Study Title: SeveriTy of Pulmonary Edema and timing of Resolution in patients with severe pre-eclampsia and eclampsia (**TIPER**) – a prospective observational study

Short title: Pulmonary edema resolution in severe pre-eclampsia and eclampsia - TIPER

SLERCSRef:

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Conflicts of Interests:	The investigators do not have any conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the authorised individuals from the University of Sierra Leone, the Investigator Team and members of the Sierra Leone Ethical Research Committee (SLERCS), unless authorised to do so.

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1. SYNOPSIS

Study Title	SeveriTy of Pulmonary Edema and timing of Resolution in patients with severe pre-eclampsia and eclampsia (**TIPER**) – a prospective observational study	
Internal ref. no. (short title)	Pulmonary edema resolution in severe pre-eclampsia and eclampsia – TIPER	
Study Design	A prospective, observational cohort study.	
Study Participants	Female subjects, hospitalized with severe preeclampsia or eclampsia	
Planned Sample Size	All eligible patients admitted to PCMH for 1 year	
Study Site	Princess Christian Maternity Hospital, Freetown, Sierra Leone	
Planned Study Period	April 2023 to April 2024.	
Inclusion criteria	All patients with severe pre-eclampsia or eclampsia admitted to hospital PCMH during the study period	
Exclusion criteria	1. Patients with chronic hypertensive disorders 2. Lung ultrasound not feasible, e.g., due to electricity breakdown, or absence of the trained sonographer or presence of subcutaneous emphysema,	
Aim	The primary aim is to describe the frequency of lung ultrasound consistent with pulmonary oedema and the timing of resolution after delivery. Secondary aims include the assessment of the frequency of acute respiratory failure, other LUS findings beyond pulmonary edema, the assessment of oxygenation, the use of respiratory organ support strategies, assessment of cardiac function, and quantification of major direct/ indirect obstetric complications and of perinatal complications.	
Hypothesis	1. A high proportion (>20%) of patients show LUS signs consistent with pulmonary edema before delivery. 2. There is incomplete resolution of both clinical and ultrasound signs of pulmonary edema 48 hours after delivery.	
	Objectives	**Outcome Measures**
Primary	Frequency of LUS consistent with pulmonary edema	Frequency endpoint: proportion of patients with a LUS positive for pulmonary edema Severity: LUS areation score
	Timing of resolution after delivery	Categorical: Fraction of patients with improvement or resolution of LUS findings. Numerical: delta LUS score between T1 and T2
Secondary	Frequency of acute respiratory failure in patients with Severe Pre eclampsia and in patients with Eclampsia	Proportion of patients with acute respiratory failure

	Frequency of other LUS findings	Proportion of patients with • consolidations • isolated pleural effusion • minor LUS findings
	Frequency of organ support strategies	Fraction of patients that receive oxygen and/or CPAP and/or mechanical ventilation
	Frequency of patients with abnormal cardiac function	Defined as low cardiac index measured by ultrasound
	Oxygenation assessment	SpO_2 to FiO_2 ratio
	Frequency of Major Direct Obstetric Complications (MDOCs)	Fraction of patients with at least one additional MDOC (antepartum hemorrhage, postpartum hemorrhage, sepsis, uterine rupture, obstructed labour)
	Frequency of Indirect Obstetric complications	Fraction of patients with at least one among stroke, severe malaria, acute kidney injury and cardiac insufficiency.
	Frequency of perinatal complications	Intra uterine fetal death (IUFD), Apgar score, Admission to special care baby unit (SCBU)
Procedures	All procedures are standard of care and routinely performed in critically ill patients: 1. Lung Ultrasound examination 2. Echocardiography and inferior vena cava ultrasound 3. Pulse oximetry 4. Urine output monitoring (when foley catheter inserted by treating team)	
Safety	The bedside non-invasive procedures pose minimal risk to the patient and do not require additional transportation.	
Benefits of study	The study will evaluate the possibility of early intercepting pre-eclamptic and eclamptic patients with pulmonary involvement. This group of patients may potentially benefit from the implementation of optimal triage and early therapeutic choices in a limited resource setting (e.g. diuretics, escalation to non-invasive or invasive ventilation, referral to HDU or ICU, dialysis) with a potential to reduce unfavourable outcomes.	

2. ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
PCMH	Princess Christian Maternity Hospital
CUAMM	Doctors with Africa – CUAMM
HDU	High Dependency Unit
FiO_2	Fraction of inspired oxygen

LUS	Lung ultrasound
SLERC	Sierra Leonel research ethics committee
SpO2	Peripheral oxygen saturation

3. BACKGROUND AND RATIONALE

3.1 Background

Obstetric critical care burden in resource–poor settings

Maternal mortality from treatable causes concerning the critical care domain in low– income countries remains strikingly high (1) . Maternal mortality in Sierra Leone is the highest in the world with 1,360 deaths per 100,000 born alive. The burden of obstetric–related critical care morbidity is also extremely high. In high–income countries less than 2% of intensive care unit (ICU) admissions relate to obstetric illnesses, but these rise to 10% in resource–limited settings. Pre-eclampsia/eclampsia are hypertensive disorders of pregnancy, one of the 3 leading causes of maternal morbidity and mortality worldwide(2).

Aims of critical care management

The aims of critical care management are to stabilize and monitor physiological parameters and support failing organ systems, thus allowing time for recovery and implementation of disease–specific therapies. Supportive management is classically divided by organ systems and may be guided by invasive or non–invasive monitoring, globally aimed at adequate oxygen delivery to the tissues. This involves several steps, at any of which deficiencies may occur, i.e., oxygen transfer to the blood in the lungs, oxygen transport from the lungs to the tissues and finally diffusion from capillary blood to the cells (3). The respiratory system is a central in this process; hence early and precise assessment of pulmonary impairment is pivotal.

Pulmonary complications associated with Severe Preeclampsia and Eclampsia

The reported incidence of eclampsia is 1.6 to 10 per 10,000 deliveries in developed countries, whereas it is 50 to 151 per 10,000 deliveries in developing countries (4–6). In addition, low-resource countries have substantially higher rates of maternal and perinatal mortalities and morbidities. This disparity in incidence and pregnancy outcomes may be related to universal access to prenatal care, early detection of preeclampsia, timely delivery, and availability of healthcare resources in developed countries compared to developing countries. Because of its infrequency in developed countries, many obstetrical providers and maternity units have minimal to no experience in the acute management of eclampsia and its complications.

Respiratory distress and pulmonary oedema are known complications of preeclampsia-eclampsia and their insurgence is a hallmark of severe disease (7,8). Pulmonary oedema is reported as a complication in 2.9% of patients with preeclampsia-eclampsia (9). Pulmonary involvement is associated with worse maternal and perinatal outcomes (10,11). Incidence is significantly higher in low income countries, rising to 12% due to poorer prenatal care and access to hospital care, and suboptimal diagnostic and management processes (12).

A retrospective study showed how the average time to resolution of pulmonary oedema for obstetric patients with different primary clinical disorders was 2.4 days (13). The preeclamptic and eclamptic patients is characterized by systemic endothelial cell dysfunction, increased systemic vascular resistance and increased capillary permeability, all leading to excessive extravasation and as such increasing the risk of pulmonary oedema (14,15). This is also why, together with the infectious cause, preeclampsia/eclampsia are the leading cause of ARDS in pregnancy (16,17).

Challenges with diagnosis and follow up of pulmonary complications

In the absence of imaging modalities (chest radiography, computed tomography) and laboratory measures (blood gas analysis) it may be difficult to quantify respiratory deterioration, or the pulmonary component in a global deterioration. Bedside clinical examination lacks sufficient sensitivity and specificity for

pulmonary edema and ARDS. Simple bedside techniques are increasingly available, such as pulse oximetry for quantification of oxygenation deficit and lung ultrasound for systemic imaging.

