Development of a sufficient design for estimation of fluconazole pharmacokinetics in people with HIV infection

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Optimal design is being employed more frequently to help reduce the number of samples taken per patient, the number of patients and number of doses to be given within a study.
- In doing this the economic and patient resources required to conduct a population pharmacokinetic or pharmacokinetic–pharmacodynamic study are reduced.

WHAT THIS STUDY ADDS

- This is the first time that healthy volunteer data (e.g. from Phase I) have been used to develop an optimal design that is to be conducted in a population with different characteristics due to disease (e.g. Phase II).

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AIMS

To assess an optimal design that is sufficient to gain precise estimates of the pharmacokinetic (PK) parameters for fluconazole in people with HIV infection.

METHODS

Two studies were identified, the first in healthy volunteers and the second in HIV patients. The investigators (J.F.R. and S.B.D.) were blinded to the second study results. The healthy volunteer study was modelled and a design was found to estimate the PK parameters. The design was evaluated by comparison of the standard errors of the parameters and the predictive performance of the optimal design. The predictive performance was assessed by comparing model predictions against observed concentrations for two models. The first model, termed 'sufficient design', was developed from data extracted from the HIV study that corresponded to the optimal design. The second model, termed 'HIV outcome model', by modelling all the data from the HIV study.

RESULTS

An optimal design HIV study was developed which had considerably fewer blood samples and dosing arms compared with the actual HIV study. The optimized design performed as well as the actual HIV study in terms of parameter precision. The performance of the design, described as the precision (mg l^{-1})² (95% confidence interval) of the predicted concentrations to the actual concentrations for the 'sufficient design' and 'HIV outcome model' models were: 0.63 (0.40, 0.87) and 0.56 (0.32, 0.79), respectively.

CONCLUSION

This study demonstrates how data from healthy volunteers can be utilized via optimal design methodology to design a successful study in the target population.

Introduction

In the development process of new drugs, Phase I clinical studies are characterized by the recruitment of healthy volunteers to provide an intensive number of samples for the study. This phase of clinical testing aims at establishing the drug's safety profile and at gathering information on the pharmacokinetic (PK) parameters of the compound for characterization of absorption, distribution and elimination by metabolism or excretion. Phase II clinical studies then follow and involve the patient population of interest. This phase of study allows initial investigation of the effectiveness of the drug, including evidence for proof of concept, and further evidence of drug safety [1]. Furthermore, it provides an opportunity to learn about the PK differences in patient populations [2].

D-optimal design of studies, in particular those pertaining to the population approach, has been purported as an appropriate method for improving parsimony and increasing the strength of studies [3, 4]. These improvements may be possible via a more economical use of resources, such as fewer samples to be taken per patient, fewer patients and fewer doses to be given within a study. While promoting parsimony, such designs may also provide precise population parameter estimates [5]. An optimal design yields the lowest possible values of the standard errors of the estimated parameters from within the practical constraints. This occurs via selection of constraining variables such as dose, number of patients and sampling times that provide the greatest amount of information about the parameters.

Using the theory of optimal design, we propose a design for fluconazole PK in people with human immunodeficiency virus (HIV) infection, using the protocol of a previously undertaken study [6]. The protocol was very intensive, so the proposed design starts with a very large number of sample collection times, and this is reduced to the minimum number of sampling times required to produce acceptable levels of standard error values while still answering the aims of the original study related to patients with HIV infection. We define this design a 'sufficient design'. The sampling times provided by the sufficient design were termed 'sufficient sampling times'. The aim of the original study was to characterize accurately the concentration–time profile of fluconazole in HIV and in healthy volunteers as well as quantifying any differences.

Fluconazole is a bis-triazole drug commonly used in the prophylaxis and treatment of fungal infections, such as *Candida* spp. and *Cryptococcus* spp., which are common infecting organisms in people with HIV infection. Fluconazole is well absorbed following oral administration, with the bioavailability from the oral route being $\geq 90\%$ of that from the intravenous route in healthy subjects [7, 8]. Fluconazole is predominantly eliminated unchanged via the renal route [9]. It has also been shown that fluconazole undergoes tubular reabsorption in the kidneys [9, 10].

It has been shown that HIV infection may alter the physiology of some organ systems [11–13]; thus, potential changes in drug input or disposition might be expected for fluconazole when administered to this patient group.

Literature evidence suggests an increase by approximately 20% in the area under the concentration–time curve (AUC) of fluconazole when administered to HIV patients [14] compared with healthy subjects. Anecdotal evidence, obtained by personal communication, suspected lower fluconazole exposure in the HIV population than in healthy subjects and that this might be due to the nonlinearity in the PK of fluconazole. It was postulated that at high doses or concentrations, the input or disposition (tubular reabsorption) of fluconazole approaches its capacity, and thus the input or disposition of fluconazole is no longer linear. Thus, lower exposure in the HIV population is seen as a reduced AUC compared with the healthy population. Thereby, a study was undertaken by Tett *et al.* [6] to address these contradictions. However, to accommodate all possible PK scenarios and that the study was to be analysed via noncompartmental analysis (NCA) methodology, the study protocol was characterized by an intensive sampling schedule with a total of 1440 samples from 20 patients. We believe that a design with fewer blood samples and dosing arms could be achieved without significant loss of information when analysed using population analysis methodology, e.g. NONMEM. Other studies characterized by an intensive sampling schedule have been analysed using population PK analysis methods [15, 16].

