Does size matter? : bridging and dose selection in paediatric trials

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Chapter 1

General introduction: what is the right dose for children?

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Br. J. Clin. Pharmacol. (2010); ***70****(4): 597-603*

1.1 Background

Irrespective of whether a drug is in development or already available on the market, the current paradigm for paediatric dose selection does not guarantee safe and effective dosing recommendation for children. The normalisation of the adult dose according to age, body weight or any other demographic covariate without prior evidence of how these factors contribute to differences in drug exposure may lead to poor and unsafe estimates of the paediatric dose. Nevertheless, the implications of such common practice remain unquestioned. No matter how easy and simple a dosing regimen may be for clinical investigators or prescribers, the continuous use of empirical approaches for dose selection cannot be justified by the current understanding of how developmental growth affects pharmacokinetics and exposure-response relationships [1]. The recent advancements in quantitative methodology for the analysis of clinical pharmacology data offer researchers and prescribers with the appropriate tools for establishing what dose is right for children.

Current paediatric prescription practice

In contrast to the entrenched clinical practice based on off-label prescription, the introduction of the paediatric regulation by the European Union, together with the renewal of the *Pediatric Rule* by the FDA on the requirements for paediatric labelling, imposes special attention to dose selection in paediatric clinical trials. The main objective of these guidelines is to ensure that effective and safe doses are evaluated in children [2, 3]. However, the design and implementation of paediatric trials remain challenging and are often difficult to accomplish. Ethical, practical and even economical considerations have caused the evaluation of efficacy and safety of drugs in children to be based on empirical extrapolations from clinical trials in adults. Despite the many flaws of this approach and mounting evidence [4–7] from quantitative pharmacological methods, very few examples exist where exposure-response relationships obtained in children are used to define dosing regimens in the paediatric population. Thus far, empirical scaling from adults to children continue to be the mainstream method for dose selection in children, with adjustment for body weight as the most commonly used approach.

The rationale for dose adjustment in paediatric indications may be determined by differences in pharmacokinetics, pharmacodynamics, disease or a combination of these factors. Pharmacokinetics of drugs in children may differ from adults for several reasons: variability due to age, gender, body composition, functionality of liver and kidneys and maturation of enzymatic systems throughout the life span from neonates to adults are all potential sources of pharmacokinetic differences [5]. Assuming similar exposure-response relationships between adult and children, efficacy in children is warranted if the same exposure can be achieved in either population. To meet this requirement, physiological differences between adults and children must be taken into account when selecting the paediatric dose [6]. In spite of the aforementioned considerations, dose scaling in paediatric trials remains an open issue, both from a clinical perspective and from a drug development standpoint. Given that children may not be subject to dose finding studies similar to those carried out in the adult population, some initial estimation of the paediatric dose must be obtained via extrapolation approaches [7]. As a consequence, the dose selected for a considerable number of drugs disseminates into clinical practice, irrespective of consensus about the appropriate dosing recommendation. This phenomenon is illustrated by scientific publications showing different dosing requirements (e.g., pain management, paediatric oncology) and by differences in prescription practice in many hospitals (e.g., heart failure, pulmonary hypertension), which have their own protocols based on the empirical experience of its staff [8, 9]. Some exceptions exist, such as the British National Formulary for Children `http://bnfc.org` and the Dutch Children's Formulary `http://www.kinderformularium.nl`, but these guidelines rely on dosing recommendations primarily from clinical experience and off-label use rather than on prospective studies or randomised clinical trials.

A similar scenario is observed in drug development, where empiricism also prevails. Usually the adult dose is divided by a fixed (scaling) factor, under the

assumption that the appropriate efficacy/safety profile can be assured. These empirical procedures are often referred to as "bridging". It is evident that such an approach has some serious disadvantages, amongst which the risk of toxicity due to the lack of understanding in the ontogeny of metabolic pathways, as for example in neonates and toddlers, or poor efficacy due to sub-optimal dosing. It is clear that a shift in paradigm is required which focuses on the differences in (physiological) function between populations, rather than differences in size between adults and children.

The correlation between dose and demographic covariates is not linear

Probably, the most common method for dose adjustment in children in paediatric clinical practice is to normalise the adult dose by body weight (i.e., mg kg^{-1}), assuming a linear relationship between weight and dose. This means that the dose doubles with a two-fold increase in the weight of a child. Another method for dose adjustment is based on age: the paediatric population is divided into sub-categories (pre-term newborns, term newborns, infants, toddlers, children and adolescents) and the dose is selected according to a child's age. This method does not take into account the changes due to developmental growth that occur within each age group. Even though the hepatic metabolic capacity of a 5-year old child is completely different from that of a neonate, this approach fails in describing the maturation of the metabolism between one and six month of age. On the other hand, no differences in drug metabolism may exist between adolescents and adults. Furthermore, categorising dosing regimens by age ranges creates an artificial discontinuity in the dose-exposure relationship across each age group, hardly substantiated by scientific evidence [10].

Scaling the dose from adults can also be performed by normalisation based on body surface area (BSA), under the assumption that metabolic processes in humans are constant when expressed as a function of BSA. However, a few disadvantages limit the application of this method: the difficulty in calculating BSA (due to the complexity and inaccuracy of the formulae that can be used) and the tendency of overdosing neonates and infants [11]. There is also little justification for BSA from a pharmacokinetic perspective: the change in PK parameters across the paediatric population does not change proportionally with the BSA, because BSA is not a descriptor of metabolic function (e.g., scaling with BSA cannot predict the lack of enzymes at birth, leading to overdosing neonates [12]).

From the above, it becomes comprehensible that the assumption of a linear relationship between body size and drug exposure or response is not always justifiable and that size itself may not be a surrogate for developmental growth. Implicitly and most importantly, one must realise that the use of demographic variables also implies unidirectional increase of the dose with body size, which constrains the paediatric dose to be always smaller than in adults, irrespective of the relevance of physiological and disease factors.

Scaling for function, not for size

Currently, evidence suggests that a more reliable way to establish how dose relates to body weight is through the use of non-linear relationships, such as, e.g., allometric scaling (see Equation 1.1) [13].

$$P_{child} = P_{adults} \cdot \left(\frac{BW}{70}\right)^{x} \tag{1.1}$$

where P is the parameter of interest, BW the bodyweight of the individual child and x the allometric exponent.

