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## Pediatric Drugs

Conference Paper  
German Paediatric Research Network (PAED-Net)

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# German Paediatric Research Network (PAED-Net)

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## Abstract

Clinical trials in children are mandatory to generate data on new drugs as well as on drugs used off-label or for unlicensed indications. The EU Paediatric Regulation introduced in 2007 provides the background, goals, and requirements for pediatric clinical trials. The German Paediatric Network (PAED-Net) was established in 2002 with a public grant from the German Ministry of Education and Research with the aim of developing competence, infrastructure, networking, and education for pediatric clinical trials. The network, consisting of six pediatric clinical units and a coordinating office, has progressed very well and has achieved valuable improvements concerning the conduct of pediatric clinical trials. In addition, training programs have encouraged knowledge about clinical trials in investigators and nurses and have made medical professionals as well as the public aware of the need and advantages of trials in children. Although these trials are still challenging from the ethical, scientific, and clinical points of view, quality-controlled data are the prerequisite for sharing therapeutic innovations for children and for applying the principles of evidence-based medicine to the youngest patient population.

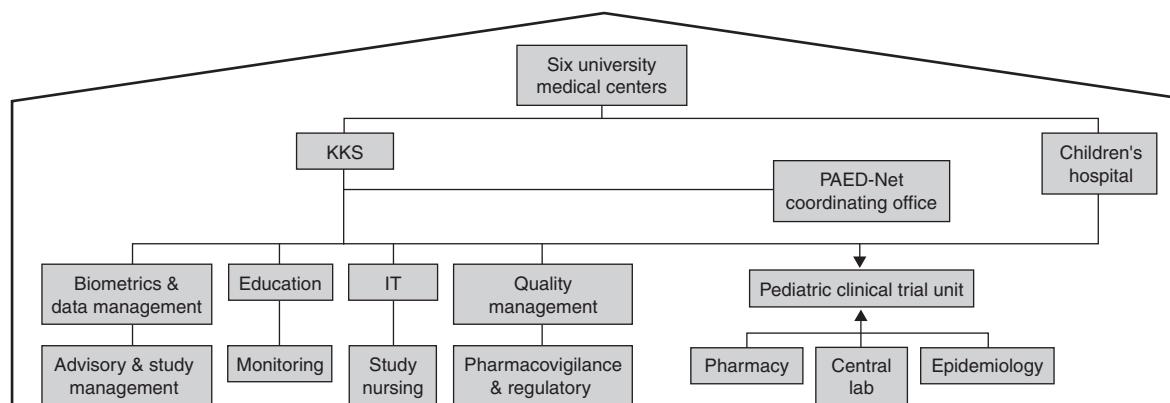
## Introduction

To improve drug therapy in children and adolescents, clinical trials are mandatory to generate data on the safety and efficacy of drugs. The Regulation (EC) No 1901/2006 of the European Parliament and of the Council on Medicinal Products for Paediatric Use that came into force in all EU member states in January 2007<sup>[1]</sup> describes, in a clear and detailed way, the necessity for clinical trials of drugs under development, for drugs for which changes in dosage forms or new indications are submitted for approval, and for off-patent drugs that are unlicensed or used off-label in pediatrics.

In order to realize these trials in Europe, networking is needed. Therefore, a European Paediatric Network was considered a prerequisite for the achievement of the goals of the paediatric regulation. The European Paediatric Network will consist of national networks either already existing or planned in the EU member states (The Network of Paediatric Networks at the EMEA, Implementing Strategy, January 2008<sup>[2]</sup>).

## Approach to Improve Conduct of Clinical Trials

The difficulties in conducting pediatric trials and the complexity of their methodological procedures as well as the lack of knowledge on conducting pediatric trials and resources led to the decision to create and fund a German Paediatric Research Network (PAED-Net),<sup>[3]</sup> which started in 2002. In response to a call from the German Ministry of Education and Research (BMBF), six university medical centers out of 36 were selected for funding, based on a competitive application process, by an independent expert board: Cologne, Freiburg, Heidelberg, Leipzig, Mainz, and Muenster with a coordinating office in Mainz. Overall, BMBF funding for the network was €5.4 million for 6 years plus funding for a trial in neonatology investigating the reduction of analgesic and sedative agents in ventilated neonates by continuous infusion of clonidine.<sup>[4]</sup> All six pediatric trial units are integrated in the previously established Coordination Centres for Clinical Trials (KKS)<sup>[5]</sup> and are in close collaboration with the respective pediatric university hospital. The advantage of being linked to the KKS as well as to the pediatric university hospital is the direct access to



**Fig. 1.** Organizational structure of the German Paediatric Research Network (PAED-Net). The structure is identical at all involved universities but the coordinating office is only located in Mainz. **IT** = information technology; **KKS** = Coordination Centres for Clinical Trials; **lab** = laboratory.

all pediatric subdisciplines and their patients, and the support from the KKS (quality management, logistics, biometrics, data management, monitoring, regulatory, and pharmacovigilance) [figure 1].

