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Research Article

# Children in clinical trials: survey on the current situation in paediatric university clinics in Germany

## Kinder in klinischen Studien: Umfrage zur Situation in universitären Kinderkliniken in Deutschland

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## Abstract

Many prescribed treatments for children have not been adequately tested in children, sometimes resulting in harmful treatments being given and beneficial treatments being withheld. In the absence of specific trial-based data in children, results of studies in adults are extrapolated, which is often inappropriate because children have different range of diseases and metabolize medications differently. Trials in children are more challenging than those in adults and the pool of eligible children entering trials is often small. Children must have at last the same rights as adults in relation to receiving treatment with medicinal products that have been fully tested. The need for more studies to obtain paediatric information for medicines used in children is now a matter of consensus on a global basis and is considered a public health priority.

Therfore a survey was performed in university hospitals in Germany targeting the current and future situation of children in clinical trials. The questionnaire of this survey was sent to 68 paediatric departments in 31 university clinics in Germany with a respond rate of 27% with respect to 18 returned questionnaires.

With regard to new laws, guidelines and strong governmental support and funding an increasing number of clinical trials is expected. Surprisingly, the number of trials in the paediatric population remains unchanged within a period of 4 years (2005-2008). Added to the surveys performed within the pharmaceutical industry from Heinrich and Hark the number of trials in children remains unchanged even within a period of 9 years (2000-2008). The efforts undertaken by the government regarding funding and supporting KKS (Coordinating Centers for Clinical Trials) and affiliated PAED-Net (Pediatric Network on Medication Development and Testing in Children and Adolescents at KKS) appear to be insufficient. Beginning of this year the legal framework with the urgent expected “Paediatric Regulation” was established. May be the implementation by clinicians and pharmaceutical industry will improve the current situation.

**Keywords:** survey, paediatric trials, paediatric regulation, KKS, PAED-Net

## Zusammenfassung

Zahlreiche Medikamente wurden bisher nicht ausreichend an Kindern untersucht, dies kann zu einer gesundheitsgefährdenden Behandlung von Kindern führen bzw. es werden Kindern wichtige Medikamente vorenthalten. In Ermangelung von studienspezifischen Daten in der Pädiatrie werden Ergebnisse aus Studien mit Erwachsenen auf Kinder übertragen. Dies ist oft unsachgemäß, da z.B. Kinder gegenüber Erwachsenen unterschiedliche Erkrankungsbereiche haben sowie Medikamente unterschiedlich abbauen. Weiterhin sind Studien mit Kindern, im Vergleich zu Studien mit Erwachsenen, schwieriger durchzuführen, zumal

die Zahl an geeigneten Kindern oft sehr gering ist. Trotzdem müssen Kindern die gleichen Rechte zugestanden werden wie Erwachsenen in Bezug auf sorgfältig entwickelte Arzneimittel. Der Bedarf an klinischen Studien in der Pädiatrie ist internationaler Konsens und zu einer Priorität der Volksgesundheit geworden.
Zur Situation und Teilnahme von Kindern in klinischen Studien wurde im Frühjahr 2007 eine Befragung in universitären Kinderkliniken in Deutschland durchgeführt. Ein Fragebogen wurde an 68 Kinderkliniken in 31 Universitätskliniken gesandt, davon antworteten 18 Kliniken, dies entspricht einer Rücklaufrate von 27%.
Unter Berücksichtigung der aktuellen Gesetzgebung, EU-Richtlinien, staatlicher Unterstützung und Finanzierung, wurde eine Zunahme an klinischen Studien in der Pädiatrie erwartet. Erstaunlicherweise verändert sich die Anzahl der pädiatrischen Studien in einem Zeitraum von 4 Jahren (2005-2008) nicht. Die Ergebnisse sind vergleichbar mit denen der Befragungen von Heinrich und Hark, die 2000 und 2005 innerhalb der pharmazeutischen Industrie durchgeführt wurden. Werden die entsprechenden Befragungsperioden zusammengefaßt, bleibt die Anzahl von klinischen Studien mit Kindern über einen Zeitraum von 9 Jahren (2000-2008) unverändert.
Die staatlichen Bemühungen, Institute wie KKS und PAED-Net (in Universitätskliniken auf Studien spezialisierte Zentren) zu unterstützen und zu finanzieren scheinen nicht ausreichend zu sein. Die dringend erwartete „Paediatric Regulation“ wurde Anfang 2007 eingeführt; damit wird die Durchführung von klinischen Studien an Kindern für die meisten Arzneimittel zur Pflicht. Deren Umsetzung von Seiten der Kliniker und der pharmazeutischen Industrie sollte eine Verbesserung der Situation zur Folge haben.

# Introduction

The use of unlicensed and off label medicine in children is widespread and is still an increasing concern within the last years. In the EU 50% or more of medicines used in children have never been studied in this population [1], [2], but only in adults, not necessarily in the same indication (or the same disease). Studies have brought to light a high proportion on unlicensed and off-label use, reaching up to 72% of all prescriptions and 93% of all paediatric patients [3], [4]. Sick children have a right to treatment with medications for which the dosage, effectiveness and side effects have been systematically investigated. However, the majority of medications that are regularly given to children have not been tested and officially approved for this special age group. It is typical to transfer the results collected in adults onto children. However, due to differences in metabolism and body structure of children compared with adults [5], this practice does not ensure that children are being treated according to the current level of medical knowledge and with the minimum possible risk of side effects.
Certain diseases are characteristically childhood diseases and so meaningful research on them needs to be conducted on children. Furthermore, there are well known problems in extrapolating pharmacological data from adults to children owing to metabolic differences between children and adults. The responses of adults and children to many drugs have much in common, but children are certainly not small adults. There are particular examples which illustrate that the response can differ markedly between adults and children: Different pathophysiology (e.g. surfactant deficiency), different variant of disease (e.g. migraine, epilepsy), different pharmacodynamics (e.g. ciclosporin), different “host” response (e.g. pneumonia, leukaemia), different adverse drug reactions (e.g. thalidomide, tetracycline).
Children must have at last the same rights as adults in relation to receiving treatment with medicinal products that have been fully tested. To ensure that children are not exposed to unnecessary risks, controlled clinical trials are required to determine the most appropriate dose in children of different ages. Paediatric trials are costly in time and money, may need a new formulation, and are fraught with ethical challenges.
Given the rare occurrence of most diseases in childhood, especially in oncology, conducting clinical trials is expensive and interminable due to the limited number of patients. In addition the conduct of clinical trials in Germany has become more difficult and, at least in the preparation of a trial, also more timeconsuming since August 2004 as a consequence of the 12$^{th}$ revision of the German Drug Law (AMG) – based on the Directive 2001/20/EC [6]. Especially the preparation of an Investigational Medicinal Product Dossier (IMPD) is an additional task, which could be difficult to perform for sponsors of non commercial trials. Nothing has changed by the implementation of the Directive 2005/28/EC [7] regarding the conduct of non commercial trials and no specific regulation on EC level in this respect can be expected as still of today only a

"Draft Guidance on 'specific modalities' for non commercial trials" (June 2006) is available.

In addition, historically several patient populations, children and women most prominently, have been underrepresented in clinical investigations [8]. In 1995 70-80% of all new medicinal products approved were still not labelled for use in children [9].

The need for more studies to obtain paediatric information for medicines used in children is now a matter of consensus on a global basis and is considered a public health priority.

The Paediatric Regulation (EC) No 1901/2006, entered into force on 26 January, 2007, aims to improve the health of Europe's children by stimulating research and development of medicines for use in children, ensuring that medicines used to treat children are appropriately tested and authorised. All new applications for MA (Marketing Authorisation) must include results of studies conducted in compliance with a PIP (Paediatric Investigation Plan), except for those with a waiver or deferral. The PIP should be submitted no later than the completion of the relevant human pharmacokinetic studies in adults. This obligation applies 18 months after entry into force of the Paediatric Regulation, as of July 2008. From now on Pharmaceutical Companies will be required by this European law to provide paediatric data for all new MAA (Marketing Authorisation Applications) with the exemption of: generics, hybrid medicinal products, biosimilars and medicinal products containing one or more active substances of well-established use, homeopathic and (traditional) herbal medicines [10].

Implementation of the KKS (Coordinating Centres for Clinical Trials) and PAED-Net, a "Pediatric Network on Medication Development and Testing in Children and Adolescents at KKS" is an initiative of the Federal Ministry for Education and Research in Germany (BMBF). PAED-Net is a network of experts to professionally plan and perform paediatric studies. Paediatric trials are supported in separate special modules. The centers are administrated by a central coordinating unit in Mainz [11]. It is intended to be a platform for transparent, patient-oriented development of new drugs and therapeutic principles in Germany [12].

The German Federation of the pharmaceutical industry (BPI) disseminated a questionnaire to 330 pharmaceutical companies concerning experience with clinical trials and children in 1998. The feedback rate was significant low, only 10.6% responded accounting for 35 companies [13], as a consequence the answers were not representative.

In 2000 and 2005 two surveys on clinical trials in children were carried out among companies belonging to the German association of research-based pharmaceutical companies (VFA). The objective was to collect the extent of clinical trials conducted in children and the evaluation of the experience the pharmaceutical industry made in this respect [14], [15]. Both surveys, with a good response rate, have shown, that the amount of studies might stay at a constant level from 2000-2005.

# Methods

To provide a status report on the current and future situation of clinical trials in children a survey was performed in paediatric departments of university clinics in Germany, covering a time period of at least 4 years (last 2 years, current status and planned next 2 years). The questionnaire was based on the surveys performed by Heinrich and Hark within the pharmaceutical industry but was modified in cooperation with the PAED Net according to clinical requirements. It consists of 21 questions and the processing time was assumed by 15-30 minutes.

In February 2007 the questionnaire was sent to 68 paediatric departments in 31 university clinics in Germany and 18 (27%) centers responded to the survey.

## Questionnaire

The paediatricians were asked, if clinical trials with children were conducted currently, within the last 2 years or if clinical trials are planned within the next 2 years. For each time period the number of trials and indications was asked for. Further on the respondent was asked if the trials were conducted with or without support of PAED-Net/KKS and/or CROs (Clinical Research Organisations), if the trials were Investigator Sponsored Trials (IST) or Investigator Initiated Trials (IIT) and/or if the trial were in cooperation with the pharmaceutical industry. Further on it was asked for reasons of good or bad conduct of trials, difficulties to recruit suitable patients and if and why a trial was refused by the Ethic Committees (EC) and/or the German Federal Institute for Drugs and Medical Devices (BfArM)/Paul Ehrlich Institute (PEI).

# Results

18 questionnaires were sent back from the following faculties: general paediatrics (7), paediatric cardiology (4), paediatric psychiatry (2), neonatology (2), paediatric surgery (1), paediatric neurology (1) and paediatric oncology (1). In total 2 KKS were involved in answering the questionnaire.

## Conduct of clinical trials in children within 2005-2006

All 18 centers responding to the survey performed clinical trials in children within 2005-2006. A total of at least 229 studies in 18 centers were reported, but in case of multicenter studies multiple mentions from different centers are possible. 56% (10/18) of the centers performed up to 5 trials, 6% (1/18) of the centers conducted up to 10 trials, 11% (2/18) of the centers performed up to 20 trials and in 17% (3/18) of the centers were up to 65 trials performed (mean: 14, median: 4, missing data in 2 cases).

Seven centers (39%) performed the studies without participation of PAED-Net/KKS, and/or CROs. Eleven centers

(61%) were supported by these organisations whereas 5 centers worked with PAED-Net/KKS and 4 centers with CROs (multiple mentions were possible, 2 centers with missing data). Support of PAED-Net/KKS and/or CROs is nearly equal distributed per center but the total number of trials was much higher in the PAED-Net/KKS group than in the CRO group (93 versus 27).

## Current situation

Currently, two centers do not conduct any trial in children, but in the remaining sixteen centers a total of at least 135 studies were reported, in case of multicenter studies multiple mentions were possible. 56% (10/18) of the centers perform up to 5 trials, 6% (1/18) of the centers conduct up to 10 trials, 11% (2/18) of the centers perform up to 20 trials and in 6% (1/18) of the centers up to 40 trials and up to 65 trials respectively are performed (mean: 9, median: 3, missing data in 1 case). Six centers (38%) performed the trials without participation of PAED-Net/KKS, and/or CROs. Ten centers (62%) were supported by these organisations whereas 5 centers worked with PAED-Net/KKS and 4 centers with CROs (multiple mentions were possible, 2 centers with missing data). Support of PAED-Net/KKS and/or CROs is equally distributed per center but the total number of trials was much higher in the PAED-Net/KKS group than in the CRO group (52 versus 11).

## Conduct of clinical trials in children planned within 2007-2008

Only two centers have no trials planned for the forthcoming 2 years but in the remaining sixteen centers a total of at least 124 studies are planned to conduct (in case of multicenter studies multiple mentions were possible). 44% (8/18) of the centers have planned to conduct up to 5 trials, 11% (2/18) of the centers will perform up to 20 trials, and 6% (1/18) of the centers plan up to 40 trials (mean: 6, median: 4, missing data in 5 cases (28%)). Six centers (38%) plan to perform the trials without participation of PAED-Net/KKS, and/or CROs. Nine centers (56%) will conduct the trials supported by these organisations (1 (6%) center with missing data). Four centers will work with PAED-Net/KKS and two centers with CROs (multiple mentions were possible, 3 centers with missing data). Support of PAED-Net/KKS is double as high as support by CROs which is represented by the total number of studies (35 versus 3).

No increase in clinical trials with children in the last years is indicated (Figure 1). Indeed, it seems to be a slight decrease in the future which could be explained by an incomplete or unknown planning of clinical trials for the next years. With respect to new laws, guidelines and strong governmental support an increasing number of clinical trials in children could have been expected. Surprisingly the number of trials seems to be unchanged or even decreasing within a period of at least 4 years.

As factors of success or failure for conduct of paediatric trials the items in Table 1 and Table 2 were listed.

**Table 1: Items of success for conduct of clinical trial**

| Reasons for a good conduct of trials | Number of answers |
|---|---|
| good coordination in department | 10 |
| good training of investigators | 9 |
| contribution by parents | 8 |
| well equipped centers | 6 |
| good organisation by pharmaceutical industry | 5 |
| good organisation by PAED-Net/KKS | 4 |
| high investigator fee | 4 |
| no other therapy possible | 2 |
| good organisation by CRO | 2 |

**Table 2: Items of failure for conduct of clinical trial**

| Reasons for a bad conduct of trials | Number of answers |
|---|---|
| few suitable patients | 10 |
| bad coordination in department | 6 |
| resistance of parents | 4 |
| resistance of nursing staff | 4 |
| placebo controlled trial | 2 |
| wrong choice of competitive drug | 1 |

Further on reasons for a good conduct of clinical trials in the paediatric field were mentioned additionally: rapid availability of staff that cares on potential patients for inclusion, convincing study design and motivation of participating physicians.

Reasons for a bad conduct of clinical trials in the paediatric field were mentioned also: untypical setting/study design for paediatric indications, no money for GCP conform studies (oncology), lack of motivation, physicians not interested in project and political decisions.

50% of the responders had no difficulties to include patients, whereas 50% of the responders had difficulties to include suitable patients into the studies for the following reasons: complex study design, enrolment period too short and prohibited concomitant medication.

The question, if clinical trials were refused by the Ethical Committee or by the German Health Authorities (Federal Institute for Drugs and Medical Devices, BfArM/Paul Ehrlich Institute, PEI) was clearly answered with no by 89% (16/18); only one center (1/18) had experienced that a project was refused, and there was one missing answer (1/18).

Surprisingly, although the number of answers is limited, only one single project was rejected by EC or Health Authority in only 6% of the studies. This could demonstrate

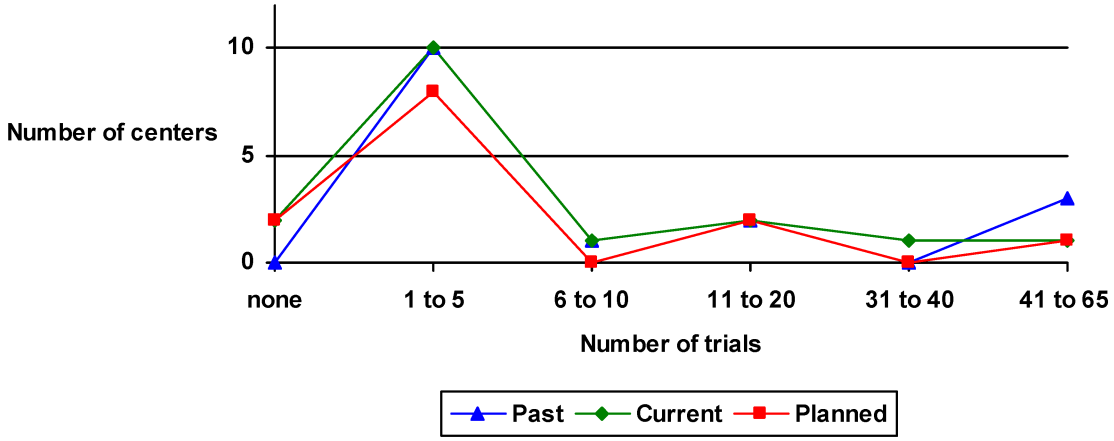


**Figure 1: Progression of trials in children (2005-2006/2007-2008)**

a good quality of the study preparation (e.g. quality of medicinal product, study design and study protocol, informed consent) and good collaboration with EC and competent authority.

To identify the purpose of the clinical trials in children, the question was asked if the results of these clinical trials were used for initial registration of a medicinal product or if the results were used for an extension of indication in children. 67% (12/18) of the responders answered this question: 33% (6/18) used the trials for an initial registration and in 56% (10/18) the result of the trials were intended for an extension of the indication for children (with 28% (5/18) missing data). Nearly twice of the clinical trials conducted in children are performed with medicinal products already registered in adults or in other indications.

## Discussion

The questionnaire of this survey was sent to 68 paediatric departments in 31 university clinics in Germany, unfortunately there was only a response of 18 paediatric departments although the centers were reminded by mail and additionally contacted by phone. Despite the lack of time which some of the centers mentioned, what are the reasons for such a low and disappointing response? Similar surveys were performed within the pharmaceutical industry with a much better response rate. It could be assumed that the pharmaceutical industry is more interested in showing that they are conducting clinical trials in children than the treating paediatricians. The results of both surveys from Heinrich and Hark performed within the pharmaceutical industry were confirmed by each other. Furthermore this survey undertaken within German university departments shows similar results. Therefore it can be concluded that the collected data are reliable.

The three surveys consulted both relevant kinds of institutions and can therefore adequately mirror clinical research in the paediatric population in Germany within a time frame from 2000-2008. Hark and Heinrich have shown in their surveys performed within the pharmaceutical industry that the number of trials in the paediatric population seems to stay constant for a time period from 2000-2005. The interpretation of the results of this survey within paediatric departments of German university hospitals indicates that the amount of studies in Germany might also stay at a constant level within the next 2 years. There is a slight trend in decreasing the number of trials which could be explained by an incomplete or unknown planning for the next years. But with respect to new laws, guidelines and strong governmental support an increasing number of clinical trials in children was and is expected. Surprisingly the number of trials seems to be unchanged within a period of at least 4 years (this survey) and added to the surveys from Heinrich and Hark, within a period of 9 years (2000-2008).

The results of these three surveys show that the Clinical Trial Directive (2001/20/EC), implemented in 2004 had no increasing effect on the number of clinical trials performed in Germany in the paediatric population so far.

The European Organisation for Research and Treatment of Cancer (EORTC), the largest independent cancer research network in Europe, recently analysed the effect of the EU Clinical Trial Directive: The number of new trials fell from 19 in 2004 to 7 in 2005 (63%), and a third fewer patients were enrolled. Simultaneously, trial costs increased by 85%. Trial initiation was about 5 months slower than in 2004, mostly the result of increased workload of Ethic Committees [16].

The EU Clinical Trial Directive was implemented to improve the quality of clinical trials and assure the safety and well-being of trial subjects. The decrease of new non-commercial paediatric trials in Europe – essential for optimising paediatric treatments – since implementation of the EU Clinical Trial Directive is also confirmed by Cannell 2007 [17].

On the one hand, the EU Clinical Trial Directive certainly improves the quality of clinical trials and assures the safety and well-being of trial subjects. It emphasises that children represent an especially vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development-related research important for their benefit. On the other

hand requirements on research are increasing and for example pharmaceutical industry has to build up paediatric expertise and has to train the various development departments within the relevant aspects of paediatric drug development [18].

Only few trained paediatric clinical pharmacologists are available in the European Union [19]. Additionally, Assael confirmed that compared to the US, most studies have been performed by general paediatricians and not by physicians specialised in paediatric pharmacology [20]: there is an urgent need to train paediatric physician scientists in clinical pharmacology.

