

# Population pharmacokinetics and dose rationale for deferasirox in the treatment of iron overload in paediatric patients undergoing haematopoietic stem cell transplantation

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## Introduction

Iron overload (IO) is common in haematological malignancies due to prior transfusion burden and has a detrimental impact on the outcome of allogeneic haematopoietic stem cell transplantation (aHSCT). The use of iron chelation constitutes an alternative in patients for whom phlebotomy is not recommended.

Current guidelines suggest the use of deferasirox (DFX), at half of the approved dose for patients with beta thalassaemia major (i.e., 7 or 10 mg/kg, for film-coated or dispersible tablet, respectively). This initial regimen has been used despite the lack of a clear correlation between IO reduction and DFX exposure. Moreover, trough concentrations at steady-state ( $C_{trough,ss}$ ) < 10 µg/mL have been proposed as a reference threshold associated with lower incidence of adverse events in this population.

There is an opportunity to optimise treatment outcome in aHSCT patients by evaluating the underlying pharmacokinetic-pharmacodynamic relationship of DFX using ferritin as a proxy for IO.

## Methods

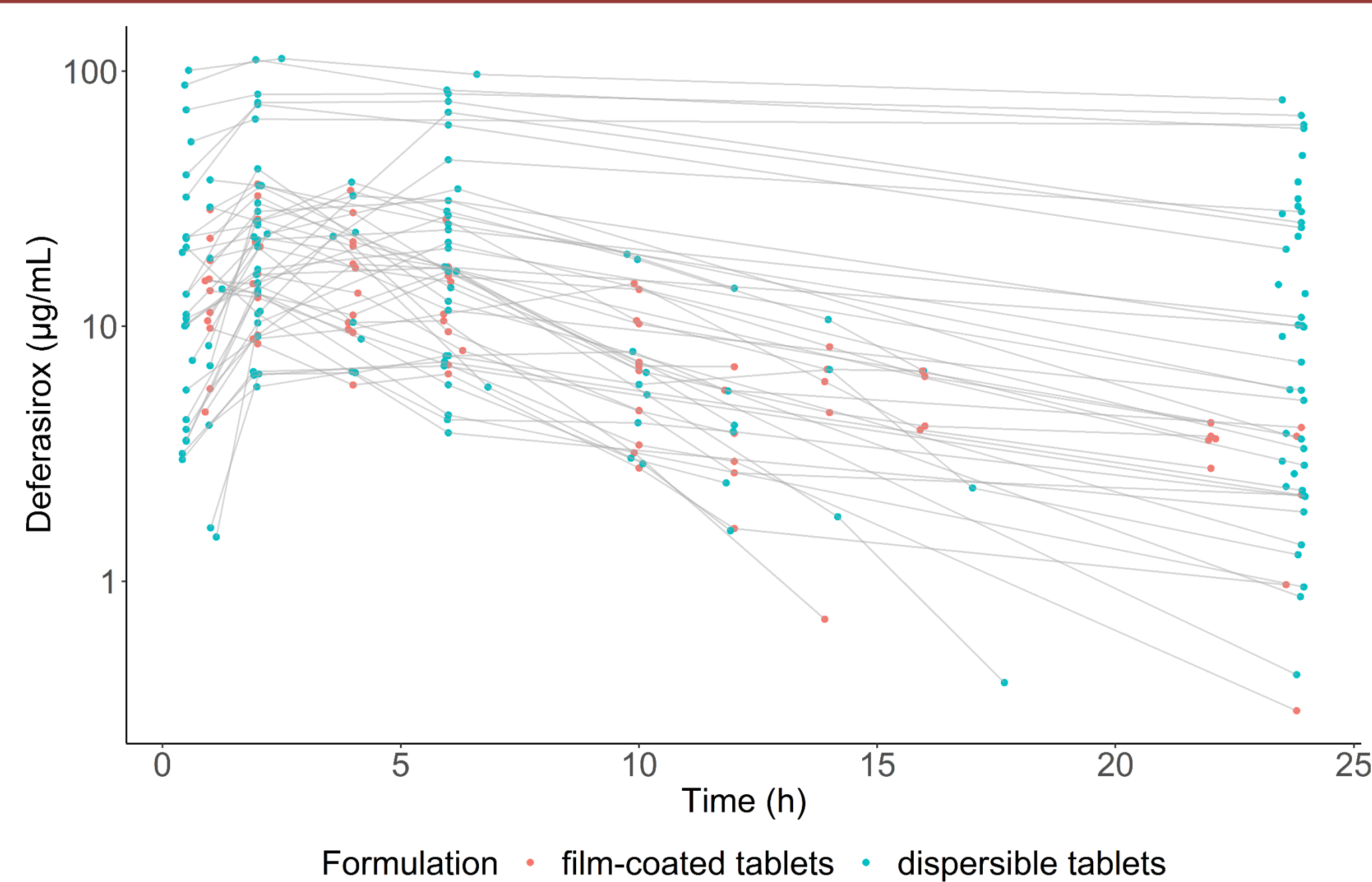


**Figure 1.** Individual concentration vs time profile of DFX in plasma following oral administration of film-coated or dispersible tablets to paediatric patients undergoing aHSCT (n=36).

