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NOn-invasive Ventilation In Children with CErebral_Malaria Phase I Trial

(NOVICE_M trial)

Statistical Analysis Plan			
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Revision History

Version	Author	Date	Reason for Revision
Draft 0.1			Protocol version 1.0
Draft 0.2	Elizabeth George	12th March 2020	Elizabeth George first draft
Draft 0.3	Elizabeth George	19th March 2020	Edits after comments from Sarah Walker
Draft 0.4	Elizabeth George	2nd April	Edits after clarifications from Kathryn Maitland and Obonyo Nchafatso
Draft 0.5	Elizabeth George	24th January 2022	Edits after comments from Roisin Connon
Draft 0.6	Roisin Connon	25th August 2023	Updated after discussions regarding neurological sequelae
Version 1.0	Roisin Connon	25th August 2023	Accepted all changes from v0.6.
Version 1.1	Roisin Connon	6th March 2024	Updated primary endpoint for protocol v2.0

Version 2.0	Roisin Connon	6th March 2024	Incorporated comments from EG on version 1.1 and upversioned.

1) Trial Design

Trial Outline

NOVICE is a Phase I feasibility and safety trial exploring the potential benefits of negative pressure ventilation (NPV) in combination with prophylactic anticonvulsants to ameliorate the adverse outcomes secondary to cerebral malaria (CM). The trial will enroll 30 children aged 3 months to 12-years (up to 40 kg in weight) hospitalised with cerebral malaria (rapid diagnostic test (RDT) positive or positive malaria slide) plus Blantyre Coma Score <=2 and a history of seizures in this illness.

The interventions will be given in a phased evaluation with 10 children per phase.

- First phase: Biphasic Cuirass Ventilation (BCV) for respiratory support, then
- Second phase: BCV plus additional prophylactic anticonvulsants (levetiracetam (LVT) 40 mg/kg loading dose and 30mg/kg every 12 hours given via nasogastric tube for 72 hours or until coma resolution), then
- Third phase: BCV plus additional prophylactic anticonvulsants (LVT 60 mg/kg loading dose and 45mg/kg every 12 hours given via nasogastric tube for 72 hours or until coma resolution)

Trial population

Eligibility for the trial is based on the child meeting all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

1. Aged 3 months and 12 years (up to 40 kg in weight for paediatric dosing of LVT) admitted to the paediatric wards
2. Current or recent evidence of *P. falciparum* malaria (slide or rapid diagnostic test (RDT) positive)
3. Blantyre Coma Score 2 or less that persists even after correction for concurrent hypoglycaemia (defined as glucose <3 mmol/l)
4. History of seizures in this illness
5. Guardian or parent willing and able to provide consent

Exclusion criteria:

1. Known cerebral palsy or significant neuro-development delay (which will affect endpoint assessment)
2. Skin disease or burns preventing use of the BCV
3. Respiratory or cardio-respiratory arrest prior to enrolment
4. A comorbidity which clinician believes has a significant risk of poor outcome e.g. malignancy, end-stage renal failure, major cardiac condition

Primary analysis will be intention to treat. Children for whom assent was given but subsequent full consent refused will be excluded. Children where assent was given but then absconded (so full consent was not obtained) will be included.

2) Interim reviews

In addition to assessing whether or not the 150% higher LVT dose should be tested, that is whether the third phase should proceed after the second phase, the Data Monitoring Committee (DMC) will also review the accumulating data and safety data after each adverse event potentially related to the intervention (as defined below) occurs, using a Bayesian continuous monitoring approach for safety. The Bayesian approach uses information from other studies to define a prior distribution for an expected rate of an adverse event before the trial starts, thus formally incorporating available knowledge about children with cerebral malaria in these settings. After each child completes 72 hours from enrolment, they will be defined as having had a clinically important adverse event potentially related to the intervention or not. This information is used to update the prior distribution and to estimate a posterior distribution. The posterior distribution is then used to estimate the probability of the clinically important adverse event rate being higher than a defined threshold, and is continually updated throughout the trial. If the probability reaches a specific pre-defined value, then the DMC is prompted to consider stopping the trial. Thus, the decision rule to be used by the DMC to consider stopping the trial is based on a high posterior probability (τ) that the estimated percentage of children with clinically important adverse events is above a threshold R (equivalently: $Pr(P_{events}>R \mid data)>\tau$). Thus this way of monitoring uses both available knowledge from previous studies and accruing data to inform decisions.

