

Electronic Supplementary Material

REstrictive fluid management VERSus usual carE in Acute Kidney Injury (REVERSE-AKI) A pilot randomized controlled feasibility trial

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Table S1. Inclusion criteria with definitions

#	Criterion	Detailed definition
1.	18-years or older and admitted to a critical care unit with an arterial line in place	Age on the day of randomization. Critical care unit: a unit where respiratory support (invasive or non-invasive) and haemodynamic support can be provided
2.	The patient has been in critical care for at least 12 hours but no more than 72 hours ^a	Randomization must occur within these time limits
3.	The patient has AKI but is not receiving acute renal replacement therapy (RRT): For the purpose of the study AKI is defined by the following criteria: a. Increase in serum creatinine over 1.5-times above baseline ^b without a decline of 27 $\mu\text{mol/l}$ or more from the last preceding measurement (at least 12 hours apart) AND/OR b. Overall urine output less than 0.5ml/kg/h (or 6ml/kg) for the previous 12h (with urine catheter in place for the period)	Either a or b or both must be fulfilled. a. The patient must have at least two available creatinine values. b. Based on the weight recorded at ICU admission preferably by weighting the patient.
4.	The patient is judged by the treating clinician not to be intravascularly hypovolemic	The attending clinician's opinion to be asked before randomization. If necessary, please refer to the site-specific decision algorithm ^c
5.	The patient is likely to remain in critical care for 48 hours after randomization	The attending clinician's opinion to be asked before randomization.

^a The maximum allowed length of ICU stay pre-randomization was amended from 48 hours to 72 hours in a protocol amendment in April 2018 due to slow recruitment.

^b Baseline creatinine: The last outpatient recording within 7-356 days preceding current episode of critical illness. If not available, the lowest creatinine during current hospitalization.

^c According to local practice, sites can use algorithms to assess volume status, for example passive leg raising test

Table S2. Exclusion criteria with definitions ^a

#	Criterion	Detailed definition
1.	Active bleeding necessitating transfusion	Clinical signs of active bleeding, patient is transfused, or red cells have been ordered. Patients with a previous bleeding episode that has resolved should not be excluded.
2.	Maintenance fluid therapy is necessary due to diabetic ketoacidosis, non-ketotic coma, severe burns or other clinical reason determined by the medical staff	The attending clinician's opinion to be asked before randomization. Other clinical reasons include post-liver transplant protocols in some institutions.
3.	Need for RRT due to intoxication of a dialyzable toxin	The clinical team is planning (recorded in the medical records or asked directly from the team) commencing RRT any time to remove a dialyzable toxin such as lithium or myoglobin
4. ^b	Commencement of RRT is expected in the next 6 hours	The clinical team is planning (recorded in the medical records or asked directly from the team) commencing RRT within the next 6 hrs from the time of screening. If plans change, and the patient did not commence RRT, patient may be reconsidered for randomization within the study randomization window (12 to 72 hrs from ICU admission) given other eligibility criteria are still ok.
5.	On chronic RRT (maintenance dialysis or renal transplant)	Mentioned in the medical records
6.	Presence or a strong clinical suspicion of parenchymal AKI (for example glomerulonephritis, vasculitis, acute interstitial nephritis) or post-renal obstruction	Mentioned in the medical records or the clinical team has expressed concerns about it. Patients who are admitted post-nephrectomy (within the previous 7 days) are excluded based on this criterion.
7. ^b	Severe hyponatremia (Na <125mmol/L) or hypernatremia (Na >155mmol/L)	The last value before screening. If this resolves during the randomization window (from 12 to 72 hrs from ICU admission), patient may be randomized given that all other criteria are still ok.
8.	Need for extracorporeal membrane oxygenation or molecular absorbent recirculating system (MARS-therapy)	In place or planned
9.	Pregnant or lactating	Condition is known
10.	Patients who are not to receive full active treatment	Limitation of treatment orders that restrict the intensity of interventions are in place
11. ^b	No baseline creatinine available	The patient has only one Cr measurement during the current hospitalization. Later with more Cr measurements, the patient

		may be reconsidered for randomization within the study randomization window (12 to 72 hrs from ICU admission) given other eligibility criteria are ok.
12.	Lack of consent	Obtaining the approval to randomize the patient that is locally required will not be possible for this patient.

