The ECUSTEC Trial

Overview of protocol

THE great north CHILDREN'S HOSPITAL

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

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The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

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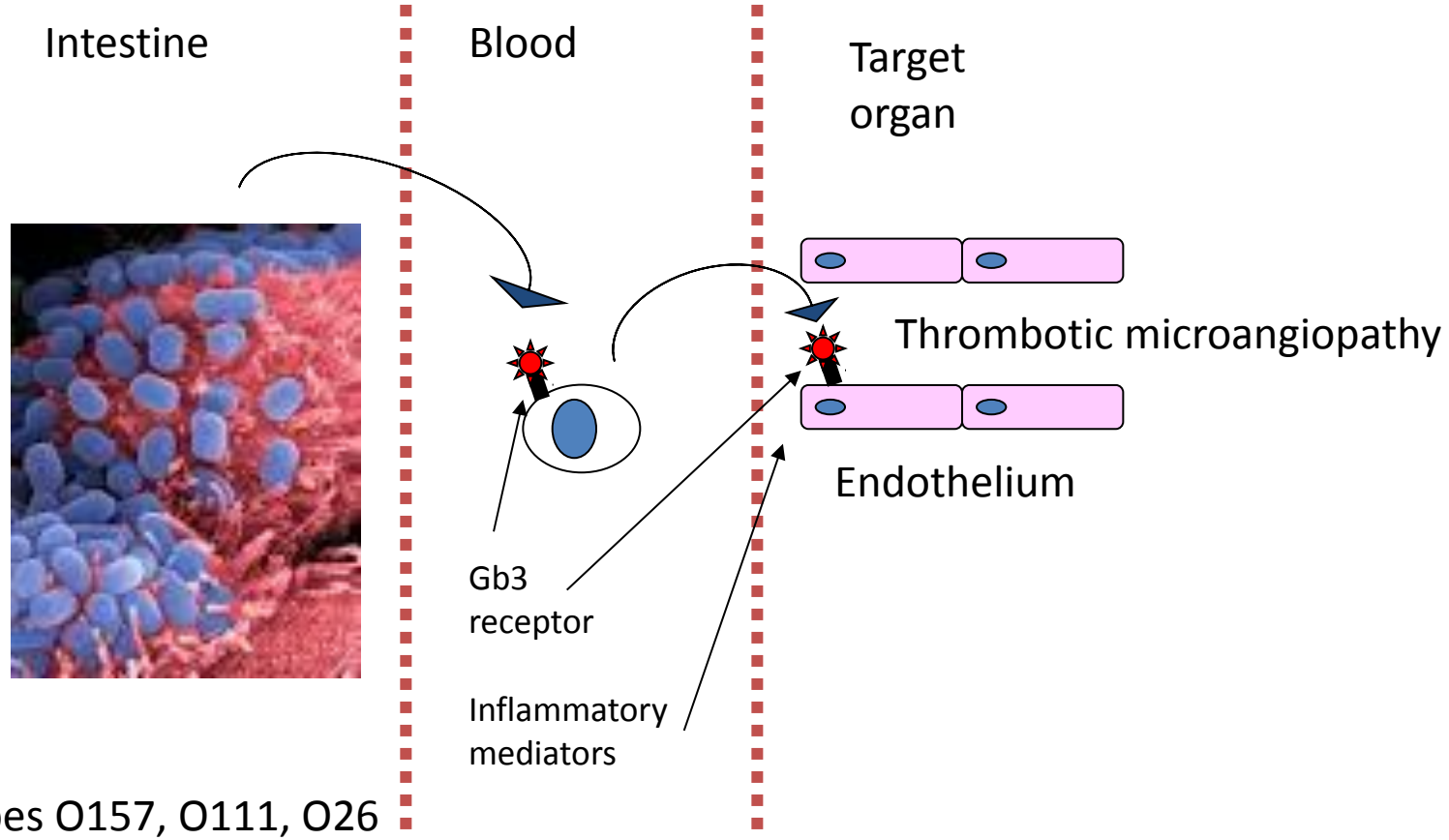
The ECUSTEC Trial

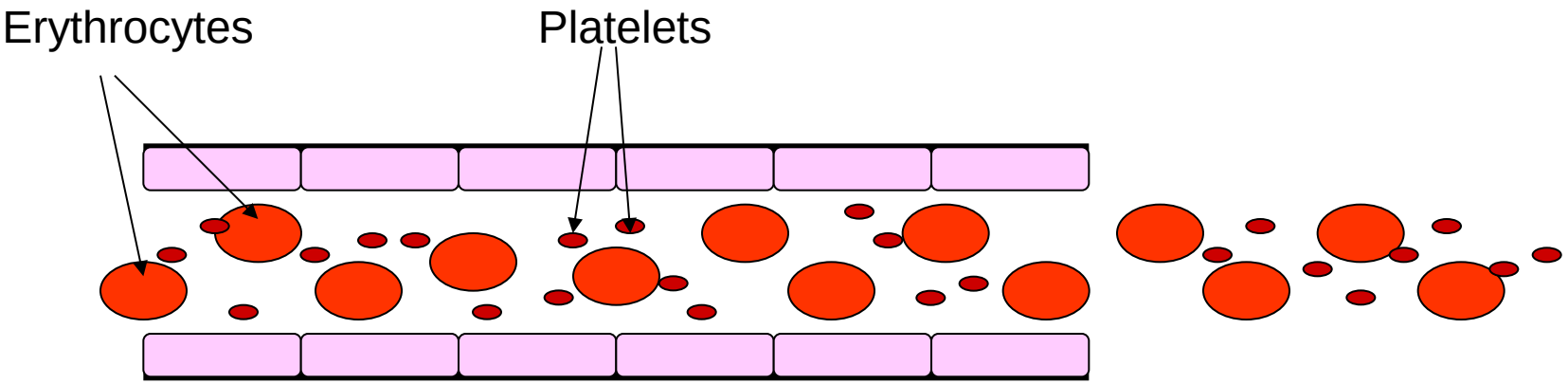
Eculizumab in Shiga-Toxin producing E. Coli Haemolytic Uraemic Syndrome (ECUSTEC): A Randomised, Double-Blind, Placebo-Controlled Trial