Initially, the pharmacokinetics of DFX was characterised in a population of children (n=36) affected by haematological malignancies and subjected to aHSCT (Figure 1). Plasma DFX concentrations (n=252) were evaluated using a nonlinear mixed effects approach in conjunction with prior parameter distributions (\$PRIOR) to overcome limitations due to the number of samples available per patient. Final parameter estimates were then used to simulate the impact of different DFX regimens on exposure and subsequently on serum ferritin profiles over the course of therapy. Optimisation criteria focused first on the identification of starting doses that are associated with low incidence of adverse events ( $C_{trough,ss}$  < 10 µg/mL). This was followed by an evaluation of up-titration steps that maximise serum ferritin reduction using a previously published drug-disease model describing the effects of iron chelation on serum ferritin [Borella, E. et al. (2022)]. Finally, simulation scenarios were implement taking into account a wider paediatric patient population.

Standard diagnostics, graphical and statistical criteria were used for model evaluation. All modelling and simulation procedures were implemented in NONMEM v7.5./Pirana, whilst R version 4.3.2 was used for data formatting, graphical and statistical summaries.

## Objectives

To characterise the population pharmacokinetics of DFX in paediatric patients undergoing aHSCT and identify an optimised DFX dosing regimen that takes into account patient baseline characteristics known to affect drug disposition and ferritin homeostasis.

