The Elements Requiring Particular Attention while Conducting Clinical Trials in a Paediatric Population

Introduction
Children account for 20-40 % of the global population depending on the region[1], but only a third of all medications are officially approved to treat children[2]. A significant amount of medications are used in children off-label, which leads to the development of adverse reactions[3, 4]. Only 7.4 % of clinical trials for medications are conducted in paediatric populations[5]. The development, research and approval of the use of new medications in children are significantly behind the current need.

Based on our experience, we would like to outline and review the elements to which particular attention should be paid when planning and conducting paediatric clinical trials.

When writing this article, we analysed the results of paediatric clinical studies involving over 1400 patients. The indications for these studies included complicated and non-complicated community-acquired pneumonia, preventing post-operative nausea and vomiting, preventing chemotherapy-induced nausea and vomiting, preventing neutropenia in patients with rabdomyosarcoma and solid tumours, etc. The age of patients, depending on the study, was between 1-18 years old.

We have identified several elements which require our special attention when planning and conducting these clinical trials:-

1. Obtaining approvals from regulatory and ethics bodies.

Clinical trials in a paediatric patient population are closely monitored by the ethics and regulatory bodies which justly apply strict requirements to clinical trial protocols. Obviously, it is most difficult to obtain the approval of a clinical trial using placebo as a comparator, or if the new medication is being studied in children and it is a first-in-human study and not enough data has been accumulated on its safety.

From an ethical point of view, placebo is justified in situations for particular indications with no proven effective treatment where an investigational drug may potentially have a significant therapeutic effect. If the drug is being researched first-in-human and there is not enough data on its safety, we recommend involving leading specialists in a particular therapeutic area to prepare independent expert opinions and append these opinions to the regulatory/ethics submission package. It is preferable to address the key opinion leaders in each particular country in which the study is planned to be conducted. At the same time, it should be taken into consideration that the expert providing an independent opinion must not participate in the study himself, and preferably, should not represent an institution expected to participate in the study. He/she must not be a consulting expert of the sponsoring company. It must be noted that the provision of a positive independent expert opinion does not guarantee the approval of the study, but may help the experts to get a more detailed concept on whether the study is feasible and appropriate in a particular country.

A regulatory submission in each particular country should be prepared separately and thoroughly. We would like to draw your attention to the fact that regulatory and ethics bodies in each particular country act independently of each other, and obtaining approvals in certain countries may not be a sufficient ground to obtain such approvals in other countries.

We have encountered a situation where a study approved in the USA and other countries of Western and Eastern Europe is not approved in Russia, Serbia, Bulgaria or France. At the same time, it is obvious that the opinion of a local key opinion leader, according to our experience, is always favourably taken into consideration.

2. Informed Consent Process.

Parent(s) must provide consent for their child to take part in a clinical study. At the same time, many countries require the consent of both parents - if they are married (Russia), or sometimes even if parents are divorced (Argentina). We do not doubt the legal status of these requirements, since both parents have equal rights in decisions related to their child. However, the necessity to obtain the informed consent of both parents may complicate the procedure of patient enrolment, and decrease the number of patients - especially in cases when a study takes place in an "acute clinical situation", and a decision on enrolment must be made immediately: within 24 hours or shorter time frames. It is obvious that in such cases, the number of signed informed consent forms is influenced not only by the non-willingness of one of the parents to sign the consent, but also by logistical reasons, i.e. the absence of one of the parents at the time of informed consent signing, and the impossibility to speedily get in touch with him/her.

For example, in a clinical trial of an antibiotic for the treatment of pneumonia in hospitalised patients, not more than four hours should have passed from the moment a patient was diagnosed with pneumonia until the beginning of antibacterial treatment, in accordance with the international treatment guidelines[6]. This period of time was often not sufficient to establish communication with the second parent of a child, if the child was admitted to hospital accompanied by only one of the parents.

On the other hand, when conducting a study of a medication for preventing chemotherapy-induced nausea and vomiting in children, investigators had sufficient time, because there is always a time slot of a few days between the diagnosis of cancer in a child and the start of treatment.

These few days are used for required diagnostic procedures and both parents have time to visit the clinic, discuss the study, and make a decision.

This is why, when selecting countries for clinical trials where screening procedures are allotted a short period of time, local legislation regulating the process of obtaining informed consent and possible complications should be taken into consideration.

3. Choice of comparator.

Standard therapy is most commonly used as a comparator in clinical trials. The likelihood of the comparator medication being administered in children "off-label" must be taken into account. This is the matter of how appropriate it is to compare the effectiveness of the study drug with a medication which is being used in children, but has no proven effectiveness in this particular indication in a paediatric population. In addition, every particular country may have approvals only for specific formulations and dosages of a certain comparator.

For example, in treating acute hematogenous osteomyelitis in children, depending on the epidemiological situation, it is recommended to use the following medications: nafcillin, first generation cephalosporins (cefalexin), vancomycin or clindamycin[7]. However, nafcillin is not approved in Europe; cefalexin is not approved in Austria, Latvia, Lithuania and Estonia. In Serbia it is approved for use only in children older than five years of age, and in Croatia in children older than seven years of age. Clindamycin is approved in Russia in children older than eight years of age, and in Serbia in children weighing more than 10 kg, i.e. older than one year of age. Linezolide is not approved to treat children in the countries of the European Union, while it is approved for use in children older than 12 years of age in Russia (but not in children with osteomyelitis).