- Background and rationale
- Eligibility
- Screening and randomisation
- IMP administration, antibiotics and meningococcal vaccinations
- Assessment visits

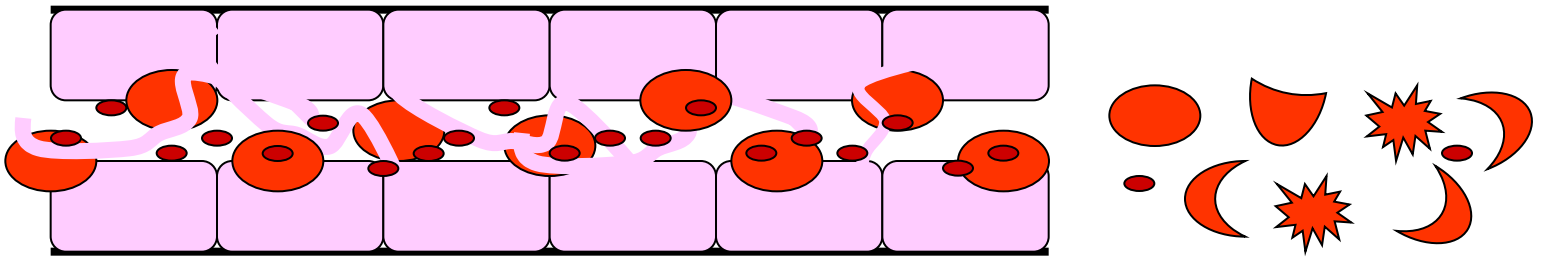
STEC HUS



- E coli Serotypes O157, O111, O26
- Prodrome of bloody diarrhoea
- Production of Shiga toxin essential