The aims of the current study were: (i) to obtain a sufficient design suitable to gain precise estimates of the PK parameters for fluconazole in people with HIV infection within the constraints of models, parameters and design space while still achieving the aims of the original study related to patients with HIV infection; and (ii) to test the performance of the sufficient design.

Methods

For this research, two studies were identified: one of fluconazole administered to healthy volunteers (analogous to a Phase I study) [10] and one of fluconazole administered to people with HIV infection (analogous to a Phase II study) [6].

In the former study (Phase I) undertaken by Gross *et al.* [10], 12 healthy male volunteers received a single oral dose of fluconazole (100 mg). An average of 15 blood samples per patient was taken between 5 min and 168 h postdose. A one-compartment model with lagged first-order input and first-order elimination provided the best description of the healthy volunteer data (Table 1).

The protocol of the second study (analogous to a Phase II study) by Tett *et al.* expected to recruit 20 patients with HIV infection (CD4 count < 200 cells mm^{-3} and CD4 count

Table 1

Parameter estimates from a healthy study population used as prior information for the sufficient design in patients with HIV infection

Parameter	Mean
Pharmacokinetic parameters	
CL (l h ⁻¹)	1.18
V (l)	55.7
K _a (h ⁻¹)	3.38
A _{lag} (h)	0.23
Between-subject variability	
BSVCL	CV%
BSVV	22.2
BSVK _a	17.4
Residual variability	
Proportional error (CV%)	14.7
Additive error (mg l ⁻¹)	0.08
Limit of quantification (mg l ⁻¹)	0.2

>200 cells mm⁻³). Three oral doses of fluconazole of 50, 100 and 400 mg were to be given to each patient. Additionally, each patient was to receive one i.v. dose of fluconazole, either 50, 100 or 400 mg. Eighteen blood samples were to be obtained following each dose administered, resulting in 72 blood samples per patient and a maximum of 1440 blood samples for the study. The range of allowable sampling times was between 5 min and 1 week postdose. We have called this protocol the 'full design'.

However, like many clinical trials, execution errors did occur, e.g. some patients did not visit the clinic for all four doses of fluconazole and/or <18 blood samples were collected from each administered dose. Thus, the actual data collected and the results obtained are called the 'HIV study outcome'.

We believe that a more parsimonious design than the 'full design' can be achieved without significant loss of information when combining optimal design methodology and using population PK methods, e.g. NONMEM for analysis. Our proposed protocol with a reduced number of blood samples and dosing arms compared with the 'full design' was called the 'sufficient design'. A flowchart representing the process of how the 'sufficient design' was obtained is shown in Figure 1. We then compare the 'sufficient design' with the 'full design' and with the 'HIV study outcome'.

In order to develop the sufficient design, information on the PK parameters of fluconazole were required. Thus, the PK parameters obtained from the Phase I study (Table 1) were the only information on the PK of fluconazole considered to be known and were used as prior information to design the Phase II study.

The sufficient design was obtained using the application software POPT® (Version 2.0; <http://www.winpop.com>). The structural models and design characteristics are user-defined in POPT (model code available by request).

During the development of the sufficient design, the design investigators (J.F.R. and S.B.D.) were blind to both the 'full design' and to the 'HIV study outcome' up to the evaluation stages of the design (see section on 'Predictive performance of the model from the sufficient design vs. the model from the HIV study outcome').

Design space

The design space is the set of all constraining variables, i.e. maximum number of patients, maximum number of dosing arms, maximum number of blood samples per patient or per visit, etc, that the design has to remain within. The design space of the sufficient design was set as the upper limit of the protocol of the 'full design'.

