PopPk analysis of a high-dose oral antineoplastic for bone marrow transplant in adults and children

Background

- Is an alkylating agent used orally for bone marrow conditioning prior to transplantation

- Standard dose of 1mg/kg q6h for 4/7 for adults and children

- Target AUC for outcome and to reduce toxicity

- Changes in AUC "observed" based on non-compartmental analysis from days 1 to 4

Aims

- To assess whether AUC changes systematically from days 1 to day 4.

- To assess for potential covariates to explain either random or systematic variability.

- To develop a limited sampling strategy to accurately predict AUC

Patient demographics

	Median	(range)
Age (yrs)	6	(1 – 50)
Weight (kg)	24	(12 – 88)
Height (cm)	116	(68 – 186)
Serum creatinine (mM)	0.04	(0.02 – 0.12)

Modelling

- Data
  - 24 patients (11 adults 13 children) (8F/16M)
  - 196 plasma drug concentrations over (up to) 3 occasions
- Base Model -1 compartment oral model (Ka,CL,V)
  - BSV & BOV (3 occasions) on Ka, CL and V
  - Parameter values similar to previous studies
- Covariate model
  - Best covariate for Vd = weight (kg)
  - Two possible covariate models for CL
    - weight$^{0.75}$ (allometric scaling)
    - body surface area (BSA)
  - Obj for allometric model -3.5 units cf BSA (BSV similarly reduced)

Which model is preferred?

CL = THETA(1)*(WT/70)**0.75

Or

CL=THETA(1)*BSA/1.9

Why?

What was done…

- 1000 non-parametric bootstrapped data sets were generated

- Both covariate models were fitted to each data set and the value of the objective function OBJF under each model was recorded

- The difference in the objective function value (ΔOBJF) between both models were computed

- The density of the ΔOBJF that is greater than zero provides the pseudoposterior probability in favour of one model over another
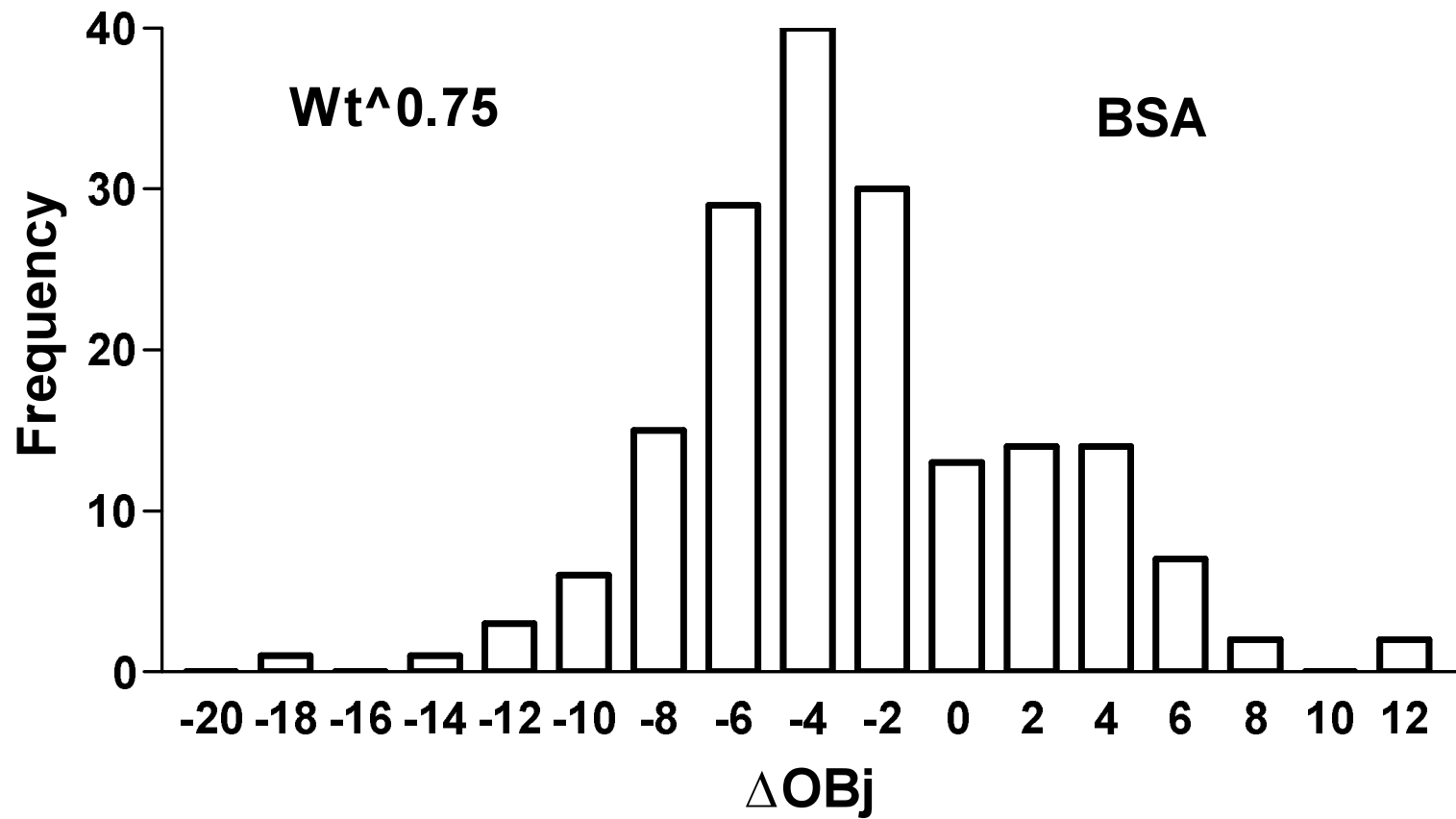
The solution

- Of 1000 randomized data sets 180 terminated successfully

- The density of the distribution of ΔOBJF < 0 was 0.75 indicating that the allometric model was preferred with a probability of 0.75 (or odds of 3)

- A visual inspection of the predictive distribution is underway…