## PK results

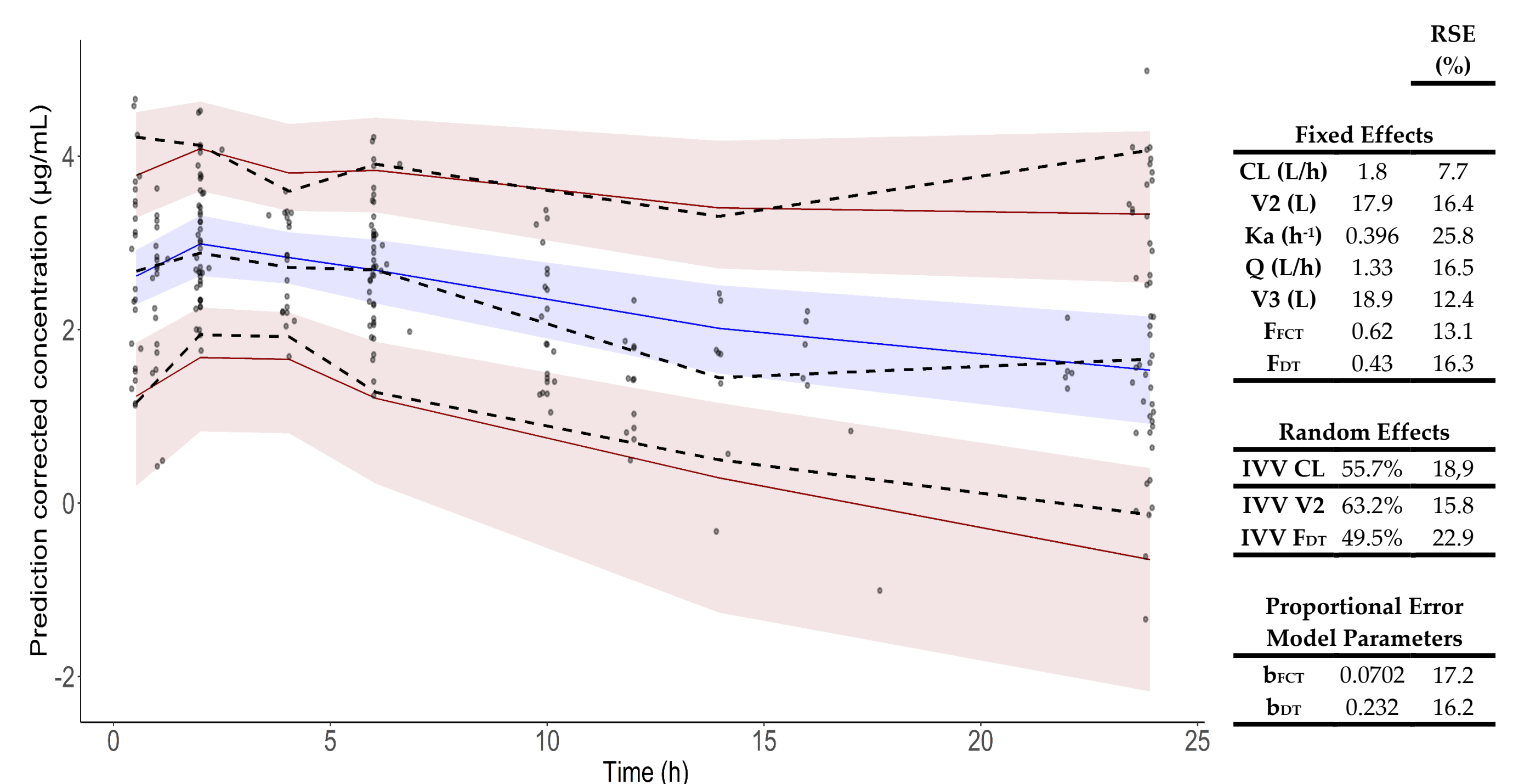


**Figure 2.** Prediction corrected visual predictive check, describing DFX concentrations in plasma. Table (right panel) summarises PK parameters along with estimates of interindividual variability. Of note are the differences in exposure due to varying bioavailability across formulations.

