Pharm Res (2012) 29:1530–1543
DOI 10.1007/s11095-011-0659-3

RESEARCH PAPER

Adaptive Optimal Design for Bridging Studies with an Application to Population Pharmacokinetic Studies

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Received: 7 April 2011 / Accepted: 19 December 2011 / Published online: 14 February 2012
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ABSTRACT

Purpose To develop and evaluate methods for conducting adaptive population pharmacokinetic bridging studies.

Methods An adaptive D-optimal design based on optimization of the population Fisher information matrix was used to determine the best sampling schedule for a target-population. Recruitment of the target-population was divided into batches and patients are assumed to enrol by batch. A prior-population model was used to determine the optimal sampling schedule for the first batch and to stabilise the data analysis in the interim iteration. Simulation studies were performed under two scenarios (1) the prior- and target-populations have similar pharmacokinetic profiles and (2) the pharmacokinetic profiles diverge significantly. A design criterion to determine early full enrolment was also proposed.

Results The target-population estimates obtained using the proposed method were compared to estimates obtained if the target-population was studied with a design optimized based on the prior-population model. The proposed method is shown to be not inferior in scenario (1) and superior in scenario (2). The criterion to determine early full enrolment was proven to be effective.

Conclusions An adaptive optimal design method together with an early full enrolment criterion were evaluated and resulted in more accurate estimates for the target-population in bridging studies.

KEY WORDS adaptive design · bridging studies · optimal design · pharmacokinetics

INTRODUCTION

As defined in the International Conference on Harmonization E5 guideline, "A bridging study is a supplementary study conducted in a new region to provide information on efficacy, safety, dosage and dosing regimen of a drug for extrapolation of foreign clinical data" (1). Data generated from the bridging study in the new region is evaluated for similarity with data from an original region for the purpose of extrapolation. In order to determine the efficacy, safety, dosage and dosing regimen of a drug, the understanding of the time course of the drug effect is essential and this knowledge is gained by modelling the pharmacokinetic-pharmacodynamic (PKPD) of the drug. In many cases it is sufficient to show the same dose-exposure relationship (Pharmacokinetic (PK)) between the original and new region (2).

Some researchers have proposed to use optimal design methods based on the Fisher information theory to find the best design for PKPD studies. These designs which allow for a parsimonious experiment provide a high level of efficiency in PKPD parameter estimation (3–5). The main drawback of optimal design in PKPD is the dependency of the design on both the model and prior parameter values due to the statistical non-linearity inherent in PK and PKPD models. Various robust design methods have been developed to address this dependency issue by incorporating a prior distribution for the parameters (6–9).

Generally, a design obtained with various optimization methods remains fixed throughout a study and data will be analysed after completion of the study. An adaptive design, as opposed to a fixed study design, involves interim data

Electronic supplementary material The online version of this article (doi:10.1007/s11095-011-0659-3) contains supplementary material, which is available to authorized users.

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analyses for data accrual during the study and provides the basis for fine tuning the design. In a clinical trial setting, adaptive designs are carried out by enrolling patients in batches. Data accumulated during the study will be analysed to determine the design for the next batch. The most common application of adaptive designs for clinical trials is to determine the maximum tolerated dose, a common endpoint in oncology studies using design methods such as the continuous reassessment method (10).

Recently adaptive design for clinical trial has sparked considerable discussion among researchers i.e., a special issue of Journal of Biopharmaceutical Statistics (11) was devoted to this topic. Application of adaptive design to improve dose-ranging in clinical development has been studied by Bornkamp *et al.* (12). They conducted a comprehensive simulation study to develop and evaluate adaptive dose finding design by comparing several methods including the traditional ANOVA method and concluded that adaptive design performed substantially better than the traditional method. Bandyopadhyay and Dragalin (13) developed an adaptive design method with sample size re-estimation and developed a stopping rule for early completion of a bioequivalence study of a test formulation to a reference formulation of a drug. They showed that the adaptive design method lead to an early stopping by demonstrating bioequivalent conclusively. In further work, Dragalin *et al.* (14) proposed a three stages adaptive design method for dose finding in a clinical trial with a continuous efficacy endpoint. D-optimal design was used to determine both dose location and patient allocation in the third stage. They demonstrated the advantage of the method with five different dose-response models. The benefit of applying optimal design in phase II clinical studies for exposure-response modelling was demonstrated by Maloney *et al.* (15) and they suggested that the optimal adaptive design approach is worth exploring as a future step.

One of the reasons for bridging studies is to minimize duplication of clinical data in the new region. Thus, knowledge of PKPD from the original region can be used to locate the optimal design to study the new region. The optimal design can be applied directly as a fixed study design where all patients in the new region will be enrolled following this design in a single-go. However, a single-go fixed study assumes the PKPD characteristics of the patients in the new region to be similar to patients in the original region otherwise the design will be suboptimal and possibly fail. Maloney *et al.* (16) demonstrated with a simulation example that optimal design methods when used adaptively were shown to perform well compared to a fixed optimal design. Thus, we will explore the applicability of adaptive-optimal design in the context of PK bridging studies.

In this project, we have applied adaptive D-optimal design to PK studies bridging from a population in an original region (termed prior-population) to a population in a new region (termed target-population). The purpose of the bridging study is to estimate the parameters of the PK model of the target-population. Our work builds on the substantial work of others in optimal design and adaptive design as mentioned in literatures in preceding paragraphs. The purpose of this study is to evaluate an adaptive D-optimal design in the setting of nonlinear mixed effects models. The D-optimal design is obtained by maximizing the determinant of the population Fisher information matrix and population approach is used in the model fitting. We want to highlight that in this project the prior-population data was not intended for extrapolation into the target-population or to be combined with the target-population data for a final pooled analysis but rather was used for the purposes of determining the initial design for the target-population and to stabilise the data analyses in the interim iteration.

This paper is organized as follows. The detailed procedure of our proposed method to perform an adaptive D-optimal design for bridging studies is presented in "Materials and Methods", where we also proposed a criterion to determine early full enrolment. Two simulation scenarios for two hypothetical examples are introduced in "Simulation Studies". The proposed methods were evaluated under these two scenarios and the results are presented which are followed by discussion and conclusion.

MATERIALS AND METHODS

We have termed our proposed procedure of the adaptive D-optimal design for bridging studies the D-optimal ABS (D-optimal Adaptive Bridging Studies). The recruitment of the target-population in the D-optimal ABS is divided into batches and patients are assumed to enrol by batch. A criterion which can be used to determine early full enrolment for all the remaining target-population patients in the interim iteration is also proposed. The performances of both methods were accessed using simulation studies of two hypothetical examples.

D-optimal ABS

In the D-optimal ABS, S_{prior} represents the total number of subjects enrolled from the prior-population, S_{target} represents the total number of subjects from the target-population which is divided equally into B batches and to be enrolled by batch.

We assumed that S_{target} has been defined *a priori* and is based on either prior experience, an agreement with the regulatory agency, based on clinical practicalities or a combination of all of these processes. It is, of course, possible to optimise the value of S_{target} but this is not the subject of the current analysis. Finally, we initiate the bridging study under the general assumption that the prior- and target-populations

are similar. However, it will be seen, that this assumption is not a requirement for the D-optimal ABS described here.

A pooled data set that combined the samples from both the prior-population patients and target-population patients is used at each iteration for both model fitting and optimal design. We use a pooled data set for the D-optimal ABS since the small number of patients at each iteration of the target-population may not provide sufficient data to get stable parameter estimates, and therefore may potentially mislead the optimal design. Two types of models are fitted to the pooled data set for the purpose of parameter estimation. One is termed the "pooled model" where prior and target patients are treated as if they arose from the same population. For the second type of model, a flag is added to the pooled data set to label whether a patient is from the prior- or the target-population. A model is then fitted to the data set (with the flag) which allows for two different sets of estimates of the PK fixed and random effects to represent the two populations of the prior and target. However, a single pooled residual variance is estimated that accounts for residual variability across both data sets. This model is termed a "covariate model", where the flag that accounts for a "population effect" is treated as a covariate in the model. All D-optimal designs in this work are based on the pooled model that arises from the pooled data. We used the covariate model for two settings (1) to illustrate the apparent properties of the D-optimal ABS method to converge to the correct solution when we used the pooled model for design and (2) to evaluate the criterion to determine early full enrolment.

Procedure for D-optimal ABS

Initialisation Step. Data from the S_{prior} patients have already been collected following a previous design $\left(\xi^{\{0\}}\right)$. A model has been fitted to the data and from this model and parameter estimates a D-optimal design ($\xi^{\{1\}}$) is determined. This D-optimal design is entirely conditioned on the model from the prior data set without, at this point, any consideration of differences that may exist between the prior and target. The total number of patients from the target-population (S_{target}) is assumed to be known *a priori* and divided into B batches. Target patients will then be enrolled by batch at each iteration b ($b = 1, \cdots, B$) in the D-optimal ABS. The first batch target-population patients is enrolled and data is collected according to $\xi^{\{1\}}$.