Different examples show that this approach yields the most accurate results in terms of exposure in children [4, 14, 15]. Nevertheless, the qualitative description of this relationship with a non-linear function is only the tip of the iceberg: how such a relationship should be described mathematically is still subject of an intense debate. Some authors defend the use of "pure" allometry, fixing the exponent in the equation (e.g., 0.75 for clearance). They are *de facto* still scaling for size, since the relationship between parameter and weight is decided *a priori* [16–18]. Other authors prefer to estimate the exponent based on the available clinical data. In this case, body weight can be considered a surrogate for the physiological function (which is not always directly measurable) [19–21].

Besides allometric scaling, a more mechanistic approach is lacking for paediatric dosing recommendation which can counter the empiricism in current clinical practice. Such an approach must identify which physiological factors alter pharmacokinetics and how these (might) differ across the paediatric population(s), without relying on *a priori* assumptions about the correlation between pharmacokinetic parameters and demographic covariates. For these reasons, we strongly suggest to use a physiologically-based scaling approach, which we describe as **scaling for function**.

The concept of scaling for function relies on inferences from pharmacokinetic parameter distributions in children. This is equivalent to the rationale for assessing drug exposure in other special populations such as obese and hepatically impaired patients. In this way, dosing requirements are derived primarily from a model-based analysis of pharmacokinetic or pharmacokinetic-pharmacodynamic data [22, 23]. In fact, it is known that under steady-state conditions, total clearance (CL) determines systemic exposure. CL itself may be dependent on liver blood flow (LBF) and/or glomerular filtration rate (GFR). These processes may however not only vary with developmental growth but also with different (patho)physiological conditions [24].

In addition to GFR and LBF, ontogeny (the development and maturation of metabolic pathways) is proved to have considerable effects on drug elimination. However, enzymatic maturation (i.e., metabolic capacity) is completely unrelated to body weight, and as such does not follow developmental growth. Each enzyme system has its own phenotype, showing different times of onset and maturation rates: some enzymes are present at birth (CYP3A7, UGT) whilst others aren't (CYP2E1, CYP2D6, CYP3A4, CYP2C9), some mature to their maximum adult activity in just a few days (UGT2B7) whilst some require months to years to

reach complete maturation (UGT1A6). Finally, some enzymes may be critical to the metabolism of certain drugs during early age, but their role may become less relevant with developmental growth in favour of other metabolic pathways (CYP3A7, CYP2C9) [6, 25]. Consequently, ontogeny cannot be described simply by body weight differences. Even if a non-linear relationship is used to correlate exposure to weight, weight alone does not capture age-dependent non-linearities in metabolic capacity.

Whilst a scientific rationale for dose recommendation in children is desirable and necessary, awareness is lacking with regard to the implications it may have on prescription practice. As stated previously, most of paediatric labels report doses normalised by body weight. Many renowned researchers and regulatory agencies still defend such normalisation, as it eliminates the apparent need for dosing algorithms [26–28]. It makes prescription easy and simple, allegedly reducing the risk of prescription errors [29].

These views ignore, however, the non-linearity in the relationship between exposure and body weight. This was the case, for example, of the accumulation of chloramphenicol, which causes the grey baby syndrome. Chloramphenicol is mainly metabolised by UDP-glucuronyl-transferase enzyme, but this system is immature in newborns and renal excretion of the un-conjugated drug is limited. When chloramphenicol is linearly scaled according to body weight, the resulting exposure in newborns is five-fold higher than the one reached in adults, causing the well known adverse reactions. Dose adjustment according to a non-linear correlation between dose and body weight (Figure 1.1) was enough to avoid the adverse events (i.e., neonates and infants up to 1 month are given half of the dose recommended to the other groups) [30–33].

On the other hand, linear scaling based on body weight may lead to sub-therapeutic exposures in children. This is illustrated by the use of carbamazepine in the treatment of epileptic seizures. Carbamazepine clearance is largely dependent on CYP3A4, which is known to show increased activity in children as compared to adults. These differences result in a higher weighted-adjusted dose of carbamazepine to achieve comparable therapeutic plasma levels [34, 35]. Other examples of common medications for which dose scaling by body weight may be inappropriate are phenytoin [6], propofol [36] and aminoglycosides [37]. One must also consider the presence of co-morbidities, which can affect pharmacokinetics and pharmacodynamics. These interactions are usually uncorrelated with and independent of demographic covariates. The use of higher doses of tobramycin in the presence of cystic fibrosis is one of the best examples of the influence of co-morbidities on pharmacokinetics [38]. The implications of non-linearity are further exemplified by busulfan, enfuvirtide, oseltamivir and nelfinavir, for which dosing algorithms have been introduced. Dosing requirements for these drugs are presented in their label as tables, categorised by weight and/or other characteristics [39–42].

It is also important to highlight that some drugs may not require scaling at all and children should receive the dose recommended for adults (e.g., vaccines, antidotes) and that there are cases in which the recommended dose is similar (e.g., telithromycin, desloratadine, olopatadine) or even higher (e.g., digoxin)

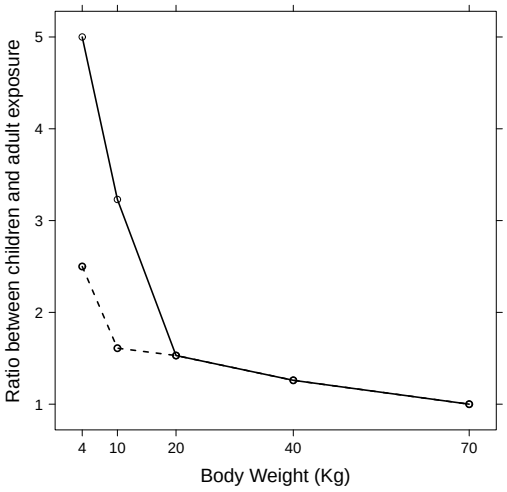

Figure 1.1: *Ratio of exposures to chloramphenicol between children and adults. Solid line: original dose (50 mg $kg^{-1}day^{-1}$). Dashed lined: dose adjustment to avoid grey baby syndrome (25 mg $kg^{-1}day^{-1}$ for babies up to 1 month). Empirical scaling of the paediatric dose based on body weight has led to overexposure to chloramphenicol*

than the dosing regimen in adults [43–47]. A summary of the paediatric dosing recommendation for these drugs is presented in Table 1.1.

Based on the evidence provided above, it is understandable that the rationale for dose adjustment entails more than the assumption of linearity between body size and drug exposure. In fact, one should not generalise the requirements for paediatric dose recommendation without further understanding of the physiological phenomena associated with developmental growth. It is evident that empiricism cannot continue as mainstream method for clinical research in children. Dosing recommendation in children must be derived from an integrated (model-based) analysis of pharmacokinetic and pharmacodynamic data, accounting for the role of disease factors as well as developmental growth. Moreover, optimal dosing in children ought to include an assessment of the impact of potential differences in mode of administration, pharmaceutical formulation and delivery devices.

