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Curriculum Development of Human Clinical Trials for the Next Generation of PhD Students and Early Career Researchers in the Medical, Science, Pharmacy and Health Professions

CHAPTER 8

PAEDIATRIC CLINICAL TRIALS

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Content

Time required to complete this chapter

Core content:	1h 00m
Additional/advanced content (yellow boxes):	15m
Activities/practical exercises (blue framed boxes):	1h 00m
Total time:	**2h 15m**

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1 Introduction to the chapter

Clinical studies in children differ from studies in adults in many aspects. The diversity of children in different age groups, the consent and recruitment process and the ethical implications are only some examples to explain why the planning and conduct of a paediatric study need particular attention. In the ethical review, paediatric expertise is required to assess and balance the benefits, risks and burden of research with minors. That is why trials with the paediatric population should be performed by trained investigators with paediatric experience. This chapter will provide you with a brief overview of clinical trials with the medicinal product intervention in the paediatric population. Further, the challenges of paediatric research are described in detail, which it is beneficial to take into consideration before the commencement of clinical study with minors as potential researchers or members of the study team. You´ll find out how to conduct a trial with specific groups of minors (neonates, healthy minors, adolescents) or what is the process of informed consent/assent in emergency situations. In the last subchapter, you will read that the involvement of parents and children in the clinical trial development process is also important so that they can adequately address and incorporate their needs and preferences.

In addition to the basic text, the chapter contains yellow boxes either with specifically focused content or to complete the topic described. They are not mandatory to study. Blue framed boxes indicate activities for independent work or teacher-led work during the lesson.

2 Paediatric regulatory framework

In the EU, the role of the regulatory body exerts a network of national agencies, coordinated by the European Medicines Agency and the European Commission.

In the past, market forces alone were not a sufficient incentive for adequate research and development of paediatric medicines. Paediatric development has depended to a considerable extent on the pharmaceutical company's product strategy with respect to the adult population. For many companies, adults represent the most economically attractive market. The consequence of this was and still is a low number of conducted paediatric clinical studies, a lack of data supporting paediatric indication and the frequent use of medication in off-label mode. In 1997, the European Commission organized a round table of experts to discuss paediatric medicines at the EMA. The experts identified the need to strengthen the legislation, in particular by introducing a system of incentives. In 1998, the Commission supported the need for international discussion on the conduct of clinical trials in children in the context of the International Conference on Harmonisation (ICH). In 2000, the harmonized tripartite E11 ICH guideline "Clinical investigation of medicinal products in the paediatric population" was finalized and subsequently became a European guideline in 2001. ICH guideline was later amended with an integrated Addendum known as **ICH E11(R1) guideline (2017)**.[1] ICH E11 serves as an international quality standard for paediatric clinical trials. The goal of this guidance

[1] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e11r1-guideline-clinical-investigation-medicinal-products-pediatric-population-revision-1_en.pdf

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is to encourage and facilitate the timely development of paediatric medicine products worldwide.

In December 2000, The European Commission was requested by the European Health Council to take specific action to remedy the problem of the usage of drugs authorized only for adults in a paediatric population. As a reaction to this request, the Commission published a consultation paper "Better medicines for children–proposed regulatory actions on paediatric medicinal products" (2002). In the following years, these proposals were assessed and resulted in new legislation governing the development and authorization of medicines for paediatric use, **Regulation (EC) No 1901/2006 on medicinal products for paediatric use**[2] (hereinafter "Paediatric Regulation", Regulation (EC) No 1901/2006). The Regulation was introduced in the European Union (E.U.) in December 2006 and entered into force in January 2007.

Another equally important legal act related to clinical trials is **Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use**.[3] Clinical Trials Regulation (hereinafter "CTR", Regulation (EU) No 536/2014) is valid from 31 January 2022 and repeals Directive 2001/20/EC (valid until 31 January 2025). CTR ensures that the rules for conducting clinical trials are identical through the EU/EEA in accordance with the highest standards of patient safety. An overview of complete paediatric legislation is given in Table 1. Documents relating to the Directive are not mentioned in this chapter because of the current validity of the new Regulation and the limited effectiveness of the Directive. More information regarding this Regulation and the transition period from the Directive to CTR can be found in Chapter 4.[4]

Table 1: Overview of paediatric legislative

Regulation (EC) No 1901/2006 on medicinal products for paediatric use
Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use
Commission Implementing Regulation (EU) 2017/556[5] on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014
Commission Delegated Regulation (EU) 2017/1569[6] supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections
Directive 2001/83/EC[7] of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
Regulation (EC) No 726/2004[8] of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

As the Directive and CTR only marginally addressed paediatric research, a recommendation of the European Commission expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 was released under the title **Ethical considerations for clinical**

[2] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R1901&qid=1621344437946
[3] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0536
[4] Insert link to Chapter 4
[5] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0556&from=EN
[6] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R1569&from=EN
[7] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083&from=en
[8] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004R0726&from=EN

trials on medicinal products conducted with minors (2017).[9]
The document provides recommendations on various ethical aspects of clinical trials performed with minors from birth up to the age of legal competence to provide informed consent. As you know, each Member State is responsible for the authorisation of clinical trials, including ethical approval. This document should facilitate a harmonised approach to the application of the Clinical Trials Regulation across the EU and thereby facilitating the conduct of clinical trials in whichever country the trial occurs. This recommendation is a part of **The rules governing medicinal products in the European Union. Volume 10**[10] – Guidance documents applying to clinical trials authorised under the Regulation. Please see Table 2 for further relevant guidelines and recommendations.

Table 2: Relevant guidelines

International and European guidelines
Clinical Investigation of Medicinal Products in the Paediatric Population (addendum E11(R1)
Paediatric extrapolation (E11A – draft version)[11]
The rules governing medicinal products in the European Union. Volume 10 – Guidance documents applying to clinical trials authorised under the Regulation[12]
Guideline for Good Clinical Practice E6(R2)[13]
Concept paper on the involvement of children and young people at the Paediatric Committee (EMA/PDCO/388684/2012)[14]
Choice of Control Group in Clinical Trials (E 10)[15]
Guideline on clinical trials in small populations, CHMP/EWP/83561/05, CHMP[16]
Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (June 2006) EMA/CHMP/EWP/147013/2004 - Corrigendum[17]
Guideline on conduct of Pharmacovigilance for medicines used by the paediatric population (June 2006) EMA/CHMP/PhVWP/235910/2005- rev.1, CHMP[18]
Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants, World Health Organization (WHO) (Geneva 2011)[19]

Paediatric clinical research started in the US a few years in advance compared to Europe. The most recent legislation ruling this subject is essentially enclosed in two main acts, i.e., the PREA, also known as 'the paediatric rule' of 2003 and the BPCA, 'paediatric exclusivity' of 2002, both amended in the FDA of 2007.

[9] https://health.ec.europa.eu/system/files/2018-02/2017_09_18_ethical_consid_ct_with_minors_0.pdf
[10] https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en
[11] https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-e11a-pediatric-extrapolation-step-2b_en.pdf
[12] https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en
[13] https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline
[14] https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-involvement-children-young-people-paediatric-committee-pdco_en.pdf
[15] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-10-choice-control-group-clinical-trials-step-5_en.pdf
[16] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-trials-small-populations_en.pdf
[17] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-role-pharmacokinetics-development-medicinal-products-paediatric-population_en.pdf
[18] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-conduct-pharmacovigilance-medicines-used-paediatric-population_en.pdf
[19] https://www.who.int/publications/i/item/9789241502948

Outside of the EU and US, there are currently no specific paediatric legislative requirements, but this may change in the future. Despite this lack of legislation, some markets do require local paediatric data for marketing authorisation.

