1. Summary of changes

Study Title: Aetiology of hyponatremia, its relation to seizures and outcome in acute febrile encephalopathy – A prospective study in Neurology intensive care unit (NICU) patients.

Sub study: Safety and efficacy of fludrocortisone in treatment of cerebral salt wasting in tuberculous meningitis

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Funded by Indian Council of Medical Research 2013-21330)
1. Summary of changes

The Project summary along with the amendments:

<table>
<thead>
<tr>
<th>Section</th>
<th>Original study</th>
<th>Changed to (amendment)</th>
<th>Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>Co-investigator Dr Sanjeev K. Bhoi, Department of Neurology, Sanjay Gandhi Post</td>
<td>Co-investigator Dr Mritunjai Kumar Department of Neurology, Sanjay Gandhi Post</td>
<td>Co-investigator change: Dr Sanjeev K. Bhoi left the study site to join another institute in a different state</td>
</tr>
<tr>
<td>Agreement</td>
<td>Graduate Institute of Medical Sciences</td>
<td>Graduate Institute of Medical Sciences</td>
<td></td>
</tr>
<tr>
<td>Date of submission</td>
<td>01-07-2013</td>
<td>Amendment submitted on 11-09-2015</td>
<td>1. Many patients with AES (presenting with fever, headache and altered sensorium within 10 days, as per definition) are diagnosed later as TB meningitis. 2. During the study, it was realised that the treatment of hyponatremia with IV saline and oral salt supplementation was not optimal. It was considered</td>
</tr>
<tr>
<td>Date of approval</td>
<td>10-10-2013</td>
<td>30-09-2015</td>
<td>Amendment approved</td>
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<tr>
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</tr>
<tr>
<td>Funding</td>
<td>ICMR</td>
<td>ICMR</td>
<td>No change</td>
</tr>
</tbody>
</table>

**Summary Protocol**

| Type of study | Prospective observational study | Sub study: Investigator initiated, open labelled, randomized controlled trial conducted during 2015 - 2017 at a tertiary care teaching hospital in north India. | Version change following discussion at ICMR head quarter in 2015. Since, hyponatremia in patients with AES including Tubercular |

appropriate to add fludrocortisone and document the results systematically under a well designed randomized Study |
Meningitis will be treated with conventional therapies which consist of IV fluids (normal saline), oral salt supplementation, and fludrocortisone. It was considered appropriate to document the results systematically under a well-designed protocol.

| Title of the project: | Aetiology of hyponatremia, its relation to seizures and outcome in acute febrile encephalopathy – A prospective study in Neurology intensive care unit (NICU) patients. | Aetiology of hyponatremia, its relation to seizures and outcome in acute febrile encephalopathy – A prospective study in Neurology intensive care unit (NICU) patients. | Sub study: Safety and efficacy of fludrocortisone in treatment of cerebral salt wasting in tuberculous meningitis | Same

| Type of patients included under the study protocol. | Patients with acute encephalitis syndrome (AES) only | Patients with **TBM were also included.** Sub study: Patients with TBM with CSW will be eligible for the fludrocortisone trial. | Version change following discussion at ICMR headquarter in 2015. Many patients with AES |
| Objectives: | a) To document the frequency of hyponatremia in acute encephalitic syndrome (AES).  

b) To evaluate the basis of hyponatremia in the patients with AES- cerebral salt wasting (CSW) versus syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in the patients with AES.  
c) To evaluate the role of hyponatremia in producing seizures and encephalopathy in AES.  
d) To evaluate the effect of hyponatremia (CSW + SIADH) on mortality and functional outcome.  
e) To recommend the treatment protocol for management of hyponatremia in AES.  

| | a) To evaluate the frequency and the basis of hyponatremia in the patients with AES and **TB Meningitis**.  
b) To classify the patients with hyponatremia into cerebral salt wasting (CSW) versus syndrome of inappropriate secretion of antidiuretic (SIADH).  
c) To evaluate the role of hyponatremia in producing seizures and encephalopathy and assess its effect on mortality and functional outcome.  
d) **To assess the Tolerability and efficacy of fludrocortisone for the treatment of hyponatremia with cerebral salt wasting in patients with AES including TB Meningitis and recommend the treatment protocol for management of hyponatremia.**  

| | Change in the objective (a) and (d).  
More accurate Wording.  
**Inclusion of patients with TBM along with AES.**
| Diagnosis of TBM | Not required. It included patients with AES only | The diagnosis of TBM was based on clinical, MRI and CSF criteria.\textsuperscript{25}  
1. Essential criteria: Features suggestive of meningitis (one or more of the following: headache, irritability, vomiting, fever, weight loss, neck stiffness, convulsions, focal neurological deficits, or altered consciousness) for more than 5 days.  
2. Supportive criteria:  
(a) CSF cells of 10 –500/\( \mu L \), with predominant lymphocytes (\( >50\% \)), protein 1 g/L and sterile bacterial and fungal culture.  
(b) Cranial CT or MRI imaging showing evidence of exudates, infarction, hydrocephalus or tuberculoma in isolation or in combinations.  
(c) Evidence of extra CNS tuberculosis (Chest radiograph suggestive of active tuberculosis or CT/ MRI/ ultrasound evidence for tuberculosis outside the CNS or Acid Fast Bacillus (AFB) identified or Mycobacterium tuberculosis cultured from another source such as sputum, lymph node, gastric washing, urine).  
(d) Exclusion of alternative diagnoses.  
Criteria for definite and highly probable TBM: Essential criteria with two supportive criteria were defined as highly probable TBM. Presence of acid fast bacilli in CSF smear, positive CSF culture or polymerase chain reaction (PCR) for M. tuberculosis was considered definite TBM.\textsuperscript{25}  
| TBM diagnostic criteria was added according to the published uniform case definition\textsuperscript{25} |

| Diagnosis of cerebral salt | Two out of 4 of the followings  
• Elevated HCT, Hb, serum | Essential: (all required)  
1. Polyuria (urine output >3L for at | More specific |
### Criteria for Wasting

<table>
<thead>
<tr>
<th>Wasting</th>
<th>Albumin, urea, autonomic changes: tachycardia, postural hypotension, CVP &lt; 6, negative fluid balance</th>
</tr>
</thead>
</table>

2. Hyponatremia: serum sodium < 135 mEq/L on 2 consecutive evaluations 24 h apart.
3. Exclusion of secondary causes like endocrine abnormalities, renal, cardiac and hepatic failure, diuretics

Supportive criteria: at least 3 out of 5 of the following

1. Clinical findings of hypovolemia such as hypotension, dry mucous membranes, tachycardia or postural hypotension.
2. Persistent negative fluid balance as determined by intake output chart and/or weight loss.
3. Laboratory evidence of dehydration such as elevated hematocrit, hemoglobin, serum albumin or blood urea nitrogen.
4. Central venous pressure (CVP) < 6 cm of water.
5. Urinary sodium > 40 mEq/L or urine osmolality > 300 mOsm/L in 2 consecutive reports.

### Criteria for Hyponatremia

<table>
<thead>
<tr>
<th>Serum sodium &lt; 135 meq/L would be taken as hyponatremia and will be categorized into mild (&gt;120 meq/L) and severe (&lt;120 meq/L). Depending on the serum chemistry, urinary intake output, urinary sodium and osmolality and central venous pressure the patients would be categorized into CSW and SIADH.</th>
</tr>
</thead>
</table>

Serum sodium < 135 meq/L would be taken as hyponatremia and will be categorized into mild (>130 meq/L) moderate (120 – 129) and severe (<120 meq/L). In case of mild hyponatremia (130-134 meq/L), serum sodium will be repeated 24 hours apart for confirmation. Depending on the serum chemistry, urinary intake output, urinary sodium and osmolality and central venous pressure (if feasible), the patients would be categorized into CSW and SIADH.

Change of wording. Grading for hyponatremia changed.
Mild hyponatremia was confirmed based on 2 reports 24 hours.
### Inclusion Criteria
All the patients with fever and altered sensorium within 10 days of their illness will be included. All patients with fever and altered sensorium within 5 days of their illness will be included in the study. The will be categorized as either acute encephalitic syndrome (AES) or tubercular meningitis (TBM) based on blood/serum/CSF criteria.

**Sub study:**
Patients with TBM with hyponatremia due to CSW will be eligible for the fludrocortisone trial.

Those with AES will be studied as before and will not be randomized.

### Exclusion Criteria
Patients with head injury, stroke, tumors, malignancy and history of chronic renal and hepatic failure will be excluded.

The patients below 10 years of age, pregnant and lactating women and those with malaria, septic, fungal or carcinomatous meningitis head injury, brain tumors, primary renal, hepatic or cardiac failure, endocrinial disorders such as adrenal failure or hypothyroidism, malignancy or any condition limiting the life expectancy to 1 year or less was excluded; however if the patients developed hepatic or renal dysfunction during treatment were not excluded. Patients not providing consent for the study will be excluded from the study.

### Examination
Detailed medical history including the demographic details, duration of illness, altered sensorium, seizures (type, frequency, duration).

Detailed medical history including the demographic details, duration of illness, altered sensorium, seizures (type, frequency, duration).

Addition of tubercular meningitis and
sensorium, seizures (type, frequency, duration and its temporal relation to hyponatremia), focal deficit, behavioural changes, headache, vomiting and features of raised intracranial pressure such as extensor posturing, pupillary asymmetry and reaction, hyperventilation and gastric hemorrhage will be noted. Presence of pallor, edema, neck vein, jaundice, petechiae, ecchymosis, ascites, hepatosplenomegaly, lymphadenopathy, chest rales and cardiac murmur will be noted. Patients’ consciousness would be recorded by Glasgow coma scale and clinical states of by APACHE-II. Presence of cranial nerve palsy and papilloedema will be recorded. Focal weakness (hemi, para or quadriplegia) will be categorized into severe and mild and tendon reflex and muscle tone will be noted. Cerebellar and sensory functions will be tested who could co-operate for the test. Evidence of TB outside the central nervous system such as lung, lymph node, bone and joint will be noted. The severity of meningitis will be graded into MRC stage 1- meningitis only; no focal signs and GCS 15. Stage 2- meningitis with either focal signs and GCS 15 or a GCS between 11 and 15; stage 3- meningitis with GCS 10 or below. Skin turgor, mucous membrane, nutritional states, measurement of weight if possible, neck vein engorgement, edema, pulse and blood pressure (if possible in lying and sitting) will be recorded daily. Other causes of hyponatremia eg. due to extra-renal loss (vomiting, diarrhea), poor intake or drugs will also be recorded. Input-output charting
APACHE will also be done daily. Daily intake output charting will be done. Total Input will include all the liquid items consumed by the patient along with intravenous fluids administered. Solid food items which cannot be measured will be excluded. Catheter, either foleys (in case of altered sensorium) or external catheters will be used to measure total daily urine output. Insensible loss of 500 ml will be added to calculate daily fluid balance. Weight will be measured using a weighing machine if patient is conscious and able to stand independently. In case of poor sensorium or unable to stand independently, beds with automated weight measurements will be used. CVP will be monitored whenever required.

| Investigations | Blood counts, hemoglobin, hematocrit, serum electrolytes (sodium, potassium, magnesium), transaminases, bilirubin, blood urea, serum creatinine, calcium, serum protein, albumin, arterial blood gas would be lactate would be estimated. 24 urinary volume, electrolyte osmolality would be measured. Chest radiograph, 12 lead ECG and cranial MRI of brain will be done. For JE, CSF IgM antibody will be done by pan-bio (Australia), for dengue serum NS1 antigen test will be done by Bio Red ELISA kit and IgM antibody by Pan-Bio (Australia). CSF IgM for VZV will be done by abcam ELISA kit, serum IgM for Chikungunya and leptospira by SD Bioline. HSV and EBV will be done by CSF PCR. Peripheral blood smear will be examined for malaria. CSF will be also examined for cryptococcal and pyogenic infection. Cerebrospinal fluid (CSF) will be examined for proteins, cells, glucose, bacteria, fungi, malignant cells and AFB staining and culture by BACTEC. CSF will also be examined for PCR for M, addition of Acid fast bacillus (AFB) culture, BACTEC and CSF polymerase chain reaction (TB-PCR) for tuberculosis. More specific monitoring of urine and serum osmolality. |
will be done by abcam ELISA kit, serum IgM for Chikungunya and leptospiro by SD Bioline. HSV and EBV will be done by CSF PCR. Peripheral blood smear will be examined for malaria. CSF will be also examined for tuberculosis, cryptococcal and pyogenic infection. Bedside EEG will be recorded in the NICU on admission using 10-20 system of electrodes placement. 1 hour EEG recording will be done at the baseline and the effect of photic stimulation and pin prick will be noted. The EEG may be categorized into normal and abnormal (focal or generalized slowing, epileptiform discharges or other abnormalities). If there is myoclonus EMG recording will be done. In the patients with hyponatremia, serum sodium will be done daily till it is corrected. In the patients with normal baseline serum sodium, twice weekly or more frequently if clinically indicated will be done for 1 week. Serum and urinary osmolality will be done at the time of hyponatremia. Urinary sodium will also be measured. ABG and intake output chart along with clinical findings will be reviewed daily.

tuberculosis. CT/MRI brain with/without contrast will be done at admission and will be repeated whenever required. In the patients with hyponatremia (sodium < 135 meq/L), serum sodium will be repeated daily till it is corrected and in patients with normal baseline serum sodium, it will be repeated twice weekly or more frequently if clinically indicated. Serum and urinary sodium and osmolality will be done at the time of hyponatremia and will be repeated every third day. Bedside EEG will be recorded in the NICU on admission using 10-20 system of electrodes placement. 1 hour EEG recording will be done at the baseline and the effect of photic stimulation and pin prick will be noted. The EEG may be categorized into normal and abnormal (focal or generalized slowing, epileptiform discharges or other abnormalities). If there is myoclonus EMG recording will be done.
| Outcome | 1. Causes of hyponatremia in patients with AES  
2. Categorization of hyponatremia into CSW and SIADH.  
3. Death in the hospital  
4. Condition at discharge-based Glasgow outcome scale  
5. Presence of encephalopathy and seizures | **Primary outcomes for the sub study:**  
- Number of days required to correct sodium to >135 meq/L.  
**Secondary outcomes for the sub study:**  
- Number of days required to attain a net positive water balance.  
- Dose of fludrocortisone required to reach primary outcome.  
- Number of patients developing adverse reactions to fludrocortisone (hypertension, hypokalemia).  
- Seizures due to hyponatremia.  
- Disability at discharge, 3 and 6 months based on modified Barthel index and m RS score. as good (mRS \( \leq 2 \)) or poor (mRS\( >2 \))  
- Mortality at 1 month, 3 months and 6 months.  
- Residual deficits in terms of seizures, cognitive, cranial nerve and motor deficits at the end of 6 months. | **Primary outcome changed.**  
Other secondary outcomes were added.  
Follow up at 3 and 6 months were added to assess the outcome. |
<table>
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<tbody>
<tr>
<td>Sample size</td>
<td>150 AES patients would be recruited</td>
<td><strong>Sample size calculation:</strong> Due to the paucity of previous studies, the number of patients needed for the study will be based on the assumption of a standard deviation of 2.5 days in the mean days to the hyponatremia correction (primary outcome) during the study period. To detect a difference of 25% between the study arm and the control arm, with a power of 80% at a significance level of 5% with the use of a two-sided test, it was calculated that 16 patients in the each arm Patients with TBM with CSW were randomized. No previous study on the role of fludrocortisone in CSW in TBM.</td>
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</tbody>
</table>
Moreover, it was felt that it may not be possible to perform a complete evaluation of 10% of patients because of the possibility of withdrawal of consent, seeking other treatment options and leaving the hospital prematurely against advice. Thus, a final sample size of 18 patients in each arm was estimated for this trial.

Patients with AES will be studied as before. They will not be randomized for fludrocortisone trial.

| Screening and Randomisation | No randomization needed. It was a prospective observational study | For sub study only: All patients with TBM without pre-existing co-morbidities (exclusion criteria) will be screened for the presence of hyponatremia (serial measurement of serum sodium) during the hospital stay. Those with hyponatremia will undergo detailed evaluation and will be categorized as having either CSW (based on predefined criteria) or other alternate cause. The patients with TBM with CSW will be randomly assigned to either control (intravenous 0.9% saline with oral salt) or experimental (fludrocortisone) group with a 1:1 allocation using computer generated random number sequence. All the patients will be given intravenous 0.9% saline with oral salt supplementation (5-12 grams/day) through naso-gastric tube or in capsule. |
The patients in the fludrocortisone arm, will receive fludrocortisone tablets (0.1 – 0.4 mg once daily, PO) which will be started at a dose of 0.1 mg once daily in the morning and will be increased every third day with an increment of 0.1 mg (D1 – 0.1 mg; D4 – 0.2 mg; D7 – 0.3 mg; D10 – 0.4 mg), till the primary endpoint is achieved or a total dose of 0.4 mg once daily is reached. Fludrocortisone will be discontinued only when 2 consecutive serum sodium values (on alternate days) are persistently normal. However, for the primary outcome analysis, we will count the earliest date to the serum sodium correction. When serum sodium fails to normalize even after 0.4 mg dose for 4 days, we will consider it as failure of the treatment and the fludrocortisone will be withdrawn. The patients will be then continued on intravenous 0.9% saline with oral salt supplementation. 3% saline will be used if there is an emergency like seizures or coma with severe hyponatremia.

<table>
<thead>
<tr>
<th>Study duration</th>
<th>Open to recruitment since 2013 2015-2017.</th>
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<tbody>
<tr>
<td>Management</td>
<td>The underlying neurological infection will be treated as per standard protocol. Patients will receive nasogastric feeding as indicated and artificial ventilation if there is respiratory failure (inability to maintain O2 saturation on ventimask, pH&lt;7.3 and PaCO2&gt;50mmHg).</td>
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<td></td>
<td>Patients diagnosed as AES will be treated with standard treatment protocol. The patients received four drug anti tubercular treatment (RHZE) for six months followed by RH for 12 months. Rifampicin was prescribed a dose of 10mg/kg (~450mg/d), isoniazide 5mg/kg (~300mg/d), pyrazinamide 25mg/kg</td>
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<td></td>
<td>Treatment of TBM included. Change in wordings.</td>
</tr>
</tbody>
</table>
The patients with CSW and SIADH will be managed as per standard protocol. Target serum sodium will be 130meq/L. (~1500mg/d) and ethambutol 15 mg/kg (~800mg/d). All patients also received prednisone 0.5 mg/kg (~40 mg/d) and aspirin up to 150mg/dorally daily, if not contraindicated (patients of uncontrolled diabetes, infection and septicaemia). The patients were subjected to ventriculo-peritoneal shunt or external ventricular drainage (EVD) or mechanical ventilation as indicated.

| Statistical analysis | The incidence of hyponatremia and its basis (SIADH Vs CSW) would be categorized. The relationship of hyponatremia with etiology of AES, presence of raised intracranial pressure, age, gender, GCS, APACHE-II, EEG changes, MRI changes and outcome will be evaluated by using various parametric and nonparametric tests. The relationship of CSW and SIADH will be evaluated with vasopressin, atrial natriuretic hormone and brain natriuretic factors by linear regression test. The statistical analysis will be done using SPSS15 version and Graphpad prism 5 |

Continuous and normally distributed variables were represented as mean±SD (standard deviation) whereas the continuous but skewed variables were represented as median and range. Normalcy of data was tested by Shapiro-Wilk test. Statistical significance was defined as two tailed $P$ value < 0.05. For normally distributed continuous variables, independent $t$-test and for skewed variables, Mann Whitney U test was used. Chi-square and Fisher’s exact tests were used to compare categorical variables. Statistical analyses were performed using SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA). Kaplan-Meier plots and explicit survival estimates at 6 months of follow-up will also be calculated for the full populations. In a second stage, time to serum sodium correction will be modeled using the Cox proportional hazards regression model following covariates (in addition to the treatment group, TBM disease severity (grade I, II, or III) and age adjustment.

Change of wordings, use of SPSS 20 version
The first study titled “Aetiology of hyponatremia, its relation to seizures and outcome in acute febrile encephalopathy – A prospective observational study in Neurology intensive care unit (NICU) patients” was an observational study approved from ICMR on 01.07.2013.

An interim analysis was done in March 2015 after recruiting 80 patients with acute febrile encephalopathy.

It revealed that many patients (12 patients out of 80) with AES (presenting with fever, headache and altered sensorium within 10 days, as per definition) were diagnosed later as TBM. The issue was discussed at ICMR headquarter. A sub group study (observational) on TBM patients started from March 2015 onwards under the same project and was approved by ICMR.

High incidence of CSW was found among patients with TBM, which were difficult to treat. Fludrocortisone was given to some of the refractory cases with good results.

First Amendment: RCT to compare the efficacy of fludrocortisone was planned and ethically cleared on 30.09.2015 from the “institute ethical committee”.

The first patient recruited under the trial was on 3 Oct, 2015.

