



Clinical Research in Paediatrics

EDITORIAL



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There are currently 5000 rare or serious diseases known to affect children. However, 80% of the medications used in paediatric cases are not licensed for use in children.

Limited basic information

This may be related to a lack of data on paediatric treatment with these medications. With fewer clinical trials conducted in children than adults, physicians are left with little choice but to prescribe treatments off-label. Also, as the paediatric market is small, it is not financially rewarding for pharmaceutical companies. This limits the information physicians / paediatricians have available when deciding on a treatment and dosage in a paediatric case. Very often they have to rely on their own prescribing experience, case reports and information the hospital has on file.

Problematic off-label medications

Significant problems arise through off-label use. It not only presents safety and efficacy concerns for the prescribing physician and family, but also legal and financial issues. The financial concerns are demonstrated by the fact that if a medication is prescribed off-label, Swiss health insurance companies are not obliged to reimburse the cost of the medicine. The Federal Supreme Court ruled this to be the case with two exceptions: firstly, if the medication is prescribed as part of a therapeutic complex; and secondly, in life-threatening cases if no other treatment method is available. Additionally, in a clinical trial scenario, a hospital / research site would normally be covered by third party insurance, whereas in off-label cases this cover may not be available. Therefore, more paediatric trials are required to assess the safety and efficacy of possible treatments.

Challenges of paediatric trials

The implementation of a paediatric trial presents various challenges, such as the recruitment of patients and the obtaining of informed consent. Parents are naturally concerned for their child's wellbeing and are reluctant to enrol them for a product of which little is known of the use in children. Disease prevalence in a paediatric population is also different to the adult population.

Relatively common diseases in adults such as cancer and heart disease are comparatively rare in children. On top of this, the number of patients potentially eligible is fewer for paediatric trials than for trials with adults. Only 15% of the Swiss population are under the age of 15. Additionally, as there has been relatively little activity in the field of paediatric trials, there are few sites / hospitals with experience in the area.

Children are not small grown-ups

Even prior to running paediatric trials, obstacles that are not present in adult trials arise. It is important to remember the fact that 'children are not small adults' and as such, a weight-based reduction in dosage compared to the adult dose cannot be applied. The paediatric studies can range from a newborn to a 17 year-old depending on protocols. As such, the fact that a paediatric population may not be a homogenous group must not be overlooked. Obviously, this presents obstacles when planning dosages for the trial as the absorption, distribution, metabolism and excretion rates will vary significantly throughout development.

Importance of paediatric trials

There is more than the safety and efficacy of new or existing drugs to consider. Paediatric research is important for the advancement of knowledge in many areas. The majority of chronic diseases have their early origin in childhood, so in order to better understand and prevent the disease process, research in this early age group is mandatory. Genetics is one such area: research into genetics demonstrates links between early age illness and chronic morbidity in adult life. Developmental research, psychiatric research, the effects of abuse and the pre- and post-natal environment are all areas in which paediatric research is needed.

Promising developments

Recently, there have been a number of developments to facilitate clinical trials in paediatric patients, which will hopefully allow for greater data availability.

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1 Regulatory

Over the past few years guidance and regulations have been introduced to govern research in the paediatric field. These refer particularly to the development of new drugs and the gaining of paediatric indications for existing drugs. They also offer incentives to companies who engage in paediatric research irrespective of outcome.

Swiss Guidelines and Regulations

- SR 812.21 Swiss Law on Therapeutic Products ([LTP/HMG](#))
- SR 812.214.2 Ordinance on clinical trials with therapeutic products ([OClin/VKlin](#))

Swissmedic adopted the ICH Guideline E11 and the Paediatric Regulation (links below), they are, however, not yet legally binding.

EMA Guidance Documents

EMA provides comprehensive information and links on their websites [Medicines for Children](#) and [Paediatric Medicine Development](#), e.g.