The future

Concerted efforts into two distinct areas of paediatric pharmacology research are required to ensure accurate selection of doses for children. The first one involves revisiting dosing recommendations for those drugs which are already on the market but are used off-label in children. In this context, one should make use of the available pharmacokinetic, safety and efficacy data in adults and across the various

Table 1.1: *Examples of drugs commonly used in paediatric medicine for which the paediatric dose is not linearly correlated with body weight. References for each drug are provided in the text together with further details about the clinical implication of non-linearity between drug exposure and descriptors of body size*

Drug	**Therapeutic indication**	**Adult dose**	**Paediatric dose**
Chloramphenicol	Bacterial infection	50 mg/kg/day	50 mg/kg/day Neo: 25 mg/kg/day
Carbamazepine	Epilepsy	5-8 mg/kg/12 h	Ad: 5-8 mg/kg/12 h Ch: 3-10 mg/kg/8 h Inf: 3-10 mg/kg/8 h
Phenytoin	Epilepsy	2 mg/kg/12 h	Ch: 2.3-2.6 mg/kg/8 h Inf: 2.3 mg/kg/8 h Neo: 2.5-4.0 mg/kg/12 h
Propofol	Anesthesia	<55 y: 6-12 mg/kg/h >55 y: 3-6 mg/kg/h	2 m-16 y: 7.5-18 mg/kg/h
Busulfan	Cancer	0.8 mg/kg/6 h	<12 kg: 1.1 mg/kg/6 h >12 kg: 0.8 mg/kg/6 h
Tobramycin	Bacterial infection	3 mg/kg/day	Ch: 6-7.5 mg/kg/day Neo: 4 mg/kg/day Cy.Fib.: 10 mg/kg/day
Enfuvirtide	HIV	180 mg/day	11-15.5 kg: 54 mg/day 15.6-20 kg: 72 mg/day 20.1-24.5 kg: 90 mg/day 24.6-29 Kg: 108 mg/day 29.1-33.5 kg: 126 mg/day 33.6-38 kg: 144 mg/day 38.1-42.5 kg: 162 mg/day
Oseltamivir	Influenza	150 mg/day	<15 kg: 60 mg/day 15-23 kg: 90 mg/day 23-40 kg: 120 mg/day
Nelfinavir	HIV	2.5 g/day	7.5-8.5 kg: 0.8 g/day 8.5-10.5 kg: 1 g/day 10.5-12 kg: 1.2 g/day 12-14 kg: 1.4 g/day 14-16 kg: 1.6 g/day 16-18 kg: 1.8 g/day 18-22 kg: 2.1 g/day
Digoxin	Heart failure	1.4-4.0 μg/kg/day	Ch: 3-8 μg/kg/day Inf: 7.5-12 μg/kg/day Neo: 4-8 μg/kg/day

Neo=neonates, Inf=infants, Ch=children, Ad=adolescents, Cy.Fib.=with cystic fibrosis

age ranges in children. Used in conjunction with appropriate research tools, these data can confirm current clinical practice or provide the appropriate scaling factor to account for the differences associated with developmental growth. Critical to this evaluation are methodologies such as pharmacokinetic-pharmacodynamic modelling [48] and physiologically-based pharmacokinetic (PBPK) approaches [49–51]. It is unfortunate that a communication gap still exists between paediatricians and clinical pharmacologists, who can apply the aforementioned methodologies to validate current prescription practice, in many cases without the need for additional prospective trials. Institutional and cultural differences about the individualisation of dosing regimens, and more often ignorance of modelling & simulation concepts, prevent these efforts from becoming a paradigm in paediatric medicine.

The second area of attention refers to early drug development, for which there are no previous data in children. Not by chance, this subject has also become the focus of regulatory guidelines and policies [1–3]. Under the assumption of comparable exposure-response relationships between population adults and children, a model-based bridging approach can be used which relies on the assessment of primary pharmacokinetic parameter distributions (i.e., clearance, volume of distribution). Simulation scenarios can then be derived to explore the implications of non-linearity between exposure and demographic covariates [52]. Such scenarios can also incorporate differences in pharmacodynamics and in the exposure-response relationship, if applicable. Among other advantages, the use of modelling & simulation tools provides an algorithm for dose selection and prospective evaluation of safety and efficacy in a paediatric clinical trial. In conjunction with sparse blood sampling and adaptive trial designs, this approach ensures that accurate dosing recommendations are provided in the label at the time of launch.

Paediatric prescribers, including primary and secondary care physicians, are living in the twenty-first century, but for many diseases paediatric drug prescription still dwells in the empiricism of foregone times. It is time to change it. Despite the opportunities offered by the existing regulations and better quantitative methods in clinical pharmacology, the silent assent of current practices and beliefs in paediatric research seems to undermine the achievement of unmet medical need, i.e., allowing children to be given the right dose.

1.2 Model-based paediatric drug development: regulatory and methodological aspects

Based on the aforementioned considerations, it is now clear that the design, analysis and interpretation of clinical studies in children require specific techniques to ensure accurate decision-making regarding the pharmacokinetics, safety and efficacy of drugs in the target patient population. Modelling and simulation (M&S) techniques may allow one to circumvent some of the challenges and difficulties in the development of medicinal products in children. M&S can be applied to tackle issues in the implementation of clinical studies both from a practical and

conceptual perspective. M&S enables

- the use of sparse sampling schemes;
- the characterisation and prediction of pharmacokinetic-pharmacodynamic (PKPD) relationships;
- the systematic extrapolation and interpolation of data across populations (e.g., from adults to children);
- the use of inferential methods based on existing information from the scientific literature.

These elements are critical not only for accurately defining the dosing regimen in children. They support the assessment of the level of evidence required to characterise (potential differences in) pharmacokinetics, safety and efficacy.