Models and parameters

Five different competing structural models were considered in order to account for possible alterations in the PK of fluconazole in people with HIV infection (Table 2). The first model was a linear input and disposition model (M1) with a low drug exposure that was obtained by perturbing the drug clearance. In this model, the AUC for HIV patients was 40% lower than that for healthy volunteers. M1 is a model that explores whether a higher drug clearance of fluconazole in people with HIV infection exists compared with healthy volunteers. The second model was a linear input and disposition model (M2) with a high drug exposure that was obtained by perturbing the drug clearance. In this model, the AUC for HIV patients was 40% higher than that for healthy volunteers. M2 is a model that explores whether a lower drug clearance of fluconazole in people with HIV infection exists compared with healthy volunteers. The third model was a nonlinear input and linear disposition model (M3). In this model, the drug absorption is capacity limited and expected to increase nonlinearly with increasing doses. M3 incorporates an $E_{\max}$ model on absorption, which describes the relationship between the dose given and the fraction of the dose absorbed. When the dose approaches zero the fraction of drug absorbed (F) approaches its maximum. F_{abs} is the estimated absolute fractional absorption of fluconazole based on calculation from i.v. and oral administration. F_{min} represents the reduced fraction of fluconazole absorbed as the dose levels increase. In M3, F_{min} was set as 80% of F_{abs} . Km_n defines the degree of nonlinearity and is the drug dose at 50% of F_{min} (Figure 2). The fourth model was a nonlinear input and linear disposition model (M4) (Figure 2). In this model, F_{min} was set as 60% of F_{abs} . The reason that models M3 and M4 have two different levels of F_{min} is because it is unknown how much fluconazole absorption will be reduced as the dose increases. The remaining parameters of M4 are the same as in M3. The fifth model was a linear input and nonlinear disposition model (M5) with a low drug exposure. Fluconazole undergoes reabsorption following filtration. Thus, this model describes the nonlinear reabsorption of fluconazole as concentrations of fluconazole increase.

Figure 1

Flowchart representing the process how the 'sufficient design' was obtained. Criteria for acceptability of the design (sufficient), e.g. the average standard error (SE) of the estimated parameters to be around 25–50% [17]

Table 2, under the column named 'Models', shows the following equation to describe M5:

$$CL_{reabs} = \frac{CL_{rmax} * [central\ cpt]}{K_{m1} + [central\ cpt]} \quad (1)$$

where CL_{rmax} is the maximum fluconazole clearance due to reabsorption, [central cpt] is the concentration of fluconazole in the central compartment and K_{m1} defines the degree of nonlinearity, i.e. it is the concentration in the central compartment at 50% of CL_{rmax} . The basic clearance kinetics can be described as:

$$CL_{net} = CL_{flt} - CL_{reabs} \quad (2)$$

$$CL_{flt} = CL_{int} \times fub \quad (3)$$

where CL_{net} is the net renal clearance of fluconazole, CL_{flt} is the clearance by filtration and CL_{reabs} is the clearance of fluconazole due to reabsorption from the tubules back to the intravascular space (central compartment). CL_{int} is the intrinsic clearance, which in this case is expected to be similar to glomerular filtration rate, and fub is the fraction unbound of fluconazole, which is equal

to 0.82 [10]. It was suspected that people with HIV infection have lower exposure to fluconazole. This means that the fraction of fluconazole reabsorbed compared with healthy volunteers is lower than in people with HIV infection (Figure 3). We assumed that the maximum fraction reabsorbed ($F_{maxreabs}$) of fluconazole in people with HIV is 80% of that of healthy volunteers. It was also assumed, without loss of generality, that the concentration of fluconazole in the tubules is 10% of its concentration in blood (central compartment). The CL_{rmax} is given by:

$$CL_{rmax} = CL_{flt} \times F_{maxreabs} \quad (4)$$

The value of CL_{rmax} calculated from Equation 4 is then used in Equation 1.

Evaluation of the design

The evaluation of the sufficient design was performed using four different methods.

(1) *Comparison of standard errors, individual model criterion and efficiencies* The standard error (SE) is a measure

Table 2

Structural models considered for fluconazole pharmacokinetics

Model	Description	Exposure	Models	Parameter values
M1	One-compartment model with linear input and disposition, high CL	Low (AUC 40%↓)	$C = \frac{\text{Dose} \cdot F \cdot K_a}{V \left(K_a - \frac{CL}{V} \right)} \cdot e^{\left(-\frac{CL}{V} t \right)} - e^{(-K_a t)}$	CL = 1.32 l h ⁻¹ F = 0.8 BSVF = 32%
M2	One-compartment model with linear input and disposition, low CL	High (AUC 40%↑)	$C = \frac{\text{Dose} \cdot F \cdot K_a}{V \left(K_a - \frac{CL}{V} \right)} \cdot e^{\left(-\frac{CL}{V} t \right)} - e^{(-K_a t)}$	CL = 0.67 l h ⁻¹ F = 0.8 BSVF = 32%
M3	One-compartment model with nonlinear input and linear disposition, high $F_{\min}$	Low (AUC 40%↓) Dose = 400 mg	$C = \frac{\text{Dose} \cdot F \cdot K_a}{V \left(K_a - \frac{CL}{V} \right)} \cdot e^{\left(-\frac{CL}{V} t \right)} - e^{(-K_a t)}$ $F = F_{\text{abs}} - \frac{F_{\min} \cdot \text{Dose}}{K_{m_n} + \text{Dose}}$	CL = 0.94 l h ⁻¹ $F_{\min} = 0.8 \times F_{\text{abs}}$ $K_{m_n} = 470$ BSVF = 32%
M4	One-compartment model with nonlinear input and linear disposition, low $F_{\min}$	Low (AUC 30%↓) Dose = 400 mg	$C = \frac{\text{Dose} \cdot F \cdot K_a}{V \left(K_a - \frac{CL}{V} \right)} \cdot e^{\left(-\frac{CL}{V} t \right)} - e^{(-K_a t)}$ $F = F_{\text{abs}} - \frac{F_{\min} \cdot \text{Dose}}{K_{m_n} + \text{Dose}}$	CL = 0.94 l h ⁻¹ $F_{\min} = 0.6 \times F_{\text{abs}}$ $K_{m_n} = 470$ BSVF = 32%
M5	One-compartment model with linear input and nonlinear disposition	Low (AUC 40%↓)	$C = \frac{\text{Dose} \cdot F \cdot K_a}{V \left(K_a - \frac{CL_{\text{net}}}{V} \right)} \cdot \left[e^{\left(-\frac{CL_{\text{net}}}{V} t \right)} - e^{(-K_a t)} \right]$ $CL_{\text{reabs}} = \frac{CL_{\text{rmax}} \cdot [\text{central cpt}]}{K_{m_1} + [\text{central cpt}]}$ $CL_{\text{net}} = CL_{\text{GFR}} - CL_{\text{reabs}}$	$F_{\text{maxreabs}} = 0.8$ $K_{m_1} = 0.8$ $CL_{\text{int}} = 7.2$ F = 0.8 BSVF _{maxreabs} = 22% BSVF = 32% BSVCL _{int} = 32%