^a two exclusion criteria that were removed in a protocol amendment in April 2018: 1) Metformin-induced lactic acidosis or acute liver failure 2) AKI stage 2 or greater is known to have been present for > 48 hours

^b Criteria 4, 7, and 11 are dynamic, and, if these change, patient can be reconsidered to be enrolled in the trial given that patient is still otherwise eligible and study randomization window is still open (from 12 to 72 hrs from ICU admission).

Table S3. Definitions of adverse events

General	
Ventricular tachycardia/fibrillation*	Requiring interventions
New-onset atrial fibrillation*	Requiring medication/defibrillation
Acute myocardial infarction*	acute myocardial infarction (ST-elevation myocardial infarction and non-ST elevation myocardial infarction) OR unstable angina pectoris, according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischaemic signs on ECG, clinical presence) AND the patient receives treatment as a consequence of this (reperfusion strategies (PCI/thrombolysis) or initiation/increased antithrombotic drug treatment).
Cerebral ischemia*	verified by CT scan or MRI
Intestinal ischemia*	Verified by endoscopy or open surgery
Acute peripheral limb ischemia*	Clinical signs AND use of open/percutaneous vascular intervention, amputation or initiation/increased antithrombotic treatment.
Radiologically diagnosed pulmonary edema*	As stated in the chest x-ray report.
Other safety event*	Please describe.
Adverse reactions to furosemide	
Loss of hearing*	
Severe disturbances in electrolytes	hypokalemia <3.0 mmol/L, ionized calcium <0.90 mmol/L, hyponatremia <125mmol/L)
Severe thrombocytopenia	<50 x 10 ⁹ /L
Agranulocytosis*	
Allergic reactions*	Rash, anaphylaxis or anything that raises clinical suspicion of an allergic reaction
Adverse events related to RRT	
RRT-associated hypotension	Defined as a drop in blood pressure requiring one of: initiation of a vasopressor during RRT session or need to escalate dose of a vasopressor during the session OR premature discontinuation of the RRT session
New-onset arrhythmia during RRT	New ventricular or atrial tachyarrhythmias that develop during RRT
Allergic reaction to RRT*	Defined as clinician suspicion of allergic reaction to one or more of the components of the RRT machine
Seizure verified by the clinician related to RRT*	
Major bleeding related to RRT*	Bleeding is related to RRT:

	<p>patient was receiving systemic anticoagulation and/or there was a major problem with the RRT circuit or vascular access that resulted in major bleeding.</p> <p>Major bleeding is defined as any of these:</p> <ol style="list-style-type: none"> Life threatening bleeding and hypovolemic shock (such as ruptured abdominal aortic aneurysm, gastrointestinal bleeding) Life threatening bleeding at a critical site (intracranial, pericardial, retroperitoneal for example) Clinically important, overt bleeding with one of the following within 24 hrs of the bleed: decrease in hemoglobin > 20 g/l or transfusion of more than 2 packed red cells Bleeding at other critical sites such as epidural, intraocular, intra-articular. Bleeding requiring an invasive intervention (surgery, angiography).
<p>Complication related to dialysis catheter</p> <ul style="list-style-type: none"> - hemorrhage at the insertion site - CVC-associated bloodstream infection - confirmed thrombus related to CVC - pneumothorax related to insertion - hemothorax related to insertion - arterial puncture at the time of insertion - other (please specify) <p>Please only consider double lumen RRT catheter inserted the purpose of RRT (not other lines for other purposes).</p>	<ul style="list-style-type: none"> -Hemorrhage at the insertion site: Bleeding associated with the insertion of the dialysis catheter that necessitates transfusion of one or more packed red cells OR surgical intervention or repair within 12 hrs of insertion. -CVC-associated blood stream infection: Bacteraemia in 2 culture sets (one from the catheter and one from other site) with no proven alternative source of bacteremia. - confirmed thrombus related to CVC: Ultrasonographically confirmed occlusive or non-occlusive thrombus in the vein where CVC was placed/remains in place, further qualified by embolism as a result of thrombus in further vasculature where the vein is drained. -Pneumothorax related to catheter insertion: Air in pleural space on routine chest x-ray following the CVC insertion and chest tube placement is necessary. -Arterial puncture at time of dialysis catheter insertion: Described as the clinician and leads to serious complications (such as major bleeding, need for surgery).