Although no formal guidelines exist yet for model-based paediatric drug development [1], the usefulness of M&S techniques for protocol design, data analysis and dose selection has been recognised by industry, academia and regulatory agencies [53]. In fact, it is often the lack of a **conceptual framework** and **technical competences** that continue to hamper the widespread implementation of the approach. The process of drug evaluation is based on the degree of evidence that is gathered throughout the drug development process. In adults, this is mainly based on experimental data reflecting the proposed dosing regimen for a product in clinical practice (i.e., large phase III clinical trials). In children, however, the use of such large phase III trials may not be feasible or even implausible, as in the case of orphan drugs in rare diseases, for which the guideline for clinical trials in small populations states:

> *"Studies with few patients are often perceived as presenting a rather simple situation: there is not much information (data) and so simple (often descriptive) analyses are all that are warranted. It seems quite counterintuitive, therefore, that for 'simple' situations more complex approaches should be applied but this is exactly what is necessary. Crude (simple) methods may often be adequate when we have huge amounts of data - but when there are very few data, it is imperative that the most efficient and informative analytical methods should be used. Many of these methods involve 'statistical modelling'. Such models usually make assumptions about the data or the form of the treatment effect. With few data, these assumptions may not be testable or verifiable. However, assumptions add to the data so that more complex statistical models give us more information than simple descriptive statistics"* [54].

In the next sections, we will present an attempt to describe the scientific and clinical basis for a drug development framework in which dose rationale and protocol design are defined by M&S techniques. We show the importance of statistical concepts as the foundation for ethical clinical research in children. It should

become evident to regulators, clinical scientists and clinicians that when dealing with children the principle of *primum non nocere* must be extended to *primum non tacere*. The inability to optimally derive information from existing data or clinical protocols also represents a breach of ethical principles.

Bridging

Before discussing the potential implications of a framework for paediatric drug development, it is important to clarify some of the terms underlying the use of a model-based approach. With **evidence**, we refer to data (facts and information) generated or used to support or reject a hypothesis. Evidence is the currency by which one fulfils the burden of proof and consequently draws conclusions. In addition to evidence gathering, conclusions can also be drawn by deduction or deductive reasoning. **Deduction** is the attempt to show that a particular conclusion necessarily follows from a set of premises. **Inference** is the act of drawing conclusions by deductive reasoning. Finally, **hypothesis testing** is the method of making decisions using data, whether from a controlled experiment or an observational study. Whilst statistical hypothesis testing has been used as a key technique in frequentist statistics, it is considered sub-optimal for the purposes of decision-making.

The need for evidence based on controlled, well-designed clinical trials to obtain paediatric information for paediatric medicines is now a matter of consensus. In fact, the recent introduction of paediatric legislation in the EU, the renewal of the pediatric rule in the USA and international guidelines, such as ICH-E14, have provided the basis for the requirements for the evaluation of medicinal products in children. However, this should be done without compromising the well-being of paediatric patients participating in clinical studies. Poorly designed protocols may expose them to unwanted side effects or result in underdosing without the expected efficacy. This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole. Most importantly, these guidelines have not addressed the lack of a framework for the rationale for a clinical development plan, nor considered the role of advanced statistical modelling as the method of choice for making inferences and designing clinical trials.

The fact that paediatric development is likely to follow the adult clinical programme imposes careful consideration about the evidence level required from the target population. Medicinal products for diseases predominantly or exclusively affecting paediatric patients will be based on a development program entirely conducted in the paediatric population, except for initial safety and tolerability data. In all other situations, i.e. when a medicinal product is to be used in the paediatric population for the same indication(s) as those studied and approved in adults, one must ensure relevant information about the exposure-response (PKPD) relationship is generated in this reference population. As the evidence for PKPD relationships in adults requires a well-thought process and additional data analysis efforts (compared to what is currently demanded by regulatory guidelines), paediatric clinical development plans are faced with the need for efficacy trials,

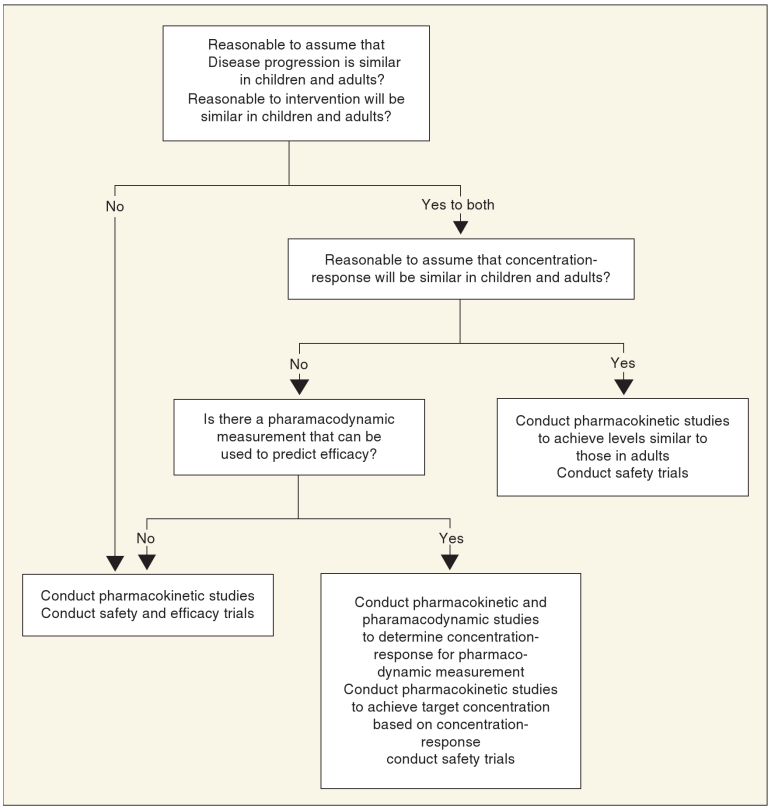

Figure 1.2: *Paediatric study decision tree (adapted from FDA's Guidance to industry: exposure-response relationships - study design, data analysis, and regulatory applications; 1993) and [55]*

which in many cases are scientifically and ethically questionable.

Hence, clarity is lacking about which evidence must be obtained directly in children and which inferences can be made based on *in vitro* or *in vivo* experiments or on data from other patient populations and indications. Bridging has been introduced as a regulatory term to refer to the extrapolation of data across populations. In paediatrics, it is promoted by the regulatory agencies (EMA and FDA) through various guidelines on clinical trials in children. In particular, the clinical investigation of medicinal products in the paediatric population (ICH E11) states that

> *"when a medicinal product is to be used in the paediatric population for the same indication(s) as those studied and approved in adults, the disease process is similar in adults and paediatric patients, and the outcome of therapy is likely to be comparable, extrapolation from*

> *adult efficacy data may be appropriate. In such cases, pharmacokinetic studies in all the age ranges of pediatric patients likely to receive the medicinal product, together with safety studies, may provide adequate information for use by allowing selection of pediatric doses that will produce blood levels similar to those observed in adults"* [56].

The same methodology of course is applicable when a medicinal product is to be used in younger paediatric patients for the same indication(s) as that studied in older paediatric patients. The possibility to investigate the pharmacokinetics properties of a drug in the paediatric population and use drug exposure to make inferences about the efficacy and safety of a treatment is therefore of pivotal importance in the development of medicinal products for children.

