Supplementary Material from Statistical Analysis

This file contains the following material.

1. Line listing of “Other” reasons why a patient was not included despite being eligible (SCR1)
2. Line listing of “Other” reasons why patient was not eligible (SCR2)
3. Baseline summary statistics (SBL1) classified by sequence and period.
4. Summary statistics of *X-A* (SPO1) classified by sequence and period.
5. Line listing of IVH adverse events which met the seriousness criteria (SAF1)
6. Details of the calculations used to compute *X* and *A* for each method of RRT.

Supplemental Table SCR1

Line listing of "Other" reasons why a patient was not included despite being eligible

Sequence	Time Period	Reason
Sequence 1	Period 1	Unable to undertake the first 6hr data collection due to not starting CRRT until after 6pm. No-one trained to undertake duties required between 6pm & 6am
Sequence 1	Period 1	only gathered 1 hour of data as patient was taken off the filter quickly, parents were not present to be able to get consent and they were discharged to oxford 25/04/2019
Sequence 1	Period 2	Patient started PD at 00:10 and then it was stopped at 03:00 as he went onto ECLS no further CRRT was required so parents weren't approached
Sequence 1	Period 3	entry into the study would mean additional access that is not clinically indicated
Sequence 1	Period 4	once nidus circuit ready to attach to patient, patient started to pass urine
Sequence 1	Period 4	NIDUS discontinued less than 30 minutes from commencement. No research tests performed. Patient passed away later that evening. Not appropriate and no research need for consent
Sequence 3	Period 4	place on ECMO- hemofilter used. patient quickly discharged next day to other centre
Sequence 3	Period 3	PD failure after 2 cycles, left on free drainage. Consultant descision not to continue PD
Sequence 3	Period 3	Consultant descision not to approach parents, already enrolled in one interventional study. Parents already very upset upset by bedside so elected not to approach for study.
Sequence 3	Period 3	Patient moribund on arrival, rapid acute deterioration. RIP.
Sequence 3	Period 3	Parents with profound learning needs, lack of capacity to recieve consent.
Sequence 3	Period 4	Infrequent parental visitation with turkish being first spoken language. Difficulty engaging with family by clinical team with issues surrounding care updates and visitation.
Sequence 2	Period 1	Patient deemed by bedside staff to be too unstable to take part
Sequence 1	Period 2	Patient on ECMO
Sequence 1	Period 2	Previously recruited to IKID
Sequence 1	Period 3	Patient on ECMO

Supplemental Table SCR2

Line listing of "Other" reasons why patient was not eligible

Sequence	Time Period	Reason
Sequence 1	Period 1	Pt not stable enough to go onto aquarius (1.2kg) Would have used NIDUS if available
Sequence 1	Period 1	Pt not stable enough for Aquaius (1kg), Consultant would have used NIDUS if available
Sequence 1	Period 1	Pt not stable enough for the Aquarius, consultant said would have used NIDUS if available
Sequence 3	Period 1	Patient not expected to survive
Sequence 3	Period 3	Patient not expected to survive
Sequence 3	Period 1	Parents unable to speak english, extensive interpretive services required. Therefore unable to give information sheet or obtain reliable informed consent.
Sequence 3	Period 1	PI descision not to recruit as patient on ECMO with difficult circuit flows and problematic CVVH access/return as a result.
Sequence 3	Period 4	Avoided need for RRT
Sequence 3	Period 4	Avoided need for RRT
Sequence 3	Period 4	Second screen of patient. Patient access extremely difficult, unable to get venous access to site cannula for nidus, patient pro-coagulant state with multiple large thromboses
Sequence 2	Period 2	Unable to complete 6h of PD - positive cycles - stopped. Second try was abandoned since U/O improved with furosemide infusion at higher dose
Sequence 1	Period 1	Discussed with CI, patient not eligible as primary indication was high lactate not fluid overload or renal failure - therefore did not meet entry criteria.
Sequence 1	Period 2	Patient only had a single lumen central line with inotropic support running through.

Supplementary Section SBL1

Additional descriptive statistics of age at screening in days (Table S1), weight at RRT initiation in kilograms (Table S2), and PIM-3 scores (Table S3) are presented here. Descriptive statistics are stratified by sequence and period. Tables are coloured according to whether a sequence was in the intervention or control phase at a particular period.

Table S1: Age at screening (days) by period and sequence

		Period 1	**Period 2**	**Period 3**	**Period 4**
Sequence 1	Mean (SD)	58.6 (101.5)	23.0 (44.6)	195.0 (186.2)	73.3 (122.5)
	Median (IQR)	13.0 (9.0, 67.0)	7.0 (5.0, 10.0)	165.0 (60.0, 330.0)	16.5 (10.5, 83.5)
	Range	9.0, 284.0	2.0, 124.0	7.0, 443.0	3.0, 362.0
	Available n	7	7	4	8
Sequence 2	Mean (SD)	47.6 (74.4)	77.5 (93.3)	62.5 (107.0)	245.7 (197.3)
	Median (IQR)	11.0 (7.0, 81.0)	34.5 (11.0, 147.0)	9.0 (6.0, 77.0)	352.0 (18.0, 367.0)
	Range	6.0, 205.0	3.0, 235.0	1.0, 273.0	18.0, 367.0
	Available n	7	6	6	3
Sequence 3	Mean (SD)	6.6 (4.8)	42.6 (108.6)	88.2 (136.9)	81.3 (144.4)
	Median (IQR)	5.5 (2.0, 12.0)	8.0 (5.0, 16.0)	19.0 (9.0, 151.0)	9.0 (7.0, 146.0)
	Range	1.0, 13.0	1.0, 466.0	6.0, 477.0	1.0, 387.0
	Available n	10	19	13	7

Values are in days. Shaded area indicates intervention arm.

Table S2: Weight (kg) by period and sequence

		Period 1	**Period 2**	**Period 3**	**Period 4**
Sequence 1	Mean (SD)	4.1 (1.8)	3.6 (1.2)	6.0 (2.0)	3.9 (2.0)
	Median (IQR)	3.3 (2.7, 6.0)	3.7 (3.0, 4.6)	6.3 (4.3, 7.6)	3.8 (2.8, 5.3)
	Range	2.6, 7.2	1.8, 5.4	3.5, 7.8	1.0, 7.0
	Available n	7	7	4	8
Sequence 2	Mean (SD)	2.9 (0.9)	4.4 (2.2)	4.1 (1.3)	5.3 (2.7)
	Median (IQR)	2.7 (2.3, 3.0)	4.0 (2.8, 6.6)	3.5 (3.2, 5.0)	6.7 (2.2, 7.0)
	Range	2.0, 4.8	1.8, 7.3	3.0, 6.2	2.2, 7.0
	Available n	7	6	6	3
Sequence 3	Mean (SD)	3.0 (0.4)	3.6 (1.1)	4.5 (2.2)	4.3 (1.5)
	Median (IQR)	3.0 (2.7, 3.2)	3.2 (2.9, 3.9)	3.6 (3.0, 5.1)	3.8 (3.1, 5.6)
	Range	2.6, 3.8	2.8, 7.6	2.4, 10.1	3.0, 7.0
	Available n	10	19	13	7

Values are in kilograms. Shaded area indicates intervention arm.

Table S3: PIM3 by period and sequence

		Period 1	**Period 2**	**Period 3**	**Period 4**
Sequence 1	Mean (SD)	0.135 (0.151)	0.104 (0.121)	0.041 (0.052)	0.074 (0.091)
	Median (IQR)	0.061 (0.015, 0.306)	0.022 (0.012, 0.213)	0.021 (0.010, 0.072)	0.041 (0.013, 0.101)
	Range	0.011, 0.376	0.009, 0.311	0.006, 0.117	0.007, 0.273
	Available n	7	7	4	8
Sequence 2	Mean (SD)	0.029 (0.025)	0.063 (0.075)	0.230 (0.369)	0.073 (0.084)
	Median (IQR)	0.016 (0.012, 0.040)	0.024 (0.017, 0.100)	0.090 (0.027, 0.186)	0.033 (0.017, 0.170)
	Range	0.011, 0.079	0.013, 0.201	0.016, 0.972	0.017, 0.170
	Available n	7	6	6	3
Sequence 3	Mean (SD)	0.107 (0.136)	0.067 (0.092)	0.034 (0.053)	0.033 (0.030)
	Median (IQR)	0.047 (0.014, 0.172)	0.025 (0.012, 0.065)	0.015 (0.010, 0.033)	0.016 (0.014, 0.051)
	Range	0.011, 0.445	0.006, 0.287	0.005, 0.204	0.011, 0.093
	Available n	10	19	13	7

Shaded area indicates intervention arm. PIM3, Paediatric Index of Mortality 3.

Supplementary Material SPO1

Additional descriptive statistics of *X-A* are presented here. Descriptive statistics are stratified by sequence and period. Tables are coloured according to whether a sequence was in the intervention or control phase at a particular period.

Table S1: Summary of first computable precision measurement *X-A* by sequence and period

		Period 1	**Period 2**	**Period 3**	**Period 4**
Sequence 1	Mean (SD)	-5.59 (5.17)	-0.75 (2.37)	-0.92 (0.67)	-1.89 (1.51)
	Median (IQR)	-5.76 (-9.36, 0.05)	-0.26 (-3.33, 1.33)	-0.92 (-1.40, -0.44)	-2.48 (-2.58, -1.48)
	Range	-14.24, 0.50	-3.33, 1.33	-1.40, -0.44	-3.30, 0.96
	n	7	3	2	6
Sequence 2	Mean (SD)	-9.89 (19.25)	19.92 (36.00)	-0.19	-0.78 (1.82)
	Median (IQR)	-2.33 (-20.33, 2.33)	12.21 (-2.57, 27.83)	-0.19	-0.02 (-2.85, 0.54)
	Range	-49.17, 6.33	-15.50, 85.32		-2.85, 0.54
	n	7	6	1	3
Sequence 3	Mean (SD)	-5.70 (8.90)	4.83 (13.03)	-10.44 (17.01)	1.66 (4.99)
	Median (IQR)	-5.92 (-9.53, -1.00)	4.67 (-3.67, 11.67)	-5.67 (-25.17, 4.33)	-0.14 (-0.65, 1.05)
	Range	-20.12, 9.44	-15.65, 32.15	-40.62, 12.83	-2.28, 10.32
	n	10	19	13	5

Data are mean (SD), median (IQR) and range. Non-shaded area indicates control arm. Shaded area indicates intervention arm. Numbers exclude participants who were the first to be recruited at transition to NIDUS at a site and those whose dialysis collection period lasted less than an hour.

Supplemental Table SAF1

Line listing of IVH adverse events which met the seriousness criteria

Index	Device	Days from RRT initiation to AE start	Days from RRT initiation to AE resolution	Adverse event	Description	Causality	Severity	Action(s) taken	Outcome
1	NIDUS	2	3	Intraventricular haemorrhage	Minor grade 1 intraventricular haemorrhages extended to severe and life-threatening intracerebral haemorrhages whilst being treated with NIDUS Clinical opinion was that this adverse event/ complication was related to the patient's sepsis and instability rather than related to the heparinisation required for the NIDUS. Patient passed away.	Unlikely	Severe	Treatment discontinued	Resolved
2	NIDUS	4		Intraventricular haemorrhage neonatal	Cranial USS documented to have altered morphology on 21/3 On 22/3 Cranial USS suspect the appearances reflect satble IVH with right lateral ventricle. Repeat Cranial ultrasound scans repeated to ensure bleeds hadn't enlarged	Possible	Moderate	None	Ongoing

Participant with index 1 subsequently passed away but this was deemed unrelated to NIDUS.

Calculation of the variables *X* and *A* used in the definition of the primary outcome variable.

The ultrafiltration measurements are computed from data collected at the bedside during RRT. The calculations used to obtain these quantities vary depending on the form of RRT being undertaken. The following pages present these calculations.

UF in PD

Using entries from the attached completed form

UF target achieved = (V2 – V1) / (D2&T2h – D1&T1h)

… where the term (D2&T2h – D1&T1h) means the interval in hours between the first and second sets of date and time entries

… and the units will be in ml/h

UF target set = A if the UF is not changed during the study period, in which case …

UF precision = ((V2 – V1) / (D2&T2h – D1&T1h)) – A

… where the units will be in ml/h

If the UF rate is changed during the study period

UF target set will be calculated from times and dates D1T1 and D2T2, plus the blue values, thus …

= (((XD1&XT1h – D1&T1h) x A) + ((D2&T2h – XD1&XT1h) x XA)) / (D2&T2h – D1&T1h)

… so this term will replace A in the final UF precision formula.

Chemical clearances in PD

The calculation of Chemical Clearance (CC) is …

CC = Q x F / P ml/min

Where Q = Quantity of waste dialysate exiting the dialysis system per minute

And F and P = Fluid and Plasma Concentration of that chemical per ml in the same units.

Thus, the Q equals the dialysate effluent volume per minute, which includes the ultrafiltrate that has joined the dialysis and replacement fluids. For PD, this is simply the per minute measured effluent rate.

So for creatinine, CC = (V2 / ((D2&T2h – D1&T1h) / 60)) x Fc / Pc

It should be expressed per kg body weight, so divide the absolute clearance by W to give the result as **ml/min per kg**.

UF in CVVH (Prismaflex & Aquarius)

** Using entries from the appended completed UF form **

UF target achieved = Increased weight of all the dialysis bags / (D2&T2h – D1&T1h)

… where the increased weight of all the dialysis bags is the increase in the weight of the bags over the study period in grams (which we are considering to be equivalent to volume in ml, so calculation assumes it is in ml), and equals (D5 + D6 +D7 + D8) – (D1 + D2 +D3 + D4)

… where the term (D2&T2h – D1&T1h) means the interval in hours between the first and second sets of date and time entries, and G is in grams, but we are assuming a specific gravity of 1.00 so

… the units will be in ml/h

UF target set For the CVVH machines, the expected increase in total bag weights will be the hourly UF target set, which is value A. (Note that we are collecting the heparin volume for the CVVH machines by default – we do this for the Nidus to adjust the expected bag weight change, but don't need to here. However, it makes it seem more consistent for the operators.)

Thus **UF precision** = (((D5 + D6 +D7 + D8) – (D1 + D2 +D3 + D4)) / (D2&T2h – D1&T1h)) – A

… where the units will be in ml/h

If the UF rate is changed during the study period …

UF target set will be calculated from times and dates D1T1 and D2T2, plus the blue values, thus …

= (((XD1&XT1h – D1&T1h) x A) + ((D2&T2h – XD1&XT1h) x XA)) / (D2&T2h – D1&T1h)

… so this term will replace A in the final UF precision formula.

Chemical clearances in CVVH (Prisma & Aquarius)

** Using entries from the appended completed UF form **

The calculation of Chemical Clearance (CC) is …

CC = Q x F / P ml/min

Where Q = Quantity of waste dialysate exiting the dialysis system per minute

And F and P = Fluid and Plasma Concentration of that chemical per ml in the same units.

Thus, the Q equals the dialysate effluent volume per minute, plus the ultrafiltrate that has joined it. The quantity of dialysate effluent per minute = the quantity pumped in per minute, so can be deduced from the dialysis and replacement fluid delivery settings on the machine,

So for creatinine, CC = ((N1 + N2) / 60) x Fc / Pc

It should be expressed per kg body weight, so divide the absolute clearance by W to give the result as **ml/min per kg**.

NOTE that the only reason for recording the times and dates D3T3 and D4T4 is to be able to correctly identify which blood test the study corresponds with, and that this was taken within an hour of the study being done.

UF in Nidus

** Using entries from the appended completed UF form **

UF target achieved = G / (D2&T2h – D1&T1h)

… where G is the increase in the weight of the bags over the study period in grams (which we are considering to be equivalent to volume in ml, so calculation assumes it is in ml), and

… where the term (D2&T2h – D1&T1h) means the interval in hours between the first and second sets of date and time entries, and G is in grams, but we are assuming a specific gravity of 1.00 so

… the units will be in ml/h

For the CVVH machines, the expected value for G will be the hourly UF target set, which is value A. This is because the heparin-in-saline syringes which these devices infuse into the circuit effectively enters the baby's blood volume, like any other IV fluid, and does not interfere with the quantity that the machine will UF. However, in the Nidus, the saline component of that infusion enters the circuit's closed system during dialysis and is directly squeezed across the dialysis membrane to enter the waste bags, and does not add to the baby's fluid volume. This means that the predicted weight of the bags for the Nidus will equal the hourly UF target A ***plus*** the hourly quantity of heparin infused. The hourly volume of heparin infused during the study period = (H2 – H1) / (D2&T2h – D1&T1h).

Taking this into account, the true hourly **UF target set** = A + ((H2 – H1) / (D2&T2h – D1&T1h))

Thus **UF precision** = (G / (D2&T2h – D1&T1h)) – (A + ((H2 – H1) / (D2&T2h – D1&T1h)))

… where the units will be in ml/h

If the UF rate is changed during the study period …

UF target set will be calculated from times and dates D1T1 and D2T2, plus the blue values, thus …

= (((XD1&XT1h – D1&T1h) x A) + ((D2&T2h – XD1&XT1h) x XA)) / (D2&T2h – D1&T1h)

… so this term will replace A in the final UF precision formula.

Chemical clearances in the Nidus

** Using entries from the appended completed UF form **

The calculation of Chemical Clearance (CC) is …

CC = Q x F / P ml/min

Where Q = Quantity of waste dialysate exiting the dialysis system per minute

And F and P = Fluid and Plasma Concentration of that chemical per ml in the same units.

Thus, the Q equals the dialysate effluent volume per minute, plus the ultrafiltrate that has joined it. The quantity of dialysate effluent per minute = the quantity pumped in per minute, so can be deduced from the dialysis and replacement fluid delivery settings on the machine,

So for creatinine, CC = ((N1 + N2) / 60) x Fc / Pc

It should be expressed per kg body weight, so divide the absolute clearance by W to give the result as **ml/min per kg**.

NOTE that the only reason for recording the times and dates D3T3 and D4T4 is to be able to correctly identify which blood test the study corresponds with, and that this was taken within an hour of the study being done.