How to Improve Clinical Research in Children

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A survey on the perception of European pediatricians and industry/CROs.

Since January 2007, the European "Pediatric Regulation"[1] has fostered ethical research and ensured appropriate authorization and information on medicines for children. The challenging nature of pediatric clinical research requires competence for a full appreciation of the evolving clinical trial methodology in this setting, and a deep knowledge of the specific regulatory requirements. The Pediatric Working Group of the European CRO Federation (EUCROF-PWG) first analyzed the status of pediatric clinical research in Europe by conducting a survey in 2007.[2] The results revealed a relatively low number of ongoing pediatric trials while it was expected that the European Pediatric Regulation would stimulate more pediatric research. Based on the information in the public European clinical trials database (EudraCT), the number of authorized pediatric trials, which were part of an agreed Pediatric Investigation Plan (PIP) was 70 in 2011, representing 19% of all pediatric studies.[3] According to the recent report of the Pediatric Medicines Section that evaluated research activities during 2011, and that was submitted to the European Medicines Agency (EMA), pharmaceutical companies seem to be meeting their clinical trial obligations in view of a marketing authorization. However, some major deviations from the rules set by the Regulation were observed, in particular, often poorly justified late submissions of PIPs/waiver applications and slow progress of the clinical trial plan.[4] Nonetheless, further research incentives are provided by the EMA through the EU Framework Program by funding studies for off-patent medicinal products, in view of the submission of a Pediatric Use Marketing Authorization (PUMA). This program will hopefully give further impulse to pediatric research, but will also amplify the need of quality improvement in pediatric clinical research.

Another survey performed by the EUCROF-PWG in 2009 aimed to determine the main difficulties and constraints in pediatric research among European CROs, pharmaceutical companies, and Institutional Review Boards/Ethics Committees (ECs).[5] Most respondents reported to have conducted less than five clinical trials in children over the last three years. From the responses, it was evident that there was space for improvement in the application of an appropriate methodology, but also a need for support. In particular, support is needed for a better understanding of how to design pediatric clinical trials, how to select appropriate and validated endpoints, how to write good Patient Information Sheets (Informed Consent and Assent Form), and, for ECs, how to gain more experience in the process of pediatric study protocol assessment.

A follow-up survey was launched in 2011 by the EUCROF-PWG to evaluate the current situation relating to pediatric clinical studies and to determine whether the concerned stakeholders had gained more experience in pediatric clinical research. The analysis involved the number of studies conducted, the difficulties encountered in conducting clinical research with children, the perception of the need for external support and the experience/competence of the ECs. This last survey was addressed to

pediatricians, pharmaceutical/biotech industry, and CROs in Europe in order to collect different points of view and provide a framework for the assessment of the status of pediatric clinical research. The present article reports the results of this last survey, and identifies current strengths and weaknesses in pediatric clinical research and the evolutionary pattern of the approach to pediatric drug development since the introduction of the European Pediatric Regulation.

Survey Results

Of the 350 questionnaires sent out (60% of these to CROs/pharma companies; 40% to pediatricians), 58 were completed and returned. The response rate was 13% from companies and 20% from pediatricians. Respondents who declared not to be involved in clinical research in pediatrics did not provide information so that they were not considered for statistical analysis (N=2).

Out of 56 respondents evaluated, 29 (51.8%) were pediatricians (mostly from academic institutions or general hospitals), 15 (26.8%) were CROs (mostly country affiliates), and 12 (21.4%) were pharmaceutical or biotech enterprises (mostly ranking within the top 10 in the local markets). The data analyses have been conducted separately for pediatricians (N=29) and sponsors/CROs together (identified hereafter as "companies:" N=27). Sponsors and CROs data were pooled because they have similar roles in carrying out clinical trials. Results are reported as percentages of responses in each category analyzed.