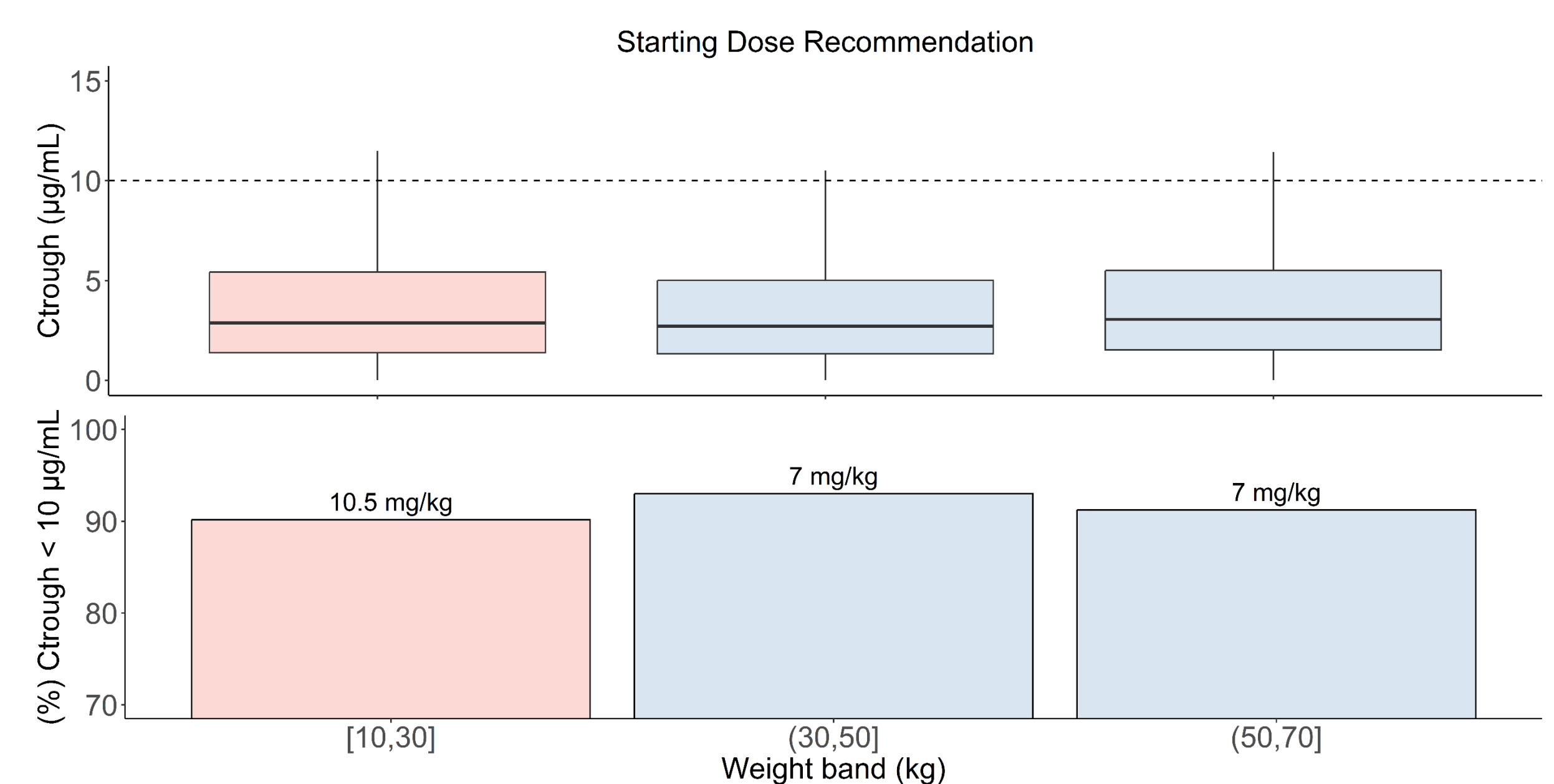


**Figure 3.** Recommended starting DFX dose associated with  $C_{trough,ss}$  < 10 µg/mL. Instead of 7 mg/kg, patients with a body weight <30 kg should initiate treatment with a DFX dose of 10.5 mg/kg. (Simulated subjects n = 1200, replicates n = 500)