Flowchart showing summary of changes and amendments in the original protocol along with the corresponding dates.
2. Original study protocol

Aetiology of hyponatremia, its relation to seizures and outcome in acute febrile encephalopathy – A prospective study in neurology intensive care unit (NICU) patients.

Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences

Original study protocol

(Funded by ICMR)

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8. Clinical study specimens
9. Publications
10. Sub-studies
11. Appendices
   - Appendix 1.1 - Diagnostic criteria for acute encephalitic syndrome (AES), cerebral salt wasting and SIADH.
   - Appendix 1.2: The Modified Rankin Scale grade Description
   - Appendix 1.3: Table of common toxicity criteria and grading
   - Appendix 1.4 Guide to management of toxicities
   - Appendix 1.5 Management of serious adverse effects of drugs requiring drug discontinuation
   - Appendix 1.6: Management of common adverse effects of AES medications
12. References
The Investigator list

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1. **Summary:**

1.1 Abstract

There is paucity of prospective study on hyponatremia in acute encephalitis syndrome. Correct management of hyponatremia is crucial for good outcome. Hyponatremia can be because of CSW or SIADH. It is proposed to document hyponatremia in AES patients admitted in Neuro ICU and will be categorize into CSW or SIADH using well defined criteria. Occurrence of seizures, EEG correlates and outcome of the AES patients with hyponatremia will be evaluated. The proportion of CSW or SIADH in specific subgroups of AES patients will also be studied. The MRI and EEG correlates of AES with and without hyponatremia will also be documented. These results of the study may lead to a simple protocol for the management of hyponatremia which would find a wide appreciation.

**Scientific Title:** Etiology of hyponatremia, its relation to seizures and outcome in acute febrile encephalopathy – A prospective study in Neurology intensive care unit (NICU) patients.

**Aim:** To document the frequency of hyponatremia in acute encephalitic syndrome (AES).

**Study design:** Prospective observational cohort study at a tertiary care teaching hospital in North India.

**Sample size calculation:** 150 consecutive patients with AES will be included.

**Inclusion criteria:** All the patients with fever and altered sensorium within 10 days of their illness will be included.

**Exclusion:** Patients with head injury, stroke, tumors, malignancy and history of chronic renal and hepatic failure will be excluded.

**Consent:** Written informed consent will be sought for all patients. In unconscious patients, family members will be approached.

**Randomization and registration:** not applicable. It is an observational study.

**Clinical monitoring:** Detailed medical history including the demographic details, duration of illness, altered sensorium, seizures (type, frequency, duration and its temporal relation to hyponatremia), focal deficit, behavioural changes, headache, vomiting and features of raised intracranial pressure such as extensor posturing, pupillary asymmetry and reaction, hyperventilation and gastric haemorrhage will be noted.

**Laboratory monitoring:** Base line tests including haemoglobin, liver function tests, (serum bilirubin, transaminases and alkaline phosphatase) serum creatinine, fasting and postprandial blood sugar, HIV serology, performed at admission. Cerebrospinal fluid (CSF) was examined for proteins, cells, glucose, bacteria, fungi, malignant cells, acid fast bacilli, BACTEC culture. Serum osmolality, urine osmolality and urine sodium were measured. Serum sodium levels were checked on alternate days till the correction of serum sodium or until the patient was discharged, whichever earlier. Daily fluid
intake and output chart was maintained and total fluid balance was calculated. Body weight was measured on admission and daily variation of weight was monitored using a special bed (LINET Eleganza3XC, Czech Republic).

**Radiology:** Patients will have a chest radiograph, Ultrasound abdomen performed on admission. A CT or MRI brain scan will also be performed in all the patients at admission. Further imaging will be performed in the event of a clinical deterioration.

**Data collection:** All information related to the study will be stored in individual patient case record forms. Data will be uploaded to the computerized database.

**Outcome measures:** The frequency of hyponatremia and the basis of hyponatremia in acute encephalitic syndrome (AES). hyponatremia related seizures and encephalopathy in AES, the effect of hyponatremia (CSW + SIADH) on mortality and functional outcome (based on GCS and m RS scale) (see appendix 1.2).

**Data analysis:** The incidence of hyponatremia and its basis (SIADH Vs CSW) would be categorized. The relationship of hyponatremia with aetiology of AES, presence of raised intracranial pressure, age, gender, GCS, APACHE-II, EEG changes, MRI changes and outcome will be evaluated by using various parametric and nonparametric tests. The relationship of CSW and SIADH will be evaluated with vasopressin, atrial natriuretic hormone and brain natriuretic factors by linear regression test. The statistical analysis will be done using SPSS15 version and Graphpad prism 5.

**Data safety and monitoring committee (DSMC):** The institute ethics committee will oversee the safety of the study.

**1.2 Background and rationale:**

Hyponatremia is the commonest electrolyte abnormality and is reported in 7-31% patients admitted in intensive care unit (ICU). Hyponatremia results in high mortality. In a study, hyponatremia resulted in 60 times more deaths compared to those without hyponatremia (Anderson 1985). Hyponatremia results in diverse neuropsychiatric symptoms and in severe cases it may result in seizures and coma. Rapid correction of hyponatremia results in osmotic demyelination of brain resulting in pontine and extrapontinemyelinolysis. These changes may add to the existing neurological dysfunction in AES. In a study on subarachnoid haemorrhage, 56 patients had hyponatremia (<135 mmeq/L); 19.6% of these patients had severe hyponatremia (<120 meq/L) (Sharlock et al 2006). Hyponatremia is attributed to syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and is thought to be a commoner cause (Serda et al 2006). Hyponatremia can also occur due to release of atrial or brain derived natriuretic factor in the patients who are mechanically ventilated and have central nervous system (CNS) insult. It results in syndrome of cerebral salt waiting. It is important to differentiate CSW from SIADH as the management of both the conditions is different and wrong management can
worsen hyponatremia and even lead to death. In 31 patients with subarachnoid haemorrhage, hyponatremia was due to high level of atrial natriuretic peptide rather due to SIADH (Kurukawa et al 1996). In another study in neuro intensive care unit (ICU) patients, 44 out of 144 patients had hyponatremia. Fluid restriction was done in 17 and majority of them developed infarcts and it was felt that many of these patients might actually have CSW (Wijdick et al 1985). These studies highlight the importance of differentiating SIADH versus CSW for preventing neurological complications. On the other hand, fluid replacement in SIADH results in further worsening of hyponatremia and its potential complications. There is very little information available on the underlying cause of hyponatremia in the patients with CNS infection, although hyponatremia has been reported in 7-32% patients. Patients with meningitis (Dodge 1975; Karar Danis and Shuklamn 1976). Traditionally SIADH is thought to be the underlying basis of hyponatremia in meningitis (Figin and Kaplan 1977; Kalan and Figin 1978). In a study, the analysis of laboratory results revealed hyponatremia and increased level of ADH but their fluid balance was negative which could explain the elevated ADH (Vianchetti et al 1996). There is increasing evidence of CSW in TBM (Nortam et al 1994; Ti et al 1998). A prospective study on fluid restriction in meningitis did not improve the outcome of meningitis and the authors suggested that fluid restriction should be avoided (Singhi et al 1995). A review of Indian studies on hyponatremia revealed that in medical tertiary center hyponatremia was present in 16.4% and one third of these patients were due to SIADH. The commonest cause was gastrointestinal, lung infection and sepsis (Chaterjee et al 2012). In pediatric ICU patients with neurological illness hyponatremia was present in 15% patients; SIADH in 33%, CSW in 17%, dehydration in 28% and drugs in 22% (Jayakumar et al 2006). It is important to evaluate the status of hyponatremia and other electrolyte changes in AES and evaluate the relative frequency of CSW and SIADH in these patients for proper management. The information generated in such a study will help in developing a protocol for the management of hyponatremia. Seizures in febrile encephalopathy occur in about 40% patients which may be due to encephalitis per se or due to hyponatremia. The management of seizure in both these conditions is different from that of seizure due to hyponatremia.

1.3 Treatment of cerebral salt wasting (CSW)

Cerebral salt wasting (CSW) is defined as renal loss of sodium due to intracranial diseases leading to hyponatremia, excessive natriuresis, volume depletion which responds to volume and salt replacement. The current management includes volume replacement with either iv 0.9% saline or oral salt supplementation for hyponatremia. In CSW, there is inhibition of renin angiotensin aldosterone system (RAAS), hence for the treatment of refractory patients with CSW, fludrocortisone has been advised.

2. Study aims:
2.1 **Primary aim:** The primary aim will be to document the frequency of hyponatremia in acute encephalitic syndrome (AES).

2.2 **Secondary aims:**
- To evaluate the basis of hyponatremia in the patients with AES- cerebral salt wasting (CSW) versus syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in the patients with AES.
- To evaluate the role of hyponatremia in producing seizures and encephalopathy in AES.
- To evaluate the effect of hyponatremia (CSW + SIADH) on mortality and functional outcome at discharge-based Glasgow outcome scale (GCS and m RS scale).
- To recommend the treatment protocol for management of hyponatremia in AES.

3. **Design:**

3.1. **Study design:** Prospective observational study in AES patients admitted to NICU.

3.2. **Randomization procedure:** Not applicable. It is an observational study.

3.3. **Target population:** All the patients with fever and altered sensorium within 10 days of their illness diagnosed as AES.

3.4. **Inclusion criteria:** All the patients with fever and altered sensorium within 10 days of their illness will be included (see appendix 1.1).

3.5. **Patients’ diagnostic categorization:** The etiology of the patients would be categorized based into encephalopathy (normal CSF) and encephalitis (CSF pleocytosis). The further categorization of encephalitis will be done based on microbiological findings (see appendix 1.1).

3.6. **Exclusion criteria:** Patients with head injury, stroke, tumors, malignancy and history of chronic renal and hepatic failure will be excluded.

3.7. **Hyponatremia and its cause:** Serum sodium < 135 meq/L would be taken as hyponatremia and will be categorized into mild (>120 meq/L) and severe (<120 meq/L). In the patients with hyponatremia, serum sodium will be done daily till it is corrected. In the patients with normal baseline serum sodium, twice weekly or more frequently if clinically indicated will be done for 1 week. Serum and urinary osmolality will be done at the time of hyponatremia. Urinary sodium will also be measured. ABG and intake output chart along with clinical findings will be reviewed daily. Depending on the serum chemistry, urinary intake output, urinary sodium and osmolality and central venous pressure the patients would be categorized into CSW and SIADH.

3.8. **Criteria for the diagnosis of Cerebral salt wasting (CSW):**

Two out of 4 of the followings will be required (see appendix 1.1):

- Elevated HCT, Hb, serum albumin, urea
- Autonomic changes: tachycardia, postural hypotension
- CVP< 6
3.9. Criteria for the diagnosis of SIADH (see appendix 1.1).

Two out of 4 of the followings will be required:

- Positive fluid balance
- CVP > 6
- Normal HCT, Hb, serum albumin, urea, HCO₃
- Absence of tachycardia and postural hypotension

4. Patient management:

4.1 Consent: A patient cannot enter the trial without informed consent. Written informed consent will be sought for all patients or their relatives entering the study.

4.2 Initial evaluation:

Detailed medical history including the demographic details, duration of illness, altered sensorium, seizures (type, frequency, duration and its temporal relation to hyponatremia), focal deficit, behavioural changes, headache, vomiting and features of raised intracranial pressure such as extensor posturing, pupillary asymmetry and reaction, hyperventilation and gastric haemorrhage will be noted. Presence of pallor, edema, neck vein, jaundice, petechiae, ecchymosis, ascites, hepatosplenomegaly, lymphadenopathy, chest rales and cardiac murmur will be noted. Patients’ consciousness would be recorded by Glasgow coma scale and clinical states of by APACHE-II.

Presence of cranial nerve palsy and Papilloedema will be recorded. Focal weakness (hemi, para or quadriplegia) will be categorized into severe and mild and tendon reflex and muscle tone will be noted. Cerebellar and sensory functions will be tested who could co-operate for the test. The etiology of the patients would be categorized based into encephalopathy (normal CSF) and encephalitis (CSF pleocytosis). The further categorization of encephalitis will be done based on microbiological findings. Serum sodium < 135 meq/L would be taken as hyponatremia and will be categorized into mild (>120 meq/L) and severe (<120 meq/L). In the patients with hyponatremia, serum sodium will be done daily till it is corrected. In the patients with normal baseline serum sodium, twice weekly or more frequently if clinically indicated will be done for 1 week. Serum and urinary osmolality will be done at the time of hyponatremia. Urinary sodium will also be measured. ABG and intake output chart along with clinical findings will be reviewed daily. Depending on the serum chemistry, urinary intake output, urinary sodium and osmolality and central venous pressure the patients would be categorized into CSW and SIADH.
4.3 Enrolment, randomisation and blinding: 150 consecutive patients with AES will be included in the study. This is a prospective observational cohort study, hence, randomisation and blinding will not be needed.

4.4 Treatment of AES:
The treatment will be based on the primary cause as follows:

- **Herpes simplex and varicella encephalitis**: Iv acyclovir 500 mg iv three times a day or gancyclovir 1000 mg three times an day with close monitoring of the renal function. In case of renal insufficiency, renal adjusted dose will be given.

- **Malaria**: Iv artesunate at a dose of 2.4 mg/kg stat followed by the same dose after 12 and 24 hours followed by 2.4 mg/kg/ day iv once daily for 7 days along with capsule doxycycline 100 mg two times a day for the same duration.

- **Scrub typhus**: Cap doxycycline 100 mg twice a day for 5 days or inj azithromycin 500 mg once daily for 5 days.

- **Pyogenic meningitis**: Iv ceftriaxone 2gm iv bd along with iv vancomycin 1 gm iv twice a day for 14-21 days. Renal functions will be closely monitored. Patients will also receive iv dexamethasone for the first 4 days with the first dose 1 hour before the antibiotics.

- **Cryptococcal and fungal meningitis** will be treated with iv amphotericin-B in a dose of 0.75 - 1mg/kg/ day along with fluconazole during the induction phase followed by only fluconazole PO during the maintenance phase.

- Patients will other aetiologies will receive symptomatic treatment. All patients will receive nasogastric feeding as indicated and artificial ventilation if there is respiratory failure (inability to maintain O₂ saturation on ventimask, pH<7.3 and PaCO₂>50mmHg).

4.5. Treatment of CSW

All the patients were given intravenous0.9% saline with oral salt supplementation (5-12 grams/day) through naso-gastric tube or in capsule. 3% saline was used if there was an emergency like seizures or coma with severe hyponatremia.

4.6 Treatment of SIADH: Patients with SIADH will be managed with free fluid restriction. Care will be taken to prevent dehydration.

4.7 Treatment of other causes of hyponatremia: Other causes of hyponatremia will be managed according to the primary cause as follows:

- **Diuretic induced**: Withdrawal of diuretics.

- **Endocrine abnormalities**: In case of hypothyroidism, patients will be supplemented with oral thyroxin and serum TSH will be monitored closely and will be maintained in between 0.5 – 5 IU/dl. Those with hyponatremia due to primary or secondary adrenal failure will be treated with maintenance steroids.
• **Heart failure/ renal failure and hepatic failure:** Hyponatremia will be managed by restriction of free water and stopping diuretics.

• **Poor intake:** Patients will be hydrated with IV 0.9% saline and oral salt supplementation.

• **Other miscellaneous causes** will receive symptomatic treatment as and when needed.

**4.8. Clinical Monitoring:** Detailed medical history including the demographic details, duration of illness, altered sensorium, seizures (type, frequency, duration and its temporal relation to hyponatremia), focal deficit, behavioural changes, headache, vomiting and features of raised intracranial pressure such as extensor posturing, pupillary asymmetry and reaction, hyperventilation and gastric haemorrhage will be noted. Presence of pallor, edema, neck vein, jaundice, petechiae, ecchymosis, ascites, hepatosplenomegaly, lymphadenopathy, chest rales and cardiac murmur will be noted. Patients’ consciousness would be recorded by Glasgow coma scale and clinical states of by APACHE-II. Presence of cranial nerve palsy and Papilloedema will be recorded. Focal weakness (hemi, para or quadriplegia) will be categorized into severe and mild and tendon reflex and muscle tone will be noted. Cerebellar and sensory functions will be tested who could co-operate for the test. Skin turgor, mucous membrane, nutritional states, measurement of weight if possible, neck vein engorgement, edema, pulse and blood pressure (if possible in lying and sitting) will be recorded daily. Other causes of hyponatremia eg. due to extra-renal loss (vomiting, diarrhoea), poor intake or drugs will also be recorded. Input-output charting and weight measurement will be done daily. Total Input will include all the liquid items consumed by the patient along with intravenous fluids administered. Solid food items which cannot be measured will be excluded. Catheter, either foleys (in case of altered sensorium) or external catheters will be used to measure total daily urine output. Insensible loss of 500 ml will be added to calculate daily fluid balance. Weight will be measured using a weighing machine if patient is conscious and able to stand independently. In case of poor sensorium or unable to stand independently, beds with automated weight measurements will be used. CVP will be monitored whenever required. Patients will have daily review until discharge from hospital. Patients will be monitored closely for

- Death (days from randomization to death)
- Neurological deterioration (onset of new focal neurological signs or fall in Glasgow coma score of >2 points.
- Drug-related adverse events (Appendix 1.5 and 1.6)

Uniform management of patients and recording of data will be ensured by the principal investigator who will make a daily round of all study participants.

**4.9 Laboratory monitoring:**
Blood counts, haemoglobin, haematocrit, serum electrolytes (sodium, potassium, magnesium), transaminases, bilirubin, blood urea, serum creatinine, calcium, serum protein, albumin, arterial blood gas would be lactate would be estimated. 24 urinary volume, electrolyte osmolality would be measured. Chest radiograph, 12 lead ECG and cranial MRI of brain will be done. For JE, CSF IgM antibody will be done by pan-bio (Australia), for dengue serum NS1 antigen test will be done by Bio Red ELISA kit and IgM antibody by Pan-Bio (Australia). CSF IgM for VZV will be done by abcam ELISA kit, serum IgM for Chikungunya and leptospira by SD Bio line. HSV and EBV will be done by CSF PCR. Peripheral blood smear will be examined for malaria. CSF will be also examined for tuberculosis, cryptococcal and pyogenic infection. Bedside EEG will be recorded in the NICU on admission using 10-20 system of electrodes placement. 1 hour EEG recording will be done at the baseline and the effect of photic stimulation and pin prick will be noted. The EEG may be categorized into normal and abnormal (focal or generalized slowing, epileptiform discharges or other abnormalities). If there is myoclonus EMG recording will be done. At the time of hyponatremia, brain natriuretic factor, vasopressin and atrial natriuretic factors will be measured. These levels will also be repeated after correction of hyponatremia. ANP, BNP will be measured by ELISA kits (RayBio ANP, BNP Enzyme Immunoassay (EIA) Kit) and vasopressin by ELISA kits (ABNOVA enzyme immunoassay kit). Other investigations are:

- Sputum, if symptomatic (routine culture, ZN stain, PCP immunofluorescence test)
- Urine culture, if urinary symptoms (urine culture)
- Stool culture, if prolonged diarrhoea (microscopy, culture and parasites)
- Blood cultures, if persistent fever (routine and mycobacterial cultures)
- Lymph node aspiration (routine and mycobacterial cultures).

4.10. Imaging
Chest and brain imaging will be performed as per the study schedule and as clinically indicated – i.e. in the event of pulmonary or neurological deterioration.

4.11 Withdrawal from the study
Patients may voluntarily withdraw from the study for any reason. If this occurs, the researchers are under no obligation to provide treatment. The patient’s withdrawal from the study will not affect their access to the best standard of care within the Institutional health system. Clinical and laboratory assessment will be performed and recorded at the time of withdrawal.

4.12 Recording and reporting of death, adverse events or protocol violations

4.12.1 Death
If the patient dies, the principal investigator should inform the institute ethical committee as soon as possible and complete the specific case report form.
4.12.2 Adverse events

If the patient dies or experiences an adverse event (serious, grade 3 or 4, or one leading to modification of treatment, see Appendix 1.3 Common Toxicity Criteria) the principal investigator should inform the institute ethical committee as soon as possible and complete the specific case report form. When applicable, adverse events will be treated as per the management guidelines in Appendix 1.5.

According to the ICH Guidelines for Clinical Safety Data Management, definitions and Standards for Expedited Reporting (1994), a serious adverse event (SAE) is defined as “any untoward medical occurrence that:

- Results in death
- Is life threatening
- Requires unplanned inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or is a congenital anomaly/ birth defect
- any other important medical condition, which, although not included in the above, may jeopardize
- the subject and may require medical or surgical intervention to prevent one of the outcomes listed.”

All SAEs will be recorded on the patient Case Report Form.

