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A Comparative Study of 12 hour versus 24 hour Modified Pritchard Regimen in the Management of Eclampsia and Preeclampsia (MOPEP STUDY): Study Protocol

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ABSTRACT

Introduction: Hypertensive disorders of pregnancy continue to be a major contributor to maternal and perinatal morbidity and mortality. Magnesium Sulfate therapy is the standard of care for seizure prophylaxis and treatment for preeclampsia and eclampsia respectively, despite wide disparities in dosing regimens and routes of administration. This study compares the clinical efficacy of Magnesium Sulfate in the reduction of seizure occurrence or recurrence with the 12 hour versus 24 hour Modified Pritchard regimens in the management of severe preeclampsia and eclampsia.

Methods and Analysis: This study is an open label randomized control trial. The study participants are patients admitted to the Korle Bu Teaching Hospital in Accra, Ghana with a diagnosis of antepartum, intrapartum, or postpartum eclampsia or preeclampsia with severe features. All study participants will be administered a loading dose of Magnesium Sulfate, followed by maintenance dosing. Participants in the Control group will receive magnesium sulfate for 24 hours after diagnosis, while those in the Treatment group will receive magnesium sulfate for 12 hours after diagnosis. The primary outcome of this study is the occurrence of a seizure any time after the completion of treatment in the assigned group. Secondary outcome measures include maternal health outcomes, Magnesium Sulfate toxicities, and fetal health outcomes. Data collection was started October 2018 with a target enrollment of 460 participants with preeclampsia and 220 participants with eclampsia with a projected study period of 1.5 years.

Ethics and Dissemination: Ethical approval was obtained from the Korle Bu Teaching Hospital IRB in Ghana. University of Michigan involvement is limited to protocol development and statistical analysis of de-identified data, and has been granted a Not Regulated Determination by the University of Michigan IRB. Results of the study will be shared at clinical forums at the Korle Bu Teaching Hospital and will be submitted for publication in an international peer-reviewed journal.

Trial Registration: The study has been registered with the Pan African Clinical Trial Registry through the South African Medical Research Council: PACTR201811515303983.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Large randomized control trial that addresses duration of administration of Magnesium Sulfate, which fills an important gap in the literature and has significant implications for management of patients with eclampsia and preeclampsia with severe features.
- The study is taking place in a low resource setting with a high incidence of preeclampsia and eclampsia and advanced disease at presentation
- Data collection in a developing country setting with no electronic medical record may contribute to missing information and become a study limitation
- Lack of blinding of patients and providers to group allocation is a study limitation, however, primary outcome (occurrence of seizure) and secondary outcomes (maternal: time to diuresis, clinical toxicities and complications; neonatal: birth outcomes) are objective measures

INTRODUCTION

Hypertensive disorders complicate 10% of pregnancies worldwide (1,2) and preeclampsia occurs in 2-8% of all pregnancies globally(1). In developing countries, hypertensive disorders account for 10-15% of maternal deaths (1,2). In Ghana, the incidence of hypertensive disorders in pregnancy has been estimated from a hospital based study as 7.6%(3). Eclampsia contributes significantly to maternal mortality in developing countries. In Ghana, a case fatality of 3.9% has been reported, and institutional reports from two major tertiary level hospitals suggest hypertensive disorders have overtaken haemorrhage as the leading cause of maternal mortality(3,4).

While preeclampsia may not be preventable, the risk of eclampsia can be significantly reduced with good obstetric management (5,6). Magnesium Sulfate has been used for decades for the management of eclampsia and preeclampsia and is the anti-convulsant of choice for the management and prevention of eclamptic seizures (7,8). Good clinical efficacy has been reported with the use of Magnesium Sulfate in the management of preeclampsia despite wide disparities the dosing regimens and routes of administration(9,6,8, 10–12).

There is lack of consensus in the existing literature about optimal duration and dosing of Magnesium Sulfate, as well as optimal therapeutic window. Therapeutic failures have been reported for doses considered both high and low(8–13). The narrow therapeutic window widely used in literature is challenged by pharmacokinetic studies that demonstrate that accepted international regimens sometimes fail to reach the minimum therapeutic threshold yet are associated with clinical efficacy(8,14,15). The duration of treatment has also been questioned, and a wide range of different regimens are currently utilized in clinical practice. Some protocols such as the Sokoto (ultra-short) protocol demonstrated that just the standard loading dose of the Prichard regimen may be sufficient (11).

In Korle Bu Teaching Hospital and other centres in Ghana, many patients do not complete the 24-hour maintenance course due to poor compliance due to discomfort associated with the repeated injections, side effects, and sometimes financial constraints; yet our observational experience has not demonstrated an increase in disease progression in this cohort of patients. Perhaps this is secondary to the efficacy demonstrated in shorter regimens like the 12- hour maintenance and ultra-short (6). The cost to the

individual and the healthcare system associated with the 24-hour maintenance course is significant. The determination of the minimum effective duration of treatment with proven clinical efficacy, minimum side effect profile and toxicity is likely to improve compliance, reduce waste and conserve resources in developing countries.

Problem Statement

Maternal morbidity and mortality resulting from preeclampsia and eclampsia remain high in many middle to low income countries. The case fatality of eclampsia is unacceptably high despite known interventions to reduce the progression to eclampsia. The current dosing regimens are at best empirical with several different regimens being utilized in clinical practice.

Previous studies comparing clinical efficacy of dosing regimens involved relatively small sample sizes and were not powered to detect clinical differences in toxicity and tolerability. Two small studies have compared outcomes using 12 hours versus 24 hours of Magnesium Sulfate using an intravenous infusion regimen (6,12). However, there are no studies that compare 12 hours versus 24 hours of Magnesium Sulfate using an intramuscular regimen, which is the most common method of administration in developing countries. Finally, the incidence of the various side effects or toxicities of magnesium sulfate with the Pritchard regimen has not been studied in the Ghanaian population, despite years of utilization of this regimen.

Justification

Magnesium sulfate remains the mainstay of treatment prevention of eclamptic seizures in patients with preeclampsia and the prevention of recurrent seizures in patients with eclampsia. The clinical efficacies reported with varying durations and routes of administration necessitates further research to determine the optimum effective duration with demonstrable clinical efficacy and low toxicity which will be cost efficient to the healthcare system, especially in low resource countries.

Our study therefore seeks to investigate and compare clinical response between the 12 hour versus 24 hour Modified Pritchard regimens. A significant reduction in cost is expected if the reduced duration of treatment proposed by this trial is adopted and there is a need to subject it to a rigorous clinical trial to assure maternal safety.

Aim and Objective

Aim: To compare the 12 hour versus 24 hour Modified Pritchard regimens of magnesium sulfate in the management of eclampsia and preeclampsia with severe features.

Objectives:

1. To compare the clinical efficacy of the 12 hour versus 24 hour Modified Pritchard regimens in the reduction of seizure occurrence in women with Eclampsia and Preeclampsia with Severe Features
2. To compare the side effect profile and toxicity of the 12 hour versus 24 hour Modified Pritchard regimens in the management of women with Eclampsia and Preeclampsia with Severe Features

3. To compare the neonatal health outcomes following treatment with 12 hour versus 24 hour Modified Pritchard regimens in women with Eclampsia and Preeclampsia with Severe Features

Hypotheses

H_0: There is no difference in clinical efficacy of Magnesium Sulfate between the 12 hour versus 24 hour Modified Pritchard regimens.