*considered as serious adverse event

Table S4. Number (%) of patients with missing baseline data

Characteristic	Restrictive fluid management (n=49)	Usual care (n=51)
Age	0	1 (2.0%)
Male sex	1 (2.0%)	0
Body mass index	1 (2.0%)	2 (3.9%)
Hypertension	1 (2.0%)	2 (3.9%)
Diabetes	1 (2.0%)	1 (2.0%)
Chronic heart failure	1 (2.0%)	1 (2.0%)
Coronary artery disease	1 (2.0%)	0
Chronic obstructive pulmonary disease	0	1 (2.0%)
Chronic kidney disease	2 (4.1%)	0
Chronic liver disease	0	1 (2.0%)
Operative ICU admission	0	1 (2.0%)
Emergency ICU admission	0	1 (2.0%)
Time from hospital admission to ICU admission (days)	0	2 (3.9%)
Time from ICU admission to randomization (hours)	0	2 (3.9%)
Simplified Acute Physiology II score ^a	11 (22.4%)	15 (29.4%)
Respiratory support -mechanical ventilation	0	1 (2.0%)

ICU; intensive care unit

^a Data from one or several of the subcomponents were missing. Calculation of the full score was not possible among these subjects.

Table S5. Suspected etiology of acute kidney injury

Risk factor	Restrictive fluid management - No / total no (%)	Usual care - No / total no (%)
Sepsis	21/46 (45.7%)	23/51 (45.1%)
Ischemia-reperfusion injury	15/46 (31.9)	13/51 (25.5)
Contrast medium	9/47 (19.6)	15/51 (29.4)
Nephrotoxic medications	3/47 (6.4)	7/50 (14.0)
Intra-abdominal compartment syndrome	3/47 (6.4)	2/51 (3.9)
Acute-on-chronic kidney disease	4/47 (8.5)	9/51 (17.6)
Major bleeding / hypoperfusion	22/47 (44.9)	20/51 (39.2)
Other	5/47 (10.6)	5/50 (10.0)

Table S6. Crude primary and secondary outcomes

Outcome	Restrictive fluid management	Usual care	Restrictive fluid management vs usual care (95% CI) ^a	P value ^b
Cumulative fluid balance at 72 hrs from randomization, mean (SD) mL ^c	-1080 (2003)	61 (3131)	-1141 (-2189; -93)	0.033
Duration of AKI (days), median [IQR] ^d	2 [1-3]	3 [2-7]	-1.0 (-2.5; 0.0)	0.046
Number of patients receiving RRT, n (%) ^e	6/46 [13.0]	15/50 [30.0]	0.43 (0.17; 0.97)	0.057
Cumulative fluid balance at 24 hrs from randomization, mean (SD) mL ^c	-416 (1194)	409 (1566)	-825 (-1380; -271)	0.004
Cumulative fluid balance at ICU discharge/day 7, mean (SD) mL ^c	-2166 (2988)	-650 (4469)	-1516 (-3031; -1)	0.050
Cumulative dose of furosemide per day, median [IQR] mg ^f	0.0 (0.0-19.0)	1.4 (0.0-26.2)	-1.4 (-13.3; 10.0)	0.719

AKI; acute kidney injury, RRT; renal replacement therapy

^a difference in means/medians or risk ratio with 95% CI

^b P value derived from regression mode without adjustment

^c The last available value for cumulative fluid balance was analyzed for all patients even if ICU discharge or consent withdrawal occurred before endpoint was fulfilled

^d truncated at 7 days, ICU discharge, or consent withdrawal. Data missing for 3 patients receiving restrictive fluid management and 1 in usual care.