2.1 Paediatric Regulation in Europe (Regulation EC No 1901/2006)

The Paediatric Regulation, introduced in 2007, combines new legal obligations with economic rewards for the pharmaceutical industry, aiming to stimulate research, innovation and development of medicinal products for children.

Since its implementation, the Paediatric Regulation has had a very positive impact on paediatric drug development. The 10-year report of the EMA has shown that it has led to more medicines for children, better and more information for prescribers and patients, better paediatric research and development, more regulatory support for paediatric matters and paediatrics now being an integral part of medicine development.[20]

The main sections ruled by the Regulation are:

- the institution of the Paediatric Committee (PDCO);
- the definition of the regulatory requirement for marketing authorization, among which is the Paediatric Investigational Plan (PIP);
- the introduction of rewards and incentives for the development of paediatric drugs, i.e., the PUMA.

2.1.1 PDCO

The Paediatric Committee is the European Medicines Agency's scientific committee. The PDCO's main role is assessment and agreement of the content of Paediatric Investigation Plans (PIPs), waivers and deferrals. The Paediatric Committee is composed of independent and impartial members appointed from Member States, health professionals, and patients' associations. You can find more information about PDCO composition and activities in the document Rules of procedures of PDCO.[21]

2.1.2 PIP

PIP is the development document which supports the use of medicine for children. The PIP covers the timing and measures proposed to generate the data to support a paediatric indication, with an age-appropriate formulation, in all relevant paediatric subsets. Guideline on the content and format[22] of PIP can be found in EUR-Lex. Applicants for PIP, including waiver of deferral, can use Templates for scientific documents[23] created by EMA and can request scientific advice from EMA in preparation for a PIP, which is free of charge for questions relating to the development of paediatric medicines.

[20] https://health.ec.europa.eu/system/files/2020-06/paediatrics_10_years_ema_technical_report_0.pdf
[21] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/pdco-rules-procedure_en.pdf
[22] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52014XC0927%2801%29&qid=1621344524564
[23] https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.ema.europa.eu%2Fen%2Fdocuments%2Ftemplate-form%2Ftemplate-scientific-document-part-b-f_en.doc&wdOrigin=BROWSELINK

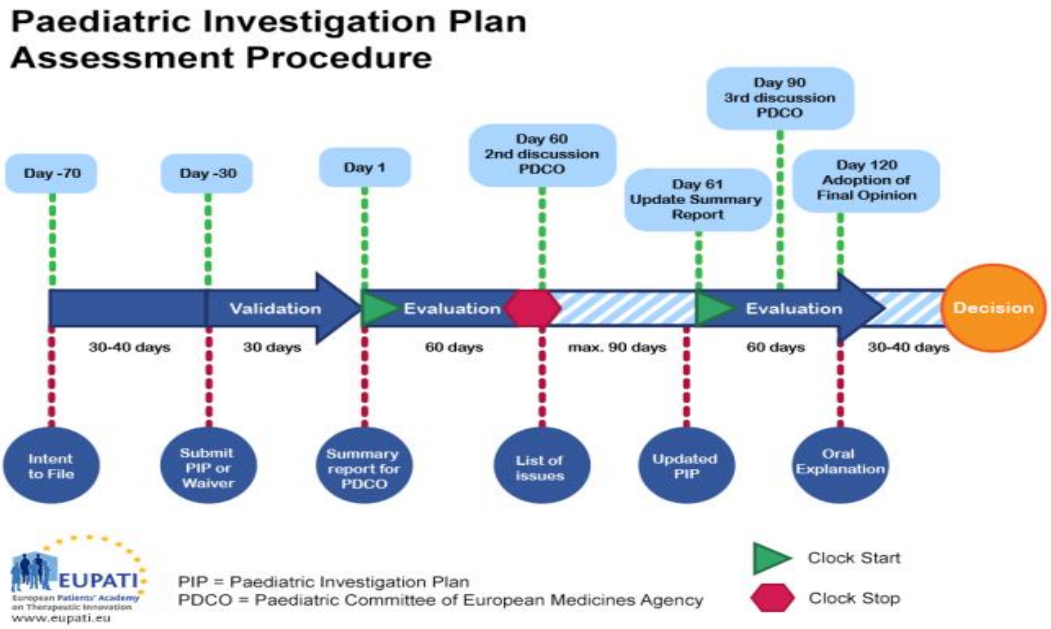
The development of this document is important for those who apply for Marketing Authorisation (MA) of a new medical product not authorised in the EU. In this case, marketing authorisation applications have to include the results of studies conducted in the paediatric population in compliance with an agreed PIP. Application for PIP should be submitted, unless duly justified, "not later than upon completion of the human pharmaco-kinetic studies", according to the Paediatric Regulation. The requirement of PIP also applies to applications to add a new indication, a new route of administration, or a new pharmaceutical form to an existing marketing authorisation.

A waiver may be granted by EMA when such paediatric development is not needed or is not appropriate. EMA can also grant a deferral, e.g. development of paediatric medicine products is deferred until there are sufficient data to demonstrate the safety and efficacy of the products in an adult population. In practice, it happens in more than 80% of cases.[24] Generics, for example, are also excluded from the PIP requirements.

PDCO´s decision on PIPs (and waivers) is made public.[25] The provisions of the regulation offer incentives since products that complete the agreed paediatric development can request an extension of patent protection for 6 months and an additional 2 years of market exclusivity for paediatric orphan medicinal products.

Practical exercise

Read articles 16 and 17 of the Paediatric Regulation (EC) 1901/2006 about the Paediatric Investigation Plan. Please try to specify how long does it take PDCO to agree on a PIP from the time that an initial application is submitted? For a better idea, you can use the diagram below.



[24] https://pubmed.ncbi.nlm.nih.gov/30924233/
[25] https://www.ema.europa.eu/en/medicines/ema_group_types/ema_pip

Read article 11 of Paediatric Regulation (EC) 1901/2006 about Waivers. Based on the information obtained, write in the text field below when Marketing Authorisation (MA) applicant can be granted a waiver for PIPs:

1) ……..
2) ……..
3) ……..

2.1.3 PUMA

The Paediatric Regulation also introduced a new type of MA, the Paediatric Use Marketing Authorisation (PUMA). This is a voluntary procedure, offering 8 years of data exclusivity plus an additional 2 years of market exclusivity to any off-patent medicinal product developed for exclusive use in the paediatric population. It is granted to investigational medicinal products that have successfully completed an agreed PIP and have set a risk management plan for the follow-up of efficacy and safety of the product.

2.2 ICH E11(R1) Guideline

To address the lack of appropriate paediatric drugs available on the global market, in 2000, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued the **ICH E11 guideline** regarding the Clinical Investigation of Medicinal Products in the Paediatric Population. It has been written specifically to harmonize, promote, and facilitate high-quality and ethical clinical research for children within the ICH regions, i.e., the United States of America (USA), the European Union (EU), and Japan.

On 6 October 2017, EMA published a revised version of the **ICH E11(R1) guideline** on the clinical investigation of medicinal products in the paediatric population in the form of an addendum. The addendum does not alter the scope of the original guideline. CH E11(R1) supplements ICH E11 in several areas, reflecting various progress in paediatric drug development, especially in extrapolation, modelling and simulation, trial methodology, and formulation. The Addendum has acknowledged the new scientific and technical advances in paediatric drug development that have occurred since the first release of the ICH E11 Guideline in 2000 and provides clarification and current regulatory perspective on topics in paediatric drug development.

3 Ethics of paediatric clinical trials

Clinical trials generally bring a lot of ethical aspects, as we know from the history of clinical trials (for more information, please see Chapter 4, CONSCIOUS project).[26] Paediatric clinical research presents multiple ethical aspects which result in the creation of many regulations and recommendations on this matter which are under constant improvement and implementation

[26] Link to Chapter 4, CONSCIOUS project

and whose common goal is to stimulate reflection on the best way to protect children´s participation in clinical research.