Allometry

The first methodological aspect pertinent to the use of inferences in a model-based approach regards the role of developmental growth on drug disposition. Often inferences about the magnitude of the differences in pharmacokinetics between adults and children are based on the assumption of a pre-defined relationship between physiological processes and body size, i.e., allometry. Given the variety of methods currently used in M&S, it is of interest to understand the different connotations of this term in biological research. From its first appearance in the XIX century, the term allometry has developed and differentiated into three main subgroups:

- static allometry;
- phylogenetic allometry;
- ontogenetic allometry.

Static allometry refers to the biological changes associated with various sizes in a given population, whilst phylogenetic allometry (also called evolutionary allometry) describes size relationships across species, and is commonly used to scale doses from pre-clinical studies to the first time in humans. Finally, ontogenetic allometry correlates the physiological changes with the growth of the individuals over time. The latter is the basis for the allometric scaling of PK parameters from adults to the paediatric population. Allometry states that metabolic rate as well as many other biological processes is related to body mass. This relationship is expressed using an exponential equation, the general form of which is the following:

$$P = a \cdot BW^b \tag{1.2}$$

where P is a physiological parameter correlated with the body weight BW, a and b are the coefficient and the exponent of the allometric equation, respectively. b is also called scaling factor, because it describes the shape of the exponential equation linking the parameter of interest to body weight: when $b = 0$, the body mass has no

effect on the parameter. When $b = 1$, the relationship is linear, and a represents the slope of the function. In paediatric pharmacology, allometry has been used to scale pharmacokinetic parameters from adults to children when paediatric data are not available, or to improve the fitting of models describing paediatric pharmacokinetics. Clearance and volume of distribution are the parameters most commonly scaled using allometry, with b being fixed respectively to 0.75 and 1, so that the equation 1.1 becomes

$$CL_{child} = CL_{adults} \cdot \left(\frac{BW}{70}\right)^{0.75} \tag{1.3}$$

$$V_{child} = V_{adults} \cdot \left(\frac{BW}{70}\right)^{1} \tag{1.4}$$

As previously mentioned, the exponent of 0.75 for clearance has been widely debated [57]. Many researchers have criticised the fixed 0.75 value of the exponent, showing that others exponents may lead to better predictions when scaling the clearance [20, 58–68]. Moreover, it is known that using a 0.75 exponent in equation 1.3 may lead to the overprediction of the clearance in younger patients [14]. Given the importance of inferential methods for accurate design of bridging studies, one needs to be aware of the limitations allometric methods represent to the prediction of pharmacokinetics in children (especially absorption and total clearance). Such limitations have been demonstrated empirically by many researchers. Here we focus on its theoretical shortcomings:

- First of all, allometry links clearance to size only. Body weight does not take into account the functional or maturation changes that occur in children (especially the younger ones). Some efforts have been made to include additional factors, so that maturation can be factored into equation 1.3 [15, 69, 70]. However, these factors didn't prove to increase the predictive power of allometry and their use remains limited. Furthermore, the need to apply "correction factors" to adjust allometric predictions implies that the assumptions underlying allometry are not necessarily correct from the very beginning.

- The slopes reflecting basal metabolism vary during the different stages of life [71]. Therefore, it makes no sense using the same exponent across different age groups to predict the clearance in children, despite the exponential nature of the function. Fixing the slope to 0.75 makes little sense if basal metabolism diverge considerably from that value [72].

- Equation 1.3 implicitly imposes bi-directionality in the relationship between clearance and body weight. In theory, if paediatric clearance can be predicted from adults, the same should apply for the prediction of adult clearance. This is seldom the case.

- Fixing the exponent to a single value of 0.75 also implies that the relationship between clearance and bodyweight remains constant across the overall range of body weights in a given population. This may appear correct when considering the population as a whole, but it ignores individual differences.

- Another issue with allometry resides in defining *a priori* the nature and extent of the relationship between parameters and covariates (e.g. clearance and body weight). Based on such a prerequisite, dose adjustment should be necessary in adults as well, since body weight in the adult population can vary considerably (e.g. obesity, cachexia). However, this does not always happen and many drugs are administered in adults as a total fixed dose, irrespective of body weight.

- Many drugs are extensively studied in adults, but show no relationship with body weight. According to allometry such circumstances do not exist, as clearance should be scaled according to the exponential equation irrespective of whether body weight plays a role in the elimination of the drug. Evidence for this discrepancy is shown by the results of a recent survey using GlaxoSmithKline's clinical data repository. We have searched drugs for which a population pharmacokinetic model in adults was developed and a full covariate analysis (including body weight) was performed. In 9 out of 10 compounds, the pharmacokinetic analysis showed that clearance was not affected by body weight at all. The remaining compound showed clearance exponentially linked to body weight with a scaling factor (allometric exponent) of 0.228, which is very different from the theoretical value. In Figure 1.3 the individual clearances versus body weight are reported, together with their estimated correlation (solid line) and the allometric correlation (dashed line). Even though the range of body weights in many is cases rather large (from 40 to 150 kg), no clear correlation between body size and pharmacokinetics is apparent in these plots.

- The concept of dose adjustment should be primarily linked to differences in physiological or functional status rather than size. For instance, special populations are dosed according to special algorithms that do not necessarily take body weight into account. The Modification of Diet in Renal Disease (MDRD) Study Group developed a four variable formula to estimate the glomerular filtration rate (GFR) without incorporation of weight as a variable, but included serum creatinine level, age, sex, and race [73]. In obese people, drugs are scaled in various fashions, depending primary on a drug's lipophilicity profile [22, 74]. Similar concepts should be incorporated into the rationale for paediatric dosing.