This simple example shows the difficulties that may be encountered when planning a clinical trial in children with acute hematogenous osteomyelitis, which undoubtedly is a serious problem in paediatric practice. As a practical recommendation, it is possible to either choose countries where one and the same medication may be used as standard treatment, or allow to compare the study drug in each country vs. its local treatment standard, which will simplify patient enrolment but will subsequently complicate statistical management of the study results.

Using placebo as a comparator in children is significantly limited. There is no doubt that prescribing placebo is not equal to the absence of treatment, because as a rule, standard treatment is prescribed along with placebo. However, it is the very word "placebo" that produces a negative attitude in parents and doctors, being associated with the absence of treatment.

For example, in a planned clinical trial of an antiviral medication for the treatment of respiratory syncytial virus in children, placebo was to be used as a comparator due to the fact that there was and still is no commonly accepted standard effective treatment of this medical condition. However, it would be more reasonable to propose a study design where commonly accepted maintenance therapy was used vs. the study drug. Such a study design would simplify both receiving study approval by ethics and regulatory bodies and obtaining informed consent from parents, because even if their child would not receive the study drug, he/she would receive maintenance therapy, which in a parent's opinion is always better than placebo.

4. Study procedures and schedule of visits.

Study procedures should be most convenient and safe for a patient.

Main points to take into consideration:

a. Invasive procedures should be minimised, and if they are unavoidable, local anesthesia should be used (e.g. local anesthetic cream).
b. Number of blood draws and the volume of blood samples must be limited. If possible, protocol-specific tests must be combined with routine tests. According to the EMA guidelines, blood loss related to clinical trials must not exceed 3 % of the circulating blood volume in four weeks and/or 1 % of circulating blood volume at any given moment[8]. For example, circulating blood volume in children less than one year of age is 80 ml/kg, i.e. in a six-month-old child weighing 8.5 kg, it will be 680 ml, and 3 % of this volume is 20.4 ml. To minimise blood loss, the minimal blood volume required for a clinical study must be defined at the stage of planning a study, and blood tests for different parameters must be combined and dry blood spot samples must be used where possible.
c. In case of repeated blood draws from a vein, it is preferable to use a peripheral catheter instead of repeated venous puncture.
d. Schedule of visits and study procedures must be most convenient for the child and his family. For example, in small children, the time of an afternoon nap must be taken into consideration. Times in class must be taken into account for children attending school.
e. Every age group has its behavioural and social particularities, which should be considered when planning a study. For example, teenage girls may be psychologically non-accepting of a pregnancy test that is part of screening procedures.

The study protocol of a paediatric clinical trial must be written with the paediatric population specifics in mind, instead of taking an adult protocol and adapting it to a study in children[9].

5. Difficulties of diagnostics.

It is common knowledge that it is more difficult to diagnose many medical conditions in children than in adults. The difficulties of diagnostics are related firstly to the physiological specifics of being a child, i.e. immaturity of organs and systems, fast generalisation of a pathological process because of the immaturity of the immune system, and vagueness of symptoms and objective signs of disease. Secondly, to the psycho-emotional age characteristics of a

child which complicate a subjective assessment of a patient. It is often necessary to use additional methods of diagnostics and laboratory tests. Unfortunately, if the time of screening is limited, diagnostic errors may take place.

For example, in the aforementioned clinical trial of a new antimicrobial drug for the treatment of community-acquired pneumonia, the period of screening would inevitably amount to only three to four hours and after it elapsed, treatment had to be started. As a result, several patients after the start of study treatment were diagnosed with other diseases: Kawasaki disease, mycoplasma pneumonia, and/or legionella infection. The clinical picture of these diseases at earlier stages is almost the same as that of a typical bacterial pneumonia, and the short screening period did not allow for a fully-fledged differential diagnostics. Even though very undesirable, this is a normal clinical situation when empirical treatment was started based on a preliminary diagnosis and the final diagnosis was established after a period of time, based on, among other factors, the response to treatment. When changing a diagnosis, treatment would need to be corrected. In clinical trials, however, this situation was regarded under a special angle. When establishing a different diagnosis, such patients were withdrawn from a study and from per protocol analysis, since they did not appear to have the studied disease. Considering that the number of patients enrolled in a paediatric clinical study (sample size) was usually smaller than the sample size of adult studies, withdrawing two to three patients from the analysis could compromise the statistical power and consequently the credibility of the study results. To avoid such a situation in paediatric trials, we can recommend using the principle of patient "substitution" more frequently.

6. Serious adverse events.

According to our experience, the frequency of serious adverse events in children is higher than in adults. This is due to more frequent hospitalisation of children because of the necessity to perform in-depth diagnostics when a clinical picture is vague, due to the inclination to generalise the pathological process and more complicated clinical course of the disease, as well as due to social reasons, i.e. young age and impossibility to provide adequate medical monitoring at home or the complexity of performing medical procedures in an outpatient setting. These factors must be taken into account both by investigators and study sponsors when planning the workload of an investigational team.

Conclusion

In recent times, there has been a tendency to increase the number of clinical studies in the paediatric population, which is also influenced by the "sticks and carrots" FDA and EMA policies. As the number of studies increases, however, the success of each particular trial depends not only on the necessity to conduct it, and on the administrative pressure by regulatory bodies such as the FDA and EMA, but also on the professional approach of the investigators and clinical research professionals who plan and conduct a study. We think that the considerations of the factors that we described in this article will increase the chances of success of clinical trials in a paediatric population.

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