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► **To cite this version:**

Paola Baiardi, Carlo Giaquinto, Silvia Girotto, Cristina Manfredi, Adriana Ceci. Innovative study design for paediatric clinical trials. *European Journal of Clinical Pharmacology*, 2011, 67 (S1), pp.109-115. 10.1007/s00228-011-0990-y . hal-00667593

HAL Id: hal-00667593

<https://hal.science/hal-00667593>

Submitted on 8 Feb 2012

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INNOVATIVE STUDY DESIGN FOR PAEDIATRIC CLINICAL TRIALS¹

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TEDDY Network of Excellence

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¹ Part of TEDDY supplement

ABSTRACT

Despite representing a fundamental step to an efficacious and safe utilisation of drugs in the paediatric population, the conduct of clinical trials in children poses several problems. Methodological issues and ethical concerns represent the major obstacles that have traditionally limited paediatric research.

The randomised clinical trial, mainstay of clinical studies to assess the effects of any therapeutic intervention, shows some weaknesses which make it scarcely applicable to the paediatric population.

Alternative and innovative approaches to clinical trial design in small populations have been developed in the last decades with the aim of overcoming the limits related to small samples and to the acceptability of the trial. These features make them particularly appealing for the paediatric population.

This systematic review describes a variety of alternative designs to assess efficacy and safety in the paediatric population, including their applicability, advantages, disadvantages and real case examples. Approaches include sequential and adaptive designs, Bayesian methods and more innovative approaches. Thanks to their features, these methods may rationally limit the amount of experimentation in children to what is achievable, necessary and ethical, and represent a reliable way of ultimately improving paediatric care.

KEYWORDS: clinical trials, paediatrics, clinical trial design, TEDDY

INTRODUCTION

Despite representing a fundamental step to an efficacious and safe utilisation of drugs in the paediatric population, the conduct of clinical trials in children still poses several problems: methodological issues, mainly related to the small sample sizes, and ethical concerns, deriving from children exposure to the potential risks of a trial, represent the major obstacles that have traditionally limited paediatric research. In addition, economical concerns in consideration of the limited paediatric medicines market, unable to guarantee adequate return on investments, have had also a crucial role in limiting drug development in children.

This situation has been tackled in the recent years at both scientific and regulatory levels: the first formal step was established in 2001 with the European Directive on clinical trials [1] and in particular with its Article 4 on the conduct of clinical trials in minors. A revolutionary change was started recently, in 2007, with the coming into force of the Paediatric Regulation [2,3] whose aim is to increase knowledge on the use of paediatric drugs, by boosting – through a system of obligations and incentives – the development of new drugs for children and ensuring at the same time a safer use of already marketed products.

The obligation of performing paediatric studies and consequently, the increased number of studies expected, and partially already observed as impact of the 2007 Regulation, has stimulated the attention on the adequate methodology for clinical trials in paediatrics. No methods exist that are relevant to paediatric trials and not also applicable to adult studies, stated that children are entitled to receive treatments tested with the same accuracy as those for adults. Clinical trial methodology to study paediatric treatments should not be different from the general methodology whenever paediatric conditions and prevalence of the diseases can ensure the use of standard methods. However, it may be that in conditions affecting small populations, innovative approaches may be pursued to ensure the feasibility of the trial and the validity of the results.

The need for alternative approaches is reported in the ICH Topic E11 guideline [4], reference document for planning and conducting clinical trials in paediatrics, and discussed in details in the

guideline for clinical trials in small populations [5], that generally faces the issue of limited sample sizes. The still open methodological debate on paediatric research is furthermore corroborated by the great number of disease-specific guidelines that EMA has been delivered in the last years [6-11].

CONVENTIONAL VERSUS ALTERNATIVE DESIGN IN PAEDIATRICS

The randomised clinical trial (RCT), mainstay of clinical studies, represents the gold standard for the assessment of the effect of any therapeutic intervention. Its strengths lie in the randomisation, aimed at avoiding bias in the allocation of subjects to treatments, the blindness, aimed at avoiding bias in the evaluation of compared treatments, and in the *a priori* choice of acceptable margins of error, specifically type I and type II errors.

However, it shows some weaknesses which make it scarcely applicable to the paediatric population. The RCT, in fact, implies a precise estimate of the sample size to guarantee that the study is powered enough to demonstrate the therapeutic superiority of one treatment compared to another. Usually such estimate leads to the determination of a bigger sample size than the samples usually available in paediatric studies. As a consequence, a paediatric RCT is often underpowered. Multicentric studies can overcome this issue, but while guaranteeing a higher generalisability of results, they introduce bigger difficulties in the management of the study and expose it to likely deviations from the research protocol.

