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*EDITORIAL*

# Clinical pharmacological studies in children: From exploratory towards confirmation driven methodology

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## Abstract

Just like children are not small adults, pediatric studies are not just subgroup-adult studies. Clinical pharmacology aims to predict these effects based on drug, population and/or patient-specific pharmacokinetics (concentration-time profiles) and -dynamics (concentration-effect profile). The most essential characteristics of childhood are growth and maturation. Both phenomena are most prominent during infancy making the claim that "an infant is not just a small child" as relevant compared to the paradigm that "a child is not just a small adult". From a clinical pharmacology perspective, the consequence of such a dynamic setting is extensive variability throughout childhood in both the pharmacokinetics and pharmacodynamics. Trial design probably has impact on recruitment to an even greater extent compared to adult studies. In general, if a study is designed well, with a clear clinical question with which parents and children can identify, they are likely to consider participation. Open communication with all stakeholders involved will most likely result in ethically correct, practically feasible, scientifically sound, and economical reasonable studies to provide children with the appropriate treatment. From an academic perspective, feasibility, relevance, applicability and costs of clinical pharmacological studies in children can be significantly improved by new sampling concepts (e.g., saliva, urine, dried spot blood) and the systematic introduction of already known information into the trial design through model based pediatric drug development, that mainly affect feasibility of pharmacokinetic studies. In contrast, for the pharmacodynamic part of pediatric studies, development and validation of population specific biomarkers or robust outcome variables is urgently needed.



**Key words:** Infant; Child; Developmental pharmacology; Trial design; Pharmacokinetics; Pharmacodynamics

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## WHY PEDIATRIC STUDIES ARE NEEDED

By virtue of their developmental and cognitive abilities, children are a vulnerable population, depending on adults for protection. This is also true when participation in a clinical trial is considered. In addition to adaptations of the clinical protocol design (e.g., drug formulation, dosing, sampling strategy, and clinical indication), recruitment and retention strategies, incentives and the process to obtain informed consent must be modified. The current limited experience with pediatric recruitment is the result of a historical swing. In the 18th and 19th century,

children were often viewed as "property" of their parents or legal representatives, and frequently recruited for research, with subsequent protection since the mid 20th century, formalized in e.g., the Helsinki declaration. Unfortunately, protecting children, got translated to excluding these populations from clinical trials, resulting in "therapeutic orphans"[1,2]. The danger of extrapolation of findings collected in adults to children has been recognized and some of the anecdotal errors (chloramphenicol in neonates, formulation errors, human immune deficiency virus related drugs in children, inappropriate questionnaires) are well known to the pediatric community. Differences in physiological responses to disease, in disease characteristics, in treatment modalities and in drug disposition necessitate collection of age-specific observations at various stages of pediatric maturation[1-3]. At present, unlicensed or off-label administration of drugs is frequent and in part depends on disease severity. Ironically, unlicensed or off-label administration is most frequent (60%-80%) the most critically ill patients (neonatal and pediatric intensive care), still 40%-60% in a pediatric hospital setting and 20%-40% in ambulatory care[1,2]. This is not without risk: unknown adverse events, poorly established efficacy, hazardous dose calculation and inappropriate formulation.

Since the late 90ies in the United States (Food and Drug Administration) and more recently (2006) in Europe (European Pediatric Regulation, 1901/2006) and in line with World Health Organization initiatives (Better medicines for children initiative/list of essential medicines), (legal) frameworks have been developed to re-launch clinical research on drugs in children. In the European Union (EU), this pediatric regulation governing the development and authorization of medicines of pediatric use (children and adolescents aged 0 to 17 years) has been introduced in December 2006 and entered into force in 2007. This regulation makes pediatric development an obligation in the EU for all new medicinal products unless a waiver has been granted. By making pediatric development mandatory, this regulation will lead to profound changes in pediatric (drug) development and will increase the number of studies performed in the pediatric population[3-5].

Effective implementation of such a launch necessitates collaboration of all stakeholders involved in search for a "good clinical practice" approach: i.e., ethically correct, practically feasible, scientifically sound, and economical reasonable. Open communication between the stakeholders (patients and their parents, academia, industry and government) will be crucial to achieve the common goal, i.e., to reduce off-label use of medicines in children so that their medical treatment is based on evidence and on understanding developmental physiology. From an industrial or clinical research organization point of view, this will necessitate networking and collaboration with health care professionals, initially and mainly trained for clinical care and parents/patients. For health care professionals, this necessitates readiness to develop clinical research networks and specific research skills in addition to the clinical care.