Normal



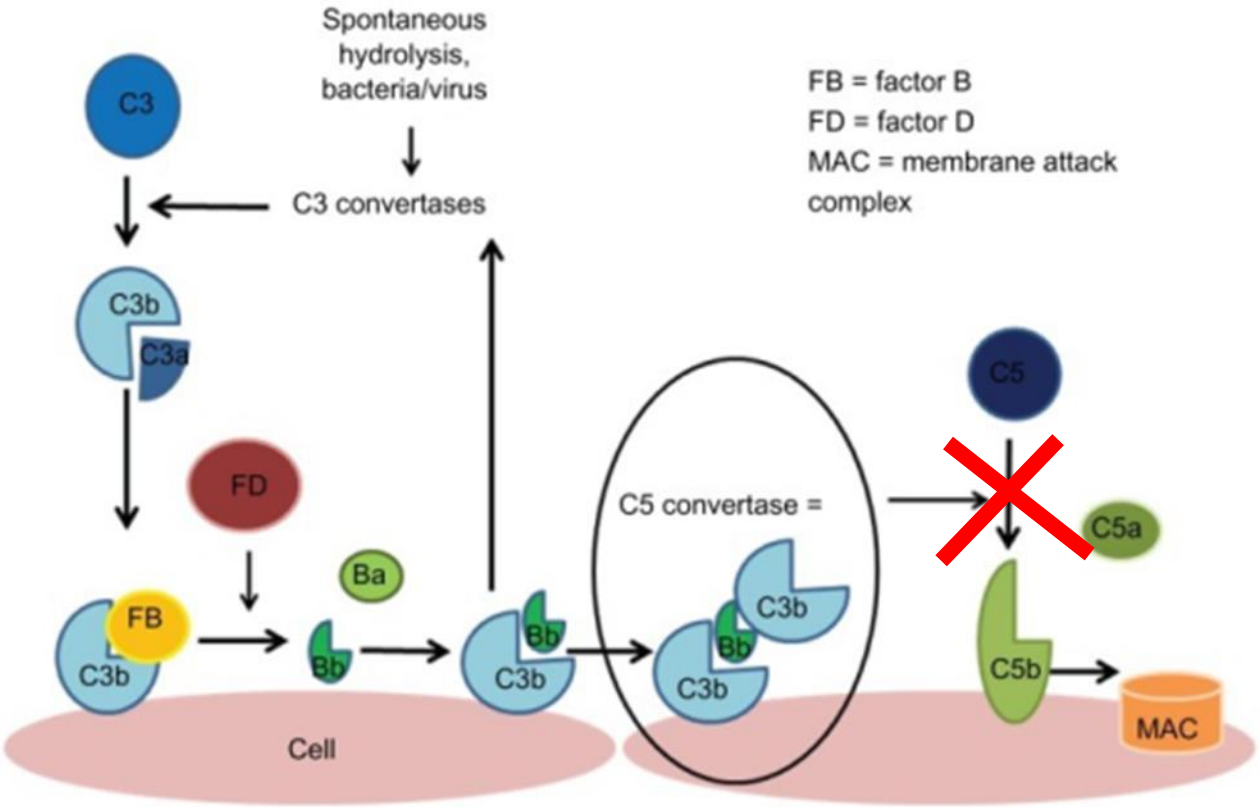
Thrombotic Microangiopathy

- Microangiopathic haemolytic anaemia
- Acute kidney injury
- Thrombocytopenia

Background and rationale

- 100-120 paediatric cases per year in UK
- 50% require renal replacement therapy (mean 10 days)
- 1-3% acute mortality
- Extra renal complications
  - 20-25% central nervous system
  - Severe colitis
  - Pancreatitis
- Outcome
  - 12% End stage renal disease or death
  - 25% Chronic kidney disease

Eculizumab blocks the complement system



Background and rationale

Eculizumab in Severe Shiga-Toxin–Associated HUS

TO THE EDITOR: The hemolytic–uremic syndrome (HUS), a thrombotic microangiopathy, most commonly occurs secondary to infection with Shiga-toxin–producing *Escherichia coli* (STEC-HUS), although rare, atypical forms are associated with abnormalities in complement-regulating proteins. The inhibition of terminal complement complex formation by the monoclonal C5 antibody eculizumab has recently been reported as a treatment for atypical HUS.[1]

We report on three 3-year-old patients with severe STEC-HUS that required hemodialysis. In Patient 1, plasma exchanges were performed because of low C3 and elevated C3d serum concentrations, which suggested complement activation. Plasma exchange was also performed in Patient 2 because of severe central nervous system involvement, a rare complication that often leads to death or permanent neurologic damage.[2] Progressive involvement of the central nervous system developed in both patients despite 5 consecutive days of plasma exchange.

Given the devastating prognosis, we administered eculizumab to these two patients, as well as to a third patient with a similar disease course, at 7-day intervals, twice in Patients 1 and 3 and four times in Patient 2. The neurologic status in all three patients improved dramatically within 24 hours after the first eculizumab infusion. let counts normalized, and lactate dehydrogenase levels decreased within 5 days in all patients (Fig. 1, and the Supplementary Appendix, available with the full text of this letter at NEJM.org).

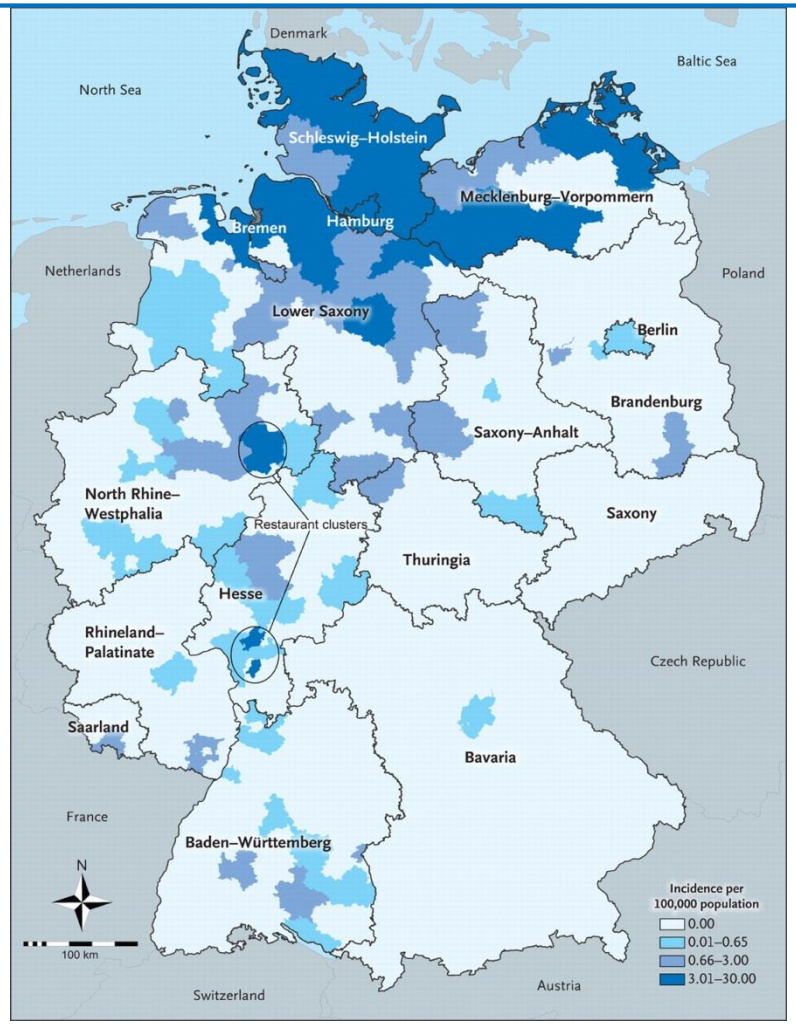
Dialysis was discontinued after 3 days in Patient 1, after 16 days in Patient 2, and after 13 days in Patient 3, and the patients were discharged with apparently normal neurologic status 9, 35, and 20 days, respectively, after the administration of the first dose of eculizumab. Renal function fully recovered, with mild residual proteinuria and hypertension in Patients 1 and 3. All patients have remained in full remission for the past 6 months. Screening for mutations in the genes encoding complement regulatory proteins (*CFH*, *CFI*, *MCP*, *C3*, *CFB*, and *THBD*) and testing for anti-CFH antibodies were negative in all patients.