Unexpected SAEs (USAEs) and events which become of concern to study investigators during the course of the study will be reported to the institute Ethics Committee within 24 hours of occurrence. Depending on the severity of USAEs the institute Ethical Committee (IEC) will be informed as follows:

a) USAEs that resulting in death or are life threatening: Initial written report will be sent as soon as possible and within 7 days of occurrence. The format and content of the initial report should follow the IEC report template and include all information available at the time of reporting. A follow up report with complete details will be sent within 15 days of the initial report.

b) For USAEs that do not result in death or not life threatening: USAE will be reported to IEC) as soon as possible and within 15 days of occurrence

5. Statistical Analysis:

150 AES patients would be recruited. The incidence of hyponatremia and its basis (SIADH Vs CSW) would be categorized. The relationship of hyponatremia with etiology of AES, presence of raised intracranial pressure, age, gender, GCS, APACHE-II, EEG changes, MRI changes and outcome will be evaluated by using various parametric and nonparametric tests. The relationship of CSW and
SIADH will be evaluated with vasopressin, atrial natriuretic hormone and brain natriuretic factors by linear regression test. The statistical analysis will be done using SPSS 15 version and Graphpad prism.

6. Ethical approval: This protocol, the informed consent form and any subsequent modifications of these documents, will be reviewed by the institutional ethical committee, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow.

7. Confidentiality: Confidentiality of the patients will be dully maintained. Clinical information will not be released without written permission of the patient.

8. Clinical study specimens
All clinical trial specimens will be labelled with the patient’s number. Samples will be transferred to the laboratories at the Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow for processing. Investigation results will be issued to the investigators in a timely manner and a hard copy of the results will be retained in the laboratory for verification.

9. Publications
Any publication or presentation during the active phase of the study must have permission from the Investigators. The investigators will define the strategy for publication, resolve any problems of authorship and maintain the quality of publications. All publications will acknowledge the appropriate funding sources. The investigators are the custodian of the data and specimens generated from this trial.

10. Sub studies
- Various causes of hyponatremia in patients with AES.
- Role of atrial and brain natriuretic peptide (ANP and BNP) in patients with CSW with TBM and AES.
- Incidence of stroke in patients with CSW in TBM and AES.

11. Appendices:
Appendix 1.1 - Diagnostic criteria for acute encephalitic syndrome (AES), cerebral salt wasting and SIADH.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES</td>
<td>AES was defined as a patient with encephalopathy (defined altered level of consciousness, lethargy, or a personality change lasting 24 h) and fever for more than 10 days (but not TBM as per case definition for clinical research\textsuperscript{16} and one of the following: seizure, focal neurological findings, CSF pleocytosis, electroencephalography or neuroimaging findings consistent with encephalitis\textsuperscript{17}. For specific diagnosis of AES, the patients were investigated for common</td>
</tr>
</tbody>
</table>
etologies such as pyogenic meningitis, Japanese encephalitis virus (JEV), herpes simplex virus (HSV), dengue, varicella zoster virus (VZV), Epstein Bar virus (EBV), Chikungunya, scrub typhus, leptospirosis and malaria. The patients without above mentioned etiology were categorized as nonspecific AES.

<table>
<thead>
<tr>
<th>Diagnosis of cerebral salt wasting</th>
<th>Two out of 4 of the followings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Elevated HCT, Hb, serum albumin, urea</td>
</tr>
<tr>
<td></td>
<td>Autonomic changes: tachycardia, postural hypotension</td>
</tr>
<tr>
<td></td>
<td>CVP&lt; 6</td>
</tr>
<tr>
<td></td>
<td>Negative fluid balance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis of SIADH</th>
<th>SIADH would be diagnosed on following (2/4 of the followings)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive fluid balance</td>
</tr>
<tr>
<td></td>
<td>CVP &gt; 6</td>
</tr>
<tr>
<td></td>
<td>Normal HCT, Hb, serum albumin, urea, HCO₃</td>
</tr>
<tr>
<td></td>
<td>Absence of tachycardia and postural hypotension</td>
</tr>
</tbody>
</table>

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**Appendix 1.2: The Modified Rankin Scale grade Description**

0 = No symptoms
1= Minor symptoms not interfering with lifestyle
2 = Symptoms that lead to some restriction in lifestyle, but do not interfere with the patient’s ability to look after themselves
3= Symptoms that restrict lifestyle and prevent totally independent living
4= Symptoms that clearly prevent independent living, although the patient does not need constant care and attention.
5 = Totally dependent, requiring constant help day and

**Appendix 1.3: Table of common toxicity criteria and grading**

ULN = upper limit of normal local reference range

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>8.0 – 9.4g/dl</td>
<td>7.0 – 7.9g/dl</td>
<td>6.5 – 6.9g/dl</td>
<td>&lt;6.5g/dl</td>
</tr>
<tr>
<td>White cell count</td>
<td>3.0 – 3.9 x 10³</td>
<td>2.0 – 2.9 x 10³</td>
<td>1.0 - 1.9 x 10³</td>
<td>&lt;1.0 x 10³</td>
</tr>
</tbody>
</table>

---

15 | Page
<table>
<thead>
<tr>
<th>Platelet Prothrombin time</th>
<th>cells/μl</th>
<th>cells/μl</th>
<th>20 - 49 x 103 cells/μl</th>
<th>&lt;20 x 103 cells/μl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75 - 99 x 103 cells/μl</td>
<td>50 - 74 x 103 cells/μl</td>
<td>&gt;1.5 – 3.0 x ULN</td>
<td>&gt;3.0 x ULN</td>
</tr>
<tr>
<td></td>
<td>&gt;1.0 – 1.25 x ULN</td>
<td>&gt;1.25 – 1.5 x ULN</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Biochemical**

<table>
<thead>
<tr>
<th>Hyponatremia</th>
<th>130 – 135 meq/l</th>
<th>120 – 129 meq/l</th>
<th>110 – 119 meq/l</th>
<th>&lt;109 meq/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypermotremia</td>
<td>146 – 150 mmol/l</td>
<td>151 – 157 mmol/l</td>
<td>158 – 165 mmol/l</td>
<td>&gt;165 mmol/l</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>3.0 – 3.4 mmol/l</td>
<td>2.5 – 2.9 mmol/l</td>
<td>2.0 – 2.4 mmol/l</td>
<td>&lt;2.0 mmol/l</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>5.6 – 6.0 mmol/l</td>
<td>6.1 – 6.5 mmol/l</td>
<td>6.6 – 7.0 mmol/l</td>
<td>&gt;7.0 mmol/l</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>3.1 – 3.6 mmol/l</td>
<td>2.2 – 3.0 mmol/l</td>
<td>1.7 – 2.1 mmol/l</td>
<td>&lt;1.7 mmol/l</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>6.5 – 9.0 mmol/l</td>
<td>9.1 – 14.0 mmol/l</td>
<td>14.1 – 28.0 mmol/l</td>
<td>&gt;28.0 mmol/l,</td>
</tr>
<tr>
<td>Urea</td>
<td>1.25 – 2.5 x ULN</td>
<td>&gt;2.5 – 5.0 x ULN</td>
<td>&gt;5.0 – 10.0 x ULN</td>
<td>&gt;10.0 x ULN</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&gt;1.0 – 1.5 x ULN</td>
<td>&gt;1.5 – 3.0 x ULN</td>
<td>&gt;5.0 – 10.0 x ULN</td>
<td>&gt;5.0 x ULN</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&gt;1.0 – 1.5 x ULN</td>
<td>&gt;1.5 – 2.5 x ULN</td>
<td>&gt;3.0 – 6.0 x ULN</td>
<td>&gt;10.0 x ULN</td>
</tr>
<tr>
<td>ALT</td>
<td>1.25 – 2.5 x ULN</td>
<td>&gt;2.5 – 5.0 x ULN</td>
<td>&gt;5.0 – 10.0 x ULN</td>
<td></td>
</tr>
</tbody>
</table>

**Gastrointestinal**

<table>
<thead>
<tr>
<th>Stomatitis/mouth ulcers</th>
<th>Mild discomfort, no limits on Activity</th>
<th>Some limits on eating or talking</th>
<th>Eating/talking very limited</th>
<th>Requiring IV fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate discomfort or significantly decreased intake for &gt; 3 days</td>
<td>Severe discomfort or minimal intake for 3 days</td>
<td>Hospitalization required</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nausea</th>
<th>Mild or transient discomfort, maintains reasonable intake</th>
<th>Moderate discomfort or significantly decreased intake for &gt; 3 days</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Vomiting</th>
<th>Mild or transient, 2-3 episodes per day or mild vomiting lasting &lt; 1 week</th>
<th>Moderate or persistent, 4-5 episodes/day or vomiting lasting&gt;1 week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe vomiting of all foods/fluids in 24 hours or orthostatic hypotension or IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypotensive shock or hospitalization required for IV fluids</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>fluids required</td>
<td></td>
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<tr>
<td>-----------------------</td>
<td>------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild, no treatment</td>
<td>Moderate or requires nonnarcotic analgesia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe or responds to first narcotic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intractable or requiring repeated narcotics</td>
<td></td>
</tr>
<tr>
<td>Consciousness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty in</td>
<td>Mild confusion or lethargy &lt;50% waking hours</td>
<td></td>
</tr>
<tr>
<td>concentration or</td>
<td>Disorientation or stupor &gt;50% of waking hours</td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>Coma or seizures</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild agitation or</td>
<td>Some limitation in activities of daily living</td>
<td></td>
</tr>
<tr>
<td>confusion</td>
<td>and minimal treatment required</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment and assistance required, severe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>agitation or confusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toxic psychosis or hospitalization</td>
<td></td>
</tr>
<tr>
<td>Clinical myopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal findings</td>
<td>Moderate myalgia or difficulty climbing stairs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or rising from sitting position, able to walk,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>may need NSAID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate to severe myalgia needing NSAID,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>assistance required for walking or general</td>
<td></td>
</tr>
<tr>
<td></td>
<td>activities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe myalgia unrelated to exercise requiring</td>
<td></td>
</tr>
<tr>
<td></td>
<td>narcotics, unable to walk or necrosis or oedema</td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild impairment</td>
<td>Moderate impairment (moderately decreased</td>
<td></td>
</tr>
<tr>
<td>(decreased sensation</td>
<td>sensation e.g. vibratory, pinprick, hot/cold</td>
<td></td>
</tr>
<tr>
<td>e.g. vibratory,</td>
<td>in great toes) in focal area or symmetrical</td>
<td></td>
</tr>
<tr>
<td>pinprick, hot/cold</td>
<td>distribution</td>
<td></td>
</tr>
<tr>
<td>in great toes)</td>
<td>Moderate impairment that is</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe impairment (decrease or loss of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sensation to knees or wrists) or loss of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sensation of moderate degree in multiple</td>
<td></td>
</tr>
<tr>
<td></td>
<td>different body areas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensory loss involves limbs and trunk</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Parasthæsia</td>
<td>Mild discomfort, no treatment</td>
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<tr>
<td></td>
<td>Moderate discomfort, requiring non-narcotic analgesia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe discomfort or symptoms respond to narcotic analgesia</td>
<td></td>
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<tr>
<td></td>
<td>Incapacitating or not responsive to narcotics</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Mild paraesthesia, numbness, pain or weakness, not treated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate paraesthesia, numbness or pain, objective weakness, requires analgesic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe, narcotic required, interferes with normal activity</td>
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<tr>
<td></td>
<td>Intolerable, incapacitating, unable to walk despite narcotics, paralysis</td>
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<tr>
<td>Respiratory</td>
<td>Transient, no treatment, 70-80% peak flow or FEV1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Requires treatment, normalizes with bronchodilator, 50-69% peak flow or FEV1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No normalization with bronchodilator, 25-49% peak flow or FEV1, retractions</td>
<td></td>
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<tr>
<td></td>
<td>Cyanosis, intubated or &lt;25% peak flow or FEV1</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Transient, increase &gt;20mm/Hg, no treatment</td>
<td></td>
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<tr>
<td></td>
<td>Recurrent, chronic increase &gt;20mm/Hg, requires treatment</td>
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<td></td>
<td>Acute treatment required, outpatient, hospitalization possible</td>
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<tr>
<td></td>
<td>Hospitalization required</td>
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<tr>
<td>Haemorrhage</td>
<td>Microscopic or occult</td>
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<td></td>
<td>Mild, no transfusion</td>
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<td></td>
<td>If Hb&lt;6.6 g/l or if Hct&lt;20% transfuse packed red cells or whole blood based on clinical care</td>
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<td></td>
<td>Massive blood loss or transfused &gt;2 units</td>
<td></td>
</tr>
<tr>
<td>Other features</td>
<td>Gross blood loss or transfused 1-2 units</td>
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<td>----------------</td>
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<td></td>
</tr>
<tr>
<td>Fever, oral, &gt; 12 hours</td>
<td>37.7-38.5°C</td>
<td>38.6-39.5°C</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Pruritus without rash</td>
<td>Localized urticaria</td>
</tr>
<tr>
<td>Rash</td>
<td>Rash, erythema or pruritus</td>
<td>Diffuse maculopapular rash or dry desquamation</td>
</tr>
</tbody>
</table>

**Appendix 1.4 Guide to management of toxicities**

- **1.4.1 Grade 1 clinical or laboratory toxicities**
  - Continue study drugs

- **1.4.2 Grade 2 clinical or laboratory toxicities**
  - Continue study drugs
  - If relevant, monitor more closely and consider more frequent laboratory assessments
  - Investigate to exclude other causes

- **1.4.3 Grade 3 clinical or laboratory toxicities**
  - Monitor more closely
  - Perform more frequent laboratory assessments
  - Investigate to exclude other causes
For AST or ALT > 5 x ULN, stop all study drugs until toxicity resolves and consider reintroduction of AES drugs sequentially.

○ For other grade 3 toxicities the clinician may immediately stop study drugs if confirmatory test cannot be performed within 72 hours or if the clinician determines that continuation of study drugs is unsafe while awaiting test results

○ Fill in an adverse event form and inform the institute ethics committee.

1.4.4 Grade 4 clinical or laboratory toxicities

○ Monitor more closely

○ Perform more frequent laboratory assessments

○ Investigate to exclude other causes

○ For all grade 4 toxicities that are attributable to AES drugs, stop all drugs until toxicity resolves and restart them slowly in low dose initially.

○ For other grade 4 toxicities the clinician may immediately stop study drugs if confirmatory test cannot be performed within 72 hours or if the clinician determines that continuation of study drugs is unsafe while awaiting test results

○ If any doubt about management discuss with the principal investigator

○ Fill in an adverse event form and inform the institute ethics committee.

Appendix 1.5 Management of serious adverse effects of drugs requiring drug discontinuation

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Possible offending Drugs</th>
<th>Clinical signs/symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe skin rash and/or Stevens-Johnson syndrome</td>
<td>Acyclovir, artesunate, gancyclovir, doxycycline, cephalosporins, vancomycin</td>
<td>All drugs may cause severe rash and/or Stevens-Johnson syndrome</td>
<td>For severe rash and/or Stevens-Johnson syndrome, stop all drugs. Once rash has improved restart AES drugs sequentially. If rash recurs, stop suspect drug permanently.</td>
</tr>
<tr>
<td>Severe anaemia</td>
<td>Acyclovir, artesunate, gancyclovir, doxycycline, cephalosporins,</td>
<td>Pallor, tachycardia, shortness of breath on exertion</td>
<td>Exclude haemolysis. Stop the drug and consider alternative drug.</td>
</tr>
<tr>
<td>Adverse Effect</td>
<td>Treatment</td>
<td>Management</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-----------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>Acyclovir, artesunate, gancyclovir, doxycycline</td>
<td>Fatigue, anorexia, gastrointestinal symptoms, jaundice, hepatomegaly, AST or ALT &gt; 5 x ULN</td>
<td>Monitor serum bilirubin and transaminases. Stop all drugs until symptoms resolve and ALT improves to &lt; 2.5 x ULN.</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Fludrocortisone</td>
<td>Palpitations, missed beats, cramps in the legs</td>
<td>Give syrup containing potassium, stop the drug in case of intractable hypokalemia</td>
</tr>
<tr>
<td>Pulmonary edema and heart failure</td>
<td>Fludrocortisone</td>
<td>Breathlessness, cough with frothy expectoration</td>
<td>Give iv furexemide and wait. Exclude neurogenic pulmonary edema. If intractable then stop fludrocortisone.</td>
</tr>
<tr>
<td>Pedal edema</td>
<td>Fludrocortisone</td>
<td>Swelling of legs</td>
<td>Monitor, give intravenous furexemide in intractable cases.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Fludrocortisone</td>
<td>Breathlessness, palpitations, signs of raised ICP.</td>
<td>Give iv furexemide. Stop the drug.</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Vancomycin, acyclovir, gancyclovir, amphotericin-B</td>
<td>Facial puffiness, pedal edema, oliguria, hematuria</td>
<td>Stop the offending drug, start a substitute and dialysis if required.</td>
</tr>
</tbody>
</table>

Appendix 1.6: Management of common adverse effects of AES medications

### Gastrointestinal symptoms
Common in the first few weeks of treatment. Liver function tests should be checked and if the AST < 2 x ULN, the symptoms are assumed not to be due to hepatic toxicity. The initial management is to change the hour of drug administration and/or to administer the drugs with food.

### Rash
If mild, affecting only a limited area or predominantly causing itching an antihistamine may be given for symptomatic relief and AES treatment (see section 4.4) may be continued. If there is a generalized erythematous rash, especially if associated with fever and/or-mucous membrane involvement, stop all drugs. Once the rash has improved restart the drugs again starting at a low dose with gradual escalation.
Drug fever  Fever may persist for 2 months after treatment has been initiated. Recurrence of fever in a patient who has been on therapy for several weeks may be due to drug fever, especially if the patient is showing clinical and microbiological improvement. Fever may also be a feature of immune reconstitution syndrome or other HIV-related infections. Potential causes should be excluded before stopping AES treatment (see section 4.4) – drug fever usually resolves in 24 hours. Once the fever has resolved restart drugs slowly at a low dose with gradual escalation.

12. References:

Bibliography:


3. Final study protocol

Aetiology of hyponatremia, its relation to seizures and outcome in acute febrile encephalopathy – A prospective study in neurology intensive care unit (NICU) patients.

Sub study: Safety and efficacy of fludrocortisone in treatment of cerebral salt wasting in tuberculous meningitis

Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences

Final study protocol

Amendment approved on 30-09-2015

(Investigator initiated, open labelled, randomized controlled trial)

(Funded by ICMR)

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2. Summary
   2.1. Abstract
   2.2. Trial flow diagram
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   3.1. Background
   3.2. Fludrocortisone for CSW
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   5.2. Secondary endpoints
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   6.1. Study design
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   7.3. Criteria for the diagnosis of CSW
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   8.10. Imaging
   8.11. Withdrawal from the trial
   8.12. Recording and reporting of death, adverse events or protocol violations
   8.12.1. Death
8.12.2. Adverse events
8.12.3. Protocol violation

9. Drug regimens
  9.1. Antituberculous therapy
  9.2. Corticosteroid therapy

10. Management of antituberculous toxicity

11. Management of adverse events

12. Data on concomitant medications

13. Statistics
  13.1. Sample size and power considerations for the sub study only
  13.2. Analysis for the sub study
    13.2.1. Analysis of the primary endpoint
    13.2.2. Analysis of secondary endpoints
  13.3. Analysis populations

14. Ethical approval

15. Confidentiality

16. Clinical trial specimens

17. Publication

18. Sub studies

19. Sampling and analysis at follow up

20. Appendices
  Appendix 1.1 - Diagnostic criteria for tuberculous meningitis and cerebral salt wasting.
  Appendix 1.2 Modified MRC grading for tuberculous meningitis
  Appendix 1.3 The Modified Rankin Scale grade Description
  Appendix 1.4 Details of ATT
  Appendix 1.5 Table of common toxicity criteria and grading
  Appendix 1.6 Guide to management of toxicities
  Appendix 1.7 Management of serious adverse effects of drugs requiring drug discontinuation
  Appendix 1.8 Management of common adverse effects of antituberculous medications
  Appendix 1.9 Reintroduction of antituberculous therapy following Drug induced hepatitis (DIH)
  Appendix 1.10 Consent forms
    1.10.1: Consent form in English (for those who can understand English)
    1.10.2: Consent form in Hindi.

References

Appendices
1. **Reason for Amendment**

1.1. The original study was an observation study to find the various causes of hyponatremia in the patients with acute encephalitis syndrome (AES). However, following the commencement of the study, it was realised that many patients with AES (presenting with fever, headache and altered sensorium within 10 days, as per definition in the protocol) turned out as Tubercular meningitis (TBM). Thus we planned to include patients with TBM separately in our study. For that, the duration of symptoms was changed from 10 days to 5 days in accordance to the uniform case definition for TBM. Finally, TBM patients were analysed separately to maintain homogeneity of the study.

1.2. During the initial study it was realized that cerebral salt wasting (CSW) was much more common in patients with TBM than AES. We also encountered difficulty in the management of hyponatremia along with severe and persistent polyuria (urine output >3.5L/day) and negative fluid balance in patients with TBM especially with conventional therapies which consisted of IV saline with oral salt supplementations was difficult.

1.3. So far, we couldn’t get any systematic study on the role of fludrocortisone in the management of CSW in patients with TBM, except for few case reports. Thus, it was considered appropriate to add fludrocortisone and document the results systematically under a well-designed randomized control trial. We included only patients with TBM for the trial because of 2 reasons a) CSW was much more common in TBM and b) to study homogenous group of patients for better generalizability of the results.