Iteration b in D-optimal ABS ($b = 1, \cdots, B$)

Step 1. The prior-population data is reduced by the same proportion as the target-population has increased. For example if S_{prior}=100 and S_{target}=50, and 20% of S_{target} (10 patients out of 50) were enrolled from the target-population at the b^{th} batch then 20% of S_{prior} (20 patients out of 100) will be removed (at random) from the prior-population. A pooled data set of patients is constructed by combining the b^{th} batch of patients from the target population with the previous batches ($b = 1, \cdots, b-1$) from the target-population, together with the reduced prior-population patients. At this point the total number of subjects in the pooled data set is denoted as $S^{\{b\}}_{\text{pooled}}$. Thus

$$S^{\{b\}}_{\text{pooled}} = \left(1 - \sum_{m=1}^{b} \alpha^{\{m\}}\right) \times S_{\text{prior}} + \sum_{m=1}^{b} \alpha^{\{m\}} \times S_{\text{target}}; \quad b = 1, \cdots, B; \quad \sum_{m=1}^{B} \alpha^{\{m\}} = 1, \tag{1}$$

where α is the proportion of accumulation in the target-population patients (α=0.2 in the previous example) and B is the total number of batches.

Two ways for reducing the proportion of the prior-population data have been considered in this study. The first is to reduce the prior-population data in each iteration arithmetically according to the number of batches of the target-population (B) where $\alpha^{\{b\}} = \frac{1}{B};\ b = 1, \cdots, B$. The second is to reduce the prior-population data geometrically where the prior-population data in the current iteration is half of the previous iteration, thus

$$\begin{aligned} \alpha^{\{1\}} &= \frac{1}{2}, \\ \alpha^{\{b\}} &= \frac{1}{2} \times \alpha^{\{b-1\}}, \quad b = 2, \cdots, B-1; \\ \alpha^{\{B\}} &= 1 - \sum_{b=1}^{B-1} \alpha^{\{b\}}. \end{aligned} \tag{2}$$

Thus we allow α to vary by iteration in the geometric accumulation and we consider α to take a fixed value in the arithmetic accumulation in this work.

Step 2. A pooled model is fitted to the pooled data set (without distinction to which population each subject arose) and a D-optimal design, $\xi^{\{b+1\}}$, is located for the new model which is then applied to collect samples from the next batch (b + 1) target-population patients. Thus

$$\xi^{\{b+1\}} = \arg\max_{\xi}\left(S^{\{b\}}_{\text{pooled}} \times \left|M(\widehat{\boldsymbol{\theta}}^{\{b\}}_{\text{pooled}}, \xi)\right|\right); \quad b = 1, \cdots, B. \tag{3}$$

where $\widehat{\boldsymbol{\theta}}^{\{b\}}_{\text{pooled}}$ is a vector of parameter estimates that were obtained by fitting the pooled model to the pooled data at iteration b and $|M(\cdot)|$ denotes the determinant of the Fisher information matrix.

Step 3. Data are collected from the $(b+1)^{\text{th}}$ batch of patients from the target-population according to $\xi^{\{b+1\}}$. Step 2 and 3 are repeated until all batches have been enrolled.

For simplicity we have assumed that there is a single sampling schedule for each batch of target-population patients where $M(\widehat{\theta},\xi)$ are elementary information matrices which characterize the information from a single individual. We also make the simplifying assumption that all patients in the prior-population arise from the same design. However, these assumptions are not a requirement of the process.

Criterion to Determine Early Full Enrolment

In this section we proposed a criterion to determine early full enrolment for the D-optimal ABS. The basis for early full enrolment is determined when the current design is sufficiently optimal that all the remaining patients in the target-population can be enrolled in the next batch. The covariate model is used for this purpose where a flag is added to the data set to indicate if a patient arises from the prior- or the target-populations. Thus after the enrolment of b^{th} batch of patients from the target-population, a covariate model is fit to the data set. A product D-optimal design $\xi_{\text{prodD}}^{\{b+1\}}$ is located for the covariate model which optimizes simultaneously across the prior-population estimates $\left(\widehat{\boldsymbol{\theta}}_{\text{prior}}^{\{b\}}\right)$ and the target-population estimates $\left(\widehat{\boldsymbol{\theta}}_{\text{target}}^{\{b\}}\right)$ in the covariate model. In addition, a local D-optimal design $\xi_{\text{target}}^{\{b+1\}}$ is located that optimizes solely at $\widehat{\boldsymbol{\theta}}_{\text{target}}^{\{b\}}$ (the estimates of the target-population in the covariate model). Thus

$$\begin{aligned}
\xi_{\text{prodD}}^{\{b+1\}} &= \arg\max_{\xi}\left\{\frac{1}{2}\left(\ln\left[\left(1-\sum_{m=1}^{b}\alpha^{\{m\}}\right)\times S_{\text{prior}}\times\left|M\left(\widehat{\theta}_{\text{prior}}^{\{b\}},\xi\right)\right|\right]\right.\right.\\
&\qquad\left.\left.+\ln\left[\sum_{m=1}^{b}\alpha^{\{m\}}\times S_{\text{target}}\times\left|M\left(\widehat{\theta}_{\text{target}}^{\{b\}},\xi\right)\right|\right]\right)\right\}\\
\xi_{\text{target}}^{\{b+1\}} &= \arg\max_{\xi}\left\{\sum_{m=1}^{b}\alpha^{\{m\}}\times S_{\text{target}}\times\left|M\left(\widehat{\theta}_{\text{target}}^{\{b\}},\xi\right)\right|\right\},\\
b &= 1,\cdots,B;\quad \sum_{m=1}^{B}\alpha^{\{m\}}=1.
\end{aligned}\tag{4}$$

Under the assumption that $\xi_{\text{target}}^{\{b+1\}}$ is the best design to study the target-population and $\widehat{\boldsymbol{\theta}}_{\text{target}}^{\{b\}}$ in the covariate model is the vector of best estimates for the target-population PK parameters, the efficiency of the product design at iteration b can then be assessed as

$$\text{D}-\text{efficiency} = \left(\frac{\left|M\left(\widehat{\boldsymbol{\theta}}_{\text{target}}^{\{b\}},\xi_{\text{prod D}}^{\{b+1\}}\right)\right|}{\left|M\left(\widehat{\boldsymbol{\theta}}_{\text{target}}^{\{b\}},\xi_{\text{target}}^{\{b+1\}}\right)\right|}\right)^{1/p},\tag{5}$$

where p is the total number of fixed and random effects parameters to be estimated in the target-population. Note, the model has the same structure for both prior and target and hence p is the same value for both populations. If the D-efficiency is not less than a predefined critical value at the current iteration then this indicates that $\xi_{\text{prod D}}^{\{b+1\}}$ has achieved the desired efficiency and all remaining patients from the target-population can be enrolled following $\xi_{\text{prod D}}^{\{b+1\}}$ as the study design.

The procedure of our proposed method for determining an early full enrolment is as follows (the initialisation step is the same as in the D-optimal ABS).

Evaluation of the Criteria

Step 1. The b^{th} batch of target-population data is combined with the previous batches $(b = 1,\cdots,b-1)$ and with the prior-population that has been reduced proportionally. A flag is added to the dataset to label which population the patient belongs to and a covariate model that allows the fixed effects and variance of the random effects estimates to differ between the prior- and target-population is fitted to the data set. Note, a single pooled residual variance is estimated that accounts for residual variability across both data sets.

Step 2. The product design $\left(\xi_{\text{prodD}}^{\{b+1\}}\right)$ and local design $\left(\xi_{\text{target}}^{\{b+1\}}\right)$ are found and the D-efficiency of the product design is calculated as in Eq. 5.

Step 3. If the D-efficiency is not less than the predefined critical value then $\xi_{\text{prodD}}^{\{b+1\}}$ is used as the study design for all the remaining patients from the target-population. If the D-efficiency is less than the predefined critical value then the next batch $(b+1)$ of target-population patients is enrolled and data is collected according to $\xi_{\text{prodD}}^{\{b+1\}}$, and steps 2 and 3 are repeated.

In this project, we have set the critical value to 0.8 in our simulation studies. The choice of 0.8 is empirical and based on previous experience of accounting for loss of optimality in the population design setting. This value should provide an overall design that performs acceptably. It is not within the scope of this project to investigate other values and indeed 0.7 or 0.9 might also achieves reasonable effects.

Simulation Studies

Simulation studies based on two different scenarios were carried out to assess the performance of the proposed methods. Both examples presented below are hypothetical and intended to provide clinical context for the simulation studies. We have considered a fixed target-population sample size thus the

number of patients in the target-population was assumed to be known and fixed in advance. The number of patients in the target-population were divided into a fixed number of batches and subsequently assumed to be enrolled by batch.