Knowledge of the Pediatric Regulation 1901/2006/EC. The knowledge of the Pediatric Regulation 1901/2006/EC is widespread among respondents (93% within companies; 83% among pediatricians), thanks to a direct involvement in pediatric studies which represent a main source for familiarization with the regulation. Although about 70% of companies and pediatricians believe that the Pediatric Regulation might eventually lead to favorable effects on the therapeutic needs of the pediatric population, it is surprising that there is moderate expectation of the Pediatric Regulation to impact effectively on the availability of new medicines authorized for children, and even less regarding the availability of new indications, new formulations, or an impact on off-patent drugs (Table 1).

It is noteworthy that the awareness of the likely increase of costs in public health, which can be an effect of the increased research activities and related costs, is evidently low (10% to 11%).

Experience in clinical research with children. 63% of companies reported to have started no more than two pediatric studies in the past three years (including 25% of companies reporting no studies at all). Data reported by pediatricians were biased by a high rate on non-responders to this question (56%); the remaining 44% of pediatricians was evenly distributed among the categories listed in Table 2.

Impact of Pediatric Regulation		
IMPACT	**COMPANIES (N=27)**	**PEDIATRICIANS (N=29)**
With regard to drug development:		
on new medicines not yet authorized	59 %	62 %
on new indications	22 %	45 %
on new formulations or dosage forms	19 %	28 %
on off patent drugs	11 %	10 %
With regard to pediatric health:		
on the development of innovative drugs	41 %	62 %
on therapeutic needs	70 %	69 %
on improving planning / managing clinical research	33 %	21 %
on increasing profitabiliity of existing drugs	26 %	21 %
on increasing work; no impact on therapeutic needs	4 %	3 %
on increasing costs in public health (multiple choices allowed)	11 %	10 %

Source: Kremer, et al.

Table 1. Expected impact of the Pediatric Regulation across drug development and pediatric health.

Because clinical research plays a dominant role in the final availability of new drugs, we have investigated the level of experience in the various phases of the clinical development. Good or fairly good experience (relating to a four-level scale: good—fairly good—poor—none) has been reported especially in Phase II and Phase III studies while Phase I has been identified as the area with less experience. Observational studies were mostly performed by pediatricians, as non-commercial sponsors of such studies. Large experience was reported by both companies and pediatricians mainly in oncology, vaccines and hematology.

Difficulties in performing clinical research with children. Difficulties related to protocol development, ethical aspects and practical issues can be encountered in this population. These were investigated (Figure 1) and both practical and methodological aspects appear to be critical while designing and carrying out a pediatric study. Obtaining the parents' understanding and consent is reported as critical and represents a frequent difficulty for the inclusion of a sufficient number of subjects in the studies, the latter being regarded as the most challenging aspect in performing clinical trials in children (74% and 59% for companies and pediatricians, respectively). An additional complication is the collection of biological samples, especially when these are frequent or invasive.

Methodological aspects are more frequently a matter of concern for the sponsoring companies/CROs, probably because they have regulatory relevance and involve the specific responsibility of the sponsor. Such critical methodological aspects include: getting appropriate patient-derived data, setting validated endpoints that are appropriate for pediatric aims and sample size calculation. Conversely, monitoring and obtaining resources dedicated to the trials, or writing a correct informed consent sheet, are felt to be major hurdles for pediatricians (Figure 1).

When exploring the need of support, as a consequence of the difficulties highlighted, pediatricians seem to be more demanding all across the wide array of items proposed, especially for the practical and administrative aspects encountered in the conduct of a clinical trial, such as "obtaining appropriate insurance," "receiving IRB approval," or having support for the trial monitoring. These outcomes reflect the difference between investigators and sponsors in terms of structure and organization, whereby the availability of dedicated and experienced staff in the companies allows clearance of such problems in a relatively easy way. The recruitment problem is the only matter of concern that is evenly distributed between companies and pediatricians (as expressed by 44% and 52% of companies and pediatricians, respectively).

