make medicines child size

Paediatric clinical trials guidance for assessors

June 2011
World Health Organization

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1. Introduction , scope and process for developing the Guideline

This guideline is intended for assessors in regulatory authorities who review protocols of clinical trials of medicines that involve children. The document is intended to complement existing guidance and documents (e.g. U.S. Food and Drug Administration, European Medicines Agency, etc.) on how to assess clinical trials protocols and will focus on paediatric-specific aspects only.

This guidance may be read in conjunction with the following:

- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E11: Guidance on clinical trials for the development of medicinal products in the paediatric population *(1)* and other relevant ICH guidance (in particular E3, E6, E9, and E10) *(1-5)*.
- Addendum to ICH E11 from Health Canada *(6)*.
- EMA guideline on clinical investigation of medicinal products in term and preterm neonates *(7)*.

In addition, a Glossary of Terms and Acronyms is included at the end of this document, beginning on page 35.

Paediatric clinical trials: Guidance for assessors was prepared from September 2010 to April 2011 on the basis of the guidance available from the European Medicines Agency (EMA) on paediatric clinical trials.

The following groups and individuals have commented on the draft:

- Steering Committee members of the Paediatric Medicines Network (PmRN).
- Department of Essential Medicines and Pharmaceutical Policies (EMP)/Medicine Access and Rational Use.
- Department of Essential Medicines and Pharmaceutical Policies (EMP)/Quality and Safety: Medicines.

2. Assessment process

The assessment of a clinical trial based on the detailed protocol, will include different steps and approaches, which are summarized below. This includes a review of ethics principles and in some cases the involvement of experts and/or the need for inspection of the trial.

2.1 Ethical review of the protocol

Ethical reviews of the protocol should be performed by an Ethics Committee, including at least one member (permanent or ad-hoc) with paediatric expertise, especially when the ethical review is not part of the scientific assessment by the regulatory authority or other authority.

2.2 *Additional expertise*

The assessment of the various elements of a paediatric trial protocol may require involving one or more experts, internal or external to the regulatory authority, such as experts in formulations, an expert in paediatric pharmacology, or experts in the relevant therapeutic area, if they are available to the regulatory authority. Conflicts of interest of experts need to be checked, documented, and managed as per applicable laws and policies *(8)*.
In case of multiple expert assessments, the assessor will then have to compile the various elements and reach a conclusion on the overall acceptability of the trial.

2.3 *Relevant documents to be provided to the paediatric clinical trial assessor and experts*

As with any clinical trial, legal requirements will apply (e.g. for medicines that are not yet registered). In addition to the full protocol and annexes, the trial sponsor must submit to the authorities an Informed Consent Form (and paediatric information and assent form, if applicable), the latest Investigator's Brochure, and/or where available, the approved product information from a stringent Regulatory Authority *(3)*.

Other legal requirements (e.g. medicine import or manufacturing authorization, trial participants insurance certificates, including premium payment documentation) may or may not be paediatric specific. Good Manufacturing Practice (GMP) standards must be met for the test and the reference medicines to be used in the trial. Similarly, Good Laboratory Practice (GLP) standards for the assays and laboratory testing must also be met *(9-10)*.

2.4 *Inspections*

Good Clinical Practice (or Good Manufacturing Practice, Good Laboratory Practice) inspections, if available, might be particularly appropriate from a risk-based approach, as the clinical trial will be performed in a vulnerable population.

2.5 *Literature search*

To ensure that all relevant data have been submitted by the sponsor, it is recommended that the assessor perform a literature search on available data on the medicine, including different salts of the same active moiety (and on the active control where relevant), and/or the condition.

3. Assessment process outcome

The outcome of the assessment of the protocol of a paediatric clinical trial by a regulator should lead to clear conclusions on its acceptability on two counts: whether the trial is capable of answering the scientific question and whether the design respects applicable ethical principles. A trial that is scientifically not valid cannot be ethical. The outcome of the assessment may be summarized in a few sentences; however, a detailed assessment of the elements of the trial is necessary in order to arrive at conclusions that are appropriate and credible. Importantly, the legal and ethical framework of research (clinical trials) differs from that of care (therapeutic guidelines) for children as for adults. There are also differences from a legal standpoint (e.g. need for informed consent), with regard to the acceptable levels of risks allowed for research as compared to standard care, and significant differences between adult research and paediatric research.

The three main questions that will need to be answered for a paediatric trial are the following:

3.1 Is the paediatric trial necessary?

- Is the trial based on a well-identified scientific question of paediatric relevance, which has not yet been answered?
- Could the trial be performed in adults or in less vulnerable subjects rather than in children?
- Is the trial responding to the needs of the paediatric population in which it will take place?

3.2 Is the trial in keeping with ethical principles (which have their origin in the Declaration of Helsinki[1]), particularly those directly applicable to paediatric trials?

- If applicable laws and policies require a favourable ethics opinion prior to regulatory approval, has a local Ethics Committee or Institutional Review Board (IRB) issued a favorable opinion of the trial?
- Does the trial meet these main ethical principles *(11-15)*?
  - Respect for the participants and their autonomy. In particular, does the protocol specify how to obtain and document informed consent of the legal representative(s) and assent of the child (beyond the age of 3-4 years, generally 6-7 years, and taking into consideration the subject's capacity to assent).
  - Distributive justice. Is there a fair distribution of the benefits and risks in the children who will be studied? Do the participants represent a cross-section of society, in terms of ethnicity and socioeconomic background *(12)*? Vulnerable subsets, such as institutionalized children, may require additional protection.
  - Beneficence and non-malevolence. Are the identified risks for children participants measured, prevented, and minimized when risks cannot be fully avoided? Are there provisions for monitoring, reporting, and taking urgent action in case of unexpected serious risks?
- Is there direct benefit for the child included in the trial? If there is no direct benefit for the child, are the risks of research no greater than minimal? Please note that applicable legislation or policies may be more restrictive and may require a direct benefit for the child.
- Does the protocol require timely publication of the results (and communication of these results to the participant[s]) even if the outcomes are negative?

3.3 Is the trial scientifically sound?

- Is the trial methodologically acceptable?
- Is the trail able to answer the question it aims to answer?
- Is the trial going to be performed and monitored according to GCP, i.e. with sufficient quality?

[1] Declaration of Helsinki (2008). World Medical Association. http://www.wma.net/en/30publications/10policies/b3/index.html

4. Specific areas of assessment

The following sections describe specific information that should be provided by the sponsor and assessed by the assessor. It is important that the assessor is able to consider critical questions and determine if he or she finds the sponsor's response acceptable.

4.1 Description of the medicine under investigation

Regulatory status of the medicine

As the risks of the trial depend on the available experience in adults and in children, the regulatory status of the medicine should be described by the sponsor of the clinical trial. The assessor may check websites of stringent regulatory authorities for similar information. Table 1 illustrates the details that should be included by the sponsor.

Table 1: Regulatory status of the medicine

Trial Sponsor/Company		
Active ingredient(s), INN		
Brand name		
Regulatory status of the medicine in the country of the trial	Unapproved, Approved, Refused, On hold, Withdrawn/Restrictions of use	
Regulatory status of the medicine in other countries <Country>	Unapproved, Approved, Refused, On hold, Withdrawn/Restrictions of use	
Approved use/indication(s)		
Therapeutic area(s) for the trial ATC code		
Proposed Indication for the trial (prevention, treatment, diagnosis of <>, bioequivalence)		
Dosage form(s) already approved	In adults: In children:	
Dosage form(s) in trial	In children:	
Strength(s) already approved	In adults: In children:	
Strength(s) in the trial	In children:	
Route(s) of administration already approved	In adults: In children:	
Route(s) of administration in the trial	In children:	
Comments		

Evidence of regulatory rejection or restrictions of use should be taken into consideration for the authorization of a clinical trial, as a negative regulatory outcome generally indicates safety concerns or lack of efficacy with the medicine. In such a case, the assessor may consider refusing authorization of the clinical trial.

Regulatory information on related clinical trial(s)

Regulatory information on other clinical trials related to the paediatric development (or adult development, where relevant) with the medicine or the active ingredient(s) may inform the assessment and should be provided by the sponsor of the clinical trial. Public information is generally limited but the assessor should

check common sources of information such as the U.S. National Institute of Health's Clinicaltrials.gov[1] site and the website of the EU Clinical Trials Register (EudraCT).[2] Table 2 illustrates the minimum detail that the sponsor should provide to the assessor.

