

Design and Conduct of Early Phase Drug Studies in Children; Challenges and Opportunities

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What Already Known About This Subject

- There have been numerous ethical, scientific and pragmatic barriers to the conduct of early Phase drug studies in children.
- This has resulted in a therapeutic gap in that drugs are frequently used in children on an “off label” basis which has been associated with an increased risk for adverse effects.

What This Review Adds

- There have been a number of developments in the past decade that have addressed the ethical and feasibility barriers to conduct of drug studies in children.
- This review provides a perspective on these developments as well as the regulatory changes mandating studies in children for new therapeutic agents in Europe and the US.

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Summary

It has historically been very difficult to conduct early Phase drug studies in children for a number of reasons related to ethics, acceptability, rarity, standardization, end points, safety, dosing and feasibility. Over the past decade there have been a number of developments including novel clinical trial design, *in silico* pharmacology and microdosing that have significantly enhanced the ability of investigators to conduct early phase drug studies in children. While the evolution of drug therapy is creating a series of new challenges, there has never been a better time for conducting drug studies in children.

Introduction

The current drug development process began after the Elixir of Sulfanilamide tragedy – in which a number of children died due to the use of diethylene glycol as a solvent - triggered the passage of the US Food and Drug Act in 1938 (1). This was intended to ensure that drugs were safe and effective prior to approval for marketing. It should not be forgotten that the impetus for this act was a therapeutic disaster largely involving children. One consequence of this was the current drug development process, which after pre-clinical studies involves Phase I (first-in-man), Phase II (first-in-patient) and Phase III (comparison to standard therapy) studies. An additional tragedy that spurred changes in drug regulation was the Thalidomide Tragedy in the early 1960's that led to both the Kefauver-Harris amendments to the Food and Drug Act in 1962 and the creation of national spontaneous reporting schemes for adverse drug reactions such as the Yellow Card Scheme in the UK (2, 3). While children have benefitted from the spontaneous reporting schemes, the other changes that were intended to provide safer drug therapy for children had quite the opposite effect. The Kefauver-Harris amendments stated in order to be approved for marketing a drug must not only be safe but also have substantial evidence of benefit under the conditions of use as defined in the product monograph, and provided powers for the Food and Drug Administration to enforce this. The result was that, rather than ensuring that well designed studies were conducted in children, product monographs simply stated, in more or less similar terms, that safety and efficacy of the drug in question had not been evaluated in children along with a legal disclaimer against use in children (2). This unintended consequence of a well meaning act was best described by Shirkey who used the term “the

therapeutic orphan” to describe that the majority of drugs on the market had no labeling for use in children – despite the fact that these drugs were commonly used, often as first line therapy, in children (2,4).

Over the past 20 years there has been a concerted effort to address these problems, including development of national and international research networks to conduct drug research in children as well as changes in the drug approval process by drug regulatory authorities that have not only increased knowledge with respect to approved drugs but also have mandated inclusion of children in pre-marketing studies of drugs likely to be used by children (5). Examples include the *Best Pharmaceuticals for Children Act* and the *Pediatric Research Equity Act* that became a permanent part of American law as part of the Congressional approval of the *FDA Safety and Innovation Act* in 2012 and the European equivalent, the *Regulation on Medicines for Paediatric Use* (5,6). The regulatory agencies on both sides of the Atlantic have the ability – and indeed the mandate – to require companies making new drug submissions to provide a detailed plan (Pediatric Study Plan in USA, Paediatric Investigation Plan in Europe) for drugs likely to be used in children. New therapies that are likely to be useful in treatment of children will therefore need to include children as part of their drug development plans (7,8). This will create challenges as this has historically not been part of drug development planning for most new therapeutic entities, but there are also a number of advances that present opportunities to address this.

The conduct of early phase drug research is challenging at the best of times (9). There are a number of specific issues associated germane to enrollment of children in early phase drug trials and these will be considered in turn.

Ethics

The involvement of children in research studies has been hotly debated and this is a field in constant flux. Since the “Great Divide” after World War II that established the importance of research ethics and informed consent, there has been an on-going debate as to the ethical issues involved in the participation of children in research (9-11). This has been true in the United States, Europe (ftp://ftp.cordis.europa.eu/pub/fp7/docs/ethical-considerations-paediatrics_en.pdf), Canada (<http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/>) and many other jurisdictions (12). Historically

there has been a pendulum varying between a somewhat *lassie faire* approach to inclusion of children in drug studies with the arguably nihilistic view that children should not be involved in drug studies (9-12). Over the past decade the position has increasingly been made that drug studies in children are essential in order to provide evidence to guide safe and effective drug therapy and to facilitate the development of drugs for common and important paediatric disorders (13).