Interaction with ethics committees. Ethical aspects are critical especially in child-related research, therefore the interaction with ECs should be easy and supported by mutual trust. In general, the competence of ECs is highly appreciated.

In most cases, the protocol submitted for ethical review is eventually approved by the consulted ECs, however with substantial comments from the ECs in 63% and 45% of instances, as respectively reported by companies and pediatricians, out of the following choices: approval always/in most instances—substantial/frequent comments—frequent rejection. This outcome indicates that the preparation of the study documentation is sometimes insufficient or unclear for a smooth ethics review.

Availability of information and educational activities. In order to improve the awareness of the various aspects of pediatric research, and also to increase skills and competence in the practical aspects of trial conduct, the participation in specific training was felt as useful by most respondents. In fact, the educational support currently available through publications, seminars, trainings, guidelines has been considered inadequate ("less than needed" or "inadequate" amount of informa-

Number of Pediatric Studies

NUMBER OF STUDIES IN LAST 3 YEARS	0	1 - 2	3 - 5	>5	NO RESPONSE
Companies	25 %	38 %	7 %	5 %	25 %
Pediatricians	13 %	12 %	8 %	11 %	56 %

Source: Kremer, et al.

Table 2. The number of pediatric studies performed in the last three years.

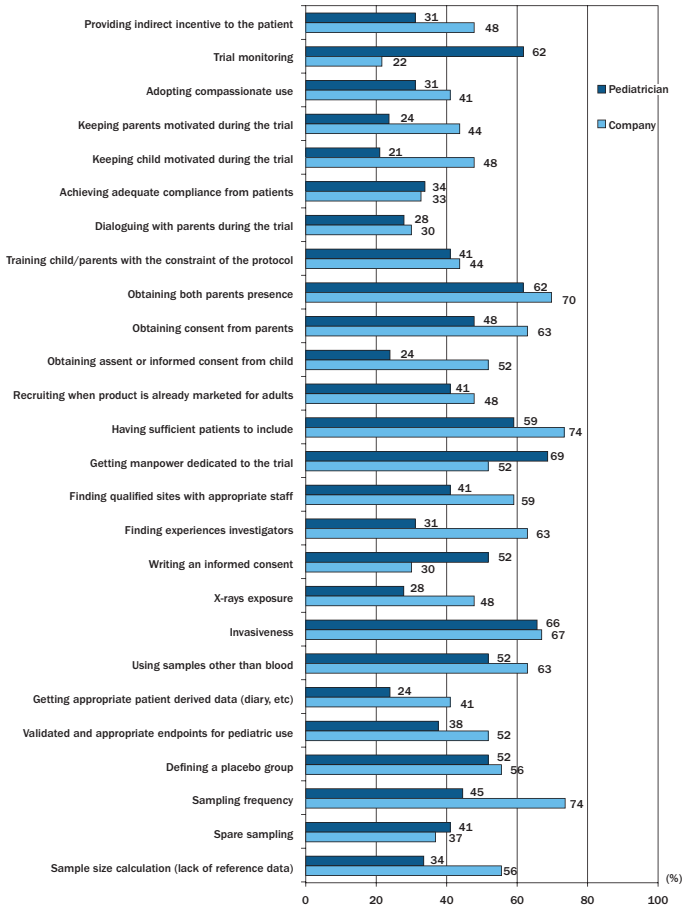
tion, out of a three-level scale: adequate—less than needed—inadequate) by 74% of companies and 69% of pediatricians. Topics most welcomed by companies were those related to compliance issues, enrollment/retention of patients, informed consent preparation and general ethical issues, pharmacokinetics, European Pediatric Regulation, and PIP preparation. Pediatricians have raised the need for advancement in informed consent preparation and general ethical issues, regulatory affairs and European Pediatric Regulation (Figure 2).