Table 2: Overview of trials with the medicine

Reference/Protocol Number	Protocol Title	Trial Country(ies)	Trial Status	Comments
Trial 1			Completed Discontinued (for safety, lack of efficacy?) On hold (reason?) Ongoing Planned, not started	If another trial with the same medicine was stopped prematurely, check whether this would impact on the trial under evaluation. If a similar trial has been completed in children, discuss whether an additional trial is necessary?
Trial 2			Completed Discontinued (for safety, lack of efficacy?) On hold (reason?) Ongoing Planned, not started	

Other questions to consider include:

- Have similar trials or trials for related medicines (e.g. same therapeutic class) been refused, discontinued or placed on hold for safety reasons?
- If similar trials in children have been approved or completed, does the particular trial represent unnecessary duplication?

Evidence of regulatory rejection, ethical refusal, or clinical hold of a trial should be taken into consideration for the authorization of a clinical trial, as a negative regulatory outcome generally indicates safety concerns or lack of efficacy with the medicine. The assessor may consider refusing authorization of the clinical trial.

If similar trials in children have been approved or completed, the assessor should consider whether the particular trial represents unnecessary duplication

Paediatric development in other regions

To help the assessor, the information assessed by other regulatory authorities should be provided by the sponsor.

[1] Available at http://www.clinicaltrial.gov.

[2] Available at https://www.clinicaltrialsregister.eu/.

Questions to consider include:

- Is there a Written Request from the US Food & Drug Administration (FDA), or a Paediatric Investigation Plan (PIP) from the European Medicines Agency (EMA) available on this medicine *(16-17)*?
- Were any waivers of the paediatric development granted for this medicine by either the FDA or the EMA? (If so, for which reason? Was it due to safety concerns?)?

Information on Written Requests, PIPs, and Waivers is available on the FDA and EMA websites for assessors to verify information.[1] In some cases, safety issues for paediatric medicines may be flagged on the Paediatric medicines Regulators' Network (PmRN) website.[2]

Relevant guidelines

The assessor should check national regulatory agencies' websites for drug development guidelines where available.

- Are there regulatory guidelines for medicines development that apply *(18-19)*? Have the guidelines, and in particular the paediatric requirements, been followed?

Similarities and differences of the disease/condition between populations (adult vs paediatric and within paediatric subsets) and possible extrapolation of efficacy

- Do differences in the disease between adults and children or between paediatric age groups, justify separate, additional trials for the demonstration of efficacy of the medicine?

Similarities between adult and childhood diseases may be identified on the basis of disease seriousness, etiology, pathophysiology, and possible variability in terms of genetic background. Other differences may be based on maturation (i.e. organ, receptor maturation). Differences may also exist between different age groups and this may have an impact on the protocol.

The need for a trial might also be justified by different measurements of efficacy (i.e. outcome measures, scales, etc.).

If there are no differences in disease characteristics, the assessor should consider whether extrapolation of efficacy from adult or older age groups is possible *(1, 20)*.

Existing paediatric data

Questions to be considered by assessors are:

- Are there existing paediatric data on the medicine (i.e. quality, non-clinical safety, clinical efficacy and safety)?

[1] Information from the US FDA is available at http://www.fda.org/, and from the EMA at http://www.ema.europa.eu/.

[2] Available at: http://www.who.int/childmedicines/paediatric_regulators/en/.

- Is the trial part of a development plan i.e., will trial results will be complemented by other data?
- How do other trial results contribute to the information needed to assess this trial?

Current methods of diagnosis, prevention, or treatment

With regard to current methods of diagnosis, prevention, or treatment in paediatric populations, the assessor should consider:

- What is the standard of care for this disease?
- If there is an active comparator, should it be used in the trial?

The standard of care may include medicines used off-label, if supported by acceptable evidence, e.g. international practice guidelines.

Determining the need for a paediatric medicine

Before performing a clinical trial, the need for the medicine should be clearly established. Examples of paediatric needs may include:

- improved efficacy in this population;
- improved safety (e.g. fewer or less serious adverse events, or fewer medication errors);
- improved dosing schemes or methods of administration (e.g. fewer doses per day, oral compared to intravenous administration, reduced treatment duration, etc.);
- new/improved clinically-relevant, age-appropriate dosage forms or formulations (e.g. devoid of toxic excipient, more palatable);
- an expected improvement in the quality of life of the child.

If the assessor concludes that all paediatric needs are covered for the condition in question, and/or the outcome of the trial is not going to meet any need, rejecting the trial should be considered if the trial is unnecessary.

Summary

The assessor should summarize conclusions made on the description, regulatory background and need for the trial:

Conclusion on the regulatory background information on the trial by the Clinical Trial assessor:
Conclusion on unmet paediatric needs:

4.2 *Clinical trial formulation and dosage form*

One of the first steps of assessment should include a review of the quantitative and qualitative composition; a review of individual components and their suitability for paediatric use; and finally the dosage form including strength, and route of administration. Note Table 3 as an example of a review, as well as the questions to consider.

Composition

Table 3: Qualitative and quantitative composition of the medicine

	Qualitative	Quantitative	Assessor's comments
Active ingredient 1			
Active ingredient 2 (etc.)			
Excipient a			
Excipient b			
Excipient c (etc.)			
Other constituents (e.g. adjuvant)			
Route of administration			

Questions to consider:

- Is the active ingredient(s) well known?
- Is each excipient appropriate and safe for children, in terms of both nature and quantity? Prior exposure of children of various ages, as relevant for the trial in question, should be documented.
- Have the excipients previously been administered to children via this route?
- Is the formulation palatable? A formulation that is unpalatable may be accepted by children for single-dose use, but not repeated dosing *(21-22)*.
- Is there a need for manipulation (compounding) or for extemporaneous preparation of the medicine before administration to the child? Who will be in charge of the preparation, parents or care givers?
- Are instructions for manipulation/preparation clear, simple, well described, and practical?
- What are the storage and stability conditions for the reconstituted formulation?

Proposed dosage form

In considering the proposed dosage form, several aspects should be considered, in particular whether the form is manageable for the intended weight or age ranges of the children. It should be of an appropriate size, composition, strength and/or concentration. Consider the following:

- If the medicine is presented in a solid form (e.g. capsule, tablet), is the size appropriate for the children to whom it will be administered?

Children below the age of approximately 5 years, but especially below 2 years, may not be able to swallow large, solid forms (unless they are dispersible) and are at risk of choking *(23)*. If the trial medication is a large solid form intended for this age group (5 years and younger), there is a need to crush the tablet, or open the capsule and mix the content with food.

- If tablets have to be cut, is there content uniformity? If tablets require that they be cut into more than halves, there is a high likelihood of dosing inaccuracy unless they are scored for this purpose.
- Can it be mixed with food? If so, which type, and does this include breast milk in neonates and infants? Does the medicine require fasting administration? Note that fasting is not acceptable for very young infants and on demand breastfed neonates.
- Are food interactions expected?
- Does the protocol specify whether there are significant differences in bioavailability due to the crushing or dissolution of tablets, or opening of capsules? Will this affect a particular subgroup of the trial? For example, such bioavailability differences may lead to differences in efficacy and/or safety between the group of older children taking whole tablets, and the younger ones receiving crushed tablets.
- If the medicine is presented as liquid form i.e., syrup, suspension, is there a need for dilution? If there is a need for dilution, is there access to clean water during the trial? Is there a risk of medication error in dilution?

Proposed strength

In reviewing the proposed strength, the assessor should consider the risk of error in delivering an accurate dose.

- Is there a risk of dosing error in the trial from the strength or concentration?
- Does the proposed strength or concentration allow for administration of accurate doses to the youngest and/or lightest children (on a mg/kg basis)?
- If this is a combination medicine, are the components dose-proportional across subsets of the paediatric population? Can the same dose (on a mg/kg basis) be administered across weight bands?

Proposed route of administration

The following questions should be answered by the assessor:

- Is the route of administration painful or hazardous in young infants, e.g. intramuscular (IM)?
- Does the administration require a delivery device?
- Is the device provided? Is it accurate and easy to use?

Summary

The assessor should summarize conclusions:

Conclusion on the acceptability of the dosage form and formulation, and on potential risks for the children to be included in the proposed trial:

4.3 Non-clinical safety

Prerequisites for the performance of a trial in human subjects are defined in the ICH M3(R2) guideline (24-25) and are more extensive for paediatric trials. Prior to exposing children in any clinical study or trial, the assessor must have access to human adult exposure data (there are very few exceptions where an active ingredient would not have been tested in adults before children) and to the following toxicology data:

- the full battery of genotoxicity (i.e. mutagenicity) studies;reproductive toxicology (i.e. fertility and peri-post natal development) studies. Embryo-fetal toxicity studies are less critical;
- repeat-dose toxicology studies of appropriate duration in relation to paediatric use;
- carcinogenicity studies, if required;
- in some cases, juvenile animal studies should be performed with a view to identify possible toxicity on developing organs.

