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Effect of pre-operative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour; A study protocol for a Randomised Controlled Trial

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Effect of pre-operative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour;
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ABSTRACT

Introduction

To improve maternal and fetal outcomes among patients with obstructed labour (OL) in low resource settings, the associated electrolyte and metabolic derangements must be adequately corrected. Oral fluid intake during labour and pre-operative intravenous fluid replacement following OL corrects the associated dehydration and electrolyte changes, but it doesn't completely reverse the metabolic acidosis which is a known cause of intrapartum birth asphyxia and a risk factor for primary postpartum haemorrhage due to uterine atony.

Sodium bicarbonate is a safe, effective, cheap and readily available acid buffer that is widely used by sportsmen to improve performance. It appears to also improve fetal and maternal outcomes in abnormally progressing labour. However, the effect of sodium bicarbonate on maternal and fetal outcomes among patients with OL is unknown. This study aims to establish the effect of a pre-operative bicarbonate infusion on maternal and perinatal outcomes among patients with OL in Mbale Regional Referral Hospital.

Methods

This will be a double blind, Randomised Controlled Clinical phase III trial. We will randomize 308 patients with OL to receive either 50mls of placebo with standard pre-operative infusion of Normal Saline (1.5 L) or 4.2g of sodium bicarbonate solution (50mls of 50mmol/L) with the pre-operative infusion of Normal Saline (1.5 L). The primary outcome will be mean lactate levels in maternal capillary blood at one hour after onset of study drug administration, and in the arterial cord blood at birth. Secondary outcomes will include maternal and fetal morbidity and mortality up to 14 days postpartum. Ethical approval has been sought from the School of Medicine Research and Ethics committee at Makerere University College of

Health Sciences, Uganda National Council for Science and Technology and the Mbale Hospital Research and Ethics Committee. The trial has been registered (PACTR201805003364421).

Strengths and limitations of this study;

Strengths,

- i. This is among the 1st studies to investigate effect of preoperative bicarbonate infusion on maternal and fetal outcomes among patients with OL.**
- ii. The primary maternal and fetal outcomes are both 'hard outcomes' (mean blood lactate levels), measured at the bedside using a hand-held device (Lactate Pro 2).**

Limitations,

- i. We will only report about the efficacy and not the effectiveness of the sodium bicarbonate**
- ii. Given the short duration of follow up, we will not have any information regarding the long-term effects of sodium bicarbonate on maternal and perinatal outcomes.**
- iii. Prior to admission at the referral hospital, patients will have received other interventions such as intravenous fluids and herbal medications which we may not be able to capture accurately.**

Introduction

Globally, the annual number of maternal deaths (MD) decreased from 532,000 in 1990 to 303,000 in 2015.[1,2] But almost all (99.6%) occur in Sub-Saharan Africa (66.3%) and South-Central Asia,[1] where it is estimated that the lifetime risk of MD is as high as 1 in 16 and 1 in 46 respectively, compared to 1 in 2,800 in developed regions.[1,2] Although primary postpartum haemorrhage (PPH) and sepsis are the leading causes of MD, obstructed labour (OL) indirectly contributes to more than 70% of these deaths. [3] Directly, OL causes 8% of all the MD[4,5] and up to 90% of the perinatal deaths due to birth asphyxia.[6] In the 2015/16 financial year, of the 246 maternal deaths reported to the Uganda Ministry of Health (MOH), 9% were due to OL, 39% were due to haemorrhage and 20% were due to sepsis.[7] In addition, 69.3% of 411 perinatal deaths were due to birth asphyxia although the contribution of OL was not specified.

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3 The prevalence of OL varies from 2– 8 % worldwide. It is highest in low and middle income countries
4 (LMICs) and is almost none-existent in developed countries. [4,5] In LMICs many patients experience
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6 delays in accessing quality emergency obstetric and neonatal care services, so they end up with
7
8 neglected OL which causes significant maternal morbidity (dehydration, uterine rupture, sepsis,
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10 vesico/rectovaginal fistulae and postpartum haemorrhage) and neonatal morbidity (asphyxia and
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12 sepsis).[3,8] Obstructed labour occurs when the fetal presenting part does not descend into the
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14 maternal pelvis despite adequate uterine contractions. [4] Usually, the obstruction can only be safely
15
16 relieved by an operative delivery.[6] In fact OL is the commonest indication for primary caesarean
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18 section and a major risk factor for infective morbidity (puerperal and neonatal sepsis) especially in
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20 LMICs.[3,9]
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26 Obstructed Labour is associated with higher levels of lactate in blood and amniotic fluid compared to
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28 normal labour, and this correlates directly with perinatal outcomes.[10] Lactate is a by-product of
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30 anaerobic respiration by both the fetus and the myometrium in response to intermittent hypoxia during
31
32 labour.[11] In OL, the episodes of hypoxia are prolonged leading to accumulation of lactic acid
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34 (metabolic acidosis) from anaerobic break down of glucose. Although impaired uterine contractility
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36 caused by myometrial acidosis increases the risk of primary PPH, it is beneficial to the fetus because it
37
38 increases feto-placental oxygenation which is protective against intrapartum birth asphyxia.[10,12] The
39
40 transfer of excess hydrogen ions across the placenta to the fetus is associated with low fetal PH, fetal
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42 distress and poor APGAR. [13]
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47 Oral bicarbonate is a widely used acid buffer in sports science, to improve physical performance in
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49 vigorous exercises because it can reverse lactic acidosis.[14] Bicarbonate does not cross the placental
50
51 barrier,[15] but it plays a key role in regulating the maternal and fetal acid-base chemistry.[13] There
52
53 are conflicting reports regarding its benefits in labour. Earlier studies involving the use of Bicarbonate in
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55 normal labour showed improvements in pH, base excess and plasma bicarbonate, but none reported
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3 APGAR scores. A recent RCT involving the use of oral bicarbonate solution in abnormal (dystocic) labour
4 reported a significant improvement in both maternal and perinatal outcomes. [14] Significantly, none of
5 these studies reported adverse maternal and perinatal effects or included participants with OL.
6
7 Currently, pre-operative intravenous infusion with at least 1.5L of fluid is recommended as a key
8 element of the standard care. This is adequate to correct the dehydration and electrolyte imbalance but
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10 it probably doesn't completely reverse the associated metabolic acidosis.[16,17]
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17 Various formulations and doses of sodium bicarbonate have been safely used for both clinical
18 indications and research purposes with no reported adverse clinical reactions. A single pre-operative
19 infusion of 4.2g of sodium bicarbonate solution (50mls of 50mmol/L) will be given as a single dose at
20 enrolment, since OL is an obstetric emergency which requires urgent intervention. [18] The same dose
21 was used orally in the recent trial in which bicarbonate solution was administered to women with
22 dystocia in labour. [14] The main outcome of this study will be to assess whether bicarbonate changes
23 the maternal and fetal lactate levels among patients with OL. Lactate is easier to measure than full blood
24 gas analysis using maintenance free, battery operated pocket size devices like the lactate Pro2 (Arkray).
25
26 Lactate is comparable to pH and base deficit with respect to sensitivity, specificity and predictive values
27 of various perinatal complications.[13] Establishing the effect of bicarbonate on maternal and fetal
28 lactate levels among patients with OL is important because it could be included in the pre-operative care
29 package as an acid buffer.
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45 We hypothesize that supplementation with preoperative sodium bicarbonate infusion as an acid buffer
46 can reduce maternal and fetal acidosis among patients with OL. Bicarbonate is safe, effective, cheap and
47 already widely used.[18] Establishing its effect on maternal and foetal outcomes following OL is
48 necessary because it could be added to the standard preoperative care package as a form of tertiary
49 prevention. This study aims to establish the effect of a single dose preoperative infusion of sodium
50 bicarbonate on maternal and fetal lactate levels and clinical outcomes among patients with OL.
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Methods/Design

Study design

This will be a superiority, double blind, Randomised Controlled Clinical phase III trial. Half of the 308 patients with OL will receive the intervention (sodium bicarbonate infusion) with pre-operative normal saline infusion, and the other half will receive the standard of care (pre-operative saline infusion) alone.

Study setting

The study will be conducted at Mbale Regional Referral Hospital located at the heart of Mbale Municipal Council, 214km to the east of the capital city Kampala. It is the main referral hospital, serving 14 districts in the Elgon zone, bordering western Kenya. This is a government run, not-for-profit, charge-free, 470-bed hospital with 52 maternity beds. The Department of Obstetrics and Gynaecology has one consultant, two specialists, three medical officers and 21 Midwives. In terms of outputs, the labour and delivery suit is only second to the Mulago National Referral Hospital labour suit. Annually, about 12,000 childbirths occur in this hospital with a caesarean section rate of 35% and nearly 500 mothers have OL. It has been ranked as the best performing regional referral hospital by the Ministry of Health in Uganda for the last 4 years.

Participants

This study will be carried out among patients with OL admitted to the labour suite in Mbale Regional Referral Hospital during the period of the study. OL will be diagnosed by either a Medical Officer or specialist on duty using the ACOG definition: in the 1st stage of labour she should have cervical dilatation >6cm with ruptured membranes, adequate contractions lasting > 4hrs with no change in cervical dilatation, OR, delay in the 2nd active stage of labour (nullipara > 2hrs, multipara > 1 hr.) with adequate uterine contractions. IN ADDITION, ANY TWO OF: the obvious signs of severe obstruction such

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3 as caput formation, severe moulding, Bandl's ring, sub-conjunctival hemorrhages, or an oedematous
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5 vulva.
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8 We will include patients with OL carrying singleton, term pregnancies (≥ 37 weeks of gestation) in
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10 cephalic presentation. We will exclude patients with other obstetric emergencies such as (ante-partum
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12 haemorrhage, Pre-eclampsia and eclampsia (defined as elevated blood pressure of at least 140/90
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14 mmHg, urine protein of at least 2+ ,any of the danger signs and fits), premature rupture of membranes
15
16 and intrauterine fetal death; comorbidities such as diabetes mellitus, Sickle cell disease, renal disease,
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18 liver disease & heart disease; and those with a hypernatraemia > 148 mmol/L and/or alkalosis $>$
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20 22mmol/L .
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24 **Randomization**

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27 A sequence of random numbers will be generated by an independent biostatistician using the online
28
29 randomisation service of www.sealedenvelop.com in permuted block sizes of four, six and eight. Based
30
31 on this sequence, OL patients will be randomly allocated to either intervention or control arms in a 1:1
32
33 ratio. Concealment will be done by an independent pharmacist not involved in the recruitment of study
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35 participants, who will prepare and label sequentially numbered, identical study drug packages each
36
37 containing five similar 10ml glass vials with all the original labels removed. After consent for inclusion
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39 has been confirmed, a study nurse will take the next study drug package and administer its contents to
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41 participant.
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46 **Intervention**

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49 The intervention will be a pre-operative infusion of 50mls of sodium bicarbonate 8.4% solution
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51 equivalent to 4.2g or 50mmol/L of bicarbonate (Martindale Pharma, Essex) in 10ml glass vials. The
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53 sodium bicarbonate will be administered intravenously as a bolus immediately after recruitment by
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3 trained research assistants who are all experienced midwives working in the labour suite, followed by
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5 1.5L of Normal Saline over the next hour.
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8 **Comparator;**