Paediatric patients were systematically given off-label medicine (intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation) before the introduction of international regulations and incentives aiming to define the need for child-specific drug development. Off-label treatment administrated to children is usually tested only on the adult population and does not possess any efficacy or safety data for their specific population. This causes an ethical problem, and that is why the need for clinical trials with children has now been widely recognised and is stimulated by European legislation, e.g. by requiring Paediatric Investigation Plans.

Children are a vulnerable population as they may be relatively incapable of protecting their own interests. Rather than being excluded from research, children deserve everyone's utmost effort to protect them from risks and burdens by minimising and mitigating those risks and burdens.

There is a useful document on the EMA website, **Ethical considerations for clinical trials on medicinal products conducted with minors**[27] (further "EMA´s Ethical consideration), a recommendation already mentioned in the Paediatric regulatory framework section. This recommendation is intended both for non-commercial clinical trials and commercial ones. It describes in detail, among other things, the process of informed consent, the participation of minors in the process of informed consent, required expertise for trial assessment, paediatric formulation, adverse effect reporting or insurance issues.

3.1 Informed consent and agreement/assent

As the child (minor) is unable to provide legal consent, informed consent must be sought from the parents/legally designated representative on the child's behalf. Articles 29 and 32 of the Clinical Trials Regulation require that specific, written informed consent of parents/legally designated representatives must be sought and obtained prior to enrolling a child in a trial.

Each Member State of the European Union and European Economic Area has national legislation and detailed requirements for informed consent and assent that are required for the conduct of paediatric clinical trials. Because these requirements vary amongst countries, researchers or sponsors must always check these national regulatory requirements when preparing consent/assent documents. Enpr-EMA´s working group prepared a **multinational overview of informed consent and assent requirements of paediatric clinical trials across Europe** in 2015, updated in 2019 (Informed consent requirements for paediatric clinical trials in Europe – ToolKit table.[28] This overview includes legal requirements for 25 countries, including, for example, the legal age of consent, number of required signatories, official language requirements, etc. You can see in the above-mentioned document that the legal age to give informed consent varies according to national laws, therefore, multinational trials may enrol children of the same age who are minors in one but able to provide informed consent in another Member State.

[27] https://health.ec.europa.eu/system/files/2018-02/2017_09_18_ethical_consid_ct_with_minors_0.pdf
[28] https://www.ema.europa.eu/en/documents/other/informed-consent-paediatric-clinical-trials-europe-2015_en.pdf

Enpr-EMA´s working group on ethics has also developed a document called **Assent / Informed Consent Guidance for Paediatric Clinical Trials with Medicinal Products in Europe**.[29]

- ✓ This document is intended to be used as an overview tool of the contents for assent/informed consent forms for all stakeholders, such as patients, sponsors and investigators.
- ✓ You can find two tables in this document, first with general information for informed consent and assent/agreements and second with trial-specific information for informed consent and assent/agreements.
- ✓ In both tables, there are separate columns for each age category (0<2, 2<6, 6<10, 10<18) and legal representative as well accompanied by 3-level recommendation symbols for all age groups.
- ✓ Review these tables to get a basic overview of what information the informed consent and assent/agreements should contain and what should not be missing from it.

Practical exercise
Open the Enpr-EMA ToolKit table to find out information about your country. Go to the discussion board and write down your selected country, the legal age of consent, mandatory / suggested age ranges defined for assent and the number of required signatories.

However, we should first specify the difference between the terms "informed consent", “agreement”, “assent”, and dissent. Please see the explanation of the terms in Table 3.

Table 3: Terms explanation

Informed consent	a subject’s free and voluntary expression of his or her willingness to participate in a particular clinical trial after having been informed of all aspects of the clinical trial that are relevant to the subject’s decision to participate	Article 2(2.21) of the Clinical Trials Regulation
Assent	“This Regulation is without prejudice to national law requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her shall also assent to participate in a clinical trial".	Article 29(8) of the Clinical Trials Regulation
Dissent	the expression of the minor’s will to refuse participation in a trial or to withdraw from, the clinical trial at any time, is respected by the investigator	Article 32(1.c) of the Clinical Trial Regulation
Agreement	used by analogy to “assent” where it is not a legal requirement	Glossary; Ethical considerations for clinical trials on medicinal products conducted with minors

[29] https://www.ema.europa.eu/en/documents/other/assent/informed-consent-guidance-paediatric-clinical-trials-medicinal-products-europe_en.pdf

3.1.1 Informed consent from the legally designated representative

The person providing the information – usually the investigator or his adequately trained delegate – should be experienced in providing tailored research information, competent in communicating and working with children and young people, and providing them and their legal representatives with the time and space to decide without pressure. When providing information, the investigator should take into consideration the fear and uncertainty of parents, especially when they are inexperienced concerning the child's condition.

The information should be given to each parent, or legally designated representative, both in oral and written form. Article 29.2(a) and (b) of CTR describe the information that should be provided, keeping it "comprehensive, concise, clear, relevant, and understandable" to obtain credible informed consent. In particular, parents/legally designated representatives should be explicitly informed of their right to refuse the child's participation and to withdraw the child from the clinical trial at any time without any resulting detriment for the child and without having to provide any justification, in line with Article 29(2aii) of the Clinical Trials Regulation.

3.1.2 Participation of minors in the informed consent process and agreement/assent

EMA´s Ethical consideration document supports the systematic request for agreement (even if the assent is not legally required) and recommends that the investigator should obtain agreement from the minor even if it is not requested by national law. The process of the agreement and providing the information about the trial for the minor should be documented in the clinical protocol.

It is very important that the minor fully participate in the informed consent process together with the parents/legally designated representative, which is adapted to the age and maturity of the child. To provide age-appropriate information and assent/agreement forms, separate material should be used for children, using language and communication tools (visuals, cartoons, videos etc.) appropriate to the participant's age and maturity.

Watch a YouTube video “Health research: making the right decision for me”[30] showing a young child's perspective on her/his potential participation in a clinical trial.

- ✓ Notice how important the communication between the investigator, the child and the parents/legally designated representatives is, passing all essential information about the study and answering any unclear questions of the child or parents/ legally designated representatives.

There are different divisions of the child population according to age: ICH E11 guideline states the age group of children (2 to 11 years) and the age group of adolescents (12-18 years), whereas EMA´s Ethical consideration of the expert group redefined those groups into pre-schoolers (2-5 years), schoolers (6-9 years) and adolescents (10-18 years). This change was made due to the WHO definition of adolescence starting at the age of 10 years.

[30] www.youtube.com/watch?v=6yaKwLG_vlE

Participation and agreement/assent according to age groups and level of maturity
It is essential to provide information to the minor individually and with respect to their level of maturity, intellectual capacities and life/disease experience. Therefore age ranges are only meant as guidance regarding the proper involvement of children in the informed consent process.

Newborns and infants (from birth to 2 years of age) – it is not expected that agreement will be obtained in this age group. Information regarding the study should be mostly aimed at preparing the child for the procedures to come. Nevertheless, any signs of protest should be discussed with parents/legally designated representatives.

Pre-schoolers (2-5 years of age) – there is more probability of giving an agreement within this age group. Visual information (videos, pictograms, cartoons or drawings) may be provided to the child for a better understanding of the given information since textual information is not very suitable for most children at this age. It is backed by research that children have the capacity to form their own opinion from the age of 4-3 years. They can also express fundamental resistance and protest beyond the usual signs of discomfort during or after unpleasant procedures. A discussion with the child and parents/ legally designated representative is needed at this expression must be valued. If the result of the discussion is dissent, it must be respected.