H_1: There is a difference in clinical efficacy of Magnesium Sulfate between the 12 hour versus 24 hour Modified Pritchard regimens.

METHODS AND ANALYSIS

Study Design

An open label randomized control trial in which the Study arm will receive 12 hours of maintenance doses of Magnesium Sulfate and the Control arm will receive 24 hours of maintenance doses of Magnesium Sulfate. Participants will be enrolled into study groups by simple randomization using a computerized random number generation table.

Study Site

The Korle Bu Teaching Hospital (KBTH) is the country's premier teaching hospital and serves as a national referral hospital for the southern half of the country. It is a tertiary hospital with a bed capacity of 2000 and an average daily Outpatient Department attendance of 1500 patients. The maternity unit conducts about 9500 deliveries per year. Current standard of care at KBTH is a Modified Pritchard regimen of Magnesium Sulfate, with administration of a loading dose followed by 24 hours of maintenance dosing, starting at the time of diagnosis of eclampsia or preeclampsia with severe features.

Study Population

Accra is a cosmopolitan city with people of varied ethnic backgrounds and social status. It is expected that the sample will represent this diversity and be reflective of the nation. Participants will be patients receiving their prenatal care at Korle Bu Teaching Hospital, as well as referral cases from peri-urban and rural communities around Accra.

Inclusion Criteria

1. Clinical diagnosis of antepartum, intrapartum, or postpartum eclampsia based on:
    a. Elevated blood pressures of 140/90 mm Hg or higher on two occasions at least 4 hours apart after 20 weeks of pregnancy
    AND
    b. Seizures not attributed to other causes.
2. Clinical diagnosis of Preeclampsia with Severe Features (definitions per ACOG Hypertension in Pregnancy Guidelines, 18) based on:
    a. Elevated blood pressures of 160/110 mm Hg or higher on two occasions at least 4 hours apart after 20 weeks of pregnancy, with proteinuria or presence of laboratory values or clinical symptoms indicating end-organ dysfunction
    OR

b. Elevated blood pressures of 140/90 mm Hg or higher on two occasions at least 4 hours apart after 20 weeks of pregnancy, with presence of laboratory values or clinical symptoms indicating end-organ dysfunction

3. Patients who receive loading dose of $MgSO_4$ at referral clinics prior to referral will be eligible for randomization if they otherwise meet the inclusion criteria
4. Age 18 years or older

Exclusion Criteria

1. Eclampsia complicated by acute renal failure, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), or pulmonary edema
2. Co-morbid maternal diagnosis of renal disease and/or seizure disorder
3. Contraindication to MgSO4 (e.g. drug hypersensitivity, myasthenia gravis, anuria, or oliguria)
4. Prior intake of any other anticonvulsant
5. Prior exposure within 72 hours to Magnesium Sulfate which was not a component of the study regimens
6. Refusal to give consent or unable to give consent (eg unconscious)
7. Age 17 or younger

Sample Size Estimation

An occurrence of a seizure is the primary outcome. In women with eclampsia, this will be a recurrent seizure and in women with preeclampsia with severe features, this will be their initial seizure. Regarding eclampsia, according to Ekele and colleagues working in an environment similar to the study site, they reported a 7.4% recurrent fit in patients with eclampsia who received only a loading dose magnesium sulfate (11). In order to find a reduction in the incidence of recurrent fits in eclamptics who receive a standard dose of magnesium sulfate from 7.4% to the 0.2% reported for the postpartum period(16), (α= 0.05 and β=0.2), a sample size of 220 women (110 in each group) with eclampsia is considered sufficient.

The occurrence of eclamptic seizures in untreated cases of severe preeclampsia is 3.2%. In order to achieve a 25% reduction in the primary outcome (α= 0.05 and β=0.2) and according to a previous study(17), 150 women will be sufficient, however to detect a 50% difference in the occurrence of side effect from 24% as reported by the Magpie trial(10) and to give the study a 90% power to detect the difference in side effects, 460 women (230 in each group) with severe preeclampsia will be sufficient. Lost to follow up is estimated as 5% in each category, therefore we will recruit 230 patients with eclampsia (115 in each group) and 480 patients with preeclampsia (240 in each group). See Figure 1.

Study Duration

Conceptualization and securing of appropriate IRB approvals and funding and organization of trial materials lasted 18 months. Trial recruitment and follow up is estimated to last 1-2 years starting October 2018.

Protocol

All women admitted the Korle Bu Teaching Hospital as a labouring or antepartum patient will be assessed by the on-call obstetric resident according to standard clinical practice. Based on initial history and physical examination, vitals signs, and laboratory values, clinical diagnoses will be made by the on-call obstetric team. If a patient has a clinical diagnosis of eclampsia or preeclampsia with severe features, she will be identified as a potential study participant. The on-call resident will review study inclusion and exclusion criteria. If a woman meets inclusion criteria, a research assistant will be notified to confirm inclusion/exclusion criteria and obtain informed consent. The participant will be randomized to the Treatment or Control group by simple randomization using a computerized random number generation table. A sticker will be placed on her chart to notify her clinical team of her participation and group assignment.

The research assistant will commence data collection by extracting relevant demographic and clinical data, such as medical history, past obstetric history, and history of the index pregnancy from the participant's antenatal record and supplemented by direct interview of participants. During the hospitalization, we will prospectively document events such as timing of Magnesium Sulfate doses, timing of any seizures, mode and timing of delivery, maternal complications and Magnesium Sulfate toxicities. Neonatal information will be collected, including gestational age at delivery, birthweight, outcome of delivery (livebirth versus stillbirth), NICU admission, APGAR score at 1 and 5 minutes, and status at discharge (alive versus dead).

According to standard protocol at Korle Bu Teaching Hospital, all participants will have a detailed history and physical examination done at the time of admission. Complete blood counts, clotting profile, liver and renal function tests, and urine protein measurements will be performed. Strict fluid input and output monitoring will be done and recorded on the study fluids chart. All patients will have urethral catheterization retained for continuous bladder drainage until the last dose of the magnesium sulfate. All participants will be monitored for the entire duration of MgSO4 treatment by the on-call obstetrics team at least every 4 hours for blood pressure, patellar reflexes, respiratory rate, urine output, and occurrence of seizures. After completion of the MgSO4 injections, patients will have their blood pressure monitored every 4 hours until normalization of blood pressure, and subsequent discharge.

Apart from the duration of Magnesium Sulfate administration, all other clinical management of study participants will be carried out by the attending on-call obstetrician in accordance with the standard institutional care protocol at KBTH. This includes administration of antihypertenisves, decision on timing and mode of delivery, induction of labor, and initiation and interpretation of fetal monitoring.