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11 Participants in the control arm will receive a pre-operative infusion of Normal Saline which is the
12
13 standard of care. Fifty mls of sodium chloride 0.9% in identical 10ml glass vials (AccuHealth Care,
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15 Gujarat) will be administered intravenously as a bolus immediately after recruitment by trained research
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17 assistants, who are all experienced midwives working in the labour suite, followed by 1.5L Normal Saline
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19 over the next hour.
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23 In addition, recruits will receive the standard pre-operative care which includes pre-operative antibiotic
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25 prophylaxis, at least 1.5L of intravenous fluids pre-operatively, bladder emptying, administration of
26
27 oxygen, and lying in left lateral position.[16]
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30 **Measurements;**

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33 The primary outcomes in this study will be the mean lactate levels in maternal capillary blood at one
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35 hour after the onset of study drug administration and in arterial cord blood within 1 minute of birth.
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37 Lactate will be measured at the bedside using a hand-held Lactate Pro 2 device (Arkray Factory Inc,
38
39 Shiga).
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43 Secondary maternal outcomes will include myometrial lactate levels at caesarean section, maternal
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45 morbidities such as primary PPH, birth canal injuries, duration of admission, puerperal sepsis (Persistent
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47 fever >38°C, Chills and general malaise, Pain in the lower abdomen, Persistent bloody/pus discharge
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49 (lochia) from genital tract, which may have an unpleasant smell, Tenderness on palpating the uterus y
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51 Uterine sub-involution, wound dehiscence/ burst abdomen),[16] fistulae, readmissions and death up to
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53 the 14 days postpartum. Secondary perinatal outcomes will include mean lactate in venous cord blood,
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3 Apgar score, admission to the NICU, asphyxia, neonatal sepsis (irritability, poorly breastfeeding, bulging
4 anterior fontanelle)[16] and perinatal death up to 7 days postpartum.
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8 **Sociodemographic, clinical and laboratory characteristics;** 9

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11 Using an interviewer administered questionnaire and available records (antenatal cards, facility registers
12 and case report files), sociodemographic and clinical characteristics will be collected by trained research
13 assistants. At baseline, 5 mls of blood will be collected in the appropriate vaccutainers for a complete
14 blood count, renal function tests, liver function tests and electrolytes. Ten mls of fresh urine will be
15 collected in a sterile container for analysis. All these specimens will be delivered to MBN clinical
16 laboratories within 1 hour of collection for analysis. Figure 1 shows the CONSORT flow diagram for this
17 study. Patients will be followed up to 14 days postnatally either by phone call if they are discharged or
18 by direct visits if they are still admitted.
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30 **Sample size and power calculation;** 31

32 We used Open Epi to detect a 15% difference in mean lactate levels between the intervention and
33 control arms, assuming an equal number of participants in each group, a two-sided significance level of
34 0.05 for a 95% confidence interval, a power of 80%, and a student's t-test for comparison of means.
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40 The mean and standard deviation (SD) of the maternal venous lactate at the end of second stage of
41 labour is 2.6 ± 1.0 mmol/L[19] without any use of bicarbonate. To detect a difference of 15%
42 (0.39mmol/L) and assuming the same S.D. of ± 1 in both arms, 278 participants will be required.
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46 Correcting for an attrition rate of 10%,[14] gives a total sample size of 308.
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50 The mean arterial cord blood lactate at 37 weeks of gestation is 4.3 ± 1.9 mmol/L[20] without any use of
51 bicarbonate. In order detect a difference of 15% (0.645mmol/L) and assuming the same S.D of ± 1.9 in
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both groups, 274 participants will be recruited. Correcting for an attrition rate of 10%, [14] gives a total sample size of 304. A sample size of 308 was therefore planned to provide power for both hypotheses.

Data collection and management;

Well trained RA will collect data using a pretested interviewer administered electronic questionnaire on password protected smart phones using the Open Data Kit software. To increase accuracy the data will be triangulated with a review of relevant health facility records such as the antenatal cards, the maternity and theatre registers, and the participants' case report forms. The questionnaire will be coded with checks for internal consistency. Data on sociodemographic, clinical and laboratory parameters will be collected at baseline, at one hour after onset of study drug administration for the primary maternal outcome, at the time of child birth for the primary neonatal outcome, and at 7 and 14 days postpartum for the secondary perinatal and maternal outcomes as summarised in table 2.[24] The PI will review the entries from the Google aggregate server every 24 hours to ensure data quality and completeness.

Table 1; Summary of the study procedures and timelines

Procedure	At admission (Baseline)	1 hour after onset of study drug administration	At birth	At 7 days postpartum	At 14 days postpartum
Assessment of eligibility	x				
Randomisation	x				
Data collection for baseline parameters	x				
Study drug administration	x				
Questionnaire administration	x	x	x	x	x
Data collection for primary outcome		x	x		
Data collection for secondary outcome			x	x	x

Statistical analysis;

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3 This will be conducted using STATA version 14 software or higher using the principle of 'intention to
4 treat'. Descriptive statistics will be used to summarise baseline characteristics of the study participants
5 and assess if randomisation was successful. The primary maternal outcome will be the difference in
6 capillary blood lactate levels at one hour after onset of study drug administration. The paired sample t-
7 test will be used to compare the difference in means at baseline and one hour after onset of study drug
8 administration within each arm. The independent student t- test will be used to compare the mean
9 lactate levels in the two arms at one hour after onset of study drug administration.

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19 For the primary fetal outcome of mean arterial cord blood lactate at birth, the independent student t-
20 test will be used to compare the mean lactate levels in the two arms within 1 minute of childbirth.

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24 The secondary outcomes will be reported as proportions in each of the two arms. Categorical variables
25 will be compared using the Chi-square and Fishers exact tests. Potential confounders and effect
26 modifiers unbalanced at baseline and associated with the outcome ($p < 0.05$) will be adjusted for using
27 multivariable linear or/and logistic regression. Proportions and the number needed to treat/harm
28 (NNT/NNH) will be reported for the secondary maternal and fetal outcomes.

35 36 **Quality control;**

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39 A dry run will be conducted for a period of one month before the intervention is introduced to train all
40 the research assistants in the study protocol procedures, filling of study questionnaires using the ODK
41 software, accurate measurement of lactate at the bedside using the Lactate Pro 2 device and the ideal
42 technique for collection of samples especially blood to avoid haemolysis. The MBN clinical laboratories
43 are internationally accredited and they are involved in regular internal and external quality control
44 checks.

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53 Ethical approval has been sought from the s

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3 School of Medicine Research and Ethics Committee (#REC REF 2017-103), the Uganda National Council
4 for Science and Technology (HS217ES), and the Mbale Regional Referral Research and Ethics Committee.
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8 **Participant safety;**

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11 All serious adverse events will be actively identified and reported to the IRB within 24 hours of
12 occurrence using the School of Medicine Research Ethics Committee reporting form throughout the
13 study period up to the end of puerperium (6 weeks after birth). The independent data monitoring
14 committee will review unblinded data when 1/3 of the participants have been enrolled and followed up
15 to completion, and at any other time that they request. In addition, only qualified health workers will be
16 recruited and trained in the protocol to work as research assistants on this trial.
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25 **Dissemination and communication of results;**

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28 Results will be disseminated to the study participants through the local radio stations and local council
29 community meeting at the village level. Findings will be shared with colleagues and administrators in
30 Mbale Regional Referral Hospital/Busitema University Faculty of Health Sciences and the Uganda
31 ministry of health through workshops and seminars. To reach the wider scientific community, the
32 findings will be published in open access peer reviewed journals and presented at both local and
33 international conferences.
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42 **Patient and Public involvement;**

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45 The patients and public were not involved in the design and conceptualisation of this study.
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48 **Discussion;**

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51 If a preoperative infusion of sodium bicarbonate is safe and it improves maternal and perinatal
52 outcomes among patients with OL, the data from this trial might facilitate the inclusion of sodium
53 bicarbonate infusion in the standard pre-operative care for patients with OL in low resource settings. Its
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3 adoption will help to mitigate adverse maternal and perinatal outcomes associated with OL as a tertiary
4 preventive measure. Obstructed labour is still an important clinical and public health problem in low
5 resource settings because of the associated maternal and perinatal morbidity and mortality caused by
6 accompanying electrolyte and metabolic changes. Therefore, identifying an effective, cheap, safe and
7 readily available acid buffer like sodium bicarbonate might offer immense health benefits.
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14 15 **Acknowledgements;**

16
17
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19 PhD fellowship awarded to me under Busitema University.
20
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22

23 **Author contributions;**

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25
26 Musaba Milton Wamboko (MMW) conceptualised, designed, developed the protocol and drafted the
27 manuscript. Justus K Barageine(JKB), Julius N Wandabwa(JNW), Grace Ndeezi (GN) and Andrew Weeks
28 (AW) all participated in the conceptualization, design, development of the protocol and writing of the
29 manuscript by providing critical review and refinement of the research idea as supervisors of my PhD
30 studies. All the authors reviewed and approved the final draft of the manuscript for submission.
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40
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51 Competing interests statement; None declared

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53 Patients consent; Required
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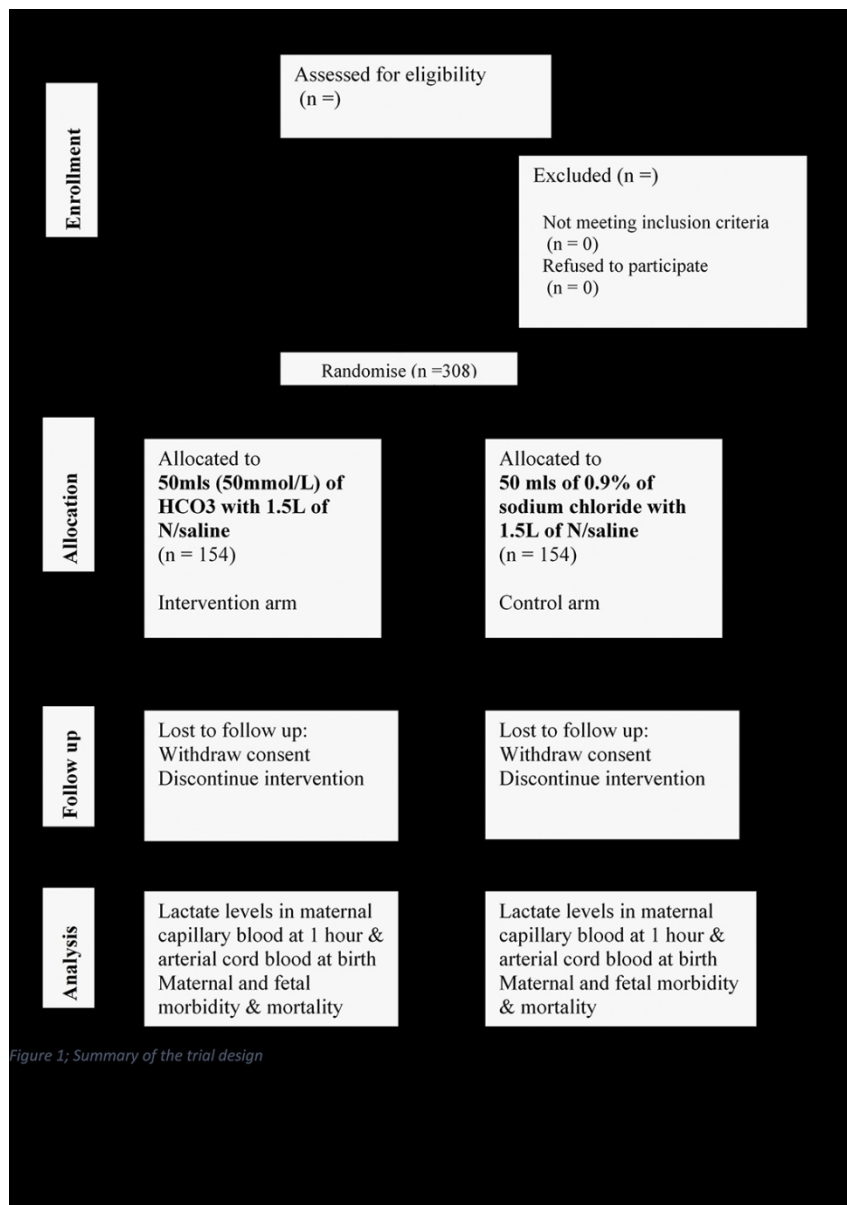


