**Supplemental Digital Content 5. Rationale and methods used for strata generation**

The rationale for stratification/grouping was based on the following assumption: since other factors such as age, comorbidities or surgical setting (i.e. clinical heterogeneity) may participate in the occurrence of adverse events (AE), it remains unclear if the observed effects of a particular transfusion regimen are the result of the transfusion strategy itself, of clinical heterogeneity, or of the combination of both. Therefore, we assumed that controlling for these factors at the analytical stage (i.e. stratification accounting for clinical heterogeneity) would yield better estimates of the true effects of transfusion strategies and allow for the identification of group-specific effects.

Strata were formed using variables known to participate in clinical heterogeneity (such as patient age, comorbidities and concomitant medication).1 The decision to use the variable “clinical setting” for strata generation was empirical and based on the assumption that patients undergoing high risk surgery (such as cardiac or vascular procedures) were more likely to develop adverse events than those in a post-partum setting, for instance. All variables used for grouping were pre-specified and described in the study protocol.

**REFERENCES**

1. Deeks J, Higgins J, Altman D. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). *The Cochrane Collaboration.* 2011; Available at: [www.cochrane-handbook.org](http://www.cochrane-handbook.org).