In the cases reported here, spontaneous recovery seemed unlikely, given the rapidly progressive course of the disease. The rapid clinical response to eculizumab in all three children supports the concept that Shiga toxin may activate complement directly,[3] providing a rationale for therapeutic complement blockade in STEC-HUS with severe complications. Complement hyperactivation was recently demonstrated in STEC-HUS,[4] and a mutation in the complement-regulating gene *MCP* was reported in a fatal case of STEC-HUS.[5] The dramatic resolution of symptoms after

Lapeyraque
NEJM May 2011

German outbreak May-July 2011

- 3816 STEC cases
- 845 (22%) developed HUS
- 54 deaths
- 88% HUS cases were adults
- E coli O104:H4
- Rapidly convened industry sponsored trial of eculizumab



Frank NEJM 2011; Wadl Euro Surveill. 2011

Background and rationale

- The use of eculizumab to treat severe STEC HUS is increasing internationally
  - No evidence of efficacy or safety in children or adults
  - Huge expense to NHS and other health services
- No published prospective, controlled evaluations of eculizumab in STEC HUS
- Very effective in treating the related condition atypical HUS (aHUS)
- If it works then the following maybe avoided in STEC HUS patients:
  - Dialysis
  - Permanent kidney damage
  - Brain damage

Trial aims and objectives

Research Objectives:

- To determine whether the severity of STEC HUS is less in those given Ecu compared to those given placebo (primary trial objective)
- To assess the safety of Ecu in STEC HUS
- To determine whether the incidence of CKD following STEC HUS is less in those receiving Ecu compared with those receiving placebo
- To evaluate the cost-effectiveness of administration of Ecu in STEC HUS from the perspective of the NHS

Exploratory objectives

Participants will be given the opportunity to participate in optional exploratory studies. The exploratory studies will include:

- Testing the hypothesis that Thrombotic Microangiopathy (TMA) in STEC HUS occurs via a Shiga-toxin- mediated reduction in podocyte Vascular Endothelial Growth Factor (VEGF) production leading to loss of key complement regulation
- Test the role of patient neutrophils in delivering Shiga-toxin to the podocyte
- Investigate genetic susceptibility to STEC HUS by determining the frequency of genetic variants associated with altered complement regulation
- To identify potential novel pathogenic mechanisms by undertaking whole exome sequencing of DNA of trial participants

Eligibility - Inclusion criteria

1. Age 6 months to <19 years
2. Weight ≥5kg
3. Diagnosis of HUS
   a. Microangiopathic haemolytic anaemia (indicated by fragmented red cells on blood film **OR** plasma lactate dehydrogenase (LDH) above local centre reference range

   AND

   b. Thrombocytopenia (platelets <150x10^9/l)

   AND

   c. Acute Kidney Injury (AKI): “injury” or “failure” category of pRIFLE criteria* despite correction of hypovolaemia**

*eGFR less than 50 or urine output <0.5ml/kg/hr for 16 hours
Ht (cm) x 36.5/pCreat – use height for weight if unable to measure

Eligibility - Inclusion criteria

4. EITHER
   - Reported diarrhoea within 14 days prior to diagnosis of HUS (defined according to WHO as "the passage of three or more loose or liquid stools per day – or more frequent passage than is normal for the individual")

   OR

   - A stool culture or Shiga-toxin polymerase chain reaction or STEC serology result indicating STEC in the patient

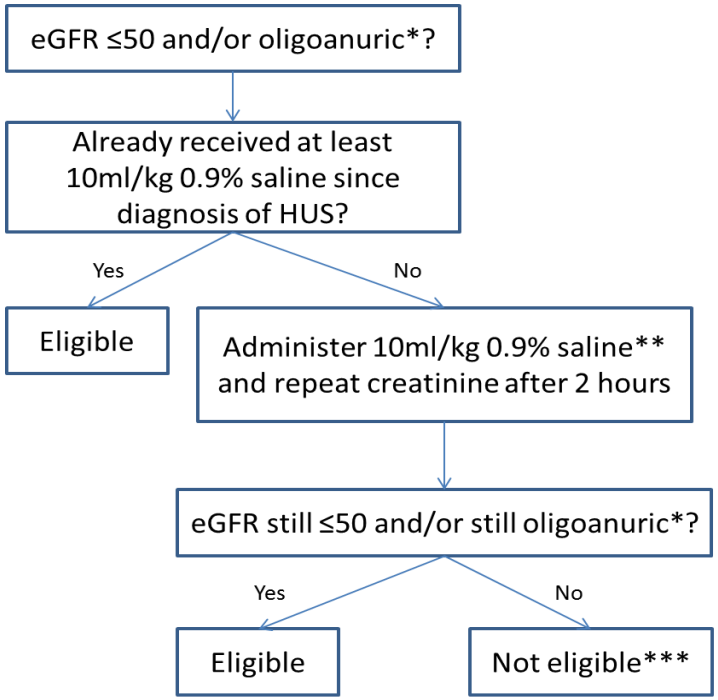
   OR

   - Household contact within 14 days prior to diagnosis of HUS
5. Patient intended to be able to receive trial drug within 48 hours of the on-call paediatric nephrologist formally taking over the care of the patient at the trial site providing inclusion criteria 3 is met, or within 48 hours of meeting inclusion criteria 3 if not met at the time the on-call paediatric nephrologist takes over the care of the patient.
6. Sexually active male or female patients must agree to practice an effective, reliable and medically approved contraceptive regimen for 6 months after enrolment.
7. Sexually active female patient has provided a negative pregnancy test ≤48 hours prior to randomisation
8. Patient/parent/guardian reported that vaccinations are up to date according to the routine UK (or equivalent) immunisation schedule
9. Written informed consent obtained from the patient's parents/guardians and written assent obtained from patient (where age appropriate). Patients aged 16 years and above will provide their own written informed consent.