All simulations were carried out in MATLAB version 2009 (a). NONMEM VI was called within MATLAB for the model fitting and the estimation method used in NONMEM is the FOCE method with interaction. The D-optimal design was obtained using POPT (17) where simulated annealing was used in simulation scenario 1 and exchange algorithm in simulation scenario 2. Each clinical study was replicated 100 times and the range of admissible sampling times was 0 to 24 h post-dose.

Simulation Scenario 1: D-optimal ABS from Adult Patient to Paediatric Patient

The first simulation scenario is a bridging study based on a hypothetical example where the prior-population is adults and the target-population is children. The drug was assumed to be a small molecule drug and was given orally. The PK model was set to follow a first-order input and first-order output one-compartment model (termed as Bateman model). In this scenario the difference between paediatric and adult patients was provided entirely by allometry. Hence in this scaled case the adult and paediatric profiles were indeed very similar (see Fig. 1a). This simulation scenario therefore provides a positive control in the sense that a study designed solely based on the prior data and applied directly to the target-population would be expected to perform well.

The PK model is defined as

$$C_{ij} = \frac{D \times ka_i}{V_i \times (ka_i - k_i)} \left[\exp\left(-k_i \times t_{ij}\right) - \exp\left(-ka_i \times t_{ij}\right)\right] \times \exp\left(\varepsilon_{p_{ij}}\right) + \varepsilon_{a_{ij}},$$
$$k_i = \frac{CL_i}{V_i}, \quad \boldsymbol{\theta}_1 = (CL_i, \quad V_i, \quad ka_i)', \quad \ln \boldsymbol{\theta}_1 \sim MVN(\ln \boldsymbol{\mu}_1, \boldsymbol{\Omega}_1). \tag{6}$$

C_{ij} is the jth observed drug concentration of ith patient at time t_{ij}. D is the given dose. The parameters ($\boldsymbol{\theta}_1$) for this model are clearance (CL), volume of distribution (V) and the absorption rate constant (ka) which were assumed to follow a multivariate lognormal distribution with nominal mean $\boldsymbol{\mu}_1$ and variance-covariance matrix $\boldsymbol{\Omega}_1$.

Values for the nominal parameter mean of adult patient and paediatric patient together with $\boldsymbol{\Omega}_1$ are given in Table I. The nominal parameter mean of CL and V for paediatric patients were scaled allometrically with exponents 0.75 and 1 respectively, i.e. CL of a 20 kg paediatric is equals to $(20\text{ kg}/70\text{ kg})^{0.75} \times CL$ of a 70 kg adult. The nominal mean of paediatric ka was assumed to be the same as the adult patient. The variances of the between subject variability were assumed to be the same with a value of 0.1 for both populations. ε_p is the proportional error and ε_a is the additive error. Both errors were assumed to be independently and identically normally distributed with $\varepsilon_{p_{ij}} \sim N(0,\ 0.1)$ and $\varepsilon_{a_{ij}} \sim N(0,\ 0.05)$.

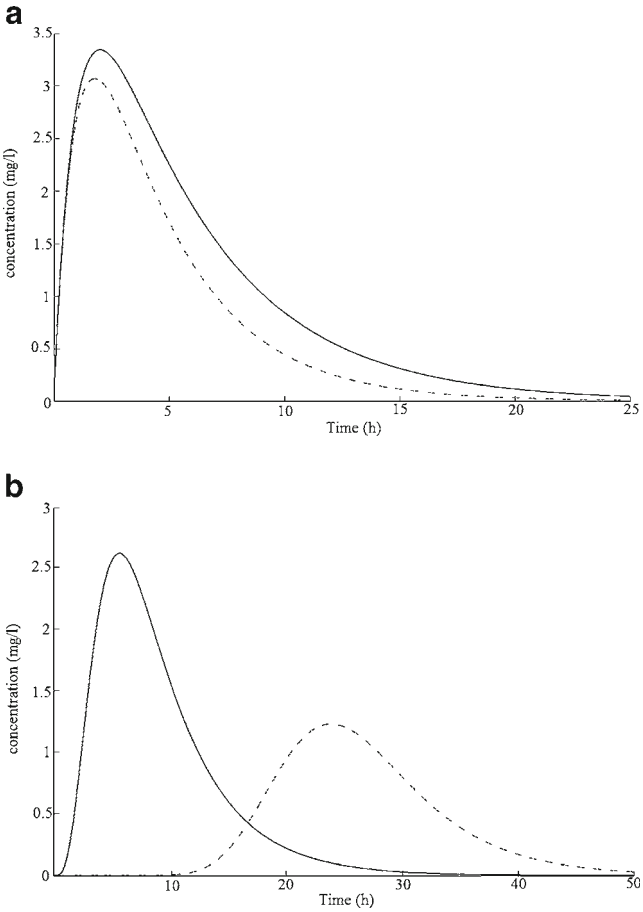

Fig. 1 (**a**) The concentration time plots for simulation scenario 1. The *solid line* is the concentration time plot for an adult patient of 70 kg and a dose of 100 mg. The *dashed line* is the concentration time plot for a paediatric patient who weighs 20 kg and a dose of 28.57 mg. (**b**) The concentration time plots for simulation scenario 2. The *solid line* is the concentration time plot for normal weight adult patient. The *dashed line* is the concentration time plot for obese adult patient. The dose was assumed to be 100 mg for both normal weight and obese patients.

We assumed a sample size of 200 adult patients and 25 paediatric patients. Arithmetic accumulation was considered in this simulation study. The 25 paediatric patients were divided into five batches with five patients in each batch. The dose was scaled based on weight only where a dose for a 20 kg child is calculated as Dose = $(20/70) \times 100$ mg; i.e., an adult weights 70 kg will be given 100 mg of the drug and scaled to 28.57 mg for a paediatric patient

Table I Nominal Parameter Mean and Variance for Adult Patient and Paediatric Patient

$\boldsymbol{\theta}_1$	$\boldsymbol{\mu}_{adult}$	$\boldsymbol{\mu}_{paediatric}$	$\boldsymbol{\Omega}_1$		
CL	4	1.56	0.1	0	0
V	20	5.71	0	0.1	0
ka	1	1	0	0	0.1

weights 20 kg. Each of the 200 adult patients were assumed to provide six blood samples following an empirical sampling schedule ($\xi^{\{0\}}$) at time 1, 2, 4, 8, 12 and 24 h post-dose. A four time point D-optimal design ($\xi^{\{1\}}$) was located based on the adult patient model. Sample data of the first batch of five paediatric patients were simulated under the design $\xi^{\{1\}}$, but using the paediatric dose and parameter values. The adult patient data was reduced by 20% $\left(\alpha = \frac{1}{5}\right)$ at each iteration. The procedure involved proportionally reducing the adult patient (prior) data, combining the remaining adult patients' data with batches of paediatric patients' data, fitting the pooled model to the pooled data set, locating a four point D-optimal design and simulating the next batch of paediatric patient data under that design. The process was repeated until the last (fifth) batch of paediatric patients. In the last iteration the data set consists of only the five batches (a total of 25) paediatric patients. Another simulation studies was also carried out for this scenario following the proposed procedure for determining the early full enrolment.

Simulation Scenario 2: D-optimal ABS from Normal Weight Adult to Obese Adult

The second simulation scenario is again a hypothetical scenario in which a bridging study was proposed from normal weight adult patients to obese adult patients for a large molecule drug given subcutaneously. We assumed that there is delayed absorption in the obese patients due to lymphatic drainage thus the input model followed a transit compartment model (18). The PK is therefore defined by a system of two ordinary differential equations (ODEs). In this scenario the two PK profiles are quite different with the peak concentration for the obese patients occurring at a point where there is expected to be negligible concentrations for the non-obese patients (see Fig. 1b). This simulation scenario provides a test case in which it would be expected that a design based solely on the prior-population would perform poorly for the target-population.

The pharmacokinetic model is given by:

$$\begin{aligned}
&\frac{dA(1)}{dt} = \frac{D \times (ktr_i \times t)^{N_i} \times e^{(-ktr_i \times t)}}{N_i!} \times ktr_i - ka_i \times A(1),\\
&\frac{dA(2)}{dt} = ka_i \times A(1) - k_i \times A(2),\\
&ktr_i = ka_i = \frac{MTT_i}{N_i}, \quad k_i = \frac{CL_i}{V_i},\\
&\boldsymbol{\theta}_2 = (CL_i,\ V_i,\ MTT_i,\ N_i)', \quad \ln \boldsymbol{\theta}_2 \sim MVN(\ln \boldsymbol{\mu}_2, \boldsymbol{\Omega}_2).
\end{aligned} \tag{7}$$

$A(1)$ and $A(2)$ are the amount of drug in the absorption and central compartment respectively. *ktr* and *ka* are the absorption rate constant of the transit compartments and the absorption compartment which were assumed to have the same values (ratio of MTT over N) in our simulation. k is the elimination rate constant and provided by the ratio of CL over V. D is the given dose and we assumed a combined error model thus the jth observed drug concentration of ith patient at time t_{ij} is $C_{ij} = \frac{A(2)_{ij}}{V_i} \times \exp\left(\varepsilon_{p_{ij}}\right) + \varepsilon_{a_{ij}}$.