↓, reduced; ↑, increased; AUC, area under the curve; $F_{\min}$, the minimum reabsorbed fraction; F_{abs} , fraction absorbed; K_{m_n} , the dose at half $F_{\min}$ in the nonlinear input and linear disposition models (M3, M4); K_{m_1} , drug concentration in central compartment at half CL_{rmax} in the linear input and nonlinear disposition model (M5); CL_{reabs} , reabsorbed clearance; CL_{rmax} , the maximum reabsorbed clearance; [central cpt], the drug concentration in the central compartment. The column 'Parameter values' shows the values of the parameters that were perturbed from the values given in Table 1.

Figure 2

Simulations for typical healthy volunteer, continuous line; vs. M3 (AUC reduced by 40%), dashed line; and vs. M4 (AUC reduced by 30%), dotted line. The value for K_{m_n} is equal to 470 mg

of the (im)precision with which a parameter is estimated (precision is the inverse of the square of the standard error). The informativeness of a design can be measured in terms of the size of the SE value of the estimate for each parameter, where the larger the standard error the less informative the design. To compute the loss of information

Figure 3

Simulations for typical healthy volunteer, continuous line; vs. M5 (AUC reduced by 40%), dashed line. The value for K_{m_1} is equal to 0.8 mg for HIV patients, dashed line

arising from performing a sufficient design vs. a full design, the SE of the parameters for M1 from the sufficient design was compared with that that arose from the full design. This procedure was repeated for models M2, M3, M4 and M5. These SEs were given by the software used to design the study (POPT).

When evaluating the SEs, an acceptable level of parameter precision was set as a percent relative SE value of <25% for fixed effects parameters and <50% for the variance of the random effects parameters [17]. These values were used as guidelines only, as it is likely that some parameters will be predicted to be estimated more precisely and some less precisely.

Figure 1 outlines how the 'sufficient design' was obtained. This sequence was followed until the design, with reduced number of doses and sampling times, was shown to have acceptable levels of SEs. On each iteration shown in Figure 1 the design was optimized given the constraints on the design variables. The overall optimal design criterion (for all models) was the product D-optimality (see ref 19 for details). Briefly, the product D-optimal criterion is given as the product of the normalized determinants for each of the competing models given the design. Each determinant is normalized by raising it to the power of the inverse of the number of parameters to be estimated. The greater the product D-optimal criterion the more informative the design for all models.

An individual model criterion value is also given by POPT when optimizing designs. It is used for the comparison of competing designs, e.g. comparing the full design with the sufficient design. The greater the individual model criterion value, the better the ability of the design to estimate the parameters of the model. In this particular case, the full design had the highest individual model criterion value. The efficiency of the design is the fraction of any two individual model criterion values where the denominator is the individual model criterion of the full design [see Equation 5 (below)]. The efficiency is expressed as a percentage, and provides an indication of the loss of the sufficient design to estimate the parameters of the model:

$$\text{Efficiency} = \frac{\text{criterion sufficient design}}{\text{criterion full design}} \cdot 100\% \quad (5)$$

(2) *Comparison of standard errors from POPT vs. NONMEM* The performance of a design can be assessed empirically by comparing the SE values predicted by POPT with those estimated by NONMEM from a simulation and estimation experiment using the suggested sampling times and doses from the design step, i.e. 'sufficient sampling times'. If SE values delivered by POPT and NONMEM are similar, then this confirms that the sufficient design performs as expected.

Using the parameter values given in Table 1, 100 simulation-estimation runs were undertaken using NONMEM (Version 5, Level 1.1; GloboMax LLC, Hanover, MD, USA) with the G77 FORTRAN compiler. The SEs given by NONMEM (using FOCE with INTERACTION) were termed 'empirical SE'. The SEs given by POPT were termed 'predicted SE'. The empirical and predicted SEs were then compared for models M1–M5.

