Clinical Studies in Infants (Pediatric Pharmacology)

Karel Allegaert

Abstract

Treatment of children with effective and safe medicines is crucial to improve their outcome. Despite this relevance, it is still common practice in children to administer medicines outside their market authorization. Even if authorized, pediatric medicines may not be age-appropriate for a broad range of therapeutic areas. This has been recognized as very unsatisfactory by all stakeholders involved and makes clinical pharmacological studies in children an obvious need.

However, clinical trials of medicines in children come with their specific burdens. These burdens can be qualified as either related to the specific aspects of pediatric pharmacokinetics (PK) and pharmacodynamics (PD) or relate to the logistics of clinical trials of medicines in children. This is followed by a stakeholder's analysis, discussing specific aspects related to parents and their children (International Children's Advisory Network, iCAN), recruitment challenges, and research capacity building. We hereby tried to focus on recent evolutions, including initiatives to further develop this research capacity (Institute for Advanced Clinical Trials, iACT for children; Innovative Medicines Initiative, IMI2).

Perhaps progress is slower than anticipated, but pediatric medicines research is evolving, and we should keep this momentum. A further structured collaboration between the different stakeholders involved (the society, parents and children, sponsors, regulatory authorities) at the international level is crucial to use the available, but limited, resources as effective as possible to further improve pharmaceutical care in children.

Contents

K. Allegaert (✉)
Intensive Care and Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

Department of Development and Regeneration, KU Leuven, Leuven, Belgium
e-mail: karel.allegaert@uzleuven.be

F.J. Hock, M.R. Gralinski (eds.), *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*,
https://doi.org/10.1007/978-3-319-56637-5_44-1

On the Knowledge Gap and the Initiatives to Close This Gap

Similar to adults, the treatment of children with effective and safe medicines is crucial to improve their outcome or protect their quality of life. Despite this relevance, it is still common practice in children to administer medicines outside their market authorization. Health care professionals routinely prescribe medicines to children off label or unlicensed, hereby using dosing regimens initially developed for adults, and extrapolating from indications initially validated in adults and based on adult – not necessary similar to pediatric – pathophysiology. As a first effort to raise awareness for this issue that is perhaps specific but not limited to pediatrics (e.g., pregnancy, geriatrics as other "special" populations), the term "therapeutic orphan" was introduced in the late 1960s by Harry Shirkey. He reported about the situation where many medicines were not labeled for prescription to children due to insufficient and inaccurate clinical evidence being available, covering aspects including dosage, efficacy but also safety. The term "therapeutic orphan" hereby refers to the deprivation of children to not have access to medicines because these have not been adequately tested in children.

Actually, to a large extent and especially in specific pediatric subpopulations like newborns or infants, this situation still exists. Even if authorized, pediatric medicines may not be age-appropriate for a broad range of therapeutic areas. To illustrate this, we refer to the study of van Riet-Nales et al. on the availability and age-appropriateness of medicines authorized for children in The Netherlands. Based on a systematic search of the national medicines database and the summary of product characteristics, 3542 pediatric medicines (703 active chemical entities) were identified (van Riet-Nales et al. 2011). This is about half of the medicines and chemical entities available for human use. Of these authorized products, about 35%, 48%, 64%, 80%, and 95% were *authorized* for use in the consecutive pediatric age categories (0–27 days, 1–23 months, 2–5 years, 6–11 years, and 12–17 years). When the *suitability of the dosage form* was also considered, this was further reduced to 27%, 37%, 52%, 70%, and 88%. This reflects both the relevance of the pediatric subpopulations and the need to develop age-appropriate formulations (van Riet-Nales et al. 2011).

As a consequence, health care professionals lack the crucial information and access to knowledge on these aspects to make the best possible, informed decision for their pediatric patients. This has resulted in extensive *unlicensed* or *off-label use* of medicines in children. This is not limited to the intensive care setting (neonatal or pediatric intensive care) or the general pediatric hospital environment, but also occurs in the outpatient or ambulatory setting. In an attempt to quantify the pediatric off-label medicines use in different areas, Mühlbauer et al. estimated that 90%, 30–70%, and 10–20% of the prescriptions were off label in the intensive care unit setting, pediatric inpatients, and outpatients, respectively (Mühlbauer et al. 2009). In the most recent meta-analysis on unlicensed and off-label medicine prescription practices in pediatric hospitals (2015), 829 studies published between 1994 and 2012 were evaluated. Unlicensed and off-label medicines prescriptions ranged from 0.2% to 48% and from 12% to 71%, respectively (Magalhaes et al. 2015). Similar to the formulation-related observations of van Riet-Nales et al., this meta-analysis reconfirmed that this practice is still widespread, and that the youngest age category, i.e., (pre)term neonates are exposed most commonly to unlicensed or off-label medicines (100% exposed to at least one unlicensed or off-label medicine) (Magalhaes et al. 2015). At least, this provides further support to improve the available knowledge and the label status for medicines administered to children.

If a medicine is used in a way that is different from that described in its license, this is called "unlicensed" or "off-license" use. This includes giving a medicine in any way or approach that is different from that described. This may involve crushing a capsule or tablet in order to turn it into a liquid to enable a toddler to take the medicine by oral route, or administer a liquid formulation intended for intravenous administration by oral route. *Off-label* medicines practice is defined as

prescribing in a different manner to label recommendations in the summary of product characteristics in a given country. This may relate to age group, dose, frequency, formulation, administration route, indication, or contraindication for use in children. The term off label refers to the use of a medicine that is not included in the package inset and does not imply in itself improper, illegal, or inaccurate use of a medicine in itself. Yet, the practice of using medicines in an off-label manner or unlicensed potentially may result in suboptimal pharmacotherapy. Although the level of evidence about harm induced by off-label and unlicensed medicines use in children is rather limited and based on association type of studies, there are indications that harm does occur and that it is still very likely underreported. The incidence of adverse events related to either labeled compared to unlabeled use of medicines was estimated to the 3.9–6% for hospitalized patients and 1.4–3.4% of out of hospital patients, suggesting that the incidence doubles in the setting of unlabeled medicines prescriptions (Horen et al. 2002).