Main Intervention: Duration of Magnesium Sulfate

1. Loading dose: All study participants will receive a loading dose of 4g of IV MgSO4 and 10mg IM MgSO4 (5g in each buttock) given at the time of antepartum, intrapartum, or postpartum diagnosis of Eclampsia or Preeclampsia with Severe Features.
2. Maintenance doses:
    a. **Treatment group (12 hour, Modified Pritchard)**: 5g MgSO4 IM every 4 hours for a total of THREE doses over TWELVE hours starting at the time of diagnosis of Eclampsia or Preeclampsia with Severe Features

b. **Control group (24 hour, Standard Pritchard)**: 5g MgSO4 IM every 4 hours for a total of SIX doses over TWENTYFOUR hours starting at the time of diagnosis of Eclampsia or Preeclampsia with Severe Features

All doses of Magnesium Sulfate will be prepared and verified by the Korle Bu Teaching Hospital in accordance with standard hospital protocols. The loading doses will be constituted as 8mls of 50% solution diluted with 12mls of sterile saline to obtain 20mls of 4g $MgSO_4$, to be administered slowly over 15-20 minutes. Maintenance doses will be constituted as 10mls of 50% $MgSO_4$ solution to obtain 5g of $MgSO_4$, to be given as deep intramuscular (IM) injection. All doses of Magnesium Sulfate will be administered by clinical hospital nursing staff in accordance with standard hospital protocols.

Treatment Failure

The occurrence of a seizure after completion of the 3rd maintenance doses and 6th maintenance doses for the study and control groups respectively will be regarded as a treatment failure. These patients will have the 24 hour Modified Pritchard protocol re-started and completed if clinical assessment permits further Magnsium Sulfate therapy. After treatment failure, the management of further Magnesium Sulfate is at the clinical discretion of the attending on-call obstetrician.

The occurrence of clinical evidence of toxicity (absent tendon reflexes, respiratory depression, coma) after initiation of maintenance doses that necessitates discontinuation of further maintenance doses will also be regarded as a treatment failure. In the case of MgSO4 toxicities, the plan of management will be to stop further administration of MgSO4 and inject 1 g of calcium gluconate (10 mL of 10% solution) intravenously. The decision to re-initiate Magnesium Sulfate is at the clinical discretion of the attending on-call obstetrician.

Outcomes Measures

The primary outcome of this study will be the clinical efficacy of the Magnesium Sulfate regimen, defined as the absence of a seizure any time after the completion of the third maintenance dose (MD3) until discharge in the Treatment (12 hour) group and after the completion of the sixth maintenance dose (MD6) until discharge in the Control (24 hour) group.

Secondary outcome measures include:

Maternal:

1. The interval from initiation of treatment to the development of diuresis (diuresis will be defined as urine output > 400ml/4 hrs)
2. Clinical evidence of toxicity (absent tendon reflexes, RR <16cpm, coma)
3. Acute renal failure (urine output <25 mls/hr) after initiation of treatment
4. Pulmonary edema
5. Cerebrovascular accident (stroke)
6. Maternal death

Neonatal:

1. Neonatal outcome at delivery (livebirth vs stillbirth)
2. APGAR scores at 1 and 5 minutes

3. Need for NICU admission
4. Duration of NICU admission
5. Neonatal outcome at discharge (alive vs dead)

Statistical Design

Data will be entered into REDCap and analyses will be carried out using STATA. Primary study aim is to determine whether use of the 12 hour versus 24 hour Modified Pritchard regimens of magnesium sulfate impacts occurence of seizure. First, independent samples *t*-tests will be conducted to determine whether there are baseline differences between conditions (12 hour regimen, 24 hour regimen) in terms of demographics, obstetric history, medical history and index pregnancy (in the case of categorical variables, chi-square test of independence will be used). Next, the primary outcome of occurrence of a maternal seizure will be examined. Given the categorical nature of this outcome variable (yes seizure, no seizure), chi-square test of independence will be used to determine whether the probability of experiencing a seizure differed by condition. Finally, analyses will be conducted to assess secondary maternal and neonatal outcomes. In the case of continuous outcome variables independent samples *t*-tests will be conducted to assess whether condition predicts the continuous secondary outcome of interest. In the case of categorical outcome variables, chi-square tests of independence will be conducted to determine whether the incidence of the categorical secondary outcome of interest differed by condition. For all analyses, Fischer's exact test will be used instead of a chi-square test of independence should the incidence of an outcome occur in less than 5 individuals per condition and corrections will be applied to correct for multiple comparisons. Of note, outcome data will be collected for participants who discontinue or deviate from intervention protocols.

Data Handling

With approval from the IRB through the Korle Bu Teaching Hospital (KBTH), Dr Titus Beyuo (primary author) will oversee the management of data collection and data safety at Korle Bu Teaching Hospital in Accra, Ghana.

Patients' data collection forms will be initially identified by their "folder number" as given at their KBTH admission, as well as their name. This will allow subsequent data collection and integration throughout their hospital course, as well as data quality control as needed. Data collection forms will only be used and accessed by authorized study co-investigators and research assistants.

Data recorded on paper data collection forms will be reviewed by Dr. Titus Beyuo and then entered into a secure electronic data organization program (REDCap) using a password protected computer. Only authorized study co-investigators and research assistants will have access to this computer. The information entered into REDCap will only include unique study numbers and will not include participants names or any other personal identifying information.

The paper data collection forms will be stored securely in a locked cabinet in a locked office in the Obstetrics and Gynecology Department at KBTH, under the direction of Dr. Titus Beyuo. The records (data collection sheets) will be retained for the entire duration of the study, during which data will be accessible only by authorized investigators. After complete cleaning and quality assurance, identification

numbers will be replaced by simple sequence numbers. This de-identified data will be exported from REDCap into STATA for statistical analysis. All authors will have access to the final study dataset.

Monitoring

Monitoring for quality and regulatory compliance will be overseen by the Korle Bu Teaching Hospital Scientific and Technical Committee in Ghana. An independent Data and Patient Safety Board was established at Korle Bu Teaching Hospital, consisting of Professor K. Nkyekyer (Consultant Obstetrician and chairman), Professor K.A. Bugyei (clinical pharmacologist and member), and Dr. Ayegua Hagan (statistician and member). The Data and Patient Safety Board was created to assess the progress of the clinical study, and will review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the study. Adverse events (anaphylaxis, allergic reaction to MgSO4, respiratory depression, coma) and severe adverse events (maternal morbidity or mortality secondary to anaphylaxis, allergic reaction to MgSO4, respiratory depression, coma) will be collected by the principal investigator, Dr. Beyuo, and reported to the Data and Patient Safety Review Board. Dr. Beyuo will also be responsible for communicating any adverse event or protocol modifications on behalf of the investigators to the Data and Patient Safety Board and the IRB.

Termination of study

The study may be terminated ahead of schedule upon recommendation of the Data and Patient Safety Board or by the IRB or by the investigators if interim analysis (planned for 6 months after initiation of study) shows greater than 1% difference in recurrent fits between the study and control arms.

Patient and Public Involvement Statement

This research was done without patient involvement. Patients were not invited to comment on the study design, interpret results, or contribute to the writing or editing of this document.

