“Recommendations on optimal designs”

Optimal designs for antimicrobial pharmacokinetic studies in children: *Translating Innovative Designs from Theory into Practice*

Lead Beneficiary
SGUL

Author(s)
Charlotte I.S. Barker, Mike Sharland

Revision date
22-12-2015

Dissemination Level
Public

Start date
01/01/2011

Duration
78 months

Project Coordinator
Dr. Carlo GIAQUINTO

Azienda Ospedaliera di Padova (AOPD)

Reference WP
WP5 – Paediatric formulations

Reference Activity
Task 5.04 – Identify the optimal dosing recommendations for common antimicrobials used in neonates and children

The research leading to these results has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 261060 (Global Research in Paediatrics – GRiP network of excellence)
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<tr>
<td>Charlotte Barker</td>
<td>St George’s, University of London</td>
</tr>
<tr>
<td>Mike Sharland</td>
<td>St George’s, University of London</td>
</tr>
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2 Abstract

The pharmacokinetic (PK) and pharmacodynamic (PD) data underpinning paediatric and neonatal antimicrobial dosing recommendations are often suboptimal, especially for older drugs. Recent advances in population pharmacokinetic methods and laboratory microanalysis have dramatically increased research in this area. However, traditional sample size calculations are not possible for these population PK studies, so historically it has been difficult to identify the ideal recruitment targets and study designs. Optimal experimental design refers to the use of mathematical optimization algorithms to identify a maximally informative study design. Optimal design theory can be applied to guide protocol design for paediatric and neonatal antimicrobial pharmacokinetic (PK) and pharmacodynamic research studies. It can inform many aspects of study design including sample size calculations, PK sample timing, and PK sample numbers per participant, which is particularly important in paediatric studies. The implementation of optimal designs can thus be used to maximise the informativeness of study design for antimicrobial PK/PD research in children and to improve the efficiency and cost-effectiveness of research delivery. For future research in this field, we must endeavour to benefit from both the refined study designs that are thus now feasible with the application of optimal design theory and also the pragmatic designs that are increasingly popular using opportunistic sampling approaches.

2.1 Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>NAPPA</td>
<td>Neonatal and Paediatric Pharmacokinetics of Antimicrobials study</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic(s)</td>
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<td>PK</td>
<td>Pharmacokinetic(s)</td>
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## 3 Receivers of the document

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<td>GRiP Beneficiaries</td>
<td>To be informed about – and disseminate awareness of – the development of pragmatic protocols for studying pharmacokinetics in children and neonates that incorporate optimal and opportunistic sampling strategies.</td>
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<tr>
<td>European Commission</td>
<td>To be informed about the development of pragmatic protocols for studying pharmacokinetics in children and neonates that incorporate optimal and opportunistic sampling strategies.</td>
</tr>
<tr>
<td>Clinical Investigators (e.g. paediatricians, methodologists, residents, PhD students)</td>
<td>Awareness of the use of study designs employing optimal design combined with opportunistic design to maximise the feasibility of delivering the protocol within routine clinical care</td>
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<td>Industry</td>
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4 Background and Introduction

In recent years it has been increasingly recognised that the pharmacokinetic (PK) and pharmacodynamic (PD) data underpinning paediatric and neonatal antimicrobial dosing recommendations are often suboptimal, especially for older drugs. Given that antibiotics are the class of medicines most widely prescribed for children globally, there is consequently a need for updated paediatric PK/PD data for these drugs to better inform current and future dosing practices. Historically, few anti-infective medicines (including antibiotic, antifungal, antiviral and antiparasitic agents) underwent large-scale or high-quality studies in children, because of practical, ethical and financial restrictions; instead these drugs were mostly studied in clinical trials in adults and then these adult PK/PD data were used to derive paediatric dosing recommendations. The paediatric dosing recommendations were typically obtained by scaling down adult doses in a linear fashion according to body weight on a mg/kg basis, which is now known to be over simplistic.

In order to improve the evidence-base for dosing medicines in children, there has been extensive research into methods that may be employed to increase the information obtained from pharmacological studies in this vulnerable population. Key strategies have included opportunistic sampling and also the use of so-called optimal design. Opportunistic sampling refers to studies undertaken in patients receiving the drug of interest as part of standard clinical care, where the research samples (for PK/PD analysis) are taken from the patient at the same time as routine blood tests that are required for routine clinical care, or leftover clinical samples are used. These opportunistic studies are increasingly popular and evidence of their success in paediatric and neonatal antimicrobial PKPD studies is already present in the scientific literature.

