

# European and non-European paediatric clinical trials

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## Abstract

Pharmaceutical companies are increasingly conducting clinical trials – including paediatric trials – in non-European countries. In much of Europe and the US, paediatric trials are associated with severe recruitment problems. Paradoxically, significantly large potential paediatric trial populations exist in Russia, Ukraine and the CIS countries, making these regions particularly attractive in terms of accommodating the forthcoming expansion of paediatric trials.

Ethics committees within the CIS countries are keen to address issues relating to the conduct of paediatric trials, and are constantly working on and revising their policies on paediatric studies.

This article outlines the advantages of conducting paediatric trials in non-European countries and the regulations involved, as well as examining the requirements of paediatric investigation plans, ethics committees and competent authorities, local insurance, import and export licences and other documentation required both in the EU and in selected non-European regions.

## Introduction

The new European regulation EC1901/2006 Medicines for Paediatric Use, which came into force in January 2007, mandates pharmaceutical companies to undertake clinical trials within the paediatric population. Europe, with its member states, has always had a solid reputation for running clinical trials because of its stringent legislation and high calibre of trial staff who maintain a good standard of quality. Increasingly, however, companies are turning to non-European countries as clinical trial sites (including paediatric trials) for a number of reasons.

Generally, it is known that there are difficulties associated with the undertaking of paediatric clinical trials, and particularly so in Western Europe. These difficulties relate to ethical, technical and logistical considerations. Many physicians are reluctant to recruit

children into clinical trials because they are seen as vulnerable subjects. Technical difficulties include obvious problems with measuring study endpoints (eg, pain or quality of life measures). The main challenge, however, is of a logistical nature, namely, that of patient recruitment and retention.

## Recruitment, retention and compliance

There are regions where paediatric trials are not associated with severe recruitment problems. One of the best examples is Eastern Europe, where a large number of paediatric trials have been conducted over the past five to ten years in all the main therapeutic areas including oncology, respiratory disease, the treatment of infectious diseases with antivirals and anti-infectives, and vaccine trials. In particular, the countries of the former Soviet Union (the CIS consists of Russia, Ukraine, and ten more of the 15 former Soviet Republics) have emerged as excellent destinations for paediatric clinical trials for several reasons:

- CIS countries have large populations. Together, the former Soviet countries have a population of around 250 million people. Around 20% of this population is represented by children under 16 years old. Compare this to Western Europe, where around 15% of the population are children.<sup>1</sup> There is also a general consensus that the decline in the child-juvenile populations in Southern and Western Europe will become more dramatic. The presence of a significantly large potential paediatric trial population makes Russia, Ukraine and the CIS countries attractive destinations to accommodate the forthcoming expansion of paediatric clinical trials.
- Comparatively rapid patient recruitment for all clinical trial patient categories (including paediatric populations). According to various published reports, the average rate of patient recruitment in Russia, for example, is up to five times faster than in the EU. This is because patients in the CIS countries are generally eager to take part in clinical trials, and compliance is very good, even with the more complex study protocols. This is also true of paediatric populations. For many parents, the participation of their children in clinical trials means that these children can gain access to free, high-quality medical care, provided by the best specialist centres in the country. This is an important motivating factor. Together with low population migration in Russia, Ukraine and other CIS countries, this contributes to excellent patient retention in clinical trials conducted in these regions.
- A centralised healthcare system. The centralised system of paediatric healthcare, with a high concentration of children in academic paediatric centres and specialised children hospitals, creates an ideal environment for recruitment into clinical trials.

- Compliance with EU legislation. Clinical research in Russia and Ukraine is conducted with strict adherence to GCP principles. Principles of ICH GCP have been integrated into national legislation for clinical trials in these countries and are strictly monitored by the national authorities. The procedures for obtaining informed consent for participation in paediatric trials are very similar to those in the US and Europe. In addition, formal US FDA inspections and numerous audits conducted by sponsor companies have allayed any concerns about the quality of clinical trial data obtained in these Eastern European countries.

### The regulations

It is known that the new paediatric regulation requires that a paediatric investigation plan (PIP) is submitted and approved by the EMEA's paediatric committee (PDCO) before a paediatric trial can commence. So how does this affect clinical trials run in non-European countries, and what considerations should be taken into account?