Eligibility - Exclusion criteria

1. Family history of aHUS
2. Previous episode of HUS
3. Known pre-existing eGFR <90ml/min/1.73m^2
4. Known or suspected pneumococcal infection
5. Known or suspected meningococcal infection
6. Prior to diagnosis, patient taking a drug known to be associated with HUS, e.g. calcineurin inhibitors, chemotherapy, quinine, oral contraceptive pill
7. Hypersensitivity to Ecu, murine proteins or any of the excipients listed in the SmPC for Ecu
8. Pregnancy or lactation
9. Malignancy
10. Known Disseminated Intravascular Coagulopathy
11. Refusal of consent, including consent for pregnancy testing, meningococcal vaccination or antibiotic prophylaxis
12. Currently participating in another clinical trial of an investigational medicinal product

Eligibility - Hypovolaemia



Continue recruitment activity whilst awaiting repeat creatinine

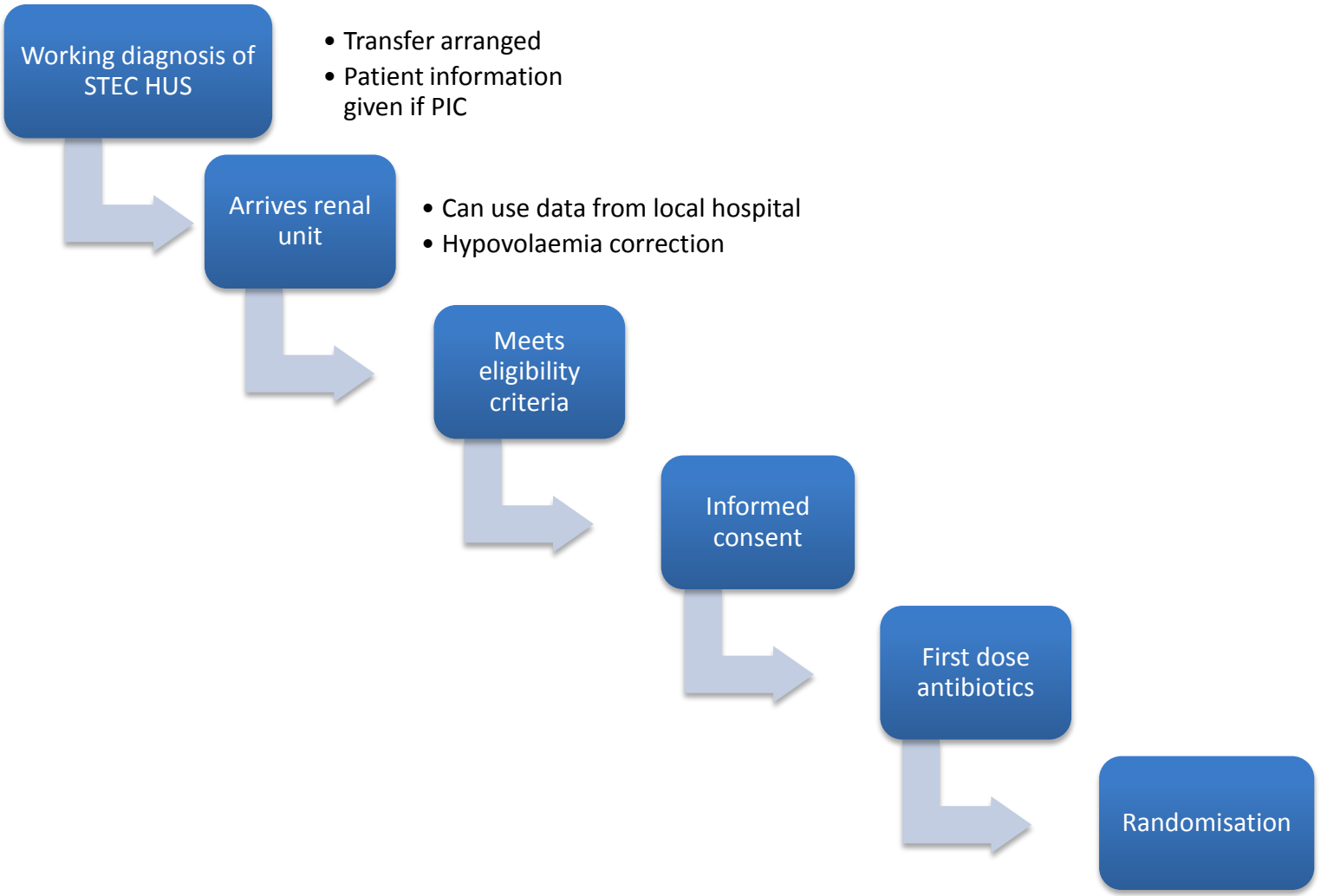
Protocol to ensure hypovolaemia is corrected. eGFR expressed as ml/min/1.73m²