ETHICS AND DISSEMINATION

Ethics approval was obtained in Ghana through the Korle Bu Teaching Hospital IRB. University of Michigan involvement is limited to protocol development and statistical analysis of de-identified data, and has been granted a Not Regulated Determination by the University of Michigan IRB. The study has been registered with the Pan African Clinical Trial Registry through the South African Medical Research Council: PACTR201811515303983.

Results of the study will be shared at clinical forums at the Korle Bu Teaching Hospital and will be submitted for publication in an international peer-reviewed journal.

AUTHORS CONTRIBUTION STATEMENT: Titus Beyuo and Samuel A. Oppong were involved in conception of this research and initial trial design. All authors were involved in review and finalization of trial protocol. Titus Beyuo and Emma Lawrence were responsible for writing this paper, with review and approval from all authors.

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COMPETING INTERESTS STATEMENT: Trial authors have no competing interests to disclose. All authors have not received support from any organization for the submitted work, and deny financial relationships with organizations that might have an interest in the submitted work in the previous three years, or other relationships or activities that could appear to have influenced the submitted work.

TRANSPARENCY STATEMENT

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING STATEMENT

Data from our clinical trial will be made available upon email request. Data that will be available includes the complete de-identified patient data set. Documents that will be available includes the Statistical code, Informed Consent form, and Case Record (data collection form).

EXCLUSIVE LICENSE STATEMENT

I, Emma Lawrence, The Corresponding Author of this article contained within the original manuscript which includes any diagrams & photographs within and any related or stand alone film submitted (the Contribution") has the right to grant on behalf of all authors and does grant on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licensees, to permit this Contribution (if accepted) to be published in the BMJ and any other BMJ Group products and to exploit all subsidiary rights, as set out in our licence set out at: http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse."

Please tick one or more boxes as appropriate:

x I am one author signing on behalf of all co-owners of the Contribution.

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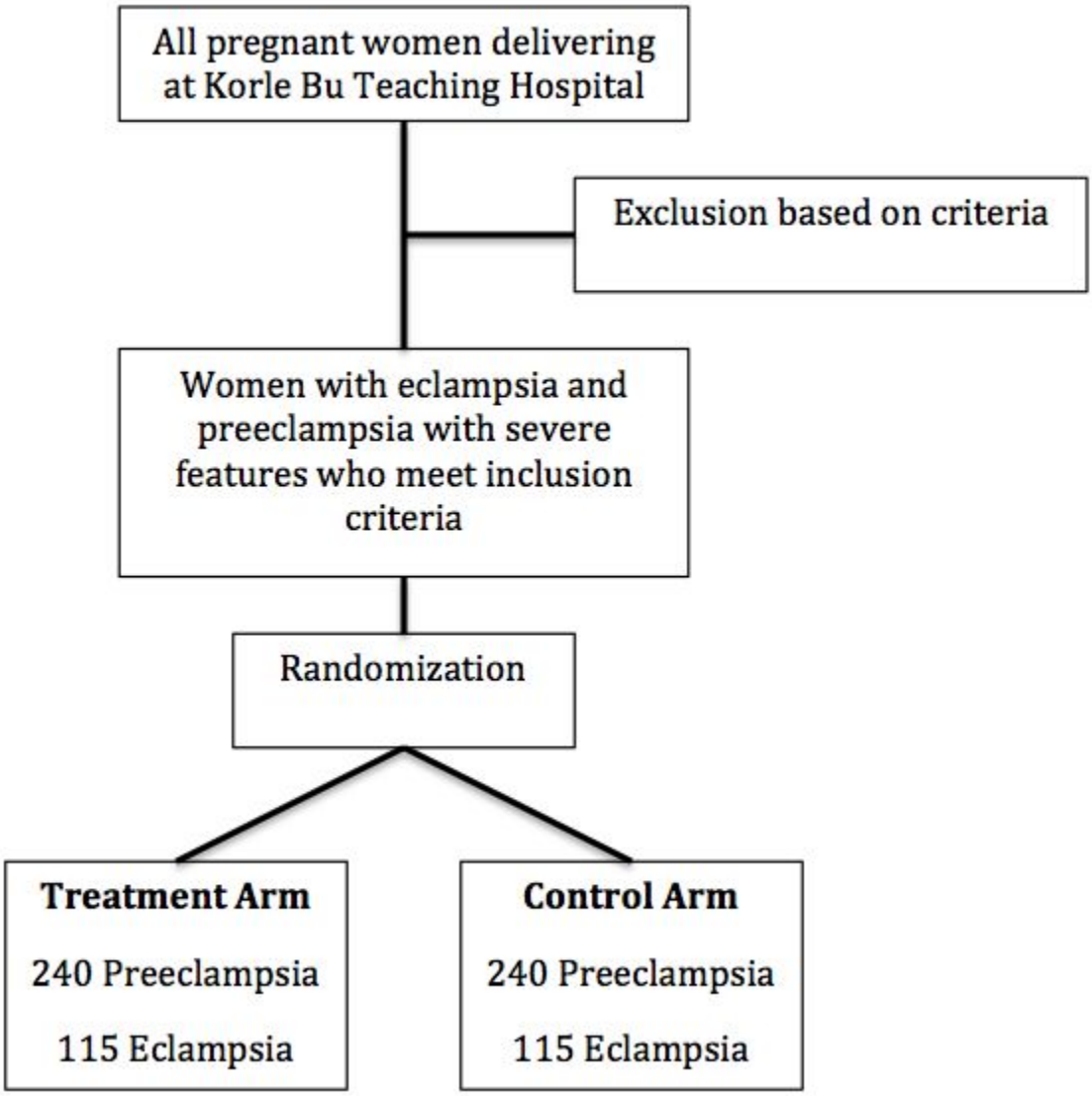
Figure 1. Recruitment and Enrollment



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	____2_____
Protocol version	3	Date and version identifier	not present because submitting as manuscript
Funding	4	Sources and types of financial, material, and other support	_____10_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1_____
	5b	Name and contact information for the trial sponsor	_____10_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____10_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____9-10____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	3-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6-7

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7, 9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	already obtained, 10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10-11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9-10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____10_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____8_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____10_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____11_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____12_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__supplementary document in this manuscript__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____n/a_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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An Open Label Randomized Control Trial of 12 hour versus 24 hour Modified Pritchard Regimen in the Management of Eclampsia and Preeclampsia in Ghana (MOPEP STUDY): Study Protocol

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An Open Label Randomized Control Trial of 12 hour versus 24 hour Modified Pritchard Regimen in the Management of Eclampsia and Preeclampsia in Ghana (MOPEP STUDY): Study Protocol

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ABSTRACT

Introduction: Hypertensive disorders of pregnancy continue to be a major contributor to maternal and perinatal morbidity and mortality. Magnesium Sulfate therapy is the standard of care for seizure prophylaxis and treatment for preeclampsia and eclampsia respectively, despite wide disparities in dosing regimens and routes of administration. This study compares the clinical efficacy of Magnesium Sulfate in the reduction of seizure occurrence or recurrence with the 12 hour versus 24 hour Modified Pritchard regimens in the management of severe preeclampsia and eclampsia.