Moreover, in the conventional approach, the noise deriving from non-systematic errors can be easily minimized in case of large samples; on the other hand, it could become serious in case of small samples and sometimes it could lead to a bias towards failing to show a difference between treatments [5].

Another limitation of RCT, when applied in paediatrics, is represented by ethics, the other crucial point in designing paediatric studies: in the past ethical concerns represented a crucial obstacle to paediatric research and this is a valid reason to explore alternatives to the typical RCT design [12].

From a statistical point of view, moral matters can be dichotomised in two categories: *individual* and *collective* ethics. When a subject is assigned to a treatment found more unfavourable at the trial end, individual ethics is sacrificed for the benefit of collective ethics [13].

If there is reason to believe that one treatment is superior to the other, the acceptability of a trial could be compromised and if the expectations for the investigational drug are so high that equipoise is lacking, a control group with placebo could be totally unaccepted. Problems with the acceptability of a study make it harder to recruit subjects, especially in case of limited populations, as in paediatrics. A trial extension, where the experimental drug is given to all patients, or a trial with unbalanced randomisation represent the traditional way of facing these issues.

Alternative approaches to clinical trial design share an underlying philosophy that combines ethical and methodological issues, and make them particularly suitable for the paediatric population. Due to their flexibility, innovative designs fit very well the requirements in the paediatric population [14], for a drug development characterised by less strict separation between phases as stated by ICH Topic E11 guideline.

Below, we describe a variety of alternative designs to determine efficacy and safety in the paediatric population, including their applicability, advantages, disadvantages and real case examples. These approaches include data-dependent designs, old methods scarcely applied both in adult and paediatric research, and innovative approaches, some of which were never applied in real contexts, to our knowledge. This paper builds on the principles of the main reference guidelines [4,5] in paediatrics and places itself as systematic review for clinical trial design in children.

SEQUENTIAL DESIGN

This is a study design with an *a priori* non fixed sample size. The trial can stop at any time during its course as soon as the scientific evidence of a superiority of one treatment against the other is proven. The number of repeated analyses during the trial has to be planned initially so that the control of the

type I and II errors is ensured together with the necessary power of the trial results. According to the scheduled data monitoring, after groups of subjects respond or after each response, we have different designs, *group sequential* or *fully sequential* designs.

Due to its nature, sequential design requires treatment outcomes to be available quickly in relation to the patient recruitment rate and this characteristic partially limits its applicability. It is not suitable for studying survival, but it could be useful to evaluate short treatments through surrogate endpoints.

The expected number of subjects is calculable and it is below the number of a comparable fixed sample size design. Some *open-ended* designs can continue to recruit patients until a conclusion about the treatments can be achieved, while *closed* designs have a fixed upper limit in the number of patients to be recruited. In any case, fewer patients are generally necessary to reach a conclusion compared to a fixed sample size design, thus guaranteeing some ethical advantages over a classical approach.

Although the approach was developed as early as the 1960s, it is not widely used in CTs. A systematic review [15] reports the application of the design in the neonatal intensive care setting: 24 trials have been performed from 1963 to 2005 that have lead to save, on average, 35% of the enrolled subjects when compared to a fixed sample size approach.

ADAPTIVE DESIGN

Adaptive design is a trial design that allows modifications to some aspects of the trial after its initiation, without invalidating the validity and integrity of the trial. Modifications of the trial can refer among others, to sample size re-estimation, early stopping and adaptive randomization.

Sample size re-estimation becomes necessary when limited evidence is available on the expected treatment effect size. In such cases, it is desirable to adjust the sample size according to the effect size for the ongoing trial thus reducing the risk of trial failure. Early stopping is pursued when the efficacy or futility of the experimental drug becomes obvious during the trial [16]. Finally, through response-adaptive randomization, allocation probability may change during the trial based on the responses of

the previous patients and more patients are expected to be randomised to the group that is proving superiority.

The possibility to make adjustments as one learns during the trial makes this approach particularly appealing in paediatric trials, due to the usual limited knowledge in this field. The flexibility of the design, however, entails more complex data analysis methods and, according to the modification of the inappropriate assumptions, the unblinding of data or the knowledge of treatment outcome before the randomization of the next patient.

The potential uses of adaptive design methods have attracted much attention, especially in the recent years and across all the development phases of drugs. Examples of applications have been reported for dose-finding studies but also for phase III trials, mainly in case of interim analyses followed by sample size re-estimation. The approach works well also in case of phase IV trials in which the method allows the saving of up to a half of the required subjects according to a traditional design [17].