* oliguria defined as urine output <0.5ml/kg/hour for ≥16 hours

** unless clinical signs of hypervolaemia

*** may become eligible if renal function deteriorates further. An alternative crystalloid or colloid to 0.9% saline may be used if clinically indicated

Screening and randomisation



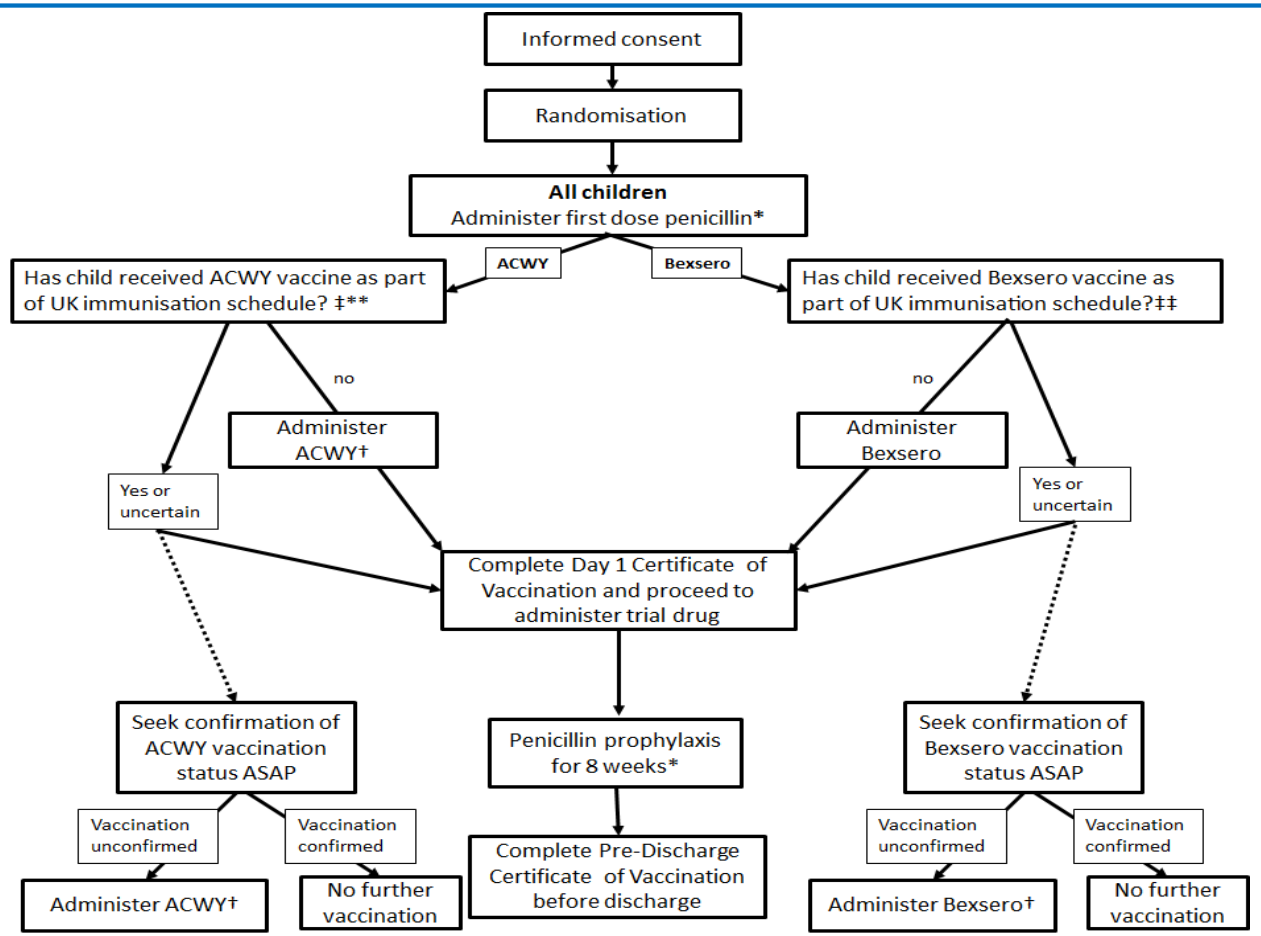
Vaccination and prophylactic antibiotics

Ecu increases children's susceptibility to meningococcal disease. To reduce the risk of meningococcal disease associated with the use of Ecu, all ECUSTEC trial participants should be given:

