Paediatric Clinical Trials in Central and Eastern Europe – Here and Now

PEER REVIEWED

Traditionally, emerging markets have lagged behind more-developed countries when it comes to paediatric trials and have, on occasion, demonstrated a reluctance to perform research on children. This comes from well-documented challenges relating to paediatric trials, such as:

- The characteristics of the study population: intrinsically more vulnerable than adults; cognitively immature; dependent on adults
- Lack of comprehensive regulations protecting children while on study
- Ethical concerns relating to some study procedures that are common for all countries
- Bad press and media activities focused on any form of child abuse in developing countries, particularly during pharmaceutical development.

Although Central and Eastern Europe has a long history of running paediatric clinical trials, particularly in those countries that are EU members such as Poland, Hungary, and the Czech Republic, the total number is still some way behind the Western world (see Table 1).

Table 1
Paediatric trials statistic based on www.clinicaltrials.gov.com
Number of ongoing trials in selected countries on April 10th 2014
*Clinicaltrials.gov data includes all trials in the US, but does not necessarily capture all ex-US studies. The US number should therefore be considered an outlier. However, relative to CEE countries, Western countries (excluding the US) are still performing vastly more paediatric trials.

US*	1354	Thailand	38
Canada	258	Finland	38
France	196	Czech	36
UK	194	Austria	31
China	154	Russia	31
Germany	134	Mexico	28
Korea South	118	South Africa	27
Spain	112	Hungary	23
Italy	107	Greece	19
Japan	93	Argentina	18
Israel	83	Slovakia	12
Denmark	78	Romania	10
Belgium	73	Slovenia	7
Turkey	72	Lithuania	6
Brazil	70	Croatia	6
Netherlands	69	Ukraine	5
Sweden	64	Bulgaria	5
India	60	Latvia	5
Australia	45	Estonia	5
Switzerland	56	Serbia	4
Norway	44	Georgia	1
Poland	43	Belarus	1

CEE countries' regulations relating to paediatric trials are not always sufficiently robust to address the most challenging aspects of trials, such as:

1. type of study/protocol into which children are permitted to be enrolled
2. early stage projects (Phase I, Phase I/II)
3. subject consenting process
4. protection of children's rights while in the study

Published regulations and their interpretations vary from country to country. The variance is mostly in the detail, but in general they lack clear answers for many hypothetical situations in which a paediatric patient might find themselves while in a clinical study. Moreover, due to lack of experience in this field, some countries' regulatory bodies have not had the opportunity to adjust their regulations or create comprehensive guidelines to meet the practical requirements. This problem is mostly related to countries that are non-EU members like Serbia, Russia, Ukraine, Georgia, and Belarus.

In countries like Poland, Hungary and the Czech Republic, there are situations in which the final decision on how to handle the paediatric subject in unusual circumstances, e.g. emergency care, is determined by the hospital local ethics committee on an "as needed" basis due to a lack of general guidelines and rules.

Not every CEE country is right for every paediatric study, and very thorough regulatory feasibility research has to be done before determining the optimal country for the project.

1. Type of clinical study with paediatric patients

EU countries have implemented regulations stating that, in general, only trials with potential therapeutic or preventive benefits are allowed. Testing of flavour, palatability or overall acceptability is not permitted.

Issues with regulatory approval arise when there is insufficient data relating to the IMP derived from adult studies. How should one define "sufficient data"? This is individual to each regulatory body and varies from country to country, but the strictest country in the region is the Czech Republic and their regulatory authority: SUKL. Sponsors should be prepared for a very long list of questions before approval is granted. There are some indications like congenital and metabolic diseases specific to the paediatric population for which adult data is not available, but for those studies, sufficient documentation has to be presented to the regulatory bodies. While doing feasibility research for such a project, it is recommended to

check whether a similar study design was approved in the past and if other factors would recommend that country.