## PD results

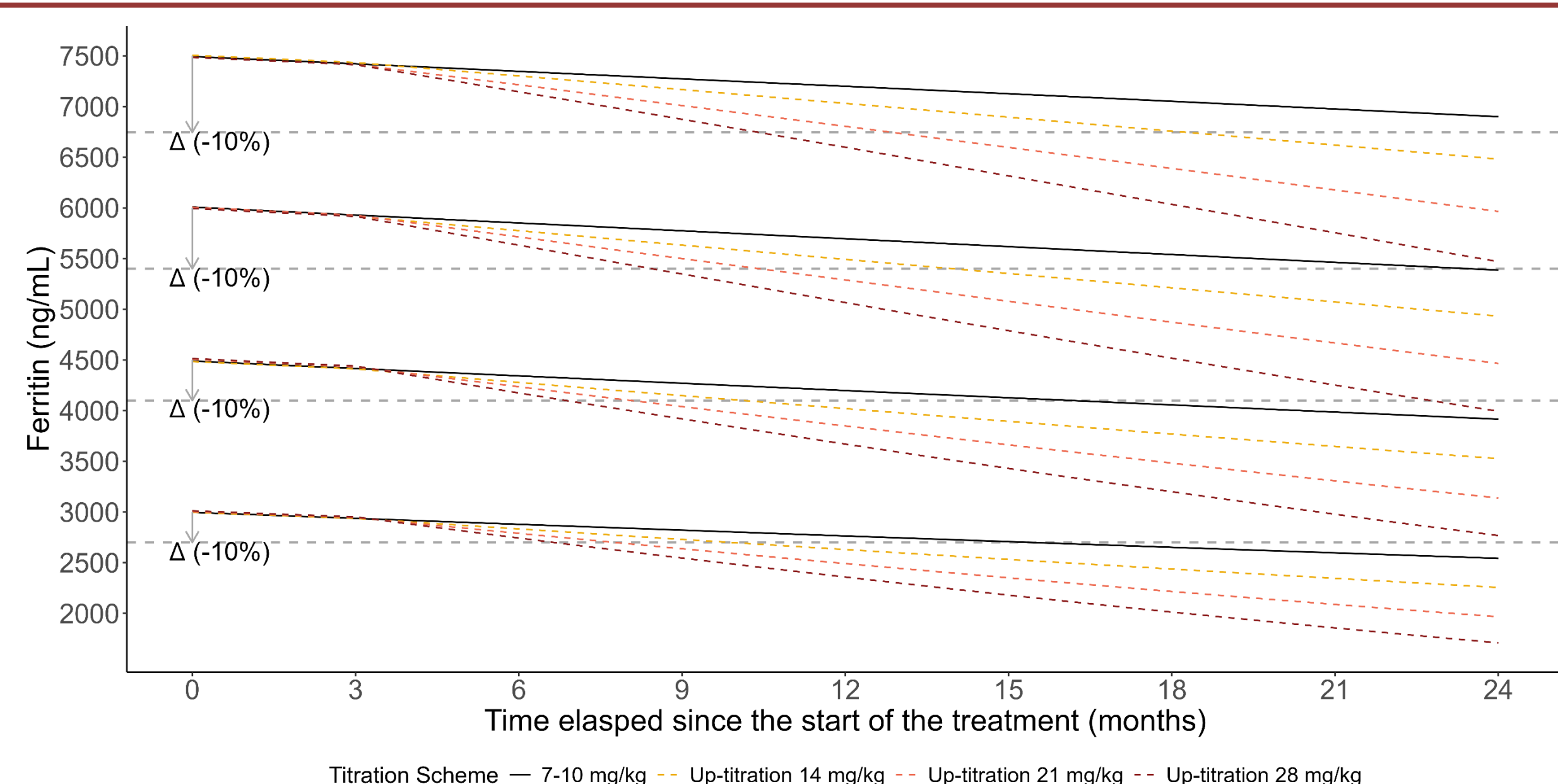


**Figure 4.** DFX-induced ferritin reduction over 24 months post transfusion phase. Solid lines depict the resulting effect of chelation based on the starting dose. Dashed lines show the importance of up-titration to maximum approved dose for effective chelation. Profiles refer to patients with a previous average transfusional burden of 10 red blood cell units and different baseline ferritin level. (Simulated subjects for each titration scheme and baseline ferritin level n = 1600, replicates n = 100).

