



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

1 September 2017  
EMA/CPMP/ICH/2711/1999  
Committee for Human Medicinal Products

## ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population

### Step 5

|  |                   |
|--|-------------------|
| Adopted by CHMP for release for consultation | 14 September 2016 |
| Start of public consultation                 | 13 October 2016   |
| End of consultation (deadline for comments)  | 13 April 2017     |
| Final adoption by CHMP                       | 14 September 2017 |
| Date for coming into effect                  | 28 February 2018  |



## Document History

| First Codification | History  | Date           | New Codification<br><b>November 2005</b> |
|--------------------|--|----------------|--|
| E11                | Approval by the Steering Committee under <i>Step 2</i> and release for public consultation.                                | 7 October 1999 | E11                                      |
| E11                | Approval by the Steering Committee under <i>Step 4</i> and recommendation for adoption to the three ICH regulatory bodies. | 19 July 2000   | E11                                      |

## Current *Step 3* version of the E11(R1)

| Code | History  | Date            |
|------|--|-----------------|
| E11  | Endorsement by the ICH Assembly under <i>Step 2</i> and release for public consultation. | 12 October 2016 |
| E11  | Adoption by the ICH Assembly under <i>Step 4</i> and release for public consultation.    | TBC 2017        |

# ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population

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# 1. Introduction

## 1.1. Scope and objective of the ICH E11 guideline addendum (R1)

Pediatric drug development has evolved since the original ICH E11 Guideline (2000), requiring consideration of regulatory and scientific advances relevant to pediatric populations. This addendum does not alter the scope of the original guideline which outlines an approach to the safe, efficient, and ethical study of medicinal products in the pediatric population. ICH E11 (2000), including the present addendum (R1) is not intended to be comprehensive; other ICH guidelines, as well as documents from regulatory authorities worldwide, the World Health Organization (WHO) and pediatric societies, provide additional detail.

The purpose of this addendum is to complement and provide clarification and current regulatory perspective on topics in pediatric drug development. The use of the word "should" means that something is suggested or recommended, but not required, unless specific regulatory or statutory requirements are specified as advised by regulatory authorities worldwide.

In this addendum, section 2 on ETHICAL CONSIDERATIONS, section 4 on AGE CLASSIFICATION AND PEDIATRIC SUBGROUPS INCLUDING NEONATES, and section 7 on PEDIATRIC FORMULATIONS, supplement the content in ICH E11 (2000). Section 3 on COMMONALITY OF SCIENTIFIC APPROACH FOR PEDIATRIC DRUG DEVELOPMENT PROGRAMS addresses issues to aid scientific discussions at various stages of pediatric drug development in different regions. Section 5 on APPROACHES TO OPTIMIZE PEDIATRIC DRUG DEVELOPMENT includes enhancement to the topic of pediatric extrapolation, and introduces modelling and simulation (M&S). Section 6 on PRACTICALITIES IN THE DESIGN AND EXECUTION OF PEDIATRIC CLINICAL TRIALS includes discussion of feasibility, outcome assessments, and long-term clinical aspects. These sections describe essential considerations intended to provide high level guidance on the implementation of these important approaches in pediatric drug development, reflecting the evolving nature of these topics. This harmonized addendum will help to define the current recommendations and reduce the likelihood that substantial differences will exist among regions for the acceptance of data generated in pediatric global drug development programs and ensure timely access to medicines for children.

## 2. Ethical considerations

ICH E11 (2000) Section 2.6 addresses relevant principles for the ethical conduct of pediatric studies, including the roles and responsibilities of the Institutional Review Board/Independent Ethics Committee (IRB/IEC), recruitment of study participants, parental (legal guardian) consent/permission and child assent (See Glossary), and minimization of risk and distress. These ethical principles are also defined in the current legal and regulatory framework of health authorities worldwide responsible for ensuring safeguards for the protection of children participating in research.