Main constraints with clinical trials in children. According to companies' respondents, clinical trials in children find constraints mainly because of recruitment issues (44%), legislative or administrative issues (30%), and difficulty in obtaining parental consent (30%). Different opinions were expressed by pediatricians, who were most worried by difficulties in obtaining ethics approval (38%), low interest of sponsors (38%), and low financial investments (31%) (Figure 3).

The future of pediatric clinical research. Like the issues described by companies as the main reasons for the slow development of pediatric research, similar concerns are also expected for the future, as being related to recruitment (63%), parental consent (41%), legislation or administrative hurdles (26%), low interest of sponsors (26%), and slow implementation of legislation (22%). Parental consent and recruitment are less frequently mentioned by pediatricians (14% and 10%, respectively), while legislation or administrative hurdles, low interest of sponsors, and slow improvement of legislation are felt by pediatricians as more critical (66%, 55%, and 31%, respectively).

Pediatrician-specific section. The majority of the pediatricians (72%) believe that their therapeutic choices would be better supported by personal updates, based on easy access to the

Main Hurdles Encountered



Source: Kremer, et al.

Figure 1. Main hurdles ("very difficult" or "difficult" tasks) encountered by pediatricians and companies in clinical research with children (multiple choices allowed).

available literature, acquisition of experts' opinion, or participation in congresses. Personal experience in clinical studies would support 55% of pediatricians in their therapeutic choices (especially by way of randomized clinical trials; much less by way of prospective or retrospective surveys), while the support given by the industry representatives' for information on therapies is felt to be marginal.

More than a half of pediatricians interviewed (56%) are of the opinion that the medical community has made insufficient collaborative efforts in the development of pediatric drugs.

Company-specific section. Thirty-three percent of companies' respondents were aware of PIPs submitted by their company. In almost all cases the PIP application was carried out by the headquarters.

Also among respondents from industry, the majority rated efforts made for development of pediatric drugs as insufficient.

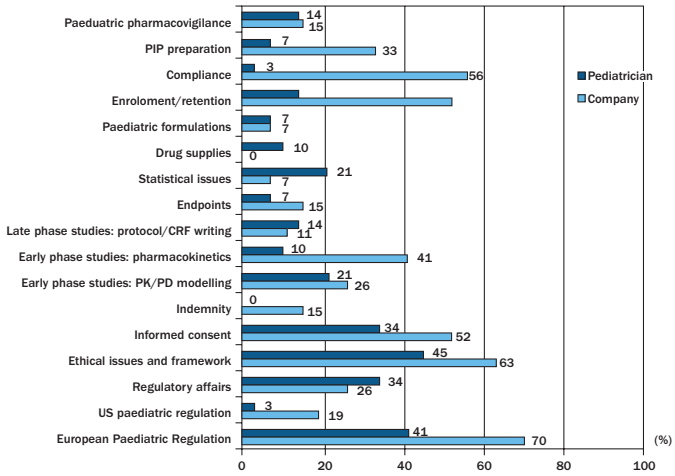
Discussion and conclusions

The results of this survey confirmed some uncertainties still dominating pediatric research among pediatricians, the pharmaceutical/biotech industry, and CROs, as were already highlighted in the previous survey conducted by EUCROF-PWG in 2009. No striking differences can be identified between the outcomes of the two surveys. Most critical difficulties reported in the previous and the current surveys are related to the protocol development, practical issues in the trial management and the need to improve parents' and patients' motivation and retention in studies. A need for support in this respect was indicated especially by pediatricians, who have to face the complex organization of a trial in addition to the daily clinical practice, often without dedicated staff. On the other hand, sponsoring companies and CROs need training on the specific regulatory, ethical, and methodological implications of the pediatric clinical development.