The values of clearance were perturbed to account for low and high drug-exposure models by setting the clearance for M1 to 40% higher and the clearance in M2 to 40% lower than clearance in healthy volunteers.

(3) *Power to discriminate between models* In addition to considering the performance of a design for estimation, it is also important to consider the performance of a design in discriminating between competing models. This is undertaken by assuming that one of the models (in turn) is the 'true' model and then simulating under this model and fitting the other competing models to each simulated dataset. The power of the design is then the proportion of times that the 'true' model has a lower objective function compared with each of the competing models.

This step was undertaken by simulating 100 datasets for each model, i.e. linear input and disposition model, nonlinear input and linear disposition model, and linear input and nonlinear disposition model using NONMEM. The simulations were carried out using the parameter values given in Tables 1 and 2. For the linear input and disposition model, the values of clearance were perturbed for low drug exposure, i.e. 40% higher than clearance in healthy volunteers. For the nonlinear input and disposition model, simulations were undertaken using $F_{\min}$ as 80% of F_{abs} .

Following the 100 simulations, the models were fitted to each set of data using NONMEM (FOCE with INTERACTION) and the 'best' model was chosen empirically as the one with the lowest objective function. The proportion of times that the sufficient design correctly discriminated between the models provides the power.

(4) *Predictive performance of the model from the sufficient design vs. the model from the HIV study outcome* The ultimate test of any design is to assess whether it actually works in practice. If the model developed from the design performs as well as the model developed from the full dataset then it is reasonable to conclude that the design worked well in practice. Performance can be assessed by considering the bias and precision of the predictions from each model.

To undertake this fourth evaluation step, two PK models were developed. The first was the model developed from the sufficient design and provided the 'sufficient model'. The 'sufficient sampling times' were extracted from the 'HIV study outcome' to build the PK model. As the exact sufficient sampling times were not always available in the 'HIV study outcome' data, the nearest sampling time was extracted in its place. For example, if a sufficient sampling time for the i.v. dose was 0.25 h but the exact sampling time was not available, then the nearest sampling time to this time point was taken. This sampling time was termed the 'near sufficient sampling time'.

A second PK model was developed using the data from the 'HIV study outcome' that provided the 'HIV outcome

model'. Using the 'HIV outcome model' and the 'sufficient model', PK parameters were estimated using popPK analysis.

Results

It was suspected that the full design with three oral doses (50, 100 and 400 mg) and one i.v. dose (either 50, 100 or 400 mg) per patient was too intensive and could be minimized without significant loss of information. This was assessed by the sequential removal of one dose at a time from the protocol without changing the intensive sampling schedule per dose (18 blood samples per dose), while comparing the SE of the parameters of the five competing models (M1–M5). The oral dose of 50 mg was shown to be the least informative dose, and its exclusion from the protocol did not change the SE of the parameters significantly. Similarly, changes due to nonlinearities in the PK profile are more likely to be seen at high doses. Therefore, of the i.v. doses only the 400-mg dose from the full design was retained in the dose schedule.

A sufficient design was subsequently obtained with a minimum number of doses and sampling times per dose to produce an acceptable level of parameter precision as defined in Methods. The sufficient design resulted in 12 blood samples per patient, corresponding to four blood samples per dose, i.e. the 400-mg i.v., 400-mg oral and 100-mg oral doses, providing a total of 240 samples from 20 patients. The sufficient sampling times identified by POPT using exchange algorithm [18] for the sufficient design are shown in Table 3. The exchange algorithm was set up by forming a $n \times n$ grid (where n is the total number of unique sampling times across all groups, e.g. 12 sampling times). The n -elements of the grid were defined to be a geometric sequence. The exchange algorithm searches across this grid. Of note, although the optimal design found exact sampling times, in clinical practice we would advocate the use of sampling windows that have been optimally determined, thus obviating the need for clinical staff to take samples at exact times.

Evaluation of the design

Comparison of SEs, individual model criterion and efficiencies Table 4 shows the SE of the parameters for each

model (M1–M5) under the sufficient design and the full design, as well as the individual model criterion and efficiency values. The SEs of the parameters were only minimally different between the sufficient design and the full design for M1 and M2 (Table 4). The same was largely true for M3 and M4, with the exception of the parameter K_{mn} that had a larger (but still acceptable) SE value from the sufficient compared with the full design. The CL_{int} and K_{ml} parameters of the linear input and nonlinear disposition model (M5) also had larger SE values than the full design.

The efficiencies of the sufficient design fell between 57 and 70% of the full design for the five models (M1–M5). As stated in Methods, efficiency provides an indication of the loss of the sufficient design to estimate the parameters of the model. Models M3 and M4 showed the lowest efficiency levels (57 and 58%, respectively) when compared with the full design. On the other hand, M1 and M2 had the least loss in ability to estimate the parameters under the sufficient design, with efficiency levels of 69 and 70%, respectively.