The clinically important adverse events potentially related to the intervention for a Bayesian monitoring approach to be considered by the DMC in this Phase I trial will be an aspiration event (defined as a sudden decrease in oxygen saturations, and/or de-novo coarse chest crepitations, with evidence of gastric reflux/aspirate in the oropharynx_. In a small Phase II trial comparing levetiracetam to standard of care (control arm) in Malawi, there were 3/21 events (15%) in the control group (NCT01982812, https://clinicaltrials.gov/ct2/show/NCT01982812). Thus, this has informed a beta prior distribution of (0.23, 1.32) with mean 0.15 (ie 15% children experiencing an event) and variance 0.05. We have defined a stopping threshold of 20%, as a previous case series identified very few aspiration events (<1%) in children with acute respiratory failure using the BCV machine[1]. The posterior probability τ was empirically set at 0.95 for the evaluation of this rule[2]. Thus, according to the derived Bayesian decision rule, enrolment will be stopped if the posterior probability of the number of clinically important adverse events being above the target threshold (20%) is higher than 0.95.

[1] Hassinger AB, Breuer RK, Nutty K, Ma CX, Al Ibrahim OS: **Negative-Pressure Ventilation in Pediatric Acute Respiratory Failure**. *Respiratory care* 2017, **62**(12):1540-1549.

[2] Richert L, Doussau A, Lelievre JD, Arnold V, Rieux V, Bouakane A, Levy Y, Chene G, Thiebaut R, Vaccine Research I: **Accelerating clinical development of HIV vaccine strategies: methodological challenges and considerations in constructing an optimised multi-arm phase I/II trial design**. *Trials* 2014, **15**:68.

3) Outcome measures

Primary outcome

Cumulative time with clinical detected epileptogenic seizure activity over 36 hours.

Secondary outcomes

Feasibility will be assessed by ability to implement/operationalise the BCV for use on the high dependency ward in Kilifi County Hospital (assessed by whether this can generate negative pressure ventilation as per specification by the Hayek recommendations and averts respiratory safety endpoints)**.**

Protocol defined safety outcomes

- Aspiration (sudden decrease in oxygen saturations, and/or denovo presence of coarse chest crepitations, with evidence of gastric reflux/aspirate in the oropharynx)
- Episodes of hypercarbia (defined as end-tidal pCO2 level of greater than 45 mmHg, and confirmed by venous pCO_2 > 6kPa).
- Episodes of bradypnoea (<10, 15 or 20 breaths/minute over 3 minutes for those aged <6m, 6-36m and >36m respectively) and hypoxaemia (oxygen saturation <92%) in a child with unrousable coma (Blantyre coma scale≤2)
- Development of hypotension (defined as systolic blood pressure <50 mm Hg in children younger than 12 months; <60 mm Hg in children 1-5 years and <70 mm Hg in children olderthan 5 years of age)
- Use of additional anticonvulsants
- Neurological sequelae at day 180
- Day 28 and day 180 mortality
- Re-admission to hospital through day 180
- Serious adverse events through day 180
- Grade 3/4 adverse events through day 180
- Length of initial hospitalisation.

Other safety outcomes

- Episodes of pH >7.45 (as an indication of respiratory alkalosis from hyperventilation) in a situation where ventilation is adequate (ie BCV-induced)

Serious adverse events will use the standardized definitions on a standardized event form.

4) Derivation of data to be analysed

Time

Time will be from enrolment for primary analysis and secondary analysis.

Definition of baseline
Baseline values for all measurements will be those recorded at screening either on the screening form, the baseline clinical evaluation form or their first blood test taken within 48 hours of admission as appropriate.

Definition of visit schedule
Analyses of measurements at a given point in follow up (weight, clinical symptoms, and neurological sequelae assessments) will use the closest available measurement to that time point in evenly spaced windows. For the day 28 visit there will be a window of ± 21 days, for the day 90 visit there will be a window of ± 30 days and for the day 180 visit there will be a window of ± 60 days.

Definition of censoring
Children lost to clinic follow up will be censored on the date they were last known alive including data from contact tracing visits. For analyses concerning events at specific time points, surviving children will be censored at that time point. That is for analyses at 28 days, censoring will occur on day 28, for analyses at 90 days censoring will occur on day 90 and for analyses at 180 days censoring will occur on day 180.