A fundamental principle in pediatric drug development requires that children should not be enrolled in a clinical study unless necessary to achieve an important pediatric public health need. When clinical studies are required to obtain information relevant to the use of a medicinal product, such studies should be conducted in pediatric populations having the disease or condition for which the investigational product is intended, unless an exception is justified. Without a prospect of direct clinical benefit from an experimental intervention or procedure, the foreseeable risks and burdens to which pediatric participants would be exposed must be low, i.e., comparable to those risks and burdens encountered in their routine clinical care. The burden of trial-related activities should also be minimized. Experimental interventions or procedures that present greater than low risk to participants must offer a sufficient prospect of clinical benefit to justify or outweigh exposure of a pediatric

population to such risk. Likewise, the balance of risk and anticipated clinical benefit must be at least comparable to the available alternative treatments, such that the child is not disadvantaged by enrollment in the research study. There should be a reasonable expectation that knowledge resulting from the clinical study will contribute to the health of the pediatric population.

The general principles of ethical considerations for parental (legal guardian) consent/permission and child assent are outlined in ICH E11 (2000) Section 2.6.3 and continue to apply. Information regarding participation in the clinical study and the process of parental (legal guardian) consent/permission and child assent must be clearly provided to the parent (legal guardian) and as appropriate to the child participant, at the time of enrollment. When obtaining child assent, relevant elements of informed consent should be provided that are appropriate to the child's capability to understand. Refusal to assent or withdrawal of assent by a child should be respected.

Over the course of a clinical study, it may be necessary to reassess the assent of a child in recognition of their advancing age, evolving maturity and competency, especially for longterm studies or studies that may require sample retention. During clinical studies there is a requirement for obtaining adequate informed consent for continued participation from pediatric participants once a child reaches the age of legal consent. Local regulations related to confidentiality and privacy of pediatric participants must be followed.

The transparency of clinical research in pediatric drug development includes the registration of clinical trials on publicly accessible and recognized databases, and the public availability of clinical trial results. Objective and unbiased information thus made available can benefit pediatric populations through enhancing clinical research, reducing unnecessary clinical trials, and informing clinical decisions in pediatric practice.

### **3. Commonality of scientific approach for pediatric drug development programs**

General principles outlined in ICH E11 (2000) Sections 1.4 and 2.1 continue to apply. Pediatric drug development programs are increasingly multiregional, and these programs face specific challenges due to regional differences in pediatric regulatory requirements, operational practicalities, standards of care, and cultural expectations. These regional differences in some instances limit the ability of health authorities to align requirements for pediatric product development. To address such differences, timely and efficient drug development requires a common scientific approach for which the following questions should be considered:

- What is the medical need in one or more pediatric populations that the drug could address?
- Who are the appropriate pediatric populations or subgroups that could be considered? (See Section 4)
- What are the key issues in the drug development program that need to be addressed based on the intended pediatric use of the drug?
- Based on the existing knowledge, including developmental physiology, disease pathophysiology, nonclinical data, data in adult or pediatric populations, or data from related compounds, what are the knowledge gaps that should be addressed to establish the safe and effective use of the drug? (See Section 5.1)
- What specific nonclinical studies could be considered?
- What clinical studies and/or methodological approaches could be considered? (See Section 5)

- What pediatric-specific clinical study design elements could be considered? (See Section 5)
- What practical and operational issues should be considered? (See Section 4 and Section 6)
- Are there different formulations/dosage forms or delivery devices that will be needed for specific pediatric subgroups, both to facilitate an optimal dose-finding strategy, and for treatment of pediatric patients in different subgroups? (See Section 7)

A common scientific approach should consider input from stakeholders (e.g., clinicians, patients, experts from academia), and should be based on scientific advances and up-to-date knowledge.

Early consideration of pediatric populations during drug development planning, along with early interactions between drug developers and regulatory authorities worldwide can facilitate agreement on a common scientific approach to a pediatric development program. When differences are identified, established regulatory pathways to minimize the impact of these differences can be utilized. Therefore, a common scientific approach, not common regional requirements, is at the cornerstone of efficient pediatric drug development and timely delivery of safe and effective medicines for children.

## **4. Age classification and pediatric subgroups, including neonates**

General principles outlined in ICH E11 (2000) Section 2.5 continue to apply. A rationale for the selection of the pediatric population to be included in clinical studies should be provided. Chronologic age alone may not serve as an adequate categorical determinant to define developmental subgroups in pediatric studies. Physiological development and maturity of organs, pathophysiology and natural history of the disease or condition, available treatment options, and the pharmacology of the investigational product are factors to be considered in determining the subgroups in pediatric studies. Further, the arbitrary division of pediatric subgroups by chronological age for some conditions may have no scientific basis and could unnecessarily delay development of medicines for children by limiting the population for study. Depending on factors such as the condition, the treatment, and the study design, it may be justifiable to include pediatric subpopulations in adult studies (See Section 6) or adult subpopulations in pediatric studies.