Comparison of standard errors from POPT vs. NONMEM The predicted SEs given by POPT were generally within 10% of the empirical SEs given by NONMEM (Table 5) for models M1–M5. The only exceptions to this are seen with M2 and M3, where the between-subject variability of K_a ($VAR(K_a)$) reached 14 and 22%, respectively. Also, for the linear input and nonlinear disposition model (M5) the SEs given by POPT for the parameters CL_{int} , K_{m1} and between-subject variability of K_a ($VAR(K_a)$) and CL_{int} ($VAR(CL_{int})$) were within 19–65% higher than the SEs given by NONMEM. For M5 the parameter $F_{maxreabs}$ (maximum fraction reabsorbed) could not be estimated and therefore was fixed. It is seen that the SE of the variance of the residual error was underestimated by the design (POPT compared with NONMEM). Although the differences are consistently smaller in this case, we believe the magnitude of the difference (within 10%) is of minor significance.

Power to discriminate between models

Generally, the sufficient design had good power to discriminate between the linear input and disposition model and the nonlinear input and disposition model with values of 96 and 100% (Table 6). When comparing between the nonlinear input and disposition model and the linear input and nonlinear disposition model, the power values were 87 and 99%. The lowest powers obtained were 50 and 68% and resulted from the comparison between linear input and disposition model and linear input and nonlinear disposition model.

Predictive performance of the model from the sufficient design vs. the model from the HIV study outcome

The data of the 'HIV study outcome' had a total of 13 recruited patients. From these patients an average of 13

Table 3

Sufficient sampling times defined by the sufficient design

Sufficient sampling times (h)				
400 mg i.v.	2.6	3.6	5.2	87.6
400 mg oral	0.1	2.8	4.6	166.3
100 mg oral	1.3	1.4	59.4	90.9

Table 4

Comparison of percent relative standard errors (expressed as coefficient of variation) given by POPT, individual model criterion and efficiencies between the sufficient and full design

Parameter	M1		M2		M3		M4		M5	
	Sufficient design	Full design	Sufficient design	Full design	Sufficient design	Full design	Sufficient design	Full design	Sufficient design	Full design
Population mean										
CL	5.5	5.1	5.6	5.2	5.6	5.1	5.6	5.1	–	–
V	4.4	3.9	4.3	3.9	4.3	3.9	4.3	3.9	4.4	3.9
K _a	42.0	41.5	42.0	41.5	42.1	41.5	42.1	41.5	42.0	41.5
F _{abs}	7.6	7.1	7.5	7.2	9.7	7.4	9.8	7.4	7.6	7.2
Km _n	–	–	–	–	35.7	11.2	50.0	15.4	–	–
CL _{int}	–	–	–	–	–	–	–	–	44.2	28.1
Km ₁	–	–	–	–	–	–	–	–	83.8	49.7
F _{maxreabs}	–	–	–	–	–	–	–	–	10.9	7.9
Between-subject variability										
VAR(CL)	38.3	33.3	39.6	34.3	39.0	33.6	38.8	33.6	–	–
VAR(V)	40.2	34.2	39.5	34.0	40.1	34.0	40.0	34.0	40.5	34.0
VAR(K _a)	32.5	31.7	32.5	31.8	32.7	31.8	32.6	31.8	32.5	31.8
VAR(F _{abs})	35.9	32.6	35.3	32.5	33.7	32.1	34.2	32.2	36.1	32.5
VAR(CL _{int})	–	–	–	–	–	–	–	–	59.9	43.6
VAR(F _{maxreabs})	–	–	–	–	–	–	–	–	37.3	33.9
Residual variability										
VAR(prop)	7.4	2.7	6.8	2.5	7.4	2.7	7.3	2.7	7.8	2.7
Individual model criterion	89.97	130.0	106.8	151.9	22.4	38.8	20.9	36.4	56.8	89.1
Efficiency	69%	100%	70%	100%	58%	100%	57%	100%	64%	100%

CL, clearance; V, central volume of distribution; K_a, absorption rate constant; F_{abs}, fraction absorbed; Km_n, drug dose at half of F_{min}; CL_{int}, intrinsic clearance; Km₁, drug dose at half of CL_{max}; F_{maxreabs}, maximum reabsorbed fraction.