The transit compartment model is used to model delayed absorption by interspersing a chain of transit compartments before the absorption. If there is significant delay in drug absorption then there will be a longer mean transit time which is assumed to be the case for obese patients in this simulation study. The parameters ($\boldsymbol{\theta}_2$) of this model are CL (clearance), V (volume of distribution), MTT (mean transit time) and N (number of transit compartments). The parameters were assumed to follow a multivariate lognormal distribution with nominal mean $\boldsymbol{\mu}_2$ and variance-covariance matrix $\boldsymbol{\Omega}_2$.

Values of $\boldsymbol{\mu}_2$ and $\boldsymbol{\Omega}_2$ are given in Table II for normal weight and obese patients. The variance of the between subject variability of CL, V and MTT were assumed to be the same for both populations with value 0.2. We assumed that there is no between subject variability for N in both populations. ε_p and ε_a were assumed to be independently and identically normally distributed with $\varepsilon_{p_{ij}} \sim N(0,\ 0.1)$ and $\varepsilon_{a_{ij}} \sim N(0,\ 0.05)$.

We assumed sample size of 60 normal weight adult patients and 60 obese adult patients. The dose was assumed to be 100 mg for both normal weight and obese patients. Both arithmetic accumulation and geometric accumulation were considered in this simulation study with five batches. The five batch arithmetic accumulation simulation study has 12 obese patients in each batch. For the geometric accumulation, the first batch of the five batches has 30 obese patients, followed by second batch 15, third batch eight, forth batch four and fifth batch the remaining three obese patients.

Data simulated for the 60 normal weight patients each assumed to provide eight blood samples following a D-optimal sampling schedule ($\xi^{\{0\}}$) optimized at the nominal mean of this prior-population, where the sampling times are 1.1, 1.6, 4.1, 4.6, 8.1, 8.6, a replicated time at 20.1 h post-dose. The model was fitted to this data set and an eight time point D-optimal design ($\xi^{\{1\}}$) was located and used to simulate the first batch of obese patients' data. We have not constrained the design to avoid replicate sampling time in this simulation scenario, but would do so for a real study. The steps of proportionally reducing the normal weight patient data, combined remaining normal weight patients' data with batches of obese patients' data, fitting pooled model to the pooled data set, locating an eight time point D-optimal design to simulate the next batch of obese patients' data, were repeated till the last batch of obese patients. Another simulation studies was also carried out for this scenario following the proposed procedure for determining the early full enrolment.

Evaluation of the Performance of D-optimal ABS and Early Full Enrolment Criterion

Estimates from the D-optimal ABS and the early full enrolment procedure were compared to estimates obtained using two local D-optimal designs where 1) the design based on the prior-population model (i.e., $\xi^{\{1\}}$) was used as the design for the whole target-population and 2) the design optimized at the target-population mean parameter values (unknown in a real life experiment) which is labelled as ξ_T.

The percentage relative error (%RE) was used to compare the bias in the estimates of each of the population PK parameters and was calculated as

$$\%\text{RE} = \frac{\widehat{\mu} - \mu_{\text{target}}}{\mu_{\text{target}}} \times 100\%, \quad (8)$$

where $\widehat{\mu}$ is the parameter estimate and μ_{target} is the nominal mean of the target-population.

RESULTS

One hundred simulations of the D-optimal ABS were run for each of the two simulation scenarios. The results of estimation error for the pooled and the covariate model with arithmetic accumulation in simulation scenario 1, and estimation error for the five batch covariate model with arithmetic accumulation in simulation scenario 2 for the 100 D-optimal ABS are presented below. The geometric accumulation in simulation scenario 2 provided similar result as the arithmetic accumulation and thus is not presented. One hundred simulations were also carried out to access the early full enrolment criterion for each of the simulation scenario and the results are presented.

Simulation Scenario 1: D-optimal ABS from Adult Patients to Paediatric Patients

The %RE of the estimates of *CL*, *V*, *ka*, ω^2_{CL}, ω^2_V, ω^2_{ka}, $\sigma^2_{\varepsilon_P}$ and $\sigma^2_{\varepsilon_a}$ in each iteration for the pooled model are shown in Fig. 2. The %RE of the estimates of *CL* and *V* were reduced and approached zero in the last (fifth) iteration. However, the %RE of the estimates of *ka* seems to increase between iterations. This is due to our choice of the nominal mean parameter value of *ka* which was assumed to be the same for both adult and paediatric. The less precise estimate was caused by the reduction in the pooled patient number from 165 (160 adults together with 5 pediatrics) in the first iteration to 25 (all five batches of paediatric) in the fifth iteration. The %RE of the estimates of ω^2_{CL} and ω^2_V did not show monotonic trend between iterations. The %RE increased from iteration 1 to 4 then reduced to around zero in the last iteration. The bias in the estimates of ω^2_{CL} and ω^2_V is large in the interim iterations because they were estimates from the pooled model that fit to the pooled data set (which consists of data simulated from two populations with same nominal variances but different nominal mean), and hence the variances estimates are inflated. The %RE of the estimates of ω^2_{ka} has the same patent as the %RE of the estimates of *ka* since the nominal mean and variance of *ka* were assumed to be the same for both populations. Again we see a reduction in the number of patient' result in less accurate estimates, which is also the same for estimates of $\sigma^2_{\varepsilon_P}$ and $\sigma^2_{\varepsilon_a}$.

The estimates of paediatric patients can be seen to approach gradually to the true parameter values when the covariate model is fitted to the same data set for the purpose of illustration (see Fig. 3). By fitting the covariate model, we allowed different estimates for adult and paediatric patients at each iteration. Boxplots in Fig. 3 are the %RE for the estimates of the paediatric patients only, where in iteration 1 we have the first batch of 5 pediatric patients, iteration 2 the first and second batch of 10 pediatric patients till iteration 5 with all the five batches of 25 paediatric patients. In our proposed D-optimal ABS, the simulation of the next batch of target-population data is under the optimal design based on the pooled model that fit to the pooled data set. The trend in Fig. 3 showed that sampling follow the design optimized at the pooled model estimates in the interim iteration result in data that stabilized the parameter estimation of the target-population with less estimation bias.

A comparison of the %RE for the parameter estimates in the last iteration of the D-optimal ABS (labelled as Iter 5), with the estimates obtained if we applied the D-optimal design located for the adult patient model $\left(\xi^{\{1\}}\right)$ directly to study the 25 paediatric patients (labelled as ND (Naive Design)), and the estimates obtained if the study design of the paediatric patients was optimized at the target-population (paediatric patients) nominal mean (labelled as T to T (Target to Target)) are shown in Fig. 4. The study design optimised at the paediatric patient nominal mean (ξ_T) is a sampling schedule at 0.41, 3.26, 10.05 and 15.23 h post-dose. The estimates in the last iteration of the D-optimal ABS are not inferior in this simulation scenario. We also see that, in this positive control scenario, optimized for the target based on a model

Table II Nominal Parameter Mean and Variance for Normal Weight Adult Patient and Obese Adult Patient

θ_2	$\mu_{\text{normal weight}}$	μ_{obese}	Ω_2			
CL	4	5.2	0.2	0	0	0
V	20	30	0	0.2	0	0
MTT	3	20	0	0	0.2	0
N	2	20	0	0	0	0

