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Challenges in Paediatric Clinical Trials: How to Make It Feasible

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Abstract

The number of paediatric clinical trials in EU has remarkably increased in the last decade in response to the implementation of the new Paediatric Regulation and incentives aiming to define the need of child-specific drug development. Nevertheless, the gap between the number of paediatric and adult-randomised controlled trials is still substantial in almost every major clinical specialty. Economic, ethical, technological, geographical and cultural factors can influence the paediatric drug development and can represent the challenges to be faced for a smooth conduction of a paediatric clinical trial. The need for trials and paediatric patient's engagement to commensurate with the approved paediatric investigation plans is so high that it is crucial to correctly address key factors. Particular care should be taken to develop well-designed studies, with efficient management plans, experienced administrative and healthcare personnel, awareness of socio-cultural features of the geographic areas involved and good communication with patients and their families in order to ensure 'trial preparedness'. A case study on a multinational paediatric clinical trial, presented within the recently ended research project 'DEferiprone Evaluation in Paediatrics (DEEP)', was reported to exemplify some of the challenges encountered by the authors and the actions taken to overcome them.

Keywords: paediatric clinical trial, children medicines development, clinical trial management, ethics, patient enrolment, trial preparedness, drug formulation, regulatory, patient engagement

1. Introduction

Paediatric clinical research was introduced in response to the increasing gaining of awareness that paediatric subjects cannot simplistically be defined as 'small-scale' adults but that possess

a unique and constantly evolving set of physiological, mental and metabolic characteristics that require a dedicated exploration to identify their appropriate needs.

Before the introduction of international regulations and incentives aiming to define the need of child-specific drug development, paediatric subjects were systematically given off-label treatments, which did not possess any efficacy or safety data for their specific population but that were only tested in adults. The reason for this lack of interest lies on a lower market appeal, together with the fact that the design and execution of clinical trials in children have always been on one hand a controversial matter, with very delicate ethical implications to be considered and consequently regulated, and on the other hand a difficult process, with low number of patients, intrinsically fragmented in further subgroups and with a need of tailored formulations.

2. Historical perspectives

The milestone that signed the beginning of the modern paediatric clinical research, with care in defining the proper requirements and ethical issues related to this vulnerable population, was represented by the introduction of the first international regulations on paediatric subjects.

These regulations have been defined independently in the most developed countries, but in accordance to unified guidelines suggested by the ICH, an organization working on the harmonization of pharmaceutical regulatory requirements within the EU, Japan and the USA.

2.1. Definition of paediatric population

Defining the paediatric population is a very complex task, as it encloses a very broad and multifaced spectrum of subjects. The international regulation on paediatric clinical trials [1] has subdivided it in further four subsets: pre-term and term neonates (0–27 days), infants (1–23 months), children (2–11 years) and adolescents (12–18 years). According to the recently revised EMA guideline ‘Ethical considerations for clinical trials on medicinal products conducted with minors’ issued on September 2017, the age groups of children and adolescents have been further redefined into pre-schoolers (2–5 years), schoolers (6–9 years) and adolescents (10–18 years) [2]. The latter age group is based on the WHO definition of adolescence starting at the age of 10 years but maybe it has to be further subdivided into two subgroups because it seems to the authors to be too wide. Age groups can be differently subdivided, and often these categories are only used to provide guidance for regulatory and clinical reasons but do not reflect the maturity of the individuals, which is something that is generally recognized as crucial aspect to be taken into account during the conduct of paediatric clinical trials. Given these uniqueness, nonetheless, international paediatric regulations try to create a unified system of rules and laws, aiming to define the needs and protect the entire paediatric population.

2.2. European Paediatric Regulation

The European Paediatric Regulation was adopted in 2006 and entered into force in 2007. It ‘lays down rules concerning the development of medicinal products for human use in order

to meet the specific therapeutic need of the paediatric population, without subjecting the paediatric population to unnecessary clinical or other trials and in compliance with Directive 2001/20/EC' ([3], Article 1).

Since its implementation, the Paediatric Regulation has a very positive impact on paediatric drug development. The 10-year report of the EMA has shown that it has led to more medicines for children, better and more information for prescribers and patients, better paediatric research and development, more regulatory support for paediatric matters and paediatrics now being an integral part of medicine development [4].

Main sections ruled by the Regulation are:

- the institution of the PDCO;
- the definition of the regulatory requirement for a marketing authorization, among which the PIP;
- the introduction of rewards and incentives for the development of paediatric drugs, i.e., the PUMA.

2.2.1. PDCO

The Paediatric Committee is composed of independent and impartial members appointed from Member States, health professionals, and patients' associations. In its whole, the PDCO provides scientific competences on the main areas of the paediatric medicines, such as drug development, paediatric medicine, physics, paediatric pharmacology, pharmacovigilance, ethics and public health. Its main roles are:

- to assess and give a final opinion on the content and compliance of PIPs, waivers and deferrals;
- to give advice on issues related to surveys on the use of medicinal products in paediatric patients, to the establishment of a European network for paediatric research (EnprEMA) and to the elaboration of documents related to the Regulation;
- to establish a specific and updated inventory of paediatric medicinal product needs.

2.2.2. PIP

The Paediatric Investigation Plan is a document that describes timing and measures by which the developer of an IMP proposes the assessment of quality, safety and efficacy of that IMP in all the concerned subsets of paediatric population, giving also indications of the measures to be taken to adapt the formulation of the product to the needs of each paediatric population. It must be drawn up and submitted to the PDCO at the EMA with a request of agreement before any application for marketing authorisation and possibly not later than upon completion of the human pharmacokinetic studies in adults. The PDCO is in charge

of the assessment of the PIP and may request further clarifications and modifications to the applicant. The final opinion can be either positive or negative.

The developer will be granted a *waiver*, if:

- the IMP and the proposed plan are judged unsafe or ineffective in some subset or in the whole paediatric population;
- the IMP does not represent a significant therapeutic benefit over other existing treatments for paediatric patients.