The assessor should consider the following questions:

- What is known from juvenile animal studies *(26)* and animal models, if available?
- Is there an indication that effects on growth and/or maturation may be a concern?
- Is the medicine considered 'high-risk' (see for example the EMA guideline on 'first in man') *(27)*?
- Are there any safety signals in toxicology studies with possible impact on development in children?
- Will these signal toxicity concerns prevent performing the paediatric trial because the risks cannot be prevented or minimized?

Summary

The assessor should summarize conclusions:

Conclusion on the acceptability of the non-clinical safety elements of the trial for the paediatric population:

4.4 Pharmacology of the medicine

If they are known at the time of assessment, the following characteristics would impact on the paediatric clinical trial: absorption; distribution; metabolism; and elimination. In particular in children, a modification of any of the pharmacokinetic (PK) or pharmacodynamic (PD) parameters due to maturation may have significant consequences on the PK or PD profile of the medicine *(28-33)*. The following provides a list of questions and information to consider.

Absorption:

- Is there active transport? Location: intestine, other? Type of transporter mainly involved? Influence of maturation on the absorption?
- What is the influence of food on absorption? Food includes milk for neonates and infants, if the medicine is going to be used in these groups.
- Is there first-pass effect? Bioavailability will be affected by gut microflora, cytochrome P450 (CYP) maturation, or liver disease.

Distribution

- Does the medicine bind to red blood cells and plasma proteins? The medicine-free fraction may be increased by anemia, in the former, and by malnutrition, in the latter case, for example.
- What is the influence of maturation on the distribution? Is there active transport?
- Where does it take place? (e.g. in the intestine, blood-brain barrier, placenta, breast milk, other)?
- Which type of transporter is mainly involved? Are pharmacogenetics of transporters involved?
- Are there any anomaly affecting the active transport or transporter may affect the PK characteristics of the medicine and may affect activity, and/or safety?

Metabolism

- What are the main metabolic routes?[1]
- Are CYP isoenzymes involved? Are there conjugation enzymes involved?
- Is the medicine a pro-drug devoid of activity, or is it mainly responsible for the activity? Does it have active metabolite(s)?
- Are the pharmacogenetics of metabolism known?
- What is the influence of size or weight, and maturation on the metabolism?
- Are there any anomaly of the metabolism that may affect the PK characteristics of the medicine and may affect activity and safety? The abundance of receptors and organ maturation may differ across age groups and can impact the PK/PD relationship, resulting in different efficacy and safety with the same drug exposure.
- Are co-medications expected in the trial?

Elimination

- What are the main routes of elimination?[2]
- Is there renal clearance in adults?
- Is there tubular handling?
- Is there influence of maturation on elimination/renal clearance? Anomalies resulting in decreased elimination (e.g., renal insufficiency or liver disease) may alter the activity and/or safety of the medicine.

Pharmacodynamics

- Are there PD data (i.e. effect of interest and other effects) in animals and/or in adults?
- How do size or weight and maturation influence the PK/PD relationship?
- Are there data on the age at which 90-100% of adult maximum PD response as a function of plasma concentration is reached?
- Are the main available PK parameters presented and discussed?

The sponsor should discuss linearity of the kinetics, and indicate Tmax, Cmax, absolute bio-availability, volume of distribution, plasma clearance, half-lives (T½, terminal T½), and hepatic extraction ratio for medicines primarily eliminated through the liver (i.e. comparison of plasma clearance to normal liver blood flow).

[1] Refer to studies with labeled compounds in adults, or in vitro studies with human liver cell preparations, or human microsomes, with recombinant cDNA.

[2] Refer to studies with labeled compounds in adults.

Accordingly, the PD and PK/PD relationship should be characterized through preclinical (in vitro and in vivo models) adult and/or paediatric data. PD biomarkers that describe the pharmacological mechanism of the intervention should be evaluated. The PD markers should be linked to the pharmacology of the drug, being easily measured and ideally correlated with clinical outcome data. PD parameters to be calculated include but should not be limited to Emax, EC50, Imax, IC50. Every effort should be made to identify the effect of size, maturation and extrinsic factors on the PK and PK/PD relationship, in particular malnutrition. Ideally, an integrative analysis of all data available in different age groups and in vitro, using modeling and simulation techniques, should be used to identify the effects of different covariates (i.e. age, size, weight, food, sex) on PK/PD.

If PK data are not available in children, they should be generated prior to exploratory or confirmatory trials.

All parameters potentially affecting PK and PD should be recorded and analyed; e.g. failure to identify food interactions may lead to unreliable PK data and failure to measure the weight of the child will prevent any PK analysis that would require normalization by weight.

If the trial aims at defining doses, the range of doses explored should be sufficiently wide to establish a dose-response relationship, or exposure-response relationship. However, high doses may lead to unacceptably high rates of adverse events.

Mechanism of action

The mechanism of action will drive the indication and use of the medicinal product. The assessor should consider the following questions:

- Is there a proof of concept for this medicine?
  Are PK/PD and disease models available, under development, or not feasible for this paediatric disease?
- Is the mechanism of action clearly described (as much as is currently known)?
- How closely is the action directed at the disease or condition in children?
- What are the main sites of action, expected PD drug interactions (i.e. medicines used primarily in children in this condition, or in related or frequently coexisting conditions), and potential expected adverse reactions?
- How does this medicine compare to what is known about other medicines of the same class and same indication (if any)?
- Can the assessor agree with the trial sponsor that the medicine is expected to act in the same or different way in adults and children?
- Are there elements of the development that are unnecessary? Conversely, are there elements that are missing?
- Is the sponsor using all available data to avoid unnecessary studies?

Summary

The assessor should summarize conclusions:

Conclusion on the acceptability of pharmacology of the medicines for the paediatric population:

4.5 Clinical efficacy, safety, and PK trials

The protocol of paediatric trials should address the same elements as in an adult trial protocol (elements are described, for example, in ICH E3 on clinical study reports *(2)* and in the CONSORT statement, which has a different objective but highlights what defines the quality of a trial).

Some elements differ and are paediatric-specific, while some are additions to adult protocols *(34-35)*.

Models and simulations can be used to optimize PD and efficacy trials with a view to limiting the number of children participants, timing of evaluation, or design *(31,36)*.

The following questions and issues should be considered in assessing this area of the proposed trial.

Type of trial, study design

- Monotherapy, or add-on (combination), or multiple doses.
- Parallel group, or Cross-over.
- Multicenter, single center.
- Multinational.
- Blind or Unblind.
- Controlled or Uncontrolled trial.
- Consecutive phases or periods.

These characteristics represent examples of design but other designs are possible. As in the case of adult trials, the design should match the objective of the trial.

There is nothing inherently specific to the design of paediatric trials. However, the following may be of interest in paediatric trials:

- Adaptive design. This technique allows adapting the trial while it progresses based on predefined rules. Its advantage is the possibility of decreasing the number of participants during the trial, which is a desirable objective for paediatric trials.
- Age-staggered inclusion. In order to protect the most vulnerable participants, the trial starts in older children before including the younger groups.

Systematic bias reduction measures

Reduction measures are not paediatric specific. They mainly include randomization and blinding (preferably double-blind, although partial blinding may be unavoidable in some instances).

Bias reduction measures are necessary to demonstrate efficacy in paediatric and adult trials. Bias reduction measures may raise issues of feasibility e.g. increasing complexity) for paediatric trials, but must be included as part of good methodology and ethical requirements in a vulnerable population i.e.., children who cannot legally consent. The need for bias reduction increases with the subjectivity of the type(s) of endpoint(s) studied, e.g., in the case of patient-reported outcomes (PRO) or outcomes assessed by each of the different investigators (e.g. disease progression).

The main objective of the study

The main objective(s) of a trial are generally to demonstrate efficacy, safety or tolerability, or to study PK. The objectives should include whether the trial is designed as a superiority, a non-inferiority, or an equivalence trial, and the reasons for the choice.

The primary endpoint(s) should reflect the main objective. For example, in a study aiming at showing efficacy of a medicine in a paediatric infectious disease, a PK parameter would generally be irrelevant as the primary endpoint; mortality/survival or cure would be more relevant. However, if the endpoint is a surrogate marker of the clinical outcome in children (e.g. viral load in HIV treatment), this is acceptable for children as for adults.

Study population

- Is the study population in line with the proposed indication for the medicine?

  The study population of relevance may be described in therapeutic guidelines in terms of severity, stage of the disease, treatment resistance, or associated risk factors.

  The protocol should describe the patients/subjects who will be targeted (e.g. children with pneumonia), gender, age groups, demographic characteristics among which weight should be included, nutritional status, breastfeeding, and whether children with coexisting conditions will be included (e.g. children with HIV infection or hemoglobinopathies).

  The age groups should be defined in relation to physiological maturation. Weight for the children must be recorded and included as weight normalization of PK characteristics might have major importance for the evaluation of the results.