1.4. Thus amendment was done in the same study (same title) to include patients with TBM with CSW, and a randomized controlled trial using fludrocortisone was started.
2. **Summary**

2.1 **Abstract**

Cerebral salt wasting (CSW) is defined as renal loss of sodium due to intracranial diseases leading to hyponatremia, excessive natriuresis, volume depletion which responds to volume and salt replacement. The majority of patients with hyponatremia with normal renal functions were initially attributed to the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) which was reported seven years after CSW. Cerebral salt wasting was reintroduced by Nelson in 1981 and has been increasingly reported in a number of neurological conditions. Cerebral salt wasting has been reported to be more common than SIADH in stroke, acute encephalitis syndrome, tuberculous meningitis (TBM), traumatic brain injury and aneurismal subarachnoid haemorrhage (SAH). In the patients with SAH, delayed cerebral ischemia is a major concern and has been attributed to excessive natriuresis and hyponatremia and is associated with increased risk of infarction probably because of associated volume contraction. In TBM, CSW has been reported in 22.4% patients and stroke in up to 45%. Stroke in TBM may be attributed to volume contraction due to CSW, at least in some cases, especially those located in the internal border zone (Misra et al 2017 Unpublished observation). In CSW, there is inhibition of renin angiotensin aldosterone system (RAAS), hence for the treatment of refractory patients with CSW, fludrocortisone has been advised. There is limited experience on the role of fludrocortisone in the treatment of CSW which is mainly based upon isolated case reports. The only randomized control trial on the role of fludrocortisone, thus far has been done in patients with SAH which revealed benefit of fludrocortisone on sodium balance and reduction in delayed stroke. There is no randomized controlled trial, on the role of fludrocortisone in CSW associated with TBM. In the present study, we report the efficacy and safety of fludrocortisone in CSW associated with TBM.

**Scientific Title:** Etiology of hyponatremia, its relation to seizures and outcome in acute febrile encephalopathy – A prospective study in Neurology intensive care unit (NICU) patients.

**Title of the sub-study:** Safety and efficacy of fludrocortisone in treatment of cerebral salt wasting in tuberculous meningitis

**Aim:** To evaluate the efficacy and safety of fludrocortisone in the management of CSW in TBM vs. saline.

**Study design:** Investigator initiated, single centre, open labelled, randomized controlled trial conducted during 2015-2017 at a tertiary care teaching hospital in North India.

**Sample size calculation:** Due to the paucity of previous studies, the number of patients needed for the study was based on the assumption of a standard deviation of 2.5 days in the mean days to the hyponatremia correction (primary outcome) during the study period. To detect a difference of 25% between the study arm and the control arm, with a power of 80% at a significance level of 5% with
the use of a two-sided test, it was calculated that 16 patients in the each arm would be needed (Zhou X-H et al, Statistical Methods in Diagnostic Medicine. New York, NY: Wiley; 2002). Moreover, it was felt that it may not be possible to perform a complete evaluation of 10% of patients because of the possibility of withdrawal of consent, seeking other treatment options and leaving the hospital prematurely against advice. Thus, a final sample size of 18 patients in each arm was estimated for this trial.

**Inclusion criteria:** Age > 10 years; patients with TBM, who had CSW according to the predefined criteria, were included (see appendix 1.1).

**Exclusion criteria:** The patients below 10 years of age, pregnant and lactating women and those with malaria, septic, fungal or carcinomatous meningitis, head injury, brain tumors, primary renal, hepatic or cardiac failure, endocrinial disorders such as adrenal failure or hypothyroidism, malignancy or any condition limiting the life expectancy to 1 year or less was excluded; however if the patients developed hepatic or renal dysfunction during treatment were not excluded, lack of consent.

**Consent:** Written informed consent will be sought for all patients. In unconscious patients, authorized representatives will be approached for consent. For those below 20 years, written consent will be taken from their parents (appendix 1.10).

**Randomization and registration:** Diagnosed patients with TBM having CSW will be randomized to 0.9% IV saline with oral salt supplementation (5-12 grams/day) only or additional fludrocortisones (0.1-0.4 mg/day/PO) groups. Four drugs anti tubercular treatment with prednisolone and aspirin will be prescribed. All patients will also received four drugs anti tubercular treatment (RHZE) for six months followed by RH for 12 months. Rifampicin will be prescribed a dose of 10mg/kg (~450mg/d), isoniazide 5mg/kg (~300mg/d), pyrazinamide 25mg/kg (~1500mg/d) and ethambutol 15 mg/kg (~800mg/d). All patients will also receive prednisone 0.5 mg/kg (~40 mg/d) and aspirin up to 150mg/dorally daily, if not contraindicated. The patients will be subjected to ventriculo-peritoneal shunt or external ventricular drainage (EVD) or mechanical ventilation as indicated.(See Appendix 1.4)

**Clinical monitoring:** Patients will be monitored closely for drug toxicity, neurological deterioration and other clinical parameters. All patients will be reviewed daily as an inpatient until discharge. Study investigators will make a daily round of all inpatients to ensure uniformity of management and accurate recording of data. Once discharged, patients will be followed up at 1, 3 and 6 months.

**Laboratory monitoring:** Base line tests including hemoglobin, liver function tests, (serum bilirubin, transaminases and alkaline phosphatase) serum creatinine, fasting and postprandial blood sugar, HIV serology, performed at admission. Cerebrospinal fluid (CSF) will be examined for proteins, cells, glucose, bacteria, fungi, malignant cells, acid fast bacilli, BACTEC culture. Serum osmolality, urine osmolality and urine sodium will be measured. Serum sodium levels were checked on alternate days till the correction of serum sodium or until the patient is discharged, whichever earlier. Daily fluid
intake and output chart will be maintained and total fluid balance was calculated. Body weight was measured on admission and daily variation of weight will be monitored using a special bed (LINET Eleganza3XC, Czech Republic).

**Radiology:** Patients will have a chest radiograph, Ultrasound abdomen performed on admission. A CT or MRI brain scan will also be performed in all the patients at admission. Further imaging will be performed in the event of a clinical deterioration.

**Data collection:** All information related to the study will be stored in individual patient case record forms. Data will be uploaded to the computerized database.

**Outcome measures:** The primary endpoint was time to correct serum sodium and secondary endpoints were in-hospital deaths, disability at three and six months according to the “simple question” and the Rankin score (see appendix 1.3), frequency of stroke and grade 3&4 adverse events (appendix 1.5) of treatment. Survivors will be censored at the date they were last known to be alive.

**Data analysis** for the primary endpoint: Analysis will be based on the per-protocol and intention to treat principle including all randomized patients. The comparison of the primary endpoint will be done by Kaplan-Meier estimates, Cox regression models as described in the statistical section of the protocol.

**Data safety and monitoring committee (DSMC):** The institute ethics committee will oversee the safety of the trial.
2.2 Trial flow diagram

93 patients with suspected TBM were assessed for eligibility

Excluded (n = 4)
Uncertain diagnosis (n = 2); Neurocystercosis (n = 2)

89 patients were diagnosed with TBM

Hyponatremia (n = 48)

Patients with CSW fulfilling the inclusion criteria (n = 37)

Alternate cause of hyponatremia (n = 11)

Refused to participate (n = 1)

36 patients with TBM and CSW underwent randomization

Assigned to fludrocortisone with 0.9% iv saline and oral salt supplementation

Lost to follow up at 3 months (n = 0)
Included for Per Protocol analysis (n = 18)
Lost to follow up at 6 months (n = 3)
Included for Per Protocol analysis (n = 15)

Assigned to 0.9% iv saline and oral salt supplementation only

Lost to follow up at 3 months (n = 1)
Included for Per Protocol analysis (n = 17)
Lost to follow up at 6 months (n = 1)
Included for Per Protocol analysis (n = 17)

2.3 Trial flow chart
<table>
<thead>
<tr>
<th>Parameters /time</th>
<th>Admissi</th>
<th>Week</th>
<th>Week</th>
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<th>Week</th>
<th>Week</th>
<th>Dischar</th>
<th>1 mo</th>
<th>3 mo</th>
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</tr>
<tr>
<td>Input and output measurement</td>
<td>Daily</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>Patient or their relatives will be advised to maintain a notebook with 24 hours input output charts once every week. These charts will be reviewed at each follow up visit.</td>
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<td></td>
<td>Weekly (and may be repeated as when needed)</td>
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<tr>
<td>CBC (Hb, TLC, plt)</td>
<td>Weekly (and may be repeated as when needed)</td>
<td>2</td>
<td>2</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>Bili, AST, ALT, ALP, creat, urea, glucose, Albumin/ protein</td>
<td>Weekly (and may be repeated as when needed)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Serum Na, K</td>
<td>Alternate day (and may be repeated)</td>
<td></td>
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<tr>
<td>Test</td>
<td>As when needed</td>
<td>Weekly 1</td>
<td>Weekly 2</td>
<td>Weekly 3</td>
<td>Weekly 4</td>
<td>Weekly 5</td>
<td>Weekly 6</td>
<td>Weekly 7</td>
<td>Weekly 8</td>
<td>Weekly 9</td>
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<tr>
<td>HIV/ HbsAg, HCV</td>
<td>1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Blood cultures</td>
<td>2</td>
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<tr>
<td>CSF gram stain</td>
<td>2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>CSF India ink/ cryptococcal antigen</td>
<td>2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>CSF fungal culture, malignant cells</td>
<td>1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>CSF TB PCR</td>
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<tr>
<td>CSF TB smear, culture, DST</td>
<td>1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Chest X-ray/ USG abdomen</td>
<td>1</td>
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<tr>
<td>CT/ MRI brain with contrast</td>
<td>1</td>
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<td>ECG</td>
<td>1</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Urine osmolality and sodium</td>
<td>Twice weekly</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>X</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>Twice weekly</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>X</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Body weight</td>
<td>Daily</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>1</td>
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Note: the numbers denotes the number of times the assessment or the clinical tests will be done in a week. X denotes that the tests were not done. Mo= months

3. **Background and rationale**

3.1 **Background**

AES and Tuberculosis affects one third of world’s population and is a leading cause of human mortality and morbidity. AES and Tubercular meningitis usually present with similar symptoms of meningitis headache, fever, vomiting; seizures, cranial nerve palsy, focal neurological deficits and urinary symptoms. Hyponatremia is a commonly seen in patients with AES and TB meningitis and a major cause of encephalopathy, seizures or both. Hyponatremia is generally multifactorial. It may be due to poor intake, extra renal loss due to recurrent vomiting (raised intracranial pressure) or drug induced. Cerebral salt wasting and SIADH are other common but unrecognized causes of hyponatremia in patients with AES including TB meningitis. It is often difficult to distinguish between both, either clinically or bio-chemically. Cerebral salt wasting syndrome is characterized by natriuresis, hyponatremia and volume contraction in response to cerebral pathology. Differentiating it
from SIADH is key in managing a patient with CSWS as both are managed paradoxically but present somewhat similarly. The usual management of hyponatremia associated with CSW is IV fluids with oral salt supplementation and fludrocortisone.

**Hyponatremia in patients with AES including TB meningitis is multifactorial.** It may be due to poor intake, extra renal loss due to recurrent vomiting (raised intracranial pressure) or drug induced. Cerebral salt wasting and SIADH are other common but unrecognized causes of hyponatremia in such patients. Cerebral salt wasting syndrome is characterized by natriuresis, hyponatremia and volume contraction in response to cerebral pathology. Correct management of hyponatremia is crucial for good outcome. The original study was an observation study to find the various causes of hyponatremia in the patients with acute encephalitis syndrome (AES). However, following the commencement of the study, it was realised that many patients with AES (presenting with fever, headache and altered sensorium within 10 days, as per definition in the protocol) were diagnosed later as Tubercular meningitis (TBM). Thus we planned to include patients with TBM separately in our study. For that, the duration of symptoms was changed from 10 days to 5 days in accordance to the uniform case definition for TBM. Finally, they were analysed separately for the purpose of homogeneity of the patients. Also, it soon became apparent that cerebral salt wasting (CSW) was much more common in patients with TBM than AES. We also encountered difficulty in the management of hyponatremia along with severe and persistent polyuria (urine output >3.5L) and negative fluid balance in patients with TBM especially with conventional therapies which consisted of IV fluids (normal saline), oral salt supplementations was difficult. So far, we couldn’t get any systematic study on the role of fludrocortisone in the management of CSW in patients with TBM, except for few case reports. Thus, it was considered appropriate to add fludrocortisone and document the results systematically under a well-designed randomized control trial. We included only patients with TBM for the trial because of 2 reasons a) CSW was much more common in TBM and b) to study homogenous group of patients for better generalizability of the results. Thus amendment was done in the same study (same title) to include patients with TBM with CSW, and a randomized controlled trial using fludrocortisone was commenced.

Cerebral salt wasting (CSW) is defined as renal loss of sodium due to intracranial diseases leading to hyponatremia, excessive natriuresis, volume depletion which responds to volume and salt replacement. The current management includes volume replacement with either iv 0.9% saline or oral salt supplementation for hyponatremia. However, the polyuria generally responds poorly to this treatment. In CSW, there is inhibition of renin angiotensin aldosterone system (RAAS), hence for the treatment of refractory patients with CSW, fludrocortisone has been advised. There is limited experience on the role of fludrocortisone in the treatment of CSW which is mainly based upon isolated case reports. The only randomized control trial on the role of fludrocortisone, thus far has been done in patients with SAH which revealed benefit of fludrocortisone on sodium balance and
reduction in delayed stroke. There is no randomized controlled trial to guide treatment of CSW associated with TBM. This study will compare the role of fludrocortisone with convective therapy (iv saline with oral salt supplementation) for the treatment of CSW in TBM.

3.2 Fludrocortisone for CSW:
Mechanism of action: Fludrocortisone and other steroids with mineralocorticoid activity increase the reabsorption of Na+ from the urine, sweat, saliva, and the contents of the colon. Thus, mineralocorticoids cause retention of Na+ in the ECF. This expands ECF volume. In the kidneys, they act primarily on the principal cells (P cells) of the collecting ducts. Under the influence of fludrocortisone, increased amounts of Na+ are in effect exchanged for K+ and H+ in the renal tubules, producing a K+ diuresis and an increase in urine acidity.

Like many other steroids, fludrocortisone binds to a cytoplasm receptor, and the receptor-hormone complex moves to the nucleus where it alters the transcription of mRNAs. This in turn increases the production of proteins that alter cell function. The fludrocortisone - stimulated proteins have two effects—a rapid effect, to increase the activity of epithelial sodium channels (ENaCs) by increasing the insertion of these channels into the cell membrane from a cytoplasmic pool; and a slower effect to increase the synthesis of ENaCs. Among the genes activated by aldosterone is the gene for serum- and glucocorticoid-regulated kinase (sgk), a serine-threonine protein kinase. The gene for sgk is an early response gene, and sgk increases ENaC activity. Fludrocortisone also increases the mRNAs for the three subunits that make up ENaCs. The fact that sgk is activated by glucocorticoids as well as fludrocortisone is not a problem because glucocorticoids are inactivated at mineralocorticoid receptor sites. However, fludrocortisone activates the genes for other proteins in addition to sgk and ENaCs and inhibits others. Therefore, the exact mechanism by which fludrocortisone –induced proteins increase Na+ reabsorption is still unsettled.

Evidence is accumulating that fludrocortisone also binds to the cell membrane and by a rapid, nongenomic action increases the activity of membrane Na+/K+ exchangers. This produces an increase in intracellular Na+, and the second messenger involved is probably IP3. In any case, the principal effect of aldosterone on Na+ transport takes 10–30 min to develop and peaks even later, indicating that it depends on the synthesis of new protein by the genomic mechanism.

Metabolism: Fludrocortisone is metabolized in the liver to inactive glucuronide and sulfate metabolites. Fludrocortisone concentrations are best described by a one-compartmental model with first-order absorption, lag time, and first-order elimination. The peak plasma concentration is obtained almost 3 h after administration. Available data were assessed in healthy volunteers but using higher single doses (between 100μg and 2 mg) and found a wide range of plasma half-lives between 0.5 h and 3.6 h (Banda J et al 2015, Mitsky VP 1994). Inactive metabolites and small amounts of unmetabolized drug are excreted by the kidneys. Insignificant quantities of drug are also excreted in faeces. Biologic half-life is 18 to 36 hours.
**Pharmacokinetics:** Fludrocortisone is absorbed readily from the GI tract. It is removed rapidly from blood and distributed to muscle, liver, skin, intestines, and kidneys. It has a plasma half-life of about 3.5 hours. It’s extensively bound to plasma proteins (transcortin and albumin). Only the unbound portion is active. Adrenocorticoids are distributed into breast milk and through the placenta (Banda J et al 2015, Laviolle B, 2010).

**Toxicity:** The most noticeable side effects are sodium and water retention, hypertension, cardiac hypertrophy, edema, heart failure hypokalemia, bruising, diaphoresis, urticaria and allergic rash (Vogt W, 1971, Banda J et al 2015).

**Dosage:** The recommended dose of fludrocortisone is 0.1 – 0.4 mg PO/ day for the treatment of hyponatremia. In children below 18 years (but > 10 years), the dose should be reduced to 0.05 – 0.1 mg PO/ day.

**Interactions:** Amphotericin B and thiazide diuretics may enhance hypokalemia. Monitoring of electrolytes is essential in such cases. Barbiturates, phenytoin and rifampin decreases corticosteroid effects. Careful monitoring is required. The toxicity of Cardiac glycosides increases in the presence of hypokalemia. Isoniazid and salicylates increases the metabolism of fludrocortisone. Sodium-containing drugs or foods may increase blood pressure needing adjustment of sodium intake.

### 3.3 Proposed treatment protocol for fludrocortisone:

All the patients will receive intravenous 0.9% saline with oral salt supplementation (5-12 grams/day) through naso-gastric tube or in capsule. The patients in the fludrocortisone arm, will receive fludrocortisone tablets (0.1 – 0.4 mg once daily, PO) which will be started at a dose of 0.1 mg once daily in the morning and will be increased every third day with an increment of 0.1 mg (D1 – 0.1 mg; D4 – 0.2 mg; D7 – 0.3 mg; D10 – 0.4 mg), till the primary endpoint is achieved or a total dose of 0.4 mg once daily is reached or patients develops an adverse reaction. Fludrocortisone will be discontinued only when 2 consecutive serum sodium values (on alternate days) are persistently normal. However, for the primary outcome analysis, we will count the earliest date to the serum sodium correction. When serum sodium fails to normalize even after 0.4 mg dose for 4 days, we will consider it as failure of the treatment and the fludrocortisone will be withdrawn. The patients will then be continued on intravenous 0.9% saline with oral salt supplementation.

### 4. Study Aims

a) To evaluate the frequency and the basis of hyponatremia in the patients with AES and TB Meningitis.

b) To classify the patients with hyponatremia into cerebral salt wasting (CSW) versus syndrome of inappropriate secretion of antidiuretic (SIADH).

c) To evaluate the role of hyponatremia in producing seizures and encephalopathy and
assess its effect on mortality and functional outcome.

d) To assess the Tolerability and efficacy of fludrocortisone for the treatment of hyponatremia with cerebral salt wasting in patients with AES including TB Meningitis and recommend the treatment protocol for management of hyponatremia.

5. **Endpoints (for sub study)**

5.1. **Primary end points:**

5.1.1. No of days required to correct sodium to >135 meq/L.

5.1.2. No of days required to attain a net positive water balance.

5.2. **Secondary endpoints:**

5.2.1. Dose of fludrocortisone required to reach primary outcome.

5.2.2. No. of patients developing adverse reactions to fludrocortisone (hypertension, hypokalemia).

5.2.3. Seizures due to hyponatremia.

5.2.4. Disability at discharge, 3 and 6 months based on modified Barthel index and mRS score. as good (mRS \( \leq 2 \)) or poor (mRS>2)

5.2.5. Mortality at 28 days, 3 months and 6 months.

5.2.6. Residual deficits in terms of seizures, cognitive, cranial nerve and motor deficits at the end of 6 months.

6. **Design (for sub study only)**

6.1. **Study design:** Investigator initiated, open labelled, randomized controlled trial conducted during 2015-2017 at a tertiary care teaching hospital in north India.

6.2. **Randomization procedure:** Randomization will be in 1:1 ratio using computer generated random number sequence.

7. **Target Population:** All patients with fever and altered sensorium within 5 days of their illness and diagnosed as tubercular meningitis based on blood/serum/CSF criteria. Only the patients with TBM with CSW will be included in the trial.

7.1. **Inclusion criteria**

- Age >10 years
- Clinical diagnosis of TBM

7.2. **Criteria for the diagnosis of tubercular meningitis (TBM) (Appendix 1.1).**

The diagnosis of TBM was based on clinical, MRI and CSF criteria as follows:25

**Essential criteria:**
Features suggestive of meningitis (one or more of the following: headache, irritability, vomiting, fever, weight loss, neck stiffness, convulsions, focal neurological deficits, or altered consciousness) for more than 5 days.