2.2.3. PUMA

The Paediatric Use Marketing Authorisation is a marketing authorisation that gives supplementary protection to a medicinal product for human use exclusively developed for its indication/formulation for paediatric use, where this same medicinal product was already authorized and is not covered anymore by a patent. It is granted to IMPs that have successfully completed an agreed PIP and have set a risk management plan for the follow-up of efficacy and safety of the product. It warrants data and market protection for 10 years.

2.3. American Paediatric Regulations

Paediatric clinical research started in the US few years in advance compared to Europe. The most recent legislation ruling this subject is essentially enclosed in two main acts, i.e., the PREA, also known as ‘the paediatric rule’ of 2003 [5] and the BPCA, ‘paediatric exclusivity’ of 2002 [6], both amended in the FDAAA of 2007 [7].

2.3.1. PREA

The Paediatric Research Equity Act defines the regulations on the subject of research into paediatric uses for drugs and biological products. The organ assigned to the assessment and supervision of the paediatric drug development is the Secretary of Health and Human Services, which acts in collaboration with a designated internal committee within the FDA with expertise in paediatrics, biopharmacology, statistics, chemistry, legal issues, paediatric ethics, and appropriate expertise on the products under assessment.

They assess and review application on drugs for paediatric use and are entitled to grant approvals or, in well justified cases, deferrals for the performance of the study in paediatric patients, or even waivers for products not suitable for children or in which the performance of the study is proven highly impracticable. The cases in which the disease and the effects of the drug are similar enough in adults and paediatric patients, an opinion can be issued in which paediatric effectiveness will be extrapolated from well-designed studies in adult patients, maybe with the addition of supplementary data obtained in paediatric subjects such as pharmacokinetics studies.

In addition, the PREA highlights the necessity of a transparent public dissemination of paediatric data obtained either from new products or from marketed drugs for use in adults. It

is also duty of the secretary to perform periodic surveys and reviews, analyse data and create statistics on paediatric studies in terms of number of assessments, authorizations, waivers and deferrals, paediatric plans and timelines, formulations, labelling changes and recommendations and report them to the Congress. The suggested channel for the public dissemination of data is the FDA website ([7], title IV).

2.3.2. *BPCA*

The Best Pharmaceutical for Children Act establishes an incentive system for the performance of paediatric studies with the aim of expanding the number of labels, indications and safety and efficacy information in the different paediatric subgroups. In this case, when the secretary judges that information related to the use of a new drug or an already-marketed drug in the paediatric population would be beneficial on public health, it issues a written request to the sponsor, that for completing such study in a defined timeframe and providing the information requested will be granted an extension of 6 months on market exclusivity ([7], title VI). The BPCA can be considered one of the most successful legislative initiatives, which brought a huge increase in the paediatric studies and the subsequent assignment of paediatric labelling.

3. Challenges in paediatric drug development

Paediatric drug development is hampered by many factors that historically have made it a neglected subject in the pharmaceutical industry's scenario. These factors are of different nature and altogether contribute to the challenge that a sponsor has to face in order to perform and complete a PCT. This section describes these main challenging factors, as a practical overview of the crucial aspects to be considered before the initiation of a PCT, in a perspective of "trial preparedness" (also categorized in **Figure 1**).

3.1. Economic burdens

Drug development is a long, extremely expensive process, with low percentages of success, i.e., final market authorization. The last decades have seen an intensification of the economic challenges, with R&D costs constantly increasing and successfully commercialized products regularly decreasing. In the paediatric research, the economic factor represents a big barrier, as the returns promised by the paediatric market are even more disadvantageous compared to the burden that has to be undertaken. Crucial factors that make paediatric investigation economically more challenging and therefore less profitable are as follows:

- small patient population, which is further fractioned in several subgroups and strongly reduces market's size;
- under-developed infrastructures, which undermine a timely and cost-effective performance of PCTs, i.e., properly GCP-trained paediatric investigators, investigation sites, centralized laboratories and contract research organizations with specific expertise in paediatric trials;