Advances in medical care have led to better survival of high risk newborn infants, especially preterm newborn infants, which makes drug development research in newborn infants or “neonates” increasingly important for certain conditions. Neonates include term, post-term and preterm newborn infants. The neonatal period for term and post-term newborn infants is defined as the day of birth plus 27 days. The neonatal period for preterm newborn infants is defined as the day of birth through the expected date of delivery plus 27 days. As the neonatal population represents a broad maturational range, the conditions that affect this population can vary considerably; therefore, it is important to carefully consider the rationale for the selection of a neonatal population or subpopulation to be studied.

## **5. Approaches to optimize pediatric drug development**

The concepts presented in ICH E11 (2000) Section 2.4 continue to apply. The principles outlined in ICH E4, E5, E6, E9, and E10 should be consulted. The number of pediatric studies and knowledge in the field of pediatrics has increased since ICH E11 (2000). Respective regulations for pediatric drug development worldwide have also evolved. However, drug development in pediatrics continues to present challenges and opportunities. In some cases, there are difficulties with generating data across a pediatric population due to a variety of ethical considerations and feasibility issues. Alternative approaches may provide opportunities to address these issues when structured and integrated into the

drug development program as per the principles outlined in this addendum. Proactive multi-disciplinary dialogue regarding the acceptability of such approaches with regulatory authorities is recommended. The planning for pediatric development of the drug should be integrated into overall product development. Waiting to begin planning until adult development has concluded can limit the opportunity to generate meaningful data for pediatric drug development.

### **5.1. The use of existing knowledge in pediatric drug development**

To better inform the design of a pediatric drug development program, there is an opportunity to utilize existing knowledge. Existing knowledge about a drug under development includes evidence already or concurrently generated in adult and pediatric populations with similar or other relevant diseases or conditions. Existing knowledge also integrates nonclinical data, data about related compounds, disease pathophysiology, consideration of the developmental physiology, and clinical data from the pediatric population or subgroup. Use of such information may optimize pediatric drug development programs without reducing standards for pediatric authorization. Safety and risk considerations based on existing knowledge should guide the decision whether specific risk mitigation, such as staggered enrollment based on age group, is necessary. However, any uncertainties related to the use of existing knowledge must be identified and managed prospectively. As data are generated through the drug development cycle, it is possible that the assumptions behind the parameters that have gone into the development strategy and methodology may need to be revisited to take new information into account. This new information will continue to inform the strategy and present an opportunity to further address uncertainties.

Additional approaches to optimize pediatric drug development may include, but are not limited to, statistical and pharmacometric methods, including M&S (see Glossary) that integrate and leverage existing knowledge, as well as extrapolation of information from other populations (adults or pediatric subgroups). The following subsections provide general considerations on the use of extrapolation and M&S in pediatric drug development.

#### **5.1.1. The use of extrapolation in pediatric drug development**

The concept of “extrapolation” is used in different ways in drug development. “Pediatric extrapolation” is defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population.

When a drug is studied in a pediatric population, one should consider all factors which may result in different drug responses, such as intrinsic (e.g., developmental) and extrinsic (e.g., geographic) factors that could impact on the extrapolation of data from one population to the other.

The process of pediatric extrapolation examines several factors that support the assumptions of similarity of disease and similarity of response to therapy between the pediatric and the reference populations, including disease pathogenesis, criteria for disease diagnosis and classification, measures of disease progression, and pathophysiological, histopathological, and pathobiological characteristics. A thorough understanding of the differences between pediatric and reference populations is required relative to the pathophysiology of the disease, available biomarker/endpoints, organ systems physiology (i.e., renal, hepatic, central nervous system, skeletal, and immune systems), as well as clinical context of available therapeutics, the mechanism of action of the drug and its pharmacological behavior. As new information is generated, the process of pediatric extrapolation should be reviewed and confirmed.

Support for the assumptions of similarity of disease and response to therapy, including exposure-response relationship and prediction of an effective dose and regimen for the intended population, may be derived from existing data about the use of the drug; published literature; expert panels and consensus documents; or previous experience with other products in the same therapeutic class. All data and information gathered can either confirm the extrapolation approach or inform how it might be improved. Ultimately, the exercise should identify if there are sufficient data to support pediatric extrapolation, or if additional clinical information is needed.

