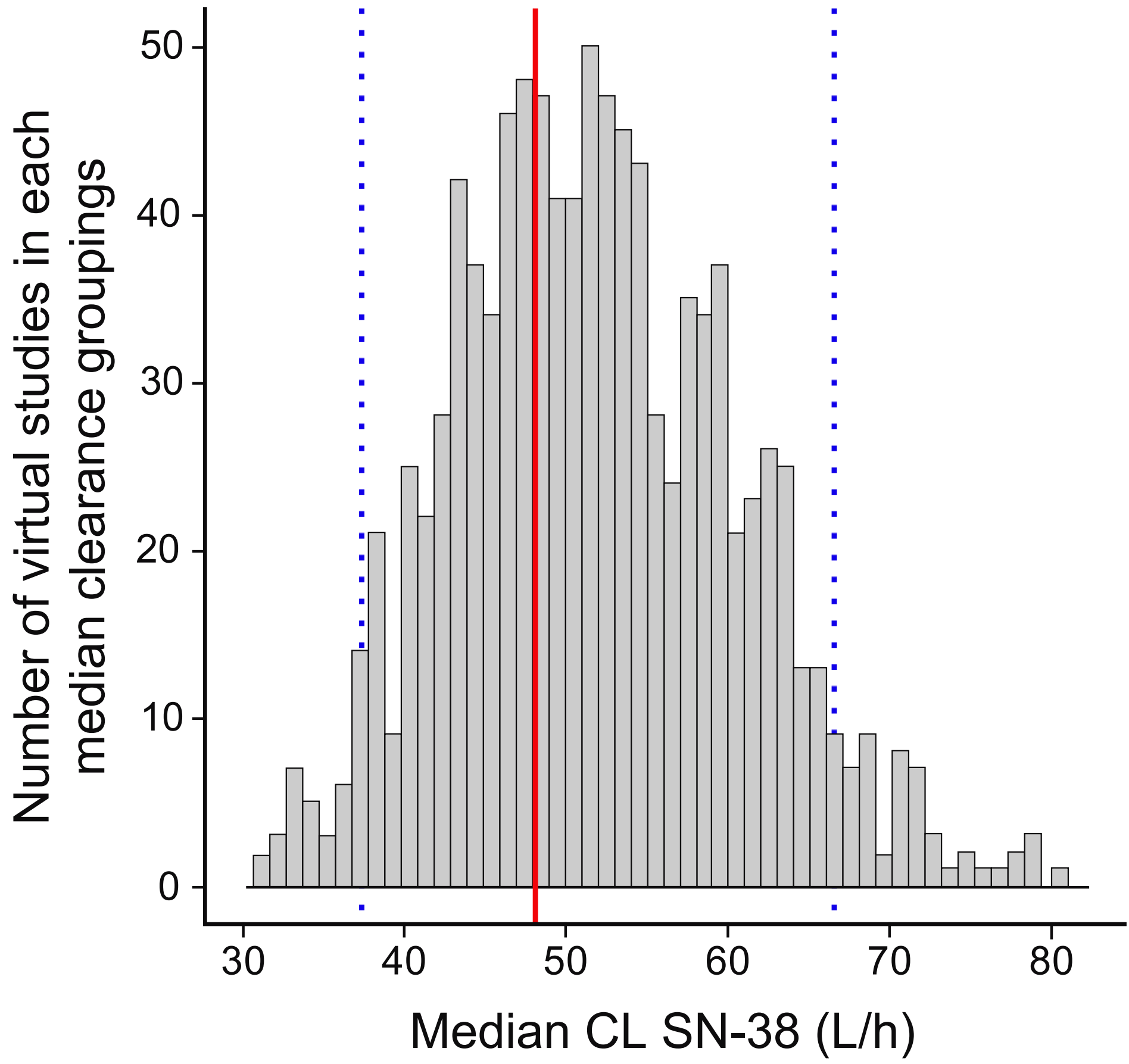
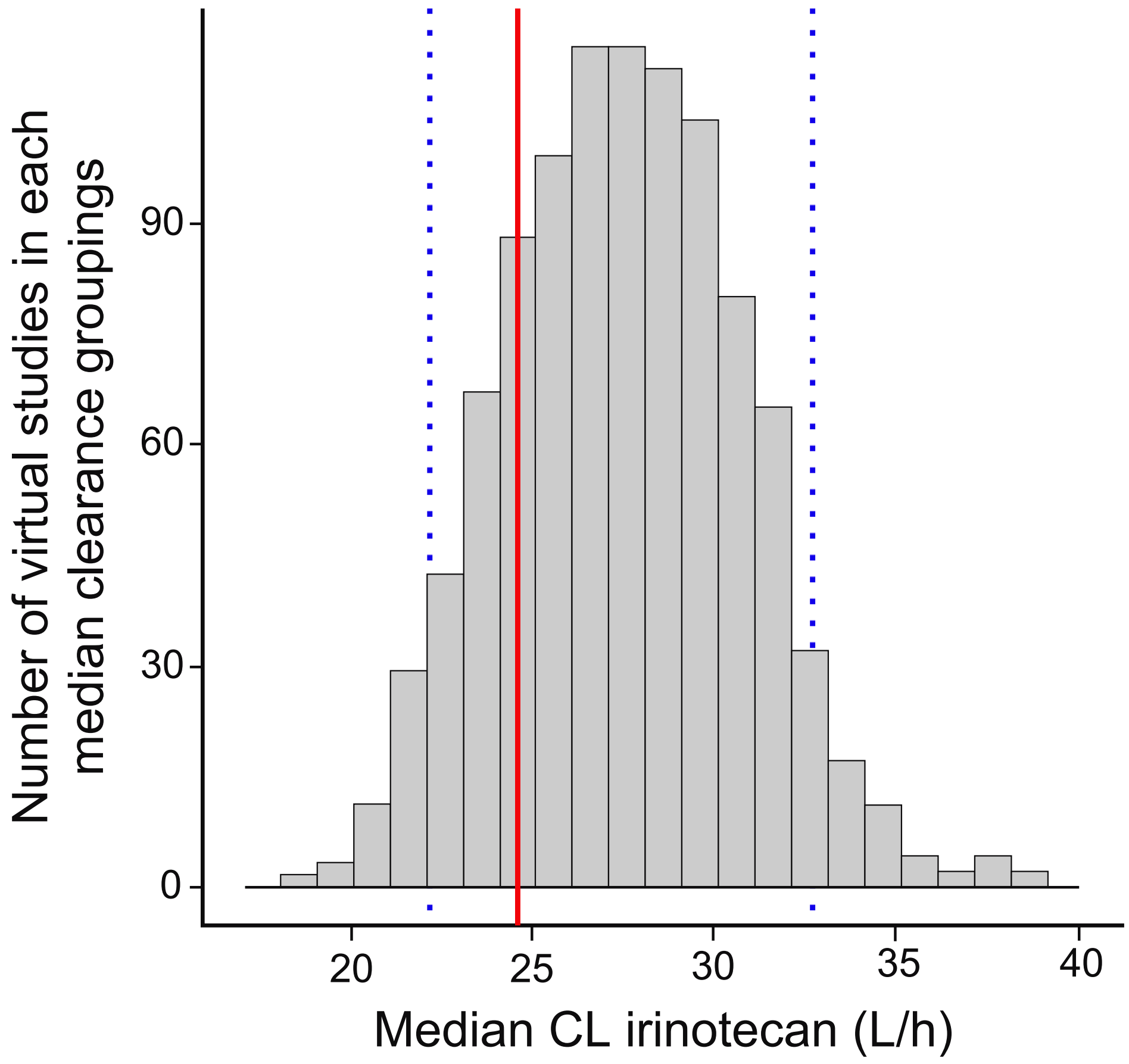


Supplementary Figure 4. Distribution of the median clearance (CL) of irinotecan (left) and its active metabolite (SN-38, right) derived from the published variability distribution of the clearances versus the estimated median clearance of irinotecan and SN-38 in this study.

The median estimated CL of irinotecan and SN-38 obtained in patients (n=19) in this study (red line) is consistent with the 90% confidence intervals obtained by resampling virtual studies with 19 subjects from the reported CL distributions in the literature (dashed blue lines) (1). Briefly, the distribution of the individual irinotecan and SN-38 clearance in the expansion phase was compared to the clearance distribution quantified by Thompson et al (1) by drawing 1000 times n=19 individual clearance values of irinotecan and SN-38 from the previously reported clearance distributions. Subsequently, the median of the clearances in the expansion phase was compared to the distribution of the medians of these virtual populations and considered comparable when the median clearance in the expansion phase was inside the 90% confidence interval of the median of the virtual populations.



Reference
1. Thompson PA, Gupta M, Rosner GL, Yu A, Barrett J, Bomgaars L, *et al.* Pharmacokinetics of irinotecan and its metabolites in pediatric cancer patients: a report from the children's oncology group. *Cancer Chemother Pharmacol* **2008**;62:1027-37.