Use of lung ultrasound to detect pulmonary complications

Point–of–care lung ultrasound (LUS) is a non–invasive, rapid and sensitive method to detect pulmonary pathology (18,19). LUS is a bedside practical and easy tool to use, and being a radiation–free investigation it can be regularly repeated. LUS may expedite etiological diagnosis in cases of undifferentiated dyspnoea (20), both in resource–rich and –poor settings (21,22). Detection of focal consolidation could suggest a diagnosis of pneumonia, whereas the visualization of multiple complex patterns could suggest ARDS (23). Simultaneous presence of pleural fluid and loss of aeration may point at fluid overload (24). Conversely, a normal lung pattern in the presence of respiratory distress would direct the clinician towards alternative diagnoses, such as respiratory compensation of a metabolic acidosis, asthma or pulmonary embolism (25).

Additional point-of-care ultrasound applications

Point-of-care *echocardiography* also represents a potential valuable adjunct to clinical care in low- and middle-income countries, with several ultrasound-based clinical algorithms proposed. Early bedside echocardiographic assessment of cardiac function is recommended to guide haemodynamic management and when combined with lung ultrasound it provides further clinically relevant information. The basic echocardiography examination consists of five standard views and allows the physician to: (i) identify imminent life-threatening causes of haemodynamic failure, (ii) recognise coexisting diagnoses that complicate management, (iii) follow the evolution of the disease process, and (iv) monitor response to treatment.

3.2 Rationale

Accurate assessment of patients with pulmonary involvement combined with LUS and echocardiography could lead to earlier detection of pre eclampsia and eclampsia associated pulmonary oedema, ARDS and other pulmonary complications. As there is currently limited evidence regarding the features, severity, aetiology and history of pulmonary oedema in this kind of people (26,27), the data from this prospective, cohort study might facilitate the early intercepting pre-eclamptic and eclamptic patients with pulmonary involvement to implement optimal triage and early therapeutic choices in a limited resource setting (diuretics, escalation to non invasive or invasive ventilation, referral to HDU or ICU, dialysis) could reduce unfavourable outcomes.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures
Primary objective	
To describe the frequency of LUS abnormalities consistent with pulmonary oedema	Frequency endpoint: proportion of patients with LUS consistent with pulmonary edema Severity endpoint: LUS aeration score (numerical 0 to 36)
To describe the timing and entity of edema resolution after delivery	Frequency endpoint: Fraction of patients with improvement or resolution of LUS findings. Quantitative endpoint: delta LUS score between T1 and T2
Secondary objectives:	
To describe the frequency of acute respiratory failure in patients with Severe Pre-eclampsia and in patients with Eclampsia	Proportion of patients with acute respiratory failure (see definition)
Frequency of other LUS findings	Proportion of patients with: • consolidations • isolated pleural effusion • minor LUS findings Calculation of the LUS ARDS score
Frequency of organ support strategies	Fraction of patients that receive: - oxygen - CPAP - Mechanical ventilation
Frequency of patients with abnormal cardiac function	Defined as either low cardiac output measured by ultrasound
Oxygenation assessment	SpO_2 to FiO_2 ratio
Frequency of Major Direct Obstetric Complications	Fraction of patients with at least one additional MDOC (APH, PPH, sepsis, uterine rupture, obstructed labour)
Frequency of Indirect Obstetric complications	Fraction of patients with at least one among stroke, severe malaria, acute kidney injury and cardiac insufficiency
Frequency of perinatal complications	IUFD, Apgar score, Admission to special care baby unit (SCBU)

4.1 Hypothesis

1. A high proportion (>20%) of patients show LUS signs consistent with pulmonary edema before delivery.
2. There is a resolution of both clinical and ultrasound signs after in the 48 hours after delivery.