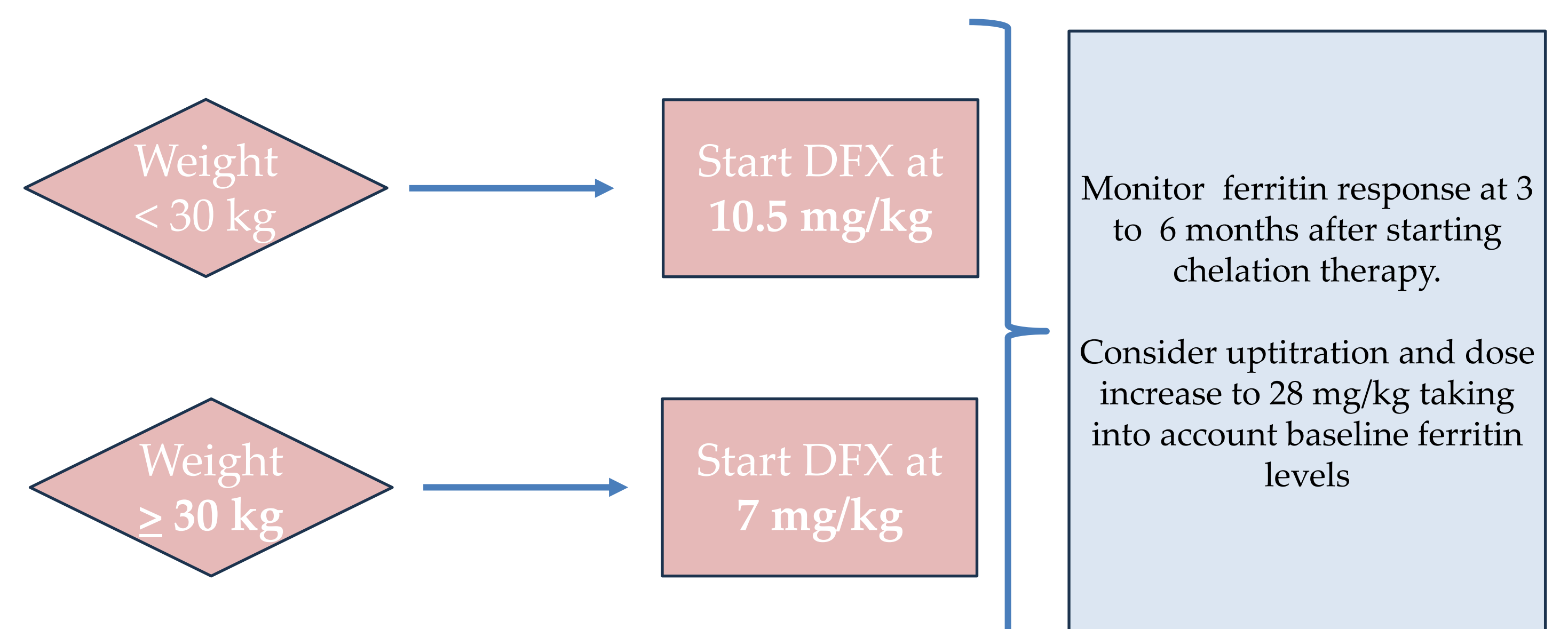


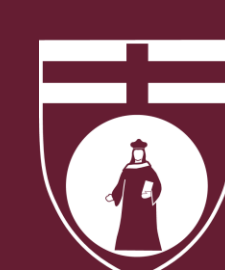
**Figure 5.** Suggested starting doses and clinical management of aHSCT patients following the initiation of chelation therapy.

## Conclusion

Starting doses DFX were identified, which are likely to minimise adverse events and drug-induced tolerability issues. However, chelation therapy should proceed with titration steps of 3.5 mg/kg up to 28 m/kg, taking into account ferritin levels at baseline. In addition, monitoring of DFX concentrations and serum ferritin shortly after initiation of treatment may offer an opportunity to assess the probability adverse events and establish up-titration requirements for effective iron chelation. These steps may also eliminate the need short term assessment of liver iron concentrations through magnetic resonance imaging or by chemical analysis of needle biopsy specimens. Further *in silico* evaluation of the effect of deferiprone on IO in aHSCT patients should be considered as an alternative for patients who show poor tolerability to DFX or have high ferritin levels at baseline.



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