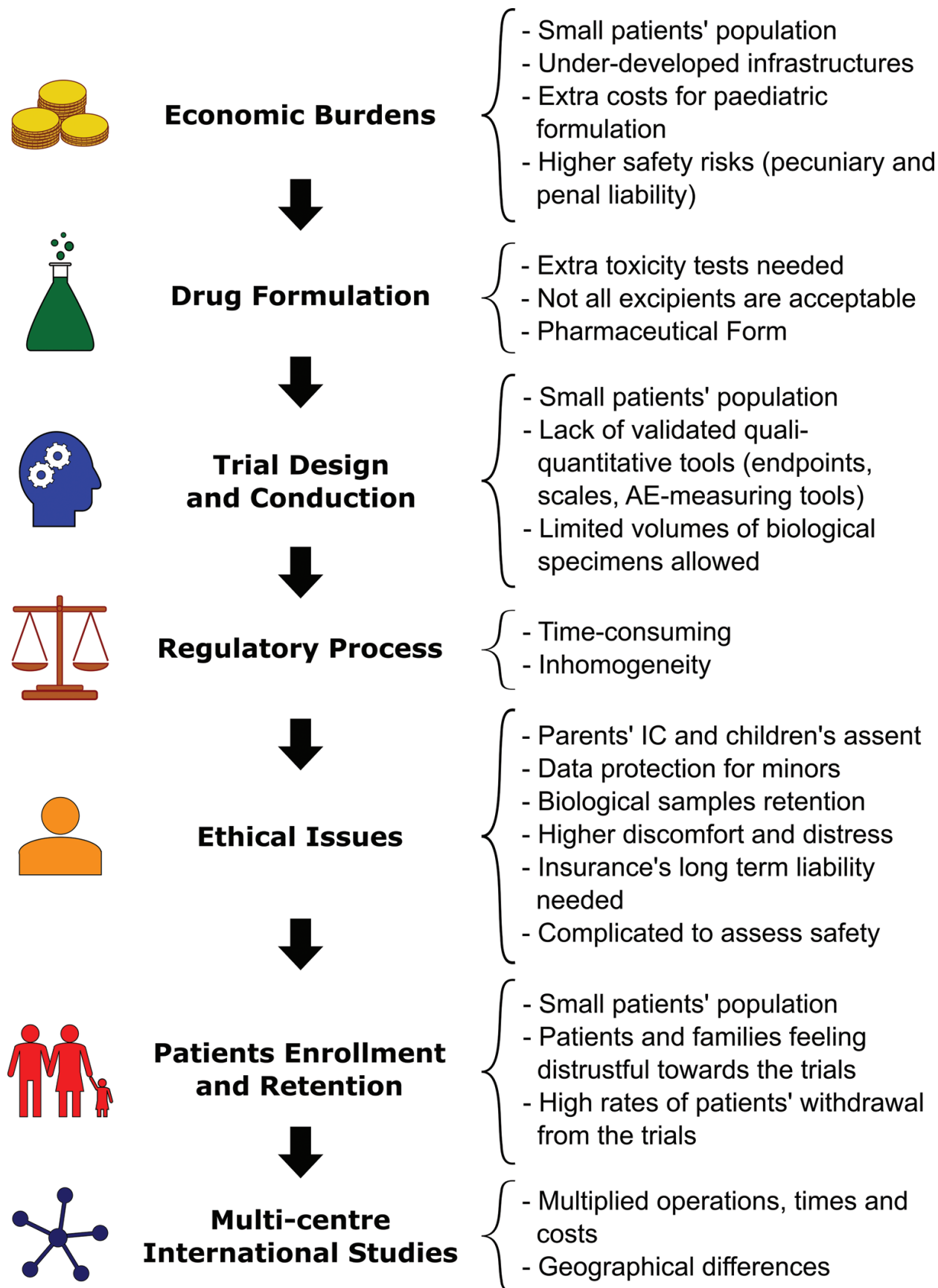


Figure 1. Aspects to consider for trial design. The flowchart summarises the most common drawbacks that can be encountered during the conduct of a paediatric clinical trial.

- need of age-appropriate formulations, that are often very difficult to develop because of the chemical-physical characteristics of the active moieties, the possible adverse reactions of the excipients, the taste, total volume etc. This process is therefore very challenging on a technical point of view, taking long time to complete and making the cost/profit ratio of the drug disadvantageous;
- risks in children can be higher than in adults, with unpredictable serious adverse reactions and long-term effects. These risks may result in pecuniary liability, which represents a strong deterrent for all the parties involved, i.e. sponsors, producers, all levels of healthcare as well as liability insurers.

3.2. Drug formulation

The technological development of a drug for paediatric use is very demanding, and it has to take into consideration many aspects that could be of potential harm for minors or act as a deterrent for a correct and continued administration of the treatment. Therefore, many guidelines have been disseminated by EMA and WHO [8–11] that identify acceptable paediatric drugs' features in terms of quality and formulation.

3.2.1. Drug quality

This aspect is of high importance if we consider the fact that children can be more susceptible to chemicals and bioactive substances, hence it is crucial that the composition of the drug is well known and characterized. ICH provides several guidelines regarding the limits for potentially harmful chemicals to be found in API in the form of impurities, degradation products and solvent residuals [12–15]. These limits apply for both adults and children, with the idea that less quantity will be administered to children. Most of the times, drugs to be used in the younger children's subgroups, i.e., neonates, toddlers, infant and young kids, need further attention, as they require preclinical studies to be performed first on juvenile animals in order to assess possible short- and long-term toxicities, thus increasing the time spent on the final formulation of the drug.

3.2.2. Excipients

According to the working document on paediatric medicines development of the WHO, for the choice of excipients to be used for a paediatric formulation, there should be a consideration on different aspects, e.g., the safety in the target age group, based on the route of administration and the frequency, duration and dosage of treatment [10]. The risks are higher for liquid formulations, but in general, the number of excipients used for a paediatric formulation should be kept to a minimum, as safety data in younger children are mostly limited if not totally missing. Colouring agents and antimicrobial preservatives have quite often toxic and allergenic potential and should be avoided as far as possible, e.g., favouring solid formulations to the liquid ones. This last solution has however negative consequences on the appropriateness of intake by younger children, as they could badly accept them due to the inability to swallow tablets. Sweetening agents are another delicate aspect. On one hand, they are often required in liquid formulations to mask an otherwise unpleasant taste of the drug that could compromise the adequate administration and intake of the treatment. On the other

hand, sweeteners' possible side effects should be kept in consideration, i.e., cariogenicity, laxative effects, glycaemic spikes in patients with diabetes, inflammatory reactions in patients with fructose intolerance, etc.

3.2.3. *Dosage forms*

Strength and dosage forms of paediatric drugs are important aspects to ensure a precise and manageable administration of treatment. Ideal formulation should warrant a ready-to-use shape, ideally adjusted on an age-specific need base, meaning more than one dosage form or more than one strength of a dosage form of the API. A minimal dosing frequency should be attempted, therefore favouring prolonged-release to immediate release formulations.

3.3. Trial design

The phase of planning is the most crucial for the smooth and prompt conduct of a clinical trial. Therefore, it requires a consistent amount of groundwork, logical thinking and awareness of the possible risks and complications. This can be even more true in the case of PCT, where the sensible factors to be considered are usually many more and more difficult to solve than for the clinical trials to be performed in adults.