There are now ethical constructs that permit and even encourage involvement of children in drug research, notably when this will be of material benefit to children with disorders targeted by the agent in question. There is on-going discourse and evolution that increasingly this has included discussion of ensuring that being involved in research would not involve more than minimal risk. While avoiding minimal risk usually means that with the exception of children with cancer it is unlikely children will be involved in Phase I studies children would certainly be ethically eligible for Phase II and Phase III studies. There has been an increasingly call that ethical approval would require not only consent from parents but also assent from the children, certainly for adolescents (14-16). The question of how best to secure informed consent for drug research in adolescents remains problematic, in that in many jurisdictions informed minors can consent to significant medical procedures – including those associated with significant risk – but often cannot themselves consent for participation even in very low risk research studies. This remains an area of active debate and discussion.

Acceptability

The issue of acceptability alludes to questions with the child's family and also with clinicians, institutions and investigators. Historically there has been believed to be reluctance for parents to enroll children in clinical trials. Recent work has suggested that this may be more perception than reality (17-19). A multi-centre study in France demonstrated that refusal rate for clinical studies in children was related to the perceived burden on the family on the part of the paediatrician charged with enrolling patients in the study (20). This supports our finding in an earlier Anglo-Canadian study that showed that paediatricians with limited training in ethics were very reluctant to enroll children in clinical trials (19). The degree of comfort of study personnel in working with children and families appears to be a key factor in success or failure of drug studies in children with respect to enrollment or lack

thereof. It is also increasingly evident that children are interested in being involved in studies for altruistic reasons with respect to the well being of other children.

In addition to individual investigators the degree of comfort with drug studies in children varies considerably between institutions, sometimes with no clear link between experience in child health care and degree of comfort for recruiting children to drug studies. In this context, the creation of regional and national networks for children's research has been a great opportunity in terms of providing standards and resources to enhance the design and conduct of clinical research – including drug research – in children. An early example was the National Institutes of Health Pediatric Pharmacology Research Network linking research units throughout the United States while a more recent example germane to the UK is the Medicines for Children Research Network created by the National Health Service which brought together expertise in paediatric drug studies across the United Kingdom (22). In the latter case this has been merged with the Paediatric Specialty Group to create a community of clinical practice that provides national research expertise in studies involving children, including drug studies (<https://www.crn.nihr.ac.uk/children/>). This creates the opportunity for shared expertise and more rapid translation of best practices.

Rarity

The issue of rarity speaks to a dichotomous reality in paediatric health care, in that many disorders are rare at any individual institution but are collectively reasonably common. We demonstrated this in a study of drug utilization in a cohort of one million Canadian children followed for a year, in which 70% of drug use was among 20% of children, these children representing a number of serious and chronic conditions (23). We also found that these children were largely cared for in 16 academic health science centres across the country. Hence clinical trials of new therapies are clearly needed but it is difficult to use a single centre and sample size was been a frequently cited problem for drug studies in children (6).

Thus in addition to acceptance the development of regional, national and international networks have been instrumental in providing mechanisms for timely recruitment of large numbers of patients using common instruments and with the evaluation of common outcomes. This has been most successful in paediatric Haematology-Oncology and Neonatology, as both fields have made considerable progress in assessing therapy and

developing evidence-based treatment protocols which have resulted in the survival of very small pre-term infants and a very high rate of cure for many childhood cancers (6, 24, 25). Increasingly other groups – including academic general paediatricians and critical care paediatricians – are developing networks to apply the strength of synergy to problems within their care and research domains (26, 27). The existence and development of these networks provides a much improved platform to support drug research in children. Additionally, these networks can support highly specialized units such as Phase I units for childhood cancer, facilities that are uncommon but very important (28, 29).

Standardization, End Points and Safety

One of the key elements in drug research is the clinical trial. Since the first curative clinical trial - conducted in 1946-47 by the MRC Tuberculosis Research Unit to study streptomycin in the management of pulmonary tuberculosis – the randomized clinical trial has become a gold standard in the drug development process (6, 30, 31). For many years a randomized placebo-controlled double blind clinical trial was considered essential to the drug development and approval process. This has been a problem in drug studies in children for several reasons (6). There have been issues with ethical approval and conduct as noted above. As well, there has been reluctance to use placebos during drug research in children. As the number of effective therapies has evolved, this question has become germane as well to clinical trials involving adults.