^e truncated at 14 days (RRT provided post-ICU discharge included)

^f per oral furosemide dose divided by 2 to make it comparable to intravenous doses. Data available from all patients.

Table S7. Crude exploratory outcomes

Outcome	Restrictive fluid management	Usual care	Restrictive fluid management vs usual care (95% CI)^a	P value^b
Days alive and free of mechanical ventilation, median [IQR] ^c	13.0 [9.0-14.0]	11.5 [1.5-14.0]	1.5 (-0.5; 7.0)	0.111
Days alive and free of vasopressors, median [IQR] ^c	12.0 [10.0-14.0]	11.5 [7.0-13.0]	0.5 (0.0; 3.0)	0.062
Days alive and free of ICU treatment, median [IQR] ^c	8.0 [3.0-11.0]	2.5 [0.0-11.0]	5.5 (-1.0; 9.0)	0.195
Days alive and free of RRT at 90 days, median [IQR] ^d	90.0 [85.0-90.0]	90.0 [33.0-90.0]	0.0 (0.0; 17.0)	0.125
Dialysis dependence at 90-days, n (%)	0/46 (0.0)	1/49 (2.0)	0.34 (0.01; 8.55)	1.000
90-day mortality, n (%)	9/46 (19.6)	13/49 (26.5)	0.74 (0.33; 1.54)	0.425

^a difference in medians or risk ratio with 95% CIs.

^b P value derived from regression model without adjustment

^c truncated at 14 days or ICU discharge. Potential ICU readmissions not accounted. Data not available for 2 patients receiving restrictive fluid management and for 1 receiving usual care.

^d Data not available for 2 patients in both groups.

Table S8. Safety outcomes

Event	Restrictive fluid management		Usual care		P value
	events/days	rate per 100 days	events/days	rate per 100 days	
Ventricular tachycardia/fibrillation	1/227	0.4 (0.0; 2.5)	3/252	1.2 (0.2; 3.5)	0.389
New-onset atrial fibrillation	4/227	1.8 (0.5; 4.5)	9/252	3.6 (1.6; 6.8)	0.240
Acute myocardial infarction	0/227	0.0 (0.0; 1.6)	0/252	0.0 (0.0; 1.5)	1.000
Cerebral ischemia	0/227	0.0 (0.0; 1.6)	2/252	0.8 (0.1; 2.9)	1.000
Intestinal ischemia	0/227	0.0 (0.0; 1.6)	0/252	0.0 (0.0; 1.5)	1.000
Acute peripheral limb ischemia	0/227	0.0 (0.0; 1.6)	1/252	0.4 (0.0; 2.2)	1.000
Radiologically diagnosed pulmonary edema	1/227	0.4 (0.0; 2.5)	8/252	3.2 (1.4; 6.3)	0.063
Hypokalemia (K<3.5)	22/223	9.9 (6.2; 14.9)	23/244	9.4 (6.0; 14.1)	0.879
Hypomagnesemia (Mg<0.8)	39/159	24.5 (17.4; 33.5)	11/201	5.5 (2.7; 9.8)	<0.001
Alkalosis pH > 7.5	33/214	15.4 (10.6; 21.7)	34/234	14.5 (10.1; 20.3)	0.808
Other safety event	2/225	0.9 (0.1; 3.2)	1/252	0.4 (0.0; 2.2)	0.510
Events related to diuretics (only assessed on days when patient received diuretics)					
Loss of hearing	0/118	0.0 (0.0; 3.1)	0/123	0.0 (0.0; 3.0)	1.000
Severe disturbances in electrolytes (hypokalemia <3.0 mmol/L, ionized calcium <0.90 mmol/L, hyponatremia <125mmol/L)	0/118	0.0 (0.0; 3.1)	0/123	0.0 (0.0; 3.0)	1.000
Severe thrombocytopenia (<50 x 10 ⁹ /L)	7/117	6.0 (2.4; 12.3)	5/119	4.2 (1.4; 9.8)	0.546
Agranulocytosis	0/118	0.0 (0.0; 3.1)	0/123	0.0 (0.0; 3.0)	1.000
Allergic reactions	0/118	0.0 (0.0; 3.1)	0/123	0.0 (0.0; 3.0)	1.000
Events related to RRT (only from those receiving RRT on that day)					
RRT-associated hypotension	3/19	15.9 (3.3; 46.1)	5/46	10.9 (3.5; 25.4)	0.609
Severe hypophosphatemia (<0.5 mmol/L)	1/19	5.3 (0.1; 29.3)	0/46	0.0 (0.0; 8.0)	1.000
Severe hypokalemia (<3.0 mmol/L)	0/19	0.0 (0.0; 19.4)	0/46	0.0 (0.0; 8.0)	1.000
Severe hypocalcemia (Ionized calcium <0.90 mmol/L)	0/19	0.0 (0.0; 19.4)	4/46	8.7 (2.4; 22.3)	0.329
Allergic reaction to RRT	0/19	0.0 (0.0; 19.4)	0/46	0.0 (0.0; 8.0)	1.000
Arrhythmia during RRT	2/19	10.5 (1.3; 38.0)	4/46	8.7 (2.4; 22.3)	0.825