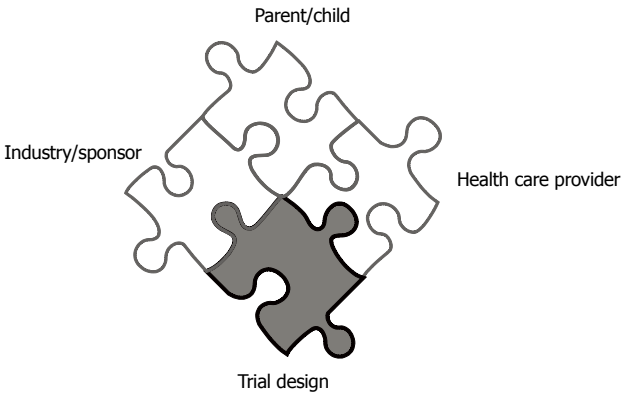


**Figure 1 Stakeholder approach in studies related to pediatric clinical pharmacology.**

## TRIAL DESIGN, A STAKEHOLDER APPROACH

Besides regulatory requirements for receiving approval and final marketing authorization, the clinical trial design of pediatric studies probably effects recruitment to a greater extent than in adult studies (Figure 1). In general, the more complex and the more invasive, the harder to recruit. To enhance recruitment, the study should aim to use patients as close to the clinical situation as possible. Potential risks and inconveniences perceived to be of relevance in children include discomfort, inconvenience, pain, fear, separation from parents and family, effects on growing and developing organs, and size or volume of biological samples[1-3]. A feasible trial design, which do not impose a burden markedly beyond routine clinical care should be aimed for. Use of placebo in children is more restricted, because children cannot consent. Placebo should not be used when it means withholding effective treatment[2,5]. As the level of evidence in favour of an effective treatment increases, the ethical justification for placebo decreased. Placebo use in not equivalent to absence of treatment, but could be used on top of standard care. As many medicines used in children have not been fully assessed and authorized, medicinal products without marketing authorisation may be considered suitable as controls if they represent standard of care. The inclusion of an active control product not authorised in a clinical trial to be entered in a marketing authorisation file, should always be discussed with a scientific body of a (national) competent authority. In this editorial, we would like to focus on the contributions that can be made by academic research centers to further improve the study design, both for aspects of pharmacokinetics as well as -dynamics[6-13].

## HOW CAN ACADEMIA IMPROVE THE CLINICAL TRIAL DESIGN IN PEDIATRIC CLINICAL PHARMACOLOGY?

When a drug is prescribed, it is with the intention to attain a proportional therapeutic effect, preferably without

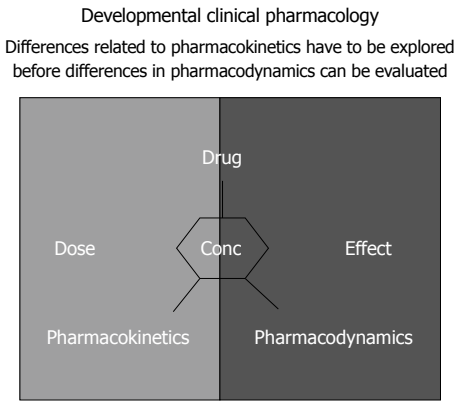


**Figure 2 Developmental pharmacology covers both developmental pharmacokinetics (concentration-time) as well as developmental pharmaco-dyn-amics (concentration-effect).**

side-effects. Clinical pharmacology aims to predict these effects based on drug, population and/or patient-specific pharmacokinetics (concentration-time profiles) and -dynamics (concentration-effect profile) (Figure 2). The most essential characteristics of childhood are growth and maturation. Both phenomena are most prominent during infancy making the claim that "an infant is not just a small child" as relevant compared to the more commonly used paradigm that "a child is not just a small adult". From a clinical pharmacology perspective, the consequence of such a dynamic setting is extensive variability throughout childhood in both the pharmacokinetics and pharmacodynamics[1].

### *Pharmacokinetics*

Differences related to pharmacokinetics have to be explored before differences in pharmacodynamics can be evaluated (Figure 2). The feasibility to perform studies in children relates in part to the introduction of adapted sampling techniques (e.g., saliva samples, dried spots blood) and more accurate quantification of metabolites in low volume samples. In addition, the burden for each individual infant can be further minimized by modeling and simulation approaches using non-linear mixed effect modeling to develop effective and safe dosing regimens since these population pharmacokinetic approaches result in the capability to analyze sparse, unbalanced datasets[7-11]. The variability can - to a certain extent - be anticipated. We would like to raise awareness in the pediatric clinical research community for the relevance of "rich data sets" that contain clinical characteristics and concentration-time (pharmacokinetics) or concentration-effect (pharmacodynamics) profiles: the description of a compound specific pattern is beyond compound specific relevance since it reflects maturational changes[7-11].