When efficacy in the pediatric population can be extrapolated from data obtained in the reference populations, leveraging of safety data from the reference to the pediatric population may be utilized; however, additional pediatric safety data are usually required, as existing data may only provide some information about potential safety concerns related to the use of a drug in the pediatric population [See ICH E11 (2000) Section 2.4].

When pediatric extrapolation is considered in a pediatric drug development strategy, the following framework of questions should be assessed to identify what additional supportive data are needed:

1. What evidence supports a common pathophysiology of disease, natural history, and similarity of the disease course between the reference and pediatric population(s)?
2. What is the strength of the evidence of efficacy in the reference populations?
3. Is there a biomarker or surrogate endpoint in the reference populations that is relevant in the pediatric population?
4. What evidence supports a similar exposure-response between the reference and intended populations?
5. What uncertainties and/or limitations do the existing data (e.g., clinical or historical data and published literature) have, and what uncertainties about the pediatric population remain?
6. If uncertainties remain, what additional information should be generated (e.g., information from M&S, animal, adult, pediatric subgroup studies) in order to inform the acceptability of the extrapolation approach?

As evidence builds, the acceptability of the proposed extrapolation approach should be reassessed and it may be appropriate to change the extrapolation approach.

### **5.1.2. The use of modelling and simulation in pediatric drug development**

Advancement in clinical pharmacology and quantitative M&S techniques has enabled progress in utilizing model-informed approaches (e.g., mathematical/statistical models and simulations based on physiology, pathology and pharmacology) in drug development. M&S can help quantify available information and assist in defining the design of pediatric clinical studies and/or the dosing strategy. Considering the limited ability to collect data in the pediatric population, pediatric drug development requires tools to address knowledge gaps. M&S is one such tool that can help avoid unnecessary pediatric studies and help ensure appropriate data are generated from the smallest number of pediatric patients. The usefulness of M&S in pediatric drug development includes, but is not limited to, clinical trial simulation, dose selection, choice and optimization of study design, endpoint selection, and pediatric extrapolation. With M&S, quantitative mathematical models are built with all available and relevant sources of existing knowledge. Well conducted M&S can inform on the pharmacokinetics, pharmacodynamics, efficacy and safety of a drug.

The incorporation of M&S into pediatric drug development should be based on a strategic plan established through multidisciplinary discussions outlining objectives, methods, assumptions, deliverables and timelines.

When building a model, it is important to consider several elements, including the context of use of the model, the quality and the extent of the existing data, and the assumptions made. Assumptions are usually structured around five main areas: pharmacology, physiology, disease considerations, existing data, as well as the mathematical and statistical assumptions underpinning the model.

Complexity in M&S requires a careful assessment of the impact of each of the above assumptions because the impact of each one on model building can vary between populations. In pediatrics, it is particularly critical to consider the maturation of organ systems with the understanding that data from older subgroups may not necessarily be informative for the younger subgroups. Once assumptions are set, different scenarios should be defined and tested to support the analysis of the impact of potential uncertainty in existing knowledge.

Emerging knowledge is incorporated into the model in an iterative approach to revisit and improve the model. A series of “learn and confirm” cycles should be used for model building and simulation/prediction, and be confirmed as soon as new information is generated. Several models may be needed to support a given pediatric drug development program depending on the question(s) to be addressed, the credibility of the model, and the emerging data generated.

Risk assessment is a critical part of M&S. The clinical and statistical consequences of a specific approach should be discussed with experts to define the risks to be handled. The risks associated with accepting the model depend on the relative contribution of the model in making a decision during product development and its consequences. These risks should be assessed and weighed against the credibility of the model for the context of use.

## **6. Practicalities in the design and execution of pediatric clinical trials**

Before deciding which types of methodological approaches are to be used in clinical trial design and execution, one should consider several practical factors that influence the design and execution of pediatric clinical trials. Three key practical factors to consider are feasibility, outcome assessments, and long-term clinical aspects, including safety.