Number of study participants

The protocol should specify the numbers by treatment group and stratum, and by other characteristics, which may be paediatric specific (e.g. age or weight bands, nutritional status).

The study power and the sample size calculation, including the formula used for the calculation, should, as for adult trails, be provided for paediatric trials. Consider whether there is a need for stratification in terms

of genetic background (e.g. sickle-cell disease), standard of care, in-patient/out-patient, or other scientific reasons. Depending on the objective of the trial, the power and sample size may need to be calculated for a particular subgroup of children.

As for adult trials, absolute participant numbers have little value if not justified. The sample size depends on a realistic, expected effect of the medicine and variability of the outcome measure in the population studied.

The calculation should include an estimated proportion of children who will drop out or be lost to follow-up. The protocol should specify how missing values will be handled statistically (e.g. non-completer = failure).

Inclusion criteria

Inclusion criteria define the characteristics of the paediatric participants who may take part in the trial. The objective is to have a reasonably homogenous population in the trial, in particular with respect to severity of the disease, age groups, maturation, and nutritional status. From a pragmatic perspective, inclusion criteria that are too stringent may increase the recruitment time, rendering the trial infeasible and/or poorly generalizable. If the criteria are not stringent enough, the patients will be more heterogeneous (i.e. have increased variability), and this may compromise the interpretation of the trial results.

The requirement to use birth control measures, which is near systematic in adult trials, is irrelevant in trials that only involve children before puberty. Delayed effects on fertility and future pregnancies should not be underestimated for medicines that can be stored in body organs (e.g. bones) and released over decades (e.g. biphosphonates).

Exclusion criteria

Exclusion criteria define the paediatric patients or subjects who may not take part because of higher risk, concomitant conditions that would make the results difficult to interpret, or who are unlikely to complete the trial. Specific exclusion criteria should be included to reflect safety issues that have been identified for the test or control medicine.

These criteria must include refusal by the legal representative(s) to consent. There are differences of opinion as to whether a child should have the right to refuse participation. Taking into account the child's capacity to assent on the one hand, and on the other hand, any cultural differences in approaches to a child's right to make a decision for him- or herself, it is nonetheless recommended that the assessor respect the will of the child.

Usual exclusion criteria apply to paediatric trials. These may include multiple trial participation, short-life expectancy and, unless the medicine is intended for these conditions, cancer or immune suppression.

In the case of trials in adolescents, females of child-bearing potential may participate provided the same relevant safety precautions are taken as for adults (i.e. contraception, if it is justified by the safety profile of the medicine).

Location of the trial

The location of the various centers (e.g. different regions, settings, countries) may impact the trial results and is not paediatric specific.

Study duration

If the trial includes several phases, the duration should be specified by phase. The assessor should identify the run-in period (e.g. wash-out period), active treatment comparison, and follow-up with or without treatment (i.e. for efficacy and/or safety) phases.

The study duration — generally the active treatment phase comparison in a comparative trial – should be long enough to demonstrate a clinically-relevant effect and should match the recommended treatment duration in children. In some cases, the medicine may require several days or weeks to be fully effective and the time point for measuring the endpoint should take this into consideration. (See also therapeutic guidelines).

Dose

Were there dose-finding studies in animals, adults, or children? Does the available pharmacology data (in vitro and in vivo) and covariate analysis support the doses proposed for the different age subsets? Do dose-finding studies support the proposed doses in the paediatric trial? Dosing should be determined on the basis of the PK and dose-finding results.

Is the dose proposed on a weight basis (e.g. mg/kg) or body surface area (BSA)?

The mg/kg basis is preferred because it only requires a scale to measure the weight of the child, whereas the BSA calculation (weight in kg/height in meters squared) is more complex to obtain, subject to calculation errors, and therefore prone to prescription errors.

Dose selection for a first-in-children trial generally tries to emulate the adult exposure that produced effective and safe outcomes.

Whereas for PK and PD studies, relatively wide ranges of doses are desirable. For safety and efficacy trials a more homogeneous exposure is desirable and some means of dose normalization or narrow dose bands should be used.

The risk of selecting the wrong dose, in particular a dose that is too low, may be higher in children. This is due to different PK characteristics related to maturation and disease, as well as the desire to protect children from what are perceived as high doses compared to adult doses *(37)*.

The dose normalization proposed should be a compromise between optimal efficacy and safety and ease-of-dose adjustments.

The protocol should specify the individual dose, how often the medicine is given daily, and the route of administration.

Route of administration

The protocol should specify whether special preparation and manipulation (i.e. compounding) are necessary to administer small doses to young children.

Such preparation should remain simple and easy to accomplish in order to avoid medication error.

The route of administration should result in minimal pain and distress for the child. Intramuscular (IM) and intravenous (IV) routes are painful and should only be used where unavoidable.

Control(s)

A controlled trial may include one or more of the following:

- placebo;
- active control (i.e. approved medicine, or medicine used off-label, if supported by available evidence);
- different doses of the test medicine. Uncontrolled trials are subject to systematic bias.

When creating a controlled trial, the assessor should refer to ICH E10 *(5)*.

To choose the appropriate control for paediatric trials, it is important to consider the setting and standard of care wherein the trial is taking place.

Many medicines are used off-label in children, but belong to the standard of care. Therefore, in contrast to adult trials, the active comparator in the trial may be used off-label, provided that this use is supported by strong published evidence, such as Cochrane reviews or their equivalent, meta-analysis, randomized controlled trials, and published literature. In the case of published literature, the assessor should be aware of the selection and publication bias.

When using an active control in children as in adults, it should be ensured that effective doses of the active control are used for the comparison: an insufficient dose would bias the comparison in favor of the test medicine. However, very often doses in children have been poorly established and this may add to the difficulty of choosing the effective dose(s) in the comparison.

Because of the vulnerability of the children and the lack of legal capacity to consent, the use of placebo in children is even more debated than use in adults. The use of placebo in the trial should not place children at increased risk *(12)*. All the conditions for the use of placebo, in particular those aiming at protecting the participants included in the research, should be provided for by the protocol *(11-15)*.

Comparison of different doses may be very informative with respect to the dose-response curve and benefit/risk balance in a superiority trial. In children, this can be part of the dose-finding strategy.

Historical data only may be available in some cases in children. There are many pitfalls in using historical data, including the inability to control bias and the lack of initial comparability of the groups (e.g. age

groups), as historical data may have been collected in different situations from that of the trial under assessment. There is no other difference from adult trials with respect to historical data.

Pharmacokinetic (PK) studies

The objective is to characterize the PK of the medicine, including the following parameters: AUC, T1/2, Cmax, and Clearance. The two main options include the use of non-compartmental techniques and PK modeling. Non-compartmental models have the advantage of unbiased PK parameter estimates, but require rich sampling, which is a concern in paediatric trials. Compartmental population models enable the use of sparse sampling, but might introduce bias. Model validation is important when models are used. Consider the following:

- Has the model been validated in children?
- Identify whether the PK study uses non-compartmental, compartmental PK, or compartmental population PK analyses
- Identify whether the PK study uses rich or sparse sampling

Rich sampling will require several blood samples (i.e. between 6 and 12) in the same child to determine the blood level curve, and in practice only about 12-20 children in the study (depending on measurement variability).

In rich sampling, a calculation of total blood sampling volume should be made. This should include the volume of blood that must be discarded to avoid remnant blood from the line if an in-situ catheter is used. The total volume should not exceed 'safe' volumes according to age or weight *(13, 35)*.

The volume and concentration of heparin used to keep the line open, if accessed frequently, should be defined in the protocol.

Sparse sampling means that only one or two samples will be collected from each child, and repeated in many more children, in the range of 100-300 (pop PK). There are obvious advantages to sparing children from multiple blood sampling. However, this means that the trial should include enough children *(36)*.

Pharmacodynamics and efficacy trials

For PD or efficacy, the endpoint should be validated in children. Non-invasive measures should always be preferred in children to minimize pain and distress.

The endpoint should match the objective of the trial and should be relevant to the child's health. Clinical outcomes are typically better than biological parameters in this respect, but may take longer (sometimes a lifetime) to be measured.

The outcome measure should be validated, but validation should not take place during the trial under assessment. However, very often there are no validated endpoints available for children in general, or for the age group(s) of the trial. In this case, the outcome measure(s) should be well-established in the published literature.

The time point at which efficacy is measured should match the duration of the disease or the expected outcome.

For example, cure of urinary infections should be measured after discontinuation of antibacterial treatment. This is not paediatric specific, but the duration of disease might differ in children.

What is the expected difference in the primary endpoint measure, which is due to the test medicine? This should be based on prior evidence, meta-analysis, Cochrane reviews, randomized controlled trials, literature, etc. However, data in children might be lacking because either they have only been generated in adults, or in different age groups, or with different therapeutic classes. The expected difference will be used for the sample size calculation.