Figure 1; Summary of the trial design

90x126mm (300 x 300 DPI)



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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym YES on the title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry YES at the end of the abstract
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier Yes
Funding	4	Sources and types of financial, material, and other support Yes on page 14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Yes on the title page
	5b	Name and contact information for the trial sponsor Yes page 14
	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 Yes page 14
	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) NA
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 Yes page 3 to 5
	6b	Explanation for choice of comparators Yes 6&7
Objectives	7	Specific objectives or hypotheses Yes page 5

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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) Yes page 6
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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 Yes page 6
---------------	---	--

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) Yes Page 6&7
----------------------	----	--

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Yes page 7 & 8
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	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) NA
--	-----	--

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) NA
--	-----	---

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial NA
--	-----	---

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 Yes page 8
----------	----	--

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 2)
----------------------	----	---

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 Yes page 11&10
-------------	----	---

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size NA
-------------	----	---

Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions Yes see page 7 under randomisation
8			
9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
11	mechanism		describing any steps to conceal the sequence until interventions are
12			assigned Yes see page 7 under randomisation
13			
14	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
15			and who will assign participants to interventions Yes see page 7
16			under randomisation
17			
18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20			how Yes see page 7 under randomisation
21			
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial Yes see page 7 under randomisation
26			

Methods: Data collection, management, and analysis

27			
28			
29	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
30	methods		trial data, including any related processes to promote data quality (eg,
31			duplicate measurements, training of assessors) and a description of
32			study instruments (eg, questionnaires, laboratory tests) along with
33			their reliability and validity, if known. Reference to where data
34			collection forms can be found, if not in the protocol Yes see page 11
35			
36			
37		18b	Plans to promote participant retention and complete follow-up,
38			including list of any outcome data to be collected for participants who
39			discontinue or deviate from intervention protocols NA
40			
41	Data	19	Plans for data entry, coding, security, and storage, including any
42	management		related processes to promote data quality (eg, double data entry;
43			range checks for data values). Reference to where details of data
44			management procedures can be found, if not in the protocol Yes see
45			page 11
46			
47	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
48	methods		Reference to where other details of the statistical analysis plan can be
49			found, if not in the protocol Yes see page 12
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52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses) NA
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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) **NA**

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 **Yes see page 13**

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 **Yes see page 13**

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 **Yes see page 13**

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Yes see page 13**

Ethics and dissemination

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Yes see page 11**

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) **NA**

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (**see attached consent**)

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **NA**

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 **Yes see page 11**

Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site **see page 14**

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 **NA**

1			
2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation (see
4			attached consent form)
5			
6	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
7	policy		participants, healthcare professionals, the public, and other relevant
8			groups (eg, via publication, reporting in results databases, or other
9			data sharing arrangements), including any publication restrictions Yes
10			see page 13
11			
12		31b	Authorship eligibility guidelines and any intended use of professional
13			writers NA
14			
15		31c	Plans, if any, for granting public access to the full protocol, participant-
16			level dataset, and statistical code NA
17			
18	Appendices		
19			
20	Informed consent	32	Model consent form and other related documentation given to
21	materials		participants and authorised surrogates (Attached to submission)
22			
23	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
24	specimens		specimens for genetic or molecular analysis in the current trial and for
25			future use in ancillary studies, if applicable (Yes see attached
26			consent)
27			

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29 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013

30 Explanation & Elaboration for important clarification on the items. Amendments to the

31 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT

32 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)"

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BMJ Open

Effect of pre-operative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour; A study protocol for a Randomised Controlled Trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026675.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Dec-2018
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Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	sodium bicarbonate, obstructed labour, blood lactate level, Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS

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Title:

Effect of pre-operative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour;
A study protocol for a Randomised Controlled Trial

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ABSTRACT

Introduction

To improve maternal and fetal outcomes among patients with obstructed labour (OL) in low resource settings, the associated electrolyte and metabolic derangements must be adequately corrected. Oral fluid intake during labour and pre-operative intravenous fluid replacement following OL corrects the associated dehydration and electrolyte changes, but it doesn't completely reverse the metabolic acidosis which is a known cause of intrapartum birth asphyxia and a risk factor for primary postpartum haemorrhage due to uterine atony.

Sodium bicarbonate is a safe, effective, cheap and readily available acid buffer that is widely used by sportspeople to improve performance. It appears to also improve fetal and maternal outcomes in abnormally progressing labour. However, the effect of sodium bicarbonate on maternal and fetal outcomes among patients with OL is unknown. This study aims to establish the effect of a pre-operative bicarbonate infusion on maternal and perinatal outcomes among patients with OL in Mbale Regional Referral Hospital.

Methods and analysis

This will be a double blind, randomised controlled clinical phase III trial. We will randomize 308 patients with OL to receive either 50mls of placebo with standard pre-operative infusion of Normal Saline (1.5 L) or 4.2g of sodium bicarbonate solution (50mls of 50mmol/L) with the pre-operative infusion of Normal Saline (1.5 L). The primary outcome will be mean lactate levels in maternal capillary blood at one hour after onset of study drug administration, and in the arterial cord blood at birth. We will use the intention to treat analysis approach. Secondary outcomes will include maternal and fetal morbidity and mortality up to 14 days postpartum.

Ethics and Dissemination

This protocol is approved by the Makerere University School of Medicine Research and Ethics Committee and Uganda National Council for Science and Technology. Each participant will give informed consent at enrollment. The trial registration number is PACTR201805003364421.

Strengths and limitations of this study;

Strengths,

- i. This is among the 1st studies to investigate effect of preoperative bicarbonate infusion on maternal and fetal outcomes among patients with OL, using a randomized control design.
- ii. Measurement of maternal lactate levels and fetal cord blood lactate at the bedside using a hand-held device (Lactate Pro 2), instead of a blood gas analyser that is expensive to acquire and operate in a resource-limited setting.

Limitations,

- i. This study will only ascertain the efficacy and not the effectiveness of the preoperative sodium bicarbonate infusion
- ii. Given the short duration of follow up, we will not have any information regarding the long-term effects of sodium bicarbonate on maternal and perinatal outcomes.
- iii. Improving maternal and fetal lactate levels may not improve the fetal outcome in Obstructed Labour, as the tocolytic effect of the lactate may be a fetal protective mechanism.

Introduction

Globally, the annual number of maternal deaths (MD) decreased from 532,000 in 1990 to 303,000 in 2015.[1,2] But almost all (99.6%) occur in Sub-Saharan Africa (66.3%) and South-Central Asia,[1] where it is estimated that the lifetime risk of MD is as high as 1 in 16 and 1 in 46 respectively, compared to 1 in 2,800 in developed regions.[1,2] Although primary postpartum haemorrhage (PPH) and sepsis are the leading causes of MD, obstructed labour (OL) indirectly contributes to more than 70% of these deaths. [3] Directly, OL causes 8% of all the MD[4,5] and up to 90% of the perinatal deaths due to birth asphyxia.[6] In the 2015/16 financial year, of the 246 maternal deaths reported to the Uganda Ministry of Health

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2
3 (MOH), 9% were due to OL, 39% were due to haemorrhage and 20% were due to sepsis.[7] In addition,
4
5 69.3% of 411 perinatal deaths were due to birth asphyxia although the contribution of OL was not
6
7 specified.
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10 The prevalence of OL varies from 2– 8 % worldwide. It is highest in low and middle income countries
11 (LMICs) and is almost none-existent in developed countries. [4,5] In LMICs many patients experience
12
13 delays in accessing quality emergency obstetric and neonatal care services, so they end up with neglected
14
15 OL which causes significant maternal morbidity (dehydration, uterine rupture, sepsis, vesico/rectovaginal
16
17 fistulae and postpartum haemorrhage) and neonatal morbidity (asphyxia and sepsis).[3,8] Obstructed
18
19 labour occurs when the fetal presenting part does not descend into the maternal pelvis despite adequate
20
21 uterine contractions. [4] Usually, the obstruction can only be safely relieved by an operative delivery.[6]
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23
24 In fact OL is the commonest indication for primary caesarean section and a major risk factor for infective
25
26 morbidity (puerperal and neonatal sepsis) especially in LMICs.[3,9]
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31 Obstructed Labour is associated with higher levels of lactate in blood and amniotic fluid compared to
32
33 normal labour, and this correlates directly with perinatal outcomes.[10] Lactate is a by-product of
34
35 anaerobic respiration by both the fetus and the myometrium in response to intermittent hypoxia during
36
37 labour.[11] In OL, the episodes of hypoxia are prolonged leading to accumulation of lactic acid (metabolic
38
39 acidosis) from anaerobic break down of glucose. Although impaired uterine contractility caused by
40
41 myometrial acidosis increases the risk of primary PPH, it is beneficial to the fetus because it increases fetoplacental
42
43 oxygenation which is protective against intrapartum birth asphyxia.[10,12] The transfer of
44
45 excess hydrogen ions across the placenta to the fetus is associated with low fetal PH, fetal distress and
46
47 poor APGAR. [13]
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52 Oral bicarbonate is a widely used acid buffer in sports science, to improve physical performance in
53
54 vigorous exercises because it can reverse lactic acidosis.[14] Bicarbonate does not cross the placental
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3 barrier,[15] but it plays a key role in regulating the maternal and fetal acid-base chemistry.[13] There are
4
5 conflicting reports regarding its benefits in labour. Earlier studies involving the use of Bicarbonate in
6
7 normal labour showed improvements in pH, base excess and plasma bicarbonate, but none reported
8
9 APGAR scores. A recent RCT involving the use of oral bicarbonate solution in abnormal (dystocic) labour
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11 reported a significant improvement in both maternal and perinatal outcomes. [14] Significantly, none of
12
13 these studies reported adverse maternal and perinatal effects or included participants with OL. Currently,
14
15 pre-operative intravenous infusion with at least 1.5L of fluid is recommended as a key element of the
16
17 standard care. This is adequate to correct the dehydration and electrolyte imbalance but it probably
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19 doesn't completely reverse the associated metabolic acidosis.[16,17]
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24 Various formulations and doses of sodium bicarbonate have been safely used for both clinical indications
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26 and research purposes with no reported adverse clinical reactions. A single pre-operative infusion of 4.2g
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28 of sodium bicarbonate solution (50mls of 50mmol/L) will be given as a single dose at enrolment, since OL
29
30 is an obstetric emergency which requires urgent intervention. [18] The same dose was used orally in the
31
32 recent trial in which bicarbonate solution was administered to women with dystocia in labour. [14] The
33
34 main outcome of this study will be to assess whether bicarbonate changes the maternal and fetal lactate
35
36 levels among patients with OL. Lactate is easier to measure than full blood gas analysis using maintenance
37
38 free, battery operated pocket size devices like the lactate Pro2 (Arkray). This device produces accurate
39
40 results in a short time with a high intraclass correlation coefficient (ICC) which is comparable to that of
41
42 gold standard in a given population i.e. 0.90 versus 0.92.[18]Lactate is comparable to pH and base deficit
43
44 with respect to sensitivity, specificity and predictive values of various perinatal complications.[13]
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46 Establishing the effect of bicarbonate on maternal and fetal lactate levels among patients with OL is
47
48 important because it could be included in the pre-operative care package as an acid buffer.
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54 We hypothesize that supplementation with preoperative sodium bicarbonate infusion as an acid buffer
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56 among patients with OL can reduce maternal acidosis at one hour after administration, while their
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3 newborns in the bicarbonate group will have less acidosis in cord blood at birth. Bicarbonate is safe,
4 effective, cheap and already widely used.[19] Establishing its effect on maternal and fetal outcomes
5 following OL is necessary because it could be added to the standard preoperative care package as a form
6 of tertiary prevention. This study aims to establish the effect of a single dose preoperative infusion of
7 sodium bicarbonate on maternal and fetal lactate levels and clinical outcomes among patients with OL.
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14 **Methods/Design**