Methods and Analysis: This study is an open label randomized control trial. The study participants are patients admitted to the Korle Bu Teaching Hospital in Accra, Ghana with a diagnosis of antepartum, intrapartum, or postpartum eclampsia or preeclampsia with severe features. All study participants will be administered a loading dose of Magnesium Sulfate, followed by maintenance dosing. Participants in the Control group will receive magnesium sulfate for 24 hours after diagnosis, while those in the Treatment group will receive magnesium sulfate for 12 hours after diagnosis. The primary outcome of this study is the occurrence of a seizure any time after the completion of treatment in the assigned group. Secondary outcome measures include maternal health outcomes, Magnesium Sulfate toxicities, and fetal health outcomes. Data collection was started October 2018 with a target enrollment of 1245 participants with severe preeclampsia and 844 participants with eclampsia with a projected study period of 2-3 years.

Ethics and Dissemination: Ethical approval was obtained from the Korle Bu Teaching Hospital IRB in Ghana. University of Michigan involvement is limited to protocol development and statistical analysis of de-identified data, and has been granted a Not Regulated Determination by the University of Michigan IRB. Results of the study will be shared at clinical forums at the Korle Bu Teaching Hospital and will be submitted for publication in an international peer-reviewed journal.

Trial Registration: The study has been registered with the Pan African Clinical Trial Registry through the South African Medical Research Council: PACTR201811515303983.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Large randomized control trial that addresses duration of administration of Magnesium Sulfate, which fills an important gap in the literature and has significant implications for management of patients with eclampsia and preeclampsia with severe features.
- The study is taking place in a low resource setting with a high incidence of preeclampsia and eclampsia and advanced disease at presentation
- Data collection in a developing country setting with no electronic medical record may contribute to missing information and become a study limitation
- Lack of blinding of patients and providers to group allocation is a study limitation, however, primary outcome (occurrence of seizure) and secondary outcomes (maternal: time to diuresis, clinical toxicities and complications; neonatal: birth outcomes) are objective measures

INTRODUCTION

Hypertensive disorders complicate 10% of pregnancies worldwide [1] [2] and preeclampsia occurs in 2-8% of all pregnancies globally [1]. In developing countries, hypertensive disorders account for 10-15% of maternal deaths [1] [2]. In Ghana, the incidence of hypertensive disorders in pregnancy has been estimated from a hospital based study as 7.6% [3,4]. Eclampsia contributes significantly to maternal mortality in developing countries. In Ghana, a case fatality of 3.9% has been reported, and institutional reports from two major tertiary level hospitals suggest hypertensive disorders have overtaken haemorrhage as the leading cause of maternal mortality [3].

While preeclampsia may not be preventable, the risk of eclampsia can be significantly reduced with good obstetric management [5,6]. Magnesium Sulfate has been used for decades for the management of eclampsia and preeclampsia and is the anti-convulsant of choice for the management and prevention of eclamptic seizures [7,8]. Good clinical efficacy has been reported with the use of Magnesium Sulfate in the management of preeclampsia despite wide disparities the dosing regimens and routes of administration [5,7,9–12].

There is lack of consensus in the existing literature about optimal duration and dosing of Magnesium Sulfate, as well as optimal therapeutic window. Therapeutic failures have been reported for doses considered both high and low [7,9–12]. The narrow therapeutic window widely used in literature is challenged by pharmacokinetic studies that demonstrate that accepted international regimens sometimes fail to reach the minimum therapeutic threshold yet are associated with clinical efficacy [7,13,14]. The duration of treatment has also been questioned, and a wide range of different regimens are currently utilized in clinical practice. Some protocols such as the Sokoto (ultra-short) protocol demonstrated that just the standard loading dose of the Prichard regimen may be sufficient [11].

In Korle Bu Teaching Hospital and other centres in Ghana, many patients do not complete the 24-hour maintenance course due to poor compliance due to discomfort associated with the repeated injections, side effects, and sometimes financial constraints; yet our observational experience has not demonstrated an increase in disease progression in this cohort of patients. Perhaps this is secondary to the efficacy demonstrated in shorter regimens like the 12- hour maintenance and ultra-short [5]. The cost to the

individual and the healthcare system associated with the 24-hour maintenance course is significant. The determination of the minimum effective duration of treatment with proven clinical efficacy, minimum side effect profile and toxicity is likely to improve compliance, reduce waste and conserve resources in developing countries.

Problem Statement

Maternal morbidity and mortality resulting from preeclampsia and eclampsia remain high in many middle to low income countries. The case fatality of eclampsia is unacceptably high despite known interventions to reduce the progression to eclampsia. The current dosing regimens are at best empirical with several different regimens being utilized in clinical practice.

Previous studies comparing clinical efficacy of dosing regimens involved relatively small sample sizes and were not powered to detect clinical differences in toxicity and tolerability. Two small studies have compared outcomes using 12 hours versus 24 hours of Magnesium Sulfate using an intravenous infusion regimen [5,12]. However, there are no studies that compare 12 hours versus 24 hours of Magnesium Sulfate using an intramuscular regimen, which is a common method of administration in developing countries, particularly in Africa [15]. Finally, the incidence of the various side effects or toxicities of magnesium sulfate with the Pritchard regimen has not been studied in the Ghanaian population, despite years of utilization of this regimen.

Justification

Magnesium sulfate remains the mainstay of treatment prevention of eclamptic seizures in patients with preeclampsia and the prevention of recurrent seizures in patients with eclampsia. The clinical efficacies reported with varying durations and routes of administration necessitates further research to determine the optimum effective duration with demonstrable clinical efficacy and low toxicity which will be cost efficient to the healthcare system, especially in low resource countries.

Our study therefore seeks to investigate and compare clinical response between the 12 hour versus 24 hour Modified Pritchard regimens. A significant reduction in cost is expected if the reduced duration of treatment proposed by this trial is adopted and there is a need to subject it to a rigorous clinical trial to assure maternal safety.

Aim and Objective

Aim: To compare the 12 hour versus 24 hour Modified Pritchard regimens of magnesium sulfate in the management of eclampsia and preeclampsia with severe features.

Objectives:

1. To compare the clinical efficacy of the 12 hour versus 24 hour Modified Pritchard regimens in the reduction of seizure occurrence in women with Eclampsia and Preeclampsia with Severe Features
2. To compare the side effect profile and toxicity of the 12 hour versus 24 hour Modified Pritchard regimens in the management of women with Eclampsia and Preeclampsia with Severe Features

3. To compare the neonatal health outcomes following treatment with 12 hour versus 24 hour Modified Pritchard regimens in women with Eclampsia and Preeclampsia with Severe Features

Hypotheses

H_0: There is no difference in clinical efficacy of Magnesium Sulfate between the 12 hour versus 24 hour Modified Pritchard regimens.

H_1: There is a difference in clinical efficacy of Magnesium Sulfate between the 12 hour versus 24 hour Modified Pritchard regimens.

METHODS AND ANALYSIS

Study Design

An open label randomized control trial in which the Study arm will receive 12 hours of maintenance doses of Magnesium Sulfate and the Control arm will receive 24 hours of maintenance doses of Magnesium Sulfate. Participants will be enrolled into study groups by simple randomization using a computerized random number generation table.

