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Authors' Reply

On behalf of the entire Proactive IV IrOn Therapy in HaemodiALysis Patients (PIVOTAL) study team, we wish to thank Kshirsagar *et al.*[1] for their comments on our recently published secondary analysis of the PIVOTAL trial.[2] We agree with much of what they have said but have the following comments to make.

The choice of dosing regimens and safety cutoffs for the two arms in the PIVOTAL trial has been extensively discussed. We completely recognize that a large number of dialysis centers in the United States are already using iron protocols that are aligned to the high-dose arm.[3] However, it is important to point out that current clinical practice varies widely worldwide, and the majority of countries and dialysis centers adopt more modest iron dosing protocols than the United States. Indeed, in Japan, the standard of care is more aligned to the low-dose arm of the trial.[3,4]

The trial was originally designed to reflect the two extremes of iron dosing in the United Kingdom, and indeed, comprehensive pretrial research indicated that a ferritin safety cutoff >700 μg/L would not be acceptable to many potential investigators in the United Kingdom. We already recognized that the sample size for the study would need to be >2000 patients and that we would need "buy-in" from 40–50 centers. Thus, the choice of dosing protocols in the study was partly on the basis of current United Kingdom and European practice and partly on a pragmatic approach regarding study feasibility.

Next, we agree with Kshirsagar *et al.*[1] that the two options that dialysis physicians in the United States have are (*1*) to continue with their more aggressive iron protocols, aiming to rigorously test the benefits/safety of this approach (particularly because in the authors' own observational study of 13,249 United States patients on dialysis, intravenous iron administration strategies promoting more intensive iron treatment were associated with higher risks of mortality and infection-related events[5]); or (*2*) adopt the PIVOTAL high-dose arm approach with the corollary that dosing strategies more or less aggressive than this be halted. Which of these options to choose is not within our remit to comment, but we feel that this is where we need to defer to guideline bodies, such as Kidney Disease Improving Global Outcomes, to assess the evidence base and make recommendations because they have the expertise and methodology to do this properly.

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See related Letter to the Editor, "At the Crossroads for Intravenous Iron Dosing," on pages 1653–1654.

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