

In concert with pediatric clinical trials

Sunil Shewale*¹ & Sameer Parekh¹



Practice Points

- There is a special need for pediatric formulations because of their physiological and developmental differences from adults.
- Pharmacokinetic (absorption, distribution, metabolism and excretion) and pharmacodynamic studies are difficult to carry out as the number of parameters varies in children of various ages.
- Due to certain unique diseases in the pediatric population, extrapolation of trial results from adults is not always possible, and is sometimes confusing and questionable.
- An assent/consent process that protects the child's dignity and welfare is crucial due to several practical difficulties.
- Unavailability of laboratory reference standards creates judgmental difficulties for pediatric trials.
- Adverse event profiles for children and adults differ and their assessment is also subjective.
- The commercial pediatric market is comparatively smaller, which restricts its earning potential.
- Trials in children are statistically more complicated with respect to design, generation of outcomes, defining and measuring valid outcomes and subgroup analysis, among other factors.
- Research in the pediatric population is necessary, but it requires more robust approaches.

¹Medical Affairs & Clinical Trials, Serum Institute of India Ltd, 212/2, Off Soli Poonawalla Road, Pune 411028, Maharashtra, India

*Author for correspondence: Tel.: +91 996 098 0895; ms.shewale85@gmail.com

SUMMARY Research involving the pediatric population is essential if children are to reap the full benefits derived from advances in medical science. However, children represent a vulnerable population and thus, research with adults cannot simply be generalized or extrapolated to a pediatric population. To study this gap between adults and children for their well-being, disease prevention, diagnosis and treatment, high-quality clinical research is required. Therapeutic products that are likely to be of high clinical value in children need to be fully studied scientifically before their widespread use. Despite the need for high-quality clinical research in children, significant barriers exist, and there can be no clear-cut and easy answer that could be implemented overnight. This necessitates different approaches that fit an increasingly narrower medical profile of the pediatric population. This article describes various issues encountered by clinical studies in the pediatric population that remain to be solved.

Clinical research in the pediatric population is more complex and thus, the need to improve strategies in running such trials has been greater – to determine the value of new treatment strategies, expand pediatric research and improve clinical outcomes. At the same time due to the worldwide increase in pediatric research activities, companies are making an effort to understand the vulnerable patient population. Children are not merely little adults nor are they one homogeneous group. They are several unique subpopulations based on biosystem maturation that, in some instances, introduces technical challenges, which may limit what can be done in an experimental context. Such challenges cause practical difficulties and trials in children take much longer to carry out than clinical trials in adults. However, millions of children now need safe and effective medicines, which requires more clinical trials.

To overcome these hurdles, clinical trials in children need to be developed and adapted to the patient group as well as the disease and therapeutic area. Similarly, understanding of the key drivers such as current regulatory mandates, clinical, operational, ethical and legal challenges worldwide is necessary. Such factors play a major role in the success of clinical trials, yet they can cause uncertainty and may highlight the need for those carrying out pediatric research to have sufficient skills and knowledge in different areas of child health and research.

Pediatric formulations

Pediatric formulations are different to the adult with respect to the age-appropriate route of administration, dosing volume, ease of

dosing, patient compliance and dose flexibility, while maintaining accuracy and safety [101]. Several pediatric formulations of medications may ultimately be required; such as for acetaminophen: different strengths of chewable tablets, a low potency ‘swallowable’ tablet, syrup and drops in various concentrations for the pediatric population. Moreover, formulations suitable for use in pediatric population are often unavailable and then compensatory attempts such as blending crushed tablets into formula may not deliver the accurate dose [1]. Thus, in product development, specific consideration should be taken in terms of needs to have a global strategy, and adapt drug substance and market specificities. In addition to drug studies, devices need to be miniaturized, adapted and tested for use in children. All of the above are technical specifications, requiring application of currently available knowledge and methods to implement. All of this increases the cost and complexity of the product development.

