

Advancing paediatric practice through clinical studies

Professor Axel Franz along with Professors Dirk Bassler and Joachim Riethmueller and Dr Corinna Engel discuss their collective involvement with an organisation that conducts clinical studies in children and is engaged in the assessment of clinical trial methodology and establishment of standards for clinical research



What are your responsibilities at the Center for Pediatric Clinical Studies (CPCS)?

Professor Dirk Bassler is the Head of the CPCS. His expertise and ongoing research into factors impacting on clinical trial results ensures state-of-the-art trial methodology, whilst Professor Axel Franz oversees study planning (study design), regulatory affairs, ethical issues and good clinical practice. The regulatory work associated with the conduct of clinical trials has become increasingly complex, and even experienced scientists encounter difficulties. Franz bridges the gap between researchers and the regulatory authorities or ethics committees by combining his knowledge as a clinician-scientist with that of a senior clinical trial specialist.

Dr Corinna Engel is Head of Data Management and Biometry. Her work ensures the highest possible data quality and soundness of results and she is consequently heavily involved in study planning. Her department provides study databases in compliance with good clinical practice, which are suitable for remote data entry. Finally, Professor Joachim Riethmueller is responsible for trial conduct. He supervises the clinical monitors, research associates and study nurses in all paediatric departments, and ensures study protocols are carried out meticulously.

Each of us relies on very experienced and highly motivated research associates, monitors, data managers and secretarial staff. As a group, we are proud not only to conduct clinical trials in children but also to be involved in various educational activities such as teaching paediatricians in clinical research and the conduct of paediatric clinical trials.

Why is education an important aspect of the Center's work?

The CPCS is responsible for training paediatricians and scientists to be able to perform clinical research in the paediatric population and overcome child-specific challenges and the ever-increasing regulatory workload. It is our experience that even large and well respected contract research organisations are not familiar with the specific problems associated with clinical studies in children, especially concerning neonates.

How do the activities of the Center fit into the wider mission of the University Children's Hospital Tuebingen?

The University Children's Hospital Tuebingen is dedicated to providing the best possible care for children. The CPCS's contributions aim to increase the availability of adequately studied therapeutic interventions, hence improving the evidence-base for clinical decision making in paediatric care.

Does the Center partner with other institutions, either national or international?

The CPCS cooperates with national and European funding agencies, including the EC, German Research Foundation (DFG) and Federal Ministry of Education and Research (BMBF) as well as parent organisations and private foundations for investigator initiated trials. The CPCS also has an active role in trials sponsored by the pharmaceutical industry, acting as a contract research organisation. Finally,

the CPCS team collaborated with the pharmaceutical industry and the Paediatric Committee at the European Medicines Agency to bring together and optimise a Paediatric Investigation Plan in compliance with the Paediatric Regulation (EC) No 1901/2006.

Your background is in paediatrics. Why is this important to the work of the Center?

In recent years it has become obvious that during pregnancy, infancy and childhood, the ground is set for future health and disease. Despite its importance, health research in children has been neglected in the past; acute diseases are rare and children with them have been considered too vulnerable to research. Consequently, drugs have not been appropriately tested for children; as they do not react in the same way as adults, the drugs available and the dosing regimen extrapolated from adult data according to weight are not best-suited. During neonatal and paediatric intensive care, for example, up to 80 per cent of the drugs we use are not authorised for this age group. The lack of appropriate data



and the inappropriate extrapolation of adult data to children results in over/under-dosing, incorrect dose intervals and unnecessary or unexpected – and often unrecognised – side effects. Essentially, the same is true for non-pharmacological treatments.

What are the challenges in designing medicine and care programmes suited to children?

