

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



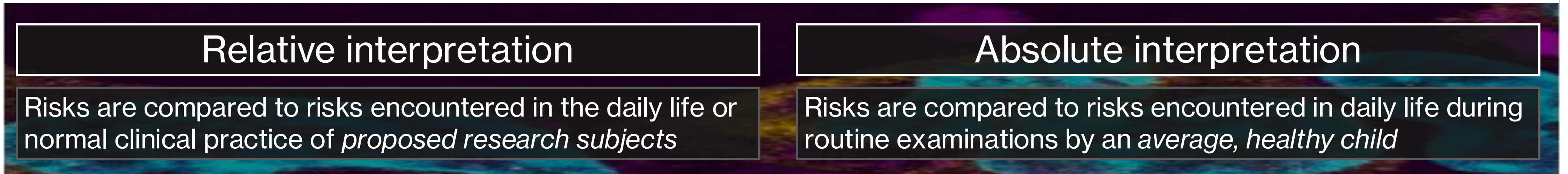
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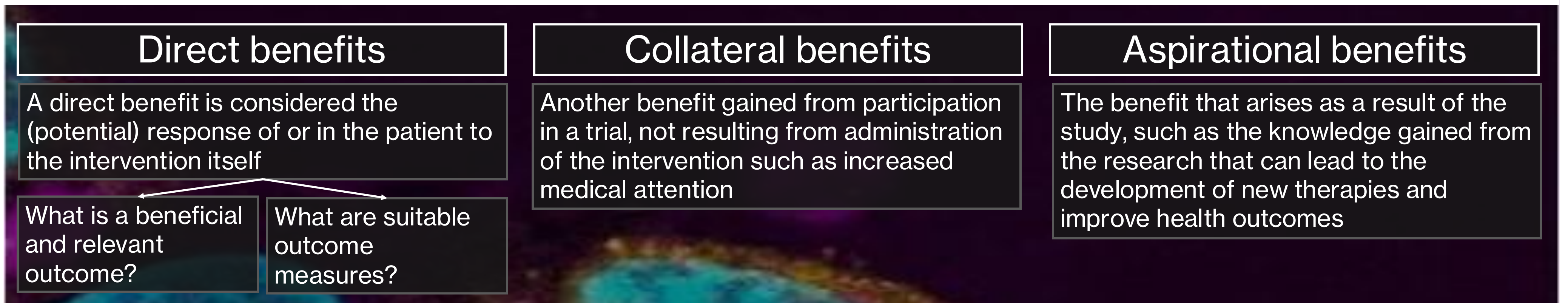
Recent developments in gene transfer and gene editing provide promising avenues for the treatment of monogenetic paediatric diseases. Some of these therapies might soon be tested in first-in-human (FIH) trials. Review of FIH paediatric gene therapy trials is complex and involves many steps in which research 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

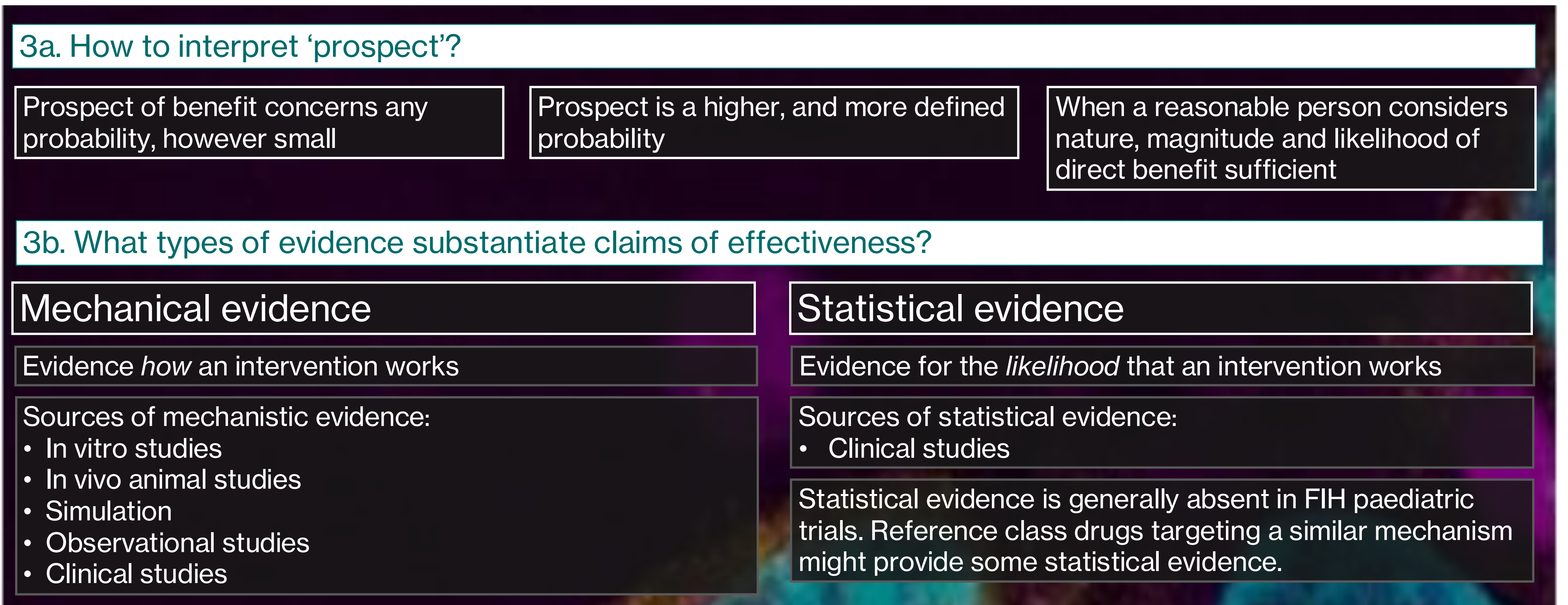
### 1. Do first-in-human paediatric gene therapy trials pose more than minimal risk?



### 2. Which benefits can justify research risks in minors?



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



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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