Future Developments of Clinical Research in Pediatrics: The Role of the Journal *Klinische Pädiatrie*

Zukünftige Entwicklungen der klinischen Forschung in der Pädiatrie: Die Rolle der Zeitschrift *Klinischen Pädiatrie*

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Bibliography
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Recently, in German a new law – "Patientenrechtegesetz" §630aBGBff – was signed by the government to strengthen patients' rights providing best care. A prerequisite for best care are conclusive information on diagnostics, treatment and prognosis. Thus, the relevance of clinical trials and clinical registries providing sufficient data for evidence-based medicine will increase during the next years. Therefore appropriate generating of the studies hypothesis, sample size calculations and study management apart from project funding as well as rapid information of the respective scientific community are of crucial importance. The lack of clinical evidence from Cochrane analyses in neonatology and other fields from pediatrics underlines this statement [12,13].

Rapid information on clinical trials

Rapid information of the respective scientific community by internationally recognized journals as well as a platform for discussions of scientific societies and working groups will help to improve the conditions for clinical research. An excellent journal for all medical disciplines fulfilling all these conditions in Germany is the Deutsche Ärzteblatt-International. However, the publication space is limited. In pediatrics several journals are existing focusing on different pediatric disciplines and different issues such as clinical practice, clinical research, or translational research in pediatrics [5].

Rapid transfer of information on new diagnostic and clinical treatment, however, may be among others limited by a long duration of the review process. Therefore Klinische Pädiatrie continuously works on improvement of the review time. The median duration from receiving a manuscript to the definitive decision improved from 61 days in 2009 to 51 days in 2012. In addition, reports on forthcoming studies seem to be an adequate instrument to inform the scientific and clinical community on new developments [17,19].

Funding resources of clinical research in pediatrics

In 2007 the Pediatric Regulations for clinical trials (Regulation (EC) No 1901/2006; http://ec.europa.eu/health/files/eudralex/vol-/reg_2006_1901/reg_2006_1901_en.pdf) were enforced in the EU. In the most recent five year report the EMA (European Medicines Agency) states on its homepage that "13 new medicines as well as 30 new indications and 9 new pharmaceutical forms of existing medicines were authorised for use in children. These authorisations were made on the basis of pediatric investigation plans (PIPs) …". By the end of 2011 29 PIP were completed and "patent offices in 16 member states granted a 6 months patent extension to 11 medicines." (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp&mid=WC0b01ac0580025b8b). Thus the new EU regulations are supporting clinical trials in children sponsored by industry and have led to an increasing access of children to new drugs. But the number of new drugs, especially for targeted therapy in oncology will increase in future [8]. Thus, a continuous and increasing effort of industry and government is needed to provide adequate numbers of clinical phase I/II trial in children that will guarantee access of these patients to new drug developments.

Excellent and innovative therapeutic and diagnostic trials are supported in Germany mainly by the Deutsche Forschungsgemeinschaft, Bundesministerium für Forschung und Bildung (BMBF) and in multinational settings also by the EU. In pediatric oncology the main supporters of clinical trials and registries in pediatric oncology are the Deutsche Kinderkrebshilfe as part of the Deutsche Krebshilfe (DKH) and the Deutsche Kinderkrebsstiftung (DKKS). Information coming from clinical trials and registries are the scientific basis for treatment and diagnostic guidelines [10,16] which could support evidence based medicine in pediatrics. In future comparisons of treatment and diagnostic guidelines in pediatrics from different countries could help physicians to inform patients about diagnostic and treatment alternatives.

On its homepage the Bundesminsterium für Bildung und Forschung (BMBF; www.bmbf.de/de/1109.php) states that today about 7000–8000 rare diseases might exist and that in Germany about 3 million people present with a rare disease. Since 2003 the BMBF supports more than 25 disease-specific networks of basic science, clinical research and supportive care for patients with rare diseases with more than 40 000 000€. Increased cooperation between basic science, translational research and clinical research as well as international networking have made major contributions to the understanding of these diseases and improvements of treatment for the respective patients. For example from 2009 on a registry for patients with primary immunodeficiencies has been supported by a BMBF grant [4]. Since then 1 368 patients have been registered, of which 1 232 were alive. Other

successful examples on an international level for increasing research in a rare disease are patients with interstitial pulmonary fibrosis. While between 1989–1999 only 114 patients with interstitial pulmonary fibrosis were enrolled in 4 studies more than 3000 patients have been enrolled in 11 trials in the decade from 2000–2010 [9]. Most of these networks benefit from translation of experimental research into health service research and thus to develop of new treatment options for patients with life-threatening or chronic diseases. Reviews of translational research in pediatrics like the contribution of different apoptotic pathways in the rhabdomyosarcomagenesis, tumor progression and treatment resistance open up new perspectives for drug development [3].

Off lable use in pediatrics

Despite these encouraging developments, still many drugs used in pediatrics are not licensed for this age. A recent report from France showed that on pediatric wards 16–62% of used drugs were either off label or unlicensed [15]. In another report it was shown that up to 93% of neonates have received at least one unlicensed or off-label drug during their stay on an NICU [1]. Since many of these drugs have been used for several years and are well investigated in adults, clinical research on drug efficacy and side effects in children, especially in neonates will neither be supported by the pharmaceutical industry nor by the above mentioned programs aiming at innovative clinical and translational research. On the other hand the Good Clinical Practice (GCP) guidelines make it nearly impossible to perform low budget studies to answer questions on these issues representing a true dilemma.

Within the last decade, however, several disease specific registries like for patients with chronic inflammatory bowel disease (CIBD) have been successfully established in various countries [2,11]. For example, the US network for CIBD registered more than 2500 patients since 2009. In Germany a similar register is supported by the Deutsche Morbus Crohn/Colitis ulcerosa Vereinigung e.V. For children with rheumatoid arthritis a register supported by the Kinder-Rheumastiftung has built up a platform to increase knowledge about course of the different rheumatoid diseases in children during long-term follow-up. Based on these experiences even some pharmaceutical companies support observational registries regarding certain treatments elements like the **Ju**venile Arthritis – **M**ethotrexate/**B**iologics long-term **O**bservation Registry which receives an unrestricted grant from Pfizer. By now more than 700 young people mostly treated with etanercept have been registered and followed for more than 5 years [14]. In addition, data from such comparable form neonatal networks in Germany e.g. German Neonatal Network (GNN) were used for improving diagnosis and treatment in neonatal intensive care [7,18].

Strategic considerations

However, still there are many unanswered questions in the fields of pediatric health services research. Thus, more registries and diagnostic studies are necessary which can successfully work with a budget far lower than required by clinical trials to fulfill the strict regulations of drug laws. The multicenter German Pediatric Surveillance Unit (ESPED) sends monthly questionnaires about rare diseases to all pediatric hospitals in Germany. Thereby data of patients with about 100 different rare diseases were recorded so far, resulting in more than 100 publications, with about 10% in high ranking international journals with an IF>10 [6]; even more important the results of these registries have supported the foundation of parents organizations e.g. for hypophosphatemia and they have led to governmental regulations such as prohibition of lamp oil after 5 toxic pneumonias with lethal outcome caused by accidental ingestion have been reported to ESPED. Low budget financing for ESPED registries were provided by research funds of participating University as well as private parent organizations. An increasing fundraising by private foundations could provide financial resources to establish more registries. The scientific societies and the Coordination Centers for Clinical Studies which have been established at several medical faculties with support of the BMBF could help to ensure appropriate spending of the donations.

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