This setting has been perceived and recognized as very unsatisfactory and substandard of care by all stakeholders, including health care professionals working with children, parents and their children, politicians, and the pharmaceutical industry. In order to move and improve this setting, there have been a number of initiatives, some of which involve legislation (United States), whereas others have taken the form of regulation (Europe). Following the US initiatives (e.g., network of Pediatric Pharmacology Research units, Best Pharmaceuticals for Children Act [BPCA], Pediatric Research Equity Act [PREA]) initiated in the late 1990s, the European Union (better medicines for children, EU Pediatric Regulation 2007) also took initiatives (Hoppu et al. 2012). The European Paediatric Regulation (EC No. 1901/2006) focuses on three main objectives: increasing the number of appropriate medicines for children, increasing the available information on these medicines, and stimulating high-quality ethical research with children. The European Medicines Agency (EMA) published a 10-year report on the experience acquired as a result of the application of the pediatric regulation and a public consultation on this document ongoing (European Medicines Agency 2016a). Simultaneously, the World Health Organization (WHO) also became active in providing incentives to improve health care through improving knowledge and access to better, tailored medicines for children. This includes issues like child friendly, age-appropriate formulations, including child-size drug campaigns, excipients, but also a list of essential medicines for children. The sixth version of this WHO model list of essential medicines for children has been published in early 2017 (WHO 2017). Finally, the latest ICH E11 guidance (International Conference on Harmonization) on pediatric studies goes back to 2000, but – to the best of our knowledge – a revision effort is ongoing.

As a reflection of the proportional efforts made to generate knowledge on pharmacotherapy in children compared to adults, Table 1 provides an overview of the number of studies registered on the clinicaltrials.gov website by July 2017, using either no specific search criteria (all studies) or "child," "infant," or "newborn." For three regions of the western world (United States, Europe, and Canada) considered in this search, there is a consistent proportional contribution of studies in these specific subpopulations when compared to the overall volume of studies (United States 40–45%, Europe 20–25%, Canada 8–10%). However, there is still an overall low number of studies in infants (3%) and newborns (2%) compared to the total number of studies (National Institutes of Health 2017).

Based on these observations, we suggest that the federal US legislation and similar European initiatives (Table 1) have indeed resulted in a substantial increase in studies on medicines in children, with a subsequent significant increase in knowledge on pharmacotherapy in children, in part reflected in label changes. Interestingly, Schachter and Ramoni reported that the pediatric legislation resulted in a significant reduction in the time interval between the new medicine application approval (in adults) and the submission of the supplemental pediatric data (median decrease from 7.2 to 4.2 years), without significant reduction in the proportion of pediatric data submitted within the first year after adult approval (0–7%)

Table 1 Number of studies and proportion of pediatric studies as retrieved on the clinicaltrials.gov website on 15 July 2017. We hereby used either no specific search criteria (all studies) and compared those retrieved when either "child," "infant," or "newborn" were entered as an additional search option. For all three regions of the western world highlighted in this table, there is a consistent proportional contribution of studies in these specific pediatric subpopulations, with still an overall low number of studies in infants (3%) or newborns (2%) compared to the total number of pediatric (23%) studies retrieved in the registry (National Institutes of Health 2017)

	all studies	'child'	'infant'	'newborn'
worldwide	249 566	55 693 (23 %)	8 557 (3 %)	5 414 (2 %)
United States	103 342 (41 %)	23 583 (42 %)	3 574 (42 %)	2 024 (38 %)
Europe	70 269 (28 %)	12 091 (22 %)	2 016 (25 %)	1 534 (28 %)
Canada	17 142 (8 %)	4 161 (7 %)	780 (9 %)	406 (8 %)

(Schachter and Ramoni 2007). The potential to update product information based on already existing – but still unpublished – information should neither be underestimated. Under article 45 of the (European) Regulation, sponsors should submit existing pediatric studies to regulatory authorities for review and potential update of the product information. Based on nearly 19,000 study reports on about 1000 active substances, 262 substances have been assessed (62 centrally, 200 nationally approved) and reviewed. Based on this review, 16 new pediatric indications were added for a variety of indications (e.g., hypertension or congestive heart failure, spasticity, constipation, laryngitis subglottica, sedation and analgesia, infectious or inflammatory diseases, or contrast medium for diagnostics) (Saint-Raymond et al. 2016).

Unfortunately, only a few limited number of label changes covered medicine label changes for neonates, reflecting the fact that neonates remain underserved. To further illustrate this: on 406 pediatric label changes (FDA, 1997–2010), only 23 medicines resulted in 11 labeled indications (e.g., remifentanil, linezolid, rocuronium, nevirapine, sevoflurane, stavudine) in neonates. The absence of label change was most commonly due to unproven efficacy, despite the fact that these medicines (e.g., valganciclovir, paracetamol, caspofungin) are very likely also relevant for this population (Stiers and Ward 2014). This largely reflects the issue to proof efficacy, based on sufficient robust clinical end points or valid biomarkers in neonates.

In an additional effort to boost research on medicines in this subpopulation, the FDASIA (Food and Drug Administration Safety and Innovation Act) initiative aligned the US setting to a certain extent with the European Regulation by introducing the requirement that clinical trials also have to be performed in neonates when relevant to this population. At the same time, the FDASIA initiative made BPCA and PREA permanent and facilitated the availability of neonatal expertise within the FDA (Gonzalez et al. 2014). Another valuable initiative to improve the setting in neonates is the International Neonatal Consortium (INC) (Critical Path Institute 2015). INC integrates stakeholders to promote clinical medicine development for neonates. The consortium hereby focuses on generalizable methods to use data to support claims that a medicine is safe and efficacious when used to treat a specific indication (Turner et al. 2017).

Pharmacokinetics (PK) and Pharmacodynamics (PD) in Pediatric Studies: Aiming for a Moving Target

Preterms are not just small neonates
Neonates are not just small children
Children are not small adults

By virtue of their developmental and cognitive abilities, children are a vulnerable population. This is also true when participation in a clinical

Table 2 Burdens that may further complicate the conduct of clinical studies in pediatrics

Pharmacokinetics/pharmacodynamics in pediatric studies: aiming of a moving target
• Sampling strategy (number of samples, volume), specific analytical techniques
• Population pharmacokinetic modeling (mechanism, physiology based) not always sufficiently validated to support study design and sampling strategy, and uncertainty about extrapolation
• Extensive variability in pharmacokinetics and pharmacodynamics. This variability is not limited to maturational changes, but also covers nonmaturational covariates like, for example, disease severity, comedication, renal or hepatic impairment, or obesity
• How to assess efficacy? Robust and relevant pharmacodynamic endpoints and validated biomarkers are needed
• The need for specific pediatric formulations
• Safety: how to assess differences in patterns of (serious) adverse reactions in the pediatric population?
Circumstances related to pediatric studies
• Pediatric drug therapy development is a perceived "must," instead of an opportunity
• Ethics, parental consent, and assent in the child
• Study facilities (investigators, research facilities) should have experience with clinical studies in children
• Recruitment challenges, the need for multicenter collaborations
• Perceived risks and fear of negative outcomes, perceptions of society
• Drug development programs initially develop for other populations, only very rarely driven by pediatric needs
• How to secure adherence and retention in the trial?
• Healthy volunteers and pediatrics
• Natural course of pediatric diseases?

trial is considered. In addition to adaptations of the clinical protocol design (e.g., medicine formulation, dosing, sampling strategy, clinical indication), recruitment and retention strategies, incentives and the process to obtain informed consent must be modified. Although obviously needed as discussed in the introduction, clinical trials of medicines in children come with their specific burdens, as illustrated in Table 2 (Reed 2011; Allegaert and van den Anker 2015). These burdens can be qualified as either related to the specific aspects of pediatric pharmacokinetics (PK) and pharmacodynamics (PD) or relate to the logistics of clinical trials of medicines in children.