3.3.1. *Innovative trial design*

Notwithstanding their little spread in the common use, innovative trial design methods are particularly suitable and powerful for facing issues related to low patients' number and control groups of PCTs. Bayesian design allows the extrapolation of results out of fewer children than in the conventional, fixed-number design, also considering evidences on adults [16]. The randomised withdrawal approach is mostly appropriate for long-term illnesses. More innovative trial design methods are being developed, thanks to the use of simulation studies. These methods, thanks to their features, represent a reliable way of ultimately improving paediatric care, by sensibly limiting the number of children required for achieving good-quality and ethical research [17].

3.3.2. *The patient's perspective*

It is crucial for clinical trial success to design a study with deep consideration of the patients' needs and perspective, such the possible pain or discomfort caused by certain invasive procedures or by interventions during a particularly difficult status of the patient, the length of assessments and interviews, the number of visits, the duration of the study and the frequency of drug intake. Not least, consideration should be given to the delicate aspect of data protection within the category of vulnerable subjects, which minors belong to.

3.3.3. *Quali-quantitative assessments*

Another obstacle that requires lots of problem-solving capacity in the design of a PCT is the lack of tools and/or methods for quantitative and qualitative assessment tailored for the

paediatric population and its subgroups. Examples in which these deficiencies can be found are as follows:

- study endpoints;
- questionnaires and scales for the measurement of psychophysical parameters;
- tools for the assessment of adverse reactions.

The use of scales and tools validated for the analysed patients' age is crucial to guarantee the proper collection and value of data for a trial. Lack of these means can imply the impossibility to proceed with a certain endpoint, thus invalidating the study.

3.3.4. Biological specimens

Many trials require the collection of patient's biological samples for the acquisition of crucial data. The aspect of the blood withdrawal in particular has to be carefully evaluated. On an ethical point of view, there is the need of avoiding as much as possible any kind of discomfort or pain to the child. On a clinical point of view, there is a very limited volume of blood (and other biological samples) that can be drawn from a child [18]. A document of recommendations, produced in 2008 and recently revised by the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC, states that trial-related blood loss should exceed neither 3% total blood volume during a period of 4 weeks nor 1% at any single time [2]. These considerations have to be carefully implemented during trial design, as it can be a reason for rejection by the ethics committee evaluating study regulatory submission.

3.4. Regulatory process

The procedures and times for regulatory approvals in different countries and investigation sites can be very inhomogeneous and time-consuming. Each regulatory body requires a separate process of revision, with comments to be addressed separately. This process is a big drawback in the case of multi-centre international studies, because it could generate different versions of the study protocol that will have to go through a further step of amendment in order to be harmonized among the investigation sites. In the European context, the new Regulation on Clinical Trials foresees the implementation of a centralized system of submissions to speed up and harmonize the process of regulatory approval of clinical studies within EU [19]. When active, this system will allow a single, fully electronic submission through the EU portal for all the Member States concerned. Technical and scientific aspects of the trial application will be discussed jointly, whereas ethical aspects will be appraised separately by the concerned Member States. They will give back opinions and requests of clarification following unified deadlines. Each Member State will then give an individual response to the sponsor through the EMA portal. In conclusion, the centralized submission will be followed by separate authorizations. Studies' information will be then accessible through a unified European database. In preparation to the implementation of this new system, a sort of test version has been introduced in the last few years by the EMA with the VHP, which

already allows a much smoother process for study approval in European investigation sites. Nonetheless, the system still needs to be followed by submissions in single countries, and country-specific requirements are still present.

3.5. Ethical issues

Paediatric clinical research has multiple ethical implications that represent a big component in the difficult process of performing paediatric clinical trials.

These implications are the centre of all the regulations that have been implemented on this matter, and still some grey areas persist and are under constant improvement and implementation. Nevertheless, ethical principles have been expressed in lots of documents produced by the most influential organizations worldwide, such as WHO, ICH and EMA [2, 20–23]. Major points are that children should not be subjects of clinical trials when the research can be performed in less vulnerable populations, and if the research is necessary, care should be taken to include first the least vulnerable subgroups. Unnecessary replication of trials in children is considered unethical too.

More generally, PCTs should be conducted following the so-called ‘Belmont principles’, which are *beneficence* (do good and avoid harm), *justice* (fair distribution of burden and benefits of research) and *respect to persons* [24], and the four healthcare ethics’ principles of *autonomy* (rights of patients to take decisions about their medical treatment), *beneficence and non-maleficence* (called just beneficence in the Belmont principle) and *justice* [25].

3.5.1. Informed consent and assent for paediatric groups

The issue of the informed consent in PCTs is very delicate because, on a legal perspective, children cannot provide a consent for themselves. For patients under legal age, informed consent has to be given by the parent(s) or a legal representative. According to the several common guidelines valid within the EU [2, 26], informed consent must be given before patient’s enrolment in the trial, and after receiving an adequate information on the purpose of the research, potential risks and benefits related to the involvement of children in the clinical trial, randomization, volunteering nature of the enrolment and absolute freedom to withdraw anytime with no consequences. This information must be provided by experienced investigators, putting no pressure whatsoever and allowing enough time for the parents/legal representative to reflect on it and ask for further information if needed. Communication must be very clear, and the comprehension of the information must be ensured even with the assistance of a mediator if necessary. Informative material must be therefore very clear, complete and easy to read, which is very much valued by ethics committees appraising PCT applications. Children able to a certain degree of understanding of the research should be, as an important principle of ethical research, involved in the process of making decisions about the enrolment in a trial. This involvement must take into consideration the maturity level of the child, so the communication and the informative material prepared must be age appropriate (this aspect is another very important step in the ethics committee evaluation process). The information can be followed by the obtainment of an assent from the child. In general, both consent and assent must be checked by the investigator as part of the normal communication with parents

and children for the entire period of the trial. Informed consent must be sought again as soon as possible where a paediatric patient is no longer a minor.