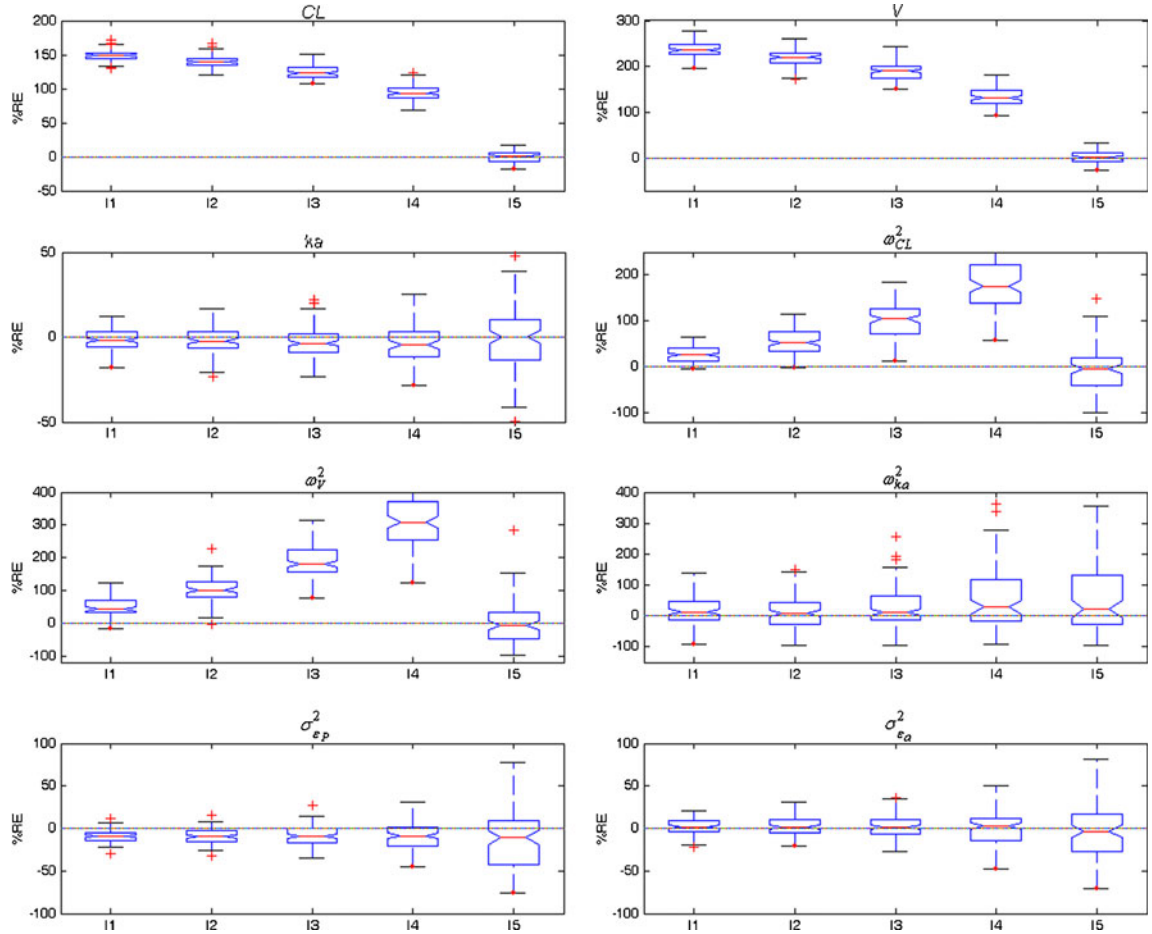

Fig. 2 Boxplots of percentage relative error (%RE) for pooled model estimates with five batches arithmetic accumulation in simulation scenario 1. *Structural parameters* clearance (*CL*), volume of distribution (*V*) and absorption rate constant (*ka*). *Statistical parameters* between subject variability (BSV) for *CL* $\left(\omega^2_{CL}\right)$, *V* $\left(\omega^2_V\right)$ and *ka* $\left(\omega^2_{ka}\right)$. *Residual unexplained variability* variance of the proportional error $\left(\sigma^2_{\varepsilon_p}\right)$ and additive error $\left(\sigma^2_{\varepsilon_a}\right)$. The *horizontal line* within each subplot is the zero percentage. There are five iterations in this simulation, which is labelled as I1 to I5.

fitted to the prior population data set (Naïve Design) was almost as accurate as if the target were known *a priori*. Since the PK profile for the prior and target in this scenario are similar as shown in Fig. 1a.

The relative standard error (RSE%) of the estimates of the parameters for the paediatric bridging study when the study design is the optimal design at adult nominal mean values (ξ_P=0.41, 3.64, 12.72 and 20.82 h post-dose) and when the study design is the optimal design at the paediatric nominal mean values (ξ_T=0.41, 3.26, 10.05 and 15.23 h post-dose) are presented in Table III. The RSE% values were computed from the Fisher information matrix given by POPT. The RSE% for all the parameters were comparable for ξ_P and ξ_T for this hypothetical example. Note in this hypothetical example a geometric six time points design was used to simulate data from the prior population instead of ξ_P.

One hundred simulations were carried out to access the criterion for the early full enrolment. We have assumed the same number of patients (200 adults and 25 paediatric) and the same number of batches (five). Seventy five simulated clinical studies had achieved 80% efficiency with the first batch paediatric patients and 25 with two batches. Thus the remaining paediatric patients can be enrolled followed the current product optimal design $\xi_{\text{prod D}}$. The adaptive design with the early full enrolment criterion allows a quick "jump" to full enrolment in this simulation study which is again due to the fact that the prior- and target-populations have similar PK profile.

Simulation Scenario 2: D-optimal ABS from Normal Weight Adult to Obese Adult

The %RE of the estimates of *CL*, *V*, *MTT*, *N*, ω^2_{CL}, ω^2_V, ω^2_{MTT}, $\sigma^2_{\varepsilon_P}$ and $\sigma^2_{\varepsilon_a}$ in each iteration of the five batches arithmetic accumulation D-optimal ABS for obese patient are shown in Fig. 5. These are the estimation result using the covariate model (The D-optimal ABS was carried out using the pooled model and the purpose of covariate model is

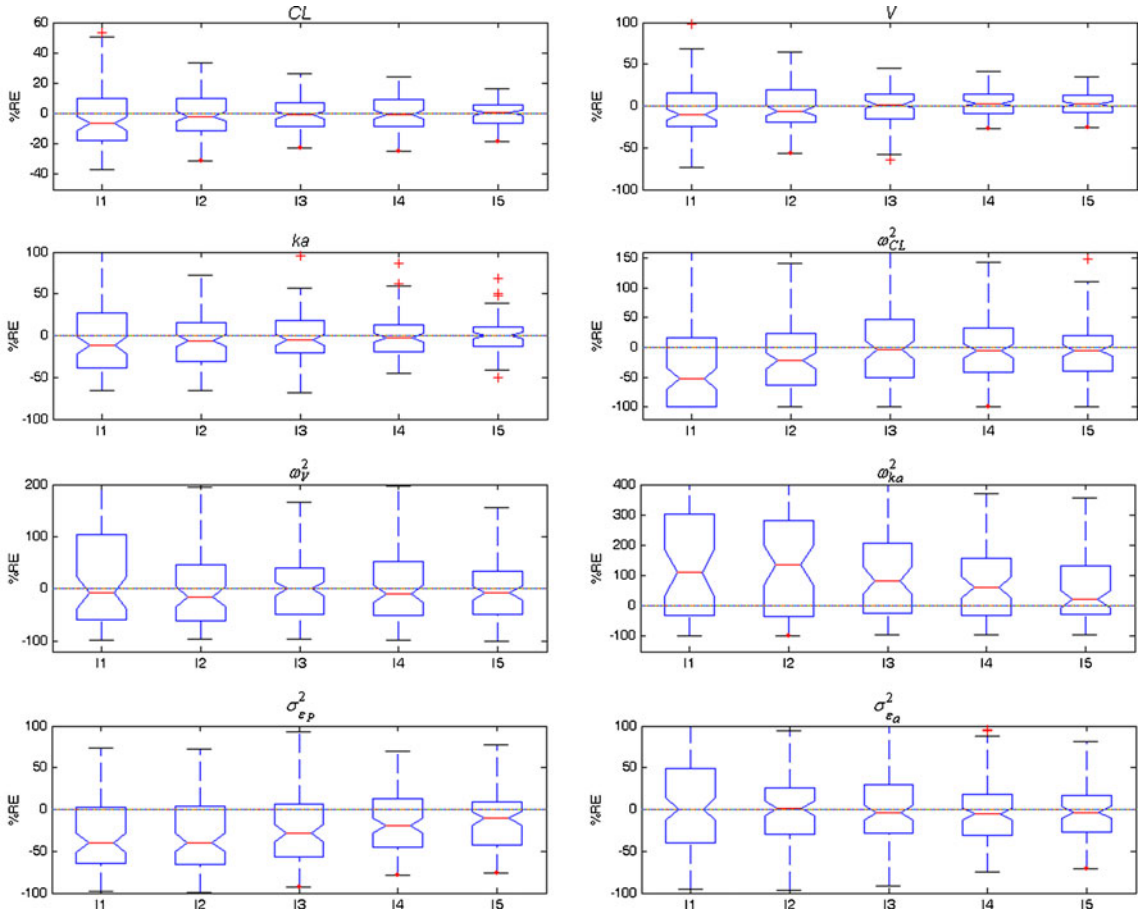

Fig. 3 Boxplots of the percentage relative error (%RE) for covariate model estimates of paediatric patients when a covariate is added to the pooled data set to indicate which population the patient belong to. *Structural parameters* clearance (*CL*), volume of distribution (*V*) and absorption rate constant (*ka*). *Statistical parameters* between subject variability (BSV) for *CL* $\left(\omega^2_{CL}\right)$, *V* $\left(\omega^2_V\right)$ and *ka* $\left(\omega^2_{ka}\right)$. *Residual unexplained variability* variance of the proportional error $\left(\sigma^2_{\varepsilon_p}\right)$ and additive error $\left(\sigma^2_{\varepsilon_a}\right)$. The *horizontal line* within each subplot is the zero percentage. There are five iterations in this simulation, which is labelled as I1 to I5.