Definition of end of time on BCV
End time for being on BCV is recorded under BCV observations but if missing then the time finished will be taken as time of last observation on BCV observation form

5) Statistical Analysis

Clinical data will be summarised using means and medians where appropriate for continuous data depending on the distribution. Analyses will follow intention-to-treat. Primary and secondary endpoints will be described using means or medians or proportions.

As this is a Phase I trial no subgroup analyses are planned.

All analysis will be included in the final report, but only analysis in bold below will be included in the DMC report.

Baseline characteristics

- **Sex: n(%) male, female**
- **Age at admission (months): median (IQR)**
- **Weight (kg): median (IQR)**
- **Heart rate (bpm), axillary temperature (˚C), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), oxygen saturation (%), respiratory rate (brpm), capillary refill time (s): median (IQR)**

- **Blantyre Coma Score (BCS): n (%) each value of score (0 to 5)**
- **Temperature gradient, weak pulse: n(%) yes, no**

Clinical history of this illness

- History of fever within 14 days, history of fever more than 14 days, history of cough, increased work of breathing, vomiting, inability to sit up right unsupported, diarrhoea, fits in this illness: n(%) yes, no, don't know
- Bloody diarrhoea: n(% of those with diarrhoea), yes, no, don't know
- **Seizures in this illness: n (%) yes, no, don't know**
- **Seizures lasting more than 30 minutes: n(%) yes, no, don't know**
- Haemoglobinuria: n(%) yes, no, don't know; median (IQR) length (days)
- Inability to sit upright unsupported (prostrate): n(%), yes, no

Treatment in this illness

- Admitted for over 24 hours into another hospital, received oral anti-malarials in last week, received oral antibiotics in last week, received traditional medicine in last week: n(%) yes, no, don't know
- N**umber of doses of IV or IM quinine/artesunate received before enrolment: median (IQR) or tabulation depending on numbers**
- **Received an anticonvulsant prior to admission: n(%) yes, no, don't know**
    - **Anticonvulsant: n(%) of each of: phenobarbitone, diazepam, don't know.**
    - **If phenobarbitone or diazepam, route of administration: n(%) oral, IM, IV.**

Past clinical history

- Two or more hospital admissions in the last year, previously received a blood transfusion (ever), received anti-helminths in last 6 months, has epilepsy, able to sit unsupported before this illness, able to walk without help before this illness: n(%) yes, no, don't know
- On regular anticonvulsants (n % of those with epilepsy) yes, no, don't know.

Child's family

- Number of siblings: median (IQR), range
- Any siblings with sickle cell disease: n(% of those with siblings) yes, no, don't know
- Father's ethnic group, mother's ethnic group
- Mother attended secondary school, child sleeps under a bed net/mosquito net: n(%) yes, no, don't know
- Parents alive: n(%) both alive, one alive, both dead
- Child's homestead: n(%) urban, semi-urban, rural

Clinical examination

- In-drawing, deep breathing, sunken eyes, decreased skin turgor, cold hands or feet only, liver size>2cm below costal margin, jaundice, very severe wasting/marasmus, generalised lymphadenopathy, flaky paint dermatitis, oral candidasis: n(%) yes, no, not assessed
- Crackles: n(%) unilateral, bilateral, none, not assessed
- Splenomegaly: n(%) not palpable, enlarged, gross

- Signs of kwashiorkor (oedema): n(%) none, pretibial (minimum), hands/legs (moderate), generalised (severe)

Neurological

- Inability to sit up right unsupported, fitting currently, neck stiffness: n(%) yes, no, not assessed
- Bulging fontanelle (infants only) : n(% infants) yes, no, not assessed
- Pupil symmetry: n(%) equal, unequal

Ward tests at admission

- HIV test result: n(%) previously positive, previously negative, tested positive today, tested negative today, tested today invalid
- **Lactate (mmol/l), glucose (mmol/l): median (IQR)**
- **Glucose given: n (%) yes, no,**
- **Blood gas: pH, bicarb, PCO_2, Base deficit (ecf), base deficit (b): median (IQR)**

Presentation

- Healthcare facility first presented to: n(%) this hospital, level II, level III, level IV, other district hospital, private hospital
- Time to enrolment since presented at other facility, time to enrolment since referred from other facility: median (IQR), range
- Distance from other facility (estimated km): median (IQR), range