However, despite internationally accepted ethical principles and the EU guidelines, special provisions for children vary between and, in some cases, within countries due to differences in national laws and practices. A unique definition of legal age of consent is lacking, and the validity of assent and age-grouping is therefore not harmonized across Europe. As the EnprEMA marked in the paper 'Informed consent for paediatric clinical trials in Europe', usually the legal age for the informed consent is 18 years, but it differs in some countries: in Austria, it is 14; in Finland and Denmark, it is 15; and in the UK, it is 16 [27]. Specific characteristics in terms of informative material to be provided as well as requirements on the matter of rights of the patient to sign informed consent or assent, whether in addition or not to the parent's consent are detected [27, 28]. Solving this issue is of primary importance in the perspective of implementing the new European Regulation, since the lack of EC practice harmonization will impede the achievement of a unified evaluation of PCT applications at central level.

3.5.2. Data protection and biological samples retention

The major concern about data protection in children regards their possible uses in the future, after the termination of a trial. In this matter personal information are included, in particular regarding sexuality or illicit substance abuse, but also biological samples collected and stored long-term. There is the need of a careful protection of these data. Retention of any material must be consented (and reconsented once the child comes of age) and confidentiality guaranteed.

3.5.3. Discomfort and distress in trial procedures

Given the vulnerable nature of paediatric patients, extra attention must be paid to the discomfort or pain caused to children by trial-related procedures. This is a very important ethical issue that has to be widely considered when designing a PCT, to take all the measures to avoid unnecessary distress in every feasible way. In any case, signs of discomfort, pain and distress must be always measured through the use of validated age-appropriate scales. Appropriate analgesia should be provided where a certain degree of pain is caused by strictly necessary procedures.

3.5.4. Insurance

Insurance is compulsory in order to safeguard patients. In the case of PCTs, it is important to make sure that insurance includes long-term liability. Since this risk is much higher in children than in clinical trials performed in adults, insurance companies are reluctant to provide this protection. Finding the right company can be therefore quite a challenging process in the start-up of a PCT.

3.5.5. Safety

As in every clinical trial, safety must be constantly evaluated and monitored, and adverse events should be always timely reported. Safety in paediatric subjects, given their vulnerability, is very important, but detecting these events can be particularly complicated. First,

because children could show effects never seen before in adults, with the consequence of unpredictable manifestations. Second, because especially in neonates and toddlers, the reaction could not be easily detectable, and they do not have the possibility to communicate their symptoms. Third, because some methods for detection of adverse reactions are not validated in children, making this assessment hard and imprecise. Consequence of this issue can be on one hand the missed detection of an adverse reaction or on the other hand (more common) the over-interpretation of symptoms as adverse events and the subsequent withdrawal of patients from studies, contributing to issue of patients' retention.

3.6. Patients enrolment and retention

The problem of low percentages in patients' enrolment and retention in PCTs is an issue that contributes to the failure in reaching the numbers for proper study's completion [29] and therefore has probably the biggest impact on the way a PCT is designed. There is a paucity of eligible paediatric subjects for the majority of studies that is dependent on epidemiologic reasons but also on a high degree of patients withdrawing from the studies as well as patients' families being wary about clinical trial's possible risks. This shortage of patients has to be compensated in most of the cases with the involvement of multiple investigation sites. This choice though is often a double-edged weapon, because on one hand, it improves the chances to reach the minimum number of patients necessary to successfully complete a study, and on the other hand, it substantially extends the time, work and costs required for the obtainment of regulatory approvals to conduct the studies in different sites and/or countries and for the study conduct.

3.6.1. Communication with patients and families

Many reasons can be identified for the scarce rate of patient's recruitment and retention in PCTs, among which the wrong approach or miscommunication with patients and their families. The wrong communication between the clinical staff and patients can be tremendously detrimental, because it can lead to the participant (or potential participant) and his family not understanding correctly the conditions of the study, its aims, benefits and potential risks. They could feel distrustful if the entire process is not explained in a transparent way, or even threatened, if they don't understand correctly the important concept of voluntary participation.

In 2012, following a large consultation phase, the PDCO issued a Concept Paper on the involvement of children and young people in its activities, with the children's best interests as primary consideration [30]. The setup of a child-friendly approach implies a collaborative and continuous action involving paediatricians and healthcare professionals, psychologists, families, and patients. Children and parents should be involved not only in the daily clinical practice but also in the whole study development, revision of clinical study protocols and use of drugs. Healthcare professionals should consider children and families' active participation as a fundamental step to reach consensus and compliance to treatments and to increment patient's enrolment and retention. Furthermore, it is necessary to recognize that a standard model of information is not valid for all age groups; therefore, in addition to parents, children, adolescent and mature minors should receive information in a clear and understandable way for their level of comprehension and maturity. These concepts are clearly underlined also in

the consultation document 'Ethical considerations for clinical trials on medicinal products conducted with minors', recently updated to be in line with the new Clinical Trials Regulation 536/2014 [2].

3.6.2. Patients' withdrawal

Many factors that could cause discomfort or be uneasy to be pursued by patients or their families have been related to patient's withdrawal. Most common reasons for withdrawing a paediatric study are the wrong formulation of the drug, i.e., the taste (too bitter or with a taste that does not match the preferences of the population the drug is used on), the pharmaceutical form (tablets, capsules, difficult to swallow for some patient's subgroups or injectable solutions that require assistance and could preclude a normal life for the patient) and the strength (not easily scalable for smaller children). Too many doses of treatment per day can cause withdrawal as well or increase the risk of lack of adherence to the study protocol. Too many hospital visits plus the lack of any form of compensation for the expenses can represent a strong deterrent for parents that have to give up on work days. Distressful procedures such as frequent blood withdrawals should be avoided as well.

3.7. Multicentre international studies

As discussed in Section 2.6, the need to increase the number of paediatric patients enrolled in a study in order to reach an adequate statistical sample, is usually managed with the design of multi-centre studies, often performed in different countries as well. This type of trials has in its turn other problematic consequences.