for the evaluation and illustration). As seen in Fig. 5, the estimates approached the true parameter values gradually at each iteration. The comparison of the %RE of estimates in the final iteration of the five batches arithmetic accumulation D-optimal ABS (labelled as Iter 5), with the %RE of estimates obtained if the eight sampling time point D-optimal design optimized at normal weight patient model $\left(\xi^{\{1\}}\right)$ was used as the study design for all the obese patients (labelled as ND), and the %RE of estimates obtained if the study design for obese patient is a eight sampling time point D-optimal design optimized at the target-population nominal mean (labelled as T to T) are shown in Fig. 6. The study design optimised at the obese patient nominal mean (ξ_T) is a sampling schedule with one sample each at 15.1, 22.6, 23.1 h post-dose, two repeated samples at 28.1 h post-dose and three repeated samples at 42.6 h post-dose. The estimates of the fifth iteration in the D-optimal ABS is less bias for all the parameters if compared to the estimates when the study design is $\xi^{\{1\}}$. The fifth iteration estimates are however not as good as the estimates obtained if the study design is the D-optimal design optimized at the obese population nominal mean (ξ_T). However, the population mean values are not known in reality and thus it is impossible to optimize a design at these values.

The relative standard error (RSE%) of the parameter estimates for the obese bridging study when the study design was the optimal design at the normal weight adults nominal mean (ξ_P, which is the same as $\xi^{\{0\}}$in this simulation scenario, with a sampling schedule at 1.1, 1.6, 4.1, 4.6, 8.1, 8.6, 20.1, 20.1 h post-dose), and when the study design is the optimal design at the obese adult nominal mean values (ξ_T, a sampling schedule with one sample each at 15.1, 22.6, 23.1 h post-dose, two repeated samples at 28.1 h post-dose and three repeated samples at 42.6 hours post-dose) were presented in Table IV. The RSE% values were computed from the population Fisher information matrix using POPT. We can clearly see that the

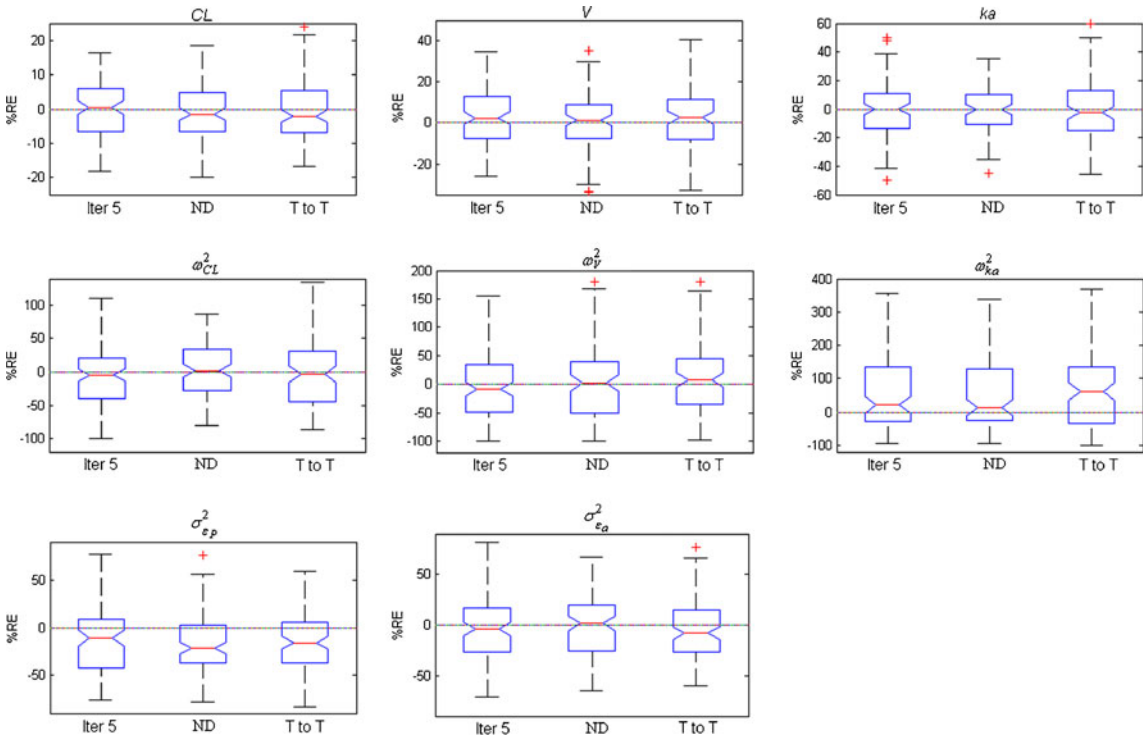

Fig. 4 Boxplots of percentage relative error (%RE) for final estimates in simulation scenario 1. "Iter 5" represents estimates obtained in the fifth iteration of the D-optimal ABS. "ND" represents estimates obtained if the four sampling time point D-optimal design located for the adult patients estimates is applied directly to study the paediatric patients. "T to T" represents estimates obtained if the study design for paediatric patients is the four sampling time point D-optimal design optimized at the paediatric population nominal mean values. *Structural parameters* clearance (*CL*), volume of distribution (*V*) and absorption rate constant (*ka*). *Statistical parameters* between subject variability (BSV) for *CL* $\left(\omega^2_{CL}\right)$, *V* $\left(\omega^2_V\right)$ and *ka* $\left(\omega^2_{ka}\right)$. *Residual unexplained variability* variance of the proportional error $\left(\sigma^2_{\varepsilon_p}\right)$ and additive error $\left(\sigma^2_{\varepsilon_a}\right)$. The *horizontal line* within each subplot is the zero percentage.

relative standard errors are large when ξ_P is applied to study the obese population.

In Fig. 6 bias is noticed in the estimates of *CL*, *V*, *N*, ω^2_{CL} and ω^2_{MTT} even when the study design for the obese patient group is the D-optimal design at the target-population nominal mean (shown as T to T in Fig. 6). A simulation-estimation study was carried out to evaluate the influence of the design on parameter estimation using NONMEM for the transit compartment model. The study design is chosen to be an intensive design with 15 samples per patient. By referring to the PK profile in Fig. 1b, the sampling times were chosen to be 10.25, 10.5, 11, 12, 13, 14, 16, 18, 20, 22, 26, 30, 36, 42 and 48 h post-dose for a design that covers the whole PK range of the obese patient. The simulation was carried out in Matlab and estimation in NONMEM (FOCE with interaction) for 100 studies. The boxplot for the %RE of the 100 estimates is provided as a supplement. There remains apparent bias in the estimates of *N* which is downwardly biased. These boxplots showed that estimates from NONMEM are reasonable with informative data that derived from an intensive design that covered the whole PK profile. The bias in *N* may be caused by the high nonlinearity associated with this parameter.

One hundred simulations were carried out for arithmetic accumulation of obese patients to access the criterion proposed for the early full enrolment. We assumed 60 obese patients which initially divided into five batches with 12 patients per batch. Ninety seven simulations achieved 80% efficiency after

Table III The Relative Standard Error (RSE%) of the Estimates on the Paediatric Population When the Study Design is the Optimal Design at Adult Nominal Mean Values (ξ_P) and When the Study Design is the Optimal Design at the Paediatric Nominal Mean Values (ξ_T). The RSE% was Computed from the Population Fisher Information Matrix and was Given by POPT

Parameter	RSE%	
	ξ_P	ξ_T
CL	9.63	8.99
V	14.2	13.8
ka	19.7	19.9
ω^2_{CL}	70.2	55.1
ω^2_V	86.4	77.9
ω^2_{ka}	196	191
$\sigma^2_{\varepsilon_p}$	26.0	24.0
$\sigma^2_{\varepsilon_a}$	14.1	18.8