Supportive criteria:

(a) CSF cells of 10 –500/μL, with predominant lymphocytes (>50%), protein 1 g/L and sterile bacterial and fungal culture.

(b) Cranial CT or MRI imaging showing evidence of exudates, infarction, hydrocephalus or tuberculoma in isolation or in combinations.

(c) Evidence of extra CNS tuberculosis (Chest radiograph suggestive of active tuberculosis or CT/ MRI/ ultrasound evidence for tuberculosis outside the CNS or Acid Fast Bacillus (AFB) identified or Mycobacterium tuberculosis cultured from another source such as sputum, lymph node, gastric washing, urine).

(d) Exclusion of alternative diagnoses.

Criteria for definite and highly probable TBM: Essential criteria with two supportive criteria were defined as highly probable TBM. Presence of acid fast bacilli in CSF smear, positive CSF culture or polymerase chain reaction (PCR) for M. tuberculosis was considered definite TBM.25

7.3. Criteria for the diagnosis of CSW (Appendix 1.1).

Essential: (all required)

1) Polyuria (urine output >3L for at least 2 consecutive days).
2) Hyponatremia: serum sodium <135 mEq/L on 2 consecutive evaluations 24 h apart.
3) Exclusion of secondary causes like endocrine abnormalities, , renal, cardiac and hepatic failure., diuretics

Supportive criteria: at least 3 out of 5 of the following

1) Clinical findings of hypovolemia such as hypotension, dry mucous membranes, tachycardia or postural hypotension.
2) Persistent negative fluid balance as determined by intake output chart and/or weight loss.
3) Laboratory evidence of dehydration such as elevated hematocrit, hemoglobin, serum albumin or blood urea nitrogen.
4) Central venous pressure (CVP) < 6 cm of water.
5) Urinary sodium >40 mEq/L or urine osmolality>300 mOsm/L in 2 consecutive reports 24 hours apart.

7.4. : Exclusion criteria
The patients below 10 years of age, pregnant and lactating women and those with malaria, septic, fungal or carcinomatous meningitis, head injury, brain tumors, primary renal, hepatic or cardiac failure, endocrinological disorders such as adrenal failure or hypothyroidism, malignancy or any condition limiting the life expectancy to 1 year or less were excluded; however if the patients developed hepatic or renal dysfunction during treatment were not excluded. Patients not providing consent for the study will be excluded from the study.

8. Patient management

8.1. Consent:
A patient cannot enter the trial without informed consent. Written informed consent will be sought for all patients or their relatives/representatives entering the trial. For those below 20 years, written consent will be taken from their parents (see appendix 1.10 for the model consent form).

8.2. Initial evaluation:
On admission all patients will have a full clinical assessment and examination to determine TBM MRC grade (see appendix 1.2). Detailed medical history including the demographic details, duration of illness, altered sensorium, seizures (type, frequency, duration and its temporal relation to hyponatremia), focal deficit, behavioural changes, headache, vomiting and features of raised intracranial pressure such as extensor posturing, pupillary asymmetry and reaction, hyperventilation and gastric haemorrhage will be noted. Presence of pallor, edema, neck vein, jaundice, petechiae, ecchymosis, ascites, hepato-splenomegaly, lymphadenopathy, chest rales and cardiac murmur will be noted. Patients’ consciousness would be recorded by Glasgow coma scale and clinical states of by APACHE-II. Presence of cranial nerve palsy and papilloedema will be recorded. Focal weakness (hemi, para or quadriplegia) will be categorized into severe and mild and tendon reflex and muscle tone will be noted. Cerebellar and sensory functions will be tested who could co-operate for the test. Evidence of TB outside the central nervous system such as lung, lymph node, bone and joint will be noted. The severity of meningitis will be graded into MRC stage 1- meningitis only; no focal signs and GCS 15. Stage 2- meningitis with either focal signs and GCS 15 or a GCS between 11 and 15; stage 3- meningitis with GCS 10 or below. Skin turgor, mucous membrane, nutritional states, measurement of weight if possible, neck vein engorgement, edema, pulse and blood pressure (if possible in lying and sitting) will be recorded daily. Other causes of hyponatremia e.g. due to extra-renal loss (vomiting, diarrhoea), poor intake or drugs will also be recorded. Input-output charting and weight measurement will be done daily. Total Input will include all the liquid items consumed by the patient along with intravenous fluids administered. Solid food items which cannot be measured will
be excluded. Catheter, either foleys (in case of altered sensorium) or external catheters will be used to
measure total daily urine output. Insensible loss of 500 ml will be added to calculate daily fluid
balance. Weight will be measure using a weighing machine if patient is conscious and able to stand
independently. In case of poor sensorium or unable to stand independently, beds with automated
weight measurements will be used. CVP will be monitored whenever required.

8.3. Screening, enrolment, randomization and blinding: (for the sub study)

The admitting physician will be responsible for ensuring the patient satisfies the entry criteria, obtain
informed consent and starts a study drug treatment package. Clinical details will be recorded in
individual patient case record form. All patients with TBM without pre-existing co-morbidities
(exclusion criteria) will be screened for the presence of hyponatremia (serial measurement of serum
sodium) during the hospital stay. Those with hyponatremia will undergo detailed evaluation and will
be categorized as having either CSW (based on predefine criteria) or other alternate cause. The
patients with CSW will be randomly assigned to either control (intravenous 0.9% saline with oral
salt) or experimental (fludrocortisone) group with a 1:1 allocation using computer generated random
number sequence. All the patients will be given intravenous 0.9% saline with oral salt supplementation
(5-12 grams/day) through naso-gastric tube or in capsule. No placebo will be given. The patients in
the fludrocortisone arm, will receive fludrocortisone tablets (0.1 – 0.4 mg once daily, PO) which will
be started in a dose of 0.1 mg once daily in the morning and will be increased every third day with
an increment of 0.1 mg (D1 – 0.1 mg; D4 – 0.2 mg; D7 – 0.3 mg; D10 – 0.4 mg), till the primary
endpoint was achieved or a total dose of 0.4 mg once daily was reached. Fludrocortisone will be
discontinued only when 2 consecutive serum sodium values (on alternate days) are persistently
normal. However, for the primary outcome analysis, we will count the earliest date to the serum
sodium correction. When serum sodium fails to normalize even after 0.4 mg dose for 4 days, we will
consider it as failure of the treatment and the fludrocortisone will be withdrawn. The patients will then
be continued on intravenous 0.9% saline with oral salt supplementation. 3% saline was used if there
was an emergency like seizures or coma with severe hyponatremia.

8.4. TB treatment

The patients will receive four drugs anti tubercular treatment (RHZE) for six months followed by RH
for 12 months. Rifampicin will be prescribed a dose of 10mg/kg (~ 450mg/d), isoniazide 5mg/kg
( ~300mg/d), pyrazinamide 25mg/kg (~1500mg/d) and ethambutol 15 mg/kg (~800mg/d).All patients
will also receive prednisone 0.5 mg/kg (~ 40 mg/ d) and aspirin up to 150mg/dorally daily, if not
contraindicated. The patients will be subjected to ventriculo-peritoneal shunt or external ventricular
drainage (EVD) or mechanical ventilation as indicated (see appendix 1.5).

8.5. Treatment of CSW:

All the patients will be given intravenous 0.9% saline with oral salt supplementation (5-12 grams/day)
through naso-gastric tube or in capsule. No placebo will be given. The patients in the fludrocortisone
arm, received fludrocortisone tablets (0.1 – 0.4 mg once daily, PO) which will be started in a dose
of 0.1 mg once daily in the morning and was increased every third day with an increment of 0.1 mg
(D1 – 0.1 mg; D4 – 0.2 mg; D7 – 0.3 mg; D10 – 0.4 mg), till the primary endpoint is achieved or a
total dose of 0.4 mg once daily is reached. Fludrocortisone will be discontinued only when 2
consecutive serum sodium values (on alternate days) are persistently normal. However, for the
primary outcome analysis, we will count the earliest date to the serum sodium correction. When
serum sodium fails to normalize even after 0.4 mg dose for 4 days, we will consider it as failure of the
treatment and the fludrocortisone will be withdrawn. The patients will then be continued on
intravenous 0.9% saline with oral salt supplementation. 3% saline was used if there was an emergency
like seizures or coma with severe hyponatremia.

8.6. Treatment of SIADH: Patients with SIADH will be managed with free fluid restriction.
Care will be taken to prevent dehydration.

8.7. Treatment of other causes of hyponatremia: Other causes of hyponatremia will be
managed according to the primary cause as follows:

8.8. Clinical monitoring
Patients will have daily review until discharge from hospital. Patients will be monitored closely for
- Death (days from randomization to death)
- Days for correction of serum sodium
- Neurological deterioration (onset of new focal neurological signs or fall in Glasgow coma
  score of >2 points).
- Patients achieving a positive fluid balance, new stroke and its location, time to get the normal
  urinary output (<3 L).
- Drug-related adverse events (Appendix 1.7)
Uniform management of patients and recording of data will be ensured by the principal investigator
who will make a daily round of all study participants. Following discharge, patients will be followed
up for 6 months. Formal outpatient review will occur at 1±7 days, 3 and 6 months± 15 days. The
patients will be advised to maintain weekly 24 hour input output chart following discharge which will
be reviewed at follow up. Urine and serum chemistry will also be reviewed on the follow up visits.

8.9. Laboratory monitoring
Inpatient laboratory monitoring will be as shown in the study schedule (section 1.3).
Other investigations may be performed as clinically indicated. Data for the following will be recorded
when analysed for clinical care:
- Blood counts including platelet count, serum chemistry, ESR, HIV serology and chest radiograph will
  be done. For JE, CSF IgM antibody will be done by pan-bio (Australia), for dengue serum NS1
  antigen test will be done by Bio Red ELISA kit and IgM antibody by Pan-Bio (Australia). CSF IgM
  for VZV will be done by abcam ELISA kit, serum IgM for Chikungunya and leptospira by SD
Bioline. HSV and EBV will be done by CSF PCR. Peripheral blood smear will be examined for malaria. CSF will be also examined for cryptococcal and pyogenic infection. Cerebrospinal fluid (CSF) will be examined for proteins, cells, glucose, bacteria, fungi, malignant cells and AFB staining and culture by BACTEC. CSF will also be examined for PCR for M. tuberculosis. CT/MRI brain with/without contrast will be done at admission and will be repeated whenever required. In the patients with hyponatremia (sodium < 135 meq/L), serum sodium will be repeated daily till it is corrected and in patients with normal baseline serum sodium, it will be repeated twice weekly or more frequently if clinically indicated. Serum and urinary sodium and osmolality will be done at the time of hyponatremia and will be repeated every third day. Bedside EEG will be recorded in the NICU on admission using 10-20 system of electrodes placement. 1 hour EEG recording will be done at the baseline and the effect of photic stimulation and pin prick will be noted. The EEG may be categorized into normal and abnormal (focal or generalized slowing, epileptiform discharges or other abnormalities). If there is myoclonus EMG recording will be done.

Other investigations include:

- Sputum, if symptomatic (routine culture, ZN stain, PCP immunofluorescence test)
- Urine culture, if urinary symptoms (urine culture)
- Stool culture, if prolonged diarrhoea (microscopy, culture and parasites)
- Blood cultures, if persistent fever (routine and mycobacterial cultures)
- Lymph node aspiration (routine and mycobacterial cultures)

Follow up Outpatient laboratory monitoring will include input output chart review, serum and urine chemistry.

8.10. Imaging

Chest and brain imaging will be performed as per the study schedule and as clinically indicated – i.e. in the event of pulmonary or neurological deterioration. The occurrence of new acute stroke and its location on repeated MRI was also noted. The diagnosis of infarction was based on MRI showing evidence of infarcts which were defined as iso to hypo intense on T1W and hyper intense on T2W/FLAIR, with diffusion restriction on diffusion-weighted imaging (DWI).

8.11. Withdrawal from the trial

Patients may voluntarily withdraw from the trial for any reason. If this occurs, the trial researchers are under no obligation to provide treatment. The patient’s withdrawal from the trial will not affect their access to the best standard of care within the national health system. Clinical and laboratory assessment should be performed and recorded at the time of withdrawal. If the patient has an unscheduled period off treatment or not in follow-up this should be recorded in the case report forms.

8.12. Recording and reporting of death, adverse events or protocol violations

8.12.1. Death
If the patient dies, the principal investigator will report to the institute ethical committee as soon as possible and complete the specific case report form.

8.12.2. **Adverse events**

If the patient dies or experiences an adverse event (serious, grade 3 or 4, or one leading to modification of treatment, see Appendix 1.5 Common Toxicity Criteria), the principal investigator will report it to the institute ethical committee as soon as possible and complete the specific case report form. When applicable, adverse events will be treated as per the management guidelines in Appendix 1.5 and 1.6.

According to the ICH Guidelines for Clinical Safety Data Management: definitions and Standards for Expedited Reporting (1994), a serious adverse event (SAE) is defined as “any untoward medical occurrence that:

- Results in death
- Is life threatening
- Requires unplanned inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect
- Any other important medical condition, which, although not included in the above, may jeopardize
- The subject and may require medical or surgical intervention to prevent one of the outcomes listed.”

All SAEs will be recorded on the patient Case Report Form.

Unexpected SAEs (USAEs) and events which become of concern to study investigators during the course of the trial will be reported to the institute Ethics Committee within 24 hours of occurrence. Depending on the severity of USAEs the institute Ethical Committee (IEC) will be informed as follows:

a) USAEs that resulting in death or are life threatening: Initial written report should be sent as soon as possible and within 7 days of occurrence. The format and content of the initial report should follow the IEC report template and include all information available at the time of reporting. A follow up report with complete details must be sent within 15 days of the initial report.

b) For USAEs that do not result in death or not life threatening: USAE must be reported to IEC) as soon as possible and within 15 days of occurrence

8.12.3. **Protocol violation**
If there is a protocol violation for any reason this will be fully recorded by the principal investigator and reported to the institute ethical committee. Protocol violations which affect patient safety will also be reported to the institute ethical committee.

9. **Drug regimens (appendix 1.4)**

Patients will be treated with anti-tuberculous therapy and adjunctive prednisolone on study entry. In addition patients will be randomized to receive intravenous 0.9% saline with oral salt supplementation (5-12 grams/day) through naso-gastric tube or in capsule. No placebo will be given. The patients in the fludrocortisone arm, will receive fludrocortisone tablets (0.1 – 0.4 mg once daily, PO) which was started at a dose of 0.1 mg once daily in the morning and was increased every third day with an increment of 0.1 mg (D1 – 0.1 mg; D4 – 0.2 mg; D7 – 0.3 mg; D10 – 0.4 mg), till the primary endpoint is achieved or a total dose of 0.4 mg once daily is reached. Fludrocortisone will be discontinued only when 2 consecutive serum sodium values (on alternate days) are persistently normal. However, for the primary outcome analysis, we will count the earliest date to the serum sodium correction. When serum sodium fails to normalize even after 0.4 mg dose for 4 days, we will consider it as failure of the treatment and the fludrocortisone will be withdrawn. The patients will then be continued on intravenous 0.9% saline with oral salt supplementation. 3% saline will be used if there is an emergency like seizures or coma with severe hyponatremia.

9.1. **Antituberculous therapy:** This will be given for the full 18 months.

### First-line antituberculous therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (H)</td>
<td>5mg/kg od po, max 300mg/day</td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td>10mg/kg od po max dose 450mg/day</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>25mg/kg od po, max 1.5g/day</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>20mg/kg od po, max 800mg/day</td>
</tr>
<tr>
<td>Streptomycin (S)</td>
<td>20mg/kg od im, max 750 mg/day</td>
</tr>
</tbody>
</table>

If the patient is comatose, the drugs can be given by nasogastric tube. After 6 months, pyrazinamide and ethambutol/streptomycin will be stopped and the patient will continue on rifampicin and isoniazid at the same doses for a further six months. Drugs will be administered orally or via nasogastric tube in unconscious patients.

### Second-line antituberculous therapy

Patients with a (1) definite or (2) clinical diagnosis of Multi Drug-Resistant (MDR) TBM will be excluded from the trial and referred to the MDR-TB department for second-line antituberculous treatment.
1. A definite diagnosis of MDR-TBM is the presence of MDR mycobacteria in the CSF, either detected by routine culture.

2. A clinical diagnosis of MDR-TBM may be suspected when the patient has recently been treated, or is still under treatment for pulmonary TB or extra-pulmonary TB (not TBM) and has been found to have MDR-TB by culture.

3. If a patient clinically is suspected of MDR-TBM, the caring clinician will consult the Principal Investigator. Referral to the MDR-TB department will be done by the PI who will consult the head of the MDR department. If patients are not eligible for treatment at the MDR-TB department of PNT hospital, appropriate treatment will be sought where possible.

9.2. Corticosteroid therapy: All patients also received prednisone 0.5 mg/kg (~ 40 mg/ d) and aspirin up to 150mg/dorally daily, if not contraindicated.

Corticosteroid schedule:

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose of prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5 mg/kg (~ 40 mg/ d)</td>
</tr>
<tr>
<td>2</td>
<td>0.5 mg/kg (~ 40 mg/ d)</td>
</tr>
<tr>
<td>3</td>
<td>0.5 mg/kg (~ 40 mg/ d)</td>
</tr>
<tr>
<td>4</td>
<td>0.5 mg/kg (~ 40 mg/ d)</td>
</tr>
<tr>
<td>5</td>
<td>0.4 mg/kg (~ 30 mg/ d)</td>
</tr>
<tr>
<td>6</td>
<td>0.3 mg/kg (~ 20 mg/ d)</td>
</tr>
<tr>
<td>7</td>
<td>0.2 mg/kg (~ 19 mg/ d)</td>
</tr>
<tr>
<td>8</td>
<td>0.1 mg/kg (~ 5 mg/ d) and stop</td>
</tr>
</tbody>
</table>

Aspirin will be continued at the dose of 150 mg once daily for 6 months.

10. Management of antituberculous toxicity
A symptom checklist will be used to determine clinical toxicity. Routine laboratory tests will be performed weekly as an inpatient and monthly as an outpatient. Clinicians may also request additional tests if clinically indicated. (For common side effects of first-line TB-drugs; see appendix 1.7 and 1.8) Therapy may need to be interrupted for severe (grade 3 or 4) adverse events (see appendix 1.6). Once clinical and laboratory features resolve, drugs may be reintroduced sequentially. For detailed management (see Appendix 1.7, 1.8 and 1.9)

11. Management of adverse events
For common side effects of corticosteroid therapy see Appendix 1.5. It is unlikely that prednisone will need to be stopped unless the patient develops severe (grade 3 or 4) adverse effects e.g. hyperglycaemia, hypertension, gastrointestinal haemorrhages (see appendix 1.6).
12. Data on concomitant medications
At each visit, information on other medications, including start dates and reason for taking them, will be documented in the case record forms.

13. Statistics:
13.1. Sample size and power considerations (for the sub study only)
Due to the paucity of previous studies, the number of patients needed for the study was based on the assumption of a standard deviation of 2.5 days in the mean days to the hyponatremia correction (primary outcome) during the study period. To detect a difference of 25% between the study arm and the control arm, with a power of 80% at a significance level of 5% with the use of a two-sided test, it was calculated that 16 patients in each arm would be needed (ref: Zhou X-H et al, Statistical Methods in Diagnostic Medicine. New York, NY: Wiley; 2002). Moreover, it was felt that it may not be possible to perform a complete evaluation of 10% of patients because of the possibility of withdrawal of consent, seeking other treatment options and leaving the hospital prematurely against advice. Thus, a final sample size of 18 patients in each arm was estimated for this trial.

13.2. Analysis: (for the sub study only)
13.2.1. Analysis of the primary endpoint:
The primary endpoint will be days for correction of serum sodium (serum sodium $\geq 135$ mEq/L). They will be represented as either mean ± SD or median (range) and will be compared using either independent t test or mann-whitney U test depending on the normalcy of the data (will be tested using Sapiro-Wilk test). The P value will be represented to the nearest 2 digits. Kaplan-Meier plots and explicit survival estimates at 6 months of follow-up will also be calculated for the full populations. In a second stage hierarchical linear regression analysis will be done in the following sequence: total oral salt given (in grams), age, TBM stage, exudates, hydrocephalus, gender, VP shunt, duration of illness, severity of hyponatremia and mechanical ventilation for deciding the best predictors (covariates) for the time to correction of hyponatremia. Only those variables showing significant change in $R^2$ with P value of < 0.05 will be used as covariates in the cox regression model. Time to correction of hyponatremia will then be modelled using the Cox proportional hazards regression model following covariates adjustment.

13.2.2. Analysis of the Secondary endpoints:
The secondary outcomes will be number of patients achieving a positive fluid balance, new stroke and its location, time to get the normal urinary output ($<3$ L), in-hospital mortality, and disability at 3 and 6 months. The disability will be assessed using modified Rankin scale (mRS) as good (mRS $\leq 2$) or poor (mRS $>2$). The adverse reactions of fludrocortisone such as hypertension, hypokalemia and pulmonary edema will be noted. The above data (except time to get the normal urinary output) will be represented as n (%) and compared using chi-square test or Fischer exact test. Time to get the normal
24

urinary output will be compared using either independent t test or mann-whitney U test depending on
the normalcy of the data (will be tested using Sapiro-Wilk test). The P value will be represented to the
nearest 2 digits.

