises as a result of the study, such as the knowledge gained from the research that can lead to the development of new therapies and improve health outcomes

3. Is there a **prospect** of direct benefit in FIH trials?

3a. How to interpret ‘prospect’?

- Prospect of benefit concerns any probability, however small
- Prospect is a higher, and more defined probability
- When a reasonable person considers nature, magnitude and likelihood of direct benefit sufficient

3b. What types of evidence substantiate claims of effectiveness?

Mechanical evidence

Evidence *how* an intervention works

Sources of mechanistic evidence:
- In vitro studies
- In vivo animal studies
- Simulation
- Observational studies
- Clinical studies

Statistical evidence

Evidence for the *likelihood* that an intervention works

Sources of statistical evidence:
- Clinical studies

Statistical evidence is generally absent in FIH paediatric trials. Reference class drugs targeting a similar mechanism might provide some statistical evidence.

The review of FIH paediatric trials is inherently complex. We show that key concepts such as "minimal risk" and "prospect of direct benefit" can be variably interpreted, which can lead to discrepancies in what is deemed acceptable. The overview presented here shows that it is important for RECs to consider *how* prospect is interpreted, and (if so) in which context (predominantly) mechanical evidence can be sufficient to substantiate claims of effectiveness and prospect of direct benefit. Based on mechanistic evidence it is difficult to provide an estimate of a size of an effect: while preclinical data can provide evidence that acting upon a specific pathway can provide a benefit, little can be said about the likelihood of it doing so.

Clarity in how key concepts are defined and applied is essential in the review process. The analysis of steps shown here can function as a guide for RECs to adopt when reviewing FIH paediatric gene therapy trials. This can increase transparency on choices and interpretations of relevant concepts that are made at every step in review of research.

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