The maturational patterns described and the extent of the impact of covariates can be used to predict *in vivo* time-concentration profiles for compounds that undergo similar routes of elimination. However, following initial development, the clinical research community still fails to a certain extent to validate such models in the clinical

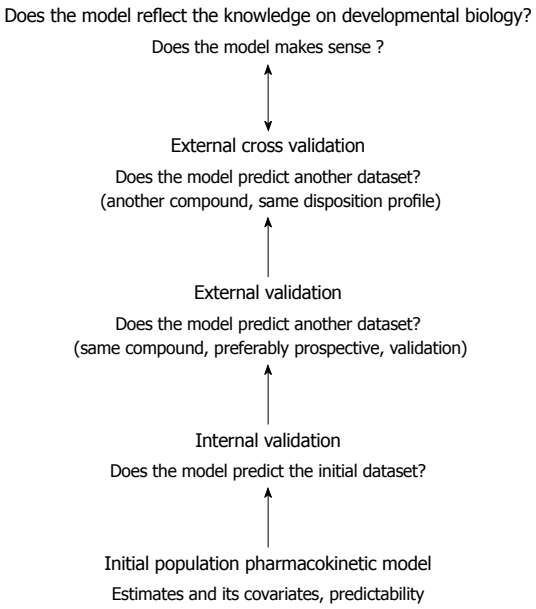


**Figure 3 Concept of stepwise integration of available pharmacokinetic knowledge into model development and validation.**

setting. Besides internal and external validation, prospective clinical trials, which allow for the evaluation of the model-based dosing regimens are needed, not only to adjust the proposed dosing regimen, but also to convince pediatricians to use the information that has been generated using these modeling exercises [7-11]. This general concept has been illustrated in Figure 3. The development and validation of analytic methods adapted for pediatric applications and the modeling and simulation concept should be further developed within the academic research groups active in the field of pediatrics.

### *Pharmacodynamics*

Improved knowledge on developmental pharmacokinetics is in the majority of drugs only a first, but essential step to describe the impact of maturation on the concentration/effect relation (Figure 2). Similar to the expansion of biomarker research in adult medicine, there is an active search for valid biomarkers to evaluate effects and side effects of interventions in children[12,13]. In essence, a biomarker is a characteristic or quantitative indicator that reflects either normal biologic processes, or pathological processes or pharmacological responses[13-16].

Since the research field of clinical pediatrics is broad, we would like to use an illustrative, anecdotal approach to make this point obvious for the readers.

**Pulmonary hypertension:** How to adapt the 6 min walking test routinely used in adults to quantify the impact of therapeutic interventions (e.g., endarterectomy, pharmacological, physiotherapy) for children, infants or even neonates[17-19]?

**Depression in children:** To quantify the severity of a depression, questionnaires are used. However, these

questionnaires (e.g., sleeping disorders, vital signs, sexual dysfunction) need validation in adolescence or childhood[20-22].

**Gastro-oesophageal reflux disease in infants:** While outcome in adults is based on subjective comfort and on findings during gastroscopy, the symptoms (crying, apnoea, milk intake) are different in infants[23-25].

**Long term neurodevelopmental outcome:** Although assessment based on Bayley scales or similar does result in quantitative results, early (first 12-18 mo) developmental assessment is only a weak (sensitivity, specificity) predictor for late neurodevelopmental outcome. This outcome is further biased by social factors and seems not to remain stable over time[26-29].

**Renal failure:** Creatinine reference values in neonates depend on birth weight, postnatal age but also on the measurement technique (either Jaffe or enzymatic quantification) applied[30-36].

**Progressive neuromuscular diseases, type Duchenne:** How to quantify the impact of a given intervention on muscular strength and to what extent is such a biomarker also of clinical relevance in children[37,38]?

**Biomarkers for patent ductus arteriosus:** How sensitive and specific are clinical symptoms, specific flow measurements by echocardiography or should we consider the N-terminal pro-brain-type natriuretic peptide measurement[15,16,39]?

### *Developmental pharmacology as a driver of clinical research in children*

Since the implementation of the pediatric regulation in the United States and the subsequent initiatives throughout the world including Europe, there is an increase in ongoing research in the field of pediatric product development[40]. The results obtained during such a pediatric product development however are beyond the compound specific observations[40-45]. Research groups are made to collaborate and to agree on assessment tools, definitions and treatment strategies, and results obtained can be extrapolated to other compounds or other subpopulation within the pediatric age range[46-50]. The advantage of such an extrapolation is that the clinical research can shift from exploratory approach to confirmation, hypothesis-driven methods[7-13]. Collaborative efforts to improve research tools on pharmacokinetics (e.g., model-based pediatric medicinal development) and -dynamics (e.g., biomarkers) likely will result not only in improved pediatric drug therapy in near future, but are also a potent drivers to learn more of the intriguing world of developmental life[7-13].