However, there are some limitations to the use of opportunistic strategies, and optimal design can play an important part in improving the design of PK and PD studies undertaken in children, in order to help ensure prospectively that the information that will be obtained from the study is maximised. Optimal design recommendations can be used exclusively or employed in conjunction with the aforementioned opportunistic strategies. This report summarises the utility of optimal design strategies for paediatric antimicrobial PK/PD studies and includes recommendations for future research in this area.
4.1 Definitions

Pharmacokinetics

Pharmacokinetics (PK) refers to absorption, distribution, metabolism and elimination, i.e. the physiological processes in the body which determine drug disposition.

Pharmacodynamics

Pharmacodynamics refers to the effects of the drug on its pharmacological target(s), including those that are beneficial (determining efficacy) and those that are harmful (determining toxicity).

Pharmacokinetic/pharmacodynamic modelling

PKPD modelling involves the use of statistical models to describe and quantify dose–concentration–effect relationships.

Population PK/PD modelling

The so-called population approach to PK/PD modelling uses the statistical method known as non-linear mixed effects (NLME) modelling. A single PK(PD) model is fitted to data from all individuals (e.g. study participants) simultaneously, which allows for two levels of random effects; this enables estimates to be obtained of the model parameter typical values and their inter-individual variability, as well as the residual unexplained variability.

Pharmacometrics

The science that quantifies drug, disease and trial information to aid efficient drug development and/or regulatory decisions, typically employing population PK/PD statistical modelling techniques, as described above.

Optimal design

Optimal design refers to the use of mathematical optimization algorithms to identify a maximally informative study design.
4.2 Optimal design: an overview

Optimal experimental design refers to the use of mathematical optimization algorithms to identify a maximally informative study design. Optimal design theory can be applied to guide protocol design for PK research studies involving human participants. While optimal design theory is also of relevance more broadly to other study types including clinical trial design and beyond, this report focusses specifically on PK study design. In statistical terms, optimal design theory for PK studies incorporates knowledge of prior information about the PK model and parameter estimates in order to mathematically optimize a function of the Fisher information matrix in order to identify the ideal combination of design factors. This strategy can be used to optimize numerous different factors relevant to study design including:

1. Required population sample size (i.e. number of study participants)
2. Timing of PK blood samples within dose interval(s)
3. Number of PK samples per participant

Optimal design methods can include additional relevant aspects such as laboratory analytical assay sensitivity, and can help to identify further factors such as the ideal range of covariates within the study population. Importantly, practical restrictions can also be incorporated into the study design such as financial limits, and the design can recognise blood volume limits that restrict sampling for research purposes, which is especially important in neonates. In order to prevent risk to neonatal and paediatric participants from excessive research sampling, the volume of additional blood taken per participant in PK studies must comply with the EMA recommendations on paediatric and neonatal research: the study-related blood loss per individual (including any losses in the manoeuvre) should not exceed 3% of the total blood volume during any 28 day period (3% is equivalent to 2.4 ml blood per kg body weight) or 1% at any single time (1 ml blood per kg body weight).

Sophisticated optimal design software is now widely available both commercially and, in some cases, free of charge. These software tools implement model-based optimal design using the same statistical modelling methods and principles employed in population PK/PD modelling (pharmacometrics) approaches.
4.3 Optimal design in paediatric antimicrobial pharmacokinetic studies

For early phase studies, optimal design can utilize knowledge available from *in vitro* or pre-clinical *in vivo* experimental work, taking advantage of the same data that can also be used for extrapolation methods prior to first-in-child studies or prior to clinical studies testing new dosing recommendations.\(^{21,22}\) The application of optimal design to paediatric antimicrobial studies has previously been demonstrated.\(^{23,24}\)

As mentioned above, the use of optimal design can also incorporate practical restrictions that are specifically important in children and neonates. For paediatric study design, it is often necessary to limit the total number of samples to that which is acceptable to children and their parents, and the healthcare professionals caring for them. To this end, the design can be restricted to a particular number of samples, enabling the ideal sampling times to be identified even if just two or three samples are feasible per patient, for example. To reflect practical study delivery in the hospital setting, sampling windows can be identified, to show the range of times that will be acceptable and to estimate the statistical impact of varied sample windows, with consideration of the effect the windows will have on the precision of parameter estimates. Since sparse sampling strategies (with few samples per patient) are now standard practice in PK research in children and neonates, the use of optimal design theory can thus ensure that these few samples are targeted towards the most information-rich sections of the drug concentration versus time profile.\(^{10,25}\) There are clear advantages to the use of optimal design in paediatric antimicrobial pharmacokinetic studies, although there are some important limitations of these methods as well, which are summarised below in Table 1.
Table 1. Advantages and limitations of implementing optimal designs for paediatric antimicrobial pharmacokinetic studies