The objectives of the PAED-Net are to develop expertise in multicenter clinical drug trials in the pediatric population and to build a network with a trial infrastructure that can act as a platform for multicenter clinical trials. The Paediatric Trial Units at the Universities of Marburg, Tuebingen, and Innsbruck, in addition to the above-mentioned six university medical centers, became associated partners of the German PAED-Net. Each Paediatric Trial Unit is staffed with a pediatrician and a study nurse who are responsible for trial conduct at the clinical site and investigator recruitment. The network is coordinated by two medical doctors working in the Coordinating Office who are responsible for organizing and performing certified training programs and network meetings, feasibility assessments, communication with industry, ethic committees, and authorities, and reports to the funding body as well as public relations.

### Achievements and Lessons Learned

An intensive collaboration with other university hospitals, non-academic hospitals, and private physicians has been established. In particular, this collaboration aims to ensure patient recruitment in clinical trials.

Harmonized standard operating procedures, a trial database (for network partners), standardized essential study documents (e.g. patient and parent information, informed consent, documents for assent), and a curriculum for training courses for pediatric investigators, study nurses, monitors, and scientists in close collaboration with KKS have been established in addition to various and manifold public works, (such as presentations, talks, articles, and interviews).

Most of the on-going or 155 completed trials since 2002 are industry driven and about one-third are investigator initiated. The majority (80%) address drugs in the following areas: gastroenterology, neonatology, allergology, metabolic diseases, cardiology, nephrology, diabetes mellitus, pulmonology, dermatology, neurology, infectious diseases, oncology, psychiatric disorders, and disease prevention.<sup>[6]</sup>

The clonidine intensive care trial (see Approach to Improve Conduct of Clinical Trials), the so-called network trial, resulted in considerable recruitment difficulties at those trial sites where the established care differed from that required by the study protocol; this contributed to the delay in the enrolment of study participants. This trial also showed that more resources, training, and communication than planned are often needed to conduct trials successfully. In addition, the contract negotiations are complex, the detection and definition of serious adverse event/suspected unexpected serious adverse reaction in patients with life-threatening diseases with co-morbidities and co-medication is difficult, and pharmacovigilance procedures have to be supplied to trial sites. Clinical trial conduct and data documentation need highly experienced and dedicated staff who feel responsible for the trial, and a lot of time input from all parties.

In order to train investigators and nurses appropriately in the principles of clinical trials, a 2-day Good Clinical Practice (GCP) pediatric trial course is performed twice a year and covers the following topics: drug therapy in children; off-label use; need for pediatric trials; preclinical and clinical drug development in industry; principles of pediatric trials (e.g. ethical standards, determination of pediatric trial population, inclusion and exclusion criteria, methods, trial medication, patients' assurance); clinical investigations of medicinal products in the pediatric population (ICH E11); Paediatric Regulation; Paediatric Investigational Plans; ethical and regulatory requirements; application for trial approval; writing a study protocol; study design and biostatistics; informed consent/

assent; clinical conduct according to GCP; responsibilities of clinical trial investigators; recruiting strategies; data documentation; monitoring; audits; pharmacovigilance; study reporting; and publication.

To meet industry interests and requests, PAED-Net members regularly advise companies with respect to planning and conduct of pediatric trials. The most frequent topics on which advice is given concern epidemiology and therapy of the disease for which the drug is planned to be developed; standard therapy; the population at risk; concomitant diseases; affected age groups; ethical aspects; minimal burden (as defined elsewhere<sup>[7]</sup>); minimal risk (as defined elsewhere<sup>[7]</sup>); pregnancy tests; sexual abstinence; blood volume (as described elsewhere<sup>[7]</sup>); venous punctures; number of required visits; physical examinations; study design (end-points, noninvasive parameters); and feasibility (number of patients, probability of realization of trial protocols).

For the past 6 years, the members of PAED-Net have had some valuable experiences in networking. It became obvious that networking requires – besides pediatric and trial excellence – team spirit, team players, and shared goals as well as trust and confidence.

To be prepared for the future the German PAED-Net will be integrated into the German Society for Paediatrics,<sup>[8]</sup> which represents all pediatric subdisciplines. More specialized pediatric clinical trial units are necessary to extend trial infrastructure and trial competence in Germany in order to produce quality-controlled data from well designed and conducted clinical trials, which will eventually lead to the ultimate goal of better medicines for children.

## Conclusion

Pediatric clinical trials are challenging and demanding but necessary and worthwhile for progress in children's care. The EU

Paediatric Regulation will result in better and more clinical pediatric trials that will generate data needed to improve drug therapy in children. Networking is mandatory to build up the necessary competencies, to facilitate co-operation, and to avoid duplication of studies.

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