BAYESIAN APPROACH

Bayesian design is the data dependent design *par excellence*. In essence, data from prior studies may be gainfully quantified to form an *a priori* probability distribution for treatment effect, and combined with the current trial data to provide an *a posteriori* distribution on which conclusions may be drawn. The approach is particularly suitable for the paediatric population. In fact, since a pediatrician's observation that a drug is effective in adults increases his/her belief in its effectiveness in the paediatric population, a quite natural approach to inference is to make these considerations explicit using Bayesian methods. Adult data can be used in designing a paediatric trial by exploiting prior information for the sample size calculation or by directly including them into the study to generate the prior distribution.

Bayesian approach can improve the power of statistical inference or can reduce the width of confidence intervals and increase the precision of statistical estimates: this is what was shown in a

recently published trial to assess the impact of a diet regimen in the management of acute lung injury and acute respiratory distress syndrome in children [18]. In the same way, a trial comparing the efficacy of immune globulin therapy with plasmapheresis in children affected by Guillan-Barré syndrome [19] proved that the construction of an evidence-based *a priori* distribution starting from adult data allowed information from adults to formally increase data from children, thus minimizing unnecessary paediatric experimentations. The consequence could be potentially smaller, more informative trials and for patients, the possibility of receiving better treatments.

However, it has to be considered that potential difficulties may arise at the end of the trial, when physicians are presented with updates on *a priori* distributions in the form of *a posteriori* distributions. In fact, since results are strongly based on the level of confidence on *a priori* distributions and on the extent to which these hypotheses apply to the current trial, some uncertainty could remain about how to translate the findings in ready to use results for changing their clinical practice.

RANDOMIZED WITHDRAWAL DESIGN

This design belongs to the category of the so-called “enrichment designs” in which the experimental drug is tested against the comparator on an “enriched population” of responders to the test compound [20]. With this approach, enrolled subjects receive initially and for an *a priori* defined period of time the trial drug in an open manner. Then, non-responders stop the trial, while responders are randomised, according to a standard design, to placebo or the trial drug after an adequate wash-out period (Figure 1).

This approach shows at least two advantages particularly appealing for the paediatric population: on the one hand it offers the patient the opportunity to experience the potential benefits of the active treatment [14], on the other hand, the design minimizes the amount of time that the individual receives a placebo . The result may be a better patient accrual, particularly in indications for which the use of placebo poses ethical concerns. In addition, the test of the experimental drug against placebo on the

selected population of responders increases the power of the comparison or alternatively, requires a smaller sample size to achieve the same power of results.

Disadvantages include carryover effects and difficulties in assessing whether the underlying disease process is still active: in fact, the design is suitable for testing drugs with short half-life and not inducing a permanent modification in the condition of the subject. Moreover, it may raise ethical concerns since the efficacy of the experimental drug can only be demonstrated by temporarily depriving patients of the benefit they had already obtained from the active drug [21].

This design has been successfully employed in studies for chronic disorders of both adults and children; it has been applied for clinical trials in childhood epilepsy [22,23] and in juvenile idiopathic arthritis [24,25]. In particular, the approach has been recognised as the most appropriate for developing new treatments for juvenile idiopathic arthritis at the Paediatric Rheumatology Expert Meeting held in London in December 2009. Its disadvantages are outweighed by its advantages even if the design does not represent the ideal method for confirmatory studies.

RANDOMIZED PLACEBO-PHASE DESIGN (RPPD)

As already mentioned, a clinical trial in paediatrics is generally more acceptable when the number of subjects assigned to the placebo arm is the least numerous possible, but also when the duration of the placebo trial is the shortest possible. The Randomized Placebo-Phase Design (RPPD) sets its innovation on this second strategy [26].

The RPPD approach is based on the consideration that if the trial drug is active, the earlier it begins, the higher the probability to observe a response in short times. Therefore, in this type of study subjects receive placebo at different times according to the treatment scheme illustrated in Figure 2.

Subjects are randomised to placebo for periods of different duration. At the end of those periods, all subjects receive the active treatment until it is possible to observe a response.

This study design belongs to the RCTs class since the treatment scheme guarantees:

- the presence of a control group according to an intra-patient scheme (each subject is the control of him/herself);
- the blindness, because subjects may begin the study directly assuming the active drug (this is the case when the placebo administration time is 0);
- the randomisation, made at the beginning of the active treatment.