- The EMA Paediatric Regulation, comprising:
 - [Regulation \(EC\) No 1901/2006](#) of the European Parliament and of the Council of December 2006 on medicinal products for paediatric use
 - [Regulation \(EC\) No 1902/2006](#), an amending regulation in which changes to the original text were introduced relating to decision procedures for the European Commission
- The Paediatric Investigational Plan ([PIP](#)), required to be submitted for all new drugs since 26 July 2008
- Paediatric-use marketing authorisation ([PUMA](#)) that can be issued for a product developed specifically use in children

The [Committee for Medicinal Products for Human Use \(CHMP\)](#) draws up scientific guidelines aimed at helping applicants prepare marketing-authorisation applications for medicinal products for human use. A summary of scientific guidelines, reflection papers and concept papers relevant to the development of medicines for children is available under [Paediatric Scientific Guidelines](#), including:

- [ICH Topic E 11: Clinical Investigation of Medicinal Products in the Paediatric Population](#)
- [Guideline on Conduct of Pharmacovigilance for medicines used by the paediatric population](#)
- [Ethical Considerations for clinical trials on medicinal products conducted with the paediatric population](#)

Additional Information and Links

- The [Better Medicines for Children](#) booklet summarises the policies and processes of the Paediatric Regulation
- [EMA scientific advice](#) is free for paediatric drug development questions
- European Union Drug Regulating Authorities Clinical Trials (EudraCT) database will publish the results of paediatric clinical trials performed both inside and outside the EU
- SwissEthics [checklist](#) for paediatric clinical research
- Swissmedic Website provides an overview of information on [Paediatrics](#) (German), e.g. [Anpassung der NAS-Anleitung - Hinweis auf pädiatrische Daten](#) and [Faktenblatt Kinder und Arzneimittel: Situation heute](#)
- Federal Office of Public Health ([FOPH](#)), links to relevant guidelines and presentations

2 Networks

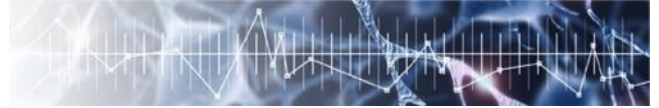
As the pool of potential participants in a paediatric trial is generally low, networks are valuable in order to share information and experience, to coordinate studies and to assist in recruitment for trials. Below are a series of links to national and international networks.

European Paediatric Networks

- European Network of Paediatric Research at the European Medicines Agency ([Enpr-EMA](#)). Promotes data exchange between national networks, hospitals and trial centres. Over 28 [networks](#) (all listed on webpage) currently work under the umbrella of Enpr-EMA

National Paediatric Networks

- Switzerland: Swiss PedNet. The Swiss Clinical Trial Organisation SCTO assists in setting up a Swiss Paediatric Network involving all leading hospitals with a paediatric department and SPOG



FACTS and INFORMATION

- Germany: **PAED-Net**
- UK: The Medicines for Children Research Network (**UK MRCN**)
- France: Réseau d'Investigation Pédiatrique des Produits de Santé (**RIPPS**)
- The Netherlands: The Medicines for Children Research Network (**NL MCRN**)
- Finland: The Finnish Investigators Network for Paediatric Medicines (**FINPEDMED**)
- Belgium: The Belgium Paediatric Drug Network (**BPDN**)

Disease-Specific Networks

- Rheumatology: The Paediatric Rheumatology International Trials Organisation (**PRINTO**)
- HIV: The Paediatric European Network for Treatments of AIDS (**PENTA**)
- Oncology: International Society of Paediatric Oncology (**SIOP**)
- Cystic Fibrosis: European Cystic Fibrosis Society (**ECFS**)
- Swiss Paediatric Oncology Group (**SPOG**): Network of clinics, cantonal hospitals and all five university hospitals, it is internationally linked and collects, analyses and shares information on treatment and illnesses
- Swiss Childhood Cancer Registry (**SCCR**): Collects information on paediatric oncology in Switzerland and shares it between cantonal cancer registries

**3 Authorities
Agencies
Committees
Organisations**

Helpful advice and guidance for paediatric clinical research and funding thereof can be found at:

- The European Commission **Cordis**
- WHO - **Medicines for Children**
- NDA - **Regulatory Consulting**
- The Drug Information Association (**DIA**)
- The Food & Drugs Administration (FDA) - **Pediatrics**
- The Clinical Trials Facilitation Group (**CTFG**)
- Priority Medicines For Children (**Priomedchild**)