5. STUDY DESIGN

This will be a single centre, prospective, cohort study of patients with severe pre-eclampsia and eclampsia. The expected duration of study is 1 year. All patients with suspected severe pre-eclampsia or eclampsia will undergo screening upon admission to HDU and the Eclamptic ward. Eligible patients will undergo a systematic clinical and LUS examination, straight after admission (**before delivery**). Clinical examination will focus on signs of respiratory, neurologic and cardiac failure. Lung ultrasound will be performed using a MyLab™Five ultrasound machine (Esaote Spa, Genova, Italy) and a low frequency (2.5–5 MHz) convex probe or a Butterfly ultrasound probe (Butterfly, USA). Lung ultrasound will be performed using the

validated 12-region method, evaluating 2 anterior regions, 2 lateral regions and 2 posterior in each hemithorax (18,28,29). As heart failure is a common finding in preeclamptic women, echocardiography performed with a cardiac sector probe, will enable real-time assessment of maternal cardiac contractility and cardiac output. The same clinical, LUS and echocardiographic assessment will be repeated between 24 h to 72 h (**after delivery)**. Whenever the pre-delivery timepoint is not feasible due to late arrival, emergency scenario or postpartum onset, the after delivery examination only will be performed.

5.1. Study Site

The study will be conducted at a single tertiary care hospital in Freetown, Sierra Leone. The Princess Christian Maternity Hospital (PCMH) is a 130-bed referral hospital. Patients will be recruited from the Eclamptic ward and the High Dependency Unit.

5.1. Sample size calculation

There is very limited data on the prevalence of pulmonary edema in eclampsia patients. For this explorative descriptive study we plan to recruit all eligible patients during a 12 months study period.

6. PARTICIPANT IDENTIFICATION AND RECRUITMENT

6.1. Study Participants

Patients hospitalized at PCMH with severe preclampsia and eclampsia will be enrolled if the applicable inclusion and exclusion criteria are met.

6.2. Inclusion Criteria

1. All patients with severe pre-eclampsia or eclampsia admitted to hospital PCMH during the study period, defined as by American College of Gynaecology and Obstetrics according to the Government of Sierra Leone Ministry of Health and Sanitation.

6.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

1. Patients with chronic hypertensive disorders;
2. LUS not feasible, e.g., due to electricity breakdown, or absence of the trained sonographer or diffuse subcutaneous emphysema.

6.4. Case definitions

Acute respiratory failure defined as RR≥30 breaths per minute AND/OR SpO_2/fraction of inspired oxygen (FiO_2) ≤ 315 AND/OR signs of difficult breathing, including the use of accessory muscles or nasal flaring. FiO_2 will be derived from the amount of oxygen the patient receives in liters.

Clinical pulmonary oedema

Defined as respiratory distress (respiratory rate >30 breaths/min and/or SpO2 <92% on room air) with bilateral fine crepitations on chest auscultation.

Lung ultrasound consistent with pulmonary oedema (categorical)

The presence of three or more B-lines (any size and any distance apart) in a particular lung region will define a positive lung region for interstitial syndrome (30) Pulmonary edema will be defined as the presence of ≥2 positive regions per side.

Abnormal lung ultrasound aeration score

The LUS aeration score (numerical) will be calculated: each lung field will be scored from 0 to 3 as follows: "0," A-pattern with ≤ 2 B-lines; "1," more than 2 separated B-lines; "2," multiple coalescent B-lines; or "3," lung consolidation, defined as anechoic or tissue-like images arising from the pleural line that is limited in depth by an irregular border. A global LUS score will be calculated at each time point and ranged from 0 to 36.

LUS ARDS score

The three variables included in the final logistic regression model for diagnosis of ARDS are: left LUS aeration score (range 0-18), right LUS aeration score (range 0-18), and the number of antero-lateral lung regions with an abnormal pleural line (range 0-8). The LUS-ARDS score can range from 0 to 91 and is computed with the formula below. (31)

$$\text{LUS-ARDS score} = 2.5 \times \text{left LUS aeration score} + 1 \times \text{right LUS aeration score} + 3.5 \times \text{no. of anterolateral regions with an abnormal pleural line}$$

Acute Respiratory Distress Syndrome (ARDS)

Defined according to the Berlin Definition or Kigali Modification as shown in **Table 1**.