Excess optimism regarding the expected effect size of the test medicine is a classic pitfall. Preliminary data or shorter term studies tend to overestimate the effect size. If the effect size is smaller in the trial than expected, the sample size will be too small, and the trial will not produce statistically significant conclusions. There is an ethical duty to perform trials that produce such conclusions.

Primary endpoint(s) with time point(s) of assessment

See relevant therapeutic guidelines (WHO, EMA, USFDA, National Medicines Regulatory Agency, etc.).

Secondary endpoint(s) with time points(s) of assessment

Secondary endpoints should provide supportive evidence to the primary endpoint with respect to the clinical benefit of the medicine for children.

A classic pitfall in trials is specifying too many secondary endpoints. Some of these endpoints will be positive by chance only (statistically about 1 in 20 endpoints at $p<0.05$). In addition, this might impose excessive burden of investigations on children participants *(4)*.

Laboratory measurements and other investigations

These could be primary or secondary endpoints, and/or part of the safety monitoring. Reference normal values (norms) should be available for the children of the trial. Microassays, which require less blood, are preferable to limit blood loss in children. Conditions for storage and transport of the biological samples should be indicated.

Dried blood spots also now offer an improved solution, particularly in places where freezing of samples and transportation is not easily accessible.

Feasibility of the laboratory measurements should be discussed. Using a centralized laboratory may offer increased consistency of analyses in multicenter trials.

Any investigation in children should be as minimally invasive as possible. Normal reference values should be available for the investigation and the children of the trial.

Follow-up for efficacy and safety

The protocol should specify the follow-up duration, organization, and milestones, and whether children are treated or not during this follow-up. All clinical trials must be managed for safety. Safety monitoring should target all appropriate subsets of children involved in the trial.

Children require long-term monitoring of safety because of delayed adverse events. The safety profile from the adult use has relevance for children, but cannot predict effects on growth and maturation.

As for adults, long-term monitoring is necessary when rebound or relapse is predicted.

Monitoring of the paediatric trial should follow the applicable requirements, policies, and laws for paediatric trials. In addition, it should be noted that younger children (below the age of 6-7 years) are unlikely to identify adverse events as such. Therefore, the primary source of reporting will be the caregivers and/or the parents, the type and frequency of monitoring of adverse events should be standardized, and their regular detection active. A data and safety monitoring board (DSMB) should be established (see below).

Although all parties who oversee or conduct clinical research have a role and responsibility for the safety of the study subjects, the clinical investigator has primary responsibility for alerting the sponsor, DSMB and the Independent Ethics Committee (IE)/institution review board (IRB) to adverse events, particularly serious or life-threatening unexpected events observed during the course of the research. The sponsor, in turn, is responsible for reporting study safety to regulatory authorities and other investigators and for the ongoing global safety assessment of the investigational product *(43-44)*.

Evaluation of the risks

Risk is defined as potential harm (real or theoretical) or potential consequence of an action. It may be physical, psychological, or social, and may be immediate or delayed. It may vary according to age groups. Risk should be assessed in terms of probability, magnitude, and duration *(13)*.

- For the children, what are the known or expected risks of the test medicine, or the control as used in the trial?
- Are the unfavorable effects reversible in children? What precautionary measures are incorporated in the protocol to minimize known or anticipated risks and prevent irreversible harm?
- Are the risks prevented, if possible? For example, maintaining sufficient hydration of the child for a medicine which can be toxic for the kidneys?
- Are the risks minimized? Are there stopping rules, rescue treatment, and measures to minimize pain and distress (see below)?

A proposal for classification of the risks in children is included in Annex 1.

Evaluation of the risks is difficult. Any evaluation should take into consideration both the known unfavorable effects and the probability of unknown effects or unexpected adverse events. This probability is reduced if the medicine has been used extensively and in a similar way (i.e. dose, duration, route) in humans, including in children.

Stopping rule(s)

Stopping rules are particularly important in paediatric trials as they represent another safeguard for the children involved in the trial.

The stopping rules can apply to an individual child participant, to a part of the trial, or to the whole trial.

1) ***Stopping rule applicable to an individual child***
If the trial is for an antibiotic, the individual stopping rule would apply if the fever in the child does not subside within 24 hours. The patient would then be switched to another proven, effective antibiotic agent.

2) ***Stopping rule applicable to a part of the trial***
The rule would apply in a trial comparing three doses, if one of the doses is too high with unacceptable adverse events. In this case, the stopping rule would require discontinuation of that arm and allow the trial to continue with the comparison of only two doses.

3) ***Stopping rule applicable to the whole trial***
This rule would apply as soon as the DSMB concludes that there is unacceptable mortality or serious adverse events in any arm of a randomized trial.

Does the protocol ensure similar follow-up of participants after stopping?

Rescue treatment

A rescue treatment should be included in the protocol to prevent maintaining the child participant in a situation of ineffective therapy for too long.

For example, in an acute pain-treatment trial, the protocol should allow for rescue medication, such as additional pain killer use, if the test medicine fails to produce pain relief after a short period of time (e.g. 2 hours) at maximum-tolerated dose.

Measures to minimize pain, distress, and parental separation

The protocol should specify the number and type of samples [e.g. blood, urine, cerebrospinal fluid (CSF)] and timing per patient, as well as the total blood volume per sample and the total for a child over the course of the trial, taken in relation to research.

The trial conditions should not compromise breastfeeding in neonates and infants. Sampling should take account of the child's feeding times or wakefulness. Waking a neonate or an infant for the purpose of sampling should be avoided, if possible.

Fasting before sampling is often recommended in adults, but is inappropriate for neonates, infants, and very young children due to the risk of hypoglycemia and dehydration *(13)*.

CSF sampling via lumbar puncture can be particularly distressing for children and parents alike. In certain conditions (e.g. cerebral malaria, increased intracranial pressure) the risks are further increased and sedation

may not be suitable if consciousness must be maintained. The protocol should include appropriate local or topical anaesthesia.

Independent Data & Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

A data and safety monitoring board (DSMB) may be constituted by the sponsor to assist in overall safety management. The establishment of such an independent committee should be systematic in all paediatric trials *(40-44)*, because children are vulnerable. It is necessary that a sponsor-independent committee be established whose responsibility is to protect the participants in the trial. However, it is important to note that a DSMB will have no time to act if the trial is brief (e.g. less than two weeks), as the trial will be completed before any decision can be made.

Statistical plan

There are no paediatric-specific statistical tests or analyses and general statistical considerations apply to paediatric trials. There is an ethical requirement to ensure good methodology. As the paediatric population available for trials are generally limited in size, the methodological considerations that apply to small trials using non-conventional design or analysis should be explicit in the protocol and preferably agreed upon with the regulatory authorities beforehand *(45)*.

As for adult trials, the protocol must specify which analysis is going to be done, at which time point(s), and using which statistical test(s). The delta should be specified and justified by evidence. The protocol must pre-define the population which will serve as reference for the statistical analysis *(4)*.

If interim analysis(es) are appropriate and necessary, they should be pre-specified in the protocol. Such analyses generally create multiplicity issues.

The interim analyses can be a safety monitoring tool for the DSMB. Unblinding or not of the trial may be decided by the DSMB.

There is no difference for a paediatric protocol with respect to missing values, drop outs, or lost-to follow-up patients *(46)*.

Proposed dates for initiation and completion of the trial

The timelines proposed should be realistic in relation to recruitment and study duration. Paediatric trials typically have longer recruitment times than adult trials. This may be explained in part by the limited number of children available for inclusion and reluctance of parents to consent to their children's participation. If timelines are too long, the trial may remain open-ended, which could be a waste of patients and resources. The consequence of lengthy timelines and open-ended trials could mean no results will be available and no conclusion drawn, therefore the trial will be unethical. If the timelines are too short, the trial quality may suffer as well, and respect for the inclusion and exclusion criteria may be at risk.

Feasibility of the trial

This includes assessment of the availability of trained investigators with experience in paediatric trials, necessary investigations (non-invasive, if possible), and effective safety monitoring. All paediatric clinical trials should be performed in accordance with commonly accepted principles of Good Clinical Practice as with adult trials *(3)*.

The feasibility assessment should come to a conclusion regarding the likelihood of completing the trial within a reasonable timeframe while producing good quality, robust results.

Summary

The assessor should summarize conclusions.

Conclusions of the assessor on efficacy safety and PK trials:

4.6 Conclusion of the assessor on the clinical trial

After reviewing the various elements of the paediatric clinical trial, the assessor should be able to answer the following questions:

- Is there a reasonable expectation of safety and efficacy of the test medicine for the children participants?
- Is there an expectation of direct benefit for the children participants?
- What is the balance of benefits and risks in the trial for the children participants?
- Is the clinical trial acceptable from both a scientific and an ethical perspective? If not, could reasonable amendments be made to render it acceptable, and if so, which ones?