A paediatric investigational plan (PIP) is of great benefit at this stage. It is a specific requirement of the EMA, but a robust PIP can also be reviewed very favourably by non-EU countries in the region. The following is an extract from the EMA's own guidelines:-

'A paediatric investigation plan (PIP) is a development plan aimed at ensuring that the necessary data are obtained through studies in children, when it is safe to do so, to support the authorisation of a medicine for children. Pharmaceutical companies submit proposals for PIPs to the European Medicines Agency's Paediatric Committee (PDCO). This Committee is responsible for agreeing or refusing the plan. The Paediatric Regulation requires PIPs to be submitted to the Agency early, wherever possible.

The normal development of a medicine requires that various studies be performed to ensure its quality, safety and efficacy. PIPs:

- *include a description of the studies and of the measures to adapt the medicine's formulation to make its use more acceptable in children, such as use of a liquid formulation rather than large tablets;*
- *cover the needs of all age groups of children, from birth to adolescence;*
- *define the timing of studies in children compared to adults.*

The development plan for a medicine can be modified at a later stage as knowledge increases. Modifications can also be made if the applicant encounters such difficulties with the implementation of a PIP, which render it unworkable or no longer appropriate.'

Another significant challenge is placebo-controlled research in paediatric populations. In some branches of medicine this cannot be avoided. In general, approval for pure placebo studies is granted only in exceptional cases. There have been examples in Hungary, Poland, Slovakia, and Romania. The strictest country in the region is often the Czech Republic. In addition, the Russian MOH rarely allows paediatric placebo trials. In order to avoid regulatory refusal which may impact approval in other countries, it is recommended to ask for a scientific hearing from the EMA or the respective local regulatory bodies. If placebo trials allow the standard treatment on top of IMP and all patients receive the standard care, then even the Czech authority can grant approval.

There is a very country-specific approach which often correlates to a country's economic standing. In Georgia, for example, if the IMP or comparator used during the study contains expensive treatment registered for a specific disease that otherwise would not be affordable and is not reimbursed, such a study may be welcomed by regulatory bodies.

Trials involving critical care of children who require emergency procedures are extremely difficult to conduct in CEE countries. For example, in Poland, which is one of the most experienced countries in paediatric trials, it is practically impossible to conduct a project with a drug that is not already registered within the EU or is planned to be administered other than for the registered indication. If the drug is registered for the studied indication, the study is possible and is considered as life-saving treatment in this particular case.

Also, protocol design and procedures have to be adjusted not only to scientific needs but also to the limitations of the paediatric patients, e.g. in terms of frequency of injection and volume of blood taken during sampling. Also, other procedures have to consider the age of children involved in the study and differentiate between those younger than 12 years and those older, or even redesign the procedures for each age group. Experience shows that the regulatory authority in the Czech Republic may require a country-specific amendment with more strict inclusion/exclusion criteria for younger children. It may also be the case that a regulatory authority gives approval for one age group only and requests that the protocol is modified for others.

2. Early-stage Projects (Phase I, Phase I/II)

Early stage trials have always been a challenge due to much greater risk to the subjects, and less provable medical benefits. For Phase I, there must be a robust rationale as to why a particular study cannot be run in an 18-65-year-old population. Typically, such a Phase I study can be proposed if the study disease is not present in the adult population, e.g. genetically-driven diseases and abnormalities. There are no strict regulations prohibiting Phase I trials in paediatric populations, but in some countries, e.g. Russia, a sponsor must prove with supporting materials that there is a clinical need for the study to be conducted in Russia. In reality, it is rare that the MOH is satisfied with these proposals.

Moreover, CEE countries do not have many qualified and certified sites that can perform Phase I trials in paediatric populations. The most advanced country is Hungary, with an established network of centres specialising in early-stage clinical trials. Examples are FUTURENEST, as well as the Phase I unit at Semmelweis University in Budapest.

Phase I trials by definition allow subject remuneration for their time spent on the trial, and this is obviously a very controversial issue when it comes to children:

- Should we pay money to parents for children's participation? If so, they might be motivated financially to offer their children for trials.
- Should we offer children some non-monetary rewards? If so, what would be most appropriate? Are sweets or toys commonly considered to be pleasant for children and are they truly valuable to them?
- Should we compensate parents for their time while assisting their child at the hospital during the study?