Simple extrapolation of PK or PD estimates initially documented in adults to pediatrics is obsolete, since both PK as well as PD processes differ considerably throughout childhood from the findings in adults because of maturational and nonmaturational changes. Throughout the pediatric life range, there is extensive maturation driven variability. This variability is also reflected in the use of different age categories for regulatory purposes and is commonly divided into the newborn period, infancy, childhood, and adolescence. Human growth and development consist of a sequence of physiologic events that link somatic growth with maturation. Weight gain hereby displays colinearity but is not similar to maturation. Across the pediatric age, both organ size and function change as well as body composition and (patho)physiology. We should be aware that these changes are most prominent – but not limited – to early infancy (Fig. 1). Across this pediatric life span, organ size and function change as does body composition, (patho)physiology, and ultimately cellular function. If we focus on weight changes to further illustrate this, there is an initial decrease (6–12%) in birth weight, with a subsequent increase of 50% in the first 6 weeks of postnatal life. Weight doubles in the first 3–4 months to result in a threefold higher weight at the end of infancy (Allegaert and van den Anker 2015). Consequently, total energy requirements change dramatically since these requirements are the sum of energy expenditure and energy deposition for growth (Fig. 1).

A rational approach to determine a safe and effective dose in an individual child necessitates understanding the PK and PD properties of a specific medicine, in combination with the clinical characteristics of a single, specific child. Developmental PK hereby represents the mathematical estimates of the concentration–time profile, while PD describes the relationship between a given

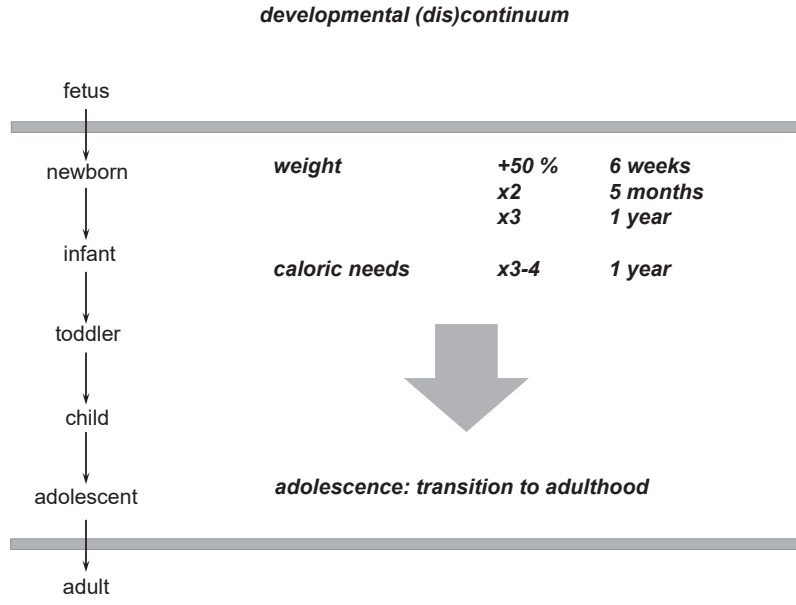

Fig. 1 Developmental discontinuum illustrated for the consecutive age subcategories in pediatrics

concentration and the extent of a given response (e.g., pain relief, blood pressure, fever reduction, improvement in asthma score). Multiple differences related to maturation but also disease (obesity, renal or liver impairment) or therapeutic interventions (e.g., drug–drug interaction, diet) will result in differences in PK and probably also PD in children compared to adults. PK (***a***bsorption, ***d***istribution, and elimination by ***m***etabolism or renal ***e***limination, ***ADME***) hereby estimate the relationship between a concentration in a given compartment (e.g., plasma, central nervous system, subcutaneous tissue, bronchial tree) and time ("*what the body does to the medicine"*).

Absorption: Following oral administration, absorption displays extensive maturation because of gastro-enteral maturation (e.g., anatomy, motility, drug metabolism or transporters), but also nonenteral routes (e.g., cutaneous, muscular size, inhalation and circulation) display age-related changes. Examples of developmental absorption are illustrated in Table 3.

Distribution: Although a "theoretical volume," this depends on physical (e.g., extra- and intracellular water, lipophilic or water soluble compound, ionization and protein binding) and physiologic (protein binding, tissue uptake, permeation to deep compartments) processes. Consequently, the distribution volume is also driven by maturational changes and disease characteristics.

Metabolism: The drug metabolizing capacity is affected by multiple covariates. Besides growth and maturation, comorbidity, pharmacogenetics, and environmental issues can explain variability.

Excretion: The most relevant route of excretion is the renal route, both through glomerular filtration rate and renal tubular transport. These processes do not mature simultaneously.

PD estimates the relationship between a concentration and (side)-effects ("*what the medicine does to the body*"). Age-dependent differences in (un)anticipated effects of medicines may have a PK basis, a PD basis, or both. Differences in developmental pharmacology result in differences in medicine potency, efficacy, and/or toxicity. However, most of the variability observed relates to differences in PK, and maturational PD can only be considered once the PK aspects have been taken into account. Table 4 provides some illustrations on developmental pharmacodynamics in neonates and infants, or children and adolescents.