14. Ethical approval: This protocol, the informed consent form and any subsequent modifications of
these documents, will be reviewed by the institutional ethical committee, Sanjay Gandhi Post
Graduate Institute of Medical Sciences, Lucknow.

15. Confidentiality
Confidentiality of the patients will be duly maintained. Clinical information will not be released
without written permission of the patient.

16. Clinical trial specimens
All clinical trial specimens will be labelled with the patient’s number. Samples will be transferred to
the laboratories at the Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow for
processing. Investigation results will be issued to the investigators in a timely manner and a hard copy
of the results will be retained in the laboratory for verification.

17. Publications
Any publication or presentation during the active phase of the study must have permission from the
Investigators. The investigators will define the strategy for publication, resolve any problems of
authorship and maintain the quality of publications. All publications will acknowledge the appropriate
funding sources. The investigators are the custodian of the data and specimens generated from this
trial.

18. Sub studies
- Various causes of hyponatremia in patients with AES.
- Role of atrial and brain natriuretic peptide (ANP and BNP) in patients with CSW with TBM
  and AES.
- Incidence of stroke in patients with CSW in TBM and AES.

19. Sampling and analysis at follow up:

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Serum bilirubin ALT</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Urine sodium | 1 | 1 | 1
Urine osmolality | 1 | 1 | 1
Weekly 24 hour input output chart maintained by the patient in a note book | Yes | yes | Yes

Note: the numbers denote the number of times the investigations will be done.

20. Appendices:

Appendix 1.1 - Diagnostic criteria for tuberculous meningitis and cerebral salt wasting.

Classification Diagnostic criteria

<table>
<thead>
<tr>
<th>Diagnosis of TBM</th>
<th>The diagnosis of TBM was based on clinical, MRI and CSF criteria.(^{25})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Essential criteria: Features suggestive of meningitis (one or more of the following: headache, irritability, vomiting, fever, weight loss, neck stiffness, convulsions, focal neurological deficits, or altered consciousness) for more than 5 days.</td>
</tr>
<tr>
<td></td>
<td>2. Supportive criteria:</td>
</tr>
<tr>
<td></td>
<td>(a) CSF cells of 10 –500/μL, with predominant lymphocytes (&gt;50%), protein 1 g/L and sterile bacterial and fungal culture.</td>
</tr>
<tr>
<td></td>
<td>(b) Cranial CT or MRI imaging showing evidence of exudates, infarction, hydrocephalus or tuberculoma in isolation or in combinations.</td>
</tr>
<tr>
<td></td>
<td>(c) Evidence of extra CNS tuberculosis (Chest radiograph suggestive of active tuberculosis or CT/ MRI/ ultrasound evidence for tuberculosis outside the CNS or Acid Fast Bacillus (AFB) identified or Mycobacterium tuberculosis cultured from another source such as sputum, lymph node, gastric washing, urine).</td>
</tr>
<tr>
<td></td>
<td>(d) Exclusion of alternative diagnoses.</td>
</tr>
<tr>
<td></td>
<td>Criteria for definite and highly probable TBM: Essential criteria with two supportive criteria were defined as highly probable TBM. Presence of acid fast bacilli in CSF smear, positive CSF culture or polymerase chain reaction (PCR) for M. tuberculosis was considered definite TBM.(^{25})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis of cerebral salt wasting</th>
<th>Essential: (all required)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Polyuria (urine output &gt;3L for at least 2 consecutive days).</td>
</tr>
<tr>
<td></td>
<td>Hyponatremia: serum sodium &lt;135 mEq/L on 2 consecutive evaluations 24 h apart.</td>
</tr>
<tr>
<td></td>
<td>Exclusion of secondary causes like endocrine abnormalities, renal, cardiac and hepatic failure, diuretics</td>
</tr>
<tr>
<td></td>
<td>Supportive criteria: at least 3 out of 5 of the following</td>
</tr>
<tr>
<td></td>
<td>Clinical findings of hypovolemia such as hypotension, dry mucous membranes, tachycardia or postural hypotension.</td>
</tr>
</tbody>
</table>
Persistent negative fluid balance as determined by intake output chart and/or weight loss.
Laboratory evidence of dehydration such as elevated hematocrit, haemoglobin, serum albumin or blood urea nitrogen.
Central venous pressure (CVP) < 6 cm of water.
Urinary sodium >40 mEq/L or urine osmolality >300 mOsm/L in 2 consecutive reports.

Appendix 1.2 Modified MRC grading for tuberculous meningitis

Grade I Glasgow coma score 15, no focal neurology
Grade II Glasgow coma score 11-14 OR Glasgow coma score 15 with focal neurology
Grade III Glasgow coma score < 10

Appendix1.3: The Modified Rankin Scale grade Description

0 = No symptoms
1= Minor symptoms not interfering with lifestyle
2 = Symptoms that lead to some restriction in lifestyle, but do not interfere with the patient’s ability to look after themselves
3= Symptoms that restrict lifestyle and prevent totally independent living
4= Symptoms that clearly prevent independent living, although the patient does not need constant care and attention.
5 = Totally dependent, requiring constant help day and

Appendix 1.4: Details of ATT

<table>
<thead>
<tr>
<th>Drug and dose</th>
<th>Side effects</th>
<th>Contraindications</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>Orange discolouration of body fluids (urine, tears, saliva), skin rash, gastrointestinal symptoms, headache, drowsiness, abnormal liver function tests, jaundice, associated with</td>
<td>Jaundice</td>
<td>Reduces efavirenz level by 25% (increase dose to 800mg). Reduces plasma concentrations of protease inhibitors and nevirapine (avoid concomitant use). Accelerates metabolism</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dose/Details</td>
<td>Side Effects</td>
<td>Interactions</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>5mg/kg 300mg od po</td>
<td>Gastrointestinal symptoms, skin rash, peripheral neuritis, optic neuritis, convulsions, psychosis, vertigo, hypersensitivity reactions, hepatitis, haemolytic anaemia, aplastic anaemia, agranulocytosis, systemic lupus erythematosus-like syndrome.</td>
<td>Drug induced liver disease increases plasma levels of prednisolone, ethionamide. Increases plasma levels of phenytoin, carbamazepine, warfarin, diazepam. Decreases plasma levels of azoles, enflurane.</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25mg/kg od po, max 1500 mg per day</td>
<td>Gastrointestinal symptoms, hepatotoxicity, skin rash, arthralgia, hyperuricaemia, gout, photosensitisation</td>
<td>Liver damage, porphyria Increases plasma levels of probenicid</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>20mg/kg od po, max 800 mg/day</td>
<td>Optic neuritis, red/green colour blindness, arthralgia, peripheral neuritis, rarely rash, pruritus, urticaria, thrombocytopenia</td>
<td>Optic neuritis, poor vision -</td>
</tr>
</tbody>
</table>
## Appendix 1.5: Table of common toxicity criteria and grading

ULN = upper limit of normal local reference range

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>8.0 – 9.4g/dl</td>
<td>7.0 – 7.9g/dl</td>
<td>6.5 – 6.9g/dl</td>
<td>&lt;6.5g/dl</td>
</tr>
<tr>
<td>White cell count</td>
<td>3.0 - 3.9 x 10^3 cells/µl</td>
<td>2.0 - 2.9 x 10^3 cells/µl</td>
<td>1.0 - 1.9 x 10^3 cells/µl</td>
<td>&lt;1.0 x 10^3 cells/µl</td>
</tr>
<tr>
<td>Platelet</td>
<td>75 - 99 x 10^3 cells/µl</td>
<td>50 - 74 x 10^3 cells/µl</td>
<td>20 - 49 x 10^3 cells/µl</td>
<td>&lt;20 x 10^3 cells/µl</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>&gt;1.0 – 1.25 x ULN</td>
<td>&gt;1.25 – 1.5 x ULN</td>
<td>&gt;1.5 – 3.0 x ULN</td>
<td>&gt;3.0 x ULN</td>
</tr>
<tr>
<td><strong>Biochemical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>130 – 135 meq/l</td>
<td>120 – 129 meq/l</td>
<td>110 – 119 meq/l</td>
<td>&lt;109 meq/l</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>146 – 150 mmol/l</td>
<td>151 – 157 mmol/l</td>
<td>158 – 165 mmol/l</td>
<td>&gt;165 mmol/l</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3.0 – 3.4 mmol/l</td>
<td>2.5 – 2.9 mmol/l</td>
<td>2.0 – 2.4 mmol/l</td>
<td>&lt;2.0 mmol/l</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>5.6 – 6.0 mmol/l</td>
<td>6.1 – 6.5 mmol/l</td>
<td>6.6 – 7.0 mmol/l</td>
<td>&gt;7.0 mmol/l</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>3.1 – 3.6 mmol/l</td>
<td>2.2 – 3.0 mmol/l</td>
<td>1.7 – 2.1 mmol/l</td>
<td>&lt;1.7 mmol/l</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>6.5 – 9.0 mmol/l</td>
<td>9.1 – 14.0 mmol/l</td>
<td>14.1 – 28.0 mmol/l</td>
<td>&gt;28.0 mmol/l,</td>
</tr>
<tr>
<td>Urea</td>
<td>1.25 – 2.5 x ULN</td>
<td>&gt;2.5 – 5.0 x ULN</td>
<td>&gt;5.0 – 10.0 x ULN</td>
<td>&gt;10.0 x ULN</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&gt;1.0 – 1.5 x ULN</td>
<td>&gt;1.5 – 3.0 x ULN</td>
<td>&gt;3.0 – 6.0 x ULN</td>
<td>&gt;6.0 x ULN</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&gt;1.0 – 1.5 x ULN</td>
<td>&gt;1.5 – 2.5 x ULN</td>
<td>&gt;3.0 – 6.0 x ULN</td>
<td>&gt;5.0 x ULN</td>
</tr>
<tr>
<td>ALT</td>
<td>1.25 – 2.5 x ULN</td>
<td>&gt;2.5 – 5.0 x ULN</td>
<td>&gt;5.0 – 10.0 x ULN</td>
<td>&gt;10.0 x ULN</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomatitis/mouth ulcers</td>
<td>Mild discomfort, no limits on</td>
<td>Some limits on eating or talking</td>
<td>Eating/talking very limited</td>
<td>Requiring IV fluids</td>
</tr>
<tr>
<td></td>
<td>Activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Mild or transient discomfort,</td>
<td>Moderate discomfort or</td>
<td>Severe discomfort or minimal</td>
<td>Hospitalization required</td>
</tr>
<tr>
<td></td>
<td>maintains reasonable</td>
<td>significantly decreased intake</td>
<td>intake for □ 3 days</td>
<td></td>
</tr>
</tbody>
</table>

28 | Page
<table>
<thead>
<tr>
<th>Intake for &gt; 3 days</th>
<th>Vomiting</th>
<th>Moderate or persistent, 4-5 episodes/day or vomiting lasting &gt; 1 week</th>
<th>Severe vomiting of all foods/fluids in 24 hours or orthostatic hypotension or IV fluids required</th>
<th>Hypotensive shock or hospitalization required for IV fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Mild, no treatment</td>
<td>Moderate or requires non-narcotic analgesia</td>
<td>Severe or responds to first narcotic</td>
<td>Intractable or requiring repeated narcotics</td>
</tr>
<tr>
<td>Consciousness</td>
<td>Difficulty in concentration or Memory</td>
<td>Mild confusion or lethargy &lt;50% waking hours</td>
<td>Disorientation or stupor &gt;50% of waking hours</td>
<td>Coma or seizures</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Mild agitation or confusion</td>
<td>Some limitation in activities of daily living and minimal treatment required</td>
<td>Treatment and assistance required, severe agitation or confusion</td>
<td>Toxic psychosis or hospitalization</td>
</tr>
<tr>
<td>Clinical myopathy</td>
<td>Minimal findings</td>
<td>Moderate myalgia or difficulty climbing stairs or rising from sitting position, able to walk, may need NSAID</td>
<td>Moderate to severe myalgia needing NSAID, assistance required for walking or general activities</td>
<td>Severe myalgia unrelated to exercise requiring narcotics, unable to walk or necrosis or oedema</td>
</tr>
<tr>
<td>Sensory</td>
<td>Mild impairment (decreased sensation e.g. vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical</td>
<td>Moderate impairment (moderately decreased sensation e.g. vibratory, pinprick, hot/cold to ankles) or joint position</td>
<td>Severe impairment (decrease or loss of sensation to knees or wrists) or loss of sensation of moderate degree in</td>
<td>Sensory loss involves limbs and trunk</td>
</tr>
<tr>
<td>Condition</td>
<td>Mild discomfort, no treatment</td>
<td>Moderate discomfort, requiring non-narcotic analgesia</td>
<td>Severe discomfort or symptoms respond to narcotic analgesia</td>
<td>Incapacitating or not responsive to narcotics</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------------------</td>
<td>-------------------------------------------------------</td>
<td>------------------------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Parasthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Mild paraesthesia, numbness, pain or weakness, not treated</td>
<td>Moderate paraesthesia, numbness or pain, objective weakness, requires analgesic</td>
<td>Severe, narcotic required, interferes with normal activity</td>
<td>Intolerable, incapacitating, unable to walk despite narcotics, paralysis</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Transient, no treatment, 70-80% peak flow or FEV1</td>
<td>Requires treatment, normalizes with bronchodilator, 50-69% peak flow or FEV1</td>
<td>No normalization with bronchodilator, 25-49% peak flow or FEV1, retractions</td>
<td>Cyanosis, intubated or &lt;25% peak flow or FEV1</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Transient, increase &gt;20mm/Hg, no treatment</td>
<td>Recurrent, chronic increase &gt;20mm/Hg, requires treatment</td>
<td>Acute treatment required, outpatient, hospitalization possible</td>
<td>Hospitalization required</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Microscopic or occult</td>
<td>Mild, no transfusion</td>
<td>If Hb&lt;6.6 g/l or if Hct&lt;20% transfuse packed red cells or whole blood based on clinical</td>
<td>Massive blood loss or transfused &gt;2 units</td>
</tr>
<tr>
<td>Other features</td>
<td>care</td>
<td>Gross blood loss or transfused 1-2 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>------</td>
<td>----------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever, oral, &gt; 12 hours</td>
<td>37.7-38.5°C</td>
<td>38.6-39.5°C</td>
<td>39.6-40.5°C</td>
<td>&gt;40.5°C</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Pruritus without rash</td>
<td>Localized urticaria</td>
<td>Generalised urticaria or angioedema</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Rash</td>
<td>Rash, erythema or pruritus</td>
<td>Diffuse maculopapular rash or dry desquamation</td>
<td>Vescication or moist desquamation or ulceration</td>
<td>Exfoliative dermatitis or mucous membrane involvement or suspected Stevens-Johnson or erythema multiforme or necrosis requiring surgery</td>
</tr>
</tbody>
</table>

**Appendix 1.6 Guide to management of toxicities**

1. **1.6.1 Grade 1 clinical or laboratory toxicities**
   1. Continue study drugs

2. **1.6.2 Grade 2 clinical or laboratory toxicities**
   1. Continue study drugs
   2. If relevant, monitor more closely and consider more frequent laboratory assessments
   3. Investigate to exclude other causes

3. **1.6.3 Grade 3 clinical or laboratory toxicities**
   1. Monitor more closely
2. Perform more frequent laboratory assessments
3. Investigate to exclude other causes
4. For AST or ALT > 5 x ULN stop all study drugs until toxicity resolves and consider reintroduction of antituberculous drugs sequentially (Appendix 1.9).
5. For other grade 3 toxicities the clinician may immediately stop study drugs if confirmatory test cannot be performed within 72 hours or if the clinician determines that continuation of study drugs is unsafe while awaiting test results
6. Fill in an adverse event form and inform the institute ethics committee.

2. Grade 4 clinical or laboratory toxicities

1. Monitor more closely
2. Perform more frequent laboratory assessments
3. Investigate to exclude other causes
4. For all grade 4 toxicities that are attributable to antituberculous drugs, stop all drugs until toxicity resolves and restart antituberculous drugs sequentially (Appendix 1.9)
5. For all grade 4 toxicities that are clearly attributable to antiretroviral drugs, stop relevant drugs until toxicity resolves and consider switching to alternative drugs as indicated in Appendix 1.7
6. For other grade 4 toxicities the clinician may immediately stop study drugs if confirmatory test cannot be performed within 72 hours or if the clinician determines that continuation of study drugs is unsafe while awaiting test results
7. If any doubt about management discuss with the principal investigator
8. Fill in an adverse event form and inform the institute ethics committee.
### Appendix 1.7 Management of serious adverse effects of drugs requiring drug discontinuation

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Possible offending Drugs</th>
<th>Clinical signs/symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe skin rash and/or Stevens-Johnson syndrome</td>
<td>Rifampicin, isoniazid, pyrazinamide, ethambutol,</td>
<td>Rifampicin may cause petechial rash due to thrombocytopenia. All TB drugs may cause severe rash and/or Stevens-Johnson syndrome</td>
<td>Stop rifampicin for petechial rash with low platelets and do not reintroduce. For severe rash and/or Stevens-Johnson syndrome, stop all drugs. Once rash has improved restart TB drugs sequentially (Appendix 1.9). If rash recurs, stop suspect drug permanently.</td>
</tr>
<tr>
<td>Severe anaemia</td>
<td>Rifampin and isoniazid may cause haemolytic anaemia</td>
<td>Pallor, tachycardia, shortness of breath on exertion</td>
<td>Exclude haemolysis. Stop the drug and consider alternative drug.</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>Rifampicin, isoniazid, Pyrazinamide</td>
<td>Fatigue, anorexia, gastrointestinal symptoms, jaundice, hepatomegaly, AST or ALT &gt; 5 x ULN</td>
<td>Monitor serum bilirubin and transaminases. Stop all drugs until symptoms resolve and AST improves to &lt; 2.5 x ULN. Then reintroduce TB drugs sequentially (Appendix 1.9)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Isoniazid, ethambutol</td>
<td>Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness, and areflexia can occur.</td>
<td>Give pyridoxine.</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Fludrocortisone</td>
<td>Palpitations, missed beats, cramps in the legs</td>
<td>Give syrup containing potassium, stop the drug in case of intractable hypokalemia</td>
</tr>
<tr>
<td>Pulmonary edema and heart failure</td>
<td>Fludrocortisone</td>
<td>Breathlessness, cough with pink frothy sputum</td>
<td>Give iv furosemide and wait. Exclude neurogenic pulmonary edema. If intractable then stop fludrocortisone.</td>
</tr>
<tr>
<td>Pedal edema</td>
<td>Fludrocortisone</td>
<td>Swelling of legs</td>
<td>Monitor, give intravenous furosemide in intractable cases.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Fludrocortisone</td>
<td>Breathlessness, palpitations, signs of raised intracranial pressure.</td>
<td>Give iv furosemide. Stop the drug.</td>
</tr>
</tbody>
</table>

**Appendix 1.8 Management of common adverse effects of antituberculous medications**

| Gastrointestinal symptoms | Common in the first few weeks of treatment. Liver function tests should be checked and if the AST < 2 x ULN, the symptoms are assumed not to be due to hepatic toxicity. The initial management is to change the hour of drug administration and/or to administer the drugs with food. |
| Rash | If mild, affecting only a limited area or predominantly causing itching an antihistamine may be given for symptomatic relief and antituberculous medications may be continued. A petechial rash may be caused by rifampicin induced thrombocytopenia – check platelet count and, and if low, stop rifampicin permanently. If there is a generalized erythematous rash, especially if associated with fever and/or mucous membrane involvement, stop all drugs. Once the rash has improved restart antituberculous drugs according to Appendix 1.7 |
| Drug fever | Fever may persist for 2 months after treatment has been initiated. Recurrence of fever in a patient who has been on therapy for several weeks may be due to drug fever, especially if the patient is showing clinical and microbiological improvement. Fever may also be a feature of immune reconstitution syndrome or other HIV-related infections. Potential causes should be excluded before stopping Antituberculous drugs – drug fever usually resolves in 24 hours. Once the fever has resolved restart drugs according to Appendix 1.7 |
| Hepatitis | Isoniazid, rifampicin or pyrazinamide can all cause drug-induced liver injury. Asymptomatic increases in AST occurs in around 20% of patients treated with 4 drugs and most resolve spontaneously. The frequency of clinical and laboratory |


monitoring should increase but therapy should not be altered. However, if AST or ALT >5 x ULN all hepatotoxic drugs (i.e. Rifampicin, Rifampicin study drug/placebo, isoniazid, pyrazinamide and any other hepatotoxic drugs) should be stopped. Levofloxacin/placebo and ethambutol/streptomycin can be continued, but if hepatitis continues to worsen stopping levofloxacin must be considered. The patient should be evaluated for other causes (viral hepatitis, alcohol intake, other hepatotoxins, biliary tract disease) before diagnosing drug-induced hepatitis. Once symptoms have resolved and AST returns to < 2 x ULN antituberculous medications may be restarted according to Appendix 1.9

**Appendix 1.9 Reintroduction of antituberculous therapy following Drug induced hepatitis (DIH)**

After improvement in the liver functions (defined as serum bilirubin <1.5 mg/dl and ALT < 80 U/L), the antitubercular drugs (ATT) were sequentially reintroduced in accordance to British Thoracic Society Guidelines for chemotherapy and management of tuberculosis as follows: H at dosage of 100 mg/day from day 1, maximum dosage (~300mg) from day 4; R at dosage of 150 mg/day from day 8, maximum dosage (~450 mg) from day 11; and Z at dosage of 500 mg/day from day 15, maximum dosage (~1500 mg) from day 18. (BTS Guidelines, Thorax 1998; 53: 536-548)
Appendix 1.10: Patient information documents and Consent forms

1.10.1: Patient information documents and Consent form in English (for those who can understand English)

Participant / Legally Acceptable Guardian AN7-V1/SGSOP 03/V1

Information Document (PID) in English

1. **Study Title:** “Etiology of hyponatremia, its relation to seizures and outcome in acute febrile encephalopathy – A prospective study in neurology intensive care unit (NICU) patients”

2. **Sub study:** “Safety and efficacy of fludrocortisone in treatment of cerebral salt wasting in tuberculous meningitis: A randomized controlled trial.”