According to Directive 2001/83/EC (as amended by Directive 2004/27/EC), clinical trials submitted as part of a marketing authorisation application (MAA) within the EU which were performed in third countries (non-EU) must meet the following requirements:

- They must be conducted in accordance with GCP principles (and compliance with GCP cited in the trial documentation)
- They must have ethical requirements equivalent to the provisions of the Clinical Trial Directive
- They must comply with the good manufacturing practice (GMP) of EU countries.

These principles are also applied to paediatric trials where the medicinal product is not studied with a view to obtaining a marketing authorisation.

In addition, it is stated that ethical standards should be no less exacting than they would be for research carried out in EU countries, and that the trial protocol should be submitted for ethical and scientific review in the EU member state in which the sponsor or its legal representative resides.<sup>2</sup>

The recommendations made within the document entitled 'Ethical Considerations for Clinical Trials on Medicinal Products conducted with the Paediatric Population' (in relation to Directive 2001/20/EC) are followed by EU researchers and sponsors carrying out trials in third countries, as well as by the ethics committees (ECs) that review these trials and their results. The laws and regulations of the countries in which the trials are conducted are to be respected, and those responsible for the trial should ensure that it responds to the public health needs and priorities of the country in which it is carried out. It is also the responsibility of all involved parties to ensure there is national compliance and that the paediatric requirements, including assent as well as consent, are obtained for children. Those conducting the trial must be properly trained and/or experienced in the study of paediatrics, and should be able to analyse and manage potential paediatric adverse events. This helps minimise risk to this particularly vulnerable population.

As a result of the new paediatric legislation, an application for a marketing authorisation of a medicinal product which is not authorised in Europe will be deemed to be valid only if it includes either:

- The results of all studies performed and details of all information collected in compliance with an agreed PIP

- A decision of the EMEA granting a product-specific or a class waiver
- A decision of the EMEA granting a deferral.

As per Article 46 of Regulation Number 1901/2006, where a study is part of a PIP agreed by the PDCO, information must be included in the line-listing along with the PIP procedure number, the EMEA decision date, number on the PIP and the date when the PIP has to be completed. The cover letter and line-listing must be submitted to the relevant member states (with a copy to the EMEA) within six months of completing the study (templates for the cover letter and line-listing are available at <http://www.hma.eu/216.html>).

### The paediatric committee (PDCO)

The PDCO is responsible for providing opinions on the development of medicines for use in children in accordance with Regulation (EC) 1901/2006 as amended. It meets on a monthly basis and its main duties are to assess the content of PIPs, applications for a full or partial waiver and applications for deferrals. The PDCO is not responsible for paediatric use marketing authorisation (PUMAs) applications. These applications remain the responsibility of the Committee for Medicinal Products for Human Use (CHMP). The CHMP (or any other competent authority), however, can ask the PDCO to prepare an opinion on the quality, safety and efficacy of a medicinal product for use in the paediatric population if these data have been generated in accordance with an agreed PIP.<sup>3</sup>

Submission of completed paediatric studies is required regardless of where they are conducted. If the medicinal product has an approved marketing authorisation within the EU, the completed study documentation should be submitted to each competent authority (CA) where the product is already authorised. The assessment itself, however, will be carried out through the work-sharing exercise for medicinal products authorised through the mutual recognition procedure/decentralised procedure (MRP/DCP) (the reference member and concerned member states) and national procedure (the national CA of the relevant member state) and by the EMEA's CHMP for centrally authorised products. The same application form is used whether requesting agreement to a PIP, waiver or deferral. Different parts (Part A to Part F) of the application are provided to fulfil the different types of request. For an application for a Waiver, Parts A and C need to be completed in full, along with some information in Part B.

In addition to the usual clinical trial documentation, a 'letter of intent' must be sent to the EMEA secretariat two months before the intended submission date of the PIP application. This application must be submitted according to the deadlines for submission, ie, 60 days prior to the PDCO meeting plus 30 days for validation and administration tasks. There are templates available for download from the EMEA website for the letter of intent and the PIP application, deferral or waiver.

Following receipt of a proposed PIP, the PDCO will appoint a rapporteur and within 60 days adopt an opinion as to whether or not the proposed studies are acceptable. Within this 60 day period the applicant or the PDCO may request a meeting. The PDCO may also request that the applicant modifies the plan. If this happens, the time given for adoption of the final opinion will be extended to an additional 60 days (maximum).

