MASTER IN BIOMEDECINE

Empowering Paediatric Research: Strategies for Involving Children and Families in Clinical Trials

GABETA, Maria

Award date:
2023

Awarding institution:
University of Namur

UNIVERSITÀ DEGLI STUDI DEL PIEMONTE ORIENTALE

"AMEDEO AVOGADRO"

EMOTION

The European Master in Translational Cosmetic and Dermatological Sciences

and

UNIVERSITÉ DE NAMUR

Master en Sciences Biomédicales, Finalité Spécialisée en Recherche Clinique

Thesis

Empowering Paediatric Research: Strategies for Involving Children and Families in Clinical Trials

Tutor

Dr./Prof. Jean-Pierre Gillet

Jean-Pierre Gillet

Training supervisor

MSc Ana Dilo

Ana Dilo Bala

Candidate

Maria Gabeta

Maria Gabeta

Academic Year 2021-2023

Session September 2023

Declaration of Authenticity

I, MARIA GABETA enrolled in the European Master in Translational Cosmetic and Dermatological Sciences at Dipartimento di Scienze del Farmaco (EMOTION), Università del Piemonte Orientale (UPO) and discussing the Thesis in September 2023 (extraordinary session)

declare that

- This thesis is my own original work, based on my personal study, experience and/or research.
- I have acknowledged all material and sources used in its preparation (*e.g.* books, articles, reports, lecture notes, and any other documents, including websites or personal communications).
- I am aware that false statements will be punished by law (art. 76 del D.P.R. 28.12.200 n.445).

Date 28/08/2023 Signature Maria Gabeta

Abstract

Conducting human clinical trials has consistently represented a highly challenging undertaking, considering regulatory and ethical factors, as well as the execution of all study stages to introduce a novel medical product to the market. When confronted with the involvement of children, this complexity is further amplified, as developing a new drug for children is not just as simple as modifying the adult's dosage. However, there has been a gradual recognition of the necessity to involve children in the process of developing pharmaceuticals in recent years.

The first part of this master thesis is an introduction to the clinical research pathway, and attempts to explain how the paediatric trials are designed and conducted, making sure that all the legal, regulatory frameworks and ethical considerations are being respected. In pediatric studies, it's essential to obtain approval from both children and parents/legal representatives in order to enroll patients in the research studies. For this reason, an important part of the thesis is dedicated to the main documents that involve children in the clinical practice: *the informed consent and assent form* (addressing their general requirements, age-based variations in consent across Europe and considerations for special cases and emergency situations).

The other part of the thesis (the subsequent analysis section) comprehensively explores strategies for integrating the participation of children, young patients, and families at various stages of the research journey. This involves identifying unmet medical needs, planning research design, including protocol design and recruitment strategies, while navigating ethical concerns and data protection. Important considerations about how to present consent information, especially according to the level of maturity and different age groups have been pointed out. A questionnaire entitled "*Parent survey: Patient Engagement in Pediatric Clinical Trials*" has been prepared and distributed to 140 participants. The main reason for engaging actual individuals in practice was to assess real parental perspectives regarding the potential inclusion of their children in clinical trials, the importance of their participation, and to get to know what practical and simple strategies to follow to enhance this participation.

The overall objective of this work was to paint a comprehensive picture of paediatric research initiatives: emphasizing the significance of developing medications and treatments tailored to children, explaining the manifold obstacles researchers encounter across study phases, and highlighting the advantages that come from involving patients and their families in the early process of trial design.

Key words: paediatric clinical research, children involvement, young patients, parents involvement, informed consent and assent

Introduction to CVBF (Consorzio per Valutazioni Biologiche e Farmacologiche)

My host organization during the past 6 months, and now my current place of work, CVBF, operates as a *consorzio*, which is the Italian term for a consortium. This collaborative structure underscores CVBF's commitment to fostering synergy between diverse stakeholders, including research institutions, pharmaceutical companies, regulatory bodies, and healthcare professionals. This approach reflects CVBF's dedication to promoting excellence in the area of biological and pharmacological assessments, contributing to the greater good of society through research, innovation, and knowledge dissemination.

Mission: Since 2000, at the core of CVBF's mission is the pursuit of advancing the development and evaluation of novel biopharmaceutical products. With an emphasis on research, collaboration, and regulatory compliance, CVBF seeks to bridge the gap between scientific discoveries and their practical applications in healthcare. This mission is underpinned by the organization's commitment to patient well-being, scientific integrity, and ethical practices.

Products and Services: CVBF offers a comprehensive array of services spanning various stages of the drug development lifecycle. These encompass regulatory consulting, clinical trial management, monitoring, pharmacovigilance, biostatistics, regulatory and quality assurance. CVBF's expertise extends to a diverse range of therapeutic areas, reflecting its adaptability to the ever-evolving landscape of medical research and innovation.

CVBF has developed significant expertise in clinical trials (CTs) since 2002. The organization possesses expertise in conducting interventional clinical trials, ranging from Phase I to Phase IV, encompassing both pharmacological and non-pharmacological domains, including medical devices and nutraceuticals. Numerous studies have been conducted in children, and this is among the factors that influenced my decision to focus my thesis on pediatric research.

Table of contents

List of abbreviations

ICH	International Council for Harmonisation
GCP	Good Clinical Practice
FDA	Food and Drug Administration
WHO	World Health Organization
EMA	European Medicines Agency
PK	Pharmacokinetics
PD	Pharmacodynamics
CYP	Children and Young Patients
PDCO	Pediatric Committee of the European Medicines Agency
CHMP	Committee for Human Medicinal Products
PRAC	Pharmacovigilance Risk Assessment Committee
SAWP	Scientific Advice Working Party
HTA	Health Technology Assesment
YPAG	Young Persons' Advisory Group
DBS	Disclosure and Barring System
CRB	Criminal Records Bureau
GDPR	General Data Protection Regulation
HLQ	Health Literacy Questionnaire
TSC	Trial Steering Committee
DMC	Data Monitoring Committee
EPAR	European Public Assessment Report
MA	Marketing Authorisation
PE	Patient Engagement
PFMD	Patient Focused Medicines Development

1 Clinical research

Clinical research is the comprehensive study of the safety and effectiveness of the most promising medical advances. In other words, it involves people who volunteer to help in better understanding how safe and effective a new medicine is. There are two main ways of carrying out clinical research:
through observational studies and through clinical trials. Clinical trials, which are also called interventional studies, test the new promising medications, tools and procedures in living people.
As defined by Johns Hopkins Medicine, clinical trials "seek to discover new and improved methods of preventing, diagnosing and treating diseases". They are not only used to test drugs or medicines, but also: medical devices, new types of surgery, new ways of changing health behaviors, new ways of using current treatments or new ways to improve quality of life.
Clinical trials are carefully designed, reviewed and completed, and need to be approved by applicable regulatory and health authorities before they can start. They follow dedicated international ethical and scientific quality standards during all phases of conduction:

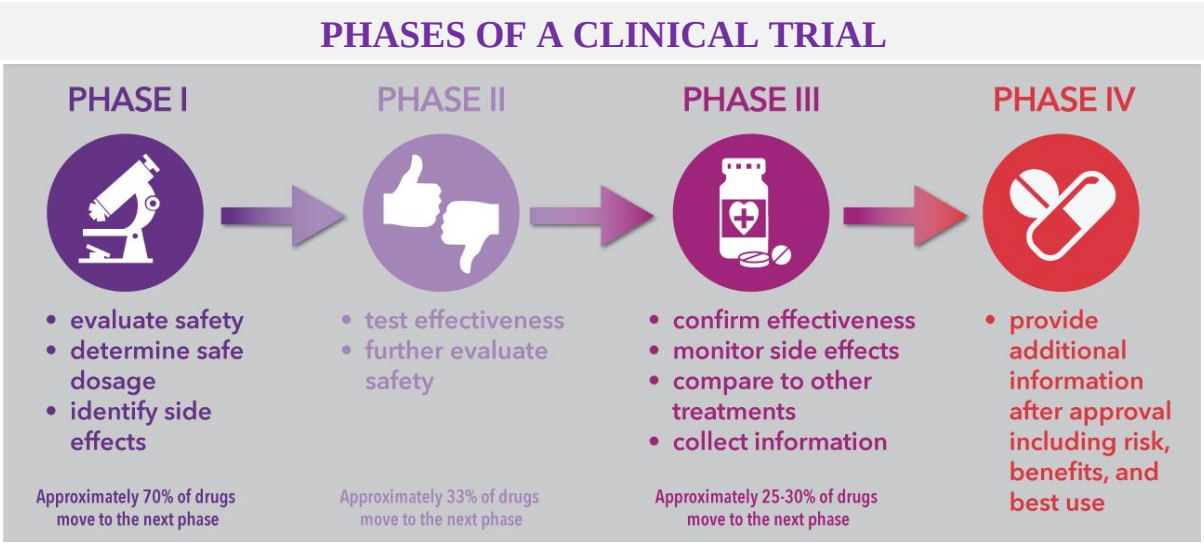
1. Phase 1 usually the first administration in humans, is conducted on a small number of healthy participants (less than 50). The primary purpose of this phase is to assess safety and determine the appropriate dose.

2. Phase 2, or first administration in patients, involves around 100 people that suffer from the study disease. The main goal of this phase is to study the effectiveness and the possible side effects.

3. Phase 3, exploring the therapeutic efficacy, is usually conducted in a larger group of people (up to 3000) and in a heterogeneous population, to confirm the effectiveness and to compare the new drug to standard or similar treatments.

4. Phase 4 or the studies conducted after the marketing authorisation, are trials performed after the drug has become available to the public. The information collected during this phase is important since even the most well-designed Phase 3 studies might not uncover a problem that could become apparent once the therapy is widely used.

Figure 1. Phases of a Clinical Trial[1]



Source: Lupus Research Alliance

People of any age can participate in a clinical trial, including children. All the experiments are governed by very strict rules in order to protect the patient's interests and dignity before any kind of scientific profit. Over the years, a unique and standardized document called ICH (R2) Good Clinical Practice has been internationally recognised as the only clinical research practice guideline. As it is quoted in the document, "Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible".

The complexibility and the long duration of the clinical trials makes them a very expensive practice, with cost estimates ranging from $48 million to $225 million. Nowdays, clinical research professionals are looking for ways to reduce these massive costs through the application of digital technologies, machine learning and artificial intelligence. Accordng to Globant (an international IT and Software Development company) there are four areas seen as key opportunities for cost reduction:

- Protocol design
- Patient identification and recruitment
- Patient retention and engagement
- Data management

"Developing a digital strategy that leads to an interoperable ecosystem where data exchange is seamless, manual processes and redundant data are eliminated, and digital technologies support patient engagement and retention will facilitate faster time to market for life-saving treatments and ultimately improve patient outcomes", quotes Globant[2].

[1] Lupus Research Alliance (no date) Phases of a Clinical Trial [Online]. Available at https://lupustrials.org/about-trials/phases-of-a-trial/ (Accessed: 17 June 2023)

[2] Basia Coulter (24 February 2023) Optimizing the cost of clinical trials [Online]. Available at https://stayrelevant.globant.com/en/technology/healthcare-life-sciences/clinical-trials-cost-breakdown/ (Accessed: 22 June 2023)

2 Paediatric clinical trials and paediatric drug development

Children are a unique population that differ from adults in terms of developmental and physiological characteristics. They deserve medicines that are adapted to their needs. The necessity to include children in drug development has been recognised increasingly over the past few decades Thus, clinical trials in paediatric populations are essential in order to develop age-specific, does-specific and empirically-verified therapies and interventions. Children are not just small adults. Their bodies and their immunity work very differently and they often go through many changes as they are still developing from infancy through adolescence. Because their bodies are very particular, it is important to create medications and treatments specifically for children rather than just reducing dosages or modifying adult's therapies.

Since children are considered a vulnerable population, paediatric clinical trials need to pass very rigorous ethical considerations and meet certain standards before being allowed to recruit young patients. The vulnerable nature of this population must be considered when balancing the need for safe and validated medicines and therapies with the high risks that come from clinical research practices.[3]

Regulatory affairs experts often talk about how clinical trials for demonstrating pediatric viability are difficult to design, get approved, conduct, manage and to be analysed. The US Food and Drug Administration (FDA) has said that "up to 50% of these trials are 'not interpretable' because sample sizes are too small, endpoints are poorly defined, pharmacokinetic (PK) and pharmacodynamic (PD) correlations are not well enough established, and that many trials have used an incorrectly identified dosage"[4].