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March 7-10, 2013
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May 2-3, 2012
1st Middle East and North Africa Pediatric Orthopaedic Surgery Conference
Dubai, United Arab Emirates

May 3-4, 2012
IPHOUM 2012 - 13th International Update Meeting Paediatric, Haematology and Oncology
Edinburgh, United Kingdom

May 3-7, 2013
PAS Annual Meeting 2013
Washington, WA, United States

May 8-12, 2012
30th Annual Meeting of the European Society of Paediatric Infectious Diseases
Thessaloniki, Greece

May 11-12, 2012
Best Practices in Primary Care (Baltimore, MD)
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May 17-20, 2012
2nd Global Congress for Consensus in Pediatrics and Child Health
Moscow, Russia

May 18-20, 2012
Mini-Fellowship in Primary Pediatric Psychopharmacology
Seattle, WA, United States

May 23-26, 2012
46th Annual Meeting of the Association for European Paediatric and Congenital Cardiology
Istanbul, Turkey

May 30 - June 1, 2012
The Contribution of Epigenetics in Pediatric Environmental Health
San Francisco, CA, United States

May 31 - June 2, 2012
Adolescent Health Care
San Francisco, CA, United States

May 31 - June 2, 2012
Spanish Society of Pediatric Neurology 36th Annual Meeting 2012
Santander, Spain

June 21-23, 2012
Pediatric - Review for Primary Care
Sedona, AZ, United States

June 4-6, 2012
Australasian Conference of Child Trauma
Queensland, Australia

June 7-9, 2012
Neonatal Pharmacology
Washington, DC, United States

June 20, 2012
9th National Neuroscience Conference: Epilepsy in Children 2012
London, United Kingdom

June 30 - July 2, 2012
11th International Congress on Pediatric Pulmonology
Bangkok, Thailand

July 2-6, 2012
20th Annual Primary Care Conference
Kiawah Island, SC, United States

July 7-14, 2012
33rd World Medical and Health Games - Antalya 2012
Antalya, Turkey

July 20-21, 2012
4th International Workshop on HIV Pediatrics
Washington DC, United States

July 23-27, 2012
3rd Essentials in Primary Care CME Conference Session One Palm Coast Florida
Palm Coast, FA, United States

July 30 - August 3, 2012
Essentials in Primary Care CME Conference Session 2 Palm Coast Florida
Palm Coast, FA, United States

August 10-22, 2012
Pediatric Emergency Medicine: Review for Primary Care
Rome, Italy

August 26-31, 2012
Pediatric Cardiology 2012 Board Review Course
Dana Point, CA, United States

September 8-9, 2012
International Congress on Paediatric Airway
Chennai, India

September 11, 2012
Developmental Behavioral Pediatrics Symposium
Riyadh, Saudi Arabia

September 19-20, 2012
4th conference of the European Paediatric Formulation Initiative
Prague, Czech Republic

September 20-21, 2012
The Pediatric Emergency Medicine Resource
Las Palmas, Spain

September 20-23, 2012
ESPE 2012 - European Society for Paediatric Endocrinology Annual Meeting
Leipzig, Germany

September 24-25, 2012
Pediatric Days 2012
Chicago, United States

October 5-9, 2012
EAPS 2012 - 4th Congress of the European Academy of Paediatric Societies
Istanbul, Turkey

October 10-13, 2012
ISPAD 2012 - 38th International Society for Pediatric and Adolescent Diabetes
Istanbul, Turkey

October 11-12, 2012
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Portland, OR, United States

October 23-28, 2012
59th AACAP Annual Meeting
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October 20-23, 2012
American Academy of Pediatrics National Conference and Exhibition
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November 7, 2012
Third Pediatric Infectious Diseases Review Course
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November 10, 2012
3rd International Saudi Pediatric Neurology Conference
Riyadh, Saudi Arabia

November 14-18, 2012
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WJCP World Journal of Clinical Pediatrics

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***Acknowledgments***

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***Format***

**Journals**

*English journal article (list all authors and include the PMID where applicable)*

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

*Chinese journal article (list all authors and include the PMID where applicable)*

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

*In press*

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

*Organization as author*

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

*Both personal authors and an organization as author*

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

*No author given*

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

*Volume with supplement*

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

*Issue with no volume*

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

*No volume or issue*

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

**Books**

*Personal author(s)*

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

*Chapter in a book (list all authors)*

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

*Author(s) and editor(s)*

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

*Conference proceedings*

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

*Conference paper*

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

**Electronic journal** (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

**Patent** (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

***Statistical data***

Write as mean ± SD or mean ± SE.

***Statistical expression***

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as $\chi^2$ (in Greek), related coefficient as *r* (in italics), degree of freedom as $\upsilon$ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

***Units***

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; $CO_2$ volume fraction, 50 mL/L $CO_2$, not 5% $CO_2$; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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***Italics***

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
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