Schoolers (6-9 years of age) – children in this age group usually understand the risks and benefits of the study. Researchers should inform children well about the research, and agreement should be obtained, preferably in writing. Research information may be enhanced by using visuals such as videos, pictograms, cartoons or drawings, even if children of this age group are able to read and write. They are also able to form their opinion, so any dissent must be respected.

Adolescents (10-18 years of age) - obtaining informed consent for this group varies across EU countries. Some countries consider that adolescents above a certain age are no longer minors and have the legal competence to give informed consent for research participation. In other EU countries, national law demands assent from all or part of this group. For more information regarding national legal requirements within EU countries plus Norway and Iceland, please see ToolKit table.[31] In general, information about research should be provided, and agreement from an adolescent who is still a minor should be sought and respected. There is also the need for informed consent from the parents/legally designated representative.

Consent, assent and agreement in emergency situations
In some emergency situations, treatment or intervention is required within minutes, and the patient's consciousness may be altered, the parents/legally designated representative may not be available to provide prior informed consent, and the children cannot be informed nor express assent or agreement. Article 35 of the CTR introduces an exemption from the informed consent requirements described above in emergency situations under strict conditions. It is necessary to say that when it is possible to delay the research decision until a parent is present to make a decision, the investigator should wait. If such delay is not possible, the trial may start without informed consent. In that case, informed consent must be obtained as soon as possible after the inclusion of the minor into the trial. This informed consent is called "deferred consent". This deferred consent must be followed by a regular informed consent procedure once parents/legally designated representatives are present. Children should be informed about the trial and involved in the informed consent procedure as soon as possible, taking into account their health condition. If the parents/legally designated representative does not wish to sign the informed consent, they should be informed of the possibility to object to the

[31] https://www.ema.europa.eu/en/documents/other/informed-consent-paediatric-clinical-trials-europe-2015_en.pdf

use of the data that have already been gathered. The conditions under deferred consent that could be allowable must be clearly described in the trial protocol.

3.2 Payment for participation

Although it is common practice to compensate trial participants for travel, parking, meal allowance and accommodation, payments for participation in trials are more controversial in children. While the European Union advocates banning all incentive payments to children, this is common practice in the United States, where almost 25% of paediatric trials offer payment.[32] This can be in the form of reimbursement, compensation, appreciation, or incentive payments. For a better explanation of these terms, please see Table 4, where you can also find examples of payments.

Clinical Trial Regulation states that there must be **no inducement** when enrolling minors in the study for both parents/legally designated representatives and minors. Only compensation for the parents´ expenses and loss of earnings which are directly related to the child´s participation in the trial, is allowed. The ethical concern about large incentive payments is that they might entice and distort the judgement and decision of the parent or child about the risks of trial participation.

A small token of appreciation for participating minors may be acceptable but needs to be explicitly allowed by ethical review. This question of any kind of payment for participation is under the huge responsibility of ethics committees which has to evaluate each clinical trial with minors individually and very carefully. Information on possible payments must be mentioned in Informed consent and assent.

Table 4: Models of payments for participation in the trial (all age groups, including adults)

Payment serves as	Amount determined by	Potential advantages	Potential disadvantages
Incentive	Market rates Supply and demand	+ More rapid recruitment + Bonuses for completion + Little or no financial sacrifice by subject	– Undue inducement possibly resulting in: incomplete assessment of risks and benefits by subject; subject concealing information to ensure enrollment/retention – Competition between studies; better-funded studies more likely to meet recruitment goals

[32] https://www.jpeds.com/article/S0022-3476(02)00063-X/fulltext

Compensation	Standardized "wage" for time and effort Additional payment for extra burdens, such as uncomfortable procedures	+ Recognizes contributions of participants + Uniform payment across studies + Equal pay for equal work + Less risk of undue inducement	− May have little impact on recruitment
Reimbursement	Expenses incurred (transport, meals,...), with or without reimbursement for lost wages	+ Makes research participation revenue neutral + Little risk of undue inducement	− May have little impact on recruitment − Uneven reimbursement from subject to subject − Financial sacrifice for the subject if lost wages are not reimbursed
Reward	Token of appreciation given at the conclusion of the study	+ Expresses gratitude for the contribution made + Not market dependent + Avoids undue inducement	− Likely to have no impact on recruitment − No basis for consistency

Quiz
Select one of the possible answers:

1. When should an initial application for PIP be submitted for new MA applications?
    a) Not later than upon completion of the human pharmaco-kinetic studies
    b) Before the completion of the human pharmaco-kinetic studies
    c) At the time of marketing authorisation submission
    d) At any time during the medical product development

2. Is PIP necessary for generics?
    Yes/No

3. Is a PIP required for an application for a new strength or presentation of a medicinal product?
    Yes/No

4. Does Clinical Trials Regulation allow payment for the participation of minors in a clinical trial?
    a) Yes, CTR says that participants and their parents can be offered a small amount of money, the amount depends on an individual clinical trial.
    b) No, CTR doesn´t allow any financial inducement during the patient´s enrolment into the trial, only compensations for the parents´ expenses and loss of earnings directly related to the participation in the clinical trial are allowed.

Co-funded by the Erasmus+ Programme of the European Union

c) No, CTR states that there must be no inducement or compensation during patients´ enrolment into the trial
d) Yes, CTR says that compensations may be offered to study participants and their parents if they are approved by the Ethics Committee

4 Study design and conduct of paediatric clinical trials

4.1 Characteristics of paediatric clinical trials

This chapter describes challenges that accompany clinical trials in children and which characterize this often overlooked subgroup of clinical trials. Despite the academic or industrial sponsor of the trial, conducting of paediatric trials is impaired by several obstacles that may lead to delay or incompletion of clinical trials and thus to waste unnecessarily included paediatric patients. Therefore it may be valuable to know the potential barriers to paediatric research before starting a trial. The challenges in paediatric clinical trials are categorized in Table 5.

One of the challenges is **the economic burden**. From a financial point of view, paediatric clinical trials are not very interesting for the industry due to the small patient population, which is further fractioned into several subgroups and strongly reduces the market's size. Economic factors may represent a big obstacle as the returns promised by the paediatric market are even more disadvantageous compared to the burden that has to be undertaken. For investigator-initiated trials could be the preparation of age-appropriate drug form a financial burden. The development process of drug forms for special age groups could be challenging, both from a technical point and from the point of cost/profit ratio.

Generally, the paediatric population refers, according to CTR, to children aged between birth and less than 18 years.

Table 5: Challenges accompanying paediatric clinical trials

Difficulties in patient recruitment and retention

The regulatory process, especially in multi-centre international trials with the participation of countries outside of the EU, could be inhomogeneous and time-consuming because each regulatory body could have specific requirements. The study must be approved by multiple competent authorities and ethics committees that can ask for different clarifications, and this can lead to nationally different versions of the study protocol. Thanks to Clinical Trial Regulation, approval by the regulatory body (EMA) is centralized (EU portal) and harmonized in the countries of the European Union. Technical and scientific aspects of the trial application are discussed jointly, whereas ethical aspects are assessed separately by the concerned Member States.

The conduction of **multi-centre international trials** in the paediatric population may also represent a challenging point. Participation of several countries in a study may be promising due better chance to achieve a higher number of enrolled patients, on the other hand, it entails an administrative and financial burden. Last but not least, the finalization of contracts between the sites, the sponsor and other subcontractors takes a very long time too and may cause a delay in the start of the study.