Considering pharmacokinetics in particular: since the process of absorption, distribution, metabolism, and elimination is different in children, the PK and PD of a drug used in paediatric populations may differ significantly from the same data gathered from adult usage. PK studies in children should permit the calculation of a dosing regimen that will achieve safe and effective therapeutic levels comparative to those approved for adult patients. Yet, each paediatric age group might need to be estimated separately because of physiological differences (newborns obviously may differ significantly from adolescents).

3 Engaging children, adolescent patients and their families in the process of shaping clinical research

Researchers' efforts to develop pediatric clinical trials should always include a patient and family–centric approach. CYP have historically been excluded from medical/clinical research as some consider them as a vulnerable group that require protection, but recent arguments have shifted and advocates for CYP inclusion believe that they have the right to the highest standards of health care, to be informed, express their views and influence decisions made about them. This approach was ratified with the introduction of the UN Convention of the Rights of the Child (2014), which sets out the civil, political and economic, social, health and cultural rights of children, advocating their right to be involved in decisions that impact on their lives.

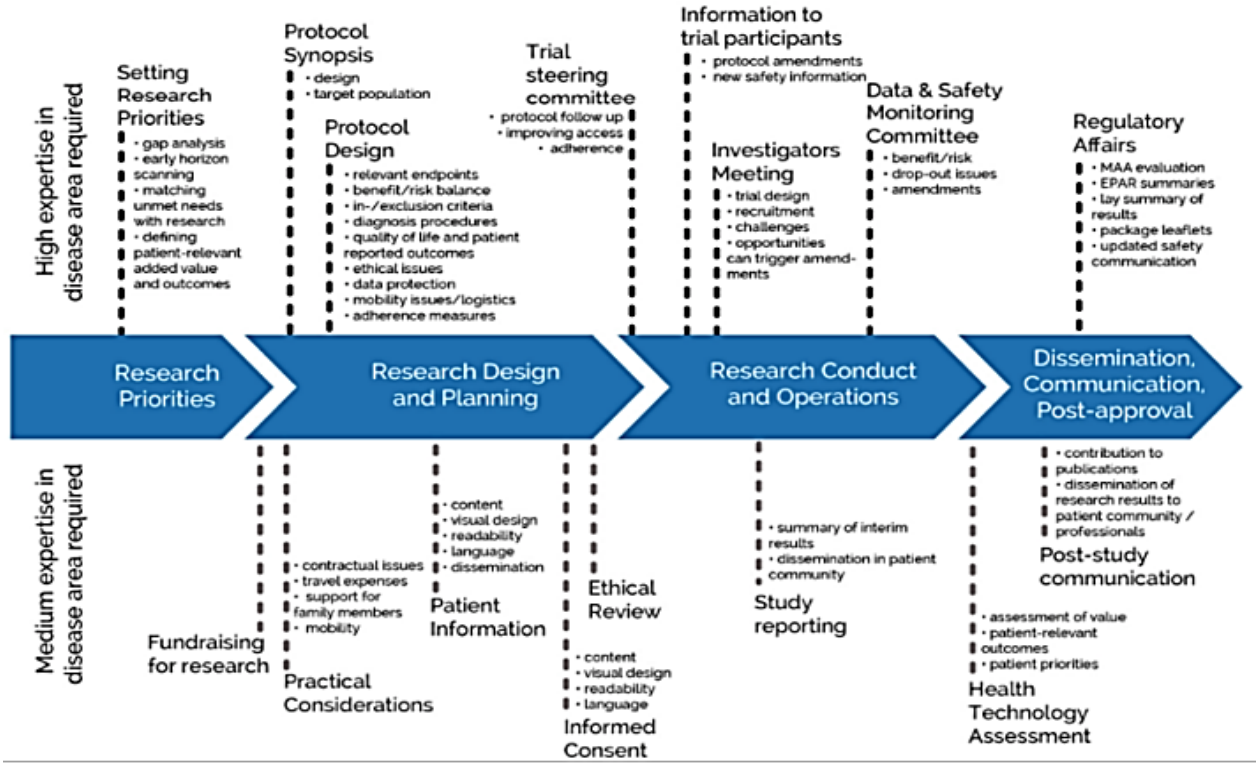
The valuable contribution that CYP and families can make, both in paediatric study design and in the review and conduct of studies is increasingly being recognized. Previous experiences suggest that involving CYP and families leads to high quality research, better accrual and

[3] World Health Organization (no date) Clinical Trials in Children [Online]. Available at https://www.who.int/clinical-trials-registry-platform/clinical-trials-in-children (Accessed: 22 June 2023)

[4] P. Joseph, J. Craig, P. Caldwell (Mar 2015) Clinical trials in children. British Journal of Clinical PharmacologyVolume 79, Issue 3: Paediatric Prescribing p.89

retention rates in clinical trials, and improved outcomes for CYP and is dependent on listening to their views and taking into account their perspectives.

Figure 2. Patient involvement in medicines research and development



Source: Warner et al., 2018[5]

3.1 Regulatory framework

3.1.1 Regulatory framework in pediatric therapeutic development and need for patient involvement

The development of therapies for the pediatric populations in Europe operates under the framework set up by the Pediatric Regulation since 2007. It has become clear over the years that, to make it successful, a patient-centered approach (rather than drug-centered approach) is needed.

In order to implement meaningful patient engagement of CYP and families, extra-care has to be taken compared to engagement of adult patients. Specifically targeted tools and resources (e.g. appropriate language and communication channels and formats) are needed on relevant legal and ethical aspects.

The engagement of CYP and families within and beyond the regulatory framework provides researchers and regulators with access to real-life experiences of living with a disease. All stakeholders, including regulators, need to be prepared to incorporate the input of CYP and

[5] Warner K, See W, Haerry D, Klingmann I, Hunter A and May M. (2018). EUPATI Guidance for Patient Involvement in Medicines Research and Development (R&D); Guidance for Pharmaceutical Industry-Led Medicines R&D. *Front. Med.* 5:270. doi: 10.3389/fmed.2018.00270

their families within their own practices, hence the importance of creating frameworks for engagement and providing training resources addressed to all stakeholders.
In the best interest of the patients, it is essential that therapeutic development takes into account the burden of living with the disease to determine to which extent a scientifically identified unmet medical need will be covered by the new medicine, whether the treatment is possibly healing or disease-modifying, whether it'll affect disease progression or basically target illness side effects and its impact on quality of life.
Within the regulatory activities, CYP and their families can provide direct experience of living with a disease or condition and align this with the clinical trial protocols, with regards to eligibility criteria, patient relevant outcome measures, acceptability of invasive procedures, and quality of life of the patients and their family.
Not only will the inclusion of the CYP and families as partners in the therapeutic development process help the recruitment, retention, and execution of the clinical trials with age-appropriate and meaningful outcome measures and trial designs (e.g. minimal use of placebo), but the involvement of patients throughout the medicine's life cycle makes the whole process more efficient and ensures that the drug will fulfill a real therapeutic need.
When developing a treatment for paediatric patients, it is fundamental to take into consideration the following points: the target age group, the environment setting where the product is likely to be utilized (e.g. clinic or community), age related activities (for example nursery or school), as well as any possible characteristic of the child that may condition their normal life activities (e.g. children with physical or mental inabilities, a high number of co-medications, incapable to swallow) and assessing the acceptability of the treatment at an early stage could be a critical step in this process[6].
These aspects involve both the treatment phase and the regulatory activities, and they become challenging due to the requirement to deliver clear information in all the conditions/ages. Within the paediatric population, it is necessary to provide enough granularity in order to recognize that a standard model of information is not applicable to all age groups and/or medical conditions, although the harmonization of some main informative materials (informed consent/assent) would be strongly recommended.

3.1.2 Framework for CYP and families engagement at European level

The Paediatric Regulation set out provisions for the creation of a Paediatric Committee within the European Medicines Agency, named the PDCO. This Committee is composed of representatives from Member States and additional experts. There are three seats for representatives of patient organizations (plus three seats for alternates). In addition, the European Medicines Agency (EMA) rules allow the participation of ad-hoc patient experts within its scientific committees and working parties (e.g. Scientific Advice Working Party). Until recently, this was tailored for adults but not for children.
In 2017, the EMA published a document entitled Principles on the involvement of young patients/consumers within EMA activities, being one of the first regulatory authorities to formally advance in this area while providing a framework that facilitates the collection of input from CYP. The purpose of the document is to encourage the involvement of CYP in EMA scientific activities and it explores:
:

[6] M.A. Turner a, M. Catapano b, S. Hirschfeld c, C. Giaquinto d, GRiP (Global Research in Paediatrics) (2014) in: Paediatric drug development: The impact of evolving regulations [Online]. Available at https://www.sciencedirect.com/science/article/pii/S0169409X14000258

- The scope of CYP involvement, highlighting the importance of identifying the most appropriate situations that may require input from CYP or their families/carers and the organisations they may be members of.
- The importance of setting clear expectations for how and when CYP are consulted, and how best to capture their opinions;
- The need to establish appropriate processes to identify, support and consult with CYP.
  With this proposed new framework, it is anticipated that the key forum where engagement with young patients/consumers/carers would occur is within the Paediatric Committee (PDCO), but could also be within the Committee for Human Medicinal Products (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC), and potentially the Scientific Advice Working Party (SAWP) when these committees/working parties review paediatric medicines. The interaction will take place either in writing, via teleconference or in person[7].

3.1.3 Other frameworks and initiatives

On a global level, the ICH guideline E11 Clinical Investigation of Medicinal Products in the paediatric populations defines the overarching rules.
This document addresses the conduct of clinical trials of medicines in paediatric populations. This document is aimed at facilitating the development of safe and effective use of medicinal product in paediatrics. It has been adopted in EU, Japan, US, Canada and Switzerland. This new ICH Guideline (R1, revised version date 20 July 2017) is proposing harmonisation of methodologies and strategies to incorporate pediatric specific aspects into overall drug development plans and therefore improve the speed of access to new drugs for paediatric patients while limiting the number of children required for enrolment in clinical trials[12].
However these guidelines do not explicitly mention any framework for patient involvement.
In addition to the framework proposed by the EMA, other regulatory agencies that play crucial roles in the evaluation, approval, and monitoring of medical products and treatments, such as the FDA and HTA bodies are considering the involvement of young people but this is still very limited and additional efforts are needed to move it forward.

3.2. Ethics

3.2.1 Ethical issues that are pertinent in involving children and young people, patients and parents in research

The duty to protect the physical, social and psychological well-being of CYP and parents involved as partners in clinical trial design and development is essential.
One way to protect well-being is to ensure CYP and families fully understand what they are getting involved in, and what their own involvement would entail. This includes understanding general codes of practice around being a YPAG member or a patient group member, in addition to being involved in a specific project or study.
This could involve an information pack detailing the types of activities that are involved, the responsibilities of the coordinator and the members.

[7] Warner K, See W, Haerry D, Klingmann I, Hunter A and May M. (2018). EUPATI Guidance for Patient Involvement in Medicines Research and Development (R&D); Guidance for Pharmaceutical Industry-Led Medicines R&D. *Front. Med.* 5:270. doi: 10.3389/fmed.2018.00270

In addition to relevant information and good communication, consent is required for certain activities such as attending meetings in another location. Who can legally provide consent is entirely dependent on national laws regarding the age of the child or young person[8].