Where the protocol or investigator's brochure is inaccurate or materially incomplete, does not adequately provide for the protection of subject rights and safety, or is deficient in design to meet its stated objectives, the regulatory authority may require protocol modification or take action to disallow the protocol to proceed in accordance with applicable laws and regulations.

Summary conclusion:

Conclusion of the assessor on the overall elements of the trial, especially related to overall safety, direct benefit and acceptability of the overall trial

5. Bioequivalence studies

Bioequivalence studies are generally not paediatric studies, even for the purpose of registration of a paediatric formulation; however, the information on bioequivalence studies is provided here in instances where assessors may have adult protocols for such studies to assess in relation to paediatric formulations and dosage forms.

5.1 Objective of a bioequivalence study

The objective of a bioequivalence study is to compare statistically the respective bioavailability of two medicines or two different dosage forms (e.g. oral, intramuscular (IM), or subcutaneous (SC) of the same active ingredient. Bioequivalence is accepted if, after administration of the same molar dose of the two medicines, their bioavailabilities lie within accepted predefined limits. Bioequivalence is not required for intravenous (IV) forms as bioavailability via the IV route is 100%. Bioequivalence may not be required between two solid oral dosage forms of immediate release (i.e. between capsule and tablet) *(47).*

5.2 Population study for bioequivalence

As a rule, bioequivalence studies are performed in healthy *adult volunteers*. If the toxicity of the medicine does not allow administering it to healthy adult subjects, then it can be done in *adult patients*.

In the rare cases where there is no indication for the medicine in adults, and only in this case would a bioequivalence study be performed in *paediatric patients* (i.e. children having the disease in question, or at risk of the disease for medicines intended for prevention).

Differences in gut blood flow of neonates and infants may generate differences in absorption between adults and younger children. However, as substitution, or interchangeability, of the neonate dosage form by the adult one during treatment is unlikely, specific studies with neonates are not warranted for the sole purpose of testing bioequivalence or determining relative bioavailability.

There is, in practice, no situation where bioequivalence should be studied in healthy children. See guidelines on bioequivalence from the EMA or FDA *(47-49)*.

6. References

1. Clinical investigation of medicinal products in the paediatric population, (ICH E11). Geneva, International Conference on Harmonisation, July 2000. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf.

2. Structure and content of clinical study reports, (ICH E3). Geneva, International Conference on Harmonisation, November 1995. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/Step4/E3_Guideline.pdf.

3. Good Clinical Practices, (ICH E6(R1)). Geneva, International Conference on Harmonisation, May 1991. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf.

4. Statistical principles for clinical trials (ICH E9). Geneva, International Conference on Harmonisation, February 1998. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf.

5. Choice of control groups and related issues in clinical trials (ICH E10). Geneva, International Conference on Harmonisation, July 2000. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf.

6. Addendum to ICH guidance document E11. Ottawa, Health Canada, December 2003. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/e11_addendum-eng.pdf.

7. Guideline on the investigation of medicinal products in the term and preterm neonate. London, European Medicines Agency, June 2007. (Doc. Ref. EMEA/536810/2008) Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003750.pdf.

8. Practical guidance for conducting a review. Regulatory support Series, No 12. Geneva, World Health Organization, 2007. Available at: http://www.who.int/medicines/areas/quality_safety/regulation_legislation/GuideAssessRegSys.pdf.

9. Good Manufacturing Practices for pharmaceutical products: main principles - Annex 4 in WHO Expert Committee on specifications for pharmaceutical preparation. 37 Report, WHO Technical Report Series, N°908. Geneva, World Health Organization, 2003. Available at: http://whqlibdoc.who.int/publications/2004/9241546190_part1.pdf.

10. Good laboratory practice: Quality practices for regulated non-clinical research and development. Geneva, World Health Organization, 2004, p 226. Available at: http://apps.who.int/tdr/svc/publications/training-guideline-publications/good-laboratory-practice-handbook-ver1.

11. American Academy of Pediatrics. Committee on Drugs. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics, 1995, 95(2):286-94. Available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;95/2/286.pdf.

12. Shaddy RE, Denne SC, and the Committee on Drugs and Committee on Pediatric Research. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics, 2010, 125:850-60. Available at: http://pediatrics.aappublications.org/content/125/4/850.full.pdf+html.

13. Ethical considerations for clinical trials with medicinal products with the paediatric population: Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. European Commission, 2008. Available at: ftp://ftp.cordis.europa.eu/pub/fp7/docs/ethical-considerations-paediatrics_en.pdf.

14. Field MJ and Behrman RE, eds. Ethical conduct of research involving children. Washington, DC, Institute of Medicine, National Academies Press, 2004. Available at: http://www.nap.edu/openbook.php?isbn=0309091810.

15. Additional Protections for Children Involved as Subjects in Research. Washington, DC, U.S. Department of Health and Human Services, U.S. Food & Drug Administration, 2001. Revised and updated 2005. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1&subpartNode=21:1.0.1.1.19.4.

16. Pediatrics. Washington, DC, U.S. Food & Drug Administration website. Available at : http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm.

17. European Paediatric Investigation Plans (PIP) guidance. London, European Medicines Agency, 2008. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580025b91.

18. Frakking FNJ, van der Lee TP, Offringa M. Survey of current guidance for child health clinical trials. Geneva, World Health Organization, 15-17 February 2010. Available at: http://www.who.int/childmedicines/publications/GUIDANCECHILDHEALTH.pdf.

19. Cramer K, Wiebe N, Moyer V et al. Children in reviews: methodological issues in child-relevant evidence syntheses. BMC Pediatr 2005;5:38. Available at: http://www.biomedcentral.com/1471-2431/5/38.

20. Sammons H. Avoiding clinical trials in children. Arch Dis Child 2011;96:291-292. Available at: http://adc.bmj.com/content/96/3/291.full.

21. Draft Guidance on paediatric formulations. Geneva, World Health Organization, 2010.

22. European Medicines Agency (EMA). (2005) Reflection paper: Formulations of choice for the paediatric population. London, European Medicines Agency, 2005. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf

23. Thomson SA, Tuleu C, Wong IC, Keady S, Pitt KG, Sutcliffe AG. Minitablets: new modality to deliver medicines to preschool-aged children. Pediatrics. 2009 Feb;123(2):e235-8.

24. Guidance on Non-clinical Safety Studies for the conduct of human clinical trials and Marketing Authorizations for Pharmaceuticals (M3(R2)). Geneva, International Conference on Harmonisation, 2009. Available at: http://www.ich.org/products/guidelines/multidisciplinary/article/multidisciplinary-guidelines.html.

25. Questions and Answers: Guidance on Non-clinical Safety Studies for the conduct of human clinical trials and Marketing Authorizations for Pharmaceuticals (M3(R2)). Geneva, International Conference on Harmonisation, 2011. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Q_As/M3_R2_Q_AStep4.pdf.

26. Silva-Lima B et al. Juvenile animal studies for the development of paediatric medicines: a description and conclusions from a European medicines agency workshop on juvenile animal testing for nonclinical assessors. Birth Defects Research Part B: Development and Reproductive Toxicology, 2010;89:467-73. Abstract available at: http://onlinelibrary.wiley.com/doi/10.1002/bdrb.20257/abstract.

27. Guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products. London, European Medicines Agency, 2007. (EMEA/CHMP/SWP/28367/2007 Corr.) Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002989.pdf.

28. Kearns G, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology: Drug disposition, action, and therapy in infants and children. N Engl J Med 2003 Sep 18;349(12):1157-67. Available at: http://www.nejm.org/doi/full/10.1056/NEJMra035092.

29. General considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products. Washington, DC, US Food & Drug Administration, 1998. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072114.pdf.

30. Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. London, European Medicines Agency, 2004. (EMEA/CHMP/EWP/147013/2004/Corr.) Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003066.pdf.

31. Kerns SE. Challenges in conducting clinical trials in children: approaches for improving performance. Expert Rev Clin Pharmacol 2009 Nov 1;2(6):609-17. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2835973/.

32. Moran C, Smith PB, Cohen-Wolkowiez M, et al. Clinical Trial Design in Neonatal Pharmacology: Effect of Center Differences, with Lessons from the Pediatric Oncology Cooperative Research Experience. Clin Pharmacol Therap 2009 Dec;86(6):589-91.

33. Ward RM, Benitz WE, Benjamin DK, et al. Criteria Supporting the Study of Drugs in the Newborn. Clin Therapeutics 2006;28(9):1385-98.

34. Saint-Raymond A, Hill S, Martines J et al. Consort 2010. Lancet 2010 Jul 24;376(9737):229-30. Available at: http://www.thelancet.com/journals/lancet/article/PIIS0140673610611348/fulltext.