4.1.1 Patients recruitment and retention

Low numbers of enrolled patients in the trial are, unfortunately, also one of the characteristics of paediatric clinical trials. Failure to achieve the target sample size can lead to a reduction in the statistical power of a study. Also, prolonged recruitment results in increased time or cost extensions and may result in premature termination of trials. Studies that terminate prematurely or fail to reach adequate statistical power raise 'ethical' concerns as trialists have exposed the participants to an intervention with uncertain benefits and may still be unable to determine whether the intervention does more harm than good at trial completion.

This shortage of patients could be compensated by conducting multinational clinical trials, but as already mentioned above, they are more difficult because of administrative requirements and procedures.

There could be many factors which can influence patient recruitment and retention in the trial. Lack of communication between the investigator, patient and parent is one of them and could lead to the participant (or potential participant) and his family not understanding correctly the conditions of the study, its aims, benefits and potential risks. They may feel distrustful if the entire process is not explained transparently. The right model of how information about the trial might be provided to participants and parents/legally designated representatives are clearly described in the EMA´s Ethical considerations, mentioned several times.

Prior to consent and assent being given, a minor and parents/legally designated representative should be made aware of the right to refuse participation in a clinical trial and entitlement to withdraw their informed consent. Freely, at any time, without having to give a reason. In paediatric clinical trials, the most common reason for withdrawing from a trial is the wrong drug formulation (e.g. the taste), the pharmaceutical form (tablets or capsules difficult to swallow for some patient´s subgroup), the strength (not easily scalable for smaller children) or too many doses of the treatment per day.

4.1.2 Drug formulations

Many medicinal products are not currently available in formulations suitable for administration to the paediatric population. Consequently, healthcare professionals frequently resort to the preparation and administration of unlicensed formulations by manipulation of adult dosage forms. Paediatric Regulation should facilitate the development and accessibility of age-appropriate paediatric medicines by requiring marketing-authorisation applicants to include in the PIP plan any efforts to adapt the formulation of the medicinal product to be age-appropriate in different subsets of the paediatric populations. For this purpose, **The Guideline on pharmaceutical development of medicines for paediatric use**[33] was developed by EMA.

Dosage forms and formulations (composition) used in a trial should be described in the study protocol, according to ICH E6. The most appropriate paediatric form and formulation should be discussed with a pharmacist when writing the protocol. In particular, the choice of excipients should match the age of the children included in the trial. For example, colouring agents and antimicrobial preservatives often have toxic and allergenic potential.

Administration of medicines in children is complex, and the trial design needs to consider the child's developmental abilities. Therefore age-appropriate dosage forms and non-invasive methods of administration should be used to avoid the risk of adverse events and the high risk of dosing errors or inaccuracy. Another reason is not to discourage the child from participating in the study, e.g. by using intramuscular injections or using large tablets for young children.

It is quite common in academic paediatric trials that extemporaneous (magistral) preparations are needed. In this case, the conditions for preparing them should follow Good Manufacturing Practice (GMP). The conditions for use should be explained in the study protocol. It is also a known fact that the lack of paediatric dosage forms caused that adult medicinal products need

[33] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf

to be manipulated into paediatric-suitable dosing forms. EMA´s Reflection paper **Formulations of choice for the paediatric population**[34] contains, among other things, a list of several manipulations with adult medicinal products which should inform physicians on the appropriateness and risks of these manipulations, which includes, e.g. splitting tablets into segments, crushing tablets, opening capsules, dispersing tablets, cutting transdermal patches or cutting suppositories. All these manipulations also come under the heading of magistral preparations, which are within the law, as foreseen in the EU legislation relating to medicinal products.

Practical exercise
Open the attached article about Paediatric oral formulations (Paediatric oral formulations: Why don't our kids have the medicines they need? - Juárez-Hernández - 2022 - British Journal of Clinical Pharmacology - Wiley Online Library)[35]

Scroll down to Table 1 a try to answer these questions:
- ✓ Which dosage form-related problems can mini-tablets solve?
- ✓ For which dosage forms is taste critical?

…….

Now go through Table 3 carefully and choose age-appropriate dosage forms for a 4-year-old child. Write down your answers.

……..

4.1.3 Trial design and conduction

The planning phase of a paediatric clinical trial is crucial for the smooth running of the clinical trial and its successful completion. Important is the question of methodology, especially regarding small sample sizes, and the question of ethics, based on the exposure of children to the potential risk of the study.

Phases of clinical trials in children are divided in the same way as in adult patients, but there are special considerations when designing a clinical trial in the paediatric population. A brief overview of the individual phases can be found in Table 6. Phase I trials, where the safety and pharmacokinetics of a new drug are tested, are not very common in the paediatric population, mainly due to the unknown effect of the intervention. The exception may be life-threatening diseases for which there is no proven treatment, or standard treatment is ineffective. Phase II trials monitoring the safety and efficacy of drugs are sometimes conducted in children and represent the first step for most drugs in terms of early phase studies in children. Generally, an earlier approach was such that studies in the paediatric population were postponed until clinical trials reached Phase III, which means that information about efficiency, acceptability and adverse effects was known. On the one hand, this approach can protect children from exposure to unnecessary harm, but on the other hand, it delays children's access to treatment and thus prolongs the off-label use of drugs in younger age groups (especially neonates).

[34] https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-paediatric-population_en.pdf
[35] https://doi.org/10.1111/bcp.15456

Phase III trials (randomized controlled trials) compare the investigational intervention with standard therapy, another effective therapy or a placebo to estimate unbiased treatment effects. Phase IV post-marketing trials are very important, especially long-term follow-up studies, because they can provide safety and/or efficacy information for subgroups within the paediatric population or additional information for the entire paediatric population. More information about safety in paediatric trials you will find in the section Safety monitoring.

Table 6: Phases of clinical drug development in humans and examples in paediatrics

Phase of drug development	Goal of trials	Examples in paediatric drug development
Phase I	First stages of drug testing in humans, typically First stages of drug testing in humans, typically	Very rarely done in children, with the exception of oncology drugs (chemotherapy) and some drugs in neonatology (surfactant)
Phase II	The first stages of drug testing for efficacy and safety, typically conducted in patients	Uncommon, and represent the first step for most drugs in terms of early phase studies in children. Regulatory advances have increased these studies for new drugs
Phase III	Effectiveness of the drug and its role in clinical practice, typically by comparison with “gold standard” therapy	Done at some times for drugs in children, most frequently for anti-infectives and increasingly for other drug classes
Phase IV	Provide information about drug safety and/or efficacy	Long-term follow-up studies

Prior to conducting a paediatric clinical trial, it is also essential to know if there are any existing data in adults. When a medicinal product is to be used in the paediatric population for the same indication(s) as those studied and approved in adults, the disease process is similar in adults and paediatric patients, and the outcome of therapy is likely to be comparable, **extrapolation** from adult efficacy data may be appropriate. This process must be followed by pharmacokinetic studies to determine the most appropriate paediatric dose. The same steps may be followed if the medicinal product was studied and approved for the older paediatric population, and we would like to use this medication for younger paediatric patients. Extrapolation could be used when all the above-mentioned conditions are fulfilled.

Clinical efficacy trials will be needed if novel indications are being sought for the medicinal product in paediatric patients or when the disease course and outcome of therapy are likely to be different in adults and paediatric patients. The principles in study design, statistical considerations and choice of control groups detailed in ICH E6[36], E9[37], and E10[38] generally apply to paediatric efficacy studies. Where efficacy studies are needed, it may be necessary to select appropriate **endpoints,** especially as this determines the sample size and analysis strategy. A characteristic point of paediatric clinical trials is that some endpoints that are

[36] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf
[37] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf
[38] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-10-choice-control-group-clinical-trials-step-5_en.pdf

commonly used in adult clinical trials have not been validated in children. For example, the evaluation of the efficacy of analgesic interventions in young children and infants was problematic as many validated instruments for the evaluation of pain involved were self-report, which could be a problem for populations that are non-verbal or who lack numerical literacy. However, there is great progress in developing and validating endpoints relevant to the paediatric population.