### **6.1. Feasibility**

Pediatric drug development faces unique feasibility issues, including a small number of eligible children for clinical research, limited pediatric specific resources at research centers, and the scarcity of dedicated pediatric trial networks. Consideration should be given to the available centers that are willing to participate, have access to eligible pediatric participants, and are appropriately staffed in research and clinical care of pediatric patients. When studying pediatric conditions, it may be necessary to consider implementing clinical trial operational strategies, including, but not limited to, the use of pediatric research coordinating centers; the development of master protocols for pediatric clinical trials or registries, planned and conducted in a collaborative manner to evaluate multiple therapies for the same disease or condition with a common control arm; and the enhancement of pediatric clinical research networks. These operational strategies and adherence to Good Clinical Practice (ICH E6) should result in improved feasibility and increase timely and efficient pediatric drug development.

The foreseeable experience of children and their parent(s)/legal guardian should be considered, including the emotional and physical burden and the convenience of participation. Current standards of

care can influence physician/patient treatment choices that may impact the design and conduct of pediatric clinical trial. Strategies that foster input from children, their caregivers, and the advocacy communities can facilitate participation, recruitment, and acceptability of a clinical study.

## **6.2. Outcome assessments**

As stated in the ICH E11 (2000) Section 2.4.2, it may be necessary to develop, validate, and employ different endpoints for specific age and developmental subgroups. The relevant endpoints and outcome measures for the pediatric population should be identified as early as possible. The standardized measurement, collection, analysis, and reporting of outcome assessments are encouraged to optimize pediatric drug development [See ICH E11 (2000) Section 2.4 and ICH E11 (R1) Section 5]. It is important to include protocol design features that allow pediatric participants at appropriate ages to contribute directly in these measures when possible. Where relevant, it may be prudent to initiate the evaluation of potential pediatric endpoints as part of the adult development program prior to their incorporation into the pediatric program.

## **6.3. Long-term clinical aspects**

The concepts on safety presented in ICH E11 (2000) Section 2.4.3 and Section 2.4.4; ICH E6 and ICH E2 topics continue to apply. It is acknowledged that rare events may not be identifiable in pre-registration development, and that pediatric-specific adverse events are unlikely to be detected in development programs that are limited in size and duration. Planned collection of safety data in nonclinical studies, adult clinical studies regardless of dose or indication, or information from other sources (e.g., M&S), should serve to improve the design of pediatric studies and pharmacovigilance activities to address specific pediatric safety concerns.

Long-term effects of drug treatment in children can include impacts on development, growth, and/or maturation of organ/system function. Therefore, adequate baseline assessments of growth/development and organ function, and regular follow-up measurements should be planned and discussed with regulatory authorities, as appropriate. Early planning for followup in a drug development program offers the opportunity to systematically capture and evaluate long-term effects in a disease or condition, and increase data interpretability.

## **7. Pediatric formulations<sup>1</sup>**

Principal considerations for the development of age-appropriate pediatric formulations to allow for safe and accurate use of pediatric medicines as outlined in ICH E11 (2000) Section 2.2 continue to apply. Additional considerations for pediatric formulations to optimize efficacy and reduce the risk for medication and dosing errors should include age-appropriate dosage forms, ease of preparations and instructions for use for caregivers, acceptability (e.g., palatability, tablet size), choice and amount of excipients, as well as use of alternative delivery systems and appropriate packaging.

Adult dosage forms are not always appropriate for use in the pediatric population, and if a product for adults is used, it may pose a safety risk. When pediatric considerations are not addressed early during drug development, the final medicinal product(s) may require such modification for use in children that the risk is increased for inaccurate dosing, changes in stability, bioavailability, or suboptimal patient acceptability. Examples of this include multiple small volume acquisitions from a vial designed for a single adult use; use of an opened adult capsule formulation or crushed tablets to mix with food for administration of a pediatric dose; and breaking tablets for dose reductions that do not have a

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<sup>1</sup> For purposes of this document, the term "pediatric formulations" includes design considerations for the dosage form, route of administration, packaging, measuring or administration device of a pediatric medicine (drug).

functional score line. When modifications of the available preparations are unavoidable, measures to minimize the impact on dose accuracy, stability, bioavailability and safety must be addressed.

Planning for development of age-appropriate dosage forms for pediatric populations should be incorporated into the earliest stages of drug development. If modifications to the available forms are necessary to allow earlier inclusion of pediatric patients in clinical trials during drug development, an age-appropriate product and the applicable bridging studies in support of its use should be planned.