Seizure	0/19	0.0 (0.0; 19.4)	0/45	0.0 (0.0; 8.2)	1.000
Major bleeding	0/19	0.0 (0.0; 19.4)	0/46	0.0 (0.0; 8.0)	1.000
Complication related to central venous access	0/20	0.0 (0.0; 18.4)	2/45	4.4 (0.5; 16.1)	1.000

P value derived from Poisson regression model and exact Poisson 95% confidence intervals for observed rates.

RRT; renal replacement therapy

Table S9. Protocol violations

Criteria	Restrictive fluid management - No / total no (%)	Usual care - No / total no (%)
Violated inclusion criteria ^a	2/49 (4.1)	1/51 (2.0)
Violated exclusion criteria	0/49 (0.0)	0/51 (0.0)
Violated stratification variables ^b	7/49 (14.3)	5/51 (9.8)
Use of excess maintenance fluid in experimental arm ^c	9/49 (18.4)	0/51 (0.0)

^aThese patients did not meet the trial inclusion criterion for acute kidney injury due

^b One patient was stratified to have mild AKI instead of severe AKI which was discovered during monitoring. The rest of violations were due to not stratifying patients into having fluid overload, albeit the trial definition for it was fulfilled (missed low P/F ratio together with positive fluid balance).

^c defined as more than 20 mL/hr crystalloid with unmet daily balance target with no contraindications for iv/po nutrition

One patient in each group had 2 separate protocol violations.

Table S10. Adjusted outcomes in the per-protocol population

Outcome	Restrictive fluid management (n=23)	Usual care (n=37)	Restrictive fluid management vs usual care (95% CI) ^a	P value ^b
Cumulative fluid balance at 72 hrs from randomization, mean (SD) mL ^c	-1360 (1916)	-427 (3145)	-877 (-2328; 575)	0.231
Duration of AKI (days), median [IQR] ^d	2.0 (1.0-4.5)	3.0 (2.0-8.0)	-2.0 (-4.0; 1.0)	0.169
Number of patients receiving RRT, n (%)	3/23 (13.0)	11/37 (29.7)	0.36 (0.09; 1.01)	0.093
Cumulative fluid balance at 24 hrs from randomization, mean (SD) mL ^c	-578 (1005)	191 (1641)	-773 (-1544; -3)	0.049
Cumulative fluid balance at ICU discharge/day 7, mean (SD) mL ^c	-2593 (2415)	-1459 (3941)	-1002 (-2770; 766)	0.261
Cumulative dose of furosemide per day, median [IQR] mg ^e	11.4 (0.0-40.0)	11.7 (0.0-33.3)	5.3 (-12.6; 20.7)	0.718

AKI; acute kidney injury, RRT; renal replacement therapy

^a difference in adjusted (severity of AKI and presence of fluid overload) means/medians with 95% CIs.