3.2.2 EU legislation, local legislation and protective measures to ensure the involvement of CYP is *ethical* and respects their needs

YPAG leaders are the responsible to coordinate the training process and the consultation sessions of the groups. They have the responsibility to ensure that CYP are safeguarded when attending group meetings or representing groups such as at a conferences. Safeguarding is making sure that staff, volunteers, programmes and performances do not expose children to the risk of distress, abuse and harm. Moreover, safeguarding ensures that any concerns from the part of the organization about children's safety within the communities they work with, are reported always on time to the appropriate authorities.
Organisations working for and with CYP, at least in EU, should not only be guided by child protection policies but also possess reporting mechanisms in place, such as:

a) National Child Protection Governance Schemes
Child protection governance schemes are frameworks and systems established by governments to ensure the safety, well-being, and rights of children. These schemes encompass policies, regulations, guidelines, and procedures aimed at preventing and responding to child abuse, neglect, exploitation, and other forms of harm. Even in clinical research practices, children must be protected at all costs. It is important to ensure that anybody who is likely to have direct contact with CYP during the studies have been cleared via the national child protection governance process. It is the responsibility of the coordinator to be aware of national policies and ensure that they are complied with[9].
It's important to note that child protection governance schemes can vary significantly from one country to another based on cultural, legal, and social factors. For examle, in England any person working with CYP should have undergone clearance via the Disclosure and Barring System (DBS), that has been previously known as a Criminal Records Bureau (CRB) check.

b) YPAG and patient group safeguarding
A Young Persons Advisory Group is made up of children and young people (aged between 8 to 18 years) that are actively involved in the decision-making processes of various organizations, particularly those related to healthcare, research, policy, and services. YPAGs aim to include the perspectives, insights, and preferences of young people in matters that directly affect them. These groups provide a space for young individuals to voice their opinions, share their experiences, and contribute to improving the outcomes and services that impact their lives. YPAGs vary in structure, frequency of meetings, and areas of focus. Some YPAGs are established within hospitals, research institutions, advocacy organizations, and government agencies. These groups can be instrumental in improving the relevance and

[8] Turner, M. A. (2015) Clinical trials of medicines in neonates: the influence of ethical and practical issues on design and conduct, *Br J Clin Pharmacol*, 79, 370–378

[9] Lucia Ruggieri, Donato Bonifazi, Annalisa Landi, Fedele Bonifazi, Franco Bartoloni, Mary Costello, Maria Grazia Felisi, Elke Gasthuys, Anila Godo, Federico Martinon Torres, David Nadal, Lieve Nuytinck, Francesca Rocchi, Mark Turner, Adriana Ceci (18 September 2019) in: Survey by TEDDY European Network of Excellence for Paediatric Clinical Research demonstrates potential for Europe-wide trials [Online]. Available at https://onlinelibrary.wiley.com/doi/10.1111/apa.15020#pane-pcw-references

effectiveness of policies and programs targeted at young individuals. Children participation in clinical research is for sure a practice that has a huge impact in their life, so many YPAGs dedicate their time to research studies. A YPAG safeguarding policy within the clinical practice will include: ensuring all staff and volunteers are vetted by the appropriate national body or scheme, as well as ensuring all staff are trained appropriately and understand the reporting procedure[10].
In Europe, the YPAG have been working to protect children's rights in clinical involvement since 2006, when the eYPAGnet was created in the UK. Nowdays, the groups are devided into two categories:

- Funder teams: Generation R, Kids Barcelona, Kids France and ScotCRN
- New teams: Kids Albania, Kids Bari, Kids Belgium, Kids Finland, Kids Germany, Kids London, Kids Madrid, Kids Portugal, Kids Rome.

4 The process to obtain the informed consent and assent

The Informed Consent is defined as "the process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form"[14]. It is important that the consent is voluntary- the investigator, nor the trial staff, should coerce or influence a subject to participate or to continue to participate in a trial. Informed means, that the participant clearly understands what participation in a trial will entail, and based on that information, can voluntarily document their willingness to participate. The documentation is important for both ethics and regulatory requirements. In the case of minors (according to EU regulations, paediatric population refers to children between birth and less than 18 years. The term minor has a more legal aspect and it can vary from country to coutry) there should be consent from their legally designated representative to include them in the clinical trial. Essentially, a parent or legal guardian is the legally designated representative of their child. They are the only ones who can provide the signed informed consent.
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/her, shall also assent in order to participate in a clinical trial according to the European law. In some cases ethics requirements may find agreement to be sufficient, but it has less of a legal value. Agreement is an analogy to "assent", where it is not a legal requirement. It is recommended by the ethics guideline that the investigator systematically requests agreement from the minor. In cases when the child, who is capable of forming and assessing the information provided to them, refuses to participate in the clincal trial, his or her wish has to be respected by the investigator[15].

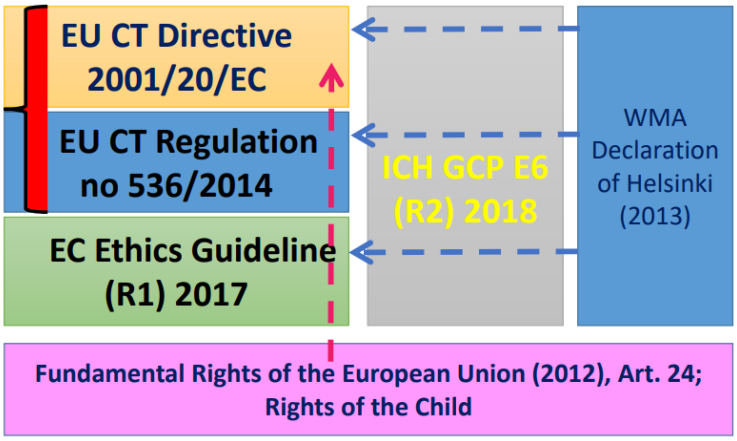
4.1 General requirements for consent

The chart below is a visual representation of the legal and ethical requirements involved in consent and assent. The general requirements are derived from the Fundamental rights of the European Union under Article 24, Rights of the Children. Going from right to left, the basis is the world medical association's Declaration of Helsinki, incorporated into the ICH Good

[10] eYPAGnet (no date) What is a Young Persons Advisory Group (YPAG)? [Online]. Available at https://eypagnet.eu/ (Acessed: 02 July 2023)

Clinical Practice[11], current version 2, which is then further incorporated into the legal texts via the new EU clinical trial regulation 536/2014, and the preceding EU Clinical trials directive. And incorporated into the ethical texts via the EU Ethics guideline that has been revised in 2017 to version 2.

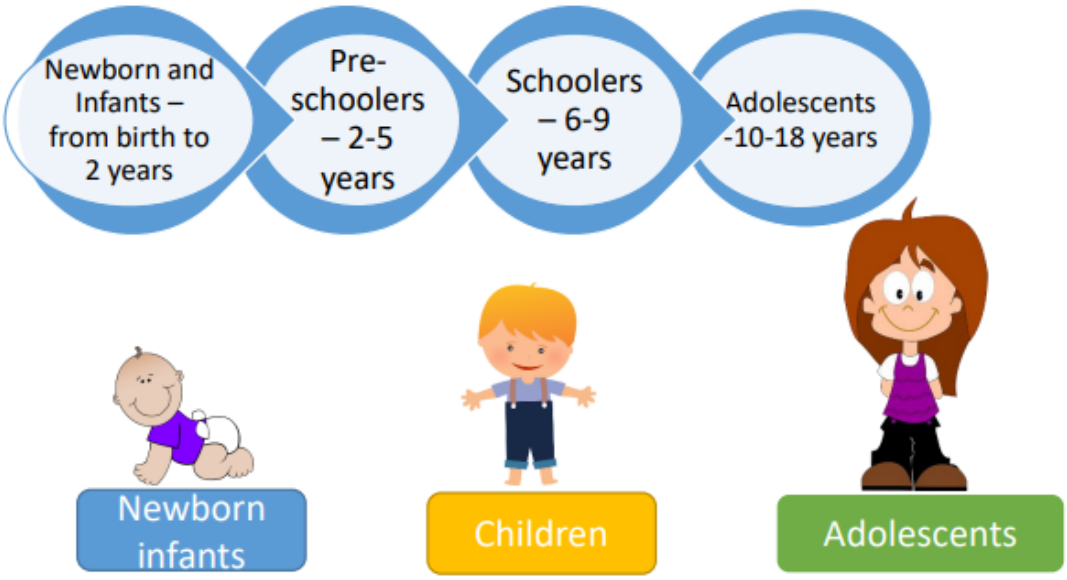
Figure 3. General requirements for consent



4.2 Consent by age in Europe

Age groups can vary depending on context, according to the World Health Organization there are 4 groups, however for the EU legal texts there are three; newborn infants, children and adolescents.

Figure 4. Age groups



[11] European Medicines Agency, Committee for Human Medicinal Products, International Council for Harmonization (1 December 2016) Guideline for good clinical practice E6(R2) [Online]. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf (Accessed: 21 June 2023)

These groups are only meant to provide guidance regarding proper involvement of minors in the informed consent process. Actual maturity and ability to assent may be different on a case-by-case basis. Two things to note, this categorization is voided in the case of emancipated minors and these age groups refer strictly to the context of assent and not to specificities of trials. Some trials will use age groups to define medical dose, inclusion criteria or outcome measures based on the physiology or drug metabolism, this does not change the consent age groups.
Anyway, maturity, in contrast to age, is not a clear-cut criterion and its evaluation can be confusing, but it used to support children involvement in research after identifying differences between them. Maturity is influenced by developmental stage, intellectual capacities (e.g. children with special needs and/or learning difficulties), and experiences that coorelate with the specific disease. The evaluation has to be documented in any case, and will rely on discussions between the investigator, the child itself and the parents/legally designated representative.
When it comes to teenagers, protection of confidentiality, especially for research on socially sensitive issues such as illegal drugs, violence or sexuallity is an added concern. In some Member States, parental discretion and the need of professional confidentiality in dealing with adolescents may tie up health professionals. Therefore, the specific aspects of disclosure to parents of any concerning information that is personal onlty to adolescents should be explicit in clinical trial protocols, and should be transparent to the concerned young people.
To conclude, legally consent is given by adults, characterized as 18 years of age or older. However, there are special circumstances that are defined by national laws and regulations. The age is 15 or 16 years for legal consent, for example in Finland, Ireland, The Netherlands and the UK. The definition of emancipated minor is also stated by national laws and regulations so it can vary between EU states.

4.3 Special cases and emergency situations

There are some cases when obtaining the informed consent is not a very smooth process.
Excluding from clinical trials those who are orphaned or those whose parents no longer possess parental rights (such as refugees without parents) is not advisable. Instead, the legally appointed representative will be asked for informed consent. This representative is responsible for safeguarding the child's interests and should consistently take into account the child's perspective.
Instances of disagreement between the minor and their parents or legally appointed representative are unique circumstances that demand careful consideration. When a minor expresses a desire to partake in an activity, even as their parents or representative object, it's important to give weight to the minor's intentions and reasoning. The researcher should strive to find a resolution for these conflicting opinions, acknowledging the developing capacity of the child to make adult-like decisions. If, despite reasonable attempts to find common ground, both sides continue to differ on the matter of participation, the dissenting stance of either party becomes decisive. Simply having the minor's consent isn't enough to permit involvement; it must always be accompanied by the informed agreement of the parents or legally designated representative.
Equal effort should be invested in reaching an agreement, even in cases where a minor declines participation in a trial despite having their parents' or legally designated representative's informed consent. It's crucial to observe any indicators of undue distress in patients who might struggle to communicate their distress explicitly. While a participant's desire to withdraw from a study should be respected, situations might arise in therapeutic studies for severe or life-threatening illnesses where, as determined by the investigator and the parent(s) or legal

guardian, the well-being of a pediatric patient could be compromised by not participating in the study. In such instances, ongoing consent from the parent(s) or legal guardian should suffice to permit the child's participation in the study.[16]
In the uncommon situation where a different legally designated representative changes during the trial, prompt action should be taken to secure informed consent from the new representative. Throughout the duration of a clinical study, it might become necessary to reevaluate a child's agreement due to their increasing age, growing maturity, and competency, particularly for studies of extended duration or those involving sample retention. In the context of clinical trials, it's essential to acquire suitable informed consent for ongoing involvement from pediatric participants once they reach the legal age of consent. It's vital to adhere to local regulations concerning the confidentiality and privacy of pediatric participants.
When addressing diverse cultural contexts, such as those involving refugees, it's important to tailor the information to the language proficiency and comprehension level of both the child and their parents or legal representative. Cultural disparities might occasionally result in misinterpretations, making it advisable to have a proficient translator and/or cultural intermediary involved in the study's preparation, as well as during the informed consent and agreement stages. This individual should possess a solid grasp of medical terminology, be skilled in the language, well-versed in societal customs, culture, traditions, religion, and specific ethnic distinctions.
During emergencies, the trial must ensure the anticipation of a direct and meaningful clinical advantage for the participant, leading to a measurable enhancement in their health-related state, thereby alleviating their distress and ultimately improving their overall health outcome. In practical terms, if it's viable to postpone research-related choices until a parent is available to make a decision, investigators should wait. In cases where such a delay is impractical, the trial might commence without obtaining informed consent, but it should be pursued promptly after the situation stabilizes; this process is referred to as deferred consent. Upon the arrival of the parents or legally appointed representative, the initial action involves furnishing details about the unfolding events and, considering the gravity of the circumstance, ensuring a thorough comprehension of the trial's nature. Following this, they should be extended an invitation to provide consent for their child's ongoing involvement in the trial, as deemed suitable. In cases where the parents or representative do not grant informed consent, they should also be informed of the option to raise objections against the utilization of data that have already been collected. Children, on the other hand, must participate in the process of informed consent, taking into account the urgency of the situation. Additional information should be presented once the child has sufficiently recovered, enabling them to express their assent or agreement. In trials of this nature, there is no exemption from the obligation to honor a child's explicit desire to decline participation.