Study Site

The Korle Bu Teaching Hospital (KBTH) is the country's premier teaching hospital and serves as a national referral hospital for the southern half of the country. It is a tertiary hospital with a bed capacity of 2000 and an average daily Outpatient Department attendance of 1500 patients. The maternity unit conducts about 9500 deliveries per year. Current standard of care at KBTH is a Modified Pritchard regimen of Magnesium Sulfate, with administration of a loading dose followed by 24 hours of maintenance dosing, starting at the time of diagnosis of eclampsia or preeclampsia with severe features.

Study Population

Accra is a cosmopolitan city with people of varied ethnic backgrounds and social status. It is expected that the sample will represent this diversity and be reflective of the nation. Participants will be patients receiving their prenatal care at Korle Bu Teaching Hospital, as well as referral cases from peri-urban and rural communities around Accra.

Inclusion Criteria

1. Clinical diagnosis of antepartum, intrapartum, or postpartum eclampsia based on:
    a. Elevated blood pressures of 140/90 mm Hg or higher on two occasions at least 4 hours apart after 20 weeks of pregnancy
    AND
    b. Seizures not attributed to other causes.
2. Clinical diagnosis of Preeclampsia with Severe Features (definitions per ACOG Hypertension in Pregnancy Guidelines [16]) based on:
    a. Elevated blood pressures of 160/110 mm Hg or higher on two occasions at least 4 hours apart after 20 weeks of pregnancy, with proteinuria or presence of laboratory values or clinical symptoms indicating end-organ dysfunction
    OR

b. Elevated blood pressures of 140/90 mm Hg or higher on two occasions at least 4 hours apart after 20 weeks of pregnancy, with presence of laboratory values or clinical symptoms indicating end-organ dysfunction

3. Patients who receive loading dose of $MgSO_4$ at referral clinics prior to referral will be eligible for randomization if they otherwise meet the inclusion criteria
4. Age 18 years or older

Exclusion Criteria

1. Eclampsia complicated by acute renal failure, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), or pulmonary edema
2. Co-morbid maternal diagnosis of renal disease and/or seizure disorder
3. Contraindication to MgSO4 (e.g. drug hypersensitivity, myasthenia gravis, anuria, or oliguria)
4. Prior intake of any other anticonvulsant
5. Prior exposure within 72 hours to Magnesium Sulfate which was not a component of the study regimens
6. Refusal to give consent or unable to give consent (eg unconscious)
7. Age 17 or younger

Sample Size Estimation

An occurrence of a seizure is the primary outcome. In women with eclampsia, this will be a recurrent seizure and in women with preeclampsia with severe features, this will be their initial seizure.

Regarding Eclampsia, we assume that the recurrent seizure rate of women receiving 12 hours of Magnesium will be halfway between the seizure of rate of women receiving 24 hours of Magnesium (13.2%) and women receiving no Magnesium (27.9%) at 20.6% [17]. To detect a difference between 20.6% recurrent seizure in the 12 hour group and 13.2% recurrent seizure in the 24 hour group, a total sample size of 804 (402 in each group) is needed, assuming a two-sided test, 5% significance level and 80% statistical power.

Regarding preeclampsia, in the subgroup analysis of the Magpie Trial, women with severe preeclampsia have a 1.1% rate of seizure if treated with 24 hours of Magnesium [10]. In our current study, with a high risk population, we anticipate a 6% rate of seizures in women who receive no Magnesium based on study site department data. In an absence of data from the literature, we assume that the seizure rate of women receiving 12 hours of Magnesium will be halfway between the seizure of rate of women receiving 24 hours of Magnesium (1.1%) and women receiving no Magnesium (6%) at 3.55%. To detect a difference between 3.55% seizures in the 12 hour group and 1.1% seizures in the 24 hour group, a total sample size of 1,186 (593 in each group) is needed, assuming a two-sided test, 5% significance level and 80% statistical power.

Assuming 5% lost to followup and intervention discontinuation, 844 women with eclampsia (422 in each group) and 1245 women with severe preeclampsia (623 in each group) will be recruited. See Figure 1 for CONSORT flow-chart .

Study Duration

Conceptualization and securing of appropriate IRB approvals and funding and organization of trial materials lasted 18 months. Trial recruitment and follow up is estimated to last 2-3 years starting October 2018.

Protocol

All women admitted to the maternity ward of Korle Bu Teaching Hospital as an antepartum, labouring or postpartum patient will be assessed by the on-call obstetric resident according to standard clinical practice. Based on initial history and physical examination, vitals signs, and laboratory values, clinical diagnoses will be made by the on-call obstetric team. If a patient has a clinical diagnosis of eclampsia or preeclampsia with severe features, she will be identified as a potential study participant. The on-call resident will review study inclusion and exclusion criteria. If a woman meets inclusion criteria, a research assistant will be notified to confirm inclusion/exclusion criteria and obtain informed consent (see consent form suppplemenary file).

Participants will be enrolled into study groups by simple randomization using a computerized random number generation table (Random Number Generator version 3.0.56 for Mac). Using the table of random sequence of numbers (1 vs 2), sequentially numbered printed data collection forms will be labeled (1=control group; 2=treatment group) by researcher TB. After a participant is recruited and consented by the research assistant, the research assistant will be given the next numbered data collection form indicating the randomization group. The research assistants are not involved in the randomization process and do not have access or knowledge of the next treatment allocation. A sticker will be placed on the participants' chart to notify her clinical team of her participation and group assignment.

The research assistant will commence data collection by extracting relevant demographic and clinical data, such as medical history, past obstetric history, and history of the index pregnancy from the participant's antenatal record and supplemented by direct interview of participants. During the hospitalization, we will prospectively document events such as timing of Magnesium Sulfate doses, timing of any seizures, mode and timing of delivery, maternal complications and Magnesium Sulfate toxicities. Neonatal information will be collected, including gestational age at delivery, birthweight, outcome of delivery (livebirth versus stillbirth), NICU admission, APGAR score at 1 and 5 minutes, and status at discharge (alive versus dead).

According to standard protocol at Korle Bu Teaching Hospital, all participants will have a detailed history and physical examination done at the time of admission. Complete blood counts, clotting profile, liver and renal function tests, and urine protein measurements will be performed. Strict fluid input and output monitoring will be done and recorded on the study fluids chart. All patients will have urethral catheterization retained for continuous bladder drainage until the last dose of the magnesium sulfate. All participants will be monitored for the entire duration of MgSO4 treatment by the on-call obstetrics team at least every 4 hours for blood pressure, patellar reflexes, respiratory rate, urine output, and occurrence of seizures. After completion of the MgSO4 injections, patients will have their blood pressure monitored every 4 hours until normalization of blood pressure, and subsequent discharge.

Apart from the duration of Magnesium Sulfate administration, all other clinical management of study participants will be carried out by the attending on-call obstetrician in accordance with the standard institutional care protocol at KBTH. This includes administration of antihypertenisves, decision on timing and mode of delivery, induction of labor, and initiation and interpretation of fetal monitoring.