15 **Study design**

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18 This will be a superiority, double blind, randomised controlled clinical phase III trial. Half of the 308
19 patients with OL will receive the intervention (sodium bicarbonate infusion) with pre-operative normal
20 saline infusion, and the other half will receive the standard of care (pre-operative saline infusion) alone.
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28 **Study setting**

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31 The study will be conducted at Mbale Regional Referral Hospital located at the heart of Mbale Municipal
32 Council, 214km to the east of the capital city Kampala. It is the main referral hospital, serving 14 districts
33 in the Elgon zone, bordering western Kenya. This is a government run, not-for-profit, charge-free, 470-
34 bed hospital with 52 maternity beds. The Department of Obstetrics and Gynaecology has one consultant,
35 two specialists, three medical officers and 21 Midwives. In terms of outputs, the labour and delivery suit
36 is only second to the Mulago National Referral Hospital labour suit. Annually, about 12,000 childbirths
37 occur in this hospital with a caesarean section rate of 35% and nearly 500 mothers have OL. It has been
38 ranked as the best performing regional referral hospital by the Ministry of Health in Uganda for the last 4
39 years.
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51 **Participants**

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3 This study will be carried out among patients with OL admitted to the labour suite in Mbale Regional
4 Referral Hospital for emergency cesarean section during the period of the study. OL will be diagnosed by
5 either a Medical Officer or specialist on duty using the ACOG definition: in the 1st stage of labour she
6 should have cervical dilatation >6cm with ruptured membranes, adequate contractions lasting > 4hrs with
7 no change in cervical dilatation, OR, delay in the 2nd active stage of labour (nullipara > 2hrs, multipara >
8 1 hr.) with adequate uterine contractions. IN ADDITION, ANY TWO OF: the obvious signs of severe
9 obstruction such as caput formation, severe moulding, Bandl's ring, sub-conjunctival hemorrhages, or an
10 oedematous vulva.
11

12 We will include patients with OL carrying singleton, term pregnancies (≥ 37 weeks of gestation) in cephalic
13 presentation. We will exclude patients with other obstetric emergencies such as (antepartum
14 haemorrhage, Pre-eclampsia and eclampsia (defined as elevated blood pressure of at least 140/90 mmHg,
15 urine protein of at least 2+ ,any of the danger signs and fits), premature rupture of membranes and
16 intrauterine fetal death. Patients with comorbidities such as diabetes mellitus, Sickle cell disease, renal
17 disease, liver disease & heart disease; and those with a hypernatraemia > 148mmol/L and/or alkalosis >
18 22mmol/L.
19

20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 **Randomization** 39

40 A sequence of random numbers will be generated by an independent biostatistician using the online
41 randomisation service of www.sealedenvelope.com in permuted block sizes of four, six and eight. Based
42 on this sequence, OL patients will be randomly allocated to either intervention or control arms in a 1:1
43 ratio. Concealment will be done by an independent pharmacist not involved in the recruitment of study
44 participants, who will prepare and label sequentially numbered, identical study drug packages each
45 containing five similar 10ml glass vials with all the original labels removed. After consent for inclusion has
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3 been confirmed, a study nurse will take the next study drug package and administer its contents to
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5 participant.
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7 8 **Intervention;** 9

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11 The intervention will be a pre-operative infusion of 50mls of sodium bicarbonate 8.4% solution equivalent
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13 to 4.2g or 50mmol/L of bicarbonate (Martindale Pharma, Essex) in 10ml glass vials. The sodium
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15 bicarbonate will be administered intravenously as a bolus immediately after recruitment by trained
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17 research assistants who are all experienced midwives working in the labour suite, followed by 1.5L of
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19 Normal Saline over the next hour.
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22 23 **Comparator;** 24

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26 Participants in the control arm will receive a pre-operative infusion of Normal Saline which is the standard
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28 of care. Fifty mls of sodium chloride 0.9% in identical 10ml glass vials (AccuHealth Care, Gujarat) will be
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30 administered intravenously as a bolus immediately after recruitment by trained research assistants, who
31
32 are all experienced midwives working in the labour suite, followed by 1.5L Normal Saline over the next
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34 hour.
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38 In addition, recruits will receive the standard pre-operative care which includes pre-operative antibiotic
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40 prophylaxis, at least 1.5L of intravenous fluids pre-operatively, bladder emptying, administration of
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42 oxygen, and lying in left lateral position.[16]
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45 **Measurements;** 46

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48 The primary outcomes in this study will be the mean lactate levels in maternal capillary blood at one hour
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50 after the onset of study drug administration and in arterial cord blood within 1 minute of birth. Lactate
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52 will be measured at the bedside using a hand-held Lactate Pro 2 device (Arkray Factory Inc, Shiga).
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3 Secondary maternal outcomes will include myometrial lactate levels at caesarean section, maternal
4 morbidities such as primary PPH, birth canal injuries, duration of admission, puerperal sepsis (Persistent
5 fever >38°C, Chills and general malaise, Pain in the lower abdomen, Persistent bloody/pus discharge
6 (lochia) from genital tract, which may have an unpleasant smell, Tenderness on palpating the uterus y
7 Uterine sub-involution, wound dehiscence/ burst abdomen), [16] fistulae, readmissions and death up to
8 the 14 days postpartum. Secondary perinatal outcomes will include mean lactate in venous cord blood,
9 Apgar score, admission to the NICU, asphyxia, neonatal sepsis (irritability, poorly breastfeeding, bulging
10 anterior fontanelle) [16] and perinatal death up to 7 days postpartum.

21 **Sociodemographic, clinical and laboratory characteristics;**

22
23 Using an interviewer administered questionnaire and available records (antenatal cards, facility registers
24 and case report files), sociodemographic and clinical characteristics will be collected by trained research
25 assistants. At baseline, 5 mls of blood will be collected in the appropriate vacutainers for a complete
26 blood count, renal function tests, liver function tests and electrolytes. Ten mls of fresh urine will be
27 collected in a sterile container for analysis. All these specimens will be delivered to MBN clinical
28 laboratories within 1 hour of collection for analysis. Figure 1 shows the CONSORT flow diagram for this
29 study. Patients will be followed up to 14 days postnatally either by phone call if they are discharged or by
30 direct visits if they are still admitted.

43 **Sample size and power calculation;**

44
45 We used Open Epi [20] to detect a 15% difference in mean lactate levels between the intervention and
46 control arms, assuming an equal number of participants in each group, a two-sided significance level of
47 0.05 for a 95% confidence interval, a power of 80%, and a student's t-test for comparison of means.

48
49 The mean and standard deviation (SD) of the maternal venous lactate at the end of second stage of labour
50 is 2.6 ± 1.0 mmol/L [21] without any use of bicarbonate. To detect a difference of 15% (0.39 mmol/L) at
51

one hour and assuming the same S.D. of ± 1 in both arms, 278 participants will be required. Correcting for an attrition rate of 10%,^[14] gives a total sample size of 308.

The mean arterial umbilical cord blood lactate at 37 weeks of gestation is 4.3 ± 1.9 mmol/L^[22] without any use of bicarbonate. In order to detect a difference of 15% (0.645 mmol/L) at birth and assuming the same S.D. of ± 1.9 in both groups, 274 participants will be recruited. Correcting for an attrition rate of 10%,^[14] gives a total sample size of 304. A sample size of 308 was therefore planned to provide power for both hypotheses.

Data collection and management;

Well trained RAs will collect data using a pretested interviewer administered electronic questionnaire on password protected smart phones using the Open Data Kit software. To increase accuracy the data will be triangulated with a review of relevant health facility records such as the antenatal cards, the maternity and theatre registers, and the participants' case report forms. The questionnaire will be coded with checks for internal consistency. Data on sociodemographic, clinical and laboratory parameters will be collected at baseline, at one hour after onset of study drug administration for the primary maternal outcome, at the time of childbirth for the primary neonatal outcome, and at 7 and 14 days postpartum for the secondary perinatal and maternal outcomes as summarised in table 1. The PI will review the entries from the Google aggregate server every 24 hours to ensure data quality and completeness.

Table 1; Summary of the study procedures and timelines

Procedure	At admission (Baseline)	1 hour after onset of study drug administration	At birth	At 7 days postpartum	At 14 days postpartum
Assessment of eligibility	x				
Randomisation	x				
Data collection for baseline parameters	x				

Study drug administration	x				
Questionnaire administration	x	x	x	x	x
Data collection for primary outcome		x	x		
Data collection for secondary outcome			x	x	x

Statistical analysis;

This will be conducted using STATA version 14 software or higher using the principle of 'intention to treat'.

Descriptive statistics will be used to summarise baseline characteristics of the study participants and assess if randomisation was successful. The primary maternal outcome will be the difference in capillary blood lactate levels at one hour after onset of study drug administration. The paired sample t-test will be used to compare the difference in means at baseline and one hour after onset of study drug administration within each arm. The independent student t- test will be used to compare the mean lactate levels in the two arms at one hour after onset of study drug administration

For the primary fetal outcome of mean arterial cord blood lactate at birth, the independent student t- test will be used to compare the mean lactate levels in the two arms within 1 minute of childbirth.

We will use the Holm-Bonferroni method to compute an adjusted P value for multiple comparisons of the dependent maternal and foetal primary outcomes.[23,24]

The secondary outcomes will be reported as proportions in each of the two arms. Categorical variables will be compared using the Chi-square and Fishers exact tests. Potential confounders and effect modifiers unbalanced at baseline and associated with the outcome ($p < 0.05$) will be adjusted for using multivariable linear or/and logistic regression. Proportions and the number needed to treat/harm (NNT/NNH) will be reported for the secondary maternal and fetal outcomes.

1
2
3 We will do a sub-group analysis of patients admitted as referrals with a diagnosis of OL (to represent
4 patients most likely to have neglected OL) to compare them with those that are diagnosed with OL within
5 the referral hospital. A second sub-group analysis will be for those patients that give birth more than two
6 hours after administration of the study drug, when we expect the effect of the intervention to have worn
7 off.
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13 14 15 **Quality control;**

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17 We run will conduct a dry run for a period of one month before introducing the intervention. To facilitate
18 the training all the research assistants in the study protocol procedures, filling of study questionnaires
19 using the ODK software,[25] accurate measurement of lactate at the bedside using the Lactate Pro 2
20 device and the ideal technique for collection of samples especially blood to avoid haemolysis. The MBN
21 clinical laboratories are internationally accredited and they are involved in regular internal and external
22 quality control checks.
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31 32 **Ethics and dissemination;**

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34 The protocol is approved by the Makerere University School of Medicine Research and Ethics Committee
35 (#REC REF 2017-103), the Uganda National Council for Science and Technology (HS217ES) and the Mbale
36 Regional Referral Research and Ethics Committee(MRRH-REC IN-COM 00/2018). Participant safety;
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41 All serious adverse events will be actively identified and reported to the IRB within 24 hours of occurrence
42 using the School of Medicine Research Ethics Committee reporting form throughout the study period up
43 to the end of puerperium (6 weeks after birth). The independent data monitoring committee will review
44 unblinded data when 1/3 of the participants have been enrolled and followed up to completion, and at
45 any other time that they request. In addition, only qualified health workers will be recruited and trained
46 in the protocol to work as research assistants on this trial.
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Dissemination plan;

Results will be disseminated to the study participants through the local radio stations and local council community meeting at the village level. Findings will be shared with colleagues and administrators in Mbale Regional Referral Hospital/Busitema University Faculty of Health Sciences and the Uganda ministry of health through workshops and seminars. To reach the wider scientific community, the findings will be published in open access peer reviewed journals and presented at both local and international conferences. The data sets will be provided free of charge by the primary author on request.