Methodology

The first part of the thesis was mainly based on the available literature found online. The information was extracted by scientific databases and official websites of prestigious companies operating in the clinical research field. The search of keywords, such as: ‘paediatric trials’, ‘paediatric clinical research’, ‘young patients involvement’, ‘informed consent and assent form’ ‘children engagement’, was the first step for accessing important scientific articles and documents to gather information from. One of the main sources of information have been the official websites of the most important institutions that cooperate in the medical setting, like EMA and WHO. All the articles have been accessed in English to avoid any kind of misunderstanding during translation.

It was considered relevant to include information about the regulatory framework and ethical considerations regarding the involvement of children in clinical research, to stress that the approval of such studies undergoes various processes and documentation in order to ensure the safety, wellbeing and the dignity of patients is protected at all costs.
Since in paediatric trials the process of obtaining the informed consent is different, an important part of this master thesis has been dedicated to this matter. During the first part, it has been explained how important this document is for the clinical practice, how clinical research professionals obtain the informed consent and assent and how it has to be proceeded in special cases and emergency situations.
During the second part, an analysis on the paediatric involvement in clinical trials has been performed. Real and practical measures on how to involve children and their families in clinical research have been pointed out. The research on this second part comes as a result of combining the relevant information found on scientific databases or websites and my personal experience gained during a six month internship performed on the clinical trials setting. Friendly interviews, personal opinions and general considerations from Principal Investigators and their staff has been a great source of information for the practical part of this thesis. The perception of professionals has been an added value and a huge help. Practical exercises during my active participation in workshops, seminars and courses have also helped me deliver additional information and interpretations.
Analysis on the latest medical needs in paediatric research; practical planning in protocol design or recruitment strategies; the importance of a proper design of the informed assent for children according to their level of maturity; the involvement of patients and their families in post-approval and communications with regulatory bodies have been the main topics of the second part of the thesis.
In the final section, the analysis contains the results from my modest questionnaire on “Parents' knowledge and possible involvement of their children in clinical trials”. After being prepared, the questionnaire was immediately submitted to one of the thesis supervisors, Ana Dilo, for approval. Right after, the process of distribution began. The questionnaire came into two versions: online (created with Typeform) and printed, on a simple white paper. The printed version was handed out to occasional parents I came across the hospital's settings when performing monitoring visits in Italy (Ancona, Bologna, Naples, Pavia, Verona). The Typeform version was distributed online with the help of the most popular social media such as: Instagram, Facebook, Whatsapp and Twitter. Further recruitment was done through a "tree system". Each parent that answered the questionnaire was invited to mention other acquaintances who could be contacted.
Finally, a personal final conclusion with future considerations on how to improve children, young patients and parents' involvement in clinical research has been written.

Analysis

1 Strategies for incorporating the participation of children, young patients, and families at various stages of the research process

1.1 Identification of unmet medical needs

The European Medcines Agency (EMA) published a list of unmet medical needs concerning paediatric patients. The EMA encourages investment and development of new research to address the specific needs of young patients and families affected by childhood diseases. It is imperative at the point of identifying unmet needs that CYP and families are consulted and taken into consideration.
There are several ways that this can be achieved.

- Surveys

Distributing targeted questionnaires to CYP and their families is one way to collect unmet needs surrounding specific conditions and the impact this has on CYPs quality of life. For example, the EMA launched in 2015 a question-based survey to collect information from CYP to:
know their views on taking medicines (e.g. practical problems with taking different types of medicines, sources to find information about medicines) and to identify the level of knowledge of/or about their participation in clinical trials.
To achieve significant outcomes with this activity, it is essential to ask the right questions that CYP and families understand. Designing a survey is not a trivial process and it can be more complex when the target population is a little child. It is crucial that time is invested in the design and the questions are piloted with the same age group before the final approval of the survey. Some top tips in the process to design a survey are:

1. Write short questionnaires in order to ensure that all the people will complete all the questions
2. Use simple vocabulary, friendly for CYP and/or parents. If it is necessary, complete your explanations with cartoons or photos.
3. Start with interesting questions in order to capture and maintain interest
4. Do not write biased questions that can have an unclear meaning for the respondent
5. Avoid negative sentences
6. Beware of too long scales
7. Do not make lists with many options
8. Avoid complex concepts
9. Include closed questions as opposed to open ones
10. Design the structure with a logical order
11. Name your survey

- Focus groups

This approach facilitates a safe place where investigators can converse with CYP and families to gather their opinions and experiences as patients and carers. Several pharmaceutical companies consider this activity valuable for protocol design in particular, but it is also an exellent way to identify unmet needs and clinical trial endpoints that are meaningful to patients.

Combining both surveys and focus groups to identify unmet needs would be considered as the gold standard. Also focus groups allow to include other complementary activities to facilitate the discussion, such as an initial activity to ‘break the ice’ for the introduction or to split into gruops the participants in the activites. It is crutial that the CYP and family members feel comfortable during the focus groups sessions.

1.2 Research design and planning

1.2.1 Protocol design

Incorporating children's involvement in the design of clinical trial protocols is a valuable and progressive approach. By including children and their families in this early stage, researchers can ensure that the trial's design is sensitive to the unique needs, preferences, and challenges faced by young patients. This involvement can lead to more patient-centered protocols, increased recruitment and retention rates, and ultimately, more relevant and effective treatments for pediatric populations. Children's perspectives can provide insights into aspects such as study procedures, treatment schedules, outcome measures, and even the overall trial environment. Their input can help identify potential barriers to participation, reduce discomfort, and enhance the overall experience for young participants. Additionally, involving families in the protocol design process allows researchers to consider the practical and emotional aspects of the trial, as families play a crucial role in supporting and facilitating children's involvement. Overall, children's engagement in protocol design ensures that clinical trials are conducted with greater consideration for the young patients' physical and emotional well-being, making research more inclusive, ethical, and impactful.
Several models for involving CYP and their families in this proces have emerged during the years to include age-appropriate focus groups; co-design workshops and simulation (mock trials).

1.2.2 Recruitment strategies

Children's engagement in recruitment strategies for clinical trials is essential for ensuring successful enrollment and meaningful participation. Involving children and their families in the development of recruitment strategies can lead to more effective and ethical approaches. There are some points to consider:

- **Understanding Target Audience:** Children and their families have insights into what appeals to their peers and community. Involving them can help tailor recruitment materials and messages that are relatable and engaging for the target audience.
- **Sensitivity to Concerns:** Children and their families can help identify potential concerns or fears that might deter participation. By addressing these concerns upfront in recruitment materials, researchers can build trust and encourage enrollment.
- **Family Networks:** Families often have extensive networks within their communities, schools, and support groups. Leveraging these networks can help spread information about the trial and encourage participation.
- **Language and Tone:** Children and families can provide feedback on the language, tone, and content of recruitment materials to ensure they are clear, respectful, and understandable.
- **Trial Design Considerations:** Children and families can offer insights into what aspects of the trial design might attract or deter participation. For example,

understanding preferences for visit schedules or trial locations can help make the trial more convenient and appealing.

- **Informed Consent:** Involving children and families in desining informed consent processes can help ensure that the information is presented in a way that is appropriate and easily comprehensible for the target age group.
- **Diverse Representation:** Children from diverse backgrounds and communities might have different perspectives on participation. Engaging a wide range of children and families can help ensure that recruitment strategies are inclusive and relevant to various groups.
- **Engaging Messaging:** Children can contribute to crafting messaging that resonates with their peers, making the trial sound exciting and beneficial.

Depending on the laws and regulations within countries, recruitment strategies can be designed and validated by CYP and families to ensure CYP and families are approached in the most appropriate manner[12]. In some countries social media strategies, campaigns on TV and other formats (leaflets, flyers, websites) are used to highlight studies to recruit patients, surely after having recieved the appropriate authorisations.

1.2.3 Ethical issues and data protection

Ethics and Research Committees have the responsibility to ensure that research projects are aligned with the rights of the patients. To achieve this commitment CYP and families can be consulted in order to help addressing any perceived ethical issues that might arise from a particular study. One of the most relevant ethical contributions in which CYP and families can participate involves the discussion about the benefit/risk of a new treatment.
In May 2018, the General Data Protection Regulation (GDPR) came into force across Europe. The regulation establishes the rights of patients regarding their clinical data and other personal information. They are the owners of this information and can use the rights of being informed, access, rectification, erasure, restrict processing, etc, against any stakeholder who may host their data.
Children's data are also protected rigorously. Patient advocates and parents need to be educated in the use of personal data and in their rights.

1.3 Patient consent and assent

CYPs are most frequently asked to provide feedback about these two important documents, which allow the expression of approval or agreement of the research participant. Important considerations regarding the assent document include:
The lack of a common framework in Europe that regulates the range of age in what is mandatory or desirable to have the assent document signature of the pediatric patient The WHO and EMA leave this decision to the discretion of the study investigators.
The disease complexity and the clinical trial complexity are factors to be taken into account in order to design the right content and format for this document. Computer-based tools are friendlier than paper-based tools and allow a holistic process to inform the patients using complementary information (videos, pictures, etc.). These resources can facilitate the process of information before the signature. Co-production of these documents with children and young

[12] Turner, M. A. (2015) Clinical trials of medicines in neonates: the influence of ethical and practical issues on design and conduct, *Br J Clin Pharmacol*, 79, 370–378

patients or YPAGs will ensure age-appropriateness of the document that will contribute to a better information process, adherence to the treatment, etc.
CYP and families can co-design activities in order to review the documents proposed by the sponsor of the trial. To do it and to prepare the consultation sessions it is essential to consider the guidelines that EnprEMA offers (that were reviewed for several YAGs members of eYPAGnet) among other guidelines. To ensure that the final assent documents are suitable for their target population it is recommended to use health literacy scales to measure the reading age of the document. This tool can be used not only for the assent document, but also for the patient information sheet and the consent document.
Most frequently used scales are:

- SAM-Sustaibility Assessment of Materials and
- Health Literacy Questionnaire when we refer to the digitalization of health services- Ref: A Multidimensional Tool Based on the Health Literacy: Development and Initial Validity Testing of the eHealth Literacy Questionnaire (eHLQ)[15]

1.3.1 How to present consent information

In pediatric clinical trials, it is most important to notice how the information is given to both child and the legal representatives, such as parents. It is always guided to use plain language, which is concise, clear, relevant, nontechnical and easily understandable. The amount of information must be adapted to the intellectual capacity of the legally designated representative and the possible participant (consider age and developmental stage), and it should be adapted to the language skills and comprehension, always using the primary language of these persons. In some case, verified translations may be used. Additional visual aids - pictures, videos, computer programs, DVD's, cartoons etc. are advised to use, when explaining information to children to support and clarify the given information. For all of this, enough time should be provided to assimilate that information and ensure to give them the opportunity and possibility to ask questions[13].