The regulatory framework for pediatric medicine development in Europe and the United States provides some guidance on how this can be addressed (Manolis and Pons 2009) as illustrated

Table 3 Illustrations on the relevance of developmental changes in absorption in infants and children

Transcutaneous	The higher surface area and the higher permeability results in extensive absorption of iodine or corticosteroids following cutaneous application and subsequent endocrine disorders
	Patches are specific formulations, developed for a continuous, stable release. Manipulations (e.g., cutting) or cutaneous lesions (e.g., eczema, burned skin) may alter this disposition
Rectal	Compared to oral, rectal administration of paracetamol results in lower and less predictable absorption
Intra-vitreal	Intra-vitreal injection of bevacizumab for retinopathy of prematurity results in appearance in the systemic circulation
Inhalational	Nonbronchial steroid disposition may result in tongue hypertrophy, oral candidiasis, or systemic effects
Buccal	Buccal midazolam (Buccolam®) formulation (PUMA product), to be used in children with seizures
Swallowing	Liquids or mini-tablets are preferred formulations in the first year of life
Gastric pH and emptying	Higher bioavailability following oral penicillin administration in newborns compared to infants or children
	The peak concentration of a given compound, e.g., paracetamol is delayed and lower in infants compared to children
Intestinal enzymatic activity	First pass effect is lower and bioavailability higher following oral midazolam in (pre)term neonates because of lower intestinal (CYP3A) drug metabolism
Pancreas activity and bile	Reduced uptake of lipophilic drugs, fat-soluble vitamins, or enteral-hepatic recirculation
Comorbidity	Bioavailability after oral administration may be different in the setting of diarrhea, or critical illness

Table 4 Illustrations on developmental pharmacodynamics in neonates and infants, or children and adolescents

Neonates and infants
• Dexamethasone and the risk for impaired neurodevelopmental outcome and cerebral palsy • Oxygenation saturation levels and the subsequent differences in mortality and morbidity (bronchopulmonary dysplasia, retinopathy of prematurity) in preterm neonates • The impact of ibuprofen or indomethacin on renal function • Exposure to antibiotics and its impact on weight gain and body composition • Neonatal hypo- and hyperglycemia, or hypothyroidism and neurocognitive outcome • Developmental toxicology for, for example, valproate (hepatic failure) or ifosfamide (renal tubular cell dysfunction, Fanconi) • The lymphocyte proliferation response is twofold lower in infants • Paradoxical seizures due to proportional excitatory GABA receptor overexpression
Children and adolescents
• Impact of steroids on growth • Impact of disease and treatment on normal pubertal development • Impact of either ethanol, nicotine, or other illicit drugs on neurodevelopmental and behavioral outcome • Limited to absent effects of tricyclic antidepressants because of a neurodevelopmental delay in the expression and activation of the norepinephrine system • Differences in oncological disease patterns between children compared to adolescents and young adults • The anticoagulant response to warfarin is higher in prepubertal children

in Fig. 2. Authorities usually consider information regarding: (i) how similar is disease progression between adults and children, (ii) how similar is the response to intervention between these populations, and (iii) which valid and relevant PD measurements (biomarkers, outcome variables) are available to decide on the type of product development program. If it is reasonable to assume that there is a similar concentration–response in children (similar disease progression, similar response to intervention) compared to data in adults, only PK and safety

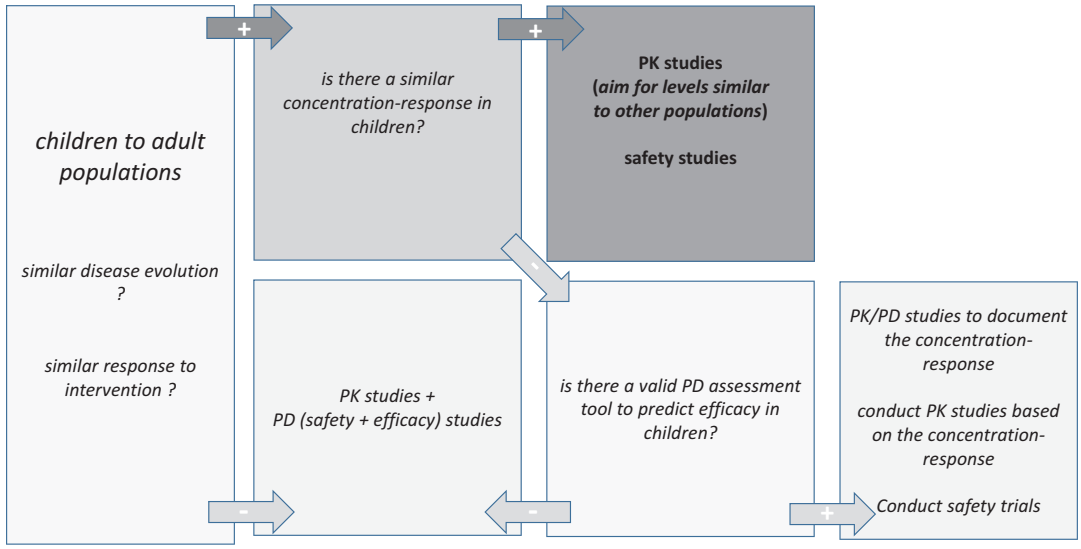

Fig. 2 Pediatric study decision tree (Manolis and Pons 2009)

studies are needed. If one does not anticipate such a similar concentration–response relationship, PK, efficacy and safety trials are needed. In the latter scenario, the availability of a PD measurement ("biomarker") to predict efficacy will determine the final study design (e.g., conduct PK/PD studies to get a concentration–response relationship for the PD measurement) (Hampson et al. 2014). Irrespective of similarity or not in concentration–response in children versus adults, this means that PK data studies are needed in the different pediatric subpopulations to provide sufficiently robust data on the maturational aspects of this concentration–time profile (Fig. 1).

Advanced techniques (dried spot blood, other bodily fluids besides plasma or blood, microanalytical techniques) and innovative trial designs (sparse sampling, scavenged sampling, opportunistic sampling) and can be very supportive to lower the burden of such studies. Modeling and simulation is one way to circumvent several difficulties in developing medicinal products in children. It allows the quantitative use of sparse sampling, characterization and prediction of PK and PD, extrapolation from adults to children, interpolation between pediatric age subsets, optimal use of scientific literature, and in vitro/preclinical data (Manolis and Pons 2009). Both for the PK analysis and also during the study design, population modeling using either nonlinear mixed effect modeling (NONMEM) or physiology-based PK (PBPK) approaches allow analysis and interpretation based on such sparse and unbalanced datasets (European Medicines Agency 2016b). It also permits exploration of the impact of different covariates such as age, weight, disease characteristics, or comedication to explain the variability in medicine disposition or effects. Similarly, *a priori* information or information collected during a previous part of a study can be used to guide the optimal design of the study in order to obtain the maximal knowledge on the PK–PD characteristics in a given subpopulation (de Cock et al. 2011). Although population PK modeling (mechanism, physiology based) is not always yet sufficiently validated to support study design, and sampling strategy and uncertainty about extrapolation remains, they do provide a valuable tool to support study design and subsequent interpretation as a "*well educated best guess*." Guidelines on the qualification and reporting of physiologically based PK (PBPK)-modeling and simulation, including on pediatric analyses, have recently been provided by EMA (European Medicines Agency 2016b).