Randomized clinical trials ("gold standard") have some weaknesses that make them hardly applicable to the paediatric population. One is the need for a larger sample size in order to prove the therapeutic superiority of one treatment compared to another, while we already know that the recruitment of paediatric patients is one of the difficulties of successfully conducting paediatric studies. Also, the perception of a lack of flexibility has historically been a problem for randomized trials in children. Therefore **innovative trial designs** were developed and used in the paediatric population. One example is *sequential design,* in which investigators conduct frequent analysis during subject enrolment to determine if the therapy of interest is superior. Due to its nature, sequential design requires treatment outcomes to be available quickly in relation to the patient recruitment rate, and this characteristic may partially limit its applicability. This design is not suitable for studying survival, but it could be useful to evaluate short treatments through surrogate endpoints. Another design used in the paediatric population is *adaptive design,* in which interim analyses are planned to inform modifications in trial design. This can permit a trial to be stopped early in the case of an intervention that is either very effective or found to be ineffective, reducing the number of children needed for the trial. *Bayesian design* works with data from previous studies, including adult studies, to inform predictions and reduce the sample size. Data gathered within the trial are also used to adjust the sample size and modify the trial's design while the trial is being carried out. You can go to Chapter 1 to get the detailed information regarding clinical trial design.[39]

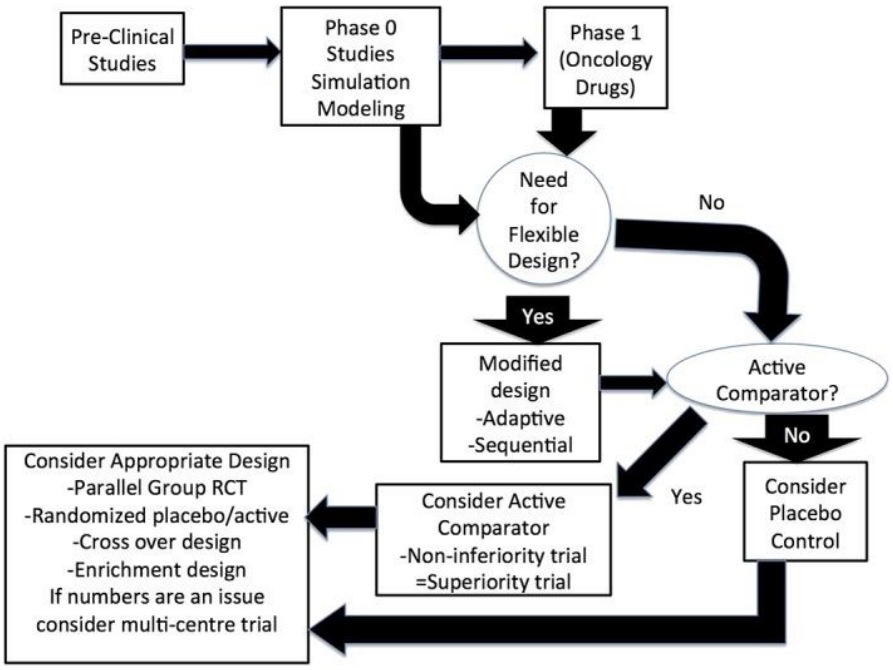


Figure 1: Key aspects in planning the design of an early phase drug trial in children

[39] Link to Chapter 1

More innovative approaches are promising thanks to the optimal results found in simulation studies. Why simulation and modelling play a role, especially in the early stage of drug development, is the ability to factor in variables such as the ontogeny of key drug clearance pathways and data derived from adult studies. The use of simulation enables a clearer estimation of drug dose and could also be used for a firmer estimation of sample size. Pharmacometrics techniques such as population pharmacokinetics, pharmacokinetic/ pharmacodynamic (PK/PD) modelling, and/or physiologically-based pharmacokinetics (PBPK) may be used to describe or predict the medicine's behaviour and select the doses in children.

In paediatric studies, the administration of a **placebo** as a control group may be a moot point. The use of a placebo is inappropriate in case it replaces an effective treatment in the trial. However, the use of a placebo may be warranted in children as in adults when evidence for an effective treatment is lacking. Also, long-term use of a placebo (between 3-6 months) may not be favourably received by patients, parents or the ethics committee. It is obvious that the question of placebo inclusion into the trial or its exclusion from the trial should be properly discussed when the trial is planned.

There is an exhaustive list of issues available in EMA´s Ethical consideration document (Annex 1),[40] which should be considered before planning a paediatric clinical trial.

- ✓ Go through this list to have a basic overview of what should be taken into account before conducting a paediatric clinical trial.
- ✓ In this chapter, only some points from the list will be mentioned in more detail.

As part of clinical trials, various **examinations** are required, which must be described in the study protocol. Their number should be reduced as much as possible (e.g. by using advanced technologies), and they should be accommodated to age and body weight (or body surface area).

If there are other possibilities, alternatives of blood (e.g. urine, saliva) should be used. If blood samples must be taken, very limited volume is accepted. EMA´s Ethical consideration document states that trial-related blood loss should not exceed either 3% of total blood volume during a period of 4 weeks or 1% at any single time. This recommendation should be taken into account during the planning of the clinical trial, failure to follow it could be a reason for rejection of the clinical trial by the Ethics Committee.

What is certainly convenient for ensuring the **feasibility** of the study is, before writing the protocol, inviting children and families to be involved in the planning, design and analysis of the clinical trial. It is always welcomed, especially in academic (non-commercial) trials, when experts are involved in a study preparation process, such as paediatric experts, medical writers (protocol writing), statisticians and data managers. The EMA guidelines on medicine development, methodology or therapeutic area should also be consulted, and it is

[40] https://health.ec.europa.eu/system/files/2018-02/2017_09_18_ethical_consid_ct_with_minors_0.pdf

recommended to obtain scientific and regulatory advice, especially when proposing to use unconventional designs, endpoints, or analyses.[41, 42]

Trials with neonates (term and preterm)
Neonates are the most vulnerable group of the paediatric population. This group suffers from specific diseases which are pharmacologically different from older children and adults. Many treatments routinely used in neonatal care are still under-researched and off-label. Therefore, trials with neonates are needed to produce evidence. Considerations and requirements for the design and conduct of clinical trials in premature and term neonates are addressed in EMA Guideline on the Investigation on Medicinal Products in the Term and Preterm Neonate.[43]

Trials with healthy minors
Generally, healthy minors should not be enrolled on trial as healthy volunteers because there is no direct benefit for them from the trial. When the study is feasible in adults, it should not be conducted in healthy minors. But there are exceptions where healthy minors are enrolled, e.g. prevention trials or paediatric vaccine trials. Healthy minors could be enrolled in this trial only if they benefit from it. Healthy minors can exceptionally participate, for example, in palatability testing such as “swill and spit tasting” for new flavoured medicine.

Trials with adolescents
Growing fertility and the potential use of drugs in adolescent are important points in trials with adolescents which deserves attention. Young females should not be excluded from the opportunity of participating in the trial due to the fact they may become pregnant during the trial. Clinical data from their group are needed too, therefore, they must be informed well about inclusion with the use of contraception by the investigator. This information must also be included in the informed consent and assent/agreement. In the case of possible teratogenic risk through sperm, young adolescents must be informed about using appropriate contraception as well.

4.2 Trial registration and publication

The registration of clinical trials on publicly accessible and recognized databases and the public availability of clinical trial results represent the transparency of clinical research and the protection of participants from unnecessary, duplicative studies. Prospective registration of trials is strongly advocated internationally by regulatory authorities, ethics committees and journals as a condition of publication.