35. Abdel-Rahman SM, Reed MD, Wells TG, et al. Considerations in the Rational Design and Conduct of Phase I/II Pediatric Clinical Trials: avoiding the Problems and Pitfalls. Clin Pharmacol Therap. 2007 Apr;81(4):483-94.

36. Manolis E, Pons G. Proposal for model based paediatric medicinal development within the current European Union regulatory framework. Br J Clin Pharmacol 2009 Oct;68(4):493-501.

37. Bartelink IH, Rademaker CMA, Schobben AFAM, et al. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacol 2006;45(11):1077-97.

38. Bankowski Z, ed. International Ethical Guidelines o Biomedical Research Involving Human Subjects. Geneva, Council for international Organizations of Medical Sciences, 1993. Available at: http://www.codex.uu.se/texts/international.html.

39. Castro-Pastrana LI, Carleton BC. Improving pediatric drug safety: need for more efficient clinical translation of pharmacovigilance knowledge. J Popul Ther Clin Pharmacol. 2011;18:e76-88. Epub 2011 Mar 21.

40. Operational guidelines for the establishment and functioning of Data and Safety Monitoring Boards (TDR/GEN/Guidelines/05.1). Geneva, World Health Organization, 2005. Available at: http://whqlibdoc.who.int/hq/2005/TDR_GEN_Guidelines_05.1_eng.pdf.

41. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products - Annex 3 in The use of essential drugs, Sixth report of the WHO Expert Committee. Geneva, World Health Organization, 1995. (WHO Technical Report Series N°850.) Available at: http://whqlibdoc.who.int/trs/WHO_TRS_850.pdf.

42. Handbook for good clinical research practice (GCP) - guidance for implementation. Geneva, World Health Organization, 2005. Available at: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/OMS-GCP.pdf.

43. Guidelines on conduct of pharmacovigilance for medicines used by the paediatric population. (EMEA/CHMP/PhVWP /235910/2005-rev1.) London, European Medicines Agency, 2005. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003764.pdf.

44. Maintenance of the ICH guideline on clinical safety data management: Data elements for transmission of individual case safety reports, (ICH E2B(R2)), Step 4 version. Geneva, International Conference on Harmonisation, 5 February 2001. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2B/Step4/E2B_R2__Guideline.pdf.

45. Guideline on clinical trials in small populations. (CPMP/EWP/83561/05.) London, European Medicines Agency, 2005. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf.

46. Guideline on Missing Data in Confirmatory Clinical Trials. London, European Medicines Agency, 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf.

47. Guideline on the investigation of bioequivalence. (CPMP/EWP/QWP/1401/98 rev.1/Corr**.) London, European Medicines Agency, 1998. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf.

48. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations. Rockville, MD, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, July 2002. Available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplication%20ANDAGenerics/UCM154838.pdf.

49. Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Rockville, MD, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, August 2000. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf.

Annex 1: Examples for levels of risks

The following list provides examples of investigations/measures that may be carried out for the purpose of a trial. The investigations have been ranked in three categories. However, this is only for general guidance, because the circumstances of the child will influence the evaluation of risks.

For example, an existing central venous line may reduce the pain and invasiveness of blood sampling, but also increases the risk of infection and of excess blood losses with line handling. Finger-stick blood sampling is acceptable if only a single sample has to be taken. If more samples are required over a period of a day, then indwelling catheters are less invasive.

The risk evaluation of some of the investigations/measures (including, but not limited to those marked §) is very much dependent on such circumstances and on the context of its use in the trial. In addition, the risk level increases with the increase in frequency of the investigations. The risk level also increases with the susceptibility to harm of any involved or exposed body organs. The categorization proposed in the table applies to single or very infrequent use of the investigation. The examples also presuppose that the measures are carried to the highest standards out by experienced investigators.

No or minimal risk

- History taking
- Clinical examination
- Growth measurements
- Tanner staging
- Behavioral testing
- Psychological testing§
- Quality of Life assessment
- Venepuncture §
- Heel prick §
- Finger prick §
- Subcutaneous injection
- Urine collection with bag §
- Breath condensate collection
- Collection of saliva or sputum
- Collection of hair sample
- Collection of tissue removed from body as part of medical treatment/care §
- Topical analgesia §
- Stool tests
- Bio-impedancemetry
- Transcutaneous oxygen saturation monitoring (pulse oxymetry) §
- Blood pressure monitoring
- Electroencephalography
- Electrocardiography
- Vision or hearing testing
- Ophthalmoscopy
- Tympanometry
- Lung function tests (peak flow, exhaled NO, spirometry)
- Oral glucose tolerance test
- Ultrasound scan
- Digitally amplified chest or limb X-ray §
- Stable isotope examination

Minor increase over minimal risk

- Urine collection via endoluminal or suprapubic catheter
- Arterial puncture
- Umbilical catheter
- pH metry
- Nasogastric tube insertion and use
- Transcutaneous oxygen or carbon dioxide tension monitoring
- Electrophysiological measurements (using stimulation)
- Exercise testing (ergometry, spiroergometry)
- Raised volume pulmonary function testing (infants)
- Peripheral venous lines
- Polysomnography
- Fasting (≥ 1 meal)
- Spinal CSF tap/lumbar puncture
- Bone marrow aspiration
- MRI scan
- X-ray other than digitally amplified chest or limb X-ray
- CT scan §
- X-ray DEXA bone density measurement
- Use of contrast media
- Paracentesis
- Skin punch biopsy
- Airways or skin hyperreactivity challenge test

Greater than minor increase over minimal risk

- Heart catheterization
- Endoscopy
- Biopsy
- Surgery or modification of standard surgical procedure carried out as part of medical treatment/care
- Sedation
- Anesthesia
- Systemic analgesia
- Hypoglycemia test
- Unstable isotope usage
- PET scanning

Glossary

Alpha	Type I error, also known as a false positive, is the error of rejecting a null hypothesis when it is actually true. Plainly speaking, it occurs when we are observing a difference when, in truth, there is none, thus indicating a test of poor specificity.
Approval **Approved medicine**	Regulatory decision authorizing the placing of the medicine on the market. Also called Registration, or Marketing Authorization in the European Union.
AUC	Area Under the Curve of plasma concentration versus time. A measure of drug exposure.
ATC code	Anatomo-Therapeutic Class (from the WHO Collaborating Centre for Drug Statistics Methodology). Classification system where active ingredients are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.
Beta	Type II error, also known as a false negative, occurs when a null hypothesis is not rejected despite being false. In other words, this is the error of failing to observe a difference when, in truth, there is one, thus indicating a test of poor sensitivity.
Bias (systematic)	External influences and factors that may distort the accuracy of statistical measurements. The purpose of conducting a clinical trial of an investigational product is to distinguish the effect of the investigational product from other factors, such as spontaneous changes in the course of the disease, placebo effects, or biased/subjective observation. Bias can be minimized in a clinical trial by designing well-controlled studies, using blinding, and using procedures to randomize subjects to the various study arms.
Bio-availability	The fraction of an administered dose of unchanged drug that reaches the systemic circulation; one of the principal pharmacokinetic properties of medicines.
cDNA	Complementary DNA (cDNA) is DNA synthesized from a mature mRNA template in a reaction catalyzed by the enzyme reverse transcriptase and the enzyme DNA polymerase.
Clinicaltrials.gov	Website developed by the U.S. National Institutes of Health through the National Library of Medicine presenting a description of clinical trial protocols and results for pharmaceuticals intended to treat serious and life-threatening diseases under an application for an Investigational New Drug (IND) to the Food and Drug Administration (FDA). It also includes voluntary registration of clinical trials. See http://www.clinicaltrials.gov.

Cmax	Maximal concentration.
Confidence interval	Indicates the reliability of an estimate. It is an observed interval (i.e. it is calculated from the observations), that, in principle, differs from sample to sample, and that frequently includes the parameter of interest, if the experiment is repeated.
CSF	Cerebrospinal fluid.
CYP	Cytochrome P. A large and diverse group of enzymes. Most CYP enzymes catalyse the oxidation of organic substances. CYPs are the major enzymes involved in drug metabolism and bioactivation, accounting for ~75% of the total metabolism. The substrates of CYP enzymes include lipids and steroidal hormones, as well as xenobiotic substances such as medicines and other chemicals.
Delta	Pre-specified margin of non-inferiority. After study completion, a two-sided 95% confidence interval (or one-sided 97.5% interval) for the true difference between the two agents will be constructed. In a non-inferiority trial, the confidence interval of the results should lie entirely on the positive side of the non-inferiority margin. Historical data are often used to determine the non-inferiority margin delta for all trials involving an active control treatment. The delta always needs to be tailored to the particular clinical context and no rule can be provided that covers all clinical situations.
DMC	Data Monitoring Committee, see also DSMB.
Dosage form	The physical form of a dose of a chemical compound used as a medicine intended for administration. Common dosage forms include pill, tablet or capsule, syrup, aerosol or inhaler, liquid (i.e. solution, powder, lyophilizate) for injection, and herbal compounds such as plants, among others. The route of administration is dependent on the dosage form of the medicine in question.
DSMB	Data and Safety Monitoring Board. A group of experts able to make decisions on whether to continue or discontinue a trial on the basis of interim analyses and regular safety (or futility)with a view to protecting the participants. Generally independent from the sponsor. May review data in a blinded or un-blinded fashion.
Ethics Committee	Ethics Committee (EU): Independent Committee in charge of providing ethical review opinion before and during a clinical trial. Called the Institutional Review Board in the United States of America.