Table 1. Berlin Criteria for ARDS and Kigali Modification of the Berlin Criteria (19,32)

Criteria	**Berlin definition of ARDS**	**Kigali modification**
Timing	Within 1 week of a known clinical insult, or new or worsening respiratory symptoms	
Oxygenation	PaO_2 /FIO_2 ≤300 mmHg	SpO_2 /FIO_2 ≤315 mmHg
PEEP requirement	Minimum 5 cm H_2O PEEP required by invasive mechanical ventilation (non-invasive acceptable for mild ARDS)	No PEEP requirement, consistent with AECC definition
Chest imaging	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or CT	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or ultrasound
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic oedema if no risk factor present)	

Bilateral opacities on ultrasound will be defined as two or more regions with a B-pattern and/or C-patterns per hemithorax bilaterally (33).

Abbreviations: ARDS, acute respiratory distress syndrome; PaO2, arterial oxygen tension; FiO_2, fraction of inspired oxygen; SpO_2, oxygen saturation as measured by pulse oximetry; AECC, American-European Consensus Conference; CT, computed tomography; PEEP, positive end-expiratory pressure.

Abnormal cardiac function

Defined as a cardiac index (CI) <2.5 l/min/m2 measured by echocardiography.

Modified Early Warning (MEWS) Score

The modified early warning score ranges from 0 to 14 and is calculated as detailed in **Table 2** (34) (35)**.**

Table 2. The Modified Early Warning Score score.

Physiological parameters	**Normal values (0 points)**	**Yellow alert (1 point)**	**Red Alert (2 points)**
Respirator rate	10- 20 breaths pwe minute	21- 30 breaths per minute	<10 or >30 breaths per minutes
Oxygen saturation	96- 100%		<95%
Temperature	36.0- 37.4°C	35- 36 or 37.5- 38°C	<35 or >38°C
Systolic blood pressure	100- 139 mmHg	150- 180 or 90- 100 mmHg	>180 or < 90 mmHg
Diastolic blood pressure	50- 89mmHg	90- 100 mmHg	>100 mmHg
Heart rate	50- 99 beats per minute	100- 120 or 40- 50 beats per minute	>120 or <40 beats per minutes
Neurological response	Alert	Voice	Unresponsive, pain

7. STUDY PROCEDURES

7.1. Recruitment

Consecutive admitted patients will be assessed for inclusion and exclusion criteria by a research physician. If eligible, the participant will be enrolled in the study. Details of those fulfilling the entry criteria will be entered onto a screening form, while reasons for non-eligibility will be added to the eligibility-screening log. It is expected that this process will take approximately 30 minutes.

7.2. Informed consent

No ethical concern is attributable to this study due to its observational nature. No direct intervention on patient is part of the study design. Personal information (name, age, community, etc.) from registries will be anonymized and no patients will be recognizable during the realization or dissemination phases of the study. Serial ultrasound examinations are standard of care in obstetric patients, while lung ultrasound is routine practice in intermediate and intensive care units, especially in the absence of alternative image modalities as chest radiography or computed tomography. For these reasons, a waiver of patient individual informed consent is requested to this EC. Sharing of patient data will follow Good Clinical Practice guidelines and ethics review committee advice.

7.3.1. Screening demographic and medical history

Basic demographic and epidemiological data (i.e. age, sex, medical history of hypertension disease) will be obtained to assess eligibility and recorded in the screening log by the study staff.

7.3.2. Screening physical exam and vital signs

Vital signs will be conducted by a research physician including Glasgow Coma Scale (GCS), pulse rate, blood pressure, respiratory rate, aural temperature (average of left and right ears), and pulmonary auscultation. The screening vital signs will be recorded in the screening log by the study staff.

7.4. Baseline Assessments

Following screening and eligibility confirmation the baseline assessments will be performed as detailed below. The duration of time to perform baseline assessment will take approximately 1 hour.