Simulation studies have shown good potential of the RPPD to evaluate treatments for chronic conditions or highly potent therapies for rare diseases [26]. Highly potent therapies simulations showed that the power of results from RPPD is comparable to that of a classical RCT, but power decreases in case of drugs with low potency. In such cases, the decision of implementing an RPPD trial would depend on the perceived acceptability of a standard RCT: with RPPD all subjects know they will receive the experimental treatment and no subjects are required to take a placebo for more than a relatively short time. Therefore, it might represent a good method for early assessment of new therapies when accrual to an RCT would be difficult or as an alternative approach to open or controlled study designs. Finally, given the characteristics of the design, it could be more accepted than a parallel group study for remission-inducing therapies using survival endpoints.

THREE-STAGE CLINICAL TRIAL DESIGN

The three-stage trial design is a methodological approach that combines the classical RCT with the randomised withdrawal trial on the same sample in order to get the maximum level of information available from each subject. The treatment scheme is depicted in Figure 3.

In the first phase, subjects are randomised according to a traditional RCT to the experimental drug or placebo. Subjects responding to placebo and those not responding to the trial treatment withdraw from the study, while responders to the active treatment enter the second phase of the trial and non-responders to placebo are assigned to the third.

Subject undergoing the second phase are randomised again to placebo or the trial drug. Subjects initially not responding to placebo, and therefore undergoing the third step, enter a randomised

withdrawal scheme: they are initially assigned to an open treatment period with the experimental drug and subsequently, only those who respond to the drug in this phase continue the study and are randomised to take either placebo or the active treatment [20].

The approach has some strengths: first of all the possibility to obtain in the same study three different evaluations of efficacy, one for each phase, and to derive a global efficacy evaluation by pooling the results. Second, the trial has improved statistical power compared to a traditional RCT: simulation studies have highlighted that this approach reduces, *ceteris paribus*, the sample size by 20-30% compared to a RCT. Third, this type of design offers some features that may address the concerns about the unnecessary exposure to placebo. In fact, all patients entered in the study have a chance to derive a therapeutic benefit from their participation in the trial (patients not responding to placebo are given the opportunity to take the active treatment in the following phases of the study) and at the same time, it is possible to avoid treating patients responding to the placebo. All these advantages make the approach particularly suitable for situations when difficulties in recruiting an adequate number of subjects have to be faced or where patient numbers are limited, both contexts being typical of the paediatric population.

The design appears useful in chronic conditions for which it is expected to return to initial conditions when the active treatment is suspended; in this case the response rates from the three phases can be pooled without bias. Other situations where the study may be potentially useful is in the determination of the therapeutic efficacy in sub-populations, when efficacy in the general population has already been proved, or in the initial stages of the drug development when it is necessary to find dosages in small patients cohorts [20].

DISCUSSION AND CONCLUSIONS

The scientific methodology and logistics of clinical research for paediatrics have greatly changed in the recent years, also following the obligation of performing paediatric clinical trials introduced by the European Paediatric Regulation [2,3] that lays down rules concerning the development of medicinal

products in order to meet the needs of the paediatric population, with the fundamental point being the avoidance of unnecessary studies in children. The binomial of obtaining evidence for drug use in paediatrics associated with the ethical issues of not exposing the paediatric population to unnecessary trials highlights more than in the past, the need for addressing new methodologies when designing paediatric trials.

When planning and analysing a clinical trial in children, crucial issues are the definition of the research question, the choice of the optimal design and outcome measure to achieve and demonstrate the objective of the study, the feasibility of the trial and the statistical validity of the findings: all characteristics that do not differ from those of adult studies, but that can pose obstacles in case of paediatric trials.

In this context, alternative approaches to study design that combine the enrolment of a limited number of subjects with measures for increasing the trial acceptability, can facilitate the carrying out of the study, particularly in those situations where a traditional RCT may be difficult to perform.

The trial designs discussed in the present paper offer opportunities for research in paediatrics: even if there is no unique rule of thumb for choosing a specific approach, each design has intrinsic features that meet the requirements of the paediatric population. Adaptive designs are very attractive due to their flexibility and can be useful especially in early clinical development. Bayesian approach generally allows to achieve greater certainty with fewer children: in this case the use of adult evidence can be also of help both in the design and in the analysis of the results. The randomised withdrawal design has been widely studied and applied in real contexts; its features make it particularly suitable for chronic conditions, specifically for juvenile arthritis. More innovative approaches are promising thanks to the optimal results found in simulation studies.