1.3.2 Acceptable compensations in trials

When developing the protocol and consent information it is important to understand that the EU laws prohibit the use of any incentives or financial inducement to enroll (recruit) children to be clinical trial participants; it is not allowed to be provided to the legally designated representatives, -nor to the participant. There should not be any suggestion about possible compensation as a reason to participate. Only some compensation may be provided, which are directly related to the child's trial conduct and visits. These are examples of such compensations; Meal coupon or equivalent for a lunch or snack for a participant during a whole day visit at clinical site. Daily allowance or equivalent compensation as defined by national laws/regulations for the legally designated representatives who need to take days off from work due to their child's clinical trial visit which is a direct loss of earnings related to the trial. Compensation for the participant for an overnight hospital stay for a longer period, usually in early phase trials. And Travel Expenses for the participant; to and from home to the clinical trial site. It is important to underline that all of these may vary according to the national laws/regulations.

[13] African Research and Innovative Initiative for Sickle cell Education: Improving Research Capacity for Service Improvement (no date) Assent form & Informative material for minors [Online]. Available at https://www.ariseinitiative.org/

1.3.3 Children's and patient's views about consent information

What children want from all the information they recieve during the process of the informed consent and assent, is to understant why they have to participate in the trial, who will the study help and how their right and dignity will be protected to all metters throughout the study period. The investigator has to be present and ready to answer all the questions the children may have, including the meaning of terms they don't understand, the procedures or even their feelings during the study. It is important that the child feels heard before participating in a trial. It is also important that the child understands and views the trial as a study that is designed to make them feel better, but it can also happen that the study could make them feel worse or make no difference at all.
When presenting the information to children it is important to include colorful photographs and images that help them to make the assent less intimidating and provide natural breaks in reading that aid comprehension. They have to know that even if they decline to participate in the study, their decision will not affect thier right to recieve the necessary medical care. Children should be thanked for considering participation, even if they decide not to sign the assent form.

1.3.4 Level of maturity and assent design according to age groups

According to children's age groups and their capibility to understand the given information, there are different ways to present the assent document to them:

- Newborns and infants (from birth to 2 years old):
  In this specific developmental stage, acquiring consent and comprehensive comprehension of the research is unattainable. The primary goal of imparting information to the child is largely focused on preparing them for the forthcoming procedures. While verbal dissent cannot be anticipated from these children, any indications of reluctance or objection should be recognized and communicated to the parents or authorized guardian. This step aims to assess whether the observed behavior merely reflects the expected but reasonable stress, or if it raises concerns warranting a reevaluation of the research's continuation.

- Children under 6 years old:
  The information must be concluded in a short document in order that the child fully understands it without getting tired or distracted. It has to be read to children because of their uncapability to read on their own. The document must contain photos and pictures related to the trial. There is no need of mentioning details like protocol title or number. A very simple text has to be used, describing only important information like the process of the IP administration, schedule of assessments, blood drawns etc. It has to be emphasized that the child has the right to think it through, and of course mum and/or dad will help the child to take the decision to participate or not. It has to be mentioned to the participant the right to say NO and that no one will be upset. Together with the benefits that the child can have during/at the end of the trial, it is important to list all the possible side effects.
  In this case, the assent is not signed by the child, but only by the parent(s) and the site personnel conducting the process.

- Children between 6-9 years old:
  The inform assent is presented into a bigger document, usually containing 5-6 pages. Even though they are able to read and write, understanding can be enhanced by reading

the information to the children. It has for sure photos and pictures to make the narrative more interesting and easier to understand. Protocol title and number as well as sponsor are mentioned. Introduction to the study, with simple text describing the IP administration, schedule of assessments, blood drawn are also mentioned and described in easy words. All the possible side effects are listed.
An important part of the document is a paragraph describing the handling of personal data. Privacy notices for minors must be presented using clear and suitable language, or in a manner that is approachable to their intellect, employing diagrams, cartoons, visuals, videos, icons, and symbols. This approach should entail explaining to them the reasons behind the need to process their personal information, detailing how this information will be used, outlining their rights concerning their personal data, and elucidating the protective measures that will be put in place to mitigate potential processing-related risks[15].
At the end of the document, it is stated that a copy will be provided to the child. It is also mentioned that the child can participate if it is agreed by the parent(s) or caregiver. As the final process, the child replies to a list of questions at the end by marking Yes or No and puts his/her name only to state that he/she agrees.

- Children between 10-12 years old:
  The assent infomation is presented in a similar way. The only difference is that, in this case, the child also signs and dates the assent form.

- Adolescents: Between 13-18 years old
  Since different Member States treat adolescents diversely (according to the respective national laws), they are considered a very particular and sensitive group. The adolescents may have the capacity to make adult decisions or independent judgments in many other areas of their life, yet they still belong to the paediatric age group[15].
  The assent form, in this case is presented in a long detailed text, that usually does not contain photos. The text contains any contact information of PI, sponsor, EC, all the processes the teen has to undertake during the study, risks and benefits from the trial, side effects and safety informations. There are also mentioned all the possible compensation forms for participation, such as transpotation costs, meals and vouchers etc.
  An important part of the assent form in adolescents is without any doubt the paragraph that describes in details the foreseen risks in case of pregnancy and breastfeeding. Part of this section is also the attention required in contraceptive methods and safe sexual intercourse. The recreational use of unprescribed drugs, alcohol, tobacco (depending on the study) is also explained. Even adolescents have a detailed view on how their confidential data is managed, who will have access to these data and how safe their information will be during and after the study. The right to withdraw the assent in any time is also mentioned, together with the section that explains the need of a new informed consent form to be signed if during the study the teen has reached the age of maturity.
  Some Member States consider adolescents that turn a certaing age of 16-17 years legally capable of giving informed consent to participate in research.

  Anex 1 contains a detailed list of requirements per country.

1.3.5 Innovative tools for patient information

As mentioned above, it is important to develop the assent process by incorporating computer-based tools, since the application of the electronic format for the consent process is becoming more frequent. Despite the need for more evidence and best practices about using innovative tools for patient information sheets and assent, CYP and families have commented that they consider electronic assent to be beneficial. Taking this into account there is a need to promote projects that evaluate digital tools and develop good practices and guidelines to facilitate their implementation. The assent process requires complementary information and educational resources that can be included in the design of the electronic assent tool. This does not need to be an exact electronic copy of the assent document, but is a good opportunity to make the process more interactive and informative. CYP can be approached to test electronic assent tools from the user experience and provide critical analysis to develop and improve the assent process.

1.3.6 Decision tools to aid participation in research studies

Materials used to educate CYP and families about health research are of great importance. Additional informative materials for children, young patients, and their families are recommended to enhance their understanding of every aspect of their involvement in the study:

- Patient Diaries: These tools are beneficial for facilitating communication about health-related events and aiding research nurses in monitoring them. Collaborating with children, young patients, and families in the development of these tools can ensure their user-friendliness and practicality.
- Leaflets/Brochures: These documents should be written in a language understandable by the general public and presented in a format that effectively conveys accurate information to all patients, including children.
- Measures for Adherence: Despite the absence of a standardized guideline for measuring medication adherence, involving patients in clinical trial design will encourage actions that promote improved adherence levels among participants.
- Drug Labeling: In studies involving investigational medicinal products, proper labeling of drugs holds great significance. Patient-centric studies will incorporate medicine labels to simplify drug administration and provide relevant information.

1.4 Research conduct and operations

Patient centered clinical trials means that the involvement of patients is ensured along the drug development process. Family involvement can be an asset to achieve this objective if they contribute in the different bodies that are working when a trial in ongoing, such as:

- Family involvement in Trial Steering Commitee[14]
- Family involvement in Data and Safety Monitoring Commitee

The primary responsibility of the Trial Steering Committee (TSC) is to exercise comprehensive oversight over the trial. Ideally, the TSC should comprise individuals who are not affiliated with the research institutions, clinical trial site personnel, sponsors, funders, and so forth. This

[14] National Institute for Health Research (NIHR) INVOLVE. (no date) Trial Steering Committee (TSC) [Online]. Available at https://www.invo.org.uk/posttypejargon/trial-steering-committee-tsc/

committee is tasked with overseeing the advancement of the trial, evaluating its conduct, and offering guidance on matters of scientific integrity[17].
The responsibilities of this committee also are connected with the Data Monitoring Committee (DMC). Also is the body responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy. The involvement of patients and families in these bodies helps to ensure the patient centricity of the paediatric clinical trials. Education to be part of these bodies can facilitate the selection of the members and ensure a meaningful participation.

1.4.1 Dissemination, Communication, Post-approval

Dissemination refers to the process of spreading research findings, information, and outcomes to a wider audience, both within the scientific community and beyond. It ensures that the knowledge generated from research is made accessible and usable for various stakeholders, including healthcare providers, policymakers, patients, and the general public. Dissemination activities can include: publications in journals, conferences and presentations, online platforms, media and press releases.
Communication involves the effective exchange of information between researchers, participants, stakeholders, and the wider community. Clear and transparent communication is essential throughout the research process, from recruitment to dissemination of results. It fosters trust, ethical conduct, and collaboration. Communication activities encompass: patient engagement, stakeholder engagement and ethical consideration.
Post-approval activities involve actions taken after a research study or clinical trial has received regulatory approval or ethical clearance. These activities ensure that the research continues to have an impact beyond its initial completion. Examples of post-approval activities include: follow-up studies, real world implementation, healthcare guidelines, patient support and education and policy advocacy.

→ Invlovement in regulatory activities

The approval of a new medicine is a commitment of the regulatory agencies. European Medicines Agency is the responsible of the approval of medicines at European level that is valid in 28 Member States of the European Union as well as Iceland, Norway and Lichtenstein. Even for orphan drugs (medicines that cure rare diseases) or for the disease areas that are developing rapidly like HIV/AIDS, diabetes, neurodegenerative disorders or cancer; the approval is a mandatory procedure. There are also some product types like those derived biotechnology and some gene therapy products that must also pass through the Agency[5].
Different types of medications are subject to various committees and procedures. In the European context, the European Medicines Agency (EMA) introduced a document in 2017 that presents the "Guidelines for Engaging Young Patients and Consumers in Marketing Authorization (MA) Processes." This document aims to simplify the procedure and define the approach for including underage individuals in regulatory activities[15].
Specifically, once a new medicine is approved there are further activities in which patients can be involved:

- EPAR (European Public Assessment Report) summaries

[15] Ceci A, Giannuzzi V, Bonifazi D, Felisi M, Bonifazi F, Ruggieri L. Clinical Trials in Paediatrics - Regulatory and Methodological Aspects. In: O Vallisuta, S Olimat, eds. Drug Discovery and Development - From Molecules to Medicine. IntechOpen; 2015: 283-285. https://doi.org/10.5772/58659

- Disseminating research results to patient communities

The European Public Assessment Report (EPAR) is published for every drug that has been given or refused a marketing authorisation is a comprehensive document produced by the European Medicines Agency (EMA) as part of its commitment to transparency and providing access to information about medicinal products authorized in the European Union (EU). The EPAR serves as a central source of information that summarizes the scientific assessment of a medicine's quality, safety, and efficacy. All the documents are always published in all official EU languages.
The European Regulation of Clinical Trials (No 536/2014) in the article 37 establishes that lay summaries need to be published in the EU data base for clinical trials in health volunteers and patient population, Phase 1 to Phase 4, conducted in at least one site in Europe. Lay summaries need to be based in the principle of offering friendly information to disseminate clinical trials results for lay persons. The involvement of patients or patients' representatives in the development and/or review of the summary to assess comprehension and the value of the information provided has to be considered. Involving Young Persons' Advisory Groups (YPAGs) in the review and understanding of the European Public Assessment Report (EPAR) can be a valuable activity. Patient involvement can be considered a win-win situation. It benefits the young participants by empowering them to become informed about their treatments and advocates for their own health, while also benefiting the healthcare system by fostering a more patient-centered and inclusive approach to medicine evaluation and communication.