A key question is selection of a suitable end point, notably as this drives sample size and analysis strategy (6, 32). These end points may include biomarkers, the validity of which may have not been established in children. Development of valid and reproducible end points has become a research field in and of itself. An issue that complicates clinical trials in children is that many end points that are commonly used in adult clinical trials have not been validated in children – or indeed may not be possible (6). As an example, the evaluation of the efficacy of analgesic interventions in young children and infants was problematic as many validated instruments for the evaluation of pain involved self-report, a problem for populations that are non-verbal or who lack numerical literacy (33). However, great progress has been made over the past two decades in developing and validating end points that are relevant to and achievable in studies involving children. To return to the issue noted above, there have been a number of scales and observation tools developed that provide investigators

with valid tools to study the effect of various interventions on pain on even the youngest of infants (33, 34).

In addition to progress in the selection of end-points there have been a number of advances in the design of clinical trials for children. Analysis of clinical trials conducted in children has suggested that many designs used to date are associated with a significant risk of bias, notably with respect to sequence generation and allocation concealment (35). As well, the perception of lack of flexibility has historically a problem for randomized drug studies in children (36). Over the past decade a number of novel trial designs have been developed to address these issues. One example is sequential design in which investigators conduct frequent analysis during subject enrollment to determine if the therapy of interest is superior (37). A type of sequential design suggested to be very useful for studies in children is adaptive design, in which planned interim analysis is used to inform modifications in trial design (38). This type of trial requires meticulous pre-trial planning and consideration for issues such as blinded versus non-blinded interim analysis (39). This can permit a trial to be stopped early in the case of an intervention that is either very effective or found to be ineffective, reducing the number of children needed for the trial. These trial designs may be unfamiliar to drug regulatory agencies and investigators planning on using them for early phase drugs studies are encouraged to discuss this with their respective drug regulatory agency.

An additional issue of key importance in any clinical trial and most certainly those involving drugs is a robust and on-going safety assessment (40). The drug approval process was designed to detect serious and common risks, and while this is generally the case it is clear from events such as the unfortunate events associated with the initial clinical trials of TGN1412 in the UK and fatty acid amide hydrolase (FAAH) inhibitors in France that serious, even fatal, adverse effects still occur (41). This is of particular importance in the drug evaluation process for children as some common and important adverse drug effects are different in both incidence and manifestation in children than in adults (42, 43). The increase in interest in drug therapy for children over the past two decades has been accompanied by the development of new instruments both clinically and *in vitro* that offer considerable promise for more rapid and focused detection of adverse drug events in children, notably for novel therapeutic agents (44, 45).

An emerging area in clinical trial design with special relevance to children is the use of simulation and modeling early in the drug development process (46, 47). The value that simulation and modeling brings is the ability to factor in variables such as ontogeny of key pathways of drug clearance and data derived from adult studies to develop estimates for drug dosing which enables a clearer estimate of dose while reducing the requirement for additional studies (47). As well, simulation can be used to provide firmer estimates of sample size and to illustrate the point at which increasing sample size does not significantly increase the precision of data gathered (47). The increasing sophistication of pharmacometrics in children also provides new opportunities.

Dosing and Feasibility

There are feasibility issues with respect to involvement of children in early phase drug studies and first among them is dose selection. The issue of dose selection for Phase I trials is problematic at the best of times and the increasing percentage of biological as new therapeutic entities has only increased this problem. A recent review of failed paediatric drug development trials has suggested that in up to a quarter of trials that fail to establish efficacy or safety the selection of the correct dose was a factor in this failure (48).

The conventional approach to developing dose considerations for children has been to extrapolate from adult dosing, often using techniques such as allometric scaling. This may be problematic in that the major issues in ontogeny directly impact on drug clearance, primarily in terms of a reduction in the capacity of children to clear drugs or drug metabolites, notably in infancy (49). While this is now well understood for drugs used in the first year of life, an under-appreciated issue is that toddlers are notably more efficient in terms of oxidative metabolism, which may increase the risk for toxicity in drugs that undergo biotransformation to active metabolites (50).