- Finally, it should be noted that allometry correlates intrinsic clearance with body weight. Scaling the dose from adults to children requires one to consider differences in total clearance rather than intrinsic clearance. Based on allometry, all other physiological factors (bioavailability, absorption, pH

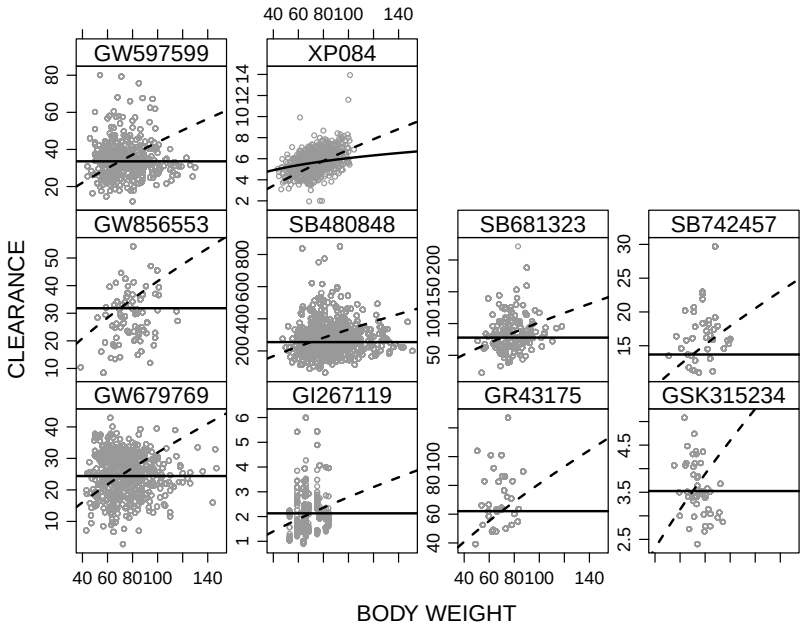

Figure 1.3: *Individual clearances* vs. *body weight as estimated in 10 drugs currently in development at GlaxoSmithKline. Solid line: mathematical correlation estimated by the models, dashed line: theoretical allometric relationship*

in the stomach, transit time, etc) must be assumed to remain constant. This is clearly not true: the younger the child, the larger the differences in physiological function as compared to adults.

The aforementioned arguments strongly suggest that there is no rationale for applying an allometric exponent of 0.75 on pharmacokinetic parameters such as clearance. Hence, a more pragmatic approach may need to be considered in which the exponent is estimated, rather than fixed during data analysis. The use of 0.75 could be considered for simulation purposes only when no other factors contraindicate its use *a priori*.

Non-linear mixed effects modelling

The second and most important aspect pertinent to the use of inferences in a model-based approach regards the choice of parameterisation and hierarchical nature of random effects so that prior knowledge can be incorporated into the analysis and conclusions about the implications of developmental growth and other age-related effects can be derived on an individual basis. It is also clear that despite practical

and ethical limitations in paediatric research protocols, accurate inferences must be made about of drug properties in the overall target population. In pharmacokinetic data analysis, it is not uncommon for the relationship between the explanatory or independent variable (i.e., time) and the response or dependent variable (i.e., drug concentration) to be handled in a non-parametric manner, as is the case of a typical non-compartmental analysis. In contrast, the use of a parametric approach based on non-linear mixed effects (NLME) models provides a tool for handling repeated-measurements data in which the relationship between the explanatory variable and the response variable can be described by a single function, allowing model parameters to differ between subjects. An immediate advantage of the approach is that the within-subject variability for a given individual can be distinguished from the differences between subjects [75].

In NLME modelling, the term *mixed* refers to the use of both fixed effects (characterising the typical individual: the mean) and random effects (describing the dispersion or parameter distribution). The latter are divided into two conceptually different levels: the difference between the individual prediction and the observation (residual error) and the variability between subjects (IIV). There may also be circumstances in which individual parameters vary longitudinally between occasions, randomly or due to some unknown physiological process. In such cases, a third level of variability can be introduced, i.e., the inter-occasion variability (IOV).

The general structure of a mixed effects model can be described as follows:

$$y_{ijk} = f\left(X_{xjk}, P_{ik}\right) + \epsilon_{ijk}, \qquad \epsilon_{ijk} \in N\left(0, \delta^2\right) \tag{1.5}$$

where y_{ijk} is the j^{th} observation at occasion k in individual i. y_{ijk} is described by a linear or non-linear function $f()$ of a vector of individual parameters P_{ik} and a vector of independent variables X_{ijk}. Typically in NLME modelling, independent variables are time (pharmacokinetic models) and dose or drug exposure (pharmacokinetic-pharmacodynamic models). X_{ijk} may also encompass other fixed effects, such as demographic covariates. The ϵ_{ijk} describes the error model, i.e., the differences between the individual prediction and the observation at each measurement (residual variability). In equation 1.5, residual variability is expressed by an additive model, but exponential and proportional models are also common [76].

The individual parameter P_{ik} for the i^{th} individual at the occasion k can be described by the expression:

$$P_{ik} = \theta_{TV} \cdot e^{\eta_i + k_i}, \qquad \eta_i \in N\left(0, \omega^2\right) \quad \text{and} \quad k_i \in N\left(0, \pi^2\right) \tag{1.6}$$

in which θ_{TV} is the typical value (fixed effect) of parameter P in the study population, and η_i and k_i are the random values (or random effects) describing the differences between the typical (population) value and the individual parameter value, respectively, relatively to the subject and occasion. In equation 1.6, the random effects are log-normally distributed with regard to the fixed effects.

The use of NLME is justified and appropriate when the data available per patient are sparse (i.e., the number of samples collected per subject is limited or insufficient to describe the overall concentration-time course). In addition, it is

recognised as the most effective method to perform meta-analysis of data arising from different studies and to incorporate prior knowledge to the estimation of model parameters. It allows one to adjust for different variances (e.g. presence of co-morbidity in a given subgroup in the population) and to explore confounding correlations, when the design of the study correlates with the outcome (e.g., effect of weight *vs.* gender).

Another appealing feature of NLME models in paediatric drug development is the possibility to handle missing data (e.g., dropout, values below the limit of quantification or when not every subject reaches a pre-defined endpoint). NLME methods also represent a major advancement for dealing with data imbalance.

Covariate selection

As highlighted in previous paragraphs, the influence of developmental growth and maturation on physiological processes cannot be ignored when considering the dose rationale for children. Such effects can be described parametrically by the incorporation of covariates on primary model parameters. A predictive model is a model in which the IIV is reduced through the use of mechanistic understanding of the pharmacokinetic system, while still adhering to the paradigm of remaining parsimonious. The inclusion of covariates which are directly linked to changes in the underlying physiological function or reflect such changes can be easily implemented in NLME models. Covariates may refer to individual characteristics (e.g., body weight, age, gender, genotype) or to external factors (e.g., concomitant medications). A third type of covariates known to influence parameter estimates is called Markovian. These covariates are data-dependent variables (e.g., time since last observation), which can be important when describing phenomena such as dropout.

To determine which covariates are influential and have a significant effect on the pharmacokinetics of a drug, a covariate analysis must be performed. Various procedures exist that enable a mechanistic or physiological basis for the evaluation of covariate effects [77–79]. From a clinical perspective, the ultimate objective of a covariate analysis is to identify sources of variability and provide the scientific basis for dosing recommendations and individualisation of dosing regimen.