Table 5

Standard errors (expressed as coefficient of variation) for the population mean and between-subject variability for parameters under the different structural models under consideration

Parameter	M1		M2		M3		M4		M5	
	POPT CV (%)	NONMEM CV (%)	POPT CV (%)	NONMEM CV (%)	POPT CV (%)	NONMEM CV (%)	POPT CV (%)	NONMEM CV (%)	POPT CV (%)	NONMEM CV (%)
Population mean										
CL	5.5	6.1	5.6	4.9	5.6	5.3	5.6	6.1	–	–
V	4.4	3.9	4.3	4.4	4.3	4.0	4.3	3.8	4.4	9.2
K _a	42	35	42	40	42	35	42	36	42	50
F _{abs}	7.6	8.7	7.5	8.1	9.7	9.6	9.8	11	7.5	8.1
Km _n	–	–	–	–	36	27	50	50	–	–
CL _{int}	–	–	–	–	–	–	–	–	44	6.2
Km ₁	–	–	–	–	–	–	–	–	84	19
F _{maxreabs}	–	–	–	–	–	–	–	–	11	FIX
Between-subject variability										
VAR(CL)	38	38	39	38	39	39	39	39	–	–
VAR(V)	40	40	39	38	40	37	40	39	40	44
VAR(K _a)	32	42	32	46	33	55	33	40	32	13
VAR(F _{abs})	36	35	35	38	34	38	34	35	36	39
VAR(CL _{int})	–	–	–	–	–	–	–	–	60	29
VAR(F _{maxreabs})	–	–	–	–	–	–	–	–	37	–
Residual variability										
VAR(prop)	7.4	14	6.8	14	7.4	14	7.3	14	7.8	12
VAR(add)	NE	19	NE	42	NE	27	NE	23	NE	32

CL, clearance; V, central volume of distribution; K_a, absorption rate constant; F_{abs}, fraction absorbed; Km_n, drug dose at half of F_{min}; CL_{int}, intrinsic clearance; Km₁, drug dose at half of CL_{max}; F_{maxreabs}, maximum reabsorbed fraction.

Table 6

Power of the sufficient design to discriminate between the models

True model	False model	Power (%)
Linear input and disposition	Linear input and nonlinear disposition	50
Linear input and nonlinear disposition	Linear input and disposition	68
Nonlinear input and linear disposition	Linear input and nonlinear disposition	87
Linear input and disposition	Nonlinear input and linear disposition	96
Linear input and nonlinear disposition	Nonlinear input and linear disposition	99
Nonlinear input and linear disposition	Linear input and disposition	100

Simulation and estimation of the model parameters have been performed under NONMEM.

Figure 4

Histogram of the relative percent difference between the time taken in the 'HIV study outcome' and the sufficient sampling time; (a) for <12 h and (b) for >12 h

Table 7

Predictive performance comparison between the 'HIV outcome model' and 'sufficient model'

	HIV outcome model	Sufficient model
ME bias (mg l ⁻¹) (95% CI)	-0.05 (-0.12, 0.01)	-0.03 (-0.09, 0.03)
MSE precision (mg l ⁻¹) ² (95% CI)	0.63 (0.40, 0.87)	0.56 (0.32, 0.79)

The lower limit of quantification of the fluconazole assay is 0.2 mg l⁻¹. ME, mean error of observed minus predicted; MSE, mean squared error of observed minus predicted.

Table 8

Pharmacokinetic parameters for 'HIV outcome model' and 'sufficient model'

Pharmacokinetic parameters	HIV outcome model	Sufficient model
Population mean	Mean (RSE %)	Mean (RSE %)
CL (l h ⁻¹)	0.8 (7.5)	0.7 (8.9)
V (l)	47 (3.8)	49 (4.6)
K _a (h ⁻¹)	8.7 (22)	15 (27)
A _{lag} (h)	0.2 (22)	0.4 (4.9)
F ₁	0.9 (3.3)	1.0 (3.7)
Between-subject variability	CV % (RSE %)	CV % (RSE %)
BSVCL	21 (36)	24 (48)
BSVV	8.4 (52)	9.9 (70)
BSVA _{lag}	42 (41)	15 (68)
BSVK _a	—*	—*
Residual variability	(RSE %)	(RSE %)
Proportional error (CV %)	24 (14)	9.5 (56)
Additive error (mg l ⁻¹)	0.02 (44)	0.16 (84)
Limit of quantification (mg l ⁻¹)	0.2	0.2

*Not able to be estimated from these data. The 'HIV outcome model' and 'sufficient model' are differentiated by their datasets, where the former is composed by the sampling times of the 'HIV study outcome' and the latter by the sufficient sampling times and near-sufficient sampling times given by the sufficient design. Coefficient of variability (CV%) and relative standard error percent (RSE) are provided.

blood samples per patient was obtained, resulting in a total of 559 samples. Thus, the 'HIV study outcome' deviated significantly from the study protocol, which expected 20 patients and 1440 samples.

Sufficient sampling times and near-sufficient sampling times extracted from the 'HIV study outcome' only provided a total of 97 samples, instead of the 240 samples intended by the sufficient design. Thus, a large number of sufficient or near-sufficient sampling times were unable to be extracted. This was due to a less than anticipated number of patients and sampling opportunities. A visual assessment of this disparity is shown in Figure 4a,b. The predictive performances for the best models are given in Table 7. The best models for each dataset with the estimated parameters are given in Table 8.

Discussion

The current study proposes that optimal design methodologies can be applied for the design of Phase II clinical trials using prior information from Phase I studies. Specifically, a sufficient design for the quantification of the population PK of fluconazole in people with HIV infection is proposed using prior population PK information from a different population group, i.e. healthy subjects. To the best of our knowledge, this is the first time that this has been described in the literature.

