Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Review article: Current opinion | Published 25 September 2014, doi:10.4414/smw.2014.14006
Cite this as: Swiss Med Wkly. 2014;144:w14006

Research dedicated to children: SwissPedNet with its international links overcomes key barriers to proper research in paediatrics

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Summary

Conducting clinical studies in the paediatric population is complex and difficult. Paediatricians deal with a vulnerable population, which primarily needs protection and where patient numbers are always low. In addition, the pharmaceutical industry often demonstrates lack of interest due to the small and non-rewarding market. Public awareness for the need of paediatric research is likewise limited. This results in lack of funding for academic studies. In Switzerland, there is a new initiative that strives to overcome the given barriers and hurdles. SwissPedNet is still in a start-up phase, but it is now ready for all collaborations of interest and keen to work together with all stakeholders on the medical progress and improvement of paediatric clinical research with the overall goal of implementing evidence-based medicine for our children (www.swisspednet.ch).

Key words: *paediatrics; clinical research; network; multicentre studies*

Introduction

Progress in medical care is tightly linked to the translation of novel findings to the management of patients. Research in paediatrics and research dedicated to children is fundamental for progress in medicine, not at least since many diseases and chronic traits first manifest themselves during childhood.

It is particularly true in paediatrics that rare diseases, congenital or acquired, often permit exceptional insights into pathophysiological mechanisms that also apply to adult patients. In addition, physicians for adults benefit from what has been learned in the sick child. Many chronic diseases originate in early childhood, and long-term observations and longitudinal paediatric cohort studies contribute greatly to the understanding of disease evolvement. Furthermore, there is increasing evidence that early infancy is a vulnerable developmental phase when many biological systems are still developing and organs finalise their development. The "Barker Hypothesis" states that during these early phases of life many environmental factors modify and program normal and abnormal organ development, respectively. A better understanding of the processes involved in this early organ development provides unique opportunities for early disease recognition using novel biomarkers and, subsequently, early preventative and therapeutic strategies. The latter are the basics for the emerging field of personalised medicine in paediatrics.

It is also particularly true that research in paediatrics is still a neglected discipline. The barriers to proper research on e.g. child drug development include several complex factors, such as lack of a suitable infrastructure and competence for conducting paediatric clinical trials, difficulties in trial design, ethical worries and many others [1].

The challenges and demands to conducting clinical trials in children have been faced by paediatricians of the five Swiss university children's hospitals (Basel, Bern, Geneva, Lausanne, and Zurich) as well as the three other class A children's hospitals (Aarau, Lucerne and St. Gallen) in Switzerland: Together they have joined their efforts and created SwissPedNet, the Swiss research network of clinical paediatric hubs in 2012. The SwissPedNet collaborates with existing paediatric research groups such as the Swiss Paediatric Oncology Group (SPOG) and the Swiss Neonatal Network & Follow-up Group (Swiss Neonet).

The emergence of paediatric research networks and their (non) funding

Paediatric research networks are emerging all over the world. The German Paediatric Network (PAED-Net) was established in 2002 with a public grant from the German Ministry of Education and Research. Six university medical centres, staffed with one MD and one study nurse each, and a coordination office built the core of PAED-Net, collaboration with other university hospitals, non-academic hospitals and private physicians ensured patient recruitment in clinical trials [2]. Securing funding for the paediatric network by the state in England has proven highly

successful, as it has allowed numerous important clinical research projects beneficial for children to be started. Moreover, securing funding has guaranteed continuation of these research projects at a high quality level. This in turn has made England an attractive partner for paediatric clinical research.

Subsequently, when the Paediatric Regulation came into force in 2007, many European networks emerged. MCRN, Medicine for Children Research Networks, perform very successfully in the UK and the Netherlands. The National Institute for Health Research NIHR MCRN is funded by the Department of Health and works in partnership with the NIHR Clinical Research Network (NIHR CRN) to improve the UK's clinical research environment and maximize the development of safe and effective medicines and formulations for children [3].

Funding or respectively non-funding remains a major issue for the endeavours of paediatric research networks. At the 5th Enpr-EMA workshop in June 2013 it was proposed that Enpr-EMA should elaborate a "business model case" for core funding, to provide estimate on overall costs, staff resources, etc. This would help networks as a basis for negotiations with potential funding sources [4].