Main Intervention: Duration of Magnesium Sulfate

1. Loading dose: All study participants will receive a loading dose of 4g of IV MgSO4 and 10mg IM MgSO4 (5g in each buttock) given at the time of antepartum, intrapartum, or postpartum diagnosis of Eclampsia or Preeclampsia with Severe Features.
2. Maintenance doses:
    a. **Treatment group (12 hour, Modified Pritchard)**: 5g MgSO4 IM every 4 hours for a total of THREE doses over TWELVE hours starting at the time of diagnosis of Eclampsia or Preeclampsia with Severe Features
    b. **Control group (24 hour, Modified Pritchard)**: 5g MgSO4 IM every 4 hours for a total of SIX doses over TWENTYFOUR hours starting at the time of diagnosis of Eclampsia or Preeclampsia with Severe Features

All doses of Magnesium Sulfate will be prepared and verified by the Korle Bu Teaching Hospital in accordance with standard hospital protocols. The loading doses will be constituted as 8mls of 50% solution diluted with 12mls of sterile saline to obtain 20mls of 4g $MgSO_4$, to be administered slowly over 15-20 minutes. Maintenance doses will be constituted as 10mls of 50% $MgSO_4$ solution to obtain 5g of $MgSO_4$, to be given as deep intramuscular (IM) injection. All doses of Magnesium Sulfate will be administered by clinical hospital nursing staff in accordance with standard hospital protocols.

Treatment Failure

The occurrence of a seizure after completion of the 3rd maintenance doses and 6th maintenance doses for the study and control groups respectively will be regarded as a treatment failure. These patients will have the 24 hour Modified Pritchard protocol re-started and completed if clinical assessment permits further Magnsium Sulfate therapy. After treatment failure, the management of further Magnesium Sulfate is at the clinical discretion of the attending on-call obstetrician.

The occurrence of clinical evidence of toxicity (absent tendon reflexes, respiratory depression, coma) after initiation of maintenance doses that necessitates discontinuation of further maintenance doses will also be regarded as a treatment failure. In the case of MgSO4 toxicities, the plan of management will be to stop further administration of MgSO4 and inject 1 g of calcium gluconate (10 mL of 10% solution) intravenously. The decision to re-initiate Magnesium Sulfate is at the clinical discretion of the attending on-call obstetrician.

Outcomes Measures

The primary outcome of this study will be the clinical efficacy of the Magnesium Sulfate regimen, defined as the absence of a seizure any time after the completion of the third maintenance dose (MD3)

until discharge in the Treatment (12 hour) group and after the completion of the sixth maintenance dose (MD6) until discharge in the Control (24 hour) group.

Secondary outcome measures include:
Maternal:

1. The interval from initiation of treatment to the development of diuresis (diuresis will be defined as urine output > 400ml/4 hrs)
2. Clinical evidence of toxicity (absent tendon reflexes, RR <16cpm, coma)
3. Side effects of Magnesium (nausea/emesis, muscle weakness, absent or reduced reflexes, respiratory depression, palpitations, dizziness, drowsiness or confusion, itching or tingling, pain and burning at the injection site, inflammation, injection abscess, bleeding or bruising, other)
4. Acute renal failure (urine output <25 mls/hr) after initiation of treatment
5. Pulmonary edema
6. Cerebrovascular accident (stroke)
7. Cardiac arrest
8. Liver Failure
9. Coagulopathy
10. Need for dialysis
11. Need for ventilation
12. Admission to ICU
13. Length of stay (antepartum, postpartum total)
14. Time from admission to delivery
15. Complications of delivery (placental abruption, retained placenta, postpartum hemorrhage)
16. Maternal death

Neonatal:

1. Neonatal outcome at delivery (livebirth vs stillbirth)
2. APGAR scores at 1 and 5 minutes
3. Need for NICU admission
4. Reason for NICU admission
5. Duration of NICU admission
6. Neonatal outcome at discharge (alive vs dead)

Statistical Design

Data will be entered into REDCap and analyses will be carried out using STATA. Primary study aim is to determine whether use of the 12 hour versus 24 hour Modified Pritchard regimens of magnesium sulfate impacts occurence of seizure. First, bivariate analysis will be performed to determine whether there are baseline differences between conditions (12 hour regimen, 24 hour regimen) in terms of demographics, obstetric history, medical history and index pregnancy. Comparisons across regimens will be performed using independent samples t-tests for normally-distributed continuous variables, Wilcoxon Rank test for non-normally distributed continuous variables, and Chi-square, and Fisher's exact tests, where appropriate in the case of categorical variables. Next, the primary outcome of occurrence of a maternal seizure will be examined. Given the categorical nature of this outcome variable (yes seizure, no seizure), chi-square test of independence will be used to determine whether the probability of experiencing a

seizure across conditions. Finally, analyses will be conducted to assess secondary maternal and neonatal outcomes. In the case of continuous outcome variables independent samples t-tests will be conducted to assess whether condition predicts the continuous secondary outcome of interest. In the case of categorical outcome variables, chi-square tests of independence will be conducted to determine whether the incidence of the categorical secondary outcome of interest differed by condition. For all analyses, Fischer's exact test will be used instead of a chi-square test of independence should the incidence of an outcome occur in less than 5 individuals per condition and [Bonferroni] corrections will be applied to correct for multiple comparisons. Number needed to treat and number needed to harm will be calculated for primary and secondary outcomes. All tests will be two-tailed. Of note, outcome data will be collected for participants who discontinue or deviate from intervention protocols.

Data Handling

With approval from the IRB through the Korle Bu Teaching Hospital (KBTH), Dr Titus Beyuo (primary author) will oversee the management of data collection and data safety at Korle Bu Teaching Hospital in Accra, Ghana.

Patients' data collection forms will be initially identified by their "folder number" as given at their KBTH admission, as well as their name. This will allow subsequent data collection and integration throughout their hospital course, as well as data quality control as needed. Data collection forms will only be used and accessed by authorized study co-investigators and research assistants.

Data recorded on paper data collection forms will be reviewed by Dr. Titus Beyuo and then entered into a secure electronic data organization program (REDCap) using a password protected computer. Only authorized study co-investigators and research assistants will have access to this computer. The information entered into REDCap will only include unique study numbers and will not include participants names or any other personal identifying information.

The paper data collection forms will be stored securely in a locked cabinet in a locked office in the Obstetrics and Gynecology Department at KBTH, under the direction of Dr. Titus Beyuo. The records (data collection sheets) will be retained for the entire duration of the study, during which data will be accessible only by authorized investigators. After complete cleaning and quality assurance, identification numbers will be replaced by simple sequence numbers. This de-identified data will be exported from REDCap into STATA for statistical analysis. All authors will have access to the final study dataset.

