Commentary

Challenges for Academic Investigator–Initiated Pediatric Trials for Rare Diseases

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ABSTRACT

Background: Clinical trials require great effort, time, expertise, and money. For clinicians at university hospitals with their full work load of teaching and medical care, the planning of an investigator-initiated clinical trial seems almost unthinkable. Despite their expertise in distinct diseases, university clinicians lack the time necessary to organize the funding and to initiate and conduct Phase III clinical trials in adults or in children.

Objective: We sought to determine whether the difficulties faced by a clinician conducting a pediatric clinical trial can be overcome by passionate motivation and external support.

Methods: Critical aspects of the application process of the world's first clinical trial in children with the rare hereditary kidney disease Alport syndrome treated with an angiotensin-converting enzyme inhibitor (Early Prospective Therapy Trial to Delay Renal Failure in Children With Alport Syndrome [EARLY PRO-TECT Alport]; http://www.clinicaltrials.gov NCT01485978; EudraCT 2010-024300-10) are described.

Results: The following crucial factors enabled the investigator to complete this trial: (1) support through clinical trial, biometrician, and regulatory experts (Institute for Applied Research and Clinical Studies [IFS], Göttingen, Germany); (2) advice from the university's ethics committee (University Medicine Göttingen, Göttingen, Germany); (3) public funding (€1 million from the German Federal Ministry of Education and Research); (4) support from the respective medical society, aiming at the resolution of an important clinical problem (German Society of Pediatric Nephrology); and (5) support from the investigator's university as the official sponsor of the trial, providing long-term commitment and covering financial risks (University Medical Center Göttingen, Göttingen, Germany).

Conclusions: The study could pave the way for approval of ramipril as a drug to treat children with Alport syndrome. Even though the study might not result in label changes, the EARLY PRO-TECT Alport trial provides the basis of an educational campaign to sensitize physicians, especially pediatricians, general practitioners, and nephrologists, to pay special attention to the early detection of kidney diseases in children, which could improve medical care for all children with kidney diseases. (*Clin Ther*. 2014;36:184–190)

Key words: COL4A5, European Alport Registry, hematuria, microalbuminuria, pediatric glomerulopathy, pediatric investigation, proteinuria, ramipril, renal failure.

INTRODUCTION

Universities have definite scientific interest in conducting investigator-initiated clinical trials (IITs). However, limited financial resources and remarkable

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regulatory requirements hamper trial conduct. In addition, the long delay from application for funding to approval and to the actual start of a clinical trial takes several years. Special legal and ethical requirements apply in clinical trials that involve minors. In addition, many of the dedicated researchers at academic institutions struggle with short-term employment contracts and the pressure to publish rapidly. Engagement in long-term strategic clinical research is therefore rather counterproductive for the individual clinician because results remain unpublishable for many years.

CHILDREN ARE NOT SMALL ADULTS

"Children are not small adults" is a doctrine in the field of pediatrics. This means, among other things, that the doses of adult medications cannot simply be downscaled to fit children because body composition and maturity of the organs in minors differ quantitatively and qualitatively from adults.[1] Yet, pediatricians are often required to use adult medications despite the lack of child-specific efficacy and tolerability data. Worldwide, only approximately 50% of the drugs used in a pediatric general ward have been tested and approved for the respective pediatric indication.[2] This off-label drug use not only poses a medical risk for the child but also creates a liability risk for the physician and an unpleasant feeling of uncertainty. Physicians are obliged to treat minors with "special and reasonable care," while at the same time they worry about being held liable for their actions by health insurance companies and lawyers.[3–8]

WHY ARE THERE NOT MORE DRUGS FOR CHILDREN?

For several decades, because of ethical concerns, minors have not been sufficiently included in drug development, which has caused the development of pediatric medicines to lag behind. Fortunately, drug development now also focuses on children. Clinical trials of pharmaceuticals in minors are now considered imperative to ensure child-friendly therapy, even if the pediatric use promises only small profits for pharmaceutical companies.[9]

CHILDREN AS ORPHANS IN MEDICAL THERAPY

Despite the recognition of a clear need for pediatric medicines, minors can still be systematically excluded from the drug development process. Ethics committees, among others, demand that drugs be tested in adults first and only then in children of decreasing ages. In Germany, despite regulations that encourage studies in children, the number of clinical trials in children did not increase at all between 2000 and 2008[10]; children are still orphans in medical therapy.

RARE AND CHRONIC DISEASES IN CHILDREN

Large gaps exist in our knowledge of medical treatment, especially of rare and chronic diseases in children, for which the number of patients is naturally small, drug development costs are high, and subsequent drug sales profits are extremely small to nonexistent.

"CARROT AND STICK" FOR THE PHARMACEUTICAL INDUSTRY

To encourage the development of medicines for children, enactment 1901/2006 of the European Parliament and of the Council on Medicines in Children came into force in 2008.[11] The enactment obliges pharmaceutical companies to test the tolerability and efficacy of new drugs in the pediatric population to obtain drug approval or authorization amendments for still patented drugs. Furthermore, evidence on the current use of approved drugs shall be collected in minors, including data on off-label use. The following incentives are being promised to the pharmaceutical industry: (1) patent extension for 6 months; (2) patent extension for drugs used in orphan diseases from 10 to 12 years; or (3) 10 years of data protection for data collected on children. To our knowledge, these incentives apply for new medications and for new indications of already approved drugs.

STRINGENT REQUIREMENTS FOR TRIALS IN A PEDIATRIC POPULATION

Today, regulatory requirements and regulatory supervision of clinical trials in minors are stringent. For example, approval by the federal authority is needed on top of all other approvals. The Central Ethics Committee of the German Medical Association has laid down principles for the protection of persons unable to give consent in biomedical research. In addition, the World Medical Association issued Declaration of Helsinki recommendations for clinical research in minors, which are designed to ensure medical protection in research and trials. All major points of these recommendations have been