Patient and Public involvement;

The patients and public were not involved in the design and conceptualisation of this study.

Discussion;

If the preoperative infusion of sodium bicarbonate is safe and effective in reducing maternal and fetal lactatemia (acidosis) among patients with OL, then the data from this trial will inform the design of future trials that will facilitate the inclusion of sodium bicarbonate infusion in the standard pre-operative care for patients with OL in low resource settings. Its adoption will help to mitigate adverse maternal and perinatal outcomes associated with OL as a tertiary preventive measure for intrauterine maternal and fetal resuscitation. Obstructed labour is still an important clinical and public health problem in low resource settings because of the associated maternal and perinatal morbidity and mortality caused by accompanying electrolyte and metabolic changes. Therefore, identifying an effective, cheap, safe and readily available acid buffer like sodium bicarbonate might offer immense health benefits.

In obstructed labour, lactatemia might be a protective mechanism to prevent uterine rupture especially in the multiparous patients and fetal hypoxia by causing relaxation of the myometrium in order to improve fetal placental circulation.[10–12] Therefore, reversal of lactic acidosis might result in stronger uterine

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3 contractions and increase the degree of fetal hypoxia or risk of uterine rupture especially if the surgical
4 intervention is delayed. Thus, although this study will help us to understand whether 50mmol of
5 bicarbonate is effective at reversing lactic acidosis, further studies will be required to ascertain its effects
6 on maternal and fetal morbidity.
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12 **Acknowledgements;**

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15 We thank the PI of the Survival Pluss Project and all his Co-Investigators for funding this work through a
16 PhD fellowship awarded to me under Busitema University.
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20 **Author contributions;**

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22
23 Musaba Milton Wamboko (MMW) conceptualised, designed, developed the protocol and drafted the
24 manuscript. Justus K Barageine(JKB), Julius N Wandabwa(JNW), Grace Ndeezi (GN) and Andrew Weeks
25 (AW) all participated in the conceptualization, design, development of the protocol and writing of the
26 manuscript by providing critical review and refinement of the research idea as supervisors of my PhD
27 studies. All the authors reviewed and approved the final draft of the manuscript for submission.
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38 This work was supported by Survival Pluss project grant number UGA-13-0030 at Makerere University.
39
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42 Cooperation (NORAD).
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48 Competing interests statement; None declared
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51 Patients consent; Required
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53 **Ethics approval;**

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3 Provenance and peer review; Not commissioned; externally peer reviewed.
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6 **Open Access;**
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9 This is an Open Access article distributed in accordance with the Creative Commons Attribution Non-
10 Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work
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12 properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>
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18 **References;**
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22 mortality between 1990 and 2015 with scenario-based projections to 2030: a systematic analysis
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Figure1 Flow diagram of study participants in the trial

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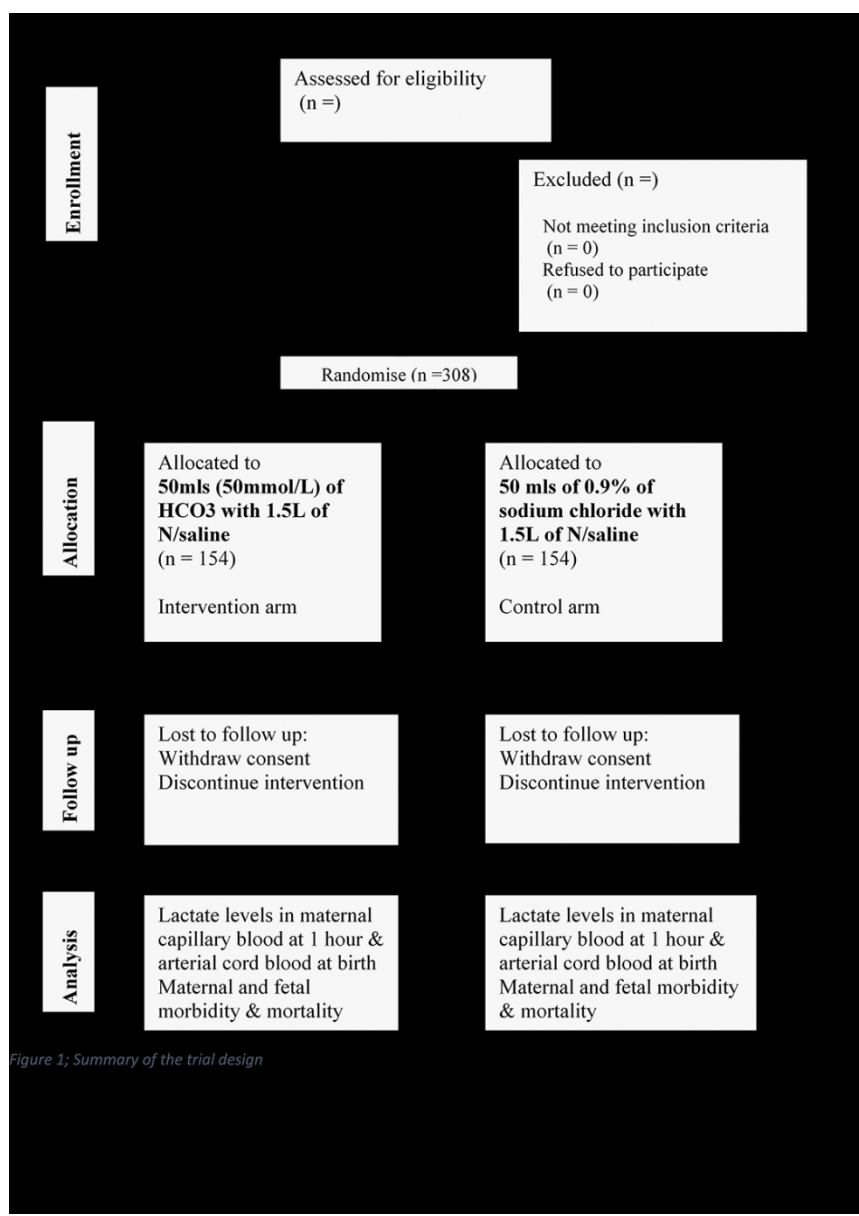


Figure 1; Summary of the trial design

90x126mm (300 x 300 DPI)



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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym YES on the title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry YES at the end of the abstract
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier Yes
Funding	4	Sources and types of financial, material, and other support Yes on page 14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Yes on the title page
	5b	Name and contact information for the trial sponsor Yes page 14
	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 Yes page 14
	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) NA
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 Yes page 3 to 5
	6b	Explanation for choice of comparators Yes 6&7
Objectives	7	Specific objectives or hypotheses Yes page 5

1 Trial design 8 Description of trial design including type of trial (eg, parallel group,
2 crossover, factorial, single group), allocation ratio, and framework (eg,
3 superiority, equivalence, noninferiority, exploratory) **Yes page 6**
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7 **Methods: Participants, interventions, and outcomes**
8

9 Study setting 9 Description of study settings (eg, community clinic, academic hospital)
10 and list of countries where data will be collected. Reference to where
11 list of study sites can be obtained **Yes page 6**
12

13 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
14 criteria for study centres and individuals who will perform the
15 interventions (eg, surgeons, psychotherapists) **Yes Page 6&7**
16

17 Interventions 11a Interventions for each group with sufficient detail to allow replication,
18 including how and when they will be administered **Yes page 7 & 8**
19

20 11b Criteria for discontinuing or modifying allocated interventions for a
21 given trial participant (eg, drug dose change in response to harms,
22 participant request, or improving/worsening disease) **NA**
23

24 11c Strategies to improve adherence to intervention protocols, and any
25 procedures for monitoring adherence (eg, drug tablet return,
26 laboratory tests) **NA**
27
28

29 11d Relevant concomitant care and interventions that are permitted or
30 prohibited during the trial **NA**
31

32 Outcomes 12 Primary, secondary, and other outcomes, including the specific
33 measurement variable (eg, systolic blood pressure), analysis metric
34 (eg, change from baseline, final value, time to event), method of
35 aggregation (eg, median, proportion), and time point for each
36 outcome. Explanation of the clinical relevance of chosen efficacy and
37 harm outcomes is strongly recommended **Yes page 8**
38

39 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
40 timeline washouts), assessments, and visits for participants. A schematic
41 diagram is highly recommended (**see Figure 2**)
42
43

44 Sample size 14 Estimated number of participants needed to achieve study objectives
45 and how it was determined, including clinical and statistical
46 assumptions supporting any sample size calculations **Yes page**
47 **11&10**
48

49 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
50 target sample size **NA**
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52 **Methods: Assignment of interventions (for controlled trials)**
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55 Allocation:
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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions Yes see page 7 under randomisation
8			
9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
11	mechanism		describing any steps to conceal the sequence until interventions are
12			assigned Yes see page 7 under randomisation
13			
14	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
15			and who will assign participants to interventions Yes see page 7
16			under randomisation
17			
18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20			how Yes see page 7 under randomisation
21			
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial Yes see page 7 under randomisation
26			

Methods: Data collection, management, and analysis

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29	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
30	methods		trial data, including any related processes to promote data quality (eg,
31			duplicate measurements, training of assessors) and a description of
32			study instruments (eg, questionnaires, laboratory tests) along with
33			their reliability and validity, if known. Reference to where data
34			collection forms can be found, if not in the protocol Yes see page 11
35			
36			
37		18b	Plans to promote participant retention and complete follow-up,
38			including list of any outcome data to be collected for participants who
39			discontinue or deviate from intervention protocols NA
40			
41	Data	19	Plans for data entry, coding, security, and storage, including any
42	management		related processes to promote data quality (eg, double data entry;
43			range checks for data values). Reference to where details of data
44			management procedures can be found, if not in the protocol Yes see
45			page 11
46			
47	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
48	methods		Reference to where other details of the statistical analysis plan can be
49			found, if not in the protocol Yes see page 12
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52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses) NA
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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) **NA**

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 **Yes see page 13**

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 **Yes see page 13**

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 **Yes see page 13**

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Yes see page 13**

Ethics and dissemination

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Yes see page 11**

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) **NA**

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (**see attached consent**)

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **NA**

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 **Yes see page 11**

Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site **see page 14**

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 **NA**

1			
2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation (see
4			attached consent form)
5			
6	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
7	policy		participants, healthcare professionals, the public, and other relevant
8			groups (eg, via publication, reporting in results databases, or other
9			data sharing arrangements), including any publication restrictions Yes
10			see page 13
11			
12		31b	Authorship eligibility guidelines and any intended use of professional
13			writers NA
14			
15		31c	Plans, if any, for granting public access to the full protocol, participant-
16			level dataset, and statistical code NA
17			
18	Appendices		
19			
20	Informed consent	32	Model consent form and other related documentation given to
21	materials		participants and authorised surrogates (Attached to submission)
22			
23	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
24	specimens		specimens for genetic or molecular analysis in the current trial and for
25			future use in ancillary studies, if applicable (Yes see attached
26			consent)
27			

28 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
 29 Explanation & Elaboration for important clarification on the items. Amendments to the
 30 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
 31 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)"
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BMJ Open

Effect of preoperative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour in Mbale Regional Referral Hospital; A study protocol for a Randomised Controlled Trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026675.R2
Article Type:	Protocol
Date Submitted by the Author:	01-Feb-2019
Complete List of Authors:	Musaba, Milton; Busitema University Faculty of Health Sciences/Mbale Regional Referral Hospital, Department of Obstetrics and Gynaecology; Makerere University College of Health Sciences, Department of Paediatrics & Child Health Barageine, Justus; Makerere University College of Health Sciences, Department of Department Obstetrics & Gynaecology Ndeezi, Grace; Makerere University College of Health Sciences, Department of Paediatrics and Child Health Wandabwa, Julius; Busitema University Faculty of Health Sciences, Department of Obstetrics and Gynaecology Weeks, Andrew; University of Liverpool, Department of Women's and Children's Health
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	sodium bicarbonate, obstructed labour, blood lactate level, Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS

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Manuscripts

Title:

Effect of preoperative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour in Mbale Regional Referral Hospital; A study protocol for a Randomised Controlled Trial

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ABSTRACT

Introduction

To improve maternal and fetal outcomes among patients with obstructed labour (OL) in low resource settings, the associated electrolyte and metabolic derangements must be adequately corrected. Oral fluid intake during labour and preoperative intravenous fluid replacement following OL corrects the associated dehydration and electrolyte changes, but it does not completely reverse the metabolic acidosis that is a cause of intrapartum birth asphyxia and a risk factor for primary postpartum haemorrhage due to uterine atony.