In contrast to the emerging knowledge about developmental PK, there is a relevant and obvious need to address the "PD gap" in pediatric medicine development. A clinical endpoint is a characteristic or variable that reflects how a patient feels, functions, or perhaps, simply survives. A biomarker is a surrogate endpoint, intended to substitute for such a clinical endpoint that predict clinical benefit, or harm, or lack of both. The US National Institute of Health (NIH) definition of a biomarker is "any characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, but also to quantify the response to a therapeutic (pharmacologic) intervention" (Regulatory Affairs Professionals Society 2016). Biomarkers can be used as surrogate endpoints, linking pathophysiological processes to clinical more relevant endpoints (e.g., blood pressure control versus long-term outcome, hemoglobin A1C versus long-term outcome of diabetes mellitus treatment). In some instances, biomarkers may serve as substitutes for clinical endpoints and may facilitate (conditional) medicine approval (Kearns 2010). Biomarkers can quantify *disease response or progression* (e.g., serum creatinine or cystatin values for renal function, exhaled nitric oxide for bronchial inflammation, 6 min walking test for cardiorespiratory or muscular strength, pulmonary function, hemoglobin A1C), to *predict a given medicine exposure or effect* (e.g., polymorphisms of medicine metabolizing enzymes or receptors), or this can be a *PD biomarker* (e.g., blood pressure, sedation or level of analgesia, neuroimaging techniques, neurocognitive outcome assessment, histamine response, pupillary diameter) (Kearns 2010).

While the concept of biomarkers can be applied to children as well as to adults, it is obvious that issues like disease severity, the natural course of a disease, and the effect of a medicine likely will be different in children, and this is even the case within the pediatric population (e.g., blood pressure, or growth velocity in preterm neonates or adolescents) (Kearns 2010). There is a huge opportunity to tailor or even to develop biomarkers for pediatric medicine development. Preferably, such biomarkers should be noninvasive, with – if any – limited discomfort, and feasible within the routine setting of clinical patient care (Kearns 2010).

Examples of PD endpoints that are somewhat specific to pediatrics are, for example, 6 min walking test in children with neuromuscular diseases, the prediction of long-term neurocognitive outcome based on the Bayley assessment tools at 18 and 24 months of life in former preterm neonates or using imaging techniques following asphyxia, body length and growth velocity assessment, or maturational and activity related differences in QT_c times to subsequently assess the impact of medicines on QT_c time intervals. Although these examples always remain disease specific, they illustrate the feasibility and relevance to validate such "surrogate" endpoints, hereby linking pathophysiological processes to clinical relevant endpoints in children.

Importantly, PD endpoints and biomarkers also cover adverse drug events and pharmacovigilance. An adverse drug reaction (ADR) has been defined by the World Health Organization (WHO) as "*any noxious or unintended medicine response at doses commonly used for prophylaxis, diagnosis, or treatment of a disease or condition*" (World Health Organization 2012). For children, it is perhaps more reasonable to consider "*an unintended and harmful effect resulting from the use of medications intended for diagnostic or therapeutic reasons (irrespective of the dose)*" as a broader definition, because of the common practice to apply off-label or unlicensed prescription of medicines, with the absence of dose guidance (Cliff-Eribo et al. 2016).

Similar to effects, medicine-related toxicity in children may also be different to that in adults. This may be due to impaired metabolism (e.g., ifosfamide-induced renal tubular cell toxicity, tolerance to paracetamol at birth, valproate toxicity in young infants) but may also be idiosyncratic or PD (e.g., more pronounced ibuprofen-related renal impairment in preterm neonates, age-related differences of cyclosporin on peripheral blood monocyte proliferation capacity, agitation after benzodiazepine administration in toddlers or young children) in its origin. It is important to recognize that the child is developing

and may be prone to different toxicities compared to adults (e.g., growth, neurodevelopment) (Cliff-Eribo et al. 2016).

Clinical trials are crucial to provide evidence-based knowledge, also on aspects of safety, since safety within clinical trials is one of the major outcome variables (Fig. 2). However, studies are commonly not sufficiently powered for safety but for efficacy. It is crucial that new but also established treatments are monitored for their effectiveness and safety under real-life conditions, including information in children (Cliff-Eribo et al. 2016). Consequently, post marketing surveillance and pharmacovigilance is essential but largely depends upon health care professionals. Sometimes, conditional approval with compulsory additional collection of data on effects or side effects is part of the product cycle with specific instructions on data collection in patients exposed to the medicine.

A Stakeholders Approach on Clinical Pharmacological Studies in Infants and Children

Pediatric Drug Therapy Is Not Yet Fully Perceived as an "Opportunity"

The success of any medicine development plan – including those in pediatrics – depends on the relevance and medical impact of the indication considered. Unfortunately, drug development programs are most commonly initially develop for other populations and "adult" indications and are not initially driven by pediatric needs. The more serious the condition and/or the lack of a satisfactory treatment will result in the perception of all stakeholders involved that a clinical trial is urgently needed and warranted. This also holds true for the investigational research boards or ethical committees (approval) and for the clinical investigators. Investigators are more likely to be recruited to study a medicine which is likely to result in significant clinical benefit to children instead of a setting one where there is already satisfactory treatment. The recent progress and ongoing studies in the field of spinal muscular atrophy (splice-switching therapy), cystic fibrosis (e.g., lumacaftor, ivacaftor), or muscular dystrophy (e.g., antisense oligonucleotides) serve as illustrations of these perceived clinical needs, but also the potential to make progress.

Parents and Their Children, Beyond Consent and Assent

The most effective way to improve consent and assent is to pay attention to the motivating and discouraging factors for research participation of parents and children. Such knowledge should enable professionals to improve and adapt the process of recruitment and informed consent to their perspectives. Using a systematic review approach, Tromp et al. documented that the most mentioned motivating factors for parents were health benefit for child, altruism, trust in research, and relation to the clinical researcher. For children, the most mentioned motivating factors for children were personal health benefit, altruism, and increasing comfort (Tromp et al. 2016). Fear of risks, distrust in research, logistical aspects, and disruption of daily life were mentioned most by parents as discouraging factors. Burden and disruption of daily life, feeling like a "guinea pig," and fear of risks were most mentioned as discouraging by children (Tromp et al. 2016). Parental drivers for consent include the perceived trust and the potential access to newer treatments. Altruism might be a soft value, but matters: the major motivation in parents to consent for their previously well child to participate in a RCT of therapy for an acute respiratory illness was to increase medical knowledge (benefit to all children 32%; improving knowledge 27%) (Sammons et al. 2007).

The legal age for consent varies in Europe (consent from the age of 14, 16, or 18 years onwards and the age at which assent is compulsory), the concept of giving assent before reaching the age of majority exist (Lepola et al. 2016). The term "informed assent" hereby describes the process whereby minors are structurally involved in the decision process about (dis)agreeing with voluntary participation in clinical trials (Lepola et al.