The following assessments by the PDCO are free of charge:

- Applications for waiver
- Applications for deferral
- Paediatric investigation plans
- Compliance with the agreed PIP

Note, however, that if scientific advice is sought for studies which also include an adult population, an appropriate fee representing the adult aspect will be charged.

The European application format submitted to the PDCO consists of six parts, A to F:

- Part A – administrative and product information
- Part B – overall development of the medicinal product, including information on the conditions
- Part C – applications product-specific waivers
- Part D – PIP
- Part E – applications deferrals
- Part F – annexes.

Specifically, part A, 'administrative and product information', must include a statement on whether or not each trial was conducted according to GCP. As already mentioned, Russia, Ukraine and other CIS countries comply with the principles of GCP and therefore reinforce their capability to conduct paediatric trials. In addition, this section must include details of any decisions, opinions or advice given by non-EU regulatory authorities on the paediatric development of the medicinal product along with copy documentation.

### Monitoring by the EMEA

Between 2005 and 2008, the EMEA has actively tracked the location of patients included in pivotal trials submitted in MAAs to the centralised procedure, and has noted increasing numbers are outside the 'traditional' Western European and North American research areas. Since 2006, a system of routine GCP inspection has been in place in these third countries and in December 2008, the EMEA published its strategy paper for the 'acceptance of clinical trials conducted in third countries'. What is interesting to note is that while the agency is focusing on third country trials, 'many of the actions that arise ... will have relevance for all clinical trials that form part of marketing authorisation applications'.<sup>4</sup>

### Ethics committees and competent authorities

The roles and responsibilities of ECs, as detailed in ICH E6, are crucial in protecting study participants. When protocols involving the paediatric population are reviewed, the EC should have members (or experts they can consult) who are knowledgeable in paediatric ethical, clinical and psychosocial issues. This applies to all ECs regardless of whether or not they are within the EU.

In Russia and Ukraine, the CAs and central ECs hold their meetings at least once a month. The time taken for assessment by the CAs can vary depending on the quality and completeness of the submitted information. As is the case in Europe, the authorities are obliged to respond to the applicant within a period of 60 days of receipt of a valid EC application. CAs charge for evaluating applications and also charge for the assessment of study amendments. Currently, ECs do not charge for their services, but there are rumours in Eastern Europe that this may well change in the future. It is possible to make

an application to the EC and the CA at the same time or in sequence. In Western Europe, you will also need to obtain a EudraCT number. This is the mandatory reference number allocated by the EMEA for the clinical trial of an investigational medical product (CTIMP) authorised on or after 1 May 2004. In the UK, details of ECs and how to apply can be found at: <http://www.nres.npsa.nhs.uk/>

Until recently, having an affiliated local EC was not mandatory for clinical trial sites in Russia and Ukraine in order to take part in clinical trials. However, lately the authorities in both countries have started implementing a strategy to make the study review by local ethics commissions an obligatory part of the approval process. Local ECs are supposed to approve studies already authorised by the central EC within a short period of time (around two weeks). Fortunately delays associated with local ethics approval are rare.

Similar to Western Europe, the regulatory dossier submitted to the CAs and national ECs (Russia and Ukraine) includes an application form, a cover letter and a set of standard essential study documents: study protocol and synopsis (including any protocol amendments, if applicable), patient information leaflet and consent form, investigator's brochure and investigational medical product dossier (IMPD). Detailed information on investigators and investigative sites participating in the trial is also submitted. The CAs must be notified if the study has already been approved in other countries, and it must be provided with the results of any clinical trials with the medicinal product which have already been conducted. If available, this information is reassuring for the CA and will help the overall approval process.

### Insurance

According to the Clinical Trial Directive, insurance is mandatory. Evidence of study insurance is required for both regulatory and ethics approval in Russia and Ukraine. In both countries, study insurance must be obtained from an accredited resident insurance company. Only insurance covering risks to study subjects is mandatory. Insurance of risks incurred by study investigators and their institutions is optional. The cost of insurance mainly depends on the phase of the study, but usually is lower than in Western European countries. It can be difficult to obtain insurance for trials performed in children, especially neonates, for two reasons. First, insurance regulations differ in the member states as well as other countries, and secondly, insurance companies have issues with long-term liability. Another aspect of insurance is that patient records should be protected by the privacy requirements of applicable national laws so that individuals are not at risk of being labelled with pre-existing conditions by insurance companies.