3.7.1. Time and costs

Performing a trial in multiple locations means that the work will be multiplied. There is the need to localize and make agreements with many structures that comply with all the requirements of the study. The study must be approved by multiple competent authorities and ethics committees that can ask for different clarifications, and this can lead to different versions of the study protocol. Submission packages for these requests of authorization must be tailored from country to country, documents for patients such as informative documents, consent and assent forms, but also labels and protocol synopsis have to be translated in the local languages. Substantial differences in the version of study protocol and documents, consequence of the discussion with the different local CAs and ECs, will probably lead to the necessity of an amendment that implements in one version all the edits and makes a right compromise with all the requirements to be submitted again to all the regulatory bodies for approval. If in some cases, a compromise is not possible because of unconcealable ethical principles, different versions have to be handled provided that the aims and GCP compliance of the study are not affected.

3.7.2. Geographic differences

The conduct of the study could be also affected by geographic issues from country to country, especially in locations outside the EU.

Cultural and social differences will cause a very different process of review of the clinical trial application by the ECs that will point out different ethical aspects also depending on the common sense in their society, filtered by cultural, religious and/or political biases. IMP's formulations could be inappropriate for certain populations, as regards taste, pharmaceutical form and/or storing conditions. Border policies could hinder the proper exchange of biological material, IMP, as well as study-specific equipment. Finding the right compromise with all the different countries' requirements and needs in order to keep a well-coordinated study planning and conduct could be therefore very demanding.

4. Overcoming different issues: a case study on a multicentre multinational PCT

As discussed in the previous section, the performance of a PCT is fulfilled with many obstacles that can compromise its success and final outcome. Good strategy, problem solving and a wide preliminary research and awareness of the issues that could present can improve the chances to successfully complete the study. In this section, we propose some solutions for the issues described above, and we use as example the case study of a recently performed research project, the DEEP. DEEP is a 6-year European Project (FP7) coordinated by Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF), a non-profit research consortium based in Italy, comprising 23 recruiting centres in European and non-European countries, scientific partners from several European countries and a pharmaceutical group based in Canada. The DEEP Project has the specific aim to produce a new oral liquid formulation of deferiprone suitable for paediatric use and to integrate the existing information on deferiprone use in iron-overloaded paediatric patients. It consisted of three studies, DEEP-1, DEEP-2 and DEEP-3 in accordance with the PIP submitted to the EMA-PDCO in February 2011 and amended and finally approved in November 2011. It is to be mentioned that the PIP has undergone several modifications upon PDCO request: the age of patients to be recruited, which was extended including all the paediatric ages (from 1 month to 17 years instead of the previously proposed 2–10 years), the sample size (from 240 patients to 310) and also the comparator (from deferoxamine to the more expensive deferasirox), with a huge increase of time and cost.

The DEEP-1 was a multi-centre, oral single dose experimental and modelling study to evaluate the pharmacokinetics of deferiprone in patients under 6 years of age affected by transfusion-dependent haemoglobinopathies (NCT01740713, *clinicaltrials.gov*). It was concluded in 2014, providing scientific evidence that the dosage per kilogram of deferiprone used in adults and older children can provide sufficient exposure to ensure efficacy also in younger children. These results allowed children aged under 6 years to start to be recruited in DEEP-2 Safety/Efficacy Study.

The DEEP-2 was a phase III multicentre, randomised, open label, non-inferiority active-controlled trial aiming at comparing the efficacy, in terms of changes of serum ferritin levels and cardiac iron overload, of deferiprone versus deferasirox in paediatric patients affected by hereditary haemoglobinopathies, requiring chronic transfusions and chelation (NCT01825512, *clinicaltrials.gov*). It has involved 393 randomized patients with the FPFV in January 2015 and

LPLV in September 2017. The DEEP-3 was a long-term observational safety study which evaluated the nature and incidence of adverse effects of deferiprone in children and adolescents with beta-thalassaemia major. Started in 2013, and ended in October 2015, with 297 patients enrolled in the study, it confirmed that the safety profile of deferiprone in children and adolescents is in accordance with the available data in adults.

4.1. Regulatory

The process for granting regulatory authorization in a multicentre multinational PCT is a big time-consuming factor. Every step (submission of PIP, study approval from CAs of every country and from ECs that can be country-specific or even local for the single centres as it is in Italy) can require several months to be completed. In addition, the legal approach is different among countries: each of them has its own rules governing the submission of CTs. On average, a large part of the regulatory bodies involved in the approval process asks for clarifications and/or changes regarding the study protocol, informative material, etc. In the case of DEEP-2, several issues raised on this topic.

In Tunisia, where trials on non-marketed drugs were not allowed on minors, a special authorization from the Ministry of Health had to be granted before ECs could approve the study. In Albania, a national Law on clinical trials was absent until July 2014; therefore, it was much harder to obtain regulatory approval there. In Egypt, despite several requests, biological samples' exportation for the centralized analyses was never authorized. In Cyprus, the eligibility of patients under 2 years of age was denied, notwithstanding the European regulation, since the study had already been approved in other European countries. For all these obstacles, it was crucial to have a dedicated regulatory team and to have appointed an external expert Ethics Board that could rapidly deal with all the actions required and solve correlated issues.

4.1.1. Ethics and safety

Since ethical and safety issues are among the major concerns in PCTs, in order to ensure a good quality conduct of the study, with focus on the safety and wellbeing of the paediatric patients, a DSMC and an EB were established for DEEP-2 study. The DSMC's main responsibility was to ensure safety monitoring of patients and quality of statistical methods, whereas EB revised the essential documents and procedures dealing with ethical aspects such as (but not limited to) documents for the ECs, Consent and Assent Forms, protocols, results and reports from the studies. In particular, it suggested interventions aimed to protect children's well-being both in the European and non-European Countries, and the use of studies results in favour of the affected populations. In addition, the EB worked in collaboration with the DSMC on all aspects of data protection and confidentiality.