2016). We should not underestimate children's capacities and should try to involve them as soon as feasible in this decision process, and perhaps even consult them for advice on how to perform clinical studies. This is because the child is not just an innocent bystander in a pediatric trial as also reflected by International Children's Advisory Network (*i*CAN) (International Children's Advisory Network 2016). This is an expanding network of local groups of children that advocates for and with children, specifically those involved in clinical trials with the aim to improve pediatric health care by providing children and families a voice in health, research, medicine, and innovation. Healthy children understand the issues related to a randomized controlled trial and clinical studies; they understand the potential risks and mainly focus on the absence of interferences in their everyday life. Children with preexisting comorbidities had better understanding of study conduct and were more likely to support children's involvement in clinical trials (Cherrill et al. 2010).

Recruitment Challenges

A sufficient number of pediatric subjects should be recruited for a given trial to draw conclusions. The variability within the pediatric age range makes it only more difficult to draw these conclusions and will further raise the number of patients needed in the different subpopulation. The limited number of children with a specific disease that will qualify indeed for recruitment, the need for consent and assent, stringent inclusion and exclusion criteria, and the limited research capacity to conduct these studies will further jeopardizes effective recruitment.

All stakeholders involved should be aware that effective recruitment and retention is not only to the benefit of the sponsor but likely will also generate new knowledge on more effective pharmacotherapy for children as soon as possible, or may document the need for new approaches. When a significant number of clinical trials are recruiting at any one time, an individual patient may meet enrollment criteria for more than one clinical trial, and co-enrollment can be considered. For specific populations with relatively small numbers, like preterm neonates, critically ill children, or children with rare diseases, co-enrollment can be considered, although this raises pertinent scientific, ethical, regulatory, and industry issues that should be taken into account when considering reenrolling into multiple clinical studies (Randolph 2009).

Recruitment and subsequent retention are perceived to be different for pediatric compared to adult trials. Besides study-related issues, the reasons for these differences are multifactorial, but also relate to the child, the parents, and health care professionals. Finally, research capacity building to conduct clinical studies for regulatory purposes is an obvious need.

Child-related issues: Knowledge on more effective recruitment strategies and motivation in children is increasing and should be considered by sponsors since initial consent and retention in the study may largely depend on the applied study design. We already referred to the *i*CAN approach early in this chapter (International Children's Advisory Network 2016). An analysis of reasons why children decide not to participate in clinical research in a cohort of 161 children in The Netherlands documented that a lower age, less experience with disease, and less complex research with lower risk were the best predictors for *not* participating. Time constraints and additional burdens were hereby used as reasons not to participate (Hein et al. 2015). These patients were initially considered for 13 different studies (ten randomized controlled trials and three observational studies in the fields of pediatric oncology, gastroenterology, ophthalmology, pulmonology). A similar pattern was observed in a study on adolescents with type 2 diabetes. In this specific setting, monetary incentives and the use of technology turned out to be most effective. Even then, recruitment remained difficult, and the authors suggested that a study design covering concerns of the adolescents (e.g., body image, weight loss, stress management), and that accommodates to their schedules, and is conducted in more convenient locations than medical facilities is much more likely to recruit (Nguyen et al. 2014).

Parent-related issues: In essence, parents consider potential clinical benefit, child safety, practicalities of participation, research for the common good, access to new medicines, and randomization (Woolfall et al. 2013). An analysis on factors that drive decisions of parents to participate or not in clinical research suggested that parents who declined had a higher socioeconomic status, were more anxious about their decision, and found it harder to make their decision compared with consenting parents. Consenting parents expressed more trust and altruism, perceived the potential for enhanced care, reflected better the concept of randomization, and were more certain about the decisions made (Hoberman et al. 2013).

Research capacity: Patient and parents factors cannot be adapted acutely at the time of the individual decision to consent or not, but we should inform public and stakeholders about the need for clinical trials of medicines in children. Consequently, the bottom up approaches to support individual motivation of patients and their parents should be combined with more top down, structural approaches like the European Network of Pediatric Research at the European Medicines Agency (Enpr-EMA) (European Network of Pediatric Research at the European Medicines Agency 2012). Enpr-EMA aims to facilitate studies by establishing a European network of national and specialty networks, investigators, and centers with expertise in performing trials in the pediatric population. Through such a network, one aims to stimulate networking and stakeholder collaboration, to build research capacity, to inform the public and the relevant stakeholders about pediatric clinical trials, and to raise awareness among health care professionals about the need for clinical trials. At a more individual level, parents and health care professionals acknowledge the influence that pediatricians have on the decisions to participate. Pediatricians believe parents balance well the perceived risks and gains when deciding about participation. They thought the child's condition, parents' health beliefs and personal attributes, and the doctors' beliefs and relationship with the investigators influenced parents' attitudes. Perceived risks included inconvenience, inadequate resources, and potential harms to the patient and doctor-patient relationship. Perceived gains included professional benefits for pediatricians, improved patient care, convenience for the families and themselves, and scientific advancement (Caldwell et al. 2002).

Especially at the level of capacity building, there are very recent initiatives in the United States and in Europe that are very promising. In the United States, Institute for Advanced Clinical Trials (iACT) is an independent nonprofit organization and believe that children of all ages deserve innovative medical therapies that are developed with the same level of urgency and commitment afforded adults (International Children's Advisory Network 2016). The institute works with others to assure that studies are designed to generate sufficient data to allow safe and effective use of new medications and devices in pediatric populations. A key factor in making this a reality is to optimize and accelerate biomedical innovation using child-centered clinical trial networks and collaboration with like-minded institutions, trial sponsors, and other stakeholders. Together with parents, patients, investigators, foundations, regulators, other government agencies, biopharmaceutical sponsors, and children's networks, Institute for Advanced Clinical Trials (iACT) for children has the ambition to catalyze improvements in the quality and timely completion of global pediatric studies to address the gap in evidence for best use of therapeutics in children (International Children's Advisory Network 2016). Strategies to achieve this relate (i) to develop a strategy and planning (independent expert advice and guidance to sponsors), (ii) to develop capabilities, tools, and best practices (streamline and improve clinical trial processes), (iii) to develop infrastructure and clinical trial execution capacity (support and manage network of prequalified trial-ready sites and collaborate with regional networks), and (iv) to foster leadership (efforts to assure early and sustained engagement of patients, caregivers, and investigators). A very similar effort is ongoing in Europe within the Innovative Medicines Initiative (IMI2), as part of the 10th call (European Commission 2016). This call explicitly stated that the paucity of patients

available to study the many pediatric indications and the need for multiple capable sites to satisfy enrolment in trials, the clinical trial infrastructure across the EU is not sufficiently organized and lacks adequate funds and scale to consistently and efficiently deliver. This deficiency in clinical research capability also negatively impacts the capacity to complete research in areas of unmet medical need. In addition to improved infrastructure for efficient study execution, collaborative efforts to maximize the coordination of pediatric networks across the EU, utilize innovative study designs, and engage regulators in planning drug development programs are all needed to guarantee that Europe can augment its current capability as a critical region for developing medicines for children.