It is obvious from these results that the different roles covered by companies sponsoring studies and investigators require mutual support, given the recognized insufficient collaboration among pediatricians and between clinicians and companies. Efforts should therefore be made towards strengthening synergies between the main stakeholders. This interplay should also include ECs, as they represent a major actor in guaranteeing the safety, rights and well being of children involved in clinical research. Such considerations mirror the results of another previous survey conducted among ECs.[6]

Specific operational, ethical and methodological aspects of pediatric research seem to represent the primary concern, in addition to the increase of the financial burden for the pharmaceutical/biotech industry imposed by the specific pediatric drug developments. Nevertheless, the stimulus given by the Pediatric Regulation to pediatric clinical research is felt as determinant for the availability of drugs specifically designed for children. The perspective of expanding the clinical research in this setting is also welcomed by the pediatric community as a way to increase their experience on specific drugs and on the pediatric clinical trial methodology. The number of pediatric studies newly registered in EudraCT has grown and has reached a level of about 350 per year.[7] However it is still uncertain whether this will eventually result in

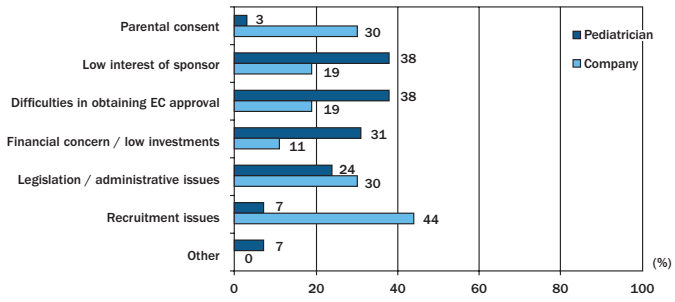
Training Topics



Source: Kremer, et al.

Figure 2. Useful topics for training (multiple choices allowed).

Observed Constraints



Source: Kremer, et al.

Figure 3. Main constraints observed in the past with clinical trials in children (multiple choices allowed).

the desired improvement in the treatment of pediatric population, provided that an improvement all across the organizational, ethical and methodological aspects of pediatric clinical research is needed. This is confirmed by the substantially unchanged perception of difficulties and needs detected in the two EUCROF-PWG surveys.

The results of this questionnaire and also the relatively limited number of responses received may reflect the marginality of pediatric research in Europe. Although such underreporting to the questionnaire represents a limitation of this work, the outcomes of the present survey may represent a basis for further improvement in pediatric research in Europe. One can conclude from the survey that further support should be given to educational initiatives focused on practical issues in the clinical trial management, ethical aspects and new methodological approaches, to overcome the challenges of drug evaluation in children and to protect them from unnecessary exposure to experimental drugs.

**More information on the survey is available in the full article online.*

References

1. Regulation (EC) No 1901/2006 of the European Parliament and of the Council on Medicinal Products for Pediatric Use, Amended by Regulation (EC) No. 1902/2006, December 12, 2006
2. M. Dehlinger-Kremer, et al., "Testing Medicines for Children," GCP *Journal*, 10-15, (2009).
3. European Medicines Agency. "Communication from the Commission—Guidance on the information concerning Pediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA), in accordance with Article 41 of Regulation (EC) No 1901/2006." *Communication* No. 2009/C 28/01.
4. European Medicines Agency. "Report to the European Commission on companies and products that have benefited from any of the rewards and incentives in the Pediatric Regulation and on the companies that have failed to comply with any of the obligations in this Regulation, covering the year 2011." EMA/480331/2012 (12 July 2012).
5. A. Svobodnik, et al., "How to Improve Children's Research," *Applied Clinical Trials*, February 2010, 46-53.
6. Altavilla A, et al., "Impact of the new European Pediatric regulatory framework on ethics committees: overview and perspectives," *Acta Pediatrica* 101(1) e27-32 (2011).
7. European Medicines Agency. "5-year Report to the European Commission. General Report on the experience acquired as a result of the application of the Pediatric Regulation." EMA/428172/2012 (8 July 2012).
8. A. Svobodnik, et al. "How to Improve Children's Research," *Applied Clinical Trials*, February 2010, 46-53.

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