→ Frameworks to involve patients in drug development as a cross-cutting activity

Regulatory bodies are highly promoting the involvement[16] of patients along the drug development process.
In June of 2018, the FDA[17] issued the "Patient-focused Drug Development: Collecting Comprehensive and Representative Input" document in the United States. This guidance is aimed at Industry, FDA personnel, and various stakeholders, with the intention of enhancing the integration of patients' perspectives into Drug Development and Regulatory Decision Making. Similarly, in July of 2017, the European Medicines Agency released the "Guidelines on Engaging Young Patients/Consumers in EMA Activities." These instances highlight the significant emphasis that regulatory bodies place on incorporating patients' insights into research. They also encourage other stakeholders to develop patient-centric frameworks, a pivotal element that ensures all parties adopt a unified approach to ensure the effectiveness of Patient Engagement[18] (PE) as a pervasive activity throughout the drug development process.
The Patient Focused Medicine Development (PFMD) is a global initiative that aims to bring together patients, caregivers, healthcare professionals, researchers, regulators, industry representatives, and other stakeholders to collaborate on advancing patient-centric approaches in medicine development. PFMD focuses on improving the way patient engagement is

[16] Public Involvement Impact Assessment Framework (PilAF) Study Group. (2013). Tabular Summary of Findings from a Review of Reported Impacts of Public Involvement in Research. Available at http://piaf.org.uk/documents/impacts-summary-1113.pdf

[17] Food and Drug Administration Staff, and Other Stakeholders. (June de 2018). (9] Patient-Focused Drug Development: Collecting Comprehensive and Representative Input Guidance for Industry. Retrieved from https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/um610442.pdf

[18] Bennett Levitan, K. G.-L. (2018). Assessing the Financial Value of Patient Engagement: A Quantitative Approach from CTTI's Patient Groups and Clinical Trials Project. Therapeutic Innovation & Regulatory Science, Vol. 52(2) 220-229. Available at: https://journals.sagepub.com/doi/10.1177/2168479017716715

integrated throughout the entire lifecycle of medicine development, from early research stages to regulatory approval and post-market activities.
The Quality Guidance for Patient Engagement has been designed with the consensus of all the stakeholders to facilite the process to design and assess activities of patient engagement. Listed below are the criteria that aid in streamlining the process:

1. Shared pursopose
2. Respect and accessiblity
3. Representativeness of stakeholders
4. Roles and responsabilities
5. Capacity and capability for engagement
6. Transparency in communication and documentation
7. Continuity and sustainability

Figure 4. Quality guidance for Patient Engagement

Source: PFMD, 2018

1.5 Results from the practical questionnaire on parent engagement

In order to better understand parent's point of views about clinical research and their children's involvement in clinical trials, I prepared a questionnaire entitled*: "Parent survey: Patient Engagement in Pediatric Clinical Trials' ' which* can be found in Annex 2. The questionnaire was prepared in order to add a real opinion from parents that come from different age groups, cultural backgrounds or educational levels. After being prepared and reviewed by my thesis supervisor, these questionnaires were distributed to a small number of people very close to me,

in order to have feedback about the organization, the design and more importantly the difficulty level of the questions. All questions were designed as *closed-ended multiple-choice* questions, a deliberate choice made to minimize confusion, enhance participant response ease, and streamline the process of answering and collecting responses. After making some minimal changes, the process of distribution began.

I distributed these questionnaires from May to July, around 40% of them to random parents I came across the hospital settings while I was performing my internship visits to the sites. The questionnaires were printed in a white paper with a large font in order to be easier for the parents to read. The hospitals I came across all the parents that participated were situated in Italy, more respectively in: Ancona (visited once), Bologna (visited 5 times), Napels (visited twice), Pavia (visited once) and Verona (visited once). All the parents received the Italian version of the questionnaire, except a pair of emigrants that were more comfortable with the English version.
The online versions of the questionnaires were distributed in social media, and since the engagement was higher, these make up 60% of the total number. The online versions were created with Typeform and the feedback was very positive, as the design was nice and eye-catching. I distributed the questionnaires to my relatives and friends that are already parents to one or more children. A 'tree system' was then used in order to have a greater engagement. Every parent who completed the questionnaire was then politely asked to provide names of other individuals they know who could potentially be reached out to. Some of the names mentioned agreed to participate and a few didn't answer.
Gathering and evaluating the responses from the questionnaires has been the most challenging aspect of this research study, yet also the most satisfying. There were 140 participants in total, 56 of them answered the printed form of the questionnaire and 84 answered the online version. Around 50% of the parents belonged to the age group of: 25-34 years old and 70% of all the participants were females. Regarding their educational background, 40% had attained a Master's degree, 30% possessed a Bachelor's degree, and 30% had completed high school or a lower level of education.
When it comes to the awareness section, almost 60% of the participants had heard of paediatric clinical trials, 60% of them declaring they had minimal understanding, 30% had moderate understanding and only 10% had advanced knowledge. Many parents, almost 40% of the participants, were positive responders, saying they would be comfortable with the idea of involving their children in clinical trials. 30% of the parents were neutral and the rest 30% were very uncomfortable with the idea. An important correlation between the attitude towards clinical research and the level of education was made. Most of the parents that were not comfortable with the idea of involving their children in clinical studies had only completed high school or a lower level of education. The main concerns and reservations of all the participants happen to be, of course, at 60% the *safety* concerns about clinical trials. Then they mentioned the potential side effects, possible long-term impacts on the child's health and lack of information about the trial. Less mentioned concerns were: financial costs (with only around 10%), ethical considerations and the fear from the unknown. The most important factors influencing decision-making in parents were, without a doubt: the potential benefits to their child's health, the trust they had in the healthcare provider/research team, the clear and understandable information about the trial and *their active involvement* in the decision-making process.
The last two questions asked to the participants were related to their practical engagement and to the ways this engagement could be improved. When asked what steps could be taken to improve the engagement and communication between parents and healthcare providers, the options that garnered the highest preference were: to offer informational sessions for parents,

providing clear and concise information about the trial; to create a user-friendly online platform for communication and to create a parent advisory board to provide feedback and suggestions. They suggested some possible tools that would help parents better understand and engage with pediatric clinical trials, and they were mainly: Parent support groups, Online forums for sharing experiences, Pediatric clinical trial brochures and Mobile apps for tracking trial progress or possible side effects in real time.

1.6 Conclusions and future considerations

This thesis emphasizes the importance of patient and family involvement in clinical trial design and offers practical steps for integrating their perspectives effectively. The study highlights the essential role of children, young patients, and their families in the process of designing clinical trials. Their direct involvement contributes to more patient-centered and relevant research, ensuring that trial protocols align with the needs and preferences of those they aim to benefit. Insights from those who directly experience the condition being studied can lead to better-designed protocols, reducing dropout rates and improving trial outcomes. Incorporating the perspectives of children, young patients, and families early in the trial design process ensures ethical considerations are addressed comprehensively. This approach helps create trials that are more sensitive to the needs and potential risks faced by these vulnerable populations. Effective collaboration among researchers, healthcare providers, patient advocacy groups, and families is crucial.

Meanwhile, it is extremely important to consider *early* engagement of children, young patients, and families in clinical trial design. Involving them from the initial stages ensures their input is integrated into trial protocols, creating studies that resonate with their experiences. It is necessary to strive for diverse representation among the involved patients and families. Different backgrounds, cultures, and experiences bring valuable insights to the table, contributing to more comprehensive trial design. As per its huge importance, considerations should be given to the ethical oversights during a study. Professionals should work closely with ethics committees to ensure the ethical implications of involving children and young patients are thoroughly considered. Addressing any potential challenges and concerns to create a well-balanced approach is a great step ahead. It is crucial to document the impact of patient and family involvement in clinical trial design and disseminate the findings. By showcasing success stories and visible improvements resulting from their input, one can inspire future trials to adopt similar approaches.

Acknowledgments

I am deeply grateful to my thesis supervisors: Prof. Jean-Pierre and Ana, who have supported and guided me throughout the journey of completing this thesis. Their contributions, suggestions and encouragement have played a crucial role in shaping this work.

I would like to acknowledge CVBF and all the people I worked with during this 6 month internship, for furnishing the necessary resources and facilities that enabled me to carry out this research. I would also like to express my appreciation to all the participants and respondents who took part in my questionnaire, providing essential data for this research. This work would not have been possible without their involvement.

My appreciation extends to all my professors, both in Italy and Belgium, for providing me with a stimulating academic environment where I could explore and expand my knowledge. Special thanks to Prof. Yves Geysels who enthusiastically imparted to me a deep understanding of clinical research. I also want to thank all my colleagues and friends from this Masters, that have shared two amazing years with me, making this journey much easier and unforgettable. Getting to know each one of them has been a privilege.

I am grateful to my partner, who has always been by my side, during my highs and lows. His encouragement and patience have been a source of comfort and strength.

Last, but not least, I would like to express my deepest gratitude to my family, who have stood by me throughout this journey. Their constant encouragement and belief in my abilities have fuelled my determination to reach this milestone. This thesis is dedicated to my parents and my sisters, whom I hope to have made proud!

Biblioghraphy

|1| African Research and Innovative Initiative for Sickle cell Education: Improving Research Capacity for Service Improvement (no date) Assent form & Informative material for minors [Online]. Available at https://www.ariseinitiative.org/

|2| Basia Coulter (24 February 2023) Optimizing the cost of clinical trials [Online]. Available at https://stayrelevant.globant.com/en/technology/healthcare-life-sciences/clinical-trials-cost-breakdown/ (Accessed: 22 June 2023)

|3| Bennett Levitan, K. G.-L. (2018). Assessing the Financial Value of Patient Engagement: A Quantitative Approach from CTTI's Patient Groups and Clinical Trials Project. Therapeutic Innovation & Regulatory Science, Vol. 52(2) 220-229. Available at: https://journals.sagepub.com/doi/10.1177/2168479017716715

|4| Ceci A, Giannuzzi V, Bonifazi D, Felisi M, Bonifazi F, Ruggieri L. Clinical Trials in Paediatrics - Regulatory and Methodological Aspects. In: O Vallisuta, S Olimat, eds. Drug Discovery and Development - From Molecules to Medicine. IntechOpen; 2015: 283-285. https://doi.org/10.5772/58659

|5| Donald Lombardi, L. S. (2017). Industry and Patient Perspectives on Child Participation in Clinical Trials: ThePediatric Assent Initiative SurveyReport. SAGE Journals, Vol. 52(1) 29-37. Available at https://link.springer.com/article/10.1177/2168479017716490

|6| European Commission in Clinical Trials [Online]. Available at https://health.ec.europa.eu/index_en

|7| European Medicines Agency, Committee for Human Medicinal Products, International Council for Harmonization (1 December 2016) Guideline for good clinical practice E6(R2) [Online]. Available at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf (Accessed: 21 June 2023)

|8| European Reference Networks (no date) What is clinical research [Online]. Available at https://www.ern-eye.eu/clinical-research/sturz (Accessed: 17 June 2023)

|9| eYPAGnet (no date) What is a Young Persons Advisory Group (YPAG)? [Online]. Available at https://eypagnet.eu/ (Acessed: 02 July 2023)

|10| Food and Drug Administration Staff, and Other Stakeholders. (June de 2018). (9] Patient-Focused Drug Development: Collecting Comprehensive and Representative Input Guidance for Industry. Retrieved from https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/um610442.pdf

|11| Lucia Ruggieri, Adriana Ceci, Franco Bartoloni, Valèry Elie, Mariagrazia Felisi, Evelyne Jacqz-Aigrain, Mariangela Lupo, Salma Malik, Cristina Manfredi, Giorgio Reggiardo, Jacques Demotes, Donato Bonifazi (2021) in: Paediatric clinical research in Europe: an insight on experts' needs and perspectives [Online]. Available at https://www.sciencedirect.com/science/article/pii/S2451865421000375

|12| Lucia Ruggieri, Donato Bonifazi, Annalisa Landi, Fedele Bonifazi, Franco Bartoloni, Mary Costello, Maria Grazia Felisi, Elke Gasthuys, Anila Godo, Federico Martinon Torres, David Nadal, Lieve Nuytinck, Francesca Rocchi, Mark Turner, Adriana Ceci (18 September 2019) in: Survey by TEDDY European Network of Excellence for Paediatric Clinical Research demonstrates potential for Europe-wide trials [Online]. Available at https://onlinelibrary.wiley.com/doi/10.1111/apa.15020#pane-pcw-references