Monitoring

Monitoring for quality and regulatory compliance will be overseen by the Korle Bu Teaching Hospital Scientific and Technical Committee in Ghana. An independent Data and Patient Safety Board was established at Korle Bu Teaching Hospital, consisting of Professor K. Nkyekyer (Consultant Obstetrician and chairman), Professor K.A. Bugyei (clinical pharmacologist and member), and Dr. Ayegua Hagan (statistician and member). The Data and Patient Safety Board was created to assess the progress of the clinical study, and will review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the study. Adverse events (anaphylaxis, allergic reaction to MgSO4, respiratory depression, coma) and severe adverse events (maternal morbidity or mortality secondary to anaphylaxis, allergic reaction to MgSO4, respiratory depression, coma) will be collected by the principal investigator,

Dr. Beyuo, and reported to the Data and Patient Safety Review Board. Dr. Beyuo will also be responsible for communicating any adverse event or protocol modifications on behalf of the investigators to the Data and Patient Safety Board and the IRB.

Termination of study

The study may be terminated ahead of schedule upon recommendation of the Data and Patient Safety Board or by the IRB or by the investigators if interim analysis (planned for 6 months after initiation of study) shows greater than 1% difference in recurrent fits between the study and control arms.

Patient and Public Involvement Statement

This research was done without patient involvement. Patients were not invited to comment on the study design, interpret results, or contribute to the writing or editing of this document.

ETHICS AND DISSEMINATION

Ethics approval was obtained in Ghana through the Korle Bu Teaching Hospital IRB. University of Michigan involvement is limited to protocol development and statistical analysis of de-identified data, and has been granted a Not Regulated Determination by the University of Michigan IRB. The study has been registered with the Pan African Clinical Trial Registry through the South African Medical Research Council: PACTR201811515303983.

Results of the study will be shared at clinical forums at the Korle Bu Teaching Hospital and will be submitted for publication in an international peer-reviewed journal.

AUTHORS CONTRIBUTION STATEMENT: Dr. Titus Beyuo and Dr. Samuel A. Oppong were involved in conception of this research and initial trial design. All authors (Dr. Titus Beyuo, Dr. Emma Lawrence, Dr. Elizabeth Langen, and Dr. Samuel A. Oppong) were involved in review and finalization of trial protocol. Dr. Titus Beyuo and Dr. Emma Lawrence were responsible for writing this paper, with review and editing from Dr. Elizabeth Langen and Dr. Samuel A. Oppong.

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COMPETING INTERESTS STATEMENT: Trial authors have no competing interests to disclose. All authors have not received support from any organization for the submitted work, and deny financial relationships with organizations that might have an interest in the submitted work in the previous three years, or other relationships or activities that could appear to have influenced the submitted work.

TRANSPARENCY STATEMENT

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING STATEMENT

Data from our clinical trial will be made available upon email request. Data that will be available includes the complete de-identified patient data set. Documents that will be available includes the Statistical code, Informed Consent form, and Case Record (data collection form).

EXCLUSIVE LICENSE STATEMENT

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Figure 1. Recruitment and Enrollment. Detailed legend: CONSORT flow diagram outlining participant flow through each stage of the randomized controlled trial (intervention allocation, follow-up and data analysis).

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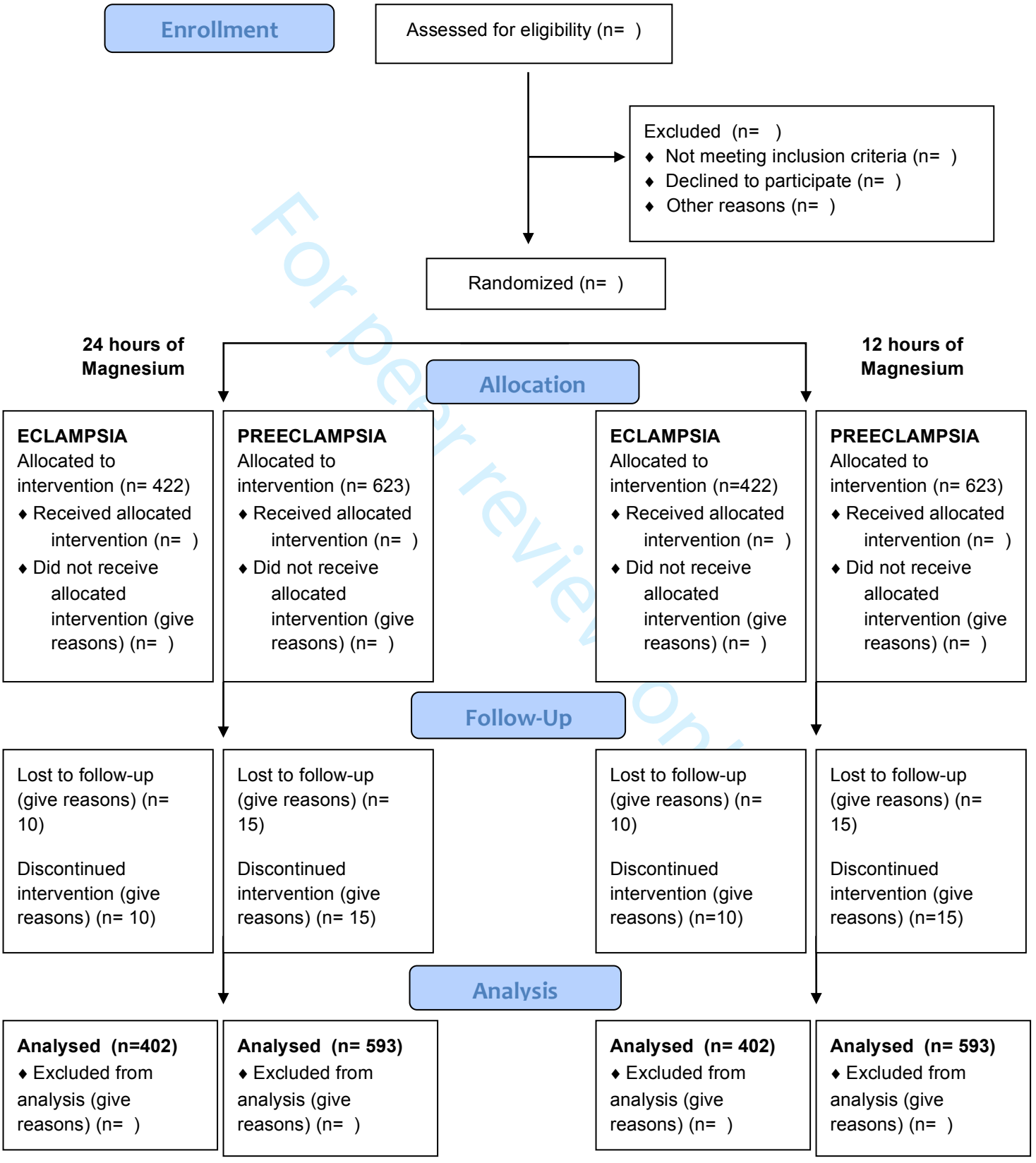
CONSORT

TRANSPARENT REPORTING of TRIALS

Figure 1. Recruitment and Enrollment



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	not present because submitting as manuscript
Funding	4	Sources and types of financial, material, and other support	10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	10
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9-10

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	3-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6-7

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7, 9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	already obtained, 10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10-11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9-10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____10_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____8_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____10_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____11_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____12_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__supplementary document in this manuscript__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____n/a_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.