Optimal design

Clinical protocols should be designed bearing in mind that the conclusions derived from an experiment depend on the accuracy of the parameter estimates obtained from the analysis of the data. Most clinical researchers often relate the degree of certainty upon which one draws conclusions about experimental data to the so-called statistical power. Little attention is paid to two other important statistical aspects, namely precision and accuracy, in particular when considering experimental conditions in which the use of hypothesis testing is not applicable or inappropriate. In addition to the empiricism in the dose rationale, the evaluation of pharmacokinetics in children is often fraught with suboptimal experimental conditions, which

can undermine the validity of inferences made from limited sampling and small number of patients. In such circumstances, optimal design theory can be used during the planning phase to ensure maximisation of the information that can be obtained from an experiment. In fact, different aspects of an experimental protocol can be considered for the purposes of optimisation. An efficient design may lead to a reduction in study costs, as fewer samples or subjects may suffice [80]. The theory of optimal design relies on the availability of a predefined model and parameter estimates or intervals. Whilst various methods and algorithms are available, which can be used as optimality criteria, from a mathematical standpoint, all of them involve the optimisation of the Fisher information matrix [81].

A discussion about the different optimality criteria and the underlying mathematical theory is beyond the scope of our review. However, it is important to understand that the most widely used methods in pharmacokinetic research are D-optimality and ED-optimality [82]. These methods consist in reducing the uncertainty associated with the parameter estimates by minimising the content of the ellipsoidal confidence region of the parameters and thereby maximising the determinant of the Fisher information matrix [83]. Various software programs are available for the optimisation of sampling times, sampling intervals, number of patients and dose levels in protocols in which the use of sparse sampling is required. Amongst others, optimisation can be performed with POPT [84], PopDes [85], PFIM [86], PkStaMP [87] and PopED [88]. An overview of the functionality available in these software programs is presented in [89].

Optimal design methods substantiate the use of sparse sampling schemes by specifying sampling points at the most information-rich areas of the drug concentration *vs.* time curve [90]. Despite the potential impact that optimality concepts can have on the design of paediatric protocols, its use remains rather limited and obscure in this field. There are only a few studies in the published literature, which mention optimal design as the basis for the choice of sampling times and number of subjects [91–93]. There are various reasons for this drawback, the most important one being the lack of a structural model in the target population and a framework to tackle model and parameter uncertainty. The use of optimal design requires well-defined structural and statistical models, which are not available in early clinical development. Theoretically, optimality concepts can be used to support the identification of the most suitable model to describe pharmacokinetics in children under the assumption of a common parameter-covariate correlation in adults and in children. Despite the uncertainty in parameter estimates, optimality has been successfully applied to mizolastine [94], famciclovir [95] and to the maturation of cytochrome P450 3A4 [96].

Analysis of pharmacokinetic data

In addition to the conceptual issues presented in the previous sections, the use of a model-based approach in early clinical development implies the availability of specific competences for the design, analysis and interpretation of clinical studies. In the next few paragraphs, we introduce some of the technical requirements for

modelling and simulation of pharmacokinetics in children. These aspects are critical for dose selection in pharmacokinetic bridging studies.

Pharmacokinetic data can be analysed by different methods. They are often classified into:

- non-compartmental;
- compartmental;
- physiologically-based pharmacokinetic (PBPK) methods.

Non-compartmental methods are descriptive and require minimal assumptions regarding drug disposition processes. Analysis results are usually summarised in terms of secondary parameters, such as C_{max}, T_{max} and area under the concentration *vs.* time curve (AUC). An important requirement for non-compartmental analysis is the need for frequent sampling schemes. In light of the challenges and difficulties in the implementation of pharmacokinetic studies in children, it is surprising to find a large number of cases in the published literature, in which non-compartmental methods are applied to the analysis of paediatric data [97–107]. Unfortunately, defenders of this method do not seem to realise that no clear distinction can be made between within and inter-individual variability. All variation is handled as residual noise.

Compartmental models and PBPK models are by far more suitable for the analysis of paediatric pharmacokinetic data. In compartmental models, different hypothetical compartments, connected through differential equations, are used to describe drug absorption and disposition into the body. A common criticism to this approach is that it is not completely mechanistic, since model compartments have no direct link with real body organs or tissues. Mammillary models and well-stirred models are examples of such simplifications. In contrast, the use of PBPK models allows one to transcribe into mathematical equations key anatomical, physiological and physicochemical properties relevant to ADME processes [108]. Compartments are used also in PBPK modelling, but in this case they correspond directly to specific organs or tissues, and the interconnection between compartments corresponds to blood and lymphatic flows. Despite some degree of simplification, PBPK models can be considered as the most mechanistic approach for the analysis of pharmacokinetic data. The main limitation for the use of PBPK models is the amount and quality of the data required, which are rarely available in paediatric trials. Therefore, the compartmental approach is currently the most used modelling tool in paediatric pharmacology. From a parameter estimation standpoint, compartmental pharmacokinetic models can be parameterised according to a hierarchical structure, which allows identification of parameter distributions and consequently of inter-individual variability. Most NLME software programs available in this field are based on maximum likelihood methods that rely on the maximisation of the likelihood of the data given the model [109–112]. Whilst these methods represent a major advancement for the analysis of pharmacokinetic data, they also impose limitations due to the very nature of the statistical theory

upon which they are based, i.e., the maximum likelihood. In other words, it should be noted that despite the characterisation of parameter distributions, the prerequisites for fitting small data sets to a hierarchical model based on maximum likelihood methods do not warrant precision or absence of bias. An additional consideration regarding the use of maximum likelihood methods concerns their role in the model selection process, as fitting and diagnostics are ultimately determined by the underlying statistical methods.