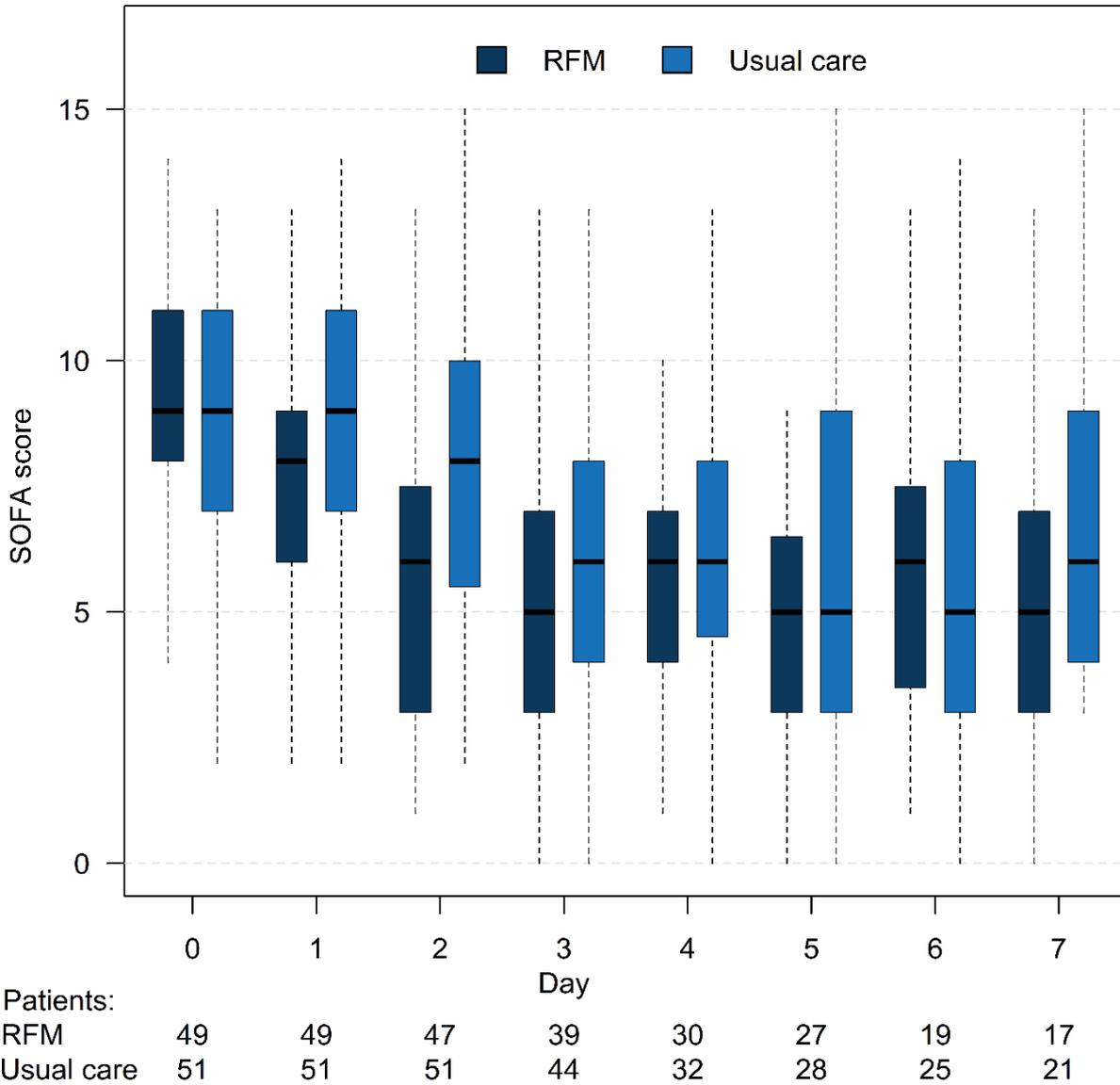
^b P value derived from regression model adjusted for stratification variables (severity of acute kidney injury and presence of fluid accumulation)