### **7.1. Dosage and administration**

In order to achieve the targeted drug exposure, more than one dosage form of the active pharmaceutical ingredient (API) and/or strengths may be needed to cover the range of pediatric populations intended to receive the medicinal product. For pediatric drugs, the setting where the product is likely to be administered should be considered when selecting the formulation for development. For example, long acting formulations may be beneficial in settings where the caregiver is not always available (e.g., school, nursery). Further, certain dosage forms that reduce the requirements for handling and storage may be more appropriate than others.

In developing a formulation for pediatric use, considerations should include the ease of accurate dose measurement and the capability to deliver small volumes of liquids to minimize the risk for dosing errors, especially in neonates, infants and young children. Such approaches could include clearly marked administration devices, and/or devices with scaling capability designed for accurate measurement of the smallest dose volume and dose increments.

### **7.2. Excipients**

Excipients may lead to adverse reactions in children that are not observed (or not to the same extent) in adults. Thus, the use of excipients in pediatric medicines should take into account factors such as age, weight, maturity (e.g., term and preterm newborns related to their physiologic development), frequency of dosing, intended duration of treatment, and potential for additional excipient exposure from commonly co-administered medicines. The use of excipients and their quantity in a formulation should minimize risk and ensure product performance, stability, palatability, microbial control, and dose uniformity. Alternatives to excipients that pose a significant risk to children should always be considered, and the risk posed by the excipient weighed against the severity of the disease and availability of alternative treatments. When selecting excipients, one should always consider the potential impact on absorption and bioavailability of the API.

### **7.3. Palatability and acceptability**

Orally administered pediatric medicines must be palatable to ensure dose acceptance and regimen adherence. A formulation strategy for developing palatable drug preparations includes minimizing/eliminating aversive attributes of the API and considering favorable flavor attributes. Taste masking is often needed to improve the palatability of the API. As pediatric drug development can benefit global populations, the target for taste masking should not only be focused on ensuring that the preparation does not taste unpleasant. Ideally, the preparation should have a neutral taste or a taste with broad cultural acceptance.

Alternative dose administration strategies should be considered for pediatric populations who cannot be accommodated by the intended dosage form (e.g., segmenting or crushing tablets, co-administration with food or liquids). Appropriateness of the alternative strategy for a pediatric population, including patient and caregiver aspects (e.g., taste/palatability, ease and accuracy of

modification, and potential changes in bioavailability due to a variety of factors) should be investigated prior to selection of the final market image formulation. Understanding real-world use behaviors in administering pediatric drugs and the mitigation of associated risks will contribute to the development of a drug product that allows for safe dose administration.

#### **7.4. Neonates**

Formulation requirements for neonates warrant special attention, such as its effects on electrolyte, fluid or nutritional balance. Intramuscular preparations should be avoided where possible due to pain, risk of over-penetration (e.g., bone, vasculature), and unpredictable drug absorption. Likewise, the tolerability of subcutaneous and intravenous preparations should be evaluated. For neonates, environmental conditions (e.g., temperature, light) and equipment used for drug administration (e.g., enteral feeding tubes) may have an effect on drug delivery and bioavailability. When developing a parenteral dosage form, compatibility with other commonly administered parenteral medicines or parenteral nutrition should also be considered and investigated as necessary, since intravenous access is often limited in neonates. While parenteral formulations may be used in neonates, it should be considered that their use often necessitates careful monitoring to minimize the risk of fluid and electrolyte disturbance.

## **8. Glossary**

### **Parental (legal guardian) consent/permission:**

Expression of understanding and agreement by fully informed parent(s) or legal guardian to permit the investigator/sponsor of a clinical study to enroll a child in a clinical investigation. The choice of the terms parental consent or parental permission in different regions may reflect local legal/regulatory and ethical considerations.

### **Child assent:**

The affirmative agreement of a child to participate in research or to undergo a medical intervention. Lack or absence of expression of agreement or disagreement must not be interpreted as assent.

### **Modelling and Simulation (M&S):**

A range of quantitative approaches, including pharmacometrics/systems pharmacology and other mathematical/statistical approaches based on physiology, pathology and pharmacology to quantitatively characterize the interactions between a drug and an organ system which could predict quantitative outcomes of the drug and/or system's behavior in future experiments. In modelling and simulation, existing knowledge is often referred to as "prior" knowledge.