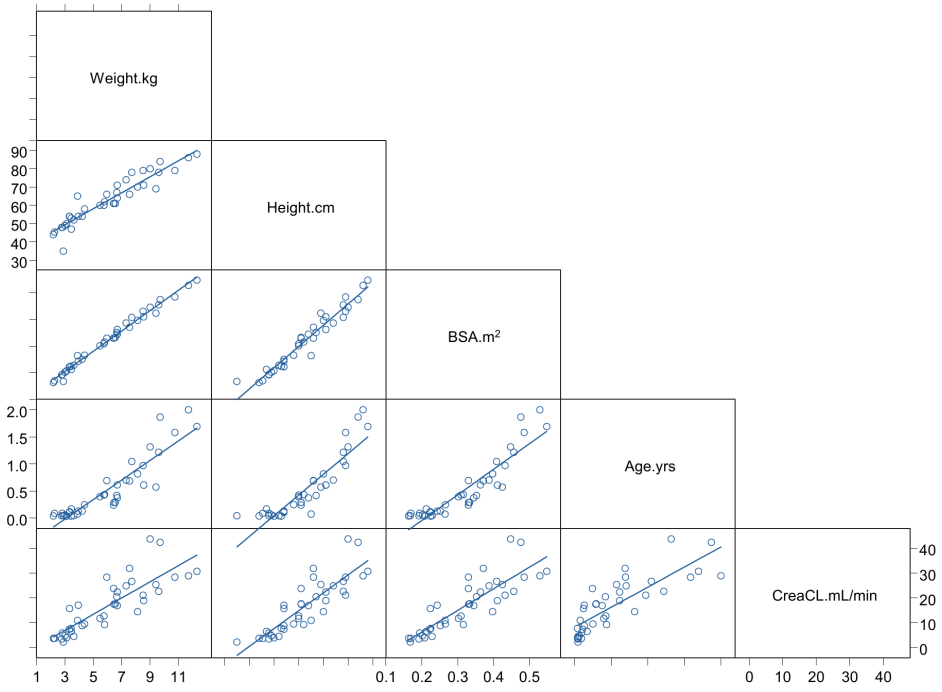

Figure 1.4: *Example for collinearity in a paediatric covariate data set (n = 40; age range 12 days to 2 years) [92]*

Of particular relevance for paediatric data is the selection of the true covariates and accurate identification of the covariate-parameter correlations. In contrast to covariate selection in adult healthy volunteers, which may represent a uniform population, children may include individuals completely different from each other, such as neonates and adolescents. Even when groups are considered within narrower age intervals (e.g., pre-term newborns, term newborns, infants, toddlers, children and adolescents) differences in drug disposition might differ considerably due to developmental growth, maturation and other factors determining changes in physiological function or disease processes. Estimation of covariate effects will therefore be highly dependent on the available data. However, the inclusion of

a wide range of patients, with sufficient representation of the covariate effect, does not automatically solve the problem, as additional data contribute in a limited way to the description of changes in pharmacokinetics on an individual level. Inevitably, the use of surrogate descriptors (i.e. demographic covariates) to describe developmental growth and maturation processes may produce biased parameter estimates [113].

Strictly correlated to the aforementioned points is the predictive performance of pharmacokinetic models. Traditionally, models selected during data fitting (i.e., parameter estimation) are considered suitable for simulations and extrapolation purposes, without formal assessment of their predictive performance. In paediatric pharmacology this represents a serious problem, given that dosing recommendations are often directly extrapolated using parameters estimated from a different paediatric group. This approach is based on the assumption that the parameter-covariate relationship remains the same across and beyond the range of covariates present in the original data set. However, it should be noted that the immediate consequences of such an assumption are the under- or overestimation of the exposure in the new population.

Clinical trial simulation

We conclude this overview on the requirements for a framework for the development of paediatric medicines emphasising the importance of simulations as the basis for the dose recommendations and study design. Relying solely on the evidence from small clinical trials may be insufficient for accurate decision making [114, 115]. Furthermore, it should be noted that even when a parametric approach is used to analyse the data, inferences made from model parameters may be irrelevant without an experimental or clinical context (i.e., protocol design, population inclusion criteria). In physics, the influence that the experimental setting may have on experimental data has since long been accepted. In paediatric research this subject is barely considered as a point for discussion in the planning and design of clinical trials.

From a conceptual standpoint, computer simulation consists in the use of mathematical and statistical models to explore, explain, and predict the behaviour of the system or process described by the model [116]. The first application to these concepts date back probably to aeronautical engineering [117]. In clinical pharmacology, the use of clinical trial simulations (CTS) is a much more recent application of such technologies. CTS allows the investigation of the impact of different design characteristics on the outcome of a trial prior to exposing patients to an experimental drug [64, 118–120]. CTS ensures the selection of protocol designs that can effectively meet the objectives of a research protocol. CTS can also be used to explore the implications of differences in (patho)physiology or pharmacological properties across patients and dose levels, thereby enabling the assessment of inefficiencies and identification of corrective measures before trial implementation [121]. In addition, CTS offers the opportunity of evaluating the influence of protocol deviations on outcomes of interest [122].

Figure 1.5: *The diagram depicts the major components of a clinical trial simulation (CTS). In model-based drug development, CTS can be used to characterise the role of developmental changes and maturation on pharmacokinetics, enabling among other things the assessment of covariate effects (e.g., age, body weight) on the overall target population. In conjunction with a trial model, CTS allows the evaluation of trial outcome taking into account uncertainty and design factors, including the implications of different statistical methods for the analysis of the data*

From a drug development perspective, it is the trial execution model that enables quantification of the effect of factors such as patient compliance, dropout, protocol deviations and covariates (i.e., inclusion/exclusion criteria). In the context of a paediatric programme, CTS can be used in conjunction with bridging studies to evaluate the implications of different dosing regimens and covariate effects across age groups [64, 118–120]. Another, even more potentially important reason for the use of CTS when planning or analysing bridging studies is the possibility to evaluate the implications of frequently observed collinearity between covariates. Collinearity refers to the correlation between covariates (e.g. BW, height and body surface area), that is, some of the covariates are nearly totally predicted by the others. In this situation, it becomes extremely difficult to estimate the contribution of individual covariates on a pharmacokinetic parameter, because no reliable estimates for individual regression coefficients can be determined (Figure 1.4). The implications of collinearity in covariates on the model-building process in non-linear mixed effect modelling are often overlooked and cannot be dissected when dealing with small data sets. Covariate model building with covariates showing a high degree of correlation ($r > 0.5$) may lead to wrong conclusions about their effect [123], i.e., one may not consider it influential even when, in fact, they are. Based on historical data, the implications of collinearity can be explored by CTS.

In fact, one can perform a virtually infinite number of "what-if" scenarios in which not only covariate effects, but also other model assumptions and design factors are tested (Figure 1.5). Such clear-cut results cannot be obtained by traditional experimental protocols or meta-analysis, because confounding factors cannot be dissected independently. Most importantly, one can assess the impact of uncertainty on model predictions and thus provide appropriate recommendations for trial design and/or dosing selection.

It is unfortunate that the application of CTS remains limited despite the practical ethical challenges associated with paediatric research protocols. In the future, it is anticipated that model-based approaches will become both the instrument and the aim of paediatric programs, yielding a more solid basis for the dose rationale and labelling recommendations without the burden of trial and error.

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