### Background
- Unfractionated heparin (UFH) is the anticoagulant of choice in paediatric patients undergoing a cardiac procedure.
- UFH is administered as a bolus intravenous (IV) injection followed by a continuous IV infusion. The bolus dose is based on the patient’s total body weight (WT) and the continuous infusion rate is adjusted based on patient’s response (aPTT).
- WT is often used to scale drug doses but it may not correlate well with drug clearance (CL) and can potentially result in over- or under-dosing.
- Recently a fat-free mass (FFM) model was developed for children and may be a suitable descriptor of size in relation to drug disposition [1].

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FFM_{\text{females}} = \left(1.11 + \frac{2}{\text{Age}^{0.71}}\right) \times 9270 \times \text{WT} \\
FFM_{\text{males}} = \left(0.88 + \frac{2}{\text{Age}^{0.71}}\right) \times 9270 \times \text{WT}
\]

### Aims
- To develop and evaluate a model to predict the dose-response of UFH in paediatrics using various size descriptors as covariates.

### Methods
- Data from 64 infants and children that received a bolus dose of UFH during cardiac angiography were analysed (Table 1).
- Blood samples were collected at baseline and at 15, 30, 45, and 120 minutes post-dose. UFH concentrations (231 measurements) were determined using protamine titration.
- aPTT (290 measurements) was determined using the PTT-A® kit (Diagnostica Stago). 43% of aPTT data were above the upper limit of quantification and were accounted for using the M3 method [2].
- Modelling was performed using NONMEM v7.2.
- PD parameters were estimated sequentially using the PPP & D method.
- Covariates tested include WT, allometric weight, body surface area, and FFM.
- The final model was evaluated using the likelihood ratio test and visual predictive check (VPC) plots.

### Results
- A one compartment PK model with linear elimination provided the best fit for the dose-concentration data (Table 2).
- Size (WT & FFM) had significant influence on model performance; FFM on CL was preferred statistically.
- The model performed well as shown on the VPC plot (Figure 1).

### References