On Early Paediatric Study Design: Sample Size Calculation using a PBPK Approach within the Simcyp Simulator

Khaled Abduljalil, Trevor N Johnson, Farzaneh Salem, Masoud Jamei

Simcyp (A Certara Company), Blades Enterprise Centre, Sheffield, UK
Khaled.Abduljalil@certara.com

Background

Powering clinical studies in advance is a prerequisite to optimize the trial and reduce both the cost and time of clinical pharmacokinetic investigation. However, the challenge is achieving this for paediatric populations without any prior clinical information. PBPK modeling provides a solution to optimally design the pediatric study plan and predict the OK based on physicochemical and *in vitro* properties together with system parameters including those that demonstrate age-dependency such as enzyme ontogeny. In addition the possibility to account for inter-individual variability in these enzymes can be a key parameter in determination of the required sample size.

The aim of this work is to investigate the required sample size for a compound eliminated mainly by UGT1A1 in a paediatric population at different ages and compare it with the adult population using either a random or enriched recruitment method with respect to UGT1A1 polymorphisms.

Methods

A hypothetical Compound-X was used with elimination pathways of 75% liver UGT1A1, 1% Renal UGT1A1, 18% additional hepatic clearance and about 6% renal filtration in healthy adult volunteers. The Simcyp Paediatric Simulator V15R1 was used to generate three populations: 0.5, 5 and 20 years old subjects with 200 virtual subjects in each group. The default UGT1A1 polymorphisms and abundances is given in Table 1.

UGT1A1 attributes	EM	PM	IM	UM
Frequency (%)	44	11	44	1
Liver abundance, pmol/mg-protein (CV)	48 (24%)	20.16 (50.8%)	34.56 (39.9%)	70.08 (30%)
Renal abundance, pmol/mg-protein (CV)	6.1 (50%)	2.56 (50%)	4.39 (50%)	8.91 (50%)

Table 1. Default frequency and abundances of UGT1A1 polymorphisms in healthy Caucasian population (EM, PM, IM and UM are Extensive, Poor, Intermediate and Ultra-rapid metabolisers, respectively).

Two recruitment designs were considered: *Random recruitment*: in this design there was no entry criteria for individuals other than their ages. *Enriched recruitment*: in this design UGT1A1 polymorphisms was considered in addition to the age as an entry criteria.

The PK parameter of interest in this work is the extrapolated AUC_{inf} calculated from plasma concentration time profiles generated with a multiplicative residual error of (Eps = 0.3 uM) sampled at 0, 0.5, 1, 3, 6,12, and 24 after single oral administration of 10 mg/kg.

The sample size calculated at significance level $\alpha=0.05$ to detect a statistical difference in AUC_{inf} for the paediatric compared with the adult population as a reference population. In the enriched design the used reference population is the EM UGT1A1 phenotype of that population.

Results

The predicted populations AUC_{inf} (mean±SD) were 538±226, 569±238 and 655±277 mg/L·h for 0.5, 5 and 20 years, respectively. Statistical power calculation indicated that the sample size differs during development. For example, about 80% of study power can be achieved to detect differences in AUC_{inf} between adult and 0.5 year population with about 30 subjects recruited randomly in each arm, while only 52% of study power can be reached with 30 subjects for the 5 years population (Figure 1).
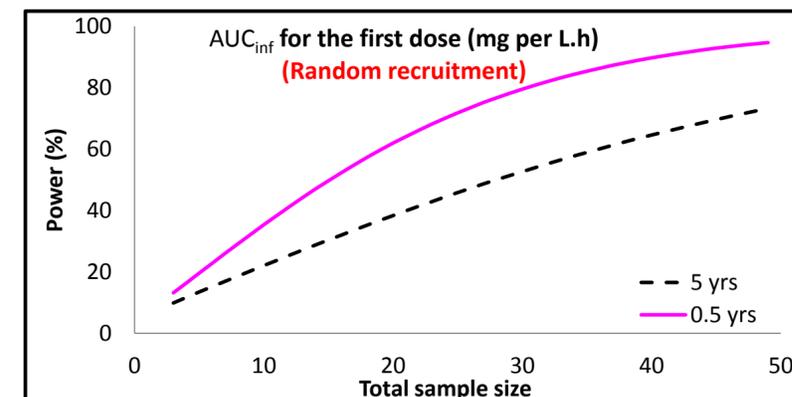

Figure 1. calculated sample size per arm in paediatric populations with reference to the adult population

The calculated sample size for each phenotype relative to the EM as a reference (the enriched recruitment design) is shown in Figure 2.

The source of variability within each sub-population that derives the sample size is the inter-individual variability in the abundance of the UGT1A1 for each phenotype. However, the driving force for differences between ages is all age-dependent system parameters, such as liver size, protein binding, and tissues composition and perfusion.

Interestingly, in adults the sample size required to detect the differences between IM and EM is larger compared to paediatric situation. Similarly, differences within the children group in sample size can be seen, for instance, at the age of 0.5 year, about 50 PM subjects are required to reach 80% power, compared with 35 PM subjects in older children to reach the same level of power.
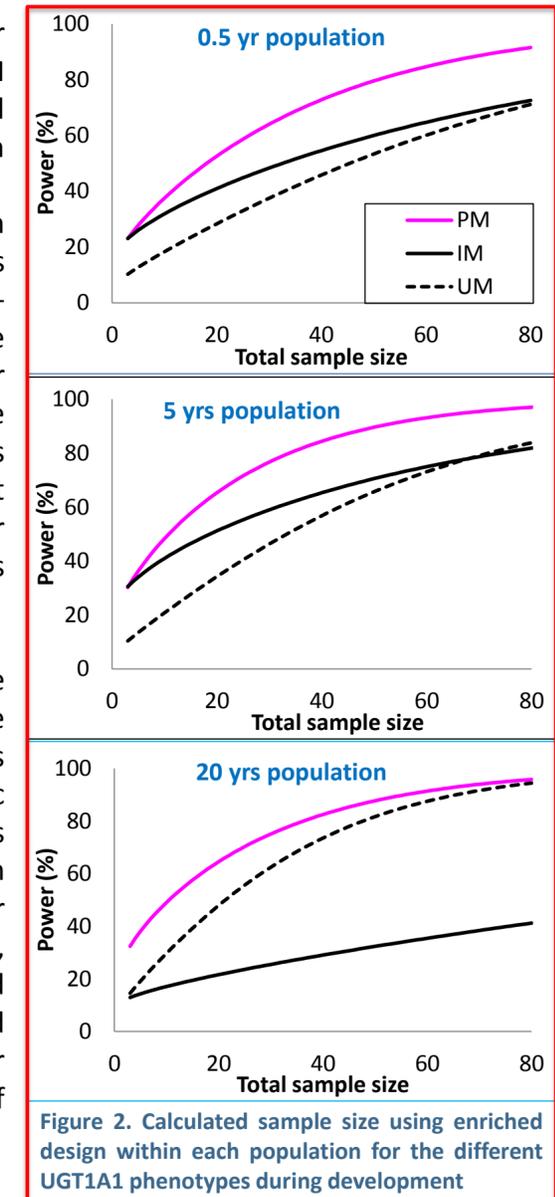

Figure 2. Calculated sample size using enriched design within each population for the different UGT1A1 phenotypes during development

Conclusions

The calculated sample size in adult can not be extrapolated to children, even for matched phenotypes as the net variability that derives the differences in children is a mixture of all system parameters, rather than the abundance or its associated variability for each phenotype.