2. **Invitation Paragraph**

You are being invited to take part in a research/trial study. Before you decide it is important for you to understand why the research/study is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your treating physician/family doctor if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

3. **What is the purpose of the study?**

Tubercular meningitis (TBM) is a very common cause of morbidity and mortality in India. Its common symptoms are fever, headache, vomiting and decreased appetite. Hyponatremia is very commonly seen in tubercular meningitis. It could be due to cerebral salt wasting (CSW) or syndrome of inappropriate secretion of antidiuretic hormone (SIADH). In such disease, patient loses salt in urine. IV fluids, oral salt supplementation and/ or fludrocortisone are the standard treatment options for the treatment of hypo-natremia associated with CSW. However, there is paucity of well-planned comprehensive study relating the comparative efficacy of saline with fludrocortisone patients with CSW in patients with TB meningitis. This study is aimed to determine the efficacy and safety of fludrocortisone in treating CSW.

4. **Why have I been chosen?**

You have been chosen because you have been diagnosed to have TB Meningitis.

5. **Do I have to take part?**

It is up to you to decide whether to take part or not. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

6. **What will happen to me if I take part?**

You will be involved in the trial for duration of 6 months. You will have to make 3 visits at 1 month, 3 months and 6 months. You will not have to visit the hospital more often than for usual treatment. On admission, your detailed history and examination will be done along with appropriate investigations including routine blood counts, haemoglobin, serum chemistry, chest x-ray, MRI of brain and CSF examination (fluid tapped from spine). You will be given treatment for TBM as per standard protocol. On visits at 1 month, 3 months and 6 months of treatment, clinical examination, routine hematolgy and blood and urine chemistry tests will be repeated. Each visit will take about 1 hour but may take sometimes longer.

Randomized Trial: Sometimes, we do not know which way of treating patients is best, we need to
make comparisons. Patients will be put into treatment groups and then compared. Patients in each
group have a different treatment and these are compared. The chance you have of getting the study
drug- one in two chances.

7. What do I have to do?
There are no lifestyle restrictions or any dietary restrictions. You can continue to take your regular
medication? You will have to comply strictly with treatment advice and will have to report side
effects if any.

8. What is the drug or procedure that is being tested?
You will be given appropriate antibiotics and 4 first line anti-tubercular drugs namely rifampicin,
isoniazide, pyrazinamide and ethambutol, prednisone and aspirin which are standard treatment. You
will also be given an oral tablet fludrocortisone. Fludrocortisone has been recommended for yhe
treatment of hyponatremia due to cerebral salt wasting.

9. What are the alternatives for diagnosis or treatment?
There is no alternate treatment of TBM.

10. What are the side effects of taking part?
Side effects of fludrocortisone can be gastric upset, hypertension, pulmonary edema, and
hypokalemia. If you suffer these or any other symptoms you should report to the principal investigator
(PI). Contact number of PI will be given to you and in case of any side affects you can inform PI on
phone

11. What are the possible disadvantages and risks of taking part?
It is possible that if the treatment is given to a pregnant woman, it may harm the unborn child.
Pregnant women must not therefore take part in this study; neither should woman who plan to become
pregnant during the study. Women who are at risk of pregnancy may be asked to have a pregnancy
test before taking part to exclude the possibility of pregnancy. Women who could become pregnant
must use an effective contraceptive during the course of this study. Any woman who finds that she
has become pregnant while taking part in the study should immediately inform the investigator.

12. What are the possible benefits of taking part?
We hope that both the treatments will help you. However, this cannot be guaranteed. The information
we get from this study may help us to treat future patients with tubercular meningitis better.

13. What if new information becomes available?
Sometimes during the course of a research project/trial, new information becomes available about the
treatment/drug that is being studied. If this happens, your research/trial doctor will tell you about it
and discuss with you whether you want to continue in the study. If you decide to withdraw, your
research/trial doctor will make arrangements for your care to continue. If you decide to continue in the
study, you may be asked to sign an updated consent form. Also, on receiving new information your
research/trial doctor might consider it to be in your best interests to withdraw you from the study.
He/she will explain the reasons and arrange for your care to continue.

14. What happens when the research/trial study stops?
Research drugs are standard drugs and are freely available in Indian market. Your standard treatment
continues unaffected even after completion of trial period.
15. What if something goes wrong?
If you have any adverse effects due to administered drug then the drug will be stopped and you will be offered alternative treatment. You can withdraw from the trial. Side effects are usually mild and subside once drug is stopped. For other side effects that persist, free treatment will be provided in department of neurology SGPGIMS Lucknow.

16. Will my taking part in this study be kept confidential?
If you consent to take part in the research/trial, any of your medical records may be inspected by the Ethics Committee of SGPGI. Your name, however, will not be disclosed outside the hospital/clinic/laboratory. All information collected about you during the course of the research/trial will be kept strictly confidential. Any information which leaves the hospital/clinic/laboratory will have your name and address removed so that you cannot be recognized from it.

17. What will happen to the results of the research/trial study?
This will be used to further refine management of tubercular meningitis. The data may be published in a medical journal. You will not be identified in any report.

18. Who is organizing and funding the research/trial?
This is an education research project that is being conducted by Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow and Indian Council of Medical Research (ICMR). None of the investigators participating in this project will get any extra payment other than salary given by this institute. This research is not funded by any agency. The investigations done on patients and treatment given will be part of routine patient management.

19. Will the drug be made available after trial is over? (new drug requires continued use, till it is marketed in India)
These drugs are already available in the Indian market.

20. Who has reviewed the study?
The study has been reviewed by Institutional Ethical Committee of SGPGIMS.

21. Contact for further information
You may contact:

1. Dr Usha Kant Misra,
   Professor and Head of department of Neurology, SGPGIMS (Tel. 0522-2494167 / 8004904627)

2. Dr Subhash Yadav
   (Member Secretary of ethical committee) SGPGIMS, Lucknow
   (Tel. 0522-2494918)

Thank you for participating in our study
You will be given a copy of this information sheet and consent form.

____________________
Signature of PI
Name: DR. U K MISRA
Date:
Version no:
Sub Study Title: “Safety and efficacy of fludrocortisone in treatment of cerebral salt wasting in tuberculous meningitis: A randomized controlled trial.”

Study Number: [2013-83-EMP-72(PGI/BE/733/2015)]

Subject’s Full Name (with father’s name)_________________________________________
Date of Birth/Age__________________________________________________________
Address of subject __________________________________________________________

Qualification____________________
Occupation: Student/self-employed/service/housewife/other (please tick as appropriate) Annual income of subjects__________________________
Name and address of nominee(s) and his relation to subject_________________________________________

1. I confirm that I have read and understood the information document dated ___________ for the above study and have had the opportunity to ask questions.

   OR I have been explained the nature of the study by the Investigator and had the opportunity to ask questions.

2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

3. I understand that the sponsor of the clinical trial/project, others working on the Sponsor’s behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. However, I understand that my identity will not be revealed in any information released to third parties or published.

4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

   I permit the use of stored sample (tissue/blood) for future research. Yes [ ] No [ ]

   I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:__________
Signatory’s Name_________________________ Date__________________
Signature of the Investigator ___________________________ Date__________________
Study Investigator’s Name ___________________________ Date__________________
Signature of the Witness ___________________________ Date__________________
Name of the Witness ______________________________

Received a signed copy of Participant Information Document and Consent Form.
Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:__________
Date______________________________
1.10.2: Patient information documents and Consent form in Hindi.

प्रतिभागी के लिए सूचनापत्र (AN9-V1/SGSOP 03/V1)

1. अध्ययन शीर्षक

मस्तिष्क ऊर्ध्व के रोगियों में रक्तद्रोह में कम नमक (Hyponatremia) के "कारण और उसकी भिन्नगी और परिणाम का संबंध: न्यूरोलैजी आईधीयू याइड्रिक लियूट्रां अध्ययन"

उप अध्ययन: TB मस्तिष्क ऊर्ध्व के रोगियों में रक्तद्रोह में कम नमक (CSW) में fludrocortisone के जरिए से उपचार तथा प्रभावकार्यता की अध्ययन: याइड्रिक लियूट्रां परिक्षण]

2. निमंत्रण अनुरूपित

उप अध्ययन / परीक्षण में भाग लेने के लिए आमंत्रित किया जा रहा है | इससे पहले आपके लिए यह समझना जरूरी है कि यह अध्ययन क्यों किया जा रहा है और उसमें क्या चीज़ शामिल है | कृपया आप अपना समय निकालकर इस सूचना को पढ़ें और अपने स्वयं के जान अपने भिन्न, परिवार और अपने विकल्पक के साथ चर्चा करें | यदि आप किसी भी जानकारी समझ में नहीं आती है तो हमसे पूछें बात | आप अपना समय निकालकर इस सूचना को पढ़ें और बताए गए आपके संदेश में भाग लेना चाहते हैं की नहीं |

3. अध्ययन का उद्देश्य क्या है?

टी बी मैनिंजाइटिस, भारत में सम्पन्न और मृत्यु दर का एक बहुत ही आम कारण है। इसके आम लक्षण बुखार, सिर दर्द, उलटी और भूख की कमी हैं। टी बी मैनिंजाइटिस में रक्तद्रोह में कम की आप (Hyponatremia) बहुत सामान्य रूप से देखा जाता है। यह Cerebral salt wasting या syndrome of inappropriate secretion of antidiuretic hormone (SIADH) के कारण हो सकता है। इस तरह के रोग में रोगी के मृत्यु से नमक निकाल जाता है। समान्य उपचार खारा अंक (saline) और अंतरिक्त मीठे नमक और fludrocortisone का सेवन है। लेकिन टी बी मैनिंजाइटिस बुखार में कम नमक के लिए प्लॉड्कोर्टिसोन (fludrocortisone) की प्रभावकारिता और सुधार की तुलना में कोई याइड्रिक लियूट्रां अध्ययन नहीं है। इस अध्ययन से उपचार में fludrocortisone की प्रभावकारिता निर्धारित करने के लिए करना चाहता है।

4. मुझे अध्ययन के लिए क्यों चुना गया है?

आपको चुना गया है क्योंकि आपको टीबी मैनिंजाइटिस का निदान किया गया है

5. क्या इसमें मुझे भाग लेना चाहिए?

"यह आप पर निर्भर है कि आपको भाग लेना चाहिए की नहीं | यदि आप भाग लेने का फैसला कर रहे हैं तो आपको अपने पास रखने के लिए एक सूचना पत्र दिया जाएगा और एक सहमति फार्म पर हस्ताक्षर करने के लिए कहा गया जाएगा | भाग लेने का निर्णय किया है, फिर भी किसी भी समय कारण बताए बिना वापस भाग न लेने के लिए आप उस्तंत्र हैं | इस कारण आप के इलाज में कोई फरक नहीं पड़ेगा। "

40 | Page
6. मुझे क्या होगा अगर मैं इस अध्ययन में भाग लेता हूँ?
अगर मैं इस अध्ययन में भाग लेता हूँ, तो आप महंगे बनाए लेनी और उच्च रक्तचाप के लावृत्तिक दवाओं से अचूक रखना होगा। इलाज के अंतर्गत अधिक बार साधन और उच्च रक्तचाप के लावृत्तिक का उपयोग किया जा सकता है।

7. मुझे क्या करना है?
आपके रोगी को दवाएं पकड़ने के लावृत्तिक बदलाव के लावृत्तिक दवाओं से अचूक रखना होगा। इलाज के अंतर्गत अधिक बार साधन और उच्च रक्तचाप के लावृत्तिक का उपयोग किया जा सकता है।

8. दवा का प्रयोग किया गया है?
प्रत्येक दवा इलाज के अंतर्गत अधिक बार साधन और उच्च रक्तचाप के लावृत्तिक का उपयोग किया जा सकता है।

9. निदान या उपचार के लावृत्तिक दवाओं का प्रयोग किया गया है?
प्रत्येक दवा इलाज के अंतर्गत अधिक बार साधन और उच्च रक्तचाप के लावृत्तिक का उपयोग किया जा सकता है।

10. इस अध्ययन में भाग लेने के लावृत्तिक दवाओं का प्रयोग किया गया है?
प्रत्येक दवा इलाज के अंतर्गत अधिक बार साधन और उच्च रक्तचाप के लावृत्तिक का उपयोग किया जा सकता है।

11. इस अध्ययन में भाग लेने के संभावित जोखिम और नुकसान क्या हैं?

यह संभव है कि अगर एक गर्भवती महिला को उपचार के लिए दिया जाता है तो अजन्में बच्चे को
नुकसान होगा | इसलिए गर्भवती महिलाओं को इस अध्ययन में भाग नहीं लेना चाहिए, जो औरत
अध्ययन के दौरान गर्भवती होने की संभावना है उन्हें भी इस अध्ययन में भाग नहीं लेना चाहिए |
जिन महिलाएं को गर्भावस्था की संभावना है ऐसे प्रतिभागियों को पहले एक गर्भावस्था परीक्षण के
लिए कहा जा सकता है | यदि संभव है तो उन्हें इस अध्ययन के दौरान एक प्रभावी गर्भजियोगक
उपयोग करना चाहिए | किसी भी औरत को पता पता है कि वह गर्भवती बन गया है, तो उसे तुरंत
अन्वेषक को सूचित करना चाहिए | गर्भावस्था के बयान को सावधानी से करें |

12. अध्ययन में भाग लेने के संबंधित लाभ क्या हैं?
हमें लाभ है कि उपचार से आपको मदद मिलगी | हालांकि, यह गारंटी नहीं हो सकती है| इस
अध्ययन से प्राप्त जानकारी हमें भविष्य में टीचर मेनिंजाइटिस के रोगियों का इलाज करने में मदद
मिल सकता है |

13. क्या होगा अगर नई जानकारी उपलब्ध हो?
कभी कभी एक अनुसंधान परियोजना / परीक्षण के दौरान इलाज/ दवा के बारे में नई जानकारी
उपलब्ध हो जाता है | आगे अगर ऐसा होता है तो आपके चिकित्सक इसके बारे में बताएंगे और आप
cे साथ चर्चा करेंगे कि क्या आप इस अध्ययन में भाग लेना जारी रखना चाहते हैं या नहीं। यदि
आप वापस लेने का निर्णय कर रहे हैं तो आपका चिकित्सक आपका दूसरा इलाज जारी रखने की
व्यवस्था करें | यदि आप अध्ययन में जारी रखने का फैसला लेते हैं, तो आप एक सहमति पावक
पर हस्तक्षेप करने के लिए कहा जा सकता है| इसके अलावा, नई जानकारी प्राप्त करने पर आपका
चिकित्सक आपके हित के लिए अध्ययन से वापस लेने के लिए कह सकता है | इन कारणों को
आपको बताएंगे और इलाज जारी रखने की व्यवस्था करें |

14. जब अनुसंधान / परीक्षण अध्ययन बंद हो जाता है तो क्या होता है?
शॉड दवाएं मानक दवाएं और भारतीय बाजार में स्वतंत्र रूप से उपलब्ध हैं। परीक्षण अवधि पूरी
होने के बाद भी आपका मानक उपचार अप्रभावित रहता है।

15. क्या होगा अगर कुछ गलत हो जाए?
यदि आपके पास प्रशासित दवा के कारण कोई प्रतिकूल प्रभाव पड़ता है तो दवा बंद कर दी जाएगी
और आपको वैकल्पिक उपचार की चेतावनी की जाएगी। आप परीक्षण से वापस भी ले सकते हैं। एक
बार दवा बंद होने के बाद सीक्वेन्स इम्युलेशन अध्ययन नहीं होते हैं और कम हो जाते हैं। जारी रखने
वाले अन्य दुफ़ेरियाँ के लिए, जिन: शुद्ध उपचार न्युरोलॉजी एम्मिजीआईएमएस लखनऊ विभाग में प्रदान किया जाएगा।

16. क्या मेरा यह अध्ययन में भाग लेने को गोपनीय रखा जाएगा?
यदि आप शोध में भाग लेने की सहमति देते हैं तो आपके मेडिकल रिकॉर्ड / परिणामों का विश्लेषण
जांच निरीक्षण दल द्वारा किया जा सकता है | यह नियमक अधिकारियों द्वारा अध्ययन सही तरीके
1100 से किया जा रहा है कि नहीं इसे देखकर के लिए किया जाता है | आपका नाम का अस्पताल /
1101 क्लिनिक और प्रयोगशाला के बाहर खुलासा नहीं किया जाएगा|सभी अनुसंधान / परीक्षण के बारे में
1102 आप के बारे में एक एक जानकारी कालई से गोपनीय रखी जाएगा| अस्पताल / क्लिनिक / प्रयोगशाला से
1103 बाहर जाना वाली कोई भी जानकारी के उपर से आपका नाम और पता हटाया जाएगा |
1104
1105 17. शोध / परीक्षण अध्ययन परिणामों का क्या होगा?
1106 इसका उपयोग टूर्नावर्क्यूल मेनिंगजाइटिस के उपचार में संशोधन करने के लिए किया गया। डेटा एक
1107 मेडिकल जर्नल में प्रकाशित किया जा सकता है | किसी भी रिपोर्ट में पहचाना नहीं जाएगा। आपकी
1108 व्यक्तिगत जानकारी गोपनीय रहेगी
1109
1110 18. इस अध्ययन को कौन आयोजित कर रहा है और इस परीक्षण के लिए घनं कहाँ से आयेगा?
1111 यह एक शिक्षा अनुसंधान परियोजना है जो संयुक्त गांधी पोस्ट ग्रेजुएट इंस्टीट्यूट तथा indian
1112 council of Medical research में द्वारा आयोजित किया गया है। इस परियोजना में भाग लेने
1113 वाले जानकारी को यह संस्थान द्वारा दिए गया वेतन के अनुसार। इस शोध के लिए किसी भी
1114 एजेंसी द्वारा अन्य किसी भी अतिरिक्त वित्त प्राप्त नहीं है | रोगियों के लिए दिया गया उपचार पर
1115 किया गया जब दिनचर्या रोगी प्रबंधन का हिस्सा है और अतिरिक्त लागत मरीज द्वारा नहीं ली
1116 जाएगी | केवल वे मरीज जो fludrocortisone का गोली भुगतान करने के लिए सहमत है, इस
1117 अध्ययन में शामिल किये जाएगे।
1118
1119 19. परीक्षण खतम हो जाने के बाद दवा उपलब्ध कराई जाएगी? (नई दवा को निरंतर उपयोग की
1120 आवश्यकता होती है, जब तक कि इसे भारत में विपणन न दिया जाए)
1121 अनुसंधान वेतन द्वारा पहले से ही भारतीय बाजार में आसानी से उपलब्ध हैं।
1122
1123 20. इस अध्ययन का पूर्वानुमान किसने किया है?
1124 अध्ययन एसजीपीजीआईएमएस, लखनऊ के संस्थागत मैथिल समिति द्वारा समीक्षा की गई है
1125
1126 21. अधिक जानकारी के लिए निम्न लोगो से संपर्क करें
1127 आप संपर्क कर सकते हैं:
1128 डॉ. उषा कौंट मिश्रा,
1129 प्रोफेसर और न्यूरोलॉजी के प्रमुख प्रमुखजीविकीआईएमएस,
1130 लखनऊ (दूरभाष 0522-2494167 / 8004904627)
1131 डॉ. सुभाष यादव
1132 (मैथिल समिति के सदस्य सचिव)
1133 एसजीपीजीआईएमएस, लखनऊ, (दूरभाष 0522-2494918)
1134 हमारे अध्ययन में भाग लेने के लिए धन्यवाद
1135 आपको इस सूचना पत्र और सहमति पत्र की एक प्रति दी जाएगी।
प्रमुख अन्वेषक के हस्ताक्षर
डा.उषाकंत भस्मा,
दिनांक:
संस्करण संख्या