7.4.1. Demographic and medical history

A detailed demographic, epidemiologic (i.e. age, sex, address, previous medications) and past-medical history will be obtained and recorded in the Case Report Form (CRF) by the research staff. All prescribed or over-the-counter drugs, traditional medications and any drug allergies will also be recorded.

7.4.2. Physical exam and vital signs

Upon enrolment, a full physical examination will be conducted by a research physician. Vital signs including GCS, pulse rate, blood pressure, respiratory rate, SpO_2, FiO_2, aural temperature (average of left and right ears), weight, height and a neurological exam will be recorded in the CRF.

7.4.3. Non-invasive investigations

Baseline investigations will include echocardiography and lung ultrasound.
Briefly, point-of-care ultrasonography will include: (1) lung ultrasound following a 12-region protocol, (2) echocardiography.

8. INVESTIGATIONS

8.1. Ultrasound Examinations

8.1.1. Lung ultrasound examination

A complete 12-region lung ultrasound examination will be conducted with a standard ultrasound machine and a low frequency (2.5–5MhZ) convex probe. The ultrasound machine, the probe and the probe holder will be cleaned before and after each use using the dedicated antiseptic detergent indicated by hospital guidelines. The patient remains in supine position and the probe will be held perpendicular to the skin. Briefly, the 12-rib interspaces will be scanned at the bedside with the ultrasound probe applied longitudinally and perpendicularly to the exterior chest wall. The left and right hemi thorax will be assessed in six areas: two anterior areas, two lateral areas, and two posterior areas. The anterior chest will be delineated as the parasternal to the anterior axillary line and divided into upper and lower halves (zones 1 and 2). The lateral area will be delineated as the anterior to the posterior axillary line and divided into upper and basal halves (zones 3 and 4). The posterior area will be considered as the zone beyond the posterior axillary line and divided into upper and lower zones (zones 5 and 6). The lung ultrasound score (sum of patterns found on each scanning site) will be recorded (score 0: pattern with less than three B-lines; score 1: Three or more separated B lines; score 2: multiple and confluent B-lines; score 3: consolidation) (36). The global lung ultrasound score will range from 0 to 36. Additional ultrasound findings include the assessment of subpleural consolidations, pleural effusions and lung sliding.

8.1.2. Cardiac echocardiographic examination

In the supine position, bedside images will be obtained using a with a low frequency (2.5-5 MhZ) sector cardiac probe. Focused echocardiographic examination will include two windows of the exterior chest wall: the parasternal long axis (PLAX) and the 4-chamber long views (4CLV). The cardiac ultrasound will obtain the real-time assessment of maternal cardiac contractility and cardiac output.

10. STATISTICS AND ANALYSIS

For descriptive purposes continuous and ordinal variables data will be expressed as median with interquartile range. For categorical variables, percentages are calculated. Student's t-test or analysis of

variance (ANOVA) will be used to compare normally distributed numerical variables. Mann Whitney U-tests and Kruskal-Wallis tests will be used to compare numerical variables when normality cannot be assumed, while chi-squared tests will be used to compare categorical variables. Univariate logistic regression analyses will be performed to identify potential factors associated with the clinical outcomes including, but not limited to, presence of interstitial syndrome, non-resolution of interstitial syndrome at 48-72h, development of ARDS and death in hospital. Multivariable logistic regression models will be used to identify independent risk factors for the same clinical outcomes. A forward and backwards stepwise approach will used to include variables into the models, with a limit of P <0.2.
Inter– observer variability of the lung ultrasound score between the study sonographer and an independent expert will be calculated on a random sample of 10 cases (120 lung regions) using Cohen K-statistics. Statistical analyses will be conducted using R (www.r-project.org). A P-value of <0.05 will be considered statistically significant. Analyses will be conducted after the end of patient recruitment and no interim analyses are planned. Statistical analysis will be performed with R software (R Foundation for Statistical Computing, Vienna, Austria).