|13| Lupus Research Alliance (no date) Phases of a Clinical Trial [Online]. Available at https://lupustrials.org/about-trials/phases-of-a-trial/ (Accessed: 17 June 2023)

|14| M.A. Turner a, M. Catapano b, S. Hirschfeld c, C. Giaquinto d, GRiP (Global Research in Paediatrics) (2014) in: Paediatric drug development: The impact of evolving regulations [Online]. Available at https://www.sciencedirect.com/science/article/pii/S0169409X14000258
|15| National Institute for Health Research (NIHR) INVOLVE. (no date) Trial Steering Committee (TSC) [Online]. Available at https://www.invo.org.uk/posttypejargon/trial-steering-committee-tsc/
|16| National Institutes of Health (no date) The Basics [Online]. Available at https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics (Accessed: 17 June 2023)
|17| P. Joseph, J. Craig, P. Caldwell (Mar 2015) Clinical trials in children. British Journal of Clinical PharmacologyVolume 79, Issue 3: Paediatric Prescribing p.89
|18| Patient Focused Medicines Development (PFMD.org) (no date) Patient Engagement [Online]. Available at https://patientfocusedmedicine.org/
|19| PFMD. (2018). *The Patient Engagement Quality Guidance*. https://patientfocusedmedicine.org/peqg/patient-engagement-quality-guidance.pdf
|20| Public Involvement Impact Assessment Framework (PilAF) Study Group. (2013). Tabular Summary of Findings from a Review of Reported Impacts of Public Involvement in Research. Available at http://piaf.org.uk/documents/impacts-summary-1113.pdf
|21| S Sam Lim, A. J. (2017). Simulating clinical trial visits yields patient insights into study design and recruitment. Patient Preference and Adherence, 11: 1295-1307. Available at: https://pubmed.ncbi.nlm.nih.gov/28814837/
|22| Susanne Schmidt (8 November 2021) Strategies for pediatric clinical trials and drug development [Online]. Available at https://www.raps.org/news-and-articles/news-articles/2021/11/strategies-for-pediatric-clinical-trials-and-drug (Accessed: 23 June 2023)
|23| Turner, M. A. (2015) Clinical trials of medicines in neonates: the influence of ethical and practical issues on design and conduct, *Br J Clin Pharmacol*, 79, 370–378
|24| Warner K, See W, Haerry D, Klingmann I, Hunter A and May M. (2018). EUPATI Guidance for Patient Involvement in Medicines Research and Development (R&D); Guidance for Pharmaceutical Industry-Led Medicines R&D. *Front. Med.* 5:270. doi: 10.3389/fmed.2018.00270
|25| WHO. (1994). Ethical Criteria for Medicinal Drug Promotion. Retrieved from http://apps.who.int/medicinedocs/en/d/Js16520e/16.1.html
|26| World Health Organization (no date) Clinical Trials [Online]. Available at https://www.who.int/health-topics/clinical-trials#tab=tab_1 (Accessed: 17 June 2023)
|27| World Health Organization (no date) Clinical Trials in Children [Online]. Available at https://www.who.int/clinical-trials-registry-platform/clinical-trials-in-children (Accessed: 22 June 2023)

APPENDICES

APPENDIX 1

23 October 2019

Informed Consent for Paediatric Clinical Trials in Europe 2015[i]

Developed by the Working Group on Ethics

			Consent from parent(s) /		
		Mandatory / suggested age ranges defined for assent (or consenti			
Austria[1]	18 years	8-13 years EC may require younger assents	One parent	German	http://www.medunigraz.at/ethikkommission/Forum/index.htm http://www.ethikkommissionen.at/ http://www.uibk.ac.at/strafrecht/scheil/scheil-einfuehrung-in-die arzneimittelpruefung-bei-kindern-und-jugendlichen---kks--kids ip.pdf For clinical trials with an IMP: AMG §42 applies. Legal age of consent is 18. One parent has to sign ("Erziehungsberechtigter"). For clinical trials with an MD: MPG §51 applies. Legal age of consent is 18. One parent has to sign ("Erziehungsberechtigter").

[1] Data for Austria were updated in May 2016.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000
An agency of the European Union

Belgium	18 years	4-11 years (some sites do not use under 12 years) 12-14 years 14-17 years	One parent at recruitment, but both parents at some point for signatures	Dutch, French German at site request	http://www.fagg afmps.be/en/human_use/medicines/medicines/research_development/ethic_committee/templates_informed_consent/ Do not have paediatric templates
Bulgaria	18 years	6-11 years 12-14 years 14-17 years – use own consent + parental signature also required	Both parents	Bulgarian	No national EC websites available in English Bulgarian Drug Agency -> clinical trials http://en.bda.bg/index.php?option=com_content&view=category&layout=blog&id=14&Itemid=34
Croatia	Nothing specified	Nothing specified	Nothing specified	Croatian	Agency for Medicinal Products and Medical Devices of Croatia -> Central Ethics Committee http://www.almp.hr/?ln=en&w=o_SEPu Information on clinical trials not available in English.
Czech Republic [2]	18 years	12-14 years 15-17 years	Both parents. Only by one parent if the other parent is not listed in the child's birth	Czech. Where the child's parents (or one of them) are foreign nationals, the information	State Institute for Drug Control -> Details of clinical trials / Guidelines and Forms / KLH-22 version 4 http://www.sukl.eu/medicines/klh-22-version-4

			certificate, has died or is younger than 18 years.	sheet shall be presented in bilingual format.	

[2] Data for the Czech Republic were updated in October 2019

Denmark	18 years	15-17 years proxy consent	Both parents Exception - no parents if aged 15-17 and non interventional no risk study (EC dispensation required)	Danish	The National Committee on Health Research Ethics -> Guidelines about Notification http://www.cvk.sum.dk/CVK/Home/English.aspx http://cvk.sum.dk/English/guidelinesaboutnotification.aspx -> 4.4. Medicinal product trials and clinical investigations of medicinal devices involving legally incompetent subjects; 4.4.1 Trials with children and young people under the age of 18 http://cvk.sum.dk/English/guidelinesaboutnotification.aspx#Afsnit %205.0 Act on Research Ethics Review of Health Research Projects
Estonia	18 years	0-7 years 7-17 years mandatory	Both parents	Estonian	State Agency of Medicine -> Clinical Trials -> Conditions and Procedure for Conducting Clinical Trials of Medicinal Products http://www.ravimiamet.ee/en/clinical-trials-medicinal-products estonia

Finland	15 years	Written separate consent as soon as child is literate; under 15 years own consent + parental consent. 15-17 years own consent + parental notification if minor can understand the significance of research + direct health benefit is expected	Parent or legal guardian and the child, when they are literate need to sign the consent. One parent by the law, but the other one can be informed (- both can sign if they want).	Finnish, Swedish	Medicines Research Act 488/1999 Medical Research Decree 986/1999 Additional info: FINPEDMED guidelines; legal and ethical regulation – templates for age groups 6-17 and parents. Regulatory requirements for clinical trials in Finland Picture Cards to support IC process

France	18 years	Based on EC – usually 2 or 3 age groups 4-6 years 7-12 years 13-17 years Picture ICFs for young children	Both Parents	French	Comité de Protection des Personnes Sud-Méditerranée II : http://www.cpp-sudmed2.fr/Information-et-autorisation des?lang=fr National Consultative Ethics Committee for Health and Life Sciences: http://www.ccne-ethique.fr/en

Germany[3]	18 years	7-11 years 12-16 years 17 years own consent + parental consent required	Both Parents	German	Permanent Working Party of Research Ethics Committees (Arbeitskreis der Medizinischen Ethik-Kommissionen) German Ethics Council http://www.ethikrat.org/ - no information for Clinical Trials Landesärztekammer Brandenburg – information available ONLY in German. https://www.laekb.de/ ICF Guidance https://www.laekb.de/files/146A97FF999/AMG_Patienteninfo_Kinder_7bis11.pdf

[3] Data for Germany were updated in November 2016

Hungary	18 years	Under 6 years 6-10 years 11-14 years 15-17 years	One Parent	Hungarian	National Institute of Pharmacy and Nutrition -> Laws and regulations (only available in Hungarian) -> Miniszteri rendeletek http://ogyei.gov.hu/search/index.php?searchPhrase=decree&from=10 http://www.ogyei.gov.hu/magyar_jogszabalyok/ -> Decree 35/2005 (VIII. 26.) of the Minister of Health on the clinical trial and application of correct clinical practices of investigational medicinal products intended for use in humans 7§ Clinical trials conducted on minors http://net.jogtar.hu/jr/gen/getdoc.cgi?docid=A0500035.eum
Iceland	18 years	Under 12 years	One parent – the EC can request both parents' signature in some cases.	Icelandic or English. The study objective in Icelandic. Materials in Icelandic. (for studies	The National Bioethics Committee (http://www.vsn.is/en/node/189) The Parliament; http://www.althingi.is/english -> http://www.althingi.is/lagasafn/log-samthykkt-a-althingi/ -> The Act of Law, No. 44/2014, on scientific research within the health sector defines the conditions for biomedical research and the role of the bioethics committees. http://www.althingi.is/lagas/nuna/20144044.html

				involving groups of other ethnicity, an appropriate language is required)	Several laws and regulations on data protection, medicines, biobanks and health information collections (2014), etc.

Ireland	16 years (Clinical trials) 18 years (all other research)	7 years, or according to capacity of child	One Parent	English	List of Research Ethics Committees for clinical trials of IMP: http://health.gov.ie/european-communities-clinical-trials-on medicinal-products-for-human-use-regulations-2004/ Research Ethics Committee Standard Application Form: http://www.molecularmedicineireland.ie/research_ethics National Consent Policy: http://www.hse.ie/eng/about/Who/qualityandpatientsafety/National_Consent_Policy/consenttrainerresource/trainerfiles/NationalConsentPolicyDOC.html Clinical Trial Regulation: S.I. No. 190/2004 - European Communities (Clinical Trials on Medicinal Products For Human Use) Regulations, 2004 http://www.irishstatutebook.ie/2004/en/si/0190.html

Italy	18 years	6-10 years 11-14 years 15-17 years with own signature No official mandatory age(s) for assent. Different age tailored assents are submitted voluntarily, and are evaluated by the ECs.	Both parents	Italian	The Italian Medicines Agency http://www.agenziafarmaco.gov.it/en/content/clinical-trials the Italian regulation on CTs include the following: D.lgs 211/2003 http://www.agenziafarmaco.gov.it/sites/default/files/decreto_2406 2003_inglese.pdf DM 21/12/07 https://www.agenziafarmaco.gov.it/ricclin/sites/default/files/files_ wysiwyg/files/Normativa/MD_21_December_2007_CTAform_English.pdf

Latvia	18 years	0-7 years 7-17 years	One parent or legal representative	Latvian	State Agency of Medicines of the Republic of Latvia -> Clinical Trials and non-interventional trials -> legislation http://www.zva.gov.lv/?setlang=en -> http://www.zva.gov.lv/?id=396&sa=396&top=386 -> http://www.zva.gov.lv/index.php?id=381&sa=381&top=333&lang http://www.zva.gov.lv/doc_upl/MK_not_289_English_02062010.pd f

Lithuania	18 years	No set ages	Both parents	Lithuanian	The Lithuanian Bioethics Committee -> Biomedical Research -> favourable opinion on Clinical Drug Trial http://bioetika.sam.lt/index.php?3202747546 Informed Consent http://bioetika.sam.lt/index.php?3221858831 -> http://bioetika.sam.lt/index.php?577320631 – information available only in Lithuanian http://bioetika.sam.lt/index.php?3202747546
Malta	18 years	6-17 years	Parents or legal representative - Practice – both parents	One of the official languages of Malta (e.g. Maltese) or in a language understandable to the clinical trial subject and, or his legal representative.	Malta Health Ethics Committee https://health.gov.mt/en/appbodies/hec/Pages/Links.aspx Maltese Clinical Trials Regulations 2004 (LN490 of 2004) MEDICINES ACT, 2003 (ACT NO. III OF 2003); http://justiceservices.gov.mt/DownloadDocument.aspx?app=lp&ite mid=16860&l=1

Netherlands[4]	16 years	12-15 years with own signature (consent) is required	Both parents	Dutch	Central Committee on Research Involving Human Subjects (CCMO) -> Human Subject -> Informed Consent – information available only in Dutch. http://www.ccmo.nl/en/ -> http://www.ccmo.nl/en/minors

Norway	18 years	12-17 years with own signature is required.	Main rule: both parents sign the consent form if they have parental responsibility for the child.	Norwegian	The Norwegian National Research Ethics Committees -> Clinical Trials -> Regulations https://www.etikkom.no/en/ethical-guidelines-for-research/ http://www.legemiddelverket.no/English/Clinical_trials/Regulations/Documents/Norwegian%20regualtion%20for%20Clinical%20Trials .pdf National database for Laws and Acts -> Lov om medisinsk og helsefaglig forskning (helseforskningsloven) – information available only in Norwegian. https://lovdata.no/dokument/NL/lov/2008-06-20-44?q=helseforskning Act on medical and health research (Helseforsknings-loven) Guidance to Helseforsknings-loven (in Norwegian only) Additional info: Norwegian Medicines Agency: Website on clinical trials.
Poland	18 years	6-11 years 12-15 years 16-17 years	One parent Practice – both parents	Polish	http://www.eurecnet.org/information/poland.html No national EC websites available in English

[4] Data for the Netherlands were updated in June 2017

Portugal[5]	18 years	0-8 years 8-12 years 12-15 years 16-17 years use adult consent and LAR	Both Parents	Portuguese	http://www.eurecnet.org/information/portugal.html CEIC – National Ethics Committee for Clinical Research http://www.infarmed.pt/portal/page/portal/CEIC/English No national regulations/acts available in English Legislation relating to consenting in Portugal (in Portuguese) http://www.ceic.pt/documents/20727/57550/Documento+Orientador+CEIC+sobre+Consentimento+Informado+%28CI%29+para+participa%C3%A7%C3%A3o+em+ensaios+cl%C3%ADnicos+em+pe diatria/15385b28-a792-4f2b-9a57-efc184f7951c
Romania	18 years	Under 6 years 6-10 years 11-14 years 15-18 years	Both Parents	Romanian	National Ethics Committee of Romania http://www.adsm.ro/ro/comisia+nationala+de+bioetica+a+medicamentului+si+a+dispozitivelor+medicale# No information available in English
Scotland	16 years	0-5 years 6-10 years 11- 15 years IC with own signature under 16 years, if they have capacity. Otherwise assent is taken	One parent	English	NRES Guidance http://www.hra-decisiontools.org.uk/consent/principles children.html and http://www.ukctg.nihr.ac.uk/default.aspx

[5] Data for Portugal were updated in June 2018

Slovakia	n.a.	n.a.	n.a.	Slovakian	The State Institute for Drug Control (SIDC) -> Clinical Trials -> Instructions http://www.sukl.sk/en?page_id=256 -> http://www.sukl.sk/en/clinical-trials/instructions?page_id=2821 No national regulations/acts available in English
Slovenia	18 years	9 years - assent 15 years - with own signature	One parent	Slovenian	Republic of Slovenia National Medical Ethics Committee -> http://kme-nmec.si/ - only front page No additional information available.
Spain[6]	18 years	0-11 years 12-17 years with own signature	One Parent	Spanish	The Agencia Española de Medicamentos y Productos Sanitarios (AEMPS); A state agency within the Spanish Ministry of Health, Social Services and Equality -> Medicines for Human use -> Clinical Research with Medicines http://www.aemps.gob.es/en/investigacionClinica/medicamentos/home.htm The Ministry of Health, section about regulation of clinical trials: http://www.aemps.gob.es/en/legislacion/espana/investigacionClinica/ensayos.htm Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry (English version)

[6] Data for Spain were updated in January 2018

Sweden	18 years	Written separate consent as soon as child is literate 6-10 years 11-14 years 15-17 years with own signature	Both parents and the child when literate, need to sign the consent	Swedish	The Central Ethical Review Board -> Documents -> Information for Research Participants http://www.epn.se/en/start/the-organisation/ -> http://www.epn.se/en/start/central-ethical-review-board documents/ -Etikprövningslagen 2008. Regulatory requiement for clinical trials LVFS 2011:19 Läkemedelslagen - 1992 Biobank law- 2002 Personal Data Act 1998 National Medicines Agency -> Legislation -> Codes of Statutes -> 1996:17 Clinical trials of medicinal products https://lakemedelsverket.se/english/ -> https://lakemedelsverket.se/english/overview/Legislation/Codes of-statutes/
UK	16 years	0-5 years 6-10 years 11- 15 years	One parent	English	NRES Guidance; http://www.hra-decisiontools.org.uk/consent/principles children.html and http://www.ukctg.nihr.ac.uk/default.aspx

[i] The accuracy of this data cannot be guaranteed but it will be updated regularly on the basis of systematic review of comments received from all stakeholders and the ToolKit users. The reason for this possible non-accuracy is the non-uniform system of the official sources for this data, including language barriers and insufficient public availability of the requirements on public websites of national ethic committees and/or authorities.

APPENDIX 2

Parent survey: Patient Engagement in Pediatric Clinical Trials (English Version) April 2023

Thank you for taking the time to participate in this survey about patient engagement in pediatric clinical trials. Your insights are valuable in understanding how parents perceive and engage with clinical trials for their children. Please answer the following questions to the best of your knowledge and experience.

Section 1: Demographic Information

1 Your age:
25-34 [ ]
35-44 [ ]
45-54 [ ]
55-64 [ ]

2 Gender:
Male [ ]
Female [ ]

3 Educational level:
High school or less [ ]
Bachelor's degree [ ]
Master's degree or higher [ ]

Section 2: Awareness and Attitudes

4. Have you heard about pediatric clinical trials before? [ ] Yes [ ] No

If yes, how would you describe your understanding of pediatric clinical trials?

Minimal [ ]
Moderate [ ]
Advanced [ ]

5. How comfortable are you with the idea of enrolling your child in a clinical trial if their medical condition required it?

Very Comfortable [ ]
Neutral [ ]
Very Uncomfortable [ ]

6. What are some of your main concerns or reservations, if any, about enrolling your child in a clinical trial?
(Choose as many as you like)

Safety concerns [ ]

Potential side effects [ ]
Long-term impacts on the child's health [ ]
Ethical considerations [ ]
Lack of information about the trial [ ]
Fear of the unknown [ ]
Financial costs [ ]
Other [ ]

Section 3: Factors Influencing Decision-making

7. Please indicate how much each of the following factors would influence your decision to enroll your child in a clinical trial. (Scale: Ranking)

Potential benefits to your child's health
Clear and understandable information about the trial
Potential risks to your child's health
Trust in the healthcare provider/research team
Involvement in the decision-making process
Compensation for particiation

Section 4: Improving Engagement

8. In your opinion, what steps could be taken to improve the engagement and communication between parents and healthcare providers when considering a clinical trial for a child? (Choose as many as you like)

Offer informational sessions for parents [ ]
Create a user-friendly online platform for communication [ ]
Provide clear and concise information about the trial [ ]
Offer translation services for non-English speaking parents [ ]
Create a parent advisory board to provide feedback and suggestions [ ]
Offer reimbursement for travel and accommodation expenses related to the trial [ ]
Provide a comprehensive consent form explaining the trial in simple terms [ ]
Offer regular updates and progress reports on the trial [ ]
Provide a dedicated helpline for parents to ask questions and seek support [ ]

9. Are there any specific resources or tools that you think would help parents better understand and engage with pediatric clinical trials? (Choose as many as you like)

Parent support groups [ ]
Pediatric clinical trial brochures [ ]
Mobile apps for tracking trial progress [ ]
Social media groups for parents of children in trials [ ]
Online forums for sharing experiences [ ]
Pediatric trial glossaries and definitions [ ]
Pediatric trial consent form templates [ ]

Thank you for participating in this survey! Your input is invaluable in enhancing our understanding of parent perspectives on patient engagement in pediatric clinical trials.

Questionario genitori: Coinvolgimento dei pazienti negli studi clinici pediatrici (Versione italiana) Aprile 2023

Grazie per dedicare del tempo a partecipare a questo questionario sul coinvolgimento dei pazienti negli studi clinici pediatrici. Le vostre opinioni sono preziose per comprendere come i genitori percepiscono e partecipano agli studi clinici per i loro bambini. Vi preghiamo di rispondere alle seguenti domande nel modo più accurato possibile, in base alla vostra conoscenza ed esperienza.

Sezione 1: Informazioni Demografiche

1 La vostra età:
25-34 [ ]
35-44 [ ]
45-54 [ ]
55-64 [ ]

2 Genere:
Maschio [ ]
Femmina [ ]

3 Livello di istruzione:
Scuola superiore, o inferiore [ ]
Laurea triennale [ ]
Laurea magistrale, o superiore [ ]

Sezione 2: Consapevolezza e Atteggiamenti

4. Avete mai sentito parlare degli studi clinici pediatrici in precedenza? [ ] Sì [ ] No
In caso affermativo, come descrivereste la vostra comprensione degli studi clinici pediatrici?

Minima [ ]
Moderata [ ]
Avanzata [ ]

5. Quanto vi sentite a vostro agio con l'idea di iscrivere vostro figlio in uno studio clinico se la sua condizione medica lo richiedesse?

Molto a mio agio [ ]
Neutrale [ ]
Molto a disagio [ ]

6. Quali sono le vostre principali preoccupazioni o riserve, se ce ne sono, riguardo all'iscrizione del vostro figlio in uno studio clinico? (Selezionare tutte quelle pertinenti)

Preoccupazioni sulla sicurezza [ ]
Potenziali effetti collaterali [ ]
Impatti a lungo termine sulla salute del bambino [ ]
Considerazioni etiche [ ]
Mancanza di informazioni sull'indagine [ ]
Paura dell'ignoto [ ]

Costi finanziari [ ]
Altro [ ]

Sezione 3: Fattori che Influenzano la Presa di Decisione

7. Vi preghiamo di indicare quanto ciascuno dei seguenti fattori influenzerebbe la vostra decisione di iscrivere il vostro figlio in uno studio clinico. (Scala: Ordinamento)

Benefici potenziali per la salute del vostro figlio
Informazioni chiare e comprensibili sull'indagine
Rischi potenziali per la salute del vostro figlio
Fiducia nel vostro medico/team di ricerca
Coinvolgimento nel processo decisionale
Compensazione per la partecipazione

Sezione 4: Migliorare il Coinvolgimento

8. Secondo la vostra opinione, quali misure potrebbero essere adottate per migliorare il coinvolgimento e la comunicazione tra i genitori e i fornitori di assistenza sanitaria quando si considera uno studio clinico per un bambino?
(Selezionare tutte quelle pertinenti)

Offrire sessioni informative per i genitori [ ]
Creare una piattaforma online user-friendly per la comunicazione [ ]
Fornire informazioni chiare e concise sull'indagine [ ]
Offrire servizi di traduzione per i genitori che non parlano inglese [ ]
Creare un consiglio consultivo genitori per fornire feedback e suggerimenti [ ]
Offrire rimborso per spese di viaggio e alloggio legate all'indagine [ ]
Fornire un modulo di consenso completo che spiega l'indagine in termini semplici [ ]
Offrire aggiornamenti regolari e rapporti di progresso sull'indagine [ ]
Fornire una linea diretta dedicata ai genitori per porre domande e chiedere supporto[ ]

9. Ci sono risorse o strumenti specifici che pensate potrebbero aiutare i genitori a comprendere meglio e a coinvolgersi negli studi clinici pediatrici?
(Selezionare tutte quelle pertinenti)

Gruppi di supporto per genitori [ ]
Brochure sugli studi clinici pediatrici [ ]
App mobili per monitorare il progresso dell'indagine [ ]
Gruppi sui social media per genitori di bambini coinvolti negli studi [ ]
Forum online per condividere esperienze [ ]
Glossari e definizioni degli studi pediatrici [ ]
Modelli di moduli di consenso per studi pediatrici [ ]

Grazie per aver partecipato a questo questionario! Il vostro contributo è prezioso per migliorare la comprensione delle prospettive dei genitori sul coinvolgimento dei pazienti negli studi clinici pediatrici.