EMA has made information on clinical trials in children (and in adults) available via the public interface, **the European Union Clinical Trial Register (EU CTR)**,[44] since March 2011. This register uses some of the information from the EudraCT database, which is an application used by national competent authorities to enter clinical trial data. EudraCT was established by clinical Trial Directive 2001/20/EC. Focused on paediatric clinical trials, EU CTR contains information on:

- a paediatric clinical trial with investigator sites in the EU/EEA,

[41] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/how-scientific-advice-works
[42] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance
[43] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-medicinal-products-term-preterm-neonate-first-version_en.pdf
[44] https://www.clinicaltrialsregister.eu/ctr-search/search

- a paediatric clinical trial that is sponsored by a marketing authorisation holder and involves the use of a medicinal product covered by an EU marketing authorisation in the paediatric population, including trials conducted outside the EU / EEA,
- trials which form part of an agreed PIP, including those where the investigator sites are outside the EU/EEA.

Besides EudraCT, EMA also manages a second clinical trial database **Clinical Trial Information System (CTIS)**. CTIS was created in line with Clinical Trial Regulation and went live on 31 January 2022.

The sponsor is responsible to register the trial. Specifically, in the EU CTR, the study information is loaded into the register by National Competent Authority (NCA) based on the information filled in by the sponsor in the Clinical Trial Application (CTA). This CTA is submitted to NCA when the sponsor asks for study approval. Therefore you can find there information from the study protocol (sponsor, study design, the investigational medicine) and study status (ongoing, completed, authorised...).

It is worth knowing that clinical trials can be registered to more than one register simultaneously. If you would like to know more about other possibilities where to register a study, please go to Chapter 4.[45]

Another sponsor´s responsibility is to publish the summary of the results of the clinical trial within the register. According to Paediatric Regulation and CTR, a summary of the results of the paediatric clinical trial should be submitted within six months from the end of the trial, accompanied by a summary understandable by laypersons, both to be included in the database. In the case of paediatric trials, efforts should be made to make the laypersons' summary understandable by children who participated in the trial (those able to read from 6 years on). Guidance on how to write Lay Summary you can find on the European Commission websites under the Public Health folder.[46]

Discussion board

Read the article dealing with Results Reporting and Publication of Paediatric Clinical Trials.[47]

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Early Discontinuation, Results Reporting, and Publication of Pediatric Clinical Trials

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https://doi.org/10.1542/peds.2021-052557 **Article history**

[45] Link to Chapter 4
[46] https://health.ec.europa.eu/latest-updates/good-lay-summary-practice-guidance-2021-10-04_en
[47] https://doi.org/10.1542/peds.2021-052557

- ✓ Go to the results section to see how small a percentage of registered trials in the Clinicaltrial.gov database have published results in the registry and in peer-reviewed journals.
- ✓ Do you have any explanation for that? Leave your comment on the discussion board/discuss it with a teacher.

It is essential for the trial's final results to be published in scientific journals since these provide evidence of whether the trial obtained a beneficial or harmful or no outcome(s). In addition, the readers will not be able to adequately critically appraise the clinical trial unless the final results are published. All approaches mentioned above should help to improve public trust and confidence in paediatric research.

5 Safety monitoring

Paediatric pharmacovigilance, in general, is a continuous process starting when a drug is administered to the first child for the first time. This may occur in the context of a clinical trial or in clinical practice and includes off-label and unlicensed use. This chapter focuses on safety monitoring before the authorization of a paediatric medicinal product. It should be emphasized that pre-registration pharmacovigilance is partially limited by the small number of patients exposed to the drug during clinical trials, therefore, some AEs (adverse events) may not be manifested. Therefore for most medicines, it is impossible to fully investigate rare ADRs (adverse reactions) prior to authorisation, as it is necessary to expose a large number of subjects to a medicinal product to elicit a reaction which occurs with a low probability in the target population. Therefore, the post-marketing assessment of medicines plays a key role in better defining drugs' safety profile in a real-world setting and filling the evidence gap of pre-marketing studies. It must also be taken into account that the response of children to medication differs not only in comparison to adults but also between different paediatric age groups (e.g., neonates and adolescents).

Paediatric drug safety activities include the description of the paediatric safety specification, which is the basis for the development of paediatric pharmacovigilance and risk minimisation activities in clinical trials. **The paediatric safety specification** (or safety profile) uses all available safety data to describe identified and potential treatment-related risks and missing safety information. Whereas safety data may originate from a variety of data sources – non-clinical studies, clinical trials, observational studies and spontaneous reports in adults and all paediatric age groups, PK and PD data, class effects and a systematic review of the safety literature, including information from health authorities. The paediatric safety specification provides the necessary evidence for study protocol sections related to drug safety, such as the benefit-risk balance, exclusion criteria, rules for stopping treatment and safety monitoring. It provides the rationale for the CRF design, management of treatment-related risks, safety data collection and analysis.

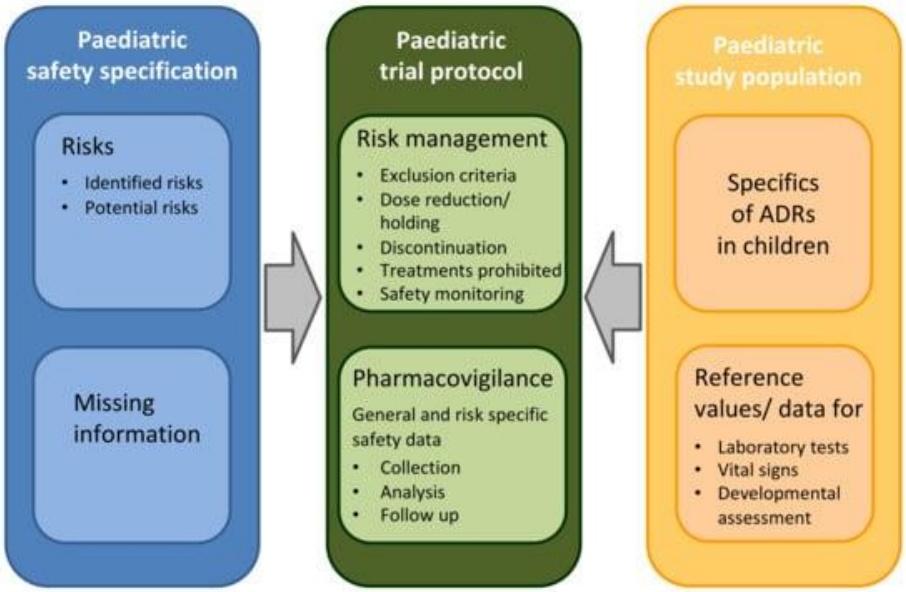

Figure 2: Relationship between paediatric safety specification and protocol development

The paediatric safety specification also informs the risk management plan (RMP), which in turn provides a systematic, evidence-based approach to risk management and pharmacovigilance in paediatric clinical trials, observational studies and clinical practice. RMPs are mandatory documents for pharmaceutical companies applying for marketing authorisation in the European Union. They include all safety-relevant information and have a specific section for children. The RMP also includes a plan on how missing safety information will be collected and the assessment of the effectiveness of risk management activities. Similar to the safety specification, the RMP is a living document. It is modified with each update of the safety specification.