^c The last available value for cumulative fluid balance was analyzed for all patients even if ICU discharge or consent withdrawal occurred before endpoint was fulfilled

^d truncated at 7 days, ICU discharge, or consent withdrawal. Data available from all patients.

^e per oral furosemide dose divided by 2 to make it comparable to intravenous doses. Data available from all patients.

Figure S1. Daily SOFA scores in restrictive fluid management versus usual care arms

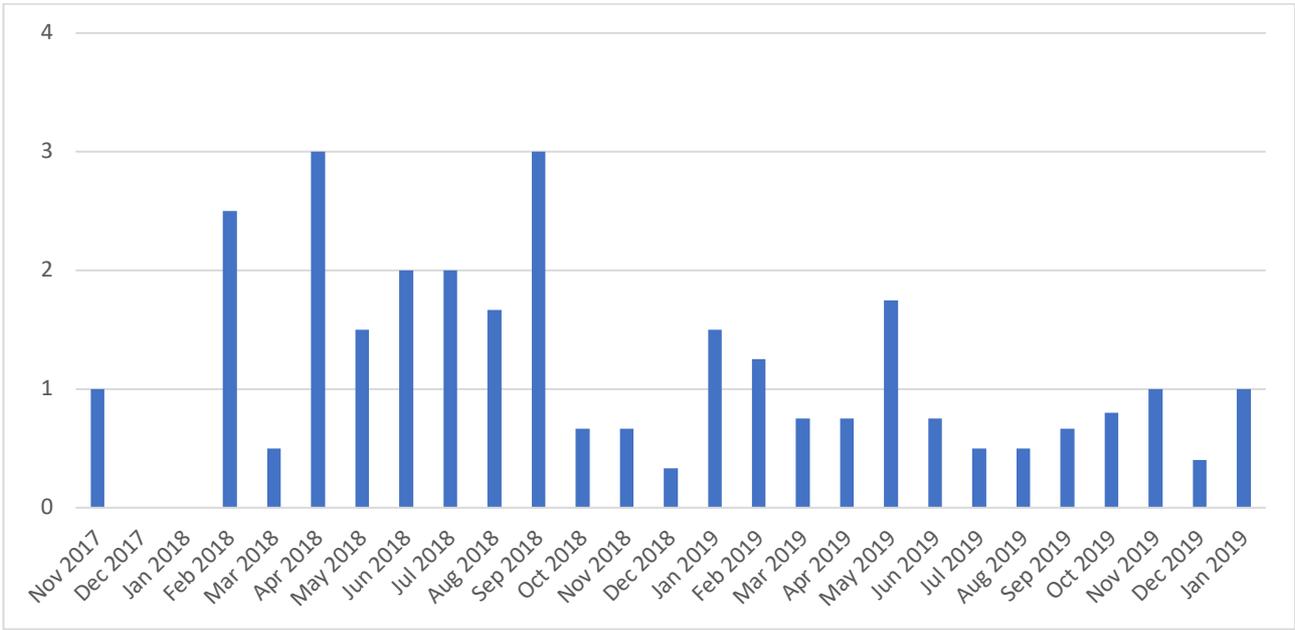


SOFA; Sequential Organ Failure Assessment

RFM; restrictive fluid management

Boxplots represent median with IQR and range in mL. Day 0 indicates baseline SOFA at randomization.

Figure S2. Number of patients recruited per active center per month



Centers stopped recruiting once their recruitment target had been met.