**AN10-V1/SGSOP 03/V2: सहमति पत्र**

उप अध्ययन शीर्षक: TB मस्तिष्क ज्वर के रोगियों में रक्तोद में कम नमक (CSW) में fludrocortisone के जरिए से उपचार तथा प्रभावकारिता की अध्ययन: याहीचिक नियंत्रित परीक्षण

अध्ययन संख्या: [2013-83-EMP-72(PGI/BE/733/2015)]

प्रतिभागी के पूर्ण नाम _________________________________

जन्म तिथि / आयु _________________________________

पता _________________________________

अहोता____________________________________

व्यवसाय: विद्यार्थी/स्वतं: नियोजित/सेवा/गृहणी/अन्य (कृपया समृद्धित पर निशान लगाये)

व्यक्ति की वार्षिक आय _________________________________

नाम मिलिंगी का नाम एवं पता उनका व्यक्ति से सम्बन्ध

1. मेरी पुष्टि है की मैं अध्ययन हेतु सूचना पत्र दिनांक __________ को पढ़ व समझा लिया तथा मुझे प्रश्न पूछने या मुझे अध्ययन अन्वेषक ने सभी तत्त्वों को समझ दिया है तथा मुझे प्रश्न पूछने के समान अवसर प्रदान किये गए।

2. मैं यहाँ समझा लिया की अध्ययन मे मेरी भागीदारी पूर्णतः स्वतंत्र है और मैं किसी भी समय किसी भी कारण के बिना, मेरे इलाज या कानूनी अधिकारों को प्रभावित किये बिना, अध्ययन मे भाग न लेने के लिए स्वतंत्र हूँ।

3. मैं यह समझा लिया है कि अध्ययन के प्रायोजक, प्रायोजक की तरफ से काम करने वाले लोग, आचार समय और नियोजक अधिकारियों को मेरे स्वास्थ्य रिकॉर्ड को वर्तमान अध्ययन या आगे के अध्ययन के सन्दर्भ में देखने के लिए मेरी अनुमति की जरूरत नहीं है, चाहे मैंने इस अध्ययन से अपना नाम वापस ले लिया हो। हालांकि, मैं यह समझता हूँ कि मेरी पहचान को किसी भी तीसरे पक्ष या प्रकाशित माध्यम मे नहीं दी जायेगी।

4. मैं इससे सहमत हूँ कि कोई भी डेटा या परिणाम जो इस अध्ययन से प्राप्त होता है उसका वैज्ञानिक उद्देश्य (ओ) के उपयोग के लिए मेरी तरफ से कोई प्रतिबंध नहीं है।

5. मैं भविष्य के अनुसंधान के लिए भंडारित नमूना (उत्तक /रक्त) पर अध्ययन के लिए अपनी सहमति देता हूँ। हाँ [ ] नहीं [ ]

6. मैं HIV परीक्षण के लिए सहमति देता हूँ।

7. मैं उपरोक्त अध्ययन में भाग लेने के लिए सहमत हूँ।

प्रतिभागी/कानूनी तौर पर स्वीकार प्रतिनिधि का हस्ताक्षर (या अंगूठे का निशान)___________

हस्ताक्षरकर्ता का नाम______________________________ दिनांक ________________________________
अन्वेषक के हस्ताक्षर ______________________ दिनांक __________________
अध्ययन अन्वेषक का नाम ______________________________________________
गवाह के हस्ताक्षर ______________________ दिनांक __________________
गवाह का नाम ________________________________________________________

मैंने हस्ताक्षर युक्त सूचना तथा सहमति पत्र प्राप्त किया | प्रतिभागी/कानूनी तौर पर प्रतिनिधि का हस्ताक्षर/अंगूठे का
निशान) _______ दिनांक _______
References:


Statistical analysis plan for the final sub-study

Aetiology of hyponatremia, its relation to seizures and outcome in acute febrile encephalopathy – A prospective study in Neurology intensive care unit (NICU) patients.

Sub study: “Safety and efficacy of fludrocortisone in treatment of cerebral salt wasting in tuberculosis meningitis [CTRI/2017/10/010255 (REF/2016/07/011822)].”

Authors: Usha K Misra, Jayantee Kalita and Mritunjai Kumar
Reviewed by S. K Mondal (Department of Biostatistics, CBMR)

Purpose
This document details the planned analyses and endpoint derivations of the sub-study Sub study: “Safety and efficacy of fludrocortisone in treatment of cerebral salt wasting in tuberculosis meningitis [CTRI/2017/10/010255 (REF/2016/07/011822)].” It focuses on the analysis for the main clinical trial publication and does not include analysis for any subsidiary studies.

Statistical software
All statistical analyses will be performed with the Package for Social Sciences 20 version (IBM, Chicago, USA) software and graphs were prepared using Graphpad Prism 5.

Analysis populations
Intention-to-treat population (ITT)
The main analysis population for all analyses is the full analysis set including all randomized patients and analysis is according to the randomized treatment arm.

Per-protocol population
The main comparison for the secondary endpoint (death and disability at 3 and 6 months) and Kaplan-Meier survival curves will also be done on the per-protocol population. The following patients from the ITT will be excluded from the per-protocol population:
1. Patients without TBM according to the diagnostic score (both unlikely TBM and confirmed other diagnosis).
2. Patients with MDR-TBM
3. Lost to follow up at or before 6 months
5. Those seeking other treatment options or any major protocol violations.
Baseline characteristics

Baseline characteristics will be summarized as either mean ± SD or median (Range) for continuous data and n (%) for categorical data. The amount of missing data for each baseline characteristic will also be displayed.

Formal comparisons of baseline characteristics between study arms are discouraged by most statisticians (see e.g. Senn SS (2008): Statistical Issues in Drug Development, 2nd Edition, Wiley [p. 98f]) but mandated by some journals. To satisfy all potential publishers, we will calculate p-values (based on the independent T/ Mann Whitney U test and Chi-square /Fisher’s exact test for continuous and categorical data, respectively) but will only report them if mandated by the journal.

Baseline/date of randomization is defined as the date of the first dose of study treatment or the date when the diagnosis of CSW is confirmed.

The following baseline characteristics will be summarized by treatment arm (with derivation rules in Brackets):

Demographics and history

1. Age [Date Birth_Y]
2. Sex [1=“male”, 2=“female”]
3. Duration of illness [Day Illness]
4. TBM symptoms: headache (1= yes, 2 = no), fever (1=yes, 2=no), vomiting (1=yes, 2=no), persistent cough for more than 2 weeks (1=yes, 2=no), weight loss (1=yes, 2=no), night sweats (1=yes, 2=no), altered sensorium (1=yes, 2=no), seizures (1=yes, 2=no), type of seizures (1=focal, 2=focal with secondary generalisation, 3= generalised).
5. General examination: Temperature [Temp], pulse [Pulse], systolic and diastolic blood pressure [SBP and SDP (recoded as “DBP”)], Chronic medical illness (1= yes, 2 = no), diabetes (Diabetes; 1=”yes”, 0=”no”), liver disease [Liver (1= yes, 2 = no)], renal disease [Renal (1= yes, 2 = no)], other disease [like COPD/brochial asthma, heart failure]: (1= yes, 2 = no).
6. Contact with someone known to have TB within the past year [Contact TB (1= yes, 2 = no),]
7. Past history of TB [Previous TB (1= yes, 2 = no),]; pulmonary TB? [ Pul TB; 1=”yes”, 2=”no”]

Neurological and TBM features

1. Cranial nerve palsy any [i.e. CNP yes=1, CNP none=0]
2. Cranial nerve palsy details [“nerve 6” if CNPLef6=1 or CNPRight6=1, “other nerve(s)”otherwise]
3. Focal weakness (1= yes, 2 = no)
4. Focal weakness type:
   1. Hemiplegia [Hemipl] (1= yes, 2 = no)
2. Paraplegia [Parapl] (1= yes, 2 = no),
3. Quadriplegia [Quadripl] (1= yes, 2 = no),

5. GCS at admission (Gcs)
6. GCS at randomization [gcs@random]
7. Worst GCS (worst GCS)
8. TBM grade at baseline [TBM Grade]
9. TBM grade at randomization (TBM grade random)
10. Worst TBM stage (TBM grade worst)
11. TBM diagnosis (1= definite, 2= highly probable, 3 = possible)
12. Extra TBM site (extra TBM) (1= yes, 2 = no)

Baseline investigations

1. Chest X-Ray at admission [X-ray Result; 1="Normal", 2="Abnormal Miliary TB", 3="Abnormal"
2. Consistent with TB", 4="Abnormal Other"]
3. Haematology at admission [all measurements in HEMAT] – closest to baseline within -2/+2 days
4. Subsequent haematology values (hemat Day 3, hemat day 7 and so on) closest to within -1/+1 days
5. Biochemistry [all measurements in BIOCHEM] – closest to baseline within -2/+2 days
6. Subsequent biochemistry values (biochemDay3, biochemDay7 and so on) closest to within -1/+1 days
7. Drug induced hepatitis (DIH 1= yes, 2 = no)
8. Serum sodium and potassium [all measurements in Na and K] closest to within -1/+1 days
9. Subsequent sodium and potassium values (NaDay2, Naday4, Kday2, Kday4 and so on) closest to within -1/+1 days
10. Hyponatremia <135meq/L (hypo Na, 1= yes, 2 = no)
11. Hyponatremia corrected (hypo Na corre, 1= yes, 2 = no)
12. Cause of hyponatremia (hypo Na cause (1= CSW, 2 = SIADH, 3= poor intake, 4= miscellaneous)
13. CSW (1= yes, 2 = no)
14. SIADH (1= yes, 2 = no)
15. Hep B/C co-infection at admission (HBsAg, HCV) – positive: (1= yes, 2 = no)
16. CSF at admission [all measurements recorded in CSF_HEMAT, CSF_BIOCHEM]
17. [CSF to plasma glucose ratio will also be calculated if there is a matching plasma glucose
measurement within +/-1 hour of the corresponding CSF measurement.]
18. Urine osmolality and sodium [all measurements in urine OSM and urine Na] – closest to baseline
within -2/+2 days
19. Subsequent Urine osmolality and sodium values (urineOSMD3, urineOSMD7, urineNaD3 and so
on) closest to within -1/+1 days
20. Urine output (litres)
21. MRI abnormal (1= yes, 2 = no)
22. Specific MRI abnormality: tuberculomas (1= yes, 2 = no), hydrocephalus (1= yes, 2 = no),
exudates (1= yes, 2 = no), meningeal enhancement (1= yes, 2 = no), infarcts (1= yes, 2 = no),
location of infarct (1= cortical, 2 = corona radiata, 3 = capsular, 4= basal ganglia, 5 =
thalamus, 6= others).
23. Border zone infarcts (1= yes, 2 = no).
24. Ventriculo peritoneal shunt and extra ventricular drainage (VP shunt 1= yes, 2 = no, EVD 1= yes,
2 = no)
25. Dose of fludrocortisone in mg/ day: (fludrodose)

**Outcome measures and adverse reactions:**
1. In hospital death (1= yes, 2 = no)
2. Adverse drug reactions (ADR 1= yes, 2 = no)
3. What ADRs (hypokalemia <3.5meq/L 1= yes, 2 = no, severe hypokalemia<2.5meq/L 1= yes, 2 =
no, acute pulmonary edema 1= yes, 2 = no, pedal edema 1= yes, 2 = no, hypertension 1= yes,
2 = no).
4. Modified Rankin score at admission, at randomisation, at discharge, at 1,3 and 6 months (m RS
admin, m RS@discharge, mRS 1M, mRS 3M, mRS 6M) scored 0-6.
5. mRS modified as good or mad defined as mRS less than equal to 2 = good and m RS >2 = bad
(good=1, bad=2).

**Planned analyses**
Baseline table for all variables as detailed above. We plan that the following variables will be
included in the baseline table of the corresponding publication:
Age, gender, diagnosis at baseline (definite, highly probable, possible, unlikely TBM according to
consensus definition), extra CNS TB, duration of illness, GCS, cranial nerve palsy, focal weakness
(hemiparesis, paraparesis, quadri-paresis), seizures, mechanical ventilator, MRI findings, CSF
findings, baseline sodium and potassium level, MRC grade, urine sodium and osmolality, serum
osmolality and urine output.

**Primary endpoint—— days to hyponatremia correction**
**Derivation:** date of diagnosis of CSW minus date of sodium correction

**Planned analyses**
Primary analysis will be done by student t test/ Mann Whitney U test. Kaplan- Meier plots will also be
calculated for the full populations. In a second stage, hierarchical linear regression analysis will be
done to decide the best predictors (covariates) for the time to correction of hyponatremia. Only those
variables showing significant change in $R^2$ with P value of <0.05 will be used as covariates in the cox
regression model. Time to correction of hyponatremia were then modelled using the Cox proportional hazards regression model following covariates adjustment.

**Secondary endpoints -**

- **Sodium corrected in \(<15\) days** – Chi-square/ Fischer exact test
- **In hospital death** – Chi-square/ Fischer exact test
- **New Stroke (infarct) after randomization** – Chi-square/ Fischer exact test
- **Achieved positive fluid balance** – Chi-square/ Fischer exact test
- **Location of new infarct** – Chi-square/ Fischer exact test
- **3 months follow up (m RS good or bad)** – chi-square/ Ficher exact test, both ITT and PPA will be performed. Kaplan- Meier plots and explicit survival estimates at 3 months will also be calculated for the full populations.

- **6 months follow up (m RS good or bad)** – chi-square/ Ficher exact test, both ITT and PPA will be performed. Kaplan- Meier plots and explicit survival estimates at 6 months will also be calculated for the full populations.

**Other exploratory analysis**

Will be performed as appropriate.
4. Statistical analysis plan for the final sub-study

Aetiology of hyponatremia, its relation to seizures and outcome in acute febrile encephalopathy – A prospective study in Neurology intensive care unit (NICU) patients.

Sub study: “Safety and efficacy of fludrocortisone in treatment of cerebral salt wasting in tuberculous meningitis [CTRI/2017/10/010255 (REF/2016/07/011822)].”

Authors: Usha K Misra, Jayantee Kalita and Mritunjai Kumar
Reviewed by S. K Mondal (Department of Biostatistics, CBMR)

Purpose
This document details the planned analyses and endpoint derivations of the sub-study Sub study: “Safety and efficacy of fludrocortisone in treatment of cerebral salt wasting in tuberculous meningitis [CTRI/2017/10/010255 (REF/2016/07/011822)].” It focuses on the analysis for the main clinical trial publication and does not include analysis for any subsidiary studies.

Statistical software
All statistical analyses will be performed with the Package for Social Sciences 20 version (IBM, Chicago, USA) software and graphs were prepared using Graphpad Prism 5.

Analysis populations
Intention-to treat population (ITT)
The main analysis population for all analyses is the full analysis set including all randomized patients and analysis is according to the randomized treatment arm.

Per-protocol population
The main comparison for the secondary endpoint (death and disability at 3 and 6 months) and Kaplan-Meier survival curves will also be done on the per-protocol population. The following patients from the ITT will be excluded from the per-protocol population:
- Patients without TBM according to the diagnostic score (both unlikely TBM and confirmed other diagnosis).
- Patients with MDR-TBM
• Lost to follow up
• Withdrawal of consent any time after randomization.
• Those seeking other treatment options.

Baseline characteristics
Baseline characteristics will be summarized as either mean ± SD or median (Range) for continuous data and n(%) for categorical data. The amount of missing data for each baseline characteristic will also be displayed.
Formal comparisons of baseline characteristics between study arms are discouraged by most Statisticians (see e.g. Senn SS (2008): Statistical Issues in Drug Development, 2nd Edition, Wiley [p. 98f]) but mandated by some journals. To satisfy all potential publishers, we will calculate p-values (based on the independent T/ Mann Whitney U test and Chi-square /Fisher’s exact test for continuous and categorical data, respectively) but will only report them if mandated by the journal.
Baseline/date of randomization is defined as the date of the first dose of study treatment or the date when the diagnosis of CSW is confirmed.
The following baseline characteristics will be summarized by treatment arm (with derivation rules in Brackets):

Demographics and history

• Age [Date Birth_Y]
• Sex [1="male", 2="female"]
• Duration of illness [Day Illness]
• TBM symptoms: headache (1= yes, 2 = no), fever (1=yes, 2=no), vomiting (1=yes, 2=no), Persistent cough for more than 2 weeks (1=yes, 2=no), weight loss (1=yes, 2=no), night sweats (1=yes, 2=no), altered sensorium (1=yes, 2=no), seizures (1=yes, 2=no), type of seizures (1=focal, 2=focal with secondary generalisation, 3= generalised).
• General examination: Temperature [Temp], pulse [Pulse], systolic and diastolic blood pressure [SBP and SDP (recoded as “DBP”)] Chronic medical illness (1= yes, 2 = no), diabetes (Diabetes; 1="yes”, 0=”no”), liver disease [Liver (1= yes, 2 = no),], renal disease [Renal (1= yes, 2 = no),], other disease [like COPD/brochial asthma, heart failure]: (1= yes, 2 = no).
• Contact with someone known to have TB within the past year [Contact TB (1= yes, 2 = no).]
• Past history of TB [Previous TB (1= yes, 2 = no).]; pulmonary TB? [ Pul TB; 1=”yes”, 2=”no”]

2
Neurological and TBM features

- Cranial nerve palsy any [i.e. CNP yes=1, CNP none=0]
- Cranial nerve palsy details ["nerve 6" if CNPL6=1 or CNPR6=1, “other nerve(s)” otherwise]
- Focal weakness (1= yes, 2 = no)
- Focal weakness type:
  - Hemiplegia [Hemipl] (1= yes, 2 = no)
  - Paraplegia [Parapl] (1= yes, 2 = no),
  - Quadriplegia [Quadripl] (1= yes, 2 = no),
- GCS at admission (Gs)
- GCS at randomization [gcs@random]
- Worst GCS (worst GCS)
- TBM grade at baseline [TBMGrade]
- TBM grade at randomization (TBMgraderandom)
- Worst TBM stage (TBM grade worst)
- TBM diagnosis (1= definite, 2= highly probable, 3 = possible)
- Extra TBM site (extraTBM) (1= yes, 2 = no)

Baseline investigations

- Chest X-Ray at admission [X ray Result; 1="Normal" ,2="Abnormal Miliary TB", 3="Abnormal Consistent with TB", 4="Abnormal Other"]
- Haematology at admission [all measurements in HEMAT] – closest to baseline within -2/+2 days
- Subsequent haematology values (hemat Day 3, hemat day 7 and so on) closest to within -1/+1 days
- Biochemistry [all measurements in BIOCHEM] – closest to baseline within -2/+2 days
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- Serum sodium and potassium [all measurements in Na and K] closest to within -1/+1 days
- Subsequent sodium and potassium values (NaDay2, Naday4, Kday2, Kday4 and so on) closest to within -1/+1 days
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- Cause of hyponatremia (hypo Na cause (1= CSW, 2 = SIADH, 3= poor intake, 4= miscellaneous)
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- Modified rankin score at admission, at randomisation, at discharge, at 1,3 and 6 months (mRS admin, m RS disc, m RS1M, m RS3M, m RS6M) scored 0-6.
- mRS modified as good or mad defined as m RS less than equal to 2 = good and m RS >2 = bad (good=1, bad=2).

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Age, gender, diagnosis at baseline (definite, highly probable, possible, unlikely TBM according to consensus definition), extra CNS TB, duration of illness, GCS, cranial nerve palsy, focal weakness (hemiparesis, paraparesis, quadri-paresis), seizures, mechanical ventilator, MRI findings, CSF findings, baseline sodium and potassium level, MRC grade, urine sodium and osmolality, serum osmolality and urine output.

Primary endpoint – days to hyponatremia correction

Derivation: date of diagnosis of CSW minus date of sodium correction

Planned analyses

Primary analysis will be done by student t test/ Mann Whitney U test. Kaplan-Meier plots will also be calculated for the full populations. In a second stage, hierarchical linear regression analysis will be done to decide the best predictors (covariates) for the time to correction of hyponatremia. Only those variables showing significant change in R^2 with P value of <0.05 will be used as covariates in the cox regression model. Time to correction of hyponatremia were then modelled using the Cox proportional hazards regression model following covariates ) adjustment.

Secondary endpoints -

Sodium corrected in <14 days – chi-square/ Ficher exact test

In hospital death – chi-square/ Ficher exact test

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Location of new infarct – chi-square/ Ficher exact test

3 months follow up (m RS good or bad) – chi-square/ Ficher exact test, both ITT and PPA will be performed. Kaplan-Meier plots and explicit survival estimates at 3 months will also be calculated for the full population.
6 months follow up (m RS good or bad) – chi-square/Ficher exact test, both ITT and PPA will be performed. Kaplan-Meier plots and explicit survival estimates at 6 months will also be calculated for the full population.

Other exploratory analysis
Will be performed as appropriate.