

# Guidelines for First-in-Children Clinical Trials of Investigational Medicinal Products

**Ethics Working Group  
of the European Academy of Paediatrics (EAP)\***

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## Introduction

These Guidelines are intended to assist the European paediatric researchers in introducing new Investigational Medicinal Products (IMPs) in the paediatric population by developing scientifically sound and ethically acceptable pathways. The Guidelines cover both IMPs that have already been introduced in an adult population as well as IMPs that have never been studied in a human population.

It is widely accepted that medicines that may be beneficial to the children should be fully studied in the paediatric populations to whom they will be administered. As a general rule, First-in-Human (FIH) or 'Phase 0/I' clinical trials are carried out only in adult populations, usually in healthy volunteers. Children are considered a vulnerable population. Children are also considered to be not mature enough to fully appreciate the objectives and risks associated with 'First-in-Human' clinical trials and similarly are not well capable of providing full informed consent.

Nonetheless, many diseases of childhood are unique to children, either not encountered in any form in adult populations or differently expressed in adults. Certain vaccines may also be developed specifically for the paediatric population. In addition, certain paediatric formulations may present such a unique situation that they can only be appropriately tested in a paediatric population. Thus, although limited, there is a clear need to provide guidance for First-in-Children (Phase 0/I) clinical trials.

FIH clinical trials are designed to evaluate limited aspects of an IMP in humans for the first time under strictly controlled conditions with sufficient medical, laboratory, and emergency back-up hospital services to ensure the safety of a limited number of research participants. FIH clinical trials focus nearly exclusively on an evaluation of the safety of an IMP in human biology, studying the human pharmacology (pharmacokinetics and pharmacodynamics) and tolerability of the IMP.

The introduction of an IMP in a FIC clinical trial is particularly challenging because of the biological variance of children across age groups. Among varying age groups, children metabolise medicines differently, expressing at times differing metabolites and toxins. These variances may significantly affect the pharmacokinetics and the pharmacodynamics of an IMP in children of differing biological age groups where the target expression, drug distribution, and primary structure may vary.

FIC clinical trials should only be carried out where there is a sufficient knowledge basis that identifies potential targeted health benefits and potential risks as well as pathways to mitigate the risks. This knowledge basis should be built upon pre-clinical in vitro studies, studies in appropriately chosen animals models and, where possible, studies in adult populations. The potential health benefits to the targeted paediatric population should be fully described, including their limitations, as well as the potential risks to the individual

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child participant. The identified risks need to be mitigated through the clinical trial design and conduct.

FIC clinical trial protocols should receive independent advice from patients and/or their associations as well as independent advice from an appropriately constituted ethics committee. FIC clinical trials should be carried out by qualified paediatricians or supported by qualified paediatricians.

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When introducing an IMP into a paediatric population, clinical trial sponsors, investigators, ethics committees, regulatory authorities, and patients & their organisations should consider the following:

1. The target disease the IMP is intended to address and the prevalence and expression of the disease in the paediatric population vs. the same in the adult population.
2. The specific intended paediatric population for which the IMP is projected as a therapeutic or prophylaxis intervention.
3. The specific paediatric cohort by means of which the IMP is to be studied and introduced into the intended paediatric population.
4. The clinical trial protocol should contain a full description of all preclinical studies and include an evaluation of the safety profile of the IMP, particularly identifying the specific risks and how the risks will be mitigated in the proposed clinical trial.
5. The clinical trial protocol should describe the animal models used to study and identify absorption, distribution, metabolism, and excretion (ADME studies) as well as the metabolites identified in safety testing (MIST) studies.
6. The protocol should discuss the manner in which the paediatric age groups were defined for the proposed clinical trial, including a discussion of the relation between chronological age and biological age for the purposes of the proposed clinical trial.
7. The protocol should clearly identify the minimum anticipated biological effect level (MABEL) for the first dose in the pre-defined biological age cohort group(s) of the study.
8. The protocol should provide a clear justification for introducing the IMP into a paediatric population at this point in its development based on a full analysis of the preclinical data. This justification should provide as full as possible a description of the mode of action of the IMP, its expression laboratory and biological models, the IMP pathways still open and needing to be explored, the level of need in the paediatric population, and the expected outcomes of the proposed clinical trial.
9. The protocol should define specifically which phase of clinical trial development the clinical trial is set at (e.g., Phase 0, Phase I, Phase II, Phase III). The protocol should clearly define the pharmacokinetic and/or pharmacodynamic characteristics of the IMP intended to be studied in the proposed clinical trial.
10. The protocol should clearly define the dose at which the IMP will be first administered in the clinical trial. The protocol should further define any changes in dosage foreseen in the proposed clinical trial, how and at what point the dosage

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variances will be introduced (e.g., the dose escalation scheme), and how this will be monitored both in the clinic and in the laboratory.

11. The protocol should clearly define decision-making rules for the start and continuation of the clinical trial, including stopping rules and the identification of responsibilities for decisions.
12. The protocol should define the clinical and laboratory facilities to be used, the emergency backup facilities, and the monitoring of the proposed clinical trial (including, if appropriate, the use of a Data & Safety Monitoring Board [DSMB]).
13. The protocol should identify the qualifications of the proposed investigator(s) and the proposed clinical trial site clinical and laboratory personnel. The protocol should also identify how input was received from a paediatrician and/or the paediatric community.
14. The protocol should identify how and when patient & their organisations input was received into the development of the protocol.
15. The protocol should identify how and when ethics advice was received into the development of the protocol, including whether advice was received from an appropriately constituted ethics committee.

### **Reference Documents**

The following documents should be consulted in relation to these Guidelines:

EMA (CHMP), Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (2017)

ICH E11 (R1), Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Paediatric Population (2017)

European Commission, Ethical considerations for clinical trials on medicinal products conducted with minors: Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. Revision 1 (2017)

EU Paediatric Regulation (2006)

EU Clinical Trials Regulation (2014)

EU General Data Protection Regulation (2016)

ICH E6 (R2), Guideline for Good Clinical Practice (2016).

ICH M3 (R2) Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (2008)

EU Directive on the protection of animals used for scientific purposes (2010)

EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines. In particular, Annex 13: Manufacture of Investigational Medicinal Products.