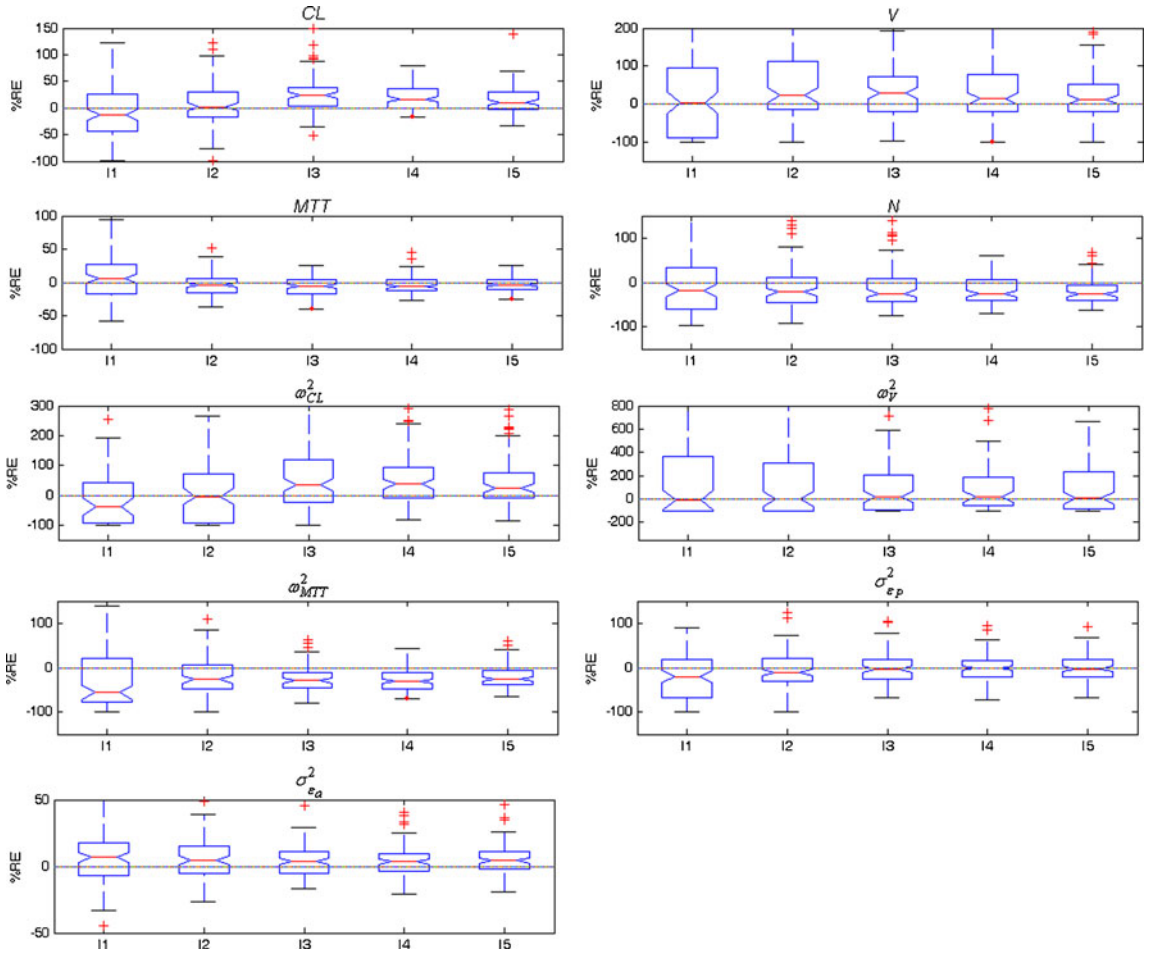

Fig. 5 Boxplots of the percentage relative error (%RE) for covariate model estimates of obese patients with five batches arithmetic accumulation. A covariate is added to the pooled data set to indicate which population the patient belong to. *Structural parameters* clearance (*CL*), volume of distribution (*V*), mean transit time (*MTT*) and number of transit compartments (*N*). *Statistical parameters* between subject variability (BSV) for *CL* $\left(\omega^2_{CL}\right)$, *V* $\left(\omega^2_{V}\right)$ and *MTT* $\left(\omega^2_{MTT}\right)$. *Residual unexplained variability* variance of the proportional error $\left(\sigma^2_{\varepsilon_p}\right)$ and additive error $\left(\sigma^2_{\varepsilon_a}\right)$. The *horizontal line* within each subplot is the zero percentage. There are five iterations in this simulation, which is labelled as I1 to I5.

the third batch of obese patients. One simulation achieved the desired efficiency after two batches and one after four batches. One simulation study will need all five batches to achieve 80% efficiency. All remaining obese patients in each of the 100 simulation studies were simulated accordingly followed the corresponding $\xi_{\text{prod D}}$ when the desired efficiency was achieved. Figure 7 compared the %RE of the final estimates obtained with the early full enrolment procedure (labelled as Final Iter) with the estimates obtained when the $\xi^{\{1\}}$ is applied to study the 60 obese patients in one-go (labelled as ND) and the estimates obtained when the study design for the 60 obese patients is the eight time point D-optimal design optimized at the obese patient nominal mean (labelled as T to T). The estimates obtained with early full enrolment procedure are more accurate as compared to the estimates using $\xi^{\{1\}}$ as the study design for all obese patients.

DISCUSSION

The current practice of PK bridging studies uses the study design based solely on the prior-population PK model. This may yield good estimates for the target-population PK if the target-population PK profile is similar to the prior-population PK as in the case of simulation scenario 1. However, if the target-population PK profile is unexpectedly divergent from the prior-population as in the case of scenario 2, the design optimized at the prior-population PK will be suboptimal and

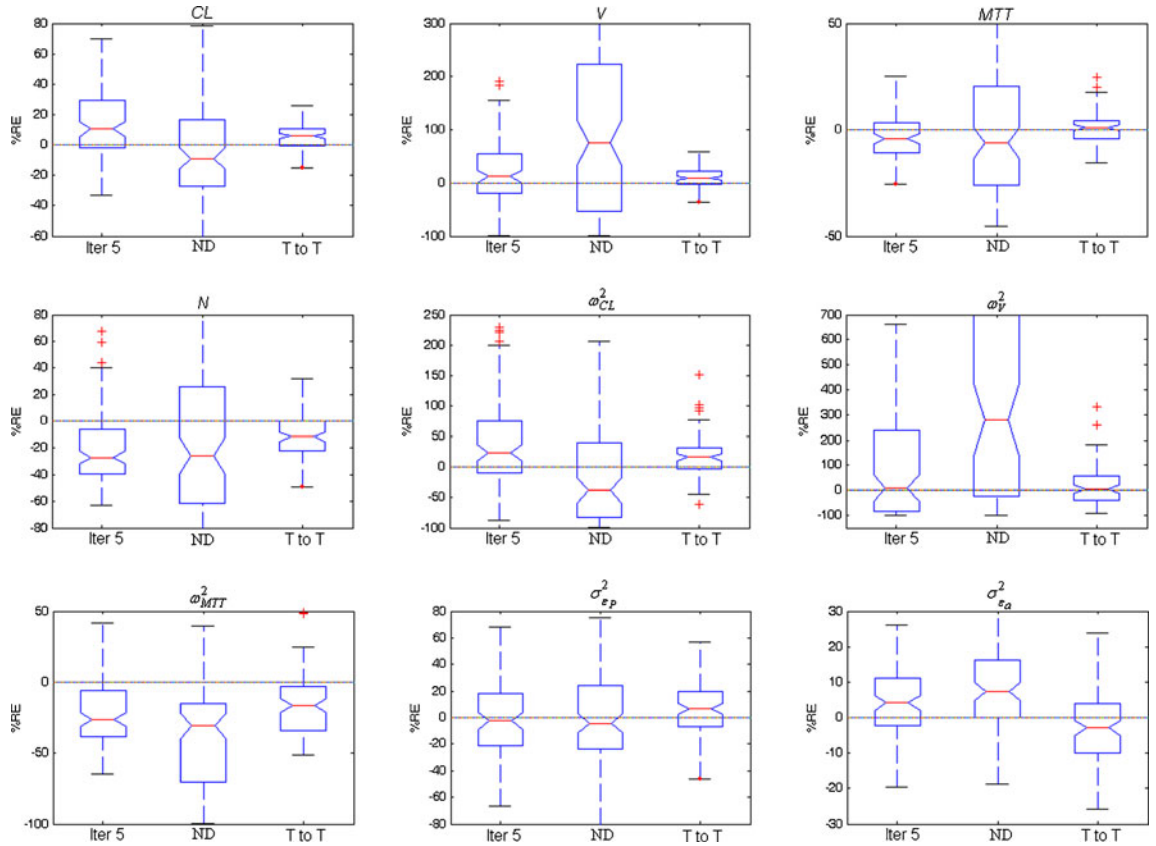

Fig. 6 Boxplots of percentage relative error (%RE) for final estimates in simulation scenario 2 with five batches arithmetic accumulation. "Iter 5" represents estimates obtained in the fifth iteration of the D-optimal ABS. "ND" represents estimates obtained if the eight sampling time point D-optimal design located for the normal weight patients estimates is applied directly to study the obese patients. "T to T" represents estimates obtained if the obese patients study design is the eight sampling time point D-optimal design optimized at the obese population nominal mean values. *Structural parameters* clearance (*CL*), volume of distribution (*V*), mean transit time (*MTT*) and number of transit compartments (*N*). *Statistical parameters* between subject variability (BSV) for *CL* $\left(\omega^2_{CL}\right)$, *V* $\left(\omega^2_V\right)$ and *MTT* $\left(\omega^2_{MTT}\right)$. *Residual unexplained variability* variance of the proportional error $\left(\sigma^2_{\varepsilon_p}\right)$ and additive error $\left(\sigma^2_{\varepsilon_a}\right)$. The *horizontal line* within each subplot is the zero percentage.

possibly result in experimental failure. Nevertheless, the scenarios are contrived and this evidence should not be used to suggest that paediatric bridging studies always show virtual superimposition of the prior and target PK profile and obese studies are always divergent.