Pediatric oncology as an illustration of the progress made and the challenges to be handled: Pediatric oncology differs from adult findings both in the patterns of their malignancies as well as in the response to pharmacotherapeutic interventions. Despite these a priori existing hurdles, the success in childhood leukemia illustrates how treatment programs and multidisciplinary, multicenter collaborative efforts were designed using clinical- and biology-based risk factors seen in the patients and resulted in impressive improvement in outcome (Ravindranath 2015). These improvements were first focused on survival, with a subsequent shift to aspects related to long-term outcome and reduced morbidity and are very well described for acute leukemia. However and similar to the setting in adults, advances in cellular and molecular techniques (mechanism of action) have boosted the field of pediatric oncology, both for leukemia, but also for pediatric oncological diseases that are still associated with poor outcome (intracranial, sarcoma). Initiatives like the SIOPE strategic plan (*seven objectives*: innovative medicine, precision medicine, knowledge on the biology, equal access, specific emphasis on adolescents, quality of life in survivors, and causes) should enable further improvement in outcome, either related to mortality (more and sooner access to novel therapies in relapse) or related to morbidity (Vassal et al. 2015).

Pediatric Medicines Research: Keep the Momentum and Aim for Improvement

Clinical trials of medicines in children have resulted in improved product labeling, have increased the identification and quantification of adverse events, and have resulted in the development of new pediatric formulations. Between 1998 and 2012, the FDA issued 401 pediatric study requests. For 189 medicines, studies were completed and exclusivity has been granted. For the majority of medicines (173; 92%), additional and relevant information specific to pediatric pharmacotherapy has been added to the summary of product characteristics, with 108 (57%) receiving a new or expanded pediatric indication (Wharton et al. 2014). The aspects (parents and their children, recruitment challenges, research capacity) earlier discussed are crucial to further boost study conduct to improve knowledge based pediatric pharmacotherapy, and additional progress can also be made by using already existing – but still unpublished – information (Saint-Raymond et al. 2016). Progress may be slower than anticipated or aimed for, but pediatric medicines research has made progress, and we should try to keep this momentum. Initiatives like iCAN, iACT, or the IMI2 are the most recent illustrations of the growing international recognition of the relevance of pediatric trials. A more structured collaboration between the different stakeholders involved (society, regulatory authorities, parents and children, sponsors) at the international level is crucial to use the available, but limited, resources as effective as possible to further improve pharmaceutical care in children.

Despite this positive evolution, still a relevant portion (42%) of completed pediatric trials failed to document either efficacy (n = 38/44) or safety (n = 7/44) (Momper et al. 2015). Interestingly, the dosing evaluated in the study turned out to be a contributing factor for trial failure (all failed efficacy) in ten of these cases. This re-stresses the relevance to explore and validate dosing (phase 2 type of studies) before initiation of larger and pivotal phase 3 trials. Testing for more than one single dose in a specific pediatric population in a

phase 2 type of study design may provide very valuable information for the pediatric medicine development plan. In eight of these development programs, it is very likely that differences in disease characteristics in pediatrics compared to adults have further contributed to the failure to document efficacy. There seems to be also a higher placebo response, resulting in failure to proof efficacy in medicines considered for bipolar disorders in children (Janiaud et al. 2017). Finally, in four cases, the study design (assay sensitivity, control group) was deficient.

An additional aspect to improve this outcome is to consider study design related issues is the use of phase 2 before phase 3 studies. Therapeutic exploratory studies or phase 2 studies may be very useful to raise the likelihood of a valid study design – including dose seeking – before conducting the pivotal phase 3 efficacy trials and are common practice in "adult" product development and should be further explored in children. The starting doses considered are hereby generally based on estimates driven modeling and simulation. It allows the quantitative use of sparse sampling, characterization and prediction of PK and PD, extrapolation from adults to children, interpolation between pediatric age subsets, optimal use of scientific literature, and in vitro/preclinical data (Manolis and Pons 2009). Population modeling, either nonlinear mixed effect modeling (NONMEM) or physiology-based PK (PBPK) approaches, allow and support the analysis and interpretation based on such sparse and unbalanced datasets (European Medicines Agency 2016b). Phase 2 can subsequently be used to validate and optimize these models to further raise the likelihood that the results of subsequent phase 3 studies are indeed valid and useful. To further stress its relevance, an EMA-based survey illustrated that single dosing are the rule (83/97 studies), with commonly (40/97) no prespecified target (40/97) and if so, decisions are guided by PK data only (33/57) (Hampson et al. 2014). This reflects the common assumption of dose proportionality and similar exposure−response relationships in adults and children (Fig. 2). Few development programs prespecify steps to verify these assumptions in children. There is scope for the use of Bayesian methods as a framework for synthesizing existing information to quantify prior uncertainty about assumptions (Hampson et al. 2014).

Importantly, the number of medicines that target major pediatric diseases is still limited. The majority of studies in children are driven by a research program initially developed for adults, with subsequent translation to pediatrics, although some specific products (e.g., lumacaftor or ivacaftor for cystic fibrosis, surfactant for hyaline membrane disease) illustrate the potential of a pediatric pathophysiology focused approach. An emerging concept to facilitate medicine development is repurposing by the use of "old" medicines for new indications, avoiding the need for time- and resource-intensive toxicity studies. The potential relevance to neonates can be illustrated by repurposing projects related to propranolol (hemangioma) or insulin-like growth factor-1 (retinopathy of prematurity) (Léauté-Labrèze et al. 2017; Hellstrom et al. 2016).

Acknowledgments The clinical research activities of Karel Allegaert are facilitated by the agency for innovation by Science and Technology in Flanders (IWT) through the SAFEPEDRUG project (IWT/SBO 130033).