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Identification of optimal sample size (overall)</td>
<td>Requires knowledge of expected inter-individual PK parameter variability in study population</td>
</tr>
<tr>
<td>Identification of optimal sample size within specific bands of prematurity in neonates</td>
<td>Requires knowledge of expected maturation-related PK parameter variability in the preterm population, and the effects of varying comorbidities and covariates in neonatal intensive care</td>
</tr>
<tr>
<td>Identification of optimum sample number</td>
<td>Actual sample number may be restricted by blood volume limitations, especially in neonates</td>
</tr>
<tr>
<td>Identification of best sampling times</td>
<td>Ideal times are not always feasible in the clinical setting, especially in critical care – this can be addressed with the use of sampling windows</td>
</tr>
<tr>
<td>Identification of preferred covariate distribution</td>
<td>Ideal samples of participants are again not always possible with real clinical patients, so recruitment of the optimum study population may not be achievable in realistic time frames</td>
</tr>
<tr>
<td>Specialist software for optimal design is now widely available</td>
<td>The use of such software requires expertise, and dedicated costs and time are associated with undertaking the optimal design in practice</td>
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Further information regarding optimal design principles for paediatric and neonatal pharmacokinetic and pharmacodynamic studies are reviewed in detail in a recent publication by Roberts et al.10
While optimal design based sampling strategies can be implemented in isolation, they can also be delivered in a flexible protocol that permits opportunistic sampling, in order to maximise the feasibility of sampling logistics in different clinical settings, and in patients with different levels of intravascular access available for sampling (e.g. with or without intravenous/arterial access, within or outside critical care environments). The feasibility of such an approach has been demonstrated within the NAPPA study, which is discussed in further detail below; these data have previously been presented as a scientific poster at the Annual Meeting of the Population Approach Group in Europe.²⁶

5 Synthesising opportunistic and optimal design: practical example from the NAPPA study

The Neonatal and Paediatric Pharmacokinetics (PK) of Antimicrobials study, NAPPA, is a multicentre population PK study evaluating six penicillins used in routine clinical care: amoxicillin, ampicillin, benzylpenicillin, co-amoxiclav (amoxicillin/clavulanate), flucloxacillin, and piperacillin/tazobactam.²⁷ All antimicrobials prescribed for study participants are given as per the normal NHS (National Health Service) standard of care, at the doses recommended by local or national guidelines. The study protocol combines opportunistic sampling strategies with optimally timed samples. The NAPPA optimal design strategy aimed to identify optimum timing recommendations grouped across all participant age-groups, from infants to adolescents, that could be applied within the pragmatic study design and be compatible with the normal care pathway.

5.1 NAPPA optimal design methods:

The optimal design exercise was implemented with PopED software (version 2.13) using the D-optimality criterion. A literature search was first undertaken to identify published population PK models of the relevant penicillins in order to select an appropriate model on which to base the optimal design. Modelled participants’ ages were defined by postmenstrual age in weeks and allocated to the mid-point of each age-group, linked with mean weight-for-age. A representative dosing strategy was selected: single intravenous flucloxacillin bolus of 25mg/kg. The number of
participants per group was set at the maximum study target. The additive residual error was adjusted to reflect anticipated assay limits (using ultra high-performance liquid chromatography with tandem mass spectrometry): 2.5mg/L. Three optimal sampling times were predicted. Sampling windows were identified to increase the feasibility of sampling in routine healthcare.

5.2 Results:
A three compartment PK model based on flucloxacillin PK data from an adult study was selected from the literature.\(^2^8\) A maturation function was added to the clearance (CL) parameter,\(^2^9\) to account for changes relating to chronological age and weight:

$$\text{CLA} = \text{CL} \times \left(\frac{\text{Weight}}{70}\right)^{0.75} \times \left(\frac{\text{Age}^3.4}{(47.7^3.4+\text{Age}^3.4)}\right)$$

The D-optimal design results were as shown in Figure 1.

![Figure 1: Graph showing the optimal times generated in the PopED optimal design using the D-optimality criterion.](image)

- The clear circles ○ show the optimum samples times for infants, children and adolescent, which were grouped together in the final design.
- The filled circles ● show the optimum sample times for neonates in the final model.

The recommended times for paediatric participants are summarised below in table 2, which also lists the associated sampling windows that were selected. The impact of these sampling windows resulted in 84% normalized efficiency. An extra trough (pre-dose) sample was also recommended for those participants receiving oral penicillin.
Table 2: D-optimal design results and selected sampling windows

<table>
<thead>
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<th>Sample number</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td><strong>Optimal Time</strong> (mins/hours post dose)</td>
<td>15 mins</td>
<td>1 hr 40 mins</td>
<td>3 hrs 30 mins</td>
</tr>
<tr>
<td><strong>Sample window</strong> (mins/hours post dose)</td>
<td>10 mins – 30 mins</td>
<td>1 hr 25 mins – 2 hrs 15 mins</td>
<td>3 hrs – 4 hrs</td>
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It can be seen from figure 1, above, that in the PopED design used with 3 sample times permitted, the third sample time in neonates differed markedly from that for the older age-groups (which were grouped together), reflecting the evolution of the penicillin pharmacokinetic profile between neonates and older children.