All these dilemmas lead to common conclusions that it is better not to offer any reimbursement for participation

in Phase I except for travel, generous meal costs and usually parents' accommodation costs to assist children in hospital. If any other material is going to be offered to support participation in clinical trials (e.g. a small backpack for carrying medication with substantial volume), this has to have a low commercial value for the subject and be approved by the relevant ethics commitee.

3. Paediatric Study Subject Consenting Process

The consenting process restrictions are the most significant factors impacting patient recruitment, and have become increasingly important during the last 25 years of cultural change in the region.

The paediatric study subject consenting process has been addressed well in the majority of CEE countries, but as always there are differences between EU countries and non-EU countries. Russia, Ukraine, Georgia, and Belarus have relatively straightforward processes in comparison to those of EU countries. Hungary and Georgia allow a one-parent signature. This is considered a significant advantage and may explain the high interest in placing paediatric trials in Hungary. Nevertheless, the majority of countries require both parents' signatures on the informed consent for their children. The law usually says that in special cases when the second parent is not available for formal reasons, one parent is sufficient. In practice, a lot of certificates and documents are required to prove the formal status of the second parent, and many people would rather give up participation in the trial than endure this bureaucratic burden, often associated with a variety of domestic problems.

To assess the impact of the single-parent factor on recruitment, we need to know the regulatory requirements as well as the prevalence of single-parent status. Analysing data from the last five years, single-parent status is highest in Russia with over 50 % of marriages ending in divorce, followed by Hungary and the Czech Republic with over 30 %, but less than 20 % in Poland.

Although in Russia both parents are required to sign the consent, there are various ways to avoid the need for both parents to be present. It is sufficient if one parent authorises another person to represent him/her at the consenting process. In Russia, the consent is taken with the presence of a witness who also has to sign and date the PIC as well. Parents are crucial for children's participation in clinical trials; for example, in Russia and Ukraine it is legally impossible for children that are deprived of parental care, adopted, fostered or orphaned, to participate in clinical trials. Advertising for paediatric patients is strictly prohibited in Russia.

Informed consent text has to be adjusted to the appropriate age level, and in Russia, Ukraine and Georgia, usually two age groups are specified – below 14 years and above 14 years. EU members have more comprehensive requirements, and the exact requirements vary from country to country with regard to age limits. Assent form requirements are not always formally stated in the local regulations, but there are usually specific recommendations. For example, in Poland it is advisable to have the following assents: below 11 years, 12-14 years, and 15-17 years; while in the Czech Republic: 6-7 years (maximum two pages, big letters, pictures as well as text), 12-14 years (maximum four pages), and 15-17 years (similar to adults' ICF, including information about contraception). The assent forms have to be adjusted according to the protocol design, and there are no specific regulations relating to this. The child's consent is always an issue as there is no strict age barrier when the child is considered capable of taking decisions about their participation in the study. It is defined that children above 12 years are able to take the relevant decision, but individual assessment by a psychologist regarding a child's cognitive abilities might be needed in the case of some specific diseases. Adolescents (>12 years) have the right to withdraw from the study whenever they wish.

Paediatric trials are a core part of clinical development. Not only is there a commercial incentive to develop paediatric treatments, but there is also a moral imperative. As discussed above, the environment for conducting paediatric research in Central and Eastern European countries is not yet as sophisticated as that of Western Europe and North America. However, they are catching up fast. Every month, new precedents are set and regulations clarified for the practical purpose of attracting high-quality clinical research.

Of course, the fact that the market for paediatric trials is not yet mature means that there are fewer competitive trials, and there remain large untapped patient populations. It is vital that detailed feasibility research is performed in advance of choosing countries. This requires investigation, not just of the epidemiology of a disease and the associated standards of care, but also the regulatory environment, precedence of similar studies and the cultural issues associated with paediatric trials. With the right partner, with the relevant experience and local expertise and the ability to negotiate the hurdles and pitfalls, sites in this region can easily enroll larger numbers of patients over shorter periods of time than their equivalents in the West. Overall, it is expected that this region will continue to make very efficient and significant contributions to paediatric research.

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