Sodium bicarbonate is a safe, effective, cheap and readily available acid buffer that is widely used by sportspeople to improve performance. It also appears to improve fetal and maternal outcomes in abnormally progressing labour. However, its effects on maternal and fetal outcomes among patients with OL is unknown. We aim at establishing the effect of a single dose preoperative infusion of sodium bicarbonate on maternal and fetal lactate levels and clinical outcomes among patients with OL.

Methods and analysis

This will be a double blind, randomised controlled clinical phase IIb trial. We will randomize 478 patients with OL to receive either 50 mls of placebo with standard preoperative infusion of Normal Saline (1.5 L) or 4.2 g of sodium bicarbonate solution (50 mls of 50 mmol/L) with the preoperative infusion of Normal Saline (1.5 L). The primary outcome will be mean lactate levels in maternal capillary blood at one hour after study drug administration and in the arterial cord blood at birth. We will use the intention to treat analysis approach. Secondary outcomes will include safety, maternal and fetal morbidity and mortality up to 14 days postpartum.

Ethics and Dissemination

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3 Makerere University School of Medicine Research and Ethics Committee and Uganda National Council for
4 Science and Technology have approved the protocol. Each participant will give informed consent at
5
6 enrollment. The trial registration number is PACTR201805003364421.
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10 Strengths and limitations of this study;

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12
13 Strengths.

- 14
15 i. This is among the first studies to investigate the effect of preoperative bicarbonate infusion on maternal and
16 fetal outcomes among patients with OL, using a randomized control design.
17
18 ii. Measurement of maternal lactate levels and fetal cord blood lactate at the bedside using a hand-held device
19 (Lactate Pro 2), instead of a blood gas analyser that is expensive to acquire and operate; in a resource-
20 limited setting.
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24 Limitations.

- 25
26 i. This study will only ascertain the efficacy and not the effectiveness of the preoperative sodium bicarbonate
27 infusion
28
29 ii. Given the short duration of follow up, we will not have any information regarding the long term effects of
30 sodium bicarbonate on maternal and perinatal outcomes.
31
32 iii. Improving maternal and fetal lactate levels may not improve the fetal outcome in OL, as the tocolytic effect
33 of the lactate may be a fetal protective mechanism.
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36
37 **Introduction**

38
39 Globally, the annual number of maternal deaths (MD) has decreased from 532,000 in 1990 to 303,000 in
40 2015.[1,2] But almost all of them (99.6%) occur in Sub Saharan Africa (66.3%) and South Central Asia,[1]
41
42 where it is estimated that the lifetime risk of MD is as high as 1 in 16 and 1 in 46 respectively, compared
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44 to 1 in 2,800 in developed regions.[1,2] Although, primary postpartum haemorrhage (PPH) and sepsis are
45
46 the leading causes of MD, obstructed labour (OL) indirectly contributes to more than 70% of these deaths.
47
48 [3] Directly, OL causes 8% of all the MD[4,5] and up to 90% of the perinatal deaths due to birth asphyxia.[6]
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50 In the 2015/16 financial year, of the 246 maternal deaths reported to the Uganda Ministry of Health
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52 (MOH), 9% were due to OL, 39% were due to haemorrhage and 20% were due to sepsis.[7] In addition,
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3 69.3% of 411 perinatal deaths were due to birth asphyxia although the contribution of OL was not
4
5 specified.
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8 The prevalence of OL varies from 2– 8 % worldwide. It is highest in low and middle income countries
9
10 (LMICs) and is almost none-existent in developed countries. [4,5] In LMICs many patients experience
11
12 delays in accessing quality emergency obstetric and neonatal care services, so they end up with neglected
13
14 OL which causes significant maternal morbidity (dehydration, uterine rupture, sepsis,
15
16 vesicovaginal/rectovaginal fistulae and postpartum haemorrhage) and neonatal morbidity (asphyxia and
17
18 sepsis).[3,8] Obstructed labour occurs when the fetal presenting part does not descend into the maternal
19
20 pelvis despite adequate uterine contractions. [4] Usually, the obstruction can only be safely relieved by
21
22 an operative delivery.[6] In fact OL is the commonest indication for primary caesarean section and a major
23
24 risk factor for infective morbidity (puerperal and neonatal sepsis) especially in LMICs.[3,9]
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29 Obstructed Labour is associated with higher levels of lactate in blood and amniotic fluid compared to
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31 normal labour, and this correlates directly with perinatal outcomes.[10] Lactate is a byproduct of
32
33 anaerobic respiration that is produced by both the fetus and the myometrium in response to intermittent
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35 hypoxia during labour.[11] In OL, the episodes of hypoxia are prolonged leading to accumulation of lactic
36
37 acid (metabolic acidosis) from anaerobic break down of glucose. Although impaired uterine contractility
38
39 caused by myometrial acidosis increases the risk of primary PPH, it is beneficial to the fetus because it
40
41 increases fetal placental circulation (oxygenation) which is protective against intrapartum birth
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43 asphyxia.[10,12] The transfer of excess hydrogen ions across the placenta to the fetus is associated with
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45 low fetal PH, fetal distress and poor APGAR. [13]
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50 Oral bicarbonate is a widely used acid buffer in sports science, to improve physical performance in
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52 vigorous exercises because it can reverse lactic acidosis.[14] Bicarbonate does not cross the placental
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54 barrier,[15] but it plays a key role in regulating the maternal and fetal acid-base chemistry.[13] There are
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3 conflicting reports regarding its benefits in labour. Earlier studies involving the use of Bicarbonate in
4 normal labour showed improvements in pH, base excess and plasma bicarbonate, but none reported
5 APGAR scores. A recent RCT involving the use of oral bicarbonate solution in abnormal (dystocic) labour
6 reported a significant improvement in both maternal and perinatal outcomes. [14] Significantly, none of
7 these studies reported adverse maternal and perinatal effects or included participants with OL. Currently,
8 preoperative intravenous infusion with at least 1.5 L of fluid is recommended as a key element of the
9 standard care. This is adequate to correct the dehydration and electrolyte imbalance but it probably
10 doesn't completely reverse the associated metabolic acidosis.[16,17]
11

12 Various formulations and doses of sodium bicarbonate have been safely used for both clinical indications
13 and research purposes with no reported adverse clinical reactions. A single preoperative infusion of 4.2 g
14 of sodium bicarbonate solution (50 mls of 50 mmol/L) will be given as a single dose at enrolment, since
15 OL is an obstetric emergency that requires urgent intervention. [18] The same dose was used orally in the
16 recent trial in which bicarbonate solution was administered to women with dystocia in labour. [14] The
17 main outcome of this study will be to assess whether bicarbonate changes the maternal and fetal lactate
18 levels among patients with OL. Lactate is easier to measure than full blood gas analysis using maintenance
19 free, battery operated pocket size devices like the lactate Pro2 (Arkray). This device produces accurate
20 results in a short time with a high intraclass correlation coefficient (ICC) which is comparable to that of
21 gold standard in a given population i.e. 0.90 versus 0.92.[18] Lactate is comparable to pH and base deficit
22 with respect to sensitivity, specificity and predictive values of various perinatal complications.[13]
23

24 We hypothesize that supplementation with preoperative sodium bicarbonate infusion as an acid buffer
25 among patients with OL can reduce maternal acidosis at one hour after administration, while their
26 newborns in the bicarbonate group will have less acidosis in cord blood at birth. Bicarbonate is safe,
27 effective, cheap and already widely used.[19] Establishing its effect on maternal and fetal outcomes
28 following OL is necessary because it could be added to the standard preoperative care package as a form
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3 of tertiary prevention. This study aims to establish the effect of a single dose preoperative infusion of
4 sodium bicarbonate on maternal and fetal lactate levels and clinical outcomes among patients with OL.
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8 **Methods/Design**

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10 **Study design**

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12 This will be a superiority, double blind, randomised controlled clinical phase IIb trial. Half of the 478
13 patients with OL will receive the intervention (sodium bicarbonate infusion) with preoperative normal
14 saline infusion, and the other half will receive the standard of care (preoperative saline infusion) alone.
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21 **Study setting**

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23 We will conduct this study in Mbale Regional Referral Hospital located at the heart of Mbale Municipality,
24 214 km to the East of the capital city, Kampala. It is the main referral hospital, serving 14 districts in the
25 Elgon zone, bordering western Kenya. This is a government run, not-for-profit, charge-free, 470-bed
26 hospital with 52 maternity beds. The Department of Obstetrics and Gynaecology has one consultant, two
27 specialists, three medical officers and 21 Midwives. In terms of outputs, the labour and delivery suite is
28 only second to the Mulago National Referral Hospital labour suite. Annually, about 12,000 childbirths
29 occur in this hospital with a caesarean section rate of 35% and nearly 500 mothers have OL. The Ministry
30 of Health has ranked it as the best performing Regional Referral Hospital in Uganda for the last four years.
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43 **Participants**

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45 This study will be carried out among patients with OL admitted to the labour suite in Mbale Regional
46 Referral Hospital for emergency cesarean section during the period of the study. Either a Medical Officer
47 or specialist on duty using the ACOG definition will make the diagnosis of OL. In the first stage of labour
48 she should have cervical dilatation >6cm with ruptured membranes, adequate contractions lasting > 4hrs
49 with no change in cervical dilatation, OR, delay in the second active stage of labour (nullipara > 2hrs,
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3 multipara > 1 hr.) with adequate uterine contractions. IN ADDITION, ANY TWO OF: the obvious signs of
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5 severe obstruction such as caput formation, severe moulding, Bandl's ring, sub-conjunctival hemorrhages,
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7 or an oedematous vulva.
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10 We will include patients with OL carrying singleton, term pregnancies (≥ 37 weeks of gestation) in cephalic
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12 presentation. We will exclude patients with other obstetric emergencies such as (ante partum
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14 haemorrhage, Pre-eclampsia and eclampsia (defined as elevated blood pressure of at least 140/90 mmHg,
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16 urine protein of at least 2+, any of the danger signs and fits), premature rupture of membranes and
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18 intrauterine fetal death. Patients with comorbidities such as diabetes mellitus, Sickle cell disease, renal
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20 disease, liver disease & heart disease. We will also exclude those patients with hypokalemia (<3.3
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22 mmol/L), hypocalcaemia (<8.2 mmol/L), hypernatraemia (> 148 mmol/L) and alkalosis (bicarbonate > 22
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24 mmol/L) because they are more likely to develop adverse drug reactions.
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29 **Randomization**