Unique pediatric diseases & early phase trials

Studies with unique pediatric indication often follow Phase I trials in adults that provide a primary assessment of the drug’s safety and pharmacokinetics. Due to safety issues or a lack of efficacy, most drugs passing through Phase I trials in adults are never approved to be further experimented on in children [102]. This may cause exposure of children to the extreme risks of early phase trials. For seriously ill children who have finished with regular medical management options and who may not stay alive until the endorsement of an investigational drug,

permission for a trial is necessary based on initial positive findings from nonclinical experiments and trials with adults. However, a big question mark remains regarding relevance of the adult safety profile for children. Thus, judgment is required in balancing conflicting concerns. During the assessment of every planned trial, the suitability and option of other therapies, disease severity, assessment of the adult safety profile and other related data, and the availability of a suitable pediatric formulation for testing should be taken into account.

Pharmacokinetic & pharmacodynamic

Pharmacokinetic studies are critical in pediatric care because the absorption, distribution, metabolism and excretion pattern in pediatric drug studies varies with age and differs among specific medicines. For example, it has been reported that sulfonamides, when administered to premature infants, may interfere with the safe removal of bilirubin (a by-product of blood metabolism) from the blood by plasma proteins. If it is allowed to accrue in the bloodstream, bilirubin can infiltrate the infant's immature blood–brain barrier, which can, in turn, lead to brain damage and/or dysfunction. Equally, genetic variations in drug metabolizing enzymes and drug transport systems affect the metabolism of medications in different pediatric populations. Similarly, the pharmacodynamic response of the drug also varies in pediatrics. Phenobarbital and antihistamines are responsible for sedation in adults but when administered in children they result in excitation and hyperactivity. Key challenges for pediatric drug development and research are thus, to build up processes and methods to: assess receptor development; craft clinical tools to evaluate the relationship between course of action of the drug in the body and what reaction it triggers in adults; and then determine whether a similar correlation holds for pediatric age group. Also, the inclusion of pharmacogenomic testing in the pediatric population helps to improve the drug efficacy (pharmacokinetic/pharmacodynamic; through identification of gene polymorphism) and to reduce the toxicity in an individual patient [2].

Intervention administration & measurement

As shown in [Table 1](#), children have to be allocated to specific age groups due to the

development of their organic functions. The most challenging aspects of running trials in children are how much blood can be collected and which sampling techniques are available. For example, pre- and post-immunization blood specimens collected throughout a vaccine trial is important to demonstrate changes in antibody titers, but trial subjects are more reluctant to give blood [3]; also, it is more difficult to draw blood since the infants have smaller veins. Furthermore, parents often refuse to give consent to take a blood sample from their child and there is a limitation for quantity of blood withdrawal due to the safety concerns. Fortunately, new analytical systems (e.g., Roche Modular, Gyrolab™ and for quantitative assays, semi-automatic devices like Liaison®, Luminex multiplexing techniques) allow precise assays using a much smaller quantity of blood than was possible in the past [4].

The behavior of children remains the other important challenge in conducting pediatric clinical trials, as this young population may not understand advice and directions. Even if they follow the protocol and instructions, often immaturity and consistent cooperation remains an issue. Certain follow-up issues, such as adverse event reporting, which depends on verbal feedback from the trial participant (e.g., more complex or complete assessments of pain, hearing, or other sensations or sensory functions), might be difficult with infants and toddlers. Older children and adolescents present a different set of challenges, for example, a rebellious attitude, especially against adult authority. Participants may need to take medications during school hours or to miss after-school activities to go to a clinic for an assessment, as that requires participants to be 'different', which can often build up peer pressure for studies and other activities. It may be useful if a child is given adequate time for training and preparation before his/her participation and initiation of study protocol.

Ethical & regulatory standards

Flawed research practice has led to the development of guidelines to safeguard human volunteers in research, with additional protections for pediatric and other vulnerable populations. In spite of the benefits, some of these practices put more administrative burdens onto research projects. For example, in a trial

Table 1. Pediatric age classes as per International Conference on Harmonisation Guidance E11.	
Age	Class
<37 weeks of gestation	Premature babies
0–27 days	Neonates
28 days to 23 months	Infants and toddlers
2–11 years	Children
12 to 16–18 years	Adolescents
Data taken from [23].	

conducted by the Pediatric Rheumatology International Trials Organization on the rare disease juvenile dermatomyositis with one of the off-label drugs, the ethical review board took more than 2 years to grant approval, despite the Pediatric Rheumatology International Trials Organization having an efficient procedure to meet the regulatory criteria [5]. The regulations check the range of clinical studies that involve the children, particularly studies that involve a comparatively larger risk for healthy subjects or those children who are not directly benefiting from participation. For example, traditional Phase I clinical trials for safety assessment that involve healthy volunteers face bigger hurdles for the granting of approval if they propose to include a pediatric population. Similarly, placebo-controlled trials to evaluate efficacy undergo detailed scrutiny when children are involved. Different countries with different cultural, ethical and regulatory understanding may have different safety criteria. For instance, in some countries it is questionable to enroll healthy children as volunteers, whereas in France and Norway approval from one of the participating centers is sufficient for the complete trial and it is not necessary to gain permission from all participating centers [5].

The ethical and regulatory standards are important for protection of trial participants from possible harm but if the system itself produces more harm than good then it needs to be modified. Meanwhile, future efforts should be directed at providing a clearer picture of the ethical and regulatory standards for this special population.

Issues with child consent/assent

The latest version of the Declaration of Helsinki suggests that, for a legally incompetent minor, the investigator must obtain informed consent from the parents or child’s legally authorized representative in accordance with the applicable law. However, children’s assent

to research is not well defined, which results in inconsistency in its pursuit and, consequently, in its usefulness [6]. If the child is 7–11 years old, assent is favored and it may require such children to sign a separate assent written at a level appropriate to their intellectual age [7]. Generally, children below 10 years of age may not fully understand the complexities of clinical trials and hence, what they are being asked to assent to. Although parents are expected to sign the consent documents, should the verbal assent of children suffice? Or should they be asked to sign something saying that they had been informed of the risks and assented, or did not dissent? An effort for parental consent differs geographically. For example, in many countries, the requirement of consent of a parent or legal guardian is for children under 18 years of age. However, in the UK the standard is 16 years and, in Japan, it is 20 years. In the USA, it generally differs from state to state, but it is usually 18 years [8]. The assent process should be conducted rightfully to discover the will of the child and his/her decision-making capability has to be respected [9]. In the same way, researchers must be well educated to explain the clinical trial and judge the child’s perception for participation [10].

Outcomes & other variable measurements

Defining appropriate outcome measures is one of the challenges faced by pediatric research. The complexity of outcome measurement differs according to age and researchers needs to develop reliable and valid ways of evaluating these outcomes. Similarly, the determination of normative data during comparison is also difficult, for example, for comparisons between healthy, suspected and/or diseased children of different ages. The effect of trial medications and other interventions should look in terms of possible physiological, anatomical, psychological risk/benefit and social developments in children. These effects should be assessed with lengthy

follow-up studies that track children for years and even decades, but again, long-term studies have an increased complexity and are difficult to carry out.

Adverse effects of medicine

The very fact that children are growing and developing automatically places them at risk for adverse effects that are not reported in adults. For example, tetracycline produces a stain on developing teeth but not teeth that are fully developed. Besides, preterm infants are at risk of suffering from any serious morbidity or death; also, most medicines administered to preterm infants lack substantial data to endorse their safety and efficacy [11]. Of the 582 pediatric drug randomized clinical trials analyzed, 36% serious adverse events and 15% mortality was reported. More than 50% of randomized clinical trials detected ADRs [12]. As adverse event assessment is very subjective in a clinical trial on children, the data really do not show the real picture. Literacy plays a very important role in adverse event monitoring because literate parents will note adverse events in documents provided to them during trial but illiterate parents may not get enough time or might not understand how to note them. Also, to date, many people record the temperature by physical touch and not by using a thermometer. Thus the parents need to be trained first, for temperature measurement or recording of other adverse events.

Likewise, as the physician relies only on the objective symptoms, in the case of a serious adverse event occurring, the social image of the sponsor and physician can get hampered, as well as the credibility of the investigational product becomes questionable. Involvement of an independent drug safety monitoring board is much needed to ensure safety in clinical drug trials. Within the UK, it is now mandatory to have a safety monitoring committee for pediatric clinical trials [13]. The alert regulatory system is needed today in infant studies, and this was evident during a clinical study in 2009, whereby the death of a child in India prompted officials to shut down the study [103].

Reference standards

Development of newer medical and diagnostic treatments often requires an evaluation of the potential benefits and safety. Thus, it becomes

critical to address the issue of analysis and normal laboratory values for a wide range of physiological variables. Such data must be age-appropriate and disease-specific. Many laboratory reference standards are based on widely available data for healthy adults. The collection of data for the development of such reference standards is not easy because routine laboratory investigations (e.g., chemistry profiles) are rarely performed in a healthy pediatric population. The nonavailability of standards becomes an even greater concern for uncommon pediatric health conditions. For example, to assess the potential toxicity of new drugs for premature infants or children with AIDS, it is essential to have baseline 'normal-for-the-population' laboratory parameters, such as white blood cell counts and liver function test results. These children may already have abnormal white blood cell counts, which makes it more difficult to monitor the effects of drugs that may have bone marrow suppression as a toxic side effect. Likewise, usefulness of microscopic examination of sputum smear in the diagnosis of tuberculosis is limited in young children as most childhood tuberculosis smears show a negative result and they are also unable to expectorate [14]. Extensive research is required for development of a reference standard or gold standard in the pediatric age group.

Difficulties with statistical analysis

Children suffering from unique medical conditions are relatively few in number. To generate statistically dependable estimates of differences between a study product and a control group, a sufficient but substantial number of participants should be available. A review of randomized controlled trials from 1982 to 1996 reported that about half of the studies recruited less than 40 children, with a median of 80 children for multicenter trials and 36 children for single-center studies. These studies may have reported false results, as the statistical power and considerations were inadequate [15]. In statistical consideration, with respect to power, sample size calculation and analyses have to be planned to accommodate children's developmental differences that often necessitate subanalyses or studies with infants, toddlers and adolescents. For example, in one of the reviews, 604 clinical trials were

found, involving more than 100,000 pediatric participants. Only approximately 7% studies were performed in neonates. Many of these trials involved both adult and pediatric patients but they inadequately describe the characteristics or eligibility criteria for volunteer children. Similarly, drug trials performed in low and low-middle income countries were of lower methodological quality, increasing difficulties in statistical analysis [16]. Consideration of statistically critical parameters and developing the trial according to their need may help to reduce the difficulties of statistical analysis.

Long-term studies in children

To assess the possible developmental effects of study drugs or interventions requires extensive follow-up, well beyond whatever the immediate study outcomes may be. For example, the adverse sequel associated with the use of cranial radiation to prevent CNS spread of leukemia in children did not become evident until many years following the introduction of this therapeutic approach [17,18]. The results of long-term studies with children involve a number of logistical and ethical challenges. The investigator should have an infrastructure that permits tracking and periodic assessment of research volunteers over the years. It is quite obvious that families may move, but within research institutions, where the investigator and study team tends to change positions over time, the clinical site must have historical data to manage interaction with volunteers and continue follow-up. In addition to being a logistical challenge, cost and expense to drive long-term studies is major concern. Study sponsors are rarely keen to provide financial support for long-term follow-up. In addition, very few institutions have the desire and wherewithal to support such studies independently. Similarly, for long-term studies, it is difficult to approach parents and children periodically for continued permission or assent, particularly if the nature or objective of the research project changes or when planned milestones are achieved. Well-planned and well-managed long-term studies can be successfully carried out in children.

Working with families

Parents are always concerned about the health and safety of their children and, hence, commonly raise several objections to enrolling their children in trials. This includes the fear of harming or

hurting, especially by invasive methods like extensive blood sampling; using children as 'guinea pigs'; misconceptions regarding the need for placebos; the increasing complexity of information sheets; and the number of visits. Language or literacy barriers make it more difficult for some people to understand the informed consent, importance and purpose of research and its benefits to the community.

People of any age may hold different values based on their ethnic background and cultural practices, leading to more faith in alternative treatments rather than scientific principles, which could ultimately reduce the attraction for clinical trial participation [19]. Joint family culture also affects the final decision of participation because in a joint family, the mother and father of the child are not the only decision makers; the elderly relatives also play an important role. Depending upon where they live or their access to transportation, people may have difficulty in bringing their child to a clinical trial site. Those with a low income may find it difficult to take time off work or find appropriate alternatives.

Migration of people from one place to another, sometimes over long distances may cause difficulties for the participation of their children. In the Indian context, this migration is very common. During pregnancy, women move to their mother's home and a few days after delivery, move to their husband's place, thus leading to an increased chance of losing them to follow-up, after participation of their child in a study. Parents may have a number of concerns about participation of their child in the study; highlighted in [Box 1](#). Educating the parents, and encouraging family involvement during study could actually encourage the participation of child. The holistic approach will include cultural and social factors, and emotional values must be considered while planning the trial.

Physician perspective

Many times, physicians don't want to take a risk because the developing system including physical, cognitive and psychological response in a pediatric age group is different from matured adults. Thus the safety and efficacy profile may differ in children [20]. Physicians also face the problem of efficacy and safety assessment in preterm and term infants as both are evaluated with a different scale. Moreover, if something happens to the patient (a serious adverse event, permanent disability or

Box 1. Parents concern about child's participation in the study.

- A distrust of medical research
- Doctors prescribe medication as a way of experimenting on unknown patients
- Medical research involves too much risk to participants
- Doctors won't make full disclosures regarding the intervention being studied
- An inherent tendency of the investigator to favor one child over another
- The social image of investigator and institution
- Investigating a new drug

death) during the trial, it has a definite impact on the physician's reputation and social network [19]. A physician may think that the intensity of counseling of parents, paperwork, extra time needed to train the staff, data collection and query resolution will increase his administrative cost/burden. On some occasions, investigators may be unexpectedly confronted by questions and criticisms from an ethics committee. These questions may include, changing schedule events for obtaining trial consent for participation, changing methodologies, redesigning protocols and delaying the enrollment. The extended time required to gain ethics committee approval for pediatric studies, even though it is necessary for participant safety, may frustrate both the investigators and the families of children with life-threatening disorders. This not infrequent scenario leads to significant disappointment among researchers and potential research participants at the site.

Despite the challenges, investigators are motivated to conduct pediatric trials by several

factors, including scientific interest, desire to provide leading-edge care to their patients and global pediatric conferences, among others.

Costing

The pediatric pharmaceutical market is small compared with the adult market, resulting in limited commercial gains and hence, worldwide pediatric trials are proportionally less in number (Figure 1). The commercial gain from various preventive, diagnostic and therapeutic treatments, especially for rare illnesses, may not be adequate to offset the expenses of developing them. For example, even though vaccines are playing an important role in saving lives in pediatrics, however both the health authorities and general public are not ready to pay the high prices and this results in a decreased profit margin for the developer. Such situation may prevent companies from recovering development cost [3]. Even for fairly familiar childhood diseases, the numbers of likely research volunteers may be small; it involves more study centers and

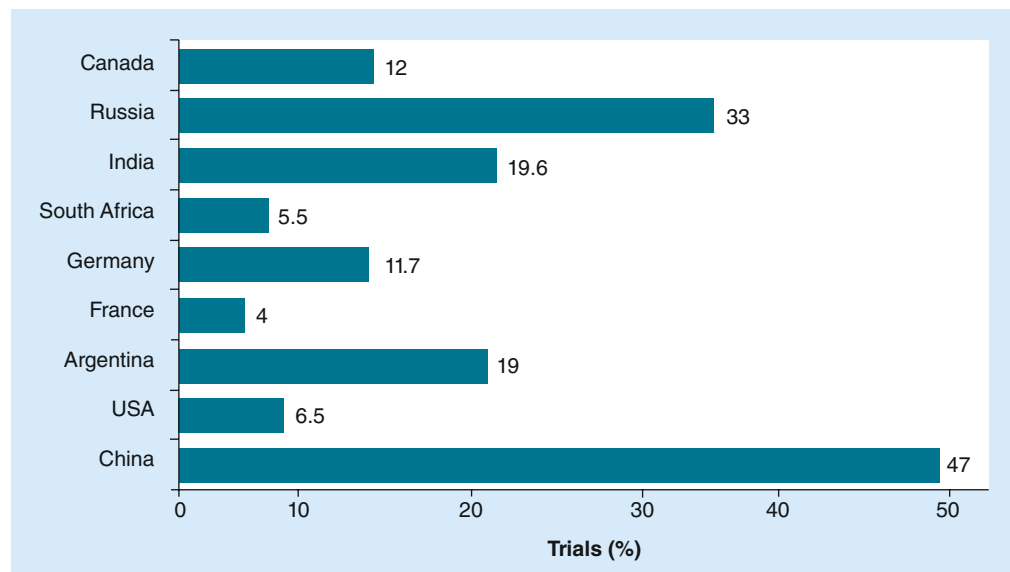


Figure 1. Percentage of number of pediatrics studies worldwide by country. Data based on trends. Data taken from [21].

additional costs for coordination. Specialized laboratory services and tests are required to examine small volume biological samples; this may increase the development costs. More time is often required per patient to complete study procedures resulting in more cost. In many countries, widespread use of off-label prescription is likely to weaken the incentives to finance pediatric research on drugs that are already approved for use by adults. Real-time comparison of various costs associated with any project is necessary to reduce the overall costing.

Looking forward

Knowing the effects of a medicinal product in a child is necessary; but this should be done without compromising their well-being. The responsibility has to be shared by pharmaceutical/biotechnology companies, regulatory authorities, health professionals and society, as a whole. The sponsor should make every effort to anticipate and reduce known hazards, as well as trying to minimize the number of participants and invasive procedures during designing itself. It is imperative that pediatric studies be performed by medical and scientific personnel who are familiar with Good Clinical Practice guidelines and are capable of a trusting relationship and communication with the child and parents. The investigator should be properly trained and experienced in studying a pediatric population, including the evaluation and management of potential adverse events. Because most pediatric conditions are sufficiently uncommon, statistically sound, ethical research requires multiple study sites, governments should continue to establish and fund discipline-specific, age-relevant research groups or consortia with the expertise and administrative infrastructure to conduct multicenter studies.

Further research should consider the role of methodological and organizational barriers to recruitment, the complexity of recruitment from a health professional perspective and developing culturally sensitive research methods. It should increase the pace of therapeutic development for rare pediatric conditions, and move toward greater consistency in the protection of child participants in research.

Future perspective

Pediatric clinical research is essential for the developing and improving the safety

of medicines. At the same time, it helps to get the best treatment choice for specific condition. There is, however, a number of challenges/issues associated with clinical trials in children. To overcome these, the future of pediatric research needs to be enhanced by strengthening the approaches and embracing emerging opportunities. Designing clinical trials in children requires taking into account specific ethical, clinical and practical pediatric considerations, and discussions on the issues of risk, benefit and burden should always be carried out on a single clinical trial basis. Sponsors should commit sufficient time and resources to formulating a strategy before beginning pediatric studies. Such a strategy must incorporate protocol design, drug formulation, consent, enrollment and many other factors. The pharmaceutical companies in collaboration with government agencies need to have more rigorous and comprehensive pediatric programs than previously. Barriers that exist at the levels of society, parents, investigator and children require collaborative networking, a culture of child-focused trial recruitment, research training and a broader distribution of research activities across the academic pediatric community. A better public awareness of the need for research in children would probably increase the level of parental commitment for the participation of children in trials, and a better understanding and compliance with the ethical and regulatory framework will ensure that safeguards are in place to protect children from unnecessary exposure to experimental drugs. The future of pediatrics is bright, but will depend on the recognition of response to a growing array of exciting opportunities.

Disclaimer

All opinions expressed in the article are those of the authors and do not reflect the views of their organization.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

■ of interest

- 1 Giacoia GP, Mattison DR. Newborns and drug studies: the NICHD/FDA newborn drug development initiative. *Clin. Ther.* 27(6), 796–813 (2005).
- 2 Cassandra M, Courtney DT, Raymond CB. Ethical considerations for pharmacogenomic testing in pediatric clinical care and research. *Pharmacogenomics* 12(6), 889–895 (2011).
- 3 Parekh S, Shewale S. Understanding the niche: the clinical development of vaccine. *J. Clin. Studies* 4(4), 52–56 (2012).
- 4 Neuer-Etscheidt K, Schulz H. Clinical trials in children challenge central laboratories. *J. Clin. Studies* 3(1), 16–19 (2011).
- **Highlights some of the practical difficulties or issues of pediatric trials that are common worldwide.**
- 5 Hannsson MG, Gattorno M, Stjernschantz Forsberg J *et al.* Ethics bureaucracy: a significant hurdle for collaborative follow-up of drug effectiveness in rare childhood diseases. *Arch. Dis. Child.* 97, 561–563 (2012).
- 6 Sterling CM, Walco GA. Protection of children's rights to self-determination in research. *Ethics Behav.* 13(3), 237–247 (2003).
- 7 Parekh S. *Pediatric consent errors*. Applied Clinical Trials (2011).
- **Highlights some of the practical difficulties or issues of pediatric trials that are common worldwide.**
- 8 Cvetkovich-Muntañola A. Pediatric clinical trials: one size doesn't fit all. *Future Foresight* 4, 2 (2011).

- **Highlights some of the practical difficulties or issues of pediatric trials that are common worldwide.**
- 9 Gross T. Challenges and practicalities of obtaining parental consent and child assent in paediatric trials. *Regulatory Rapporteur* 7, 6 (2010).
- **Highlights some of the practical difficulties or issues of pediatric trials that are common worldwide.**
- 10 Susman EJ, Dorn LD, Fletcher JC. Participation in biomedical research: the consent process as viewed by children, adolescents, young adults, and physicians. *J. Pediatr.* 121(4), 547–552 (1992).
- 11 Davis JM, Connor EM, Wood AJ. The need for rigorous evidence on medication use in pre-term infants – is it time for a neonatal rule? *JAMA* 308(14), 1436–1436 (2012).
- 12 Nor Aripin KNB, Choonara I, Sammons HM. Systematic review of safety in paediatric drug trials published in 2007. *Eur. J. Clin. Pharmacol.* 68, 189–194 (2012).
- 13 Sammons HM, Gray C, Hudson H *et al.* Safety in paediatric clinical trials – a 7 year review. *Acta Paediatr.* 97, 474–477 (2008).
- 14 Carlos M, Ben J. Current concepts tuberculosis in children. *N. Engl. J. Med.* 367, 348–361 (2012).
- 15 Campbell H, Surry SAM, Royle EM. A review of randomized controlled trials published in Archives of Disease in Childhood from 1982–1996. *Arch. Dis. Child.* 79(2), 192–197 (1998).
- 16 Nor Aripin KNB, Choonara I, Sammons HM. A systematic review of paediatric randomised controlled drug trials published in 2007. *Arch. Dis. Child.* 95, 469–473 (2010).
- 17 Cousens P, Waters B, Said J, Stevens M. Cognitive effects of cranial irradiation in leukaemia: a survey and meta-analysis. *J. Child Psychol. Psychiatry* 29, 839–852 (1988).
- 18 Roman DD, Sperduto PW. Neuropsychological effects of cranial radiation: Current knowledge and future directions. *Int. J. Radiat. Oncol. Biol. Phys.* 31, 983–998 (1995).
- 19 Shewale S, Parekh S. Reinventing patient recruitment in clinical studies. *The Monitor* 39–43 (2011).
- 20 ICH Expert Working Group. *Clinical Investigation of Medicinal Products in a Pediatrics Population. Current Step 4 Version*. 07, E11–2.4.3:11 (2000).
- 21 Thiers FA, Sinskey AJ, Ernst R. Trends in the globalization of clinical trials. *Nat. Rev. Drug Discov.* 7, 13–14 (2008).
- **Websites**
- 101 Pereira DL. Pediatric formulation development-challenges and opportunities from an industry perspective (2009). www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM197956.pdf (Accessed 5 February 2013)
- 102 Kaitin KI. Post-approval R&D raises total drug development costs to \$897 million. Tufts Center for the Study of Drug Development impact report (2003). <http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=29> (Accessed 5 February 2013)
- 103 Parker Waichman LLP. Report on Pevnar study death in India raises concern about overseas drug trials (2009). www.yourlawyer.com/articles/read/16282 (Accessed 5 February 2013)