5.3 Conclusions from the optimal design undertaken for NAPPA:

For NAPPA, D-optimality design in PopED was used to select optimal timing recommendations for a study of six penicillins in different age-groups, from infants to adolescents. The feasibility of the recommendations was enhanced by selecting practical timing windows to reflect the flexibility needed in routine healthcare for study implementation.

During a two year recruitment period, 400 children have been enrolled in the NAPPA study at nine participating NHS Hospitals in England, from whom over 1000 PK samples have been obtained. Successful recruitment and delivery of the NAPPA protocol at participating sites has clearly demonstrated that it is feasible to integrate a pragmatic population-pharmacokinetic study design utilising optimal and opportunistic sampling strategies into routine NHS care. To our knowledge, this is the first protocol to include computationally-defined optimally timed samples in the same study as opportunistic approaches including both clinical and laboratory scavenged sampling.
At the time of writing, the final study PK analyses are ongoing, and will be used to study the relative information available from both optimal and opportunistic sampling (both separately and when combined) to demonstrate the utility of this flexible, pragmatic approach for future paediatric antimicrobial PK research design.

6 Recommendations for future research

We recommend the use of optimal design for planning future paediatric antimicrobial PK/PD studies whenever it is economically feasible, given the available resources. Optimal design can help to avoid waste in research by guiding sample size calculations to avoid under- or over-recruitment in paediatric studies, and likewise can help guide sampling plans to avoid under- or over-sampling. Important areas of research for future antimicrobial PK/PD studies will be the use of optimal design theory to identify the ideal sample sizes in specific sub-population of patients, particularly in the neonatal age-group. The optimum stratification of neonates according to gestational age at birth and postnatal age warrants detailed investigation, with consideration of the rapid changes in PK/PD both in utero and during the first days of life, and optimum sample sizes are likely to vary according to specific drugs or drug classes of interest, and their respective developmental pharmacology. Likewise, these optimal design theories can then be applied to explore the ideal range of renal function (and dysfunction) that should be incorporated into a clinical trial, and other relevant pathophysiological covariates, comorbidities and concomitant medications, which may have significant influences on drug disposition. For critical care PK/PD research, innovative designs may investigate additional therapeutic interventions (such as renal replacement therapies, and cardiopulmonary bypass), which may be relevant. Given the cost of such research, these efforts will need to be prioritized in order of clinical need and importance, which will vary according to the clinical context.

It is inevitable that not all research centres have access to the in-house expertise in pharmacometrics and statistical modelling that are required to perform optimal designs independently, therefore the role of collaborative research networks to support these studies is essential. As demonstrated by the NAPPA study, such research can benefit from international Paediatric Clinical Pharmacology networks, as exemplified by the Global Research in Paediatrics
Network of Excellence, and also from national paediatric research networks. NAPPA was adopted by the Children’s section\textsuperscript{30} of the UK National Institute for Health Research (NIHR)\textsuperscript{31} Clinical Research Network Portfolio,\textsuperscript{32} which supported research infrastructure and delivery at all sites and was pivotal to the success of the study.

7 Conclusions

The use of optimal design theory can now maximise the informativeness of study design for paediatric antimicrobial PK/PD research and thus improve cost-effectiveness of research delivery. For future research in this field, we must endeavour to benefit from both the refined study designs that are now feasible with the application of optimal design theory\textsuperscript{10} and also the pragmatic designs that are increasingly popular using opportunistic sampling approaches.\textsuperscript{7} The sophistication of specialist software that is now available for optimal designs will facilitate the implementation of these approaches in a wide range of settings.\textsuperscript{10,19} Although it is essential to recognise that not all research centres will have access to the necessary expertise in pharmacometrics and statistical modelling to undertake optimal designs independently, the role of collaborative Paediatric Clinical Pharmacology networks, as demonstrated by the Global Research in Paediatrics Network of Excellence, will continue to grow and facilitate the sharing of such expertise across borders.

8 Acknowledgements

We are grateful to Dr Joe Standing for his input in the design and delivery of the NAPPA study, and to all the participants and their families, the clinical research teams at participating sites, and the co-investigators and collaborators.
9 References


16. European Medicines Agency. Guideline on the investigation of medicinal products in the term and preterm neonate. 2007. Available at:


10 Document History

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