Limited commercial interest and collaboration with pharmaceutical industry

From the perspective of paediatricians, there is a large gap in the availability of thoroughly studied and licensed diagnostic or therapeutic means for children as compared to adults. Results from studies in adults can rarely and, if at all, only barely be transposed to neonates, toddlers, children or adolescents because of the remarkable biological differences. With the adoption of the European Paediatric Regulation in January 2007, involvement of commercial interests is mandatory and has lead to the obligation to provide paediatric investigational plans (PIP) for all new drugs. Nevertheless, five years after adoption of the paediatric regulation no increase of paediatric trials in EU countries could be observed [5].

During its first six years in operation, FINPEDMED, the Finnish Investigators Network for Paediatric Medicines, received 91 trial requests, 18 trials were started, and in 24 cases, sponsors did not select Finnish investigators. This experience from Finland highlights the need for Nordic collaboration to increase expertise, recruitment base and attractiveness for sponsors [6].

It is not realistic for a paediatric research network to become self-supporting by conducting commercial paediatric studies.

Lack of suitable infrastructure and competence for conducting paediatric clinical trials

The initiators of SwissPedNet are convinced that paediatric clinical research needs a national platform to be successful and internationally competitive. The paediatric population ranging from premature babies to adolescents can neither be treated nor investigated within the adult medicine settings, which lack specialized personnel and infrastructure. Moreover, it is globally recognised that the paediatric population is a population with special legal and ethical needs. Indeed, the *Paediatric Regulation* came into force in the European Union in 2007. There is a specific ICH Guideline for clinical investigation of medicinal products in the paediatric population, and within national law, Art. 21 to 24 of the Swiss law on human research demand special requirements for research in children and adolescents. The fulfilment of these requirements has not yet been established in Switzerland. Thus, to comply with above regulations, a paediatric-specific platform matching the research efforts in adult medicine is important.

In view of the many methodological challenges and technical requirements associated with modern clinical trials, these are best and most efficiently conducted within the framework of clinical trial units (CTUs). In 2007, the Swiss National Science Foundation (SNSF) funded the establishment of six academic clinical trial units (CTUs) in Switzerland. As of May 2011, the six CTUs are operational at the University Hospitals of Basel, Bern, Geneva, Lausanne, Zurich and the Kantonsspital St. Gallen. Academic clinical research in Switzerland is profiting significantly from this infrastructure. While these CTUs advise and support paediatric clinical trials, none of them is particularly specialised in conducting clinical trials in children. They do, of course, provide knowledge and support to the best of their ability, especially in respect to design, quality, and statistics and data management. Nevertheless, being academic clinical research organisations, none of the CTUs has dedicated facilities suitable for children from the neonate to the adolescent, nor are they staffed with the paediatricians or paediatric nurses able to address these special needs.

International collaboration of SwissPedNet

SwissPedNet is tightly linked via Enpr-EMA, the European Network of Paediatric Research at the European Medicines Agency, to internationally share high quality medical expertise and robust data from Switzerland.

SwissPedNet is member of Enpr-EMA. This is a network of research networks and experts and, amongst other activities, Enpr-EMA facilitates the pharmaceutical industry's access to paediatric clinical study centres and experts. They also include their members in consultations of new guidelines and lists of development programs for drugs used in children [7].

Known hurdles in paediatric research are peculiarities in development of scientific protocols for small sample sizes and the difficulties in recruitment. For the paediatric specific standards, SwissPedNet actively searched and agreed on a collaboration with a second international body: StaR Child Health. StaR Child Health is an initiative that seeks to improve the quality of design, conduct, and reporting of clinical research by promoting the use of modern research standards [8].

Conclusion

Networks are essential to cope with the challenges in paediatric research. SwissPedNet fills the gap within Switzerland and has already established international collaborations as the paediatric population with their rare diseases is small. Proper research infrastructure within the children's hospitals is crucial for competitive and reliable study conduct in and with children. Collaboration with industry can still be improved. In Switzerland, the initiators of SwissPedNet set the course for the future nationally and internationally.

Funding / potential competing interests: P.W. is funded by the Swiss National Science Foundation.

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