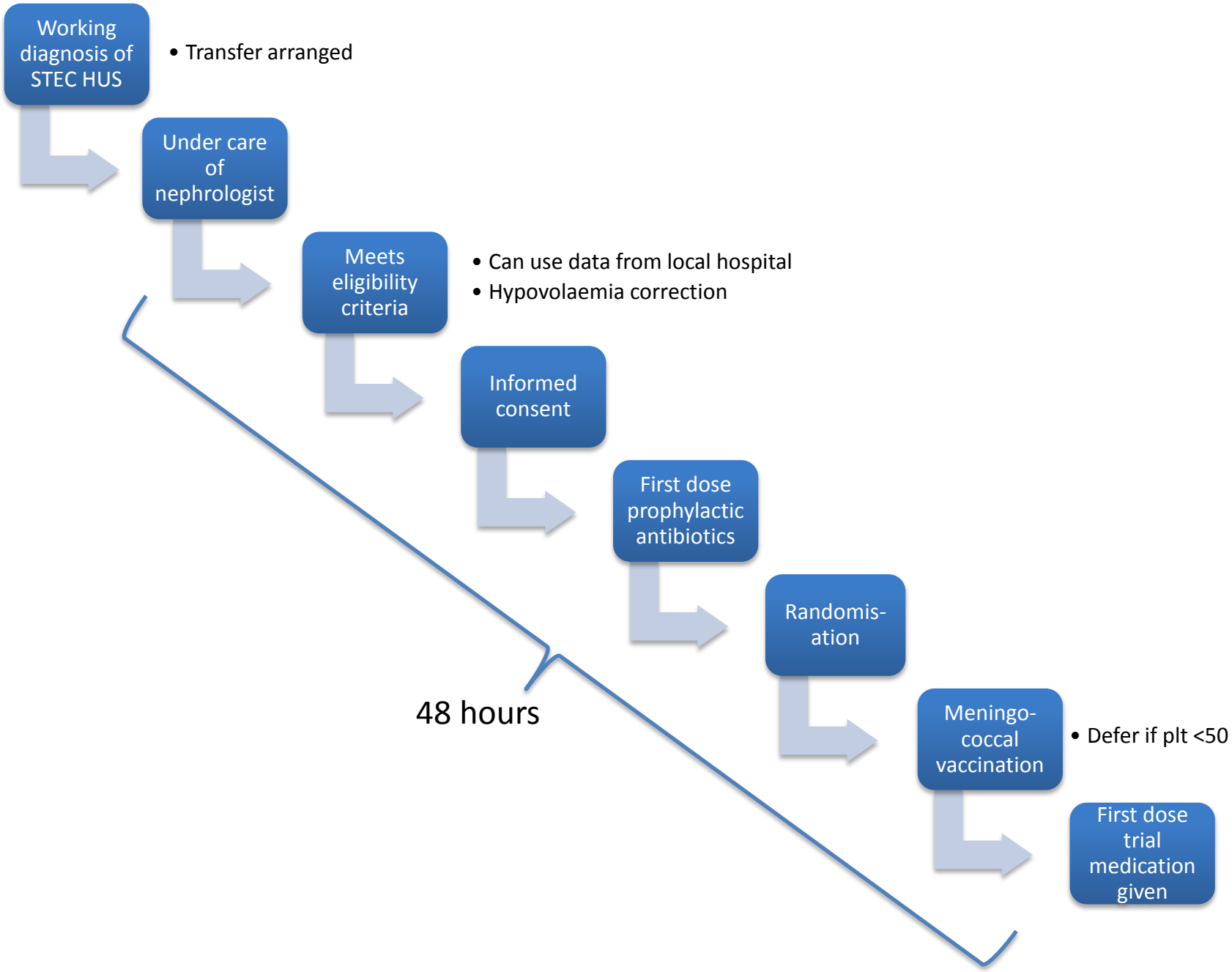
1. **Antibiotic prophylaxis**
2. **Vaccination against meningococcus**
3. **Information on early features of meningococcal disease**

Participants must start prophylactic antibiotics before they can be randomised into the ECUSTEC trial

Meningococcal vaccination process



* or erythromycin if penicillin allergic
**<2yrs Nimenrix; ≥2yrs Menveo or Nimenrix
† If platelet count <50x10⁹/l defer vaccination until platelet count >50x10⁹/l; if receiving systemic anti-coagulation defer vaccination until 24hrs after stopping anti-coagulation.
‡ ACWY is part of the UK immunisation programme for children aged 14yrs since Autumn 2015.
‡‡ Bexsero is part of the UK immunisation programme for children born on or after 30th April 2015.


Working diagnosis of STEC HUS
• Transfer arranged
Under care of nephrologist
Meets eligibility criteria
• Can use data from local hospital
• Hypovolaemia correction
Informed consent
First dose prophylactic antibiotics
Randomis-ation
Meningo-coccal vaccination
• Defer if plt <50
First dose trial medication given
48 hours

Supportive care

- Renal replacement therapy (RRT) will be initiated in the following circumstances:
  - Refractory electrolyte imbalance that poses a risk to the patient
  - Clinical signs of hypervolaemia (diuretics may be tried first if appropriate)
  - Fluid restriction preventing sufficient nutrition
  - Oligoanuria (urine output <0.5ml/kg/hr) >6 hours in the absence of hypovolaemia (diuretics may be tried first if clinically appropriate)

- Dialysis modality – local decision
- The time at which the decision is taken to commence RRT will be recorded as the start of RRT
- Stopping of RRT will be guided by the judgement of the clinical team and the reasons for stopping should be recorded
- Red cell transfusion will be performed if Hb <70g/l or if <75g/l with fall of greater than 20g/l evidenced in previous 24 hours
- A 3 month course of oral folic acid therapy will be prescribed

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
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
Gastro-intestinal	No abdominal surgery reguired (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

Primary outcome measure **Clinical severity score** assigned following D60 assessments

Secondary outcome measures

- 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)
- 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 of the presence of
  - 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/1.73m2 at 52 weeks)
  - Presence of any of these will constitute CKD at 1 year.
- eGFR measurement using a centralised cystatin C assay at 52 weeks.
- Persistent neurological defect at day 60 measured by structured expert assessment to include CNS examination, vision, hearing and neuropsychological assessment
- Economic evaluation of cost per clinical severity score point, and cost per QALY gained, using Paediatric Quality of Life Inventory (PedsQL) and Child Health Utility- 9D (CHU-9D) assessments to measure health related quality of life (HR QoL).