Thus a more parsimonious design, with blood samples collected at the sampling times that offer the greatest amount of information about the PK parameters, is achieved without losing the ability to estimate the model parameters precisely. This study has also illustrated that different scenarios, e.g. changed clearance or nonlinearity in PK, can be incorporated into the assessment of the design.

Optimizing the design of a study offers a variety of advantages, such as reducing the number of patients to be recruited in a study, the number of blood samples to be collected from the patients and the dosing arms to be administered to a patient. These are attractive advantages, not only to the industry that could anticipate a reduction in the costs of a Phase II study, but also to the patient population, who are more likely to comply with less intensive studies that offer less harm and time burden.

During the development of the design, the design investigators (J.F.R. and S.B.D.) were advised only of the 'full design' and were blind to the 'HIV study outcome'. The protocol of the full design was very intensive with an expected number of blood samples totalling 1440 from 20 patients. However, due to execution errors in the clinical trial, the 'HIV study outcome' had fewer patients and samples per patient than intended in the full design. As an example, only 10 of the 20 expected HIV patients were able to be recruited for the 100-mg oral dose. This dose had an average of five blood samples collected per patient compared with 18 required by the full design. Overall, only 39% of samples were taken as intended by the HIV study protocol. This is not uncommon in clinical studies and presents an ideal argument for optimizing and minimizing sample collection times prior to study commencement.

The construction of the sufficient design was subject to the constraining variables outlined by the full design. These constraints were not overly restrictive. However, other authors have described the successful application of optimized designs that required different design constraints, such as time constraints [19], maximum number of blood samples allowed for the study [4], constrained times for the collection of blood samples, e.g. during working hours [20], or cost limitations [21].

The application of the product D-optimality criterion has been previously shown, in a particular example, to be

efficient in terms of parameter estimation and model discrimination [19]. The incorporation of competing models is a unique point of optimal design methodologies, which allows for exploration of various structural models that might reasonably describe drug actions or exploration of disease-induced alterations in the PK of drugs. In the current study, the sufficient design provided acceptably precise parameter estimates for the majority of the model parameters and had good properties for discriminating between the 'true' and 'false' models with generally good power. Although this is encouraging for this optimality criterion, it does not constitute proof that product D-optimal designs are always efficient in this regard.

A clear advantage is that a simplification of a study protocol can be achieved without significant loss of information. The sufficient design has resulted in one less visit of the patient to the clinic, and the number of samples in the design reduced from 1440 to 240 samples. Ultimately, this means significant cost reduction and a reduction in the burden for the patient. It may mean that a study previously considered unfeasible can be successfully achieved. If it were assumed that the cost of an assay was £50, and the cost of a patient attending a clinic for dose administration and blood sampling was £1000, then the sufficient design demonstrated here could save £81 000 while providing results that were comparable to the full executed study. Of course, these values vary extensively depending on laboratory pricing differences and staff costs. Further discussion on drug development costs can be found at DiMasi *et al.* [22], DiMasi [23] and the Food and Drug Administration [24].

A limitation of the retrospective construction and application of a sufficient design is the ability to test the performance of the sufficient design, since this relies on the availability of blood samples having been taken at, or close to, the sufficient sampling times. When the exact sufficient sampling time was not available, the near-sufficient sampling time was extracted from the 'HIV study outcome', and these provided only 97 samples of the 240 samples required by the sufficient design. The histogram of the relative percent difference between the time taken in the 'HIV study outcome' and the sufficient sampling time (Figure 4a,b) shows that many near-sufficient sampling times were far from the sufficient sampling time, with a relative difference up to 12 000%. Despite this, the 'sufficient model' developed using the sufficient and near-sufficient sampling times performed indistinguishably from the 'HIV outcome model'. The parameters estimated by the popPK analysis (see Table 8) are within 20% of those found in the NCA analysis by Tett *et al.* [6]. This highlights the applicability of D-optimal designs to practical settings and shows that had the sufficient design been undertaken it might have performed as well as the actual executed study ('HIV study outcome') and possibly better had more samples been available at the appropriate times, while

being considerably more parsimonious than either the intended or actual executed study designs.

However, it was apparent that the linear input and non-linear disposition model (M5) was harder to estimate and differentiate than the other models under consideration. It seems probable that this is due to the highly nonlinear nature of this model in conjunction with the use of a first-order approximation to the likelihood. As K_m is the only parameter that defines the degree of nonlinearity, such results are not unexpected, since in this setting the non-linear model approaches its linear counterpart as K_m approaches infinity. Further work is needed to investigate this issue.

In summary, the sufficient design presented in this study illustrates that cost-effective studies that provide acceptable parameter precision are achievable even when there is considerable uncertainty in the model and parameter space. This provides a useful way for Phase II studies to be designed based on data obtained during preliminary Phase I studies.

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