### Import and export licences

As both Russia and Ukraine are outside the EU, there is a requirement to obtain a licence for the import of study medication(s) and for the export of biosamples (if analysis is to be performed by laboratories outside the countries). Licences can only be obtained after the trial has received regulatory and ethical approval, but it can normally be done in parallel with seeking the opinion of local ECs. This process normally takes about two weeks.

Once import and export licences are obtained, shipments can be arranged through any established international courier company with

regional presence in Russia or Ukraine. Shipments are inspected by Customs and it is essential for study sponsors, or CRO representatives, to appoint an experienced customs broker, as this process is not straightforward. Customs officials are well known for their rigour and pedantic approach to shipment documentation. It is also important to prepare all the shipment documents (pro forma invoices) in full compliance with Customs requirements.

### Other documentation

A GMP certificate is also required from the manufacturer; its manufacturing authorisation, certificates of analysis for both the study drug(s) and placebo (if used in the study). Labels for the study drug/placebo prepared to national standards need to be submitted for approval. If advertising is planned, advertising materials must also be formally authorised.

If submission is made by a CRO representing the study sponsor in Russia or Ukraine, a power-of-attorney letter confirming delegation of authority from the sponsor to the CRO should be submitted to the authorities. Importantly, the letter must be apostilised by a consulate of Russia or Ukraine (as applicable) in the sponsor's country of residence.

### ClinicalTrials.gov

The registry of clinical trials, ClinicalTrials.gov, supported by the US government, is a useful source of statistics on international clinical trials. It is operated by the National Library of Medicine of the National Institutes of Health (NIH) and contains listings of publicly and privately funded clinical trials from around the world. All studies conducted under the US FDA's investigational new drug (IND) application must be registered with ClinicalTrials.gov.

There are no open access official databases of clinical trials in Russia and Ukraine. According to ClinicalTrials.gov, however, there are 147 completed and ongoing paediatric clinical studies in Russia (46 of them currently recruiting patients) and 45 studies in Ukraine (17 currently recruiting). The majority of these studies are interventional treatment studies and most of them are conducted under the FDA's IND. Again using the data contained on ClinicalTrials.gov, to date we can see that in Western Europe there are more than 5,000 trials (completed or ongoing) which include the paediatric population. Around 36% of these trials are conducted in the UK, Germany and Spain.

### The future

Further growth on the number of paediatric trials run in Russia and Ukraine is expected as a direct result of the implementation of the new paediatric legislation. These countries are keen to offer their facilities and support to sponsors outside their region and, therefore, have embraced the regulations in order to conduct trials not only to an acceptable level of quality, but aiming to exceed the required standards. The ECs within the CIS countries take the challenge of paediatric trials very seriously and are constantly working on and revising their policies on paediatric trials. Combine this determination with relatively low costs, close monitoring by the EMEA and access to a steady paediatric population, and these countries are likely to become increasingly attractive locations to run paediatric trials. On

the other hand, Western Europe is a known entity and remains a centre of excellence for research and development. In addition, the EMEA is developing a European network of existing national and European networks, investigators and centres with specific expertise in the conduct of studies in the paediatric population. No doubt this level of support will prove to be attractive to sponsors.

Without doubt, ethical and moral problems associated with conducting paediatric trials are applicable throughout the world, without exception. Despite all the challenges associated with paediatric trials, however, it is important to remember that the final aim of these trials is to improve the availability of medicines formulated and tested for paediatric use all over the world. Wherever sponsors decide to conduct their trials we must not lose sight of the objective of the paediatric legislation – to provide 'a brighter future for child health'.<sup>5</sup>

### References

- 1 Source: United Nations Economic Commission for Europe
- 2 Source: [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/0/ethical\\_considerations.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/0/ethical_considerations.pdf)
- 3 Source: EMEA website, [www.emea.europa.eu](http://www.emea.europa.eu), Paediatric Committee (PDCO)
- 4 Source: EMEA strategy paper: 'Acceptance of clinical trials conducted in third countries, for evaluation in Marketing Authorisation Applications', London, 5 December 2008.
- 5 Source: EMEA website, [www.emea.europa.eu](http://www.emea.europa.eu)

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