Better appreciation of the role of ontogeny and disease enables a more rationale of drug dosing for paediatric studies (51). A technique with considerable potential is microdosing in which a pharmacokinetic study is done using a subtherapeutic dose of a ^{14}C labeled drug (52-54). This can be done as a “Phase 0” study prior to a Phase 1 or Phase 2 trial. Advances in analytical technology have been such that concerns about the volume of blood needed for

pharmacokinetic studies – once a major concern in paediatrics – is now largely a historical curiosity except for very premature infants.

Once a dose has been selected a consideration somewhat unique to paediatric drug studies is formulation. While drugs for adults – notably chronic therapy – are overwhelmingly given orally as tablets or capsules, the use of drugs in children must take into account the fact that medication naïve children under the age of 8 find it difficult to take tablets or capsules and even medication sophisticated children cannot reliably take medication in conventional tablets or capsules. The traditional approach to this problem has been to develop liquid formulations or crush the tablets (55). Over the past decade there has been an explosion in the creation of novel dosing systems designed for children, work largely driven by developments in Europe and which offers great promise for making drug research – and drug therapy – much more practical for infants and small children (56).

Moving Forward

While there have been many cultural, scientific and regulatory challenges that have made conducting early phase clinical trials in children difficult, developments over the past decade have addressed many of these issues and have provided the opportunity – indeed, in some cases the requirement – for the inclusion of children even in early stage of drug development (Figure 1). While there are new issues – such as the development of drugs for the neonate, the increasing appreciation of the importance of drug transporters in drug disposition in children and the complex issues raised by the increasing use of biologicals – that pose new and interesting challenges for paediatric pharmacy and clinical pharmacology there has never been a more promising time for drug development in children (57-60).

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Figure Legends

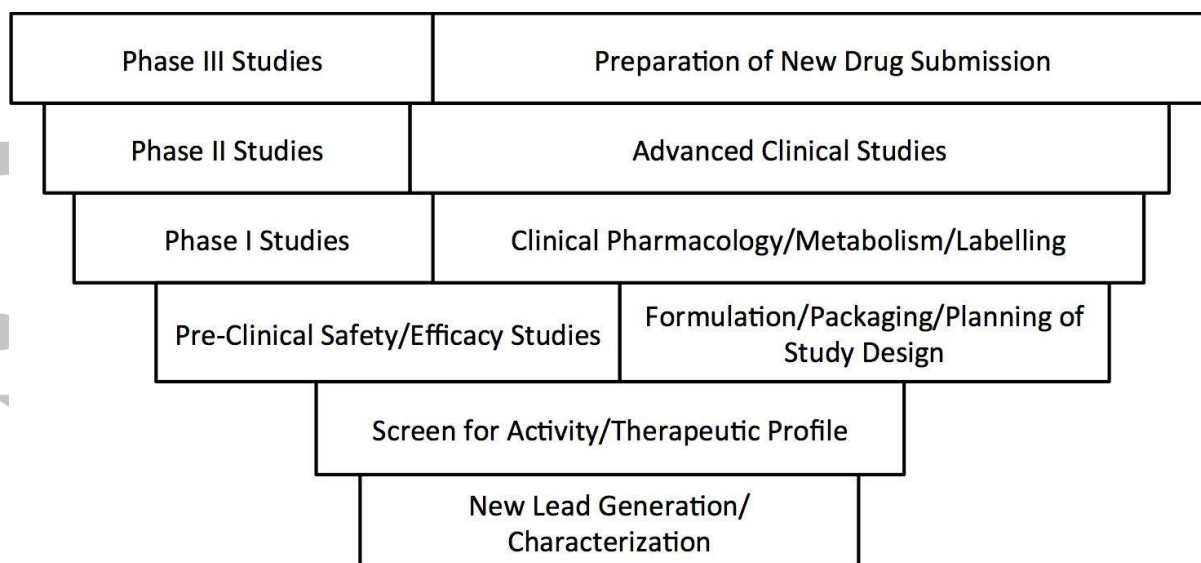


Figure 1

General overview of the Drug Development Process

Modified from Council of Canadian Academies: The Expert Panel on Therapeutic Products for Infants, Children and Youth. Improving Medicines for Children in Canada. Council of Canadian Academies, Ottawa, 2014.