During childhood, the body undergoes developmental changes that impact upon the distribution, metabolism and excretion of drugs, consequently, the body will react differently on apparently similar doses of the drug in different paediatric populations. Extrapolating dosage recommendations for adults are not suitable, and even within the paediatric population extrapolations based on weight may not be applicable. At the same time, children need age-appropriate formulations, which are often unavailable or at least inadequately tested. Finally, information and consent (or assent) by children to therapies and to participation in clinical studies is complex and requires paediatric expertise which is frequently not available in the adult clinical trial setting.

A unique paediatric clinical study centre

The Center for Pediatric Clinical Studies at the University Children's Hospital of Tuebingen, Germany conducts clinical studies, both interventional and observational, which aim to provide better and safer medicines and therapies for children

EVIDENCE-BASED PAEDIATRIC CARE is hindered by insufficient knowledge on efficacy, effectiveness and safety of commonly prescribed medications and therapeutic interventions. For example, it is inappropriate to merely scale-down adult dosages according to size and weight because a child's tolerance to medication is not directly proportional to his/her growth but rather dependent upon organ development and function. Paediatric medical care is far from optimal because the majority of medicines prescribed for children have not been appropriately studied and approved for paediatric use. There is also a need for empirical research data on child health and disease, especially because many medical conditions in children fulfil criteria of 'rare' diseases. But it is particularly difficult to conduct effective clinical research on children because they are vulnerable, small, frequently in a critical condition and cannot give consent to participate in a study themselves.

The Center for Pediatric Clinical Studies (CPCS) seeks to improve paediatric research methods and practice by promoting clinical studies of high methodological quality. It is a branch of the University Children's Hospital Tuebingen, but the work and expertise of its members are not confined to the institute as they actively promote the sharing of knowledge and resources on an international scale. Its projects are aimed at improving the design, management, execution and evaluation of paediatric clinical studies, and in doing so, the Center considers all paediatric fields and age groups.

DEPARTMENTAL STRUCTURE

The CPCS is comprised of 10 regular staff, and many visiting practitioners and academics. The Centre is split into four different departments: study methodology, planning and regulatory affairs, implementation and biometry, each overseen by a separate member of staff. Professor Dirk Bassler is Director of the Study Methodology Department, which provides methodological expertise, empirical-clinical-epidemiological research and study designs for clinical research questions and problems, while Professor Joachim Riethmueller is the Deputy Director and supervises the

Implementation Department for study execution, pharmacovigilance and monitoring. Dr Corinna Engel is in charge of Biometry and Data Management. Her department is involved in protocol design and result publication, the establishment and management of databases and preparation of biometric interim and final reports. Lastly, the Planning Department is run by Professor Axel Franz, who is responsible for the development of study designs and protocols according to good clinical practice and in compliance with both Pharmaceutical Act and Medicinal Product Act regulations in cooperation with the ethics committee and the regulatory authorities.

A UNIQUE INSTITUTION

The CPCS is unique, being a university-based trial unit, specialised in paediatric clinical studies and certified for having established a strong quality management system in compliance with ISO9001-2008. To meet requirements for drug development trials, the CPCS is regularly audited and hence can conduct trials aiming for marketing authorisation. The CPCS team also successfully elaborated, submitted and defended a Paediatric Investigation Plan to the Paediatric Committee at the European Medicines Agency in compliance with the Paediatric Regulation (EC) No 1901/2006.

CURRENT PROJECTS

Since its establishment in 2008, the Centre has led and conducted numerous investigator-initiated and industry-funded studies to develop its reputation as a leader in paediatrics. Two of the most successful research endeavours to date are the ongoing Effects of Transfusion Thresholds on Neurocognitive Outcome of infants with very low birth weights (ETTNO) study and the Neonatal European Study of Inhaled Steroids (NEuroSIS).

ETTNO is an intervention project that is coordinated by Franz and funded by the German Research Foundation (DFG). Its aim is 'to



INTELLIGENCE

CENTER FOR PEDIATRIC CLINICAL STUDIES

OBJECTIVES

To promote clinical studies of high methodological quality in children so that in the future more medicines, medicinal products and therapeutic interventions will be appropriately studied and consequently approved for use in children.