References and Further Reading

Allegaert K, van den Anker J (2015) Neonatal drug therapy: the first frontier of therapeutics for children. Clin Pharmacol Ther 98:288–297

Caldwell PH, Butow PN, Craig JC (2002) Pediatricians' attitudes toward randomized controlled trials involving children. J Pediatr 141:798–803

Cherrill J, Hudson H, Cocking C et al (2010) Clinical trials: the viewpoint of children with a chronic illness compared with healthy children. Arch Dis Child 95:229–232

Cliff-Eribo KO, Sammons H, Choonara I (2016) Systematic review of paediatric studies of adverse drug reactions from pharmacovigilance databases. Exp Opinin Drug Saf 15:1321–1328

Critical Path Institute (2015) https://c-path.org/programs/inc. Accessed 21 Jul 2017

De Cock RF, Piana C, Krekels EH et al (2011) The role of population PK–PD modelling in paediatric clinical research. Eur J Clin Pharmacol 67(Suppl 1):5–16

Doussau A, Geoerger B, Jimenez I et al (2016) Innovations for phase I dose-finding designs in pediatric oncology clinical trials. Contemp Clin Trials 47:217–227

European Commission (2016) http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/imi2-2016-10-04.html. Accessed 21 Jul 2017

European Medicines Agency (2016a) http://ec.europa.eu/health//sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf. Accessed 21 Jul 2017

European Medicines Agency (2016b) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211315.pdf. Accessed 21 Jul 2017

European Network of Paediatric Research at the European Medicines Agency (2012) http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp. Accessed 21 Jul 2017

Gonzalez D, Paul IM, Benjamin DK Jr et al (2014) Advances in pediatric pharmacology, therapeutics, and toxicology. Adv Pediatr Infect Dis 61:7–31

Hampson LV, Herold R, Posch M et al (2014) Bridging the gap: a review of dose investigations in paediatric investigation plans. Br J Clin Pharmacol 78:898–907

Hein IM, Troost PW, de Vries MC et al (2015) Why do children decide not to participate in clinical research: a quantitative and qualitative study. Pediatr Res 78:103–108

Hellstrom A, Ley D, Hansen-Pupp I et al (2016) Insulin-like growth factor 1 has multisystem effects on foetal and preterm infant development. Acta Paediatr 105:576–586

Hoberman A, Shaikh N, Bhatnagar S et al (2013) Factors that influence parental decisions to participate in clinical research: consenters vs nonconsenters. JAMA Pediatr 167:561–566

Hoppu K, Anabwani G, Garcia-Bournissen F et al (2012) The status of paediatric medicines initiatives around the world – what has happened and what has not? Eur J Clin Pharmacol 68:1–10

Horen B, Montastruc JL, Lapeyre-Mestre M (2002) Adverse drug reactions and off-label drug use in paediatric outpatients. Br J Clin Pharmacol 54:665–670

International Children's Advisory Network (2016) https://www.icanresearch.org. Accessed 21 Jul 2017

Janiaud P, Cornu C, Lajoinie A et al (2017) Is the perceived placebo effect comparable between adults and children ? A meta-regression analysis. Pediatr Res 81:11–17

Joseph PD, Craig JC, Caldwell PH (2015) Clinical trials in children. Br J Clin Pharmacol 79:357–369

Kearns GL (2010) Beyond biomarkers: an opportunity to address the 'pharmacodynamic gap' in pediatric drug development. Biomark Med 4:783–786

Léauté-Labrèze C, Harper JI, Hoeger PH (2017) Infantile haemangioma. Lancet 390:85–94

Lepola P, Needham A, Mendum J et al (2016) Informed consent for paediatric clinical trials in Europe. Arch Dis Child 101:1017–1025

Magalhaes J, Rodrigues AT, Rogue F et al (2015) Use of off-label and unlicensed drugs in hospitalized paediatric patients: a systematic review. Eur J Clin Pharmacol 71:1–13

Manolis E, Pons G (2009) Proposals for model-based paediatric medicinal development within the current European Union regulatory framework. Br J Clin Pharmacol 68:493–501

Momper JD, Mulugeta Y, Burckart GJ (2015) Failed pediatric drug development trials. Clin Pharmacol Ther 98:245–251

Mühlbauer B, Janhsen K, Pichler J et al (2009) Off-label of prescription drugs in childhood and adolescence: an analysis of prescription patterns in Germany. Dtsch Arztebl Int 106:25–31

Nguyen TT, Jayadeva V, Cizza G et al (2014) Challenging recruitment of youth with type 2 diabetes into clinical trials. J Adolesc Health 54:247–254

Randolph AG (2009) The unique challenges of enrolling patients into multiple clinical trials. Crit Care Med 37 (1 Suppl):S107–S111

Ravindranath Y (2015) Evolution of modern treatment of childhood acute leukemia and cancer: adventures and battles in the 1970s and 1980s. Pediatr Clin N Am 62:1–10

Reed MD (2011) Reversing the myths obstructing the determination of optimal age- and disease-based drug dosing in pediatrics. J Pediatr Pharmacol Ther 16:4–13

Regulatory Affairs Professionals Society (2016) http://www.raps.org/Regulatory-Focus/News/2016/01/29/24212/FDA-NIH-Unveil-Glossary-of-Clinical-Definitions. Accessed 21 Jul 2017

Saint-Raymond A, Pelle B, Zaccaria C et al (2016) Usage of unpublished paediatric data. Arch Dis Child 101:81–84

Sammons HM, Atkinson M, Choonara I et al (2007) What motivates British parents to consent for research? A questionnaire study. BMC Pediatr 7:12

Schachter AD, Ramoni MF (2007) Paediatric drug development. Nat Rev Drug Discov 6:429–430

Stiers JL, Ward R (2014) Newborns, one of the last therapeutic orphans to be adopted. JAMA Pediatr 168:106–108

Tromp K, Zwaan CM, van de Vathorst S (2016) Motivations of children and their parents to participate in drug research: a systematic review. Eur J Pediatr 175:599–612

Turner MA, Portman RJ, Davis JM (2017) Regulatory science in neonates: a framework that supports evidence-based drug therapy. JAMA Pediatr. https://doi.org/10.1001/jamapediatrics.2017.1360

United States National Institutes of Health (2017) https://www.clinicaltrials.gov/ct2/search. Accessed 15 Jul 2017

Van Riet-Nales DA, de Jager KE, Schobben AF et al (2011) The availability and age-appropriateness of medicines authorized for children in the Netherlands. Br J Clin Pharmacol 72:465–473

Vassal G, Rousseau R, Blanc P et al (2015) Creating a unique, multi-stakeholder Paediatric Oncology

Platform to improve drug development for children and adolescents with cancer. Eur J Cancer 51:218–224
Wharton GT, Murphy MD, Avant D et al (2014) Impact of pediatric exclusivity on drug labeling and demonstrations of efficacy. Pediatrics 134:e512–e518
Woolfall K, Shilling V, Hickey H et al (2013) Parents' agendas in paediatric clinical trial recruitment are different form researchers' and often remain unvoiced: a qualitative study. PLoS One 8:e67352
World Health Organization (2012) http://www.who.int/medicines/areas/quality_safety/safety_efficacy/EMP_ConsumerReporting_web_v2.pdf. Accessed 21 Jul 2017
World Health Organization (2017) http://www.who.int/medicines/publications/essentialmedicines/6th_EMLc2017.pdf. Accessed 21 Jul 2017