Although the importance of clinical trials in children is increasingly recognised by major research groups and professional bodies worldwide [21], there is still a strong need to improve the awareness not only in public but also between the paediatricians. It often seems more acceptable to use untested medications on children as "routine clinical care" rather than enrol eligible children in a relevant clinical trial. A survey among paediatricians has shown, that there is concern about off label prescribing and that there is a need for clinical trials in children, but there was only a low acceptance for such studies. During 2003-2004 all hospital based paediatricians were contacted in Scotland within a survey; this survey had a response rate of 59% (257 questionnaires were distributed and 151 were returned). Although only half of the respondents believed that the use of off label medicines disadvantages their patients, a lager number expressed concerns about safety and efficacy issues, reporting high levels of treatment failure and Adverse Drug Reactions (ADR). Unexpectedly only a third of respondents thought that specific formulations were required, highlighting an unawareness of the current situation where pharmacists overcome the lack of paediatric formulations by supplying extemporaneous preparations, imported medicines, or unlicensed special products. Only half of the respondents believed that medicines should undergo trials in children, citing as the reasons for this less enthusiastic attitude "that there was already a significant level of empirical knowledge available" [22]. Definitely, there are many other references stating that clinical trials are necessary and required in the paediatric population but there are still 30% of hospital based paediatricians within a European country treating children and believing that these trials are not essential.

Consideration of this apparent lack of enthusiasm for the necessity of clinical trials in children, actions to promote requirements for safe and efficious medicines in the paediatric population has to be strengthen particularly with regard to the "experts": the paediatricians. But not only the awareness of the "experts" but also the awareness among parents, patient groups and the public has to be increased.

"Although there is a lot to do, some of the German Paediatric Specialists are optimistic: Within the next 10 to 15 years there will be sufficient meaningful clinical trials for children and adolescents" [23]. Changes within a period of 10-15 years is interminable and not very optimistic. Additionally it is doubtful to reach this goal within the given timeframe taking into consideration that institutions like KKS and PAED-Net exists since 9 years and 6 years respectively. Further on the European Union is 13 years behind compared to the US, where the Pediatric Rule was implemented in 1994. All this indicates that there is a chance for improvement of the situation, but it will last for many years and perhaps will overrun its time. Beginning of 2007 the legal framework was established, now the implementation by clinicians and pharmaceutical industry is strongly required.

## Conclusions

It is over 30 years since the term "therapeutic orphan" was used [24], [25]. Children have the same rights as adults to receive medicines that have been formally tested to ensure efficiency and safety. To improve such situation the joint effort of paediatricians, governmental organisations, the pharmaceutical industry, and any relevant bodies or individuals is mandatory in order to ensure that children do not remain "therapeutic orphans". Common initiatives of politicians, paediatricians, pharmaceutical industry and health authorities have to enforce the necessity for clinical trials in the paediatric population. Better education of the medical community and the public is needed about the rationale and benefits of trials and the potential dangers of using health-care interventions that have not been appropriately studied. Negatively biased media coverage about clinical trials involving children needs to be balanced with public-awareness campaigns about the societal benefits of randomised controlled trials. The possible harm from unpredicted adverse events because of a lack of paediatric trials has to be highlighted. As the need and demand for paediatric clinical trials, paediatricians and researchers must find strategies to overcome both parents' and doctors' barriers to trial participation.

Testing medicinal products has historically been low on the pharmaceutical industry's priority list. This has been due to lack of legislation, financial incentives, and fear of harm to children. As the US and Europe regulators mandate and guide the legal, licensing, and ethical framework for paediatric trials, it is hoped that the situation will change now and all (pharmaceutical industry and researchers) will rise to the challenge and prepare for a new era of medicinal benefit for the children. Europe-wide clinical trials must be faster, safer, easier and cheaper for both industry and academic sponsors.

To improve this disappointing situation the following proposals are recommended:

- Create and strengthen awareness among paediatricians, parents, patient groups and public
- Build up international network and "expert" knowledge by paediatricians and pharmaceutical industry
- Increase public funding and control progress

- Establish additional incentives to compensate the increased efforts and costs in conducting clinical trials with children

**Children deserve better: Children are our future!**

# Notes

## Competing interests

The authors declare that they have no competing interests.

## Authors' contribution

The results are based on a survey performed for Jasmin Khan-Boluki's thesis as part of the Master of Science in Pharmaceutical Medicine at the University Duisburg/Essen. Both authors read and approved the final manuscript.

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