Admission blood test results and admission microbiology

- **Malaria RDT test: n(%) positive, negative, invalid or not done**
- **Malaria blood film: n(%) positive, negative, invalid or not done**
- Malaria pigment: n(%) yes, no
- Malaria species: n(% those with malaria) *P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax*
- Parasite count per 200 WBC, parasite count per 500 RBC: median (IQR)
- WBC, RBC, Hb from FBC, haematocrit, MCV, MCH, MCHC, platelets, lymphocytes, neutrophils, granulocytes, monocytes, reticulocyte count: median (IQR)
- Sodium, potassium, urea/BUN, creatinine, albumin, AST, ALT, bilirubin: median (IQR)
- Pathogens isolated: n(% samples tested) yes, no.
- List of pathogens: n(%)

Description of follow-up

Denominator in each case is those who have been enrolled long enough ago for that visit to have occurred or to have completed follow up as appropriate, including those who have been lost to follow up.

Completion of follow up visits

- **Visits considered complete, defined as attended or died before the visit took place, at 28 days, 90 days, 180 days** and overall**: n(%)**

- **Child status at 28 days, 90 days, 180 days** and overall**: n(%) visit done, died, lost to follow up, missed visit.**

Completeness of neurological assessment records

- **Symptom checklists considered complete, defined as a non-missing entry or died before the time point at 90 days and 180 days: n(%)**
- **Symptom checklists considered complete out of those alive at that time point: n(%)**
- **Neurological exam considered complete, defined as a non-missing entry or died before the time point at 90 days and 180 days: n(%)**
- **Neurological exam considered complete out of those alive at that time point: n(%)**

Adherence to treatment

BCV

- **Time spent on BCV (hours): median (IQR)**
  - **Time spent on sync mode (hours): median (IQR)**
  - **Time spent on triggered mode (hours): median (IQR)**
  - **Time spent on control mode (hours): median (IQR)**
- **Time spent on high flow oxygen (hours): median (IQR)**

Levetiracetam (LVT)

Number given loading dose of 40mg/kg: n (% of those enrolled to second phase)
Number of 30mg/kg doses given in admission: median (IQR)

Number given loading dose of 60mg/kg: n (% of those enrolled to third phase)
Number of 45mg/kg doses given in admission: median (IQR)

Primary analysis

Cumulative time with clinical detected epileptogenic seizure activity over 36 hours: median (IQR) overall and by phase of enrolment.
Number of clinical seizures: median (IQR) overall and by phase of enrolment
Number of additional anti-epiletic drugs needed: median (IQR) overall by phase of enrolment

Children who die without recovering from coma will be imputed to have a cumulative time of 36 hours (maximum expected coma duration).

Safety analysis

Number of aspiration events (defined as sudden decrease in oxygen saturations, and/or denovo presence of coarse chest crepitations, with evidence of gastric reflux/aspirate in the oropharynx).
Number of episodes of hypercarbia (defined as pCO2 level > 45mmHg from end-tidal PCO_2 confirmed by venous PCO_2 > 6kPa): median (IQR)
Number of episodes of bradypnoea (<10, 15, or 20 breaths/min over 3 minutes for those aged <6m, 6-36m, and >36m respectively) and hypoxaemia (oxygen saturation <92%) in a child with unrousable coma (BCS≤2): median (IQR)
Number of children that develop hypotension (systolic blood pressure <50mmHg, <60mmHg, <70mmHg in children <12 m, 1-5 years, >5 years respectively): n(%)

Died by day 28: n(%)
Died by day 180: n(%)
Listing of clinical summary of neurological sequelae

Number of children with a readmission by 180, number of children with a serious adverse event by 180, number of children with grade 3/4 adverse event by day 180: n(%)
Number of readmissions to hospital by day 180, number of serious adverse events by day 180, number of grade 3/4 adverse events by day 180: n
Length of initial hospitalization (days): median (IQR)

Feasibility analysis

- **Reasons for ending BCV: n (%) power cut, child unable to tolerate BCV, skin breakdown or injury, inadequate cuirass seal, other**
- **Number of times suctioning was necessary: median (IQR)**

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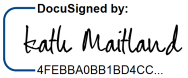
Kath Maitland kathryn.maitland@gmail.com Imperial College, London Security Level: Email, Account Authentication (Optional)	DocuSigned by:  4FEBBA0BB1BD4CC... Signature Adoption: Pre-selected Style Using IP Address: 102.222.146.1	Sent: 06 March 2024 | 14:11 Viewed: 07 March 2024 | 06:32 Signed: 07 March 2024 | 06:32
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