EMA has developed a set of guidelines for the conduct of pharmacovigilance known as **Good Pharmacovigilance Practice (GVP)**.[48] Guidelines are divided into chapters which are categorised into 2 parts: modules covering major pharmacovigilance processes (I-XIV) and product or population-specific considerations (vaccines, biological medicinal products and paediatric population). Due to the focus of this tutorial chapter, we are interested in Guideline on GVP: Product- or Population-Specific Considerations IV: Paediatric population.[49] This guideline focuses on paediatric safety specifications, such as susceptibility to an adverse reaction, limited numbers of subjects in paediatric clinical trials, medication errors, off-label use and clinical presentation of adverse reactions. It also contains paediatric-specific guidance on all major pharmacovigilance tools and processes, including a risk management plan, periodic safety update reports, post-authorisation safety studies, signal management and safety

[48] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices#introduction-section
[49] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-iv_en-0.pdf

communication. Since pharmacovigilance has special terminology, the existing Annex I[50] with definitions is certainly worth mentioning.

Collection of the safety data, reporting requirements and timing during the clinical trial are identical for paediatric and adult trials, in particular for suspected unexpected serious adverse reactions. For this reason, these topics are not further discussed here. All the necessary information can be found in Chapter 5 (Pharmacovigilance and study medication).[51]

6 Paediatric trials initiatives

It is a known fact that lots of paediatric trials fail or are not completed for different reasons described in previous subsections. Therefore guidance for paediatric drug research is very welcome. One of the pieces of advice to enhance paediatric research is to involve children and parents in the design of the clinical trials. The involvement of children/parents in research design, the preparation of patients' documentation, and information materials to improve research protocols are widely acknowledged. Early involvement of patients in the trial design may be helpful in the identification of trial aspects that are less acceptable or unclear for potential participants. This effort can ensure a greater willingness of patients to participate in the study.

International paediatric trial networks have been established in many countries to address some of the challenges by improving the infrastructure and research capacity. The US and EU created networks with specialized expertise in conducting trials in children and have dedicated funding for paediatric research and training.

6.1 Infrastructure support

The Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)[52] was established in March 2011. Enpr-EMA is a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children in collaboration with research networks, investigators and centres with recognized expertise in conducting paediatric trials. This network is working towards developing the necessary competencies and avoiding unnecessary duplication of paediatric studies, educating parents or carers and children about trials and encouraging their participation. It also raises awareness among healthcare professionals of the necessity for trials in children of all ages, supporting their involvement in such studies and engaging in dialogue with ethics committees on paediatric trial issues. Enpr-EMA maintains a fully searchable database of its member research networks and centres.[53] Further Enpr-EMA recommends to medicinal developers to involve paediatric networks when developing a PIP.

[50] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf
[51] Link to Chapter 5
[52] https://www.ema.europa.eu/en/partners-networks/networks/european-network-paediatric-research-european-medicines-agency-enpr-ema
[53] http://enprema.ema.europa.eu/enprema/search.php

Practical exercise, discussion board
Enpr-EMA maintains a database of Enpr-EMA networks.

- ✓ Enter the database and search for Enpr-EMA networks in your country. Write them down together with their specialities.
  ……..
  ……..
  ……..
- ✓ Do you know any of them? Can you say why this network could be useful for you? Leave your comment on the discussion board/discuss it with the teacher.

Besides Enpr-EMA, there are huge developed infrastructure platforms that integrate patient engagement in research, such as **Connect4children (c4c)**, **EPTRI and ECRIN (PedCRIN**). For example, c4c is a large collaborative network which includes 35 academic, 10 industry partners and around 500 affiliated partners. Briefly, c4c focuses on the promotion of innovative trial design of paediatric clinical trials and offers an education and training platform through the national hub. Those interested in the course can choose from a wide range of courses, from basic ones, including GCP in paediatrics, to more advanced courses related to, e.g. PIP and developmental pharmacology.

For more information about the c4c project, you can visit their websites[54] or watch a short YouTube video ("What is conect4children?").[55]

European Clinical Research Infrastructure Network (ECRIN) is an infrastructure which provides tailored support to facilitate trial preparation and implementation in the field of non-commercial (academic) clinical trials. PedCRIN is a four-year project which aims to develop tools for international paediatric research, for example, tools for setup and the management of paediatric clinical trials or tools which deliver consultation methods to involve children and parents in clinical research.[56] Within the PedCRIN project, 3 pilot paediatric clinical trials were funded. One of the activities in this project was consultations with patient groups where supported pilot trials were discussed. During a focus group, children and/or parents are informed about a certain topic, and they can give their views, with the idea that participants learn from each other and that, therefore, more diverse responses are generated.

6.2 Patient and parent involvement

An innovative approach to the patient's involvement in paediatric clinical research is represented by the Young Persons Advisory Groups widespread throughout the world. A **Young Persons Advisory Group (YPAG)** is an organization composed of youths, patients, carers, and people interested in a health condition or in research. They actively participate as partners, advising researchers and their teams in a full range of activities in various research projects and initiatives. After educational and training activities, the youths become able to help

[54] https://conect4children.org/
[55] https://youtu.be/ZbXu2hEB6f4
[56] https://ecrin.org/paediatric-tools

researchers in trial design, prioritizing future researches, improving communication with the target population, and increasing awareness of clinical research through different means of communication. The European Young Persons Advisory Group Network (eYPAGnet) was established to support the development of new YPAGs within Europe, for more information, you can visit their websites.[57]

Many advisory groups have been founded, and all together, they constitute the **International Children's Advisory Network (iCAN)**[58], a worldwide consortium of children's advisory groups or chapters working together to provide a voice for children and families in health, medicine and research. Within the consortium, various types of groups can be described, all working together for advocacy purposes in paediatric medicines, such as:

- Kids and families impacting disease through science (KIDS)[59]
- Young Persons Advisory Groups
- Kids Can[60]
- TEDDY[61]

Through many activities and initiatives performed, the young advisor groups spread all over the world are able to help the professionals involved in clinical trials to overcome some tough issues of clinical research. For example, they could help to open and complete the trials on time or could improve the recruitment of patients to the agreed target and the retention of patients to study completion. In general, through the YPAGs, the clinicians involved in the trials could meet the needs of the patients, designing the study according to their necessities.

Quiz

Select one of the possible answers:

1. The solution how to increase the low numbers of patients in paediatric clinical trials can be to conduct a …….. clinical trial and involve ……..and ……..in the process of the clinical trial preparation.

2. Which legal document has the potential effort to enhance the development of age-appropriate paediatric medicine?
    a) Regulation (EU) No 536/2014
    b) Paediatric Regulation (EC) No 1901/2006
    c) Directive 2001/20/EC
    d) Regulation (EC) No 726/2004

3. What is the maximum allowable blood sample volume at a single time?
    a) 1% of total blood volume
    b) 3% of total blood volume

[57] https://eypagnet.eu/
[58] https://www.icanresearch.org/
[59] https://www.ema.europa.eu/en/documents/presentation/presentation-worldwide-involvement-children-clinical-research-pamela-dicks-jenny-preston-charles_en.pdf
[60] https://www.micyrn.ca/ypag
[61] https://www.teddynetwork.net/ypag/

4. Complete the table with the remaining challenges of paediatric clinical trials:

Regulatory process		Difficulties in patient recruitment and retention	
	Multi-centre international trials		

7 Conclusion

Paediatric clinical trials can be difficult to carry out for many reasons, which have been analysed in this chapter. However, there is a need to carry out trials with children, which cannot be performed with adults, in order to obtain evidence specifically attuned to the needs of children. Without these data, clinicians are forced to treat children with a medicine prescribed off-label in many cases.

Even though the Paediatric Regulation has strengthened paediatric medicine development, there is still a need for an improved, mutual understanding of paediatric trial requirements and challenges across the regulatory network, companies, clinicians, researchers and ethics committees, as well as the public. We hope that this chapter helped you to clarify the needs of paediatric trials and provided you with the necessary links to important documents and organisations (Enpr-EMA, ECRIN, iCAN) that can facilitate the preparation and conduct of a clinical trial with minors.

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