Appendix 1 (as supplied by the authors): Justification of changes made to the published protocol of the SIRS kidney substudy

Protocol (Available in Supplement 2; also published in BMJ Open. 2014;4:e004842)[1]	Change
Page 6, under 'Secondary Questions'. "3. Does methylprednisolone versus placebo at the time of surgery alter kidney function 6 months after surgery?"	After knowledge of the primary acute kidney injury (**AKI**) substudy results, this secondary question was no longer relevant, so the investigators did not invest the resources needed to prepare this data for analysis.
Page 7. Under 'Patient selection.' "All SIRS randomized patients will be included in the AKI substudy except for the following three reasons: (1) those with end-stage renal disease prior to randomization (expected in <2% of patients), as the assessment of AKI is no longer relevant (estimated-glomerular filtration rate (eGFR) <15 mL/min per 1.73m^2 as determined by the chronic kidney disease-epidemiology collaboration (CKD-EPI) equation, receipt of chronic dialysis or a prior kidney transplant or a baseline serum creatinine >327 μmol/L; the last exclusion also enables retained patients to have their new onset AKI staged according to most recent guidelines).	We did not exclude patients based on a baseline serum creatinine >327 μmol/L. Two patients (0.03%) in the kidney substudy had a preoperative serum creatinine > 327 μmol/L; one met the criteria for stage 2 AKI or higher (and had an increase in postoperative serum creatinine concentration that was ≥ 26.5 μmol/L from the preoperative value), and the other did not meet the criteria for stage 2 AKI or higher.
Page 7. Under 'Patient selection. "We expect over 7000 SIRS patients will be eligible for the AKI substudy from 81 centres in 18 countries.	The main SIRS trial enrolled patients from 80 centres in 18 countries. All 80 centres agreed to participate in this substudy, and between June 2007 and January 2014, patients from 79 centres were enrolled in the substudy.
Page 8. Under 'Primary definition of AKI.' "We will use a mixed effects logistic regression model to obtain an estimate of the OR of AKI comparing methylprednisolone with placebo (after testing model assumptions)."	Instead of using a mixed effects logistic regression model, we used a modified Poisson regression model accounting for centre to estimate the relative risk of AKI comparing methylprednisolone with placebo. We used the latter method because an estimate of the relative risk (rather than the odds ratio) of AKI was preferred.
Page 8. Under 'Primary definition of AKI.' "In SIRS, this AKI outcome will use the most recent consensus criteria and will be defined as any of the following two criteria: (1) ≥50% change in the postoperative serum creatinine value from the preoperative value (((peak postoperative serum creatinine – preoperative serum creatinine)/preoperative serum creatinine)x100),	We also added to the primary definition of AKI the outcome of receipt of (new) acute dialysis within 30 days of surgery.

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(2) ≥26.5 μmol/L increase in serum creatinine after surgery from the preoperative value.	
Page 8. "For the primary analysis, we will treat centre as a random effect, and will adjust for the following baseline characteristics: age (per year), sex, left ventricular function (≥50%, 35-49%, 20-34%, <20%), diabetes, pre-randomization ACE inhibitor or angiotensin receptor blocker use, pre-randomization statin use, pre-randomization diuretic use, preoperative eGFR category (≥60 and <60 mL/min per 1.73 m^2), surgery type (coronary artery bypass grafting (CABG), valve, CABG and valve) and evidence of non-elective surgery (defined by either preoperative use of inotropes or vasopressors, preoperative use of an intra-aortic balloon pump or ventricular assist device or history of a myocardial infarction within the 30 days prior to surgery)."	• We changed the left ventricular ejection fraction (LVEF) categories from ≥50%, 35-49%, 20-24%, <20%, to ≥50% vs. <50% because of low count in the <20% category. • For patients missing LEVF (0.9% of patients), we used a logistic regression model with multiple imputation to estimate the LVEF category (≥50% and <50%), under the assumption that the covariate was missing at random, using all other prespecified covariates used in the adjusted analyses (see **Appendix S1** for details). • We added an extra surgery type category, "other," which includes 1) patients who may have had a CABG procedure but no valve procedure, and aorta surgery (patch enlargement, Bentall procedure, ascending aortic replacement, arch replacement, descending aortic replacement), or cardiac ablation surgery; 2) patients who may have had a valve procedure but no CABG procedure, and aorta surgery or cardiac ablation surgery; 3) patients who had neither CABG or valve procedure but did have an aorta surgery or cadiac ablation surgery; and 4) patients who had some other type of cardiac procedure. • We accounted for centre using a generalized estimating equation approach to accommodate the use of the modified Poisson regression method.
Page 8. "In patients who underwent surgery but are missing a postoperative serum creatinine value (expected in <2% of patients), we will carry the pre-randomization serum creatinine value forward which should provide a more conservative estimate of the intervention effect than the alternative of removing such patients. For patients missing a left ventricular ejection fraction measurement (at present 1.5% missing), we will impute a value of 50%. If required, for each remaining covariate, we will include a missing data indicator variable (at present <0.1% data are missing for each variable)."	For medication use, covariates used in adjusted analyses with missing values (pre-randomization ACE or angiotensin receptor blocker use, statin use, diuretic use; 0.01% missing), we assumed the patients were not using the medication (see footnote in Table 1). For preoperative use of inotropes or vasopressors and preoperative use of IABP or VAD, patients missing this variable were assumed to not have this (0.8 and 1.1% missing, respectively; see Table 1 footnote). For patients with a previous MI missing date of previous MI (1.6% missing), we assumed that the date of MI was more than 30 days before surgery (see Table 1 footnote).

Abbreviations: ACE, angiotensin converting enzyme; AKI, acute kidney injury; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; KDIGO, Kidney Disease Improving Global Outcomes; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SIRS, Steroids in Cardiac Surgery; VAD, ventricular assist device.

Reference

1. Garg AX, Vincent J, Cuerden M, et al. Steroids In caRdiac Surgery (SIRS) trial: acute kidney injury substudy protocol of an international randomised controlled trial. *BMJ Open*. 2014;4(3):e004842. doi:10.1136/bmjopen-2014-004842.