We have proposed a method to carry out bridging studies adaptively by using the pooled data set in the interim iteration to stabilize the data analysis and to avoid bias estimates caused by small numbers of target-population data in the early iterations. However, the proposed method merely provides an exploration of the design method. The statistical properties of this method have not been studied.

Two types of models were fitted to the pooled data set in the simulation studies for the D-optimal ABS. The pooled model is fitted to the data set without considering if the patient arises from the prior- or target-populations. In contrast, the covariate model is fitted to the data set that explicitly allows for the possibility that the two populations estimates may differ. In this study we have optimized the design based on the estimates from the pooled model for the D-optimal ABS. In this setting the interim estimate of variance will be inaccurate due to potential bimodality. The purpose of fitting a covariate model in the D-optimal ABS is to show how the estimates in the target-population approach to the real parameter value although the design is optimized at the estimates from the pooled model.

From the simulation studies, we see that the estimates approached to the true target-population parameter values with the accumulated target-population data replaced the prior-population data. A D-optimal design obtained by maximizing the information based on the updated estimates ensured more accurate estimation of the target-population PK model at the final iteration. The proposed D-optimal ABS was shown to be not inferior when the prior- and target-population have similar PK profile and provide better estimates when the PK profile of the target-population is widely apart from the prior-population. The geometric accumulation method (result not shown) showed the same outcome as the arithmetic accumulation when applied to scenario 2,

Table IV The Relative Standard Error (RSE%) of the Estimates on the Obese Population when the Study Design is the Optimal Design at Normal Weight Adult Nominal Mean Values (ξ_P) and When the Study Design is the Optimal Design at the Obese Adult Nominal Mean Values (ξ_T). The RSE% was Computed from the Population Fisher Information Matrix and was Given by POPT

Parameter	RSE%	
	ξ_P	ξ_T
CL	7×10^{8}	6.54
V	8×10^{8}	12.2
MTT	6×10^{7}	6.12
N	2×10^{7}	13.5
ω^2_{CL}	1×10^{7}	23.0
ω^2_{V}	8×10^{6}	46.2
ω^2_{MTT}	8×10^{4}	19.4
$\sigma^2_{\varepsilon_p}$	14.3	9.16
$\sigma^2_{\varepsilon_a}$	3.91	6.16

again the final iteration of D-optimal ABS was more accurate as compared to design the studies based solely on the prior-population estimates $\left(\xi^{\{1\}}\right)$.

Our simulation result of the proposed criterion for determining early full enrolment by comparing the D-efficiency (of a product design and a local design) after inclusion of each new batch data showed that we can achieve the desired efficiency at an earlier stage if the PK profile of the prior- and target-populations are deemed to be similar. However more batches are needed if the prior- and target-populations have widely diverged PK profile. Although here we used a value of efficiency of 0.8, the choice of efficiency will be up to the researcher and the specific case at hand. In this project we have assumed a fixed number of target-population patients but the corollary scenario could be explored where the sample size of the batch and the total sample size of the target population could be optimised.

We have used the local D-optimal design in this study which means the design for the next batch is optimized at current batch estimates without incorporate uncertainty in the estimate values. A possible variation of the method could be to use a robust optimal design on the estimates of the target-population data from the covariate model. The standard errors of the estimates can be determined at each iteration and a possible stopping criterion explored is when the standard errors are less than a preset value. However, the D-optimal ABS is naturally robust

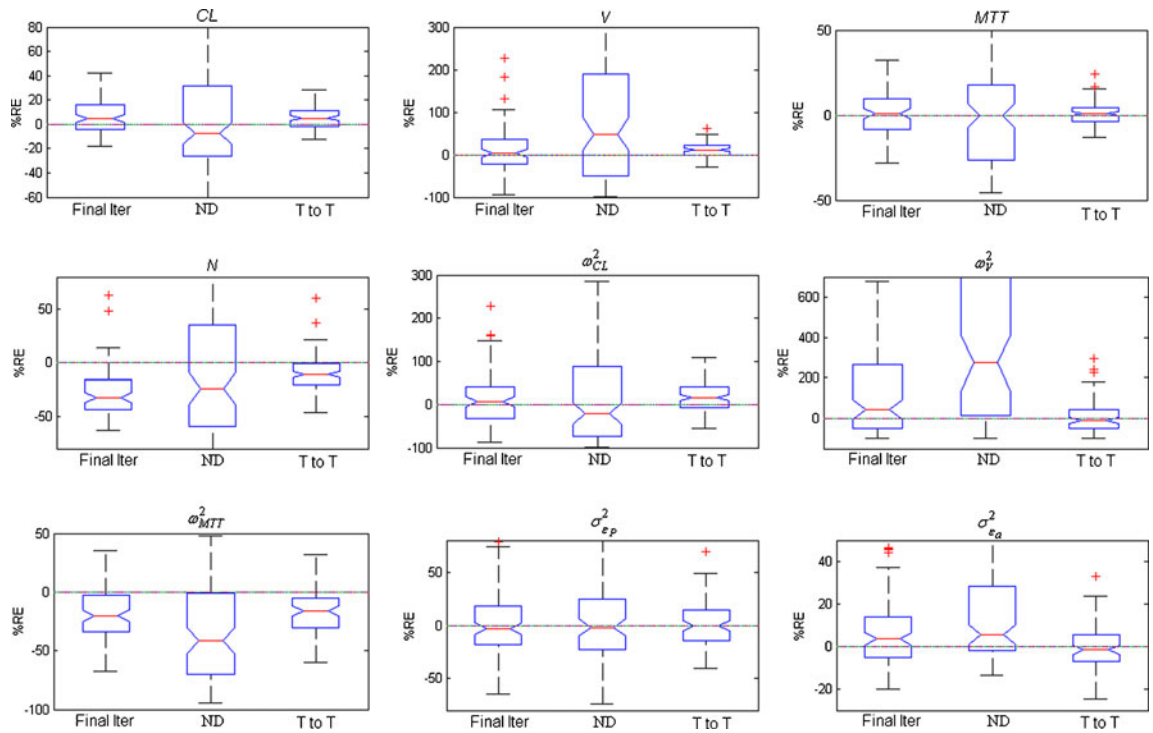

Fig. 7 Boxplots of percentage relative error (%RE) for final estimates in simulation scenario 2. "Final Iter" represents final estimates obtained with the early full enrollment criterion, "ND" represents estimates obtained if the eight sampling time point D-optimal design located for the normal weight patients estimates is applied directly to study the obese patients. "T to T" represents estimates obtained if the obese patients study design is the eight sampling time point D-optimal design optimized at the obese population nominal mean values. *Structural parameters* clearance (*CL*), volume of distribution (*V*), mean transit time (*MTT*) and number of transit compartments (*N*). *Statistical parameters* between subject variability (BSV) for *CL* $\left(\omega^2_{CL}\right)$, *V* $\left(\omega^2_{V}\right)$ and *MTT* $\left(\omega^2_{MTT}\right)$. *Residual unexplained variability* variance of the proportional error $\left(\sigma^2_{\varepsilon_p}\right)$ and additive error $\left(\sigma^2_{\varepsilon_a}\right)$. The *horizontal line* within each subplot is the zero percentage.

since it does not rely on the assumption that the prior- and target-populations are similar. Hence adding uncertainty on the updated estimate values at each iteration seems to be unnecessary and would incur extra expense to the optimal design.

CONCLUSION

In PK bridging studies it is usual to make the assumption that the PK profile of the target-population is similar to the prior-population. There is no way to test this assumption *a priori* and of concern is the risk of poorly efficient study, or perhaps study failure, if the two populations are sufficiently dissimilar. An adaptive D-optimal bridging study as described here provides an alternative approach and does not require any assumptions about the degree of similarity between the prior- and target-populations. A method to optimize the adaptive process was also explored which provide relevant early full enrolment condition for the target-population patients.

ACKNOWLEDGMENTS & DISCLOSURES

Lee Kien Foo is supported by a University of Otago post-graduate scholarship. We acknowledge helpful discussions with James McGree and at the Population Optimal Design of Experiments meeting in Berlin 2010.

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