Assessment visits

- All participants to be followed-up for 52 weeks from randomisation

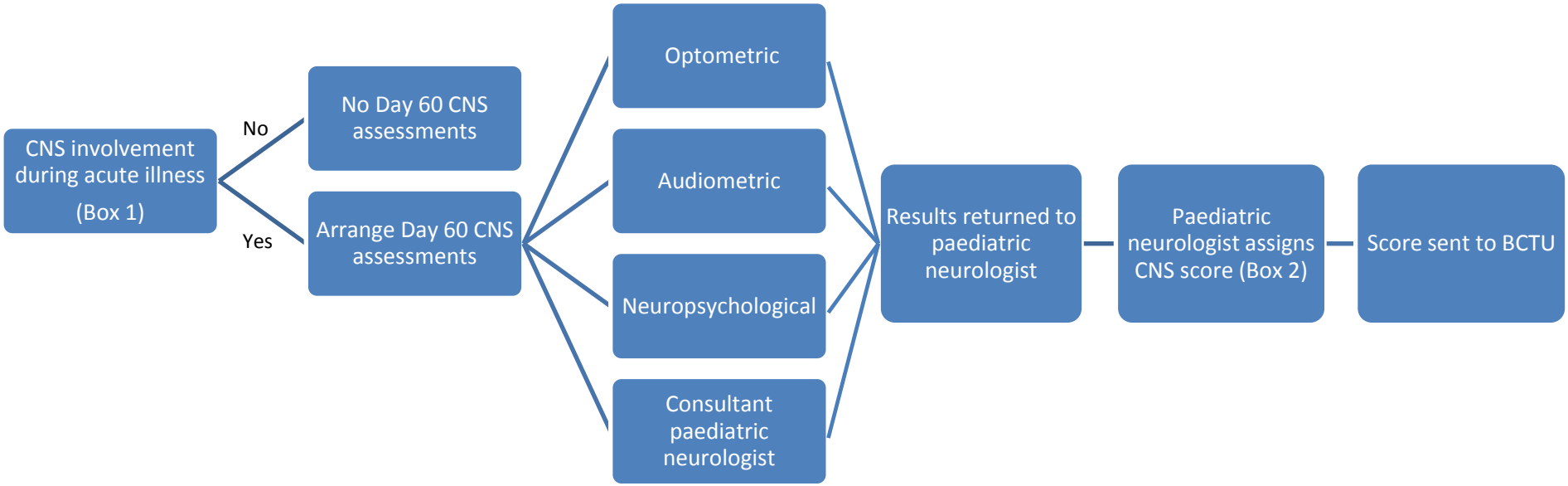
- Daily trial assessments until up to either hospital discharge or day 14 (whichever is soonest)
  - If admission is ≥14 days assessments will continue to be taken weekly to discharge or day 60 (whichever is soonest)
  - Information on the in-patient assessments will be collected in the ECUSTEC Initial Admission for Trial Treatment Form

- All participants to be assessed at:
  - 30 days
  - 60 days
  - 26 weeks
  - 52 weeks

Assessment visits

- Must be conducted by appropriate qualified health professional included on the delegation log
- Health Related Quality of Life (HR QoL) will be measured using Peds QL and CHU-9D questionnaires at baseline, day 8, days 30, day 60, 26 and 52 weeks
- Health service resource use information will be collected at each follow-up assessment visit
- On the Day 60 visit participant/parent/guardian will be invited to complete an optional anonymised ECUSTEC Trial Evaluation Questionnaire
- At 52 week visit please give the age appropriate ECUSTEC Thank You Letters or ECUSTEC Thank You Card

Day 60 CNS Assessment



Box 1. CNS features during acute illness that indicate need for Day 60 CNS assessment
Altered consciousness (Agitation, irritability, hallucinations, confusion, excessive drowsiness)
Seizure/s
Focal or global neurological defect of any duration

Box 2. CNS score (assign the highest score that applies)	
Altered consciousness (Agitation or irritability or hallucinations or confusion or 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

* Multiple seizures occurring within a 24 hr period considered part of the same event
**Todd's paresis following a seizure should resolve within 24 hrs

Assessment visits - samples

- Genetic blood sample
  - taken between day 1 and day 8
  - Sent to Bristol University
  - DNA analysis of genes previously associated with HUS
  - Whole exome sequencing optional, requires additional consent
- Day 30 stool sample
  - To determine whether Ecu leads to prolonged STEC excretion
  - Sent to Public Health England Microbiological Reference Laboratory
  - Upon discharge parent/participant should be provided with stool sample collection pot
- Week 52 Visit
  - A blood sample will be collected and sent to central laboratory for estimated GFR by creatinine and cystatin C
- Exploratory samples
  - Optional blood and urine samples to be collected
  - Day 1, 2, 4, 6, 8 and 30
  - If discharged between day 1 and day 8 participant is not required to return for urine and blood samples for the exploratory studies


Thank You!