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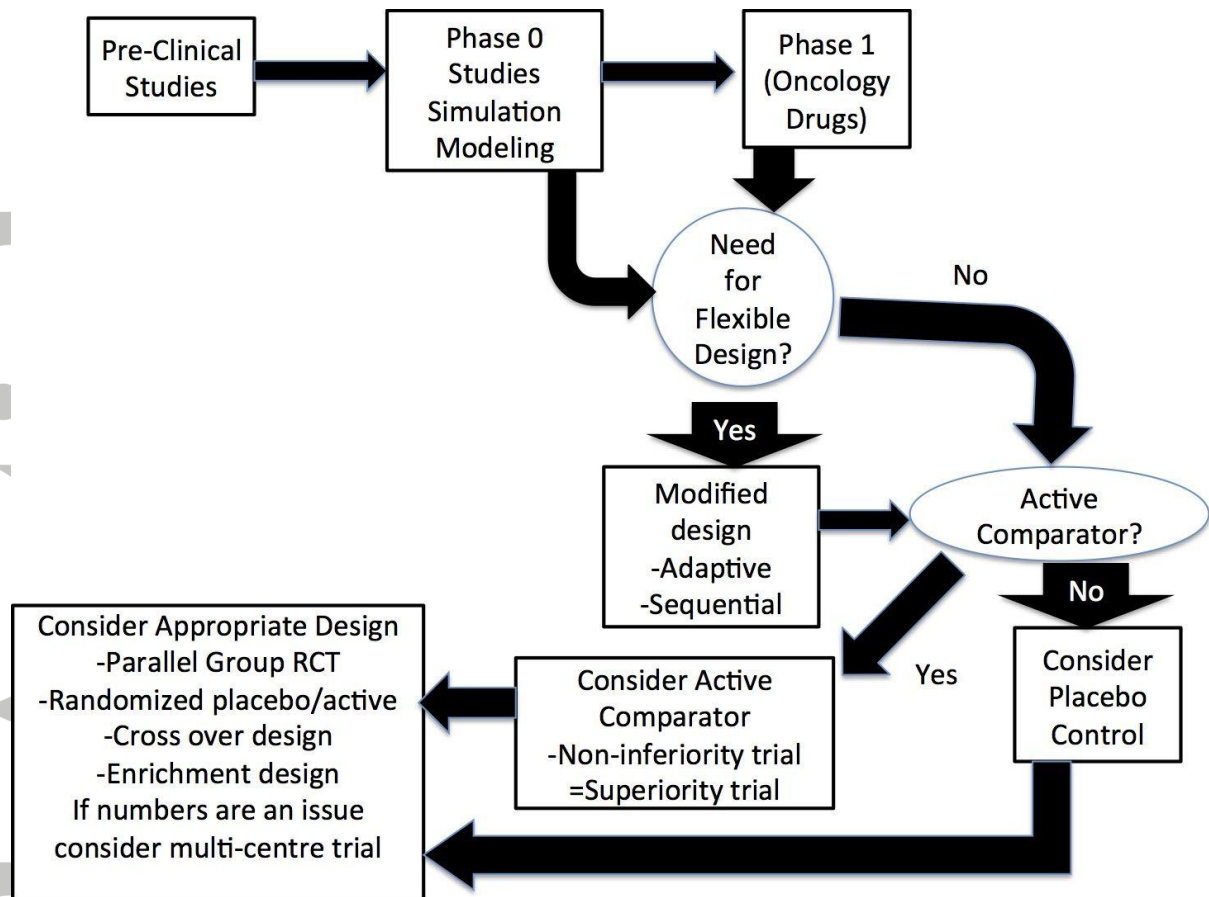


Figure 2

Considerations in planning the design of an early Phase drug trial in children. A key aspect in planning relates to early decisions as to the need for a flexible design.

Modified from Council of Canadian Academies: The Expert Panel on Therapeutic Products for Infants, Children and Youth. Improving Medicines for Children in Canada. Council of Canadian Academies, Ottawa, 2014.

Phase of Drug Development	Goal of Studies	Examples in Paediatric Drug Development
Phase I	First Stages of Drug Testing in Humans, typically conducted in health adult volunteers	Very rarely done in children with the expectation of oncology drug (chemotherapy) and some drugs in neonatology (surfactant)
Phase II	First Stages of Drug Testing for Efficacy and Safety, typically conducted in patients	Uncommon, and represent the first step for most drugs in terms of early phase studies in children. Regulatory advances have increased these studies for new drugs
Phase III	Effectiveness of the Drug and the Role in Clinical Practice, typically by comparison with “gold standard” therapy	Done at some times for drugs in children, most frequently for anti-infectives and increasingly for other drug classes

Table 1. Phases of Pre-Clinical Drug Development in Humans and Examples in Paediatrics.