However, despite the clear advantages of these innovative approaches to clinical trials design, their application in practice remains still an exception. This is probably due, among others, to obstacles in having the protocol approved [13]. Despite the increasing attention given to paediatric research at scientific, regulatory and legal levels, competencies in the field still need to be improved and deepen at every level. Protocol design requires not only solid knowledge of the methodology, but also in-depth

understanding of child physiology, psychology, the social embedding of children and many other factors [14]. A role in limiting the use of such approaches may also be attributable to reluctance by Regulatory Authorities in accepting the new study designs for registrative paediatric trials. The Paediatric Committee established with the European Regulation is making a big work in assessing paediatric research at the European level, including provisions to ensure the performance of well-designed clinical trials. These provisions cannot avoid the consideration of alternative and innovative approaches to trial design.

In summary, the availability and implementation of new methodologies for the design of paediatric clinical trial represent an opportunity for paediatric research. Thanks to their features, these methods may rationally limit the amount of experimentation in children to what is achievable, necessary and ethical and represent a reliable way of ultimately improving paediatric care.

ACKNOWLEDGEMENTS

This report is part of the Task-force in Europe for Drug Development for the Young (TEDDY) Network of Excellence supported by the European Commission's Sixth Framework Program (Contract n. 0005216 LSHBCT- 2005-005126).

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Figure 1: The randomized withdrawal design trial

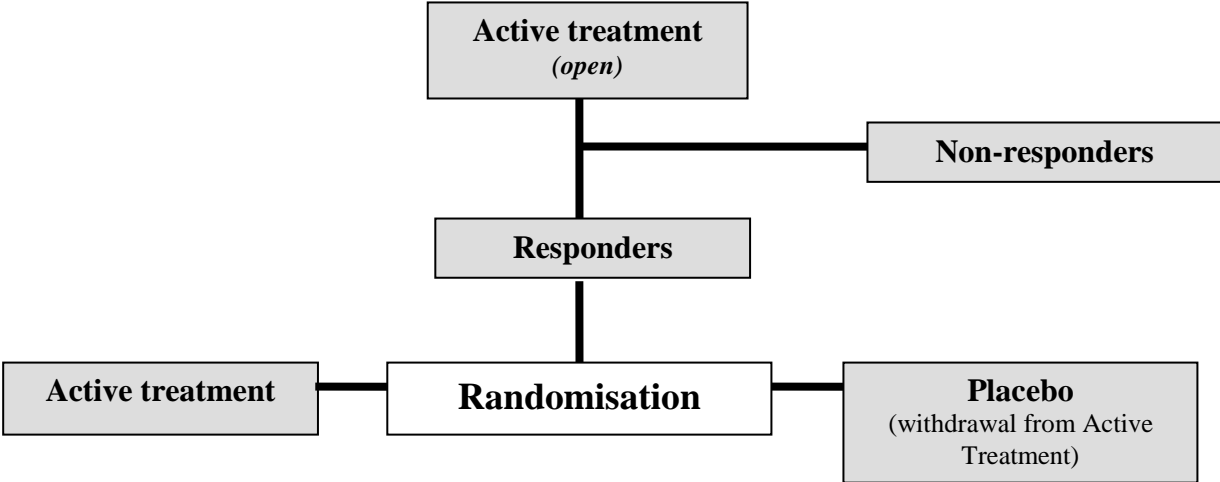


Figure 2: The Randomized Placebo-Phase Design (RPDD) trial

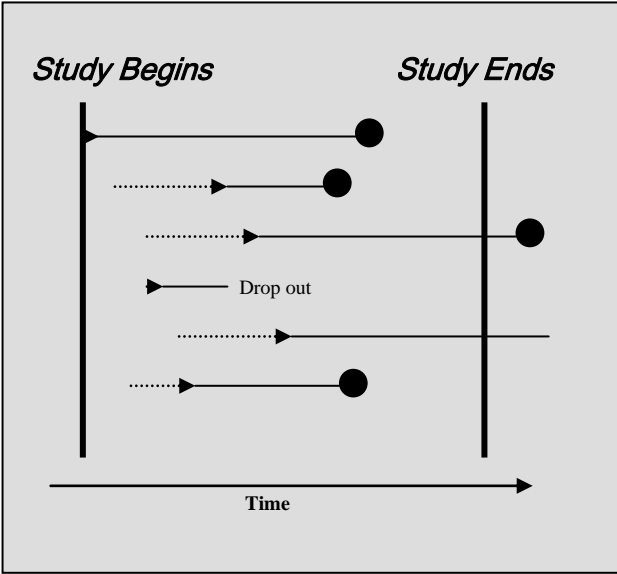


Figure 3: The three stage design trial