4.1.2. Extra-European studies

For studies outside Europe, national legislations in matter of clinical trials are still very different, and cultural and social diversity affects a lot the common sense of ethics. This issue was faced in the DEEP-2 study. Actions taken to ease the management of the trial started from the

planning of the study. An initial survey was performed to define the legal framework regulating clinical trials in different countries. SOPs were setup and followed to implement a unique procedure and a unique CTA 'package of documents'. Local CROs were employed that had the proper expertise together with the right awareness of socio-cultural and regulatory peculiarities, as well as linguistic fluency. Majority of integrations were asked by the different ethics committees regarding the content of the informed consents and assents, and one of the most controversial and dependent on country-specific cultural influences was the topic of contraception and pregnancy (informative documents for Egyptian female adolescents could not include information regarding contraception, whereas for Greek patients, the insurance had to cover foetus damages even though contraceptive measures were explicitly mentioned in the informed consent form).

4.2. Patient-oriented perspective

On the base of the ethical principles concerning patient's proper information and engagement [2, 30], age-tailored (<6, 7–11, 12–17) information booklets explaining CTs' aims and procedures and what they are going to experience, and assent forms were prepared in the framework of the DEEP-2 study. They were the result of a collaborative effort between pharmacologists, paediatricians, child psychologists, communicators and illustrators. Their aim was to inform the participant child on the study's objectives and procedures and to obtain his/her assent to participate in the study. They were translated in all the six languages of the clinical sites included in the trial (Albanian, Arabic, English, French, Greek, Italian). Furthermore patients, parents and patients' organisations were involved in creating the protocol information package, actively participating in the revision of documents for the children and contributing in the design of the dissemination strategy.

The educational part of the study towards kids and families is very important for the participation and compliance; another aspect that would be beneficial, and thus it would be worthy to contemplate it in a study, is the communication to patients and families of the trial results. In this regard, in the context of the DEEP-2 study, strong importance will be given to the establishment of an adequate form of communication of the results specifically designed for laypersons, meaning that comprehension can be reached and further transmitted by involved subjects and their families. The main principles of the lay communication will be followed, with the design of a summary that can be understood by an audience from the age of 12 years upwards. A child-friendly version of the lay summary will also be prepared to help younger children in understanding trial results.

4.3. Selection of centres

As discussed above, the choice of investigation centres can have a huge impact on the outcome of a PCT. A careful selection of the centres involved in the DEEP-2 study was aimed to involve centres complying with as many of the following criteria as possible:

- being localized in a geographical area where epidemiology of the disease under study is high, and thus many patients can be approached;

- availability of a Principal Investigator that has a relevant experience in GCP and PCTs, and is willing to collaborate with a proactive attitude;
- facilities necessary to perform all the diagnostics and procedures required by the study protocol present within the hospital/clinic;
- social and cultural features of the area in which the centre is located likely to allow a good understanding and acceptance of the study and of its requirements and characteristics.

4.4. Quality assurance

As already extensively discussed, the number of patients in PCT is a very limiting factor. It is therefore very important that solid data are collected as far as possible from every single patient enrolled in a study. To this aim, the implementation of SOPs specifically designed for paediatric studies and compliance to GCP principles during the entire duration of the clinical trial must be ensured. Proper training must be organized for all the staff involved, and constant monitoring of the activities has to be performed. The quality of the data derives also from a harmonized method of analysis. This can be achieved for example by the organized collection and analysis of samples by a centralized laboratory to rule out instrument's deviations and ensure standardized results.