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32 An independent biostatistician will generate a sequence of random numbers using the online randomisation
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34 service of www.sealedenvelope.com in permuted block sizes of four, six and eight. Based on this
35
36 sequence, OL patients will be randomly allocated to either intervention or control arms in a 1:1 ratio. An
37
38 independent pharmacist who is not involved in the recruitment of study participants, will conceal the
39
40 randomization sequence by preparing new labels with sequential numbers to be placed on identical study
41
42 drug packages each containing five similar 10 ml glass vials without the original labels. After consent for
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44 inclusion is confirmed, a study nurse will take the next study drug package and administer its contents to
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46 the participant.
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50 **Intervention;**

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53 The intervention will be a preoperative infusion of 50 mls of sodium bicarbonate 8.4% solution equivalent
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55 to 4.2 g or 50 mmol/L of bicarbonate (Martindale Pharma, Essex) in 10 ml glass vials. The sodium
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3 bicarbonate will be administered intravenously as a bolus immediately after recruitment by trained
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5 research assistants who are all experienced midwives working in the labour suite, followed by 1.5 L of
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7 Normal Saline over the next hour.
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10 **Comparator;**

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13 Participants in the control arm will receive a preoperative infusion of Normal Saline, which is part of the
14
15 current standard of care. Fifty mls of sodium chloride 0.9% in identical 10 ml glass vials (AccuHealth Care,
16
17 Gujarat) will be administered intravenously as a bolus immediately after recruitment by trained research
18
19 assistants, who are all experienced midwives working in the labour suite, followed by 1.5 L Normal Saline
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21 over the next hour.
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25 In addition, recruits will receive the standard pre-operative care which includes pre-operative antibiotic
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27 prophylaxis, at least 1.5 L of intravenous fluids pre-operatively, bladder emptying, administration of
28
29 oxygen, and lying in left lateral position.[16]
30
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32 **Measurements;**

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35 The primary outcomes in this study will be the mean lactate levels in maternal capillary blood at one hour
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37 after the onset of study drug administration and in arterial cord blood within 1 minute of birth. We will
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39 measure Lactate at the bedside using a hand-held Lactate Pro 2 device (Arkray Factory Inc. Shiga).
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43 The Secondary maternal outcomes will include myometrial lactate levels at caesarean section, maternal
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45 mortality up to 14 days postpartum. Other morbidities such as primary PPH, birth canal injuries, duration
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47 of admission, puerperal sepsis (Persistent fever $>38^{\circ}\text{C}$, Chills and general malaise, Pain in the lower
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49 abdomen, Persistent bloody/pus discharge (lochia) from genital tract, which may have an unpleasant
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51 smell, Tenderness on palpating the uterus Uterine sub-involution, wound dehiscence/ burst
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53 abdomen),[16] fistulae and readmissions. Secondary perinatal outcomes will include mean lactate in
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3 venous cord blood, Apgar score, admission to the NICU, asphyxia, neonatal sepsis (irritability, poorly
4 breastfeeding, bulging anterior fontanelle)[16] and perinatal death up to 7 days postpartum.
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8 For the secondary safety outcomes, we will monitor for the following drug reactions throughout the
9 period of the study. Frequent urge to urinate, continuing headache, continuing loss of appetite, mood or
10 mental changes, muscle pain or twitching, nausea or vomiting, stomach cramps, slow breathing, swelling
11 of feet or lower limbs, unpleasant taste, increased thirst, unusual tiredness or weakness, venous irritation,
12 cellulitis and IV site pain.[20–22]
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19 20 **Sociodemographic, clinical and laboratory characteristics;** 21

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23 Using an interviewer administered questionnaire and available records (antenatal cards, facility registers
24 and case report files), sociodemographic and clinical characteristics will be collected by trained research
25 assistants. At baseline, five mls of blood will be collected in the appropriate vacutainers for a complete
26 blood count, renal function tests, liver function tests and electrolytes. Ten mls of fresh urine will be
27 collected in a sterile container for analysis. All these specimens will be delivered to MBN clinical
28 laboratories within 1 hour of collection for analysis. Figure 1 shows the CONSORT flow diagram for this
29 study. We will follow up patients for up to 14 days postpartum either by phone call if they are discharged
30 or by direct visits if they are still admitted according to the current standard of care for patients with OL
31 in Uganda.
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44 **Sample size and power calculation;** 45

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47 We used the formula, $n \leq (Z_{1-\frac{\alpha}{2c}} + Z_{1-\beta})^2 2 \left(\frac{SD}{\Delta}\right)^2$ [23] and Open Epi [24] to detect a $\Delta = 15\%$
48 difference in mean lactate levels between the intervention and control arms. Assuming an equal number
49 of participants in each group, a two-sided significance level α of 0.05 for a 95% confidence interval, a
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3 power ($1 - \beta$) of 80%, an allowance of $c =$ two multiple comparisons and a Bonferroni-Holm method for
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5 comparison of means.
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8 The mean and standard deviation (SD) of the maternal venous lactate at the end of second stage of labour
9
10 is 2.6 ± 1.0 mmol/L[25] without any use of bicarbonate. To detect a difference of 15% (0.39 mmol/L) at
11
12 one hour and assuming the same S.D. of ± 1 in both arms, 326 participants will be required. Correcting for
13
14 an attrition rate of 10%, [14] gives a total sample size of 364.
15

16
17 The mean arterial umbilical cord blood lactate at 37 weeks of gestation is 4.3 ± 1.9 mmol/L[26] without
18
19 any use of bicarbonate. In order to detect a difference of 15% (0.645 mmol/L) at birth and assuming the
20
21 same S.D of ± 1.9 in both groups, 432 participants will be recruited. Correcting for an attrition rate of
22
23 10%, [14] gives a total sample size of 478. We therefore, chose a sample size of 478 to provide adequate
24
25 power for both hypotheses.
26
27

28 29 30 **Data collection and management;**

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32 Well trained RAs will collect data using a pretested interviewer administered electronic questionnaire on
33
34 password protected smart phones using the Open Data Kit software.[27] To increase accuracy, the data
35
36 will be triangulated with a review of relevant health facility records such as the antenatal cards, the
37
38 maternity and theatre registers, and the participants' case notes. The questionnaire will be coded with
39
40 checks for internal consistency. Data on sociodemographic, clinical and laboratory parameters will be
41
42 collected at baseline, at one hour after onset of study drug administration for the primary maternal
43
44 outcome, at the time of childbirth for the primary neonatal outcome, and at 7 and 14 days postpartum
45
46 for the secondary perinatal and maternal outcomes as summarised in table 1. The PI will review the
47
48 entries from the Google aggregate server every 24 hours to ensure data quality and completeness.
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52
53 *Table 1; Summary of the study procedures and timelines*
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Procedure	At admission (Baseline)	1 hour after onset of study drug administration	At birth	At 7 days postpartum	At 14 days postpartum
Assessment of eligibility	x				
Randomisation	x				
Data collection for baseline parameters	x				
Study drug administration	x				
Questionnaire administration	x	x	x	x	x
Data collection for primary outcome		x	x		
Data collection for secondary outcome			x	x	x

Statistical analysis;

This will be conducted using STATA version 14 software or higher using the principle of 'intention to treat'. Descriptive statistics will be used to summarise baseline characteristics of the study participants and assess if randomisation was successful. The primary maternal outcome will be the difference in capillary blood lactate levels at one hour after onset of study drug administration. The Bonferroni-Holm method[28,29] will be used to compare the difference in means at baseline and one hour after onset of study drug administration both within and between each of the two arms.

For the primary fetal outcome of mean arterial cord blood lactate at birth, The Bonferroni-Holm method will be used to compare the mean lactate levels in the two arms within 1 minute of childbirth.

The secondary outcomes will be reported as proportions in each of the two arms. Categorical variables will be compared using the Chi-square and Fishers exact tests. Potential confounders and effect modifiers unbalanced at baseline and associated with the outcome ($p < 0.05$) will be adjusted for using multivariable

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3 linear or/and logistic regression. Proportions and the number needed to treat/harm (NNT/NNH) will be
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5 reported for the secondary maternal and fetal outcomes.
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8 We will do a sub-group analysis of patients admitted as referrals with a diagnosis of OL (to represent
9
10 patients most likely to have neglected OL) to compare them with those that are diagnosed with OL within
11
12 the referral hospital. A second sub-group analysis will be for those patients that give birth more than two
13
14 hours after administration of the study drug, when we expect the effect of the intervention to have worn
15
16 off.
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19 20 **Quality control;** 21

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23 We will conduct a dry run for a period of one month before introducing the intervention. To facilitate the
24
25 training of all the research assistants in the study protocol procedures, filling of study questionnaires using
26
27 the ODK software,[27] accurate measurement of lactate at the bedside using the Lactate Pro 2 device and
28
29 the ideal technique for collection of samples especially blood to avoid haemolysis. The MBN clinical
30
31 laboratories are internationally accredited and they are involved in regular internal and external quality
32
33 control checks.
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35

36
37 The sponsor of this study (Makerere University) does not formally monitor studies to ensure compliance
38
39 and adherence to the standard operating procedures (SOP's) of the study protocol. The PI will check each
40
41 case report form (CRF) on submission for completeness and undertake regular interviews with study staff
42
43 and a sample of the study participants to check on the adherence. In addition, the regulatory bodies such
44
45 as the IRB, UNCST and National Drug Authority (NDA) also carry out regular scheduled and unscheduled
46
47 spot checks to monitor adherence of the study to the approved protocol.
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50 51 **Ethics and dissemination;** 52 53 54 55 56 57

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3 The protocol is approved by the Makerere University School of Medicine Research and Ethics Committee
4 (#REC REF 2017-103), the Uganda National Council for Science and Technology (HS217ES) and the Mbale
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7
8 Regional Referral Research and Ethics Committee(MRRH-REC IN-COM 00/2018). Participant safety;

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10
11 During the study, all the serious adverse events will be actively identified and reported to the IRB within
12
13 24 hours of occurrence. We will adopt and use the School of Medicine Research Ethics Committee
14
15 reporting form. Only qualified health workers will be recruited and trained in the protocol to work as
16
17 Research Assistants on this trial. The independent data monitoring committee will review unblinded data
18
19 when 1/3 of the participants have been enrolled and followed up to completion and report to the sponsor
20
21 of the study. If need arises such as patient safety, the study Steering Committee and the IDMC will request
22
23 the independent study biostatistician to unblind the treatment allocation for a specific patient or group
24
25 of patients without compromising the allocation concealment for the rest of the participants.
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28 29 **Dissemination plan;**

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32 Results will be disseminated to the study participants through the local radio stations and local council
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34 community meeting at the village level. Findings will be shared with colleagues and administrators in
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36 Mbale Regional Referral Hospital/Busitema University Faculty of Health Sciences and the Uganda Ministry
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38 of Health through workshops and seminars. To reach the wider scientific community, the findings will be
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40 published in open access peer reviewed journals and presented at both local and international
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42 conferences. The data sets will be provided free of charge by the primary author on request.
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46 **Patient and Public involvement;**