11. DATA MANAGEMENT

11.1. Data management

All patients will be identified with a unique study identification code. A logbook with the matching between patient number and name will be stored digitally and in paper. The paper version will be stored behind a lock and the digital form will be protected with a password. The logbook will be the only document containing patient identifier information. Data will be stored an additional 15 years after the study's completion

11.2. Access to Data

Data is collected from the patient medical chart and transcribed onto an Internet– based electronic CRF (REDCap – Research Electronic Data Capture (18), www.projectredcap.org). Access to the data–entry system is protected by a personalized username and password. The data will be kept on a central secured server. Patients are identified with a study identification code, hence there will be no patient identifier data transcribed on the online CRF.

Data derived from this study will be shared with the clinical team directly responsible for patient's care and with hospital leadership and management team for monitoring and/or audit purposes. After publication of the primary results, on request the pooled dataset will be available for secondary analysis, after judgment and approval of scientific quality and validity of the proposed analysis by the Steering Committee.

11.3. Data Handling and Record Keeping

The anonymized data will be stored in a secure database to guarantee the privacy of study subjects. Only local investigators will have access to the database and matching log–book. A copy of the LUS report will be attached to the patient's clinical chart to be visualized by the clinical team responsible for patient's care.

12. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written SOPs, the monitors will verify

that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (2008).

13.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3. Approvals

The protocol, ICF, and PIS will be submitted to SLERC, Sierra Leone Ethical Research Committee for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all amendments to the original approved documents. As lung ultrasound is standard of care in critically ill patients, especially in a setting lacking other imaging modalities and considered there are no associated risks when receiving this examination, a waiver of written informed consent is requeted from the committee. This approach was successfully used in the past in the same setting. (18)

13.4. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

13.5. Expenses and Benefits

Expenses

In-hospital costs of medications and medical supplies will be covered. No other gifts or payments will be made upon participation in this study.

Benefits

Pulmonary oedema is a life-threatening complication of severe preeclampsia and eclampsia, occurring in approximately in 2.9% of patients with preeclampsia-eclampsia and it is associated with worse maternal and perinatal outcomes. Accurate assessment of patients with pulmonary involvement combined with LUS and echocardiography could lead to earlier detection of pre eclampsia and eclampsia associated pulmonary oedema, ARDS and other pulmonary complications. As there is currently limited evidence regarding the features, severity, etiology and history of pulmonary oedema in this group of patients, the possibility of early intercepting pre-eclamptic and eclamptic patients with pulmonary involvement to implement optimal triage and early therapeutic choices in a limited resource setting (diuretics, escalation to non-invasive or invasive ventilation, referral to HDU or ICU, dialysis) could reduce unfavourable outcomes.

13.6. Reporting

The PI shall submit an Annual Progress Report to SLERC and local ethics committee on the anniversary of the date of approval of the study. In addition, the PI shall submit an End of Study Report to SLERC and to local ethics committee upon the completion of the study.

13.7. Other Ethical Considerations

13.7.1. Risks

Because all proceedings in the method of this study are based on common clinical practice and ultrasound is a non–invasive procedure that cannot injure patients, the risk of this study is considered very low. LUS and echocardiographic are standardly performed in intensive and intermediate care units to assess lung aeration and presence of pleural effusion and consolidations or cardiac contractility and cardiac output. The ultrasound examinations performed for this study are not charged to the patient or to the hospital administration. As this study aims at assessing the frequency of complications in critically ill obstetric patients, we cannot choose for another patient population. Patients included in this study may benefit in terms of increased serial monitoring events in a setting where no other onsite lung and cardiac imaging techniques is available

14. FINANCE AND INSURANCE

14.1. Funding

The study will be supported by Doctors with Africa – CUAMM using funding by a Wellcome Innovations Flagship award (Collaboration for Research, Improvement and Training in Critical CARE in ASIA grant -- ref. 215522/Z/19/Z). Waiver for costs for publication based on low–income country status will be sought from the relevant international journals.

15. PUBLICATION POLICY

The results of this study will be published in a peer–reviewed medical journal. We have no restrictions in publication of outcomes of this study

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