KEY COLLABORATORS

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FUNDING

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compare the effect of restrictive versus liberal red blood cell transfusion thresholds on long-term neurodevelopmental outcome in extremely low birth weight infants'. The study assesses premature infants with a birth weight of 400-999 g, taking into consideration mental and physical development scores from the Bayley Scales of Infant Development – a kit for identifying children who have cognitive or motor delays – as component of the primary outcome measure. ETTNO is in the process of evaluating 920 premature infants; to compare short- and long-term clinical outcomes, half will be assigned restrictive transfusion thresholds and half will have liberal transfusion thresholds (triggers) administered. The implementation of transfusion guidelines is only applied during the first 2.5-4 months, while the patients are still hospitalised. There is a planned single neurodevelopmental follow-up examination 24 months after the initial intervention from at least 780 cases and the data collection aims to be completed by the end of 2016.

NEuroSIS, meanwhile, is a study funded by the EU, under the Seventh Framework Programme (FP7), into the evaluation of premature infants who have been born prior to a 28-week gestation period. It is attempting to determine whether the early inhalation of budesonide (an anti-inflammatory agent) reduces the risk of mortality and bronchopulmonary dysplasia (BPD), a chronic lung disease exclusive to premature babies. It is a clinical trial which proposes to test a total of 850 infants born between 23 and 27 weeks postmenstrual age (PMA). Infants will be randomised into two groups within the first 12 hours of life, with one group receiving budesonide and, the other given a placebo. The neurodevelopmental outcomes of the patients will be assessed between the ages of 18-22 months. The results of NEuroSIS will provide useful indications about the effectiveness and safety of inhaled steroids in preterm infants. Information from this study will inform views on pulmonary drug distribution as well as the pharmacodynamics of budesonide in the patient population.

Concerning older children, the CPCS currently conducts several phase I to phase III studies in patients with cystic fibrosis, both with public grants and industry sponsors, and another project accompanied by the CPCS evaluates a homeopathic medication in children with recurrent acute otitis media (middle ear infection).

COLLABORATIVE WORK

The CPCS has also contributed substantially to the global Standard for Research (StaR) Child Health Initiative, funded by the World Health Organization (WHO), to help improve the quality of paediatric clinical research by promoting the use of modern, evidence-based standards. Each consists of a set of guidelines that have been approved by an international team and are established through either empirical data or a consensus of experts if research is lacking. This approach is used to construct a summary of current practice and a subsequent list of recommendations for the process of design, conduct and reporting of research with children. A research agenda is also created from the identification of gaps in evidence.

The CPCS was heavily involved in the article 'Standard 4: Determining adequate sample sizes', which identified problems with existing measures used to determine appropriate sample sizes in paediatric research. When it comes to collecting data for dosages and effective treatments in paediatrics, size is ethically difficult to determine; too small and it could lead to inaccurate findings, too large and it would expose more children than necessary to an inferior treatment. The article concluded that a combination of techniques could be used to determine appropriate sample sizes and supplement new data, thereby reducing the exposure of trial participants to needless harm. These techniques included crossover studies, repeated measures, the use of effect sizes and sequential designs. The review also proposed a further research agenda to highlight potential areas which, when developed, would contribute towards better paediatric research practice.

LONG-TERM AMBITIONS

By refining paediatrics and increasing knowledge surrounding child health, the CPCS will continue to improve methodological quality to increase the number of drugs and therapeutic interventions that are approved for use on children based on high-quality clinical studies. Additionally, its remit stretches to the wider scientific community by contributing to efforts 'to Overcome failure to Publish nEgative FINDings' (OPEN) – a systematic assessment of distorting evidence in scientific work due to publication bias. The results of OPEN will provide recommendations for implementing effective measures to avoid repeat cases of misrepresented findings.