EudraCT	A public website hosted by the European Medicines Agency (EMA) giving access to an exhaustive list of clinical trials of medicinal products, which are performed with at least one site in the European Economic Area (EEA), or of trials included in a Paediatric Investigation Plan. See https://www.clinicaltrialsregister.eu/.
First-in-man guideline	A guideline describing the transition from non-clinical to early clinical development. It provides criteria to classify new investigational medicines as potential high-risk medicines. It also gives guidance on quality aspects, non-clinical testing strategies, and designs for first-in-man clinical trials, including the calculation of the initial dose to be used in humans, the subsequent dose escalation, and the management of risk.
First-pass effect	The first-pass effect, also known as first-pass metabolism or presystemic metabolism, is a phenomenon of drug metabolism whereby the amount of a drug is greatly reduced before it reaches the systemic circulation. For oral drugs, it is the fraction of lost drug which is generally related to the liver and gut wall metabolism.
Half-life	T½, terminal T½ The period of time it takes for a substance undergoing elimination to decrease by half. Also known as exponential decay.
High-risk medicines	See first-in-man guideline.
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use "is a joint initiative involving both regulators and research-based industry representatives of the European Union, Japan and the USA in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality and efficacy of medicines." (See http://www.ich.org.)
IEC	Independent Ethics Committee.
INN	International Non-proprietary Name. Identifier of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. In lay terms, more commonly known as the generic name of a medicine.
Interim analysis	Statistical analysis made during the course of a trial, before the planned end of the trial, aiming at treatment comparison. It requires unblinding of the trial.
IRB	Institutional Review Board (US): An independent Committee in charge of providing ethical review opinion before and during a clinical trial. Called the Ethics Committee in the EU.

Medicines	For the purpose of this document, medicines include drugs, vaccines, and biologicals (different US legal frameworks). Medicines are called medicinal products in EU (single legal framework).
Modeling	The science of using mathematical language to describe and quantify a system. For example, pharmacokinetic (PK) or pharmacodynamic (PD) modeling may allow use of sparse sampling to characterize the PK and PD of a medicine and to optimize future experiments.
Multiplicity	Control of type I error by adjustment of alpha level for multiple tests. May be needed in situations such as: multiple arms; co-primary endpoints; multiple statistical approaches for the same endpoint; interim analysis; more than one dose versus placebo; meta analysis; and/or sub group analysis. The adjustment approach could be very conservative (e.g., Bonferroni) or less conservative (e.g., Hochberg).
Non-inferiority trial (see also equivalence)	A clinical trial intended to show that the test medicine (or intervention) is as efficacious (or as safe) as the comparator (active comparator). The comparison is one-sided only (two-sided in an equivalence trial). Such a trial requires defining an acceptable range of results (also called delta) within which the results are considered not different. The more serious the outcome for the patient, the smaller the delta normally considered acceptable.
Null hypothesis	The null hypothesis typically proposes a general or default position, such as that there is no relationship between two measured phenomena.
Off-label medicine	Medicine used outside the terms of the indication, route of administration, or dosing in the product information agreed by the regulatory authority.
On hold (trial/evaluation)	Temporary discontinuation of a trial or evaluation pending an answer to a regulatory request for additional information (generally for safety).
Paediatric Investigation Plan	A mandatory development plan to be carried out in children (0-18 years) in order for a medicine to be authorized in the European Union. Completion of the plan according to its timelines and defined content may be rewarded by an extension of the medicine's patent by 6 months.
Pharmacodynamics (PD)	What a medicine does to the body. Description of the pharmacological effects of a medicine on the various target organs.
Pharmacogenetics (PG)	Genetic characteristics modifying either the pharmacodynamics or pharmacokinetics of a medicine.
Pharmacokinetics (PK)	What the body does to a medicine. Description of absorption, distribution, metabolism, excretion of the medicine.
Plasma clearance	Volume of plasma cleared from the medicine by unit of time.

Population pharmacokinetics (pop PK)	The study of variability in drug concentrations between individuals (healthy volunteers or patients).
Power effect	The ability of the study to reliably detect the size of the effect of the study intervention (medicine effect). The larger the sample size or number of participants in the trial, the greater the statistical power.
Proof of concept	Early confirmation of the validity of a given hypothesis concerning a disease or its treatment, achieved through a series of techniques. The data supporting the proof of concept can be derived from: • non-clinical (tissue and animal, disease models) studies; • clinical studies in healthy volunteers; • clinical studies in patients.
Randomization	Process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias. Ensures initial comparability of the groups.
Refused	The trial or the approval of a medicine is rejected by authorities for reasons of lack of efficacy or safety, or insufficient quality of the medicine. Reasons should be provided.
Restrictions of use	Limitations to the prescription of a medicine in order to maximize efficacy and limit or prevent safety issues.
Rich (blood) sampling	In rich sampling, a calculation should be made of predicted blood sampling volume, and should not exceed safe volumes according to age. The timing of the samples and number of subjects also should be justified on the basis of models, knowledge of adult PK characteristics, or previous experience.
Sample size	The number of patients in a trial. This has to be determined according to specific formula in order for the trial to reliably conclude with statistical significance.
Simulation	Manipulation of a model in such a way that it operates statistically, or in time or space, to develop data as a basis for making decisions on medicines dosing or effect. It allows characterization of interactions that would not otherwise be apparent because of their separation in time or space. (See also Modeling).
Sparse (blood) sampling	Sparse sampling means that only one or two samples will be collected in each child, and repeated in many more children, in the range of 100-200 (see population PK). This technique has the obvious advantage of sparing children from multiple blood sampling. Models can be used to predict the optimal sampling times or windows for sparse sampling and the number of subjects.

Sponsor	ICH definition: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. WHO definition: An individual, company, institution, or organization that, either singularly or collectively, takes responsibility for the initiation, management, and/or financing of a health research project. The sponsor of a study may be composed of a number of individuals, companies, institutions, or organizations that share the responsibilities of the study. In this case, it is important that the protocol clearly defines how the sponsor responsibilities are distributed, the individual(s) or organization(s) responsible for establishing the DSMB, and to whom the DSMB reports.
Steady state	At steady state, the maintenance dose/rate of administration is equal to the rate of elimination. This leads to the steady-state concentration (Css) of a medicine.
Stratification - Stratum/a	Stratification is the process of grouping members of the population into relatively homogeneous subgroups before sampling (e.g. by randomization), based on pre-defined criteria such as age, or disease stage. The strata should be mutually exclusive: every element in the population must be assigned to only one stratum. According to the context: stratified randomization; stratified analysis (with or without randomization).
Superiority trial	A clinical trial intended to show that the test medicine (or intervention) is more efficacious (or safer) than the comparator (i.e. placebo or active comparator). By convention, superiority is agreed when the p value (alpha) is smaller than 0.05 (5%).
Surrogate marker	A biomarker used in place of a clinical endpoint to which it is correlated (e.g. blood pressure reduction instead of stroke). A surrogate marker may be more sensitive to drug effect, its change obtained over a shorter time frame (months instead of years), but it does not provide for the real clinical effect size, and the correlation may exist for some drug classes and not others (e.g., correlation between glycated hemoglobin change and diabetes mortality for metformin, but not for sulfonylureas)
Tmax	Time to reach maximum concentration.
Unlicensed medicine	Medicine used despite the lack of regulatory registration in any indication.
Volume of distribution	Quantifies the distribution of a medicine between plasma and the rest of the body after oral or parenteral dosing. It is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a medicine.
Withdrawn (regulatory application)	Application withdrawn by the sponsor/applicant. May indicate a negative opinion by regulatory authorities.

Withdrawal (patients)	Discontinuation of participation in study. Discontinuation of consent to participate.
Written Request	In the United States, a Written Request for pediatric studies may be requested under section 505A of the Federal Food, Drug, and Cosmetic Act for a particular drug. May follow a Pediatric Study Proposal Request by a sponsor. Completion of the Written Request according to its terms and timelines is rewarded by 6 months of exclusivity for the medicine.