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48
49 The patients and public were not involved in the design and conceptualisation of this study.
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51 52 **Discussion;**

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3 If the preoperative infusion of sodium bicarbonate is safe and effective in reducing maternal and fetal
4 lactatemia (acidosis) among patients with OL, then the data from this trial will inform the design of future
5 trials that will facilitate the inclusion of sodium bicarbonate infusion in the standard preoperative care for
6 patients with OL in low resource settings. Its adoption will help to mitigate adverse maternal and perinatal
7 outcomes associated with OL as a tertiary preventive measure for intrauterine maternal and fetal
8 resuscitation. Obstructed labour is still an important clinical and public health problem in low resource
9 settings because of the associated maternal and perinatal morbidity and mortality caused by the
10 accompanying electrolyte and metabolic changes. Therefore, identifying an effective, cheap, safe and
11 readily available acid buffer like sodium bicarbonate might offer immense health benefits.
12
13

14
15 In obstructed labour, lactatemia might be a protective mechanism to prevent uterine rupture especially
16 in the multiparous patients and fetal hypoxia by causing relaxation of the myometrium in order to improve
17 fetal placental circulation.[10–12] Therefore, reversal of lactic acidosis might result in stronger uterine
18 contractions and increase the degree of fetal hypoxia or risk of uterine rupture especially if the surgical
19 intervention is delayed. Thus, although this study will help us to understand whether 50 mmol of
20 bicarbonate is effective at reversing lactic acidosis; further studies will be required to ascertain its effects
21 on maternal and fetal morbidity.
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24
25 In the body, sodium bicarbonate (NaHCO_3) rapidly disintegrates into sodium and bicarbonate ions and its
26 effects wear off in 60-90 minutes. It does not cross the placenta, it is unknown if NaHCO_3 is excreted in
27 breast milk and its effects on lactation are unknown. Since we are administering a single low dose
28 preoperatively, we believe that it will have no effect on lactation. This will need further study in the future
29 even if past studies have not reported any adverse effects.[20–22]
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51 **Acknowledgements;**

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1
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4
5 PhD fellowship awarded to me under Busitema University.
6
7

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9
10 this study.
11
12

13 **Author contributions;**

14
15
16 Musaba Milton Wamboko (MMW) conceptualised, designed, developed the protocol and drafted the
17
18 manuscript. Justus K Barageine (JKB), Julius N Wandabwa (JNW), Grace Ndeezi (GN) and Andrew Weeks
19
20 (AW) all participated in the conceptualization, design, development of the protocol and writing of the
21
22 manuscript by providing critical review and refinement of the research idea as supervisors of my PhD
23
24 studies. All the authors reviewed and approved the final draft of the manuscript for submission.
25
26
27

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36
37 (NORAD).
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41 Competing interests statement; None declared
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43 Patients consent; Required
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46 **Ethics approval;**

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49 Provenance and peer review; Not commissioned; externally peer reviewed.
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52 **Open Access;**

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3 Figure1 Flow diagram of study participants in the trial
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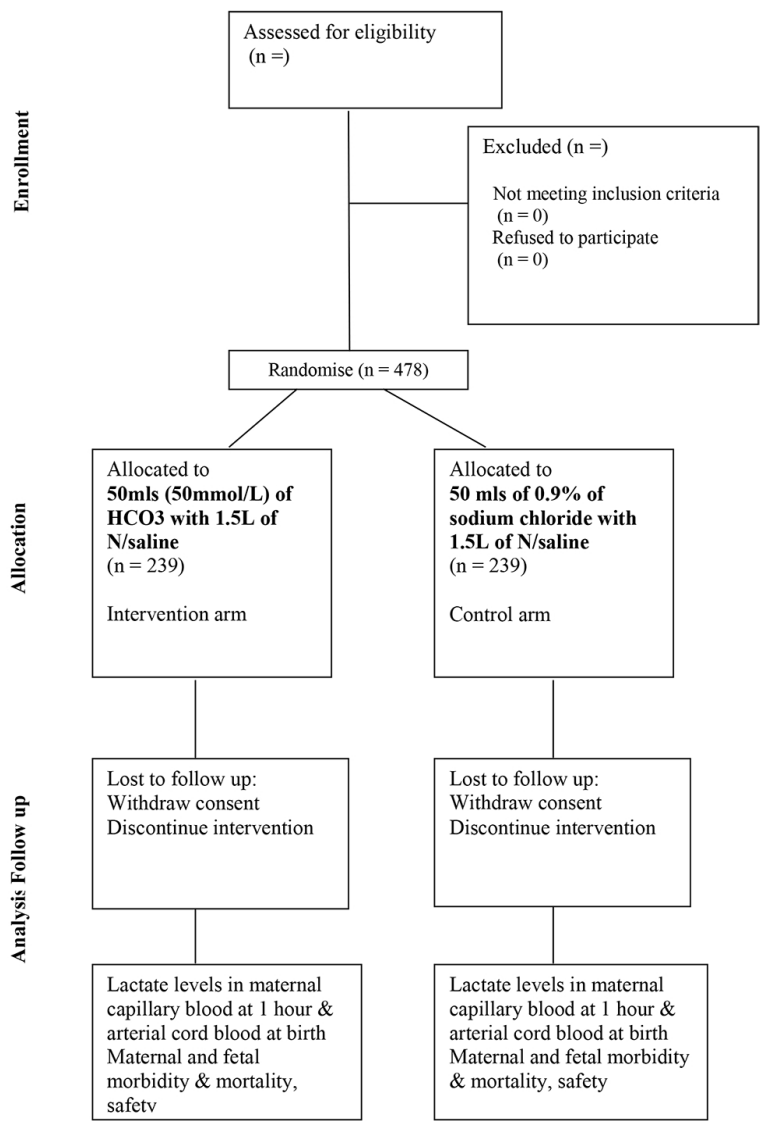


Figure 1; Flow chart of study participants



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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym YES on the title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry YES at the end of the abstract
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier Yes
Funding	4	Sources and types of financial, material, and other support Yes on page 14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Yes on the title page
	5b	Name and contact information for the trial sponsor Yes page 14
	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 Yes page 14
	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) NA
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 Yes page 3 to 5
	6b	Explanation for choice of comparators Yes 6&7
Objectives	7	Specific objectives or hypotheses Yes page 5

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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) Yes page 6
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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 Yes page 6
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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) Yes Page 6&7
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Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Yes page 7 & 8
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	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) NA
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	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) NA
--	-----	---

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial NA
--	-----	---

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 Yes page 8
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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 2)
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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 Yes page 11&10
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Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size NA
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Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions Yes see page 7 under randomisation
8			
9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
11	mechanism		describing any steps to conceal the sequence until interventions are
12			assigned Yes see page 7 under randomisation
13			
14	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
15			and who will assign participants to interventions Yes see page 7
16			under randomisation
17			
18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20			how Yes see page 7 under randomisation
21			
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial Yes see page 7 under randomisation
26			

Methods: Data collection, management, and analysis

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28			
29	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
30	methods		trial data, including any related processes to promote data quality (eg,
31			duplicate measurements, training of assessors) and a description of
32			study instruments (eg, questionnaires, laboratory tests) along with
33			their reliability and validity, if known. Reference to where data
34			collection forms can be found, if not in the protocol Yes see page 11
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36			
37		18b	Plans to promote participant retention and complete follow-up,
38			including list of any outcome data to be collected for participants who
39			discontinue or deviate from intervention protocols NA
40			
41	Data	19	Plans for data entry, coding, security, and storage, including any
42	management		related processes to promote data quality (eg, double data entry;
43			range checks for data values). Reference to where details of data
44			management procedures can be found, if not in the protocol Yes see
45			page 11
46			
47	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
48	methods		Reference to where other details of the statistical analysis plan can be
49			found, if not in the protocol Yes see page 12
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52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses) NA
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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) **NA**

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 **Yes see page 13**

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 **Yes see page 13**

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 **Yes see page 13**

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Yes see page 13**

Ethics and dissemination

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Yes see page 11**

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) **NA**

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (**see attached consent**)

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **NA**

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 **Yes see page 11**

Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site **see page 14**

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 **NA**

1			
2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation (see
4			attached consent form)
5			
6	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
7	policy		participants, healthcare professionals, the public, and other relevant
8			groups (eg, via publication, reporting in results databases, or other
9			data sharing arrangements), including any publication restrictions Yes
10			see page 13
11			
12		31b	Authorship eligibility guidelines and any intended use of professional
13			writers NA
14			
15		31c	Plans, if any, for granting public access to the full protocol, participant-
16			level dataset, and statistical code NA
17			
18	Appendices		
19			
20	Informed consent	32	Model consent form and other related documentation given to
21	materials		participants and authorised surrogates (Attached to submission)
22			
23	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
24	specimens		specimens for genetic or molecular analysis in the current trial and for
25			future use in ancillary studies, if applicable (Yes see attached
26			consent)
27			

28 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
 29 Explanation & Elaboration for important clarification on the items. Amendments to the
 30 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
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BMJ Open

Effect of preoperative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour in Mbale Regional Referral Hospital; A study protocol for a Randomised Controlled Trial

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Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	sodium bicarbonate, obstructed labour, blood lactate level, Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS

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Title:

Effect of preoperative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour in Mbale Regional Referral Hospital; A study protocol for a Randomised Controlled Trial

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ABSTRACT

Introduction

To improve maternal and fetal outcomes among patients with obstructed labour (OL) in low resource settings, the associated electrolyte and metabolic derangements must be adequately corrected. Oral fluid intake during labour and preoperative intravenous fluid replacement following OL corrects the associated dehydration and electrolyte changes, but it does not completely reverse the metabolic acidosis that is a cause of intrapartum birth asphyxia and a risk factor for primary postpartum haemorrhage due to uterine atony.

Sodium bicarbonate is a safe, effective, cheap and readily available acid buffer that is widely used by sportspeople to improve performance. It also appears to improve fetal and maternal outcomes in abnormally progressing labour. However, its effects on maternal and fetal outcomes among patients with OL is unknown. We aim at establishing the effect of a single dose preoperative infusion of sodium bicarbonate on maternal and fetal lactate levels and clinical outcomes among patients with OL.

Methods and analysis

This will be a double blind, randomised controlled clinical phase IIb trial. We will randomize 478 patients with OL to receive either 50 mls of placebo with standard preoperative infusion of Normal Saline (1.5 L) or 4.2 g of sodium bicarbonate solution (50 mls of 50 mmol/L) with the preoperative infusion of Normal Saline (1.5 L). The primary outcome will be mean lactate levels in maternal capillary blood at one hour after study drug administration and in the arterial cord blood at birth. We will use the intention to treat analysis approach. Secondary outcomes will include safety, maternal and fetal morbidity and mortality up to 14 days postpartum.

Ethics and Dissemination

1
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3 Makerere University School of Medicine Research and Ethics Committee and Uganda National Council for
4
5 Science and Technology have approved the protocol. Each participant will give informed consent at
6
7 enrollment. The trial registration number is PACTR201805003364421.
8
9

10 Strengths and limitations of this study;

11
12
13 Strengths.

- 14
15 i. This is among the first studies to investigate the effect of preoperative bicarbonate infusion on maternal and
16 fetal outcomes among patients with OL, using a randomized control design.
17
18 ii. Measurement of maternal lactate levels and fetal cord blood lactate at the bedside using a hand-held device
19 (Lactate Pro 2), instead of a blood gas analyser that is expensive to acquire and operate; in a resource-
20 limited setting.
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24 Limitations.

- 25
26 i. This study will only ascertain the efficacy and not the effectiveness of the preoperative sodium bicarbonate
27 infusