UNIVERSITY OF BIRMINGHAM

ECUSTEC – Statistical Considerations

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Outline

- Primary outcome
- Secondary outcomes
- Sample size
- Internal pilot study
- Data analysis

Primary Outcome

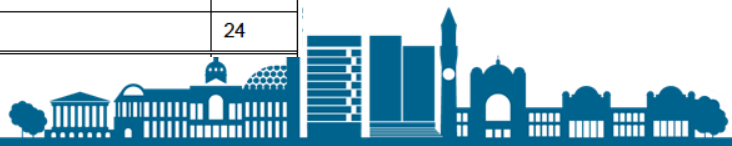
- Grant application – no obvious primary outcome measure that captured all the information
- Developed multi-domain Clinical Severity Score specifically for the study

Primary Outcome – Clinical Severity Score

- Clinical Severity Score at day 60
  - Renal
  - CNS
  - Pancreas
  - Gastrointestinal
  - Cardiac
- Single score is assigned at day 60 to reflect the cumulative morbidity up to that point

Primary Outcome – Clinical Severity Score (Renal)

Renal	Lowest eGFR >50	1
	Lowest eGFR 26-50, no oligoanuria*	2
	Lowest eGFR ≤ 25, no oligoanuria*	3
	Oligoanuria* but no dialysis (or renal replacement therapy, RRT) required	4
	Dialysis/RRT <48 hours	5
	Dialysis/RRT 2 days	6
	Dialysis/RRT 3 days	7
	Dialysis/RRT 4 days	8
	Dialysis/RRT 5 days	9
	Dialysis/RRT 6 days	10
	Dialysis/RRT 7 days	11
	Dialysis/RRT 8 days	12
	Dialysis/RRT 9 days	13
	Dialysis/RRT 10 days	14
	Dialysis/RRT 11 days	15
	Dialysis/RRT 12 to 13 days	16
	Dialysis/RRT 14 to 17 days	17
	Dialysis/RRT 18 to 20 days	18
	Dialysis/RRT 21 to 27 days	19
	Dialysis/RRT 28 to 34 days	20
	Dialysis/RRT 35 to 41 days	21
	Dialysis/RRT 42 to 48 days	22
	Dialysis/RRT 49 to 55 days	23
	Dialysis/RRT >55 days	24



Primary Outcome – Clinical Severity Score

CNS	No obvious CNS involvement	0
	Altered consciousness (Agitation, irritability, hallucinations, confusion, excessive drowsiness)	2
	Single seizure	4
	Two or more seizures 24 hrs apart**	6
	Transient focal neurological defect (>24 hrs*** but <1 week)	7
	Persistent focal neurological defect (present at day 60 and persistent for more than 1 week)	10
	Persistent global (≥ 2 brain functions - vision/hearing/cognitive/motor/sensory/memory) neurological defect at day 60	15
Pancreas	No clinical or biochemical evidence pancreatitis	0
	Raised amylase and/or lipase† without clinical symptoms/signs	2
	Hyperglycaemia without insulin requirement	6
	Pancreatitis with sequelae (laparotomy, parenteral nutrition††, insulin required)	8
	Chronic sequelae of pancreatitis at day 60 (parenteral nutrition††, insulin, other)	10

Primary Outcome – Clinical Severity Score

Gastro-intestinal	No abdominal surgery required (except related to peritoneal dialysis catheter)	0
	Laparoscopy/laparotomy required for abdominal symptoms	5
	Intestinal perforation AND/OR bowel resection required	8
	Stoma formation	10
Cardiac	No cardiac involvement (normal CVS examination - except hypertension/volume overload)	0
	Cardiac failure confirmed by ECHO††† (impaired systolic ventricular# function or chamber enlargement## or valve regurgitation###)	4
	Cardiac failure confirmed by ECHO with dilated cardiomyopathy	6
	Myocardial infarction (on standard ECG +/-° troponin +/- ECHO evidence)####	10

Score ranges from 1 to 69 with higher scores indicating greater disease severity

Primary Outcome – Clinical Severity Score

Domain	Score
Renal: Dialysis/RRT for 10 days	14
CNS: Single seizure	4
Pancreas: No clinical or biochemical evidence pancreatitis	0
Gastro-intestinal: Laparoscopy/laparotomy required for abdominal symptoms	5
Cardiac: No cardiac involvement	0
Clinical Severity Score at day 60	**23**

Single score is assigned at day 60 to reflect the cumulative morbidity up to that point

Secondary Outcomes

- Overall survival
- Duration of renal replacement therapy (days)
- Duration of thrombocytopenia
  - number of consecutive days until platelet count >150x10^9/l
- Duration of haemolysis
  - number of days until lactate dehydrogenase (LDH) within local centre reference range
- Number of packed red blood cell transfusions required and volume (ml/kg)

Secondary Outcomes

- Duration markers of inflammation present
  - number of days until neutrophil cell count and C-reactive protein are in normal range for that centre
- CKD at 52 weeks: a composite endpoint where the presence of any of the following at 1 year constitutes CKD:
  - hypertension [average of 3 readings by manual method using centile charts for age/sex/height]
  - albuminuria [urine albumin-creatinine ratio >2.5mg/mmol on early morning urine]
  - eGFR<90ml/min/1.73m^2 at 52 weeks

Secondary Outcomes

- eGFR at 52 weeks (measured using a centralised cystatin C assay)

- Persistent neurological defect at day 60
  - measured by structured expert assessment to include CNS examination, vision, hearing and neuropsychological assessment

Sample Size – Clinical Severity Score

- Sample size is based on retrospective data collected on 94 patients with STEC HUS presenting to five trial centres over several years who met the trial inclusion criteria
  - mean clinical severity score of 13.16
  - standard deviation=9.66; range: 2 to 45

Sample Size – Clinical Severity Score

- Sample size is based on detecting a 5 point difference between treatment groups in the Clinical Severity Score at day 60
- This was considered a meaningful clinical benefit, a reduction of 5 points would equate to:
  - the difference between 9 days and 4 days on dialysis
  - OR avoiding a surgical laparotomy to investigate an acutely distended abdomen
  - OR avoiding development of cardiac failure

Sample Size – 5 point difference

Renal	Lowest eGFR >50	1
	Lowest eGFR 26-50, no oligoanuria*	2
	Lowest eGFR ≤ 25, no oligoanuria*	3
	Oligoanuria* but no dialysis (or renal replacement therapy, RRT) required	4
	Dialysis/RRT <48 hours	5
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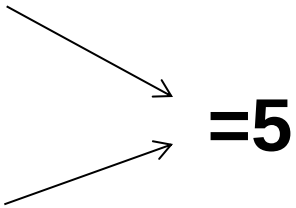
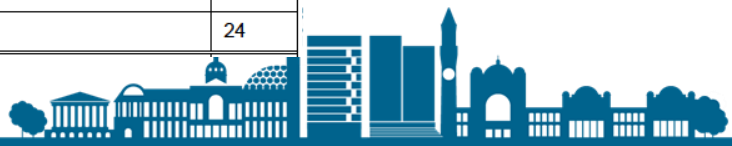




Sample Size – Clinical Severity Score

- To detect a difference of 5 points in the Clinical Severity Score between groups using a 2-sided t-test
- With 80% power and a type I error rate of 5% (α=0.05), a total of 60 participants per group need to be randomised
- Assuming and adjusting for a 10% loss to follow-up drop-out rate, 134 participants (67 per group) will need to be recruited

Internal Pilot Study

- Trial contains internal pilot phase
- Originally 18 months duration
  - 12 months recruitment, 6 months follow-up
- Extended to allow trial to recruit for whole 2018 STEC-HUS season
- Purpose of internal pilot is to determine whether substantive trial will continue

Internal Pilot Study – Stopping Rules

- 26 participants are recruited
- 20 of the 26 recruited participants (i.e. 10 of 13 participants in each arm) received the planned two doses of trial treatments as per the trial protocol
  - to assess logistics since some participants may be discharged prior to day 8, so will need to return to the renal unit to receive the second study dose
  - to assess tolerability as participants may be too unwell or may not have tolerated first dose, so do not receive the second dose

Internal Pilot Study – Stopping Rules

- At least 22 of the 26 recruited participants have completed 26 weeks follow up
- Independent Data Monitoring and Ethics Committee (DMEC) have not identified any tolerability or safety concerns (e.g. increase in meningococcal infection) in this patient population

Need to meet these criteria to justify continuation of the trial

Internal Pilot Study – EME requirement

- DMEC will also review the Clinical Severity Score at day 60
- DMEC will judge based on the interim data, whether there is sufficient evidence to support stopping the trial early as evidence of efficacy is proven or will not be proven

Internal Pilot Study

- Identify any logistical issues or barriers to recruitment, which can be addressed, and the trial protocol revised if needed
- Assess whether centres comply with their agreement to avoid giving plasma exchange in trial participants
- Review the sample size assumptions, whilst accepting that the numbers in the internal pilot are small

Data Analysis

- The primary comparison groups will be composed of those randomised to Ecustec versus those randomised to placebo
- All analyses will be based on the intention to treat principle
  - i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol violation
  - An ITT analysis gives us the ‘real life’ effect of the treatment regimen

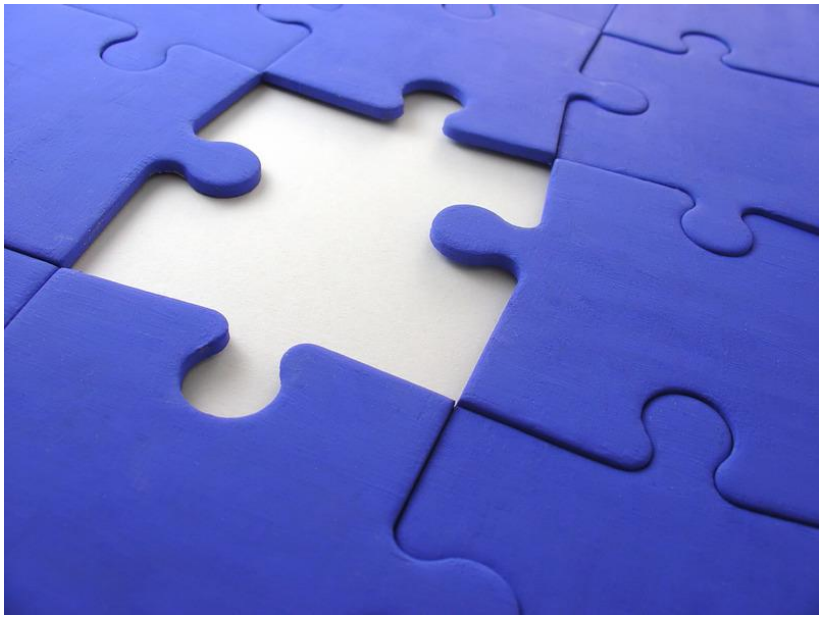
Data Analysis – Clinical Severity Score

Ecustec	Placebo	Treatment difference
Mean (standard deviation)	Mean (standard deviation)	Adjusted mean difference (95% confidence interval)

Adjusted mean difference estimated from linear regression model with the minimisation variables (centre, pRIFLE category and volume of saline received in 48h prior to randomisation) included as covariates in the model

Statistician's Plea

- Complete data for the data items that feed into the Clinical Severity Score is essential for the calculation of the Clinical Severity Score



Any Questions