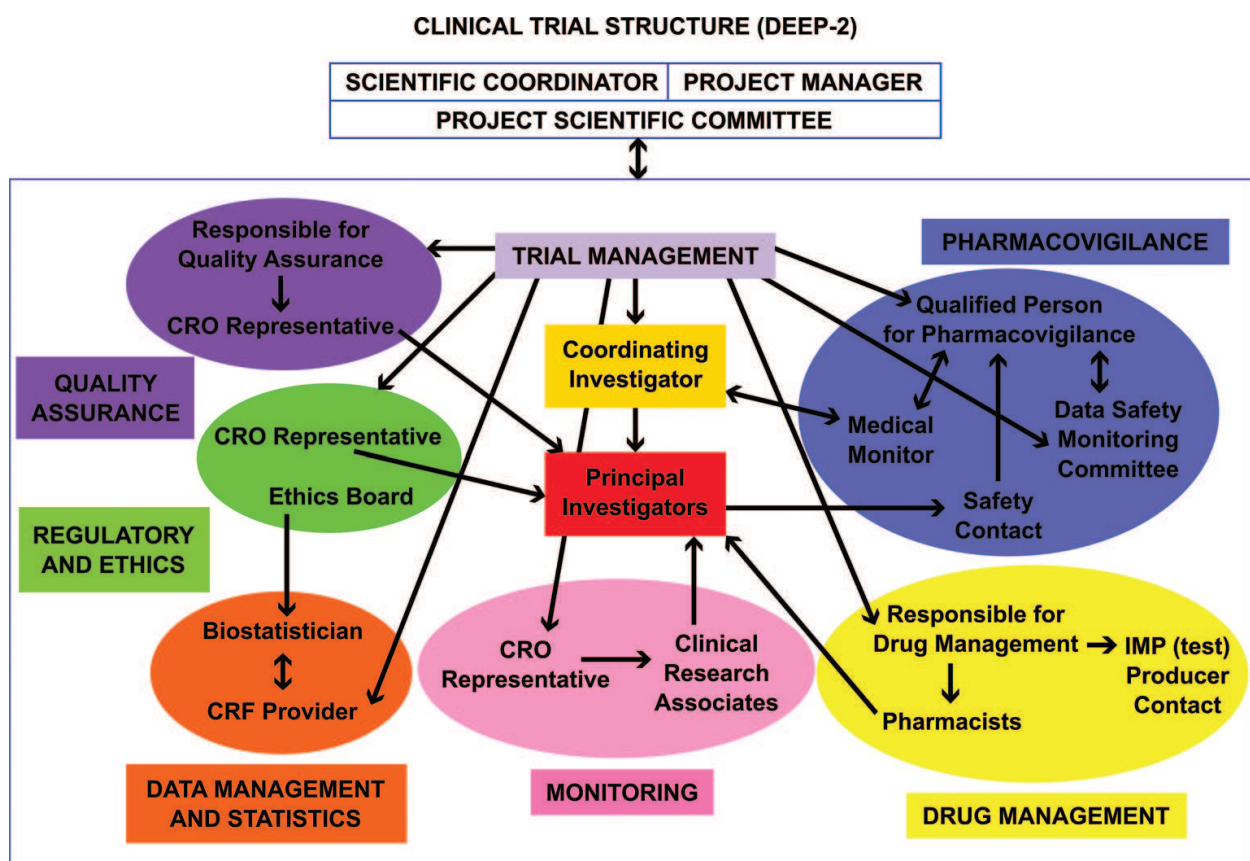


Figure 2. DEEP-2 infrastructure. This schematic depicts the set of organizations and human resources employed for the conduct of DEEP-2 clinical trial in every country it was performed.

This issue was properly addressed in the DEEP-2 study. SOPs were set-up and followed for all the aspects of the trial. A complex trial infrastructure was arranged in order to fulfil all the GCP requirements and promptly respond to all the possible issues and needs arising (**Figure 2**). This infrastructure was made through a well-defined structure of roles and responsibilities for each member of the staff.

Laboratories specialized in pharmacokinetics analysis and blood ferritin diagnostics, were employed for the centralized assessment of these parameters.

In reference to the centralized evaluation of ferritin analysis, a second laboratory was identified within Egypt area due to the impossibility to export biological samples from Egypt which, with its three investigation sites (Alexandria, Cairo and Zagazig), retained almost the 40% of the total samples collected from patients recruited in the entire study. Consistency of data obtained in the two laboratories was ensured using standard controls in both sites for all the analyses performed.

A central laboratory in Australia was assigned for the analysis of images of hepatic R2 and cardiac T2* MRIs acquired and transmitted by the investigation sites. The proper calibration of MRI machines in every centre was ensured with the use of phantoms delivered to the investigation sites.

5. Conclusions

Notwithstanding its important and noble meaning and the possible benefits deriving from its successful conclusion for either society and sponsors, the conduction of PCTs is a path undermined by obstacles and deterrents. We reported the example of DEEP, a European research Project (FP7) coordinated by CVBF and recently concluded. DEEP's final aim was to produce and get the authorization for a new oral liquid formulation of deferiprone with a paediatric indication and to extend the information available on deferiprone in iron-overloaded paediatric patients.

Although successfully completed, many issues had to be faced, and deviations from the initially planned study were the inevitable consequence of the strategies implemented to overcome them.

The first protocol's version reported a population's size of 310 evaluable patients needed for getting statistical significance of data. The estimated drop-out rate was 10%, so the calculated number of total patients to be recruited was 344. When the study started, it became clear that the actual percentage of drop-out was higher, so the protocol had to be amended, and the new number of patients to be recruited was increased to 388.

Because of the higher number of patients required, to the initial 15 centres selected for the conduct of the study, other 8 centres had to be added to allow the recruitment of the 388 patients needed. In actual facts, at the end of the study, 393 patients were randomized, of whom 316 completed the study.

The enrolment rate of patients at different sites was really heterogeneous. In particular, the involvement of two centres respectively in Cairo and Tunis allowed a tremendous number of

patients to be recruited because of the high epidemiology of haemoglobinopathies in those countries. On the other hand, in other countries like Greece and Italy, the same successful recruitment rate was not achieved in the same way; possible explanations are a superior diffusion of the prenatal prevention and the presence of more parallel paediatric studies, which have caused a further shrinking of the eligible population.

All the above-mentioned variation to the trial caused an increase in times and costs that were not easily accepted by the European Commission who was funding the initial study program: while a 20 months' project extension was agreed, no additional resources were granted. This caused a tremendous financial stress to all the 16 private and public partners involved in the project (most of them big public hospitals) and only thanks to the contribution from the same partners participating to the project, it was possible to efficaciously conclude it. The anticipated cost of the overall project increased from 7 to 10 million euros.

The study was supposed to be conducted in 3 years, but it took instead 4.5 years in total, plus preliminary activities from PIP submission to study protocol drafting: their duration was supposed to be 1 year long, but it took 3 years instead.

In this chapter, we tried to give the reader a more detailed overview of what obstacles can be encountered during the conduction of a paediatric clinical trial and suggested feasible ways to deal with them, hoping that this under-developed branch of the pharmaceutical research may grow further, providing challenges and opportunities for the next future, and may lead to the successful labelling of new treatments for the paediatric population.

List of abbreviations

API	active pharmaceutical ingredients
BPCA	Best Pharmaceutical for Children Act
CA	Competent authority
CRO	Contract Research Organization
CT	Clinical trial
DEEP	DEferiprone Evaluation in Paediatrics
DSMC	Data Safety Monitoring Committee
EB	Ethics Board
EC	Ethics Committee
EMA	European Medicines Agency
EnprEMA	European network for paediatric research at the European Medicines Agency
EU	European Union

FDAAA	Food and Drug Administration Amendments Act
FPFV	First patient first visit
GCP	Good clinical practice
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
LPLV	Last patient last visit
MRI	Magnetic resonance imaging
PCT	Paediatric Clinical Trial
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PREA	Paediatric Research Equity Act
PUMA	Paediatric Use Marketing Authorisation
SOP	Standard operating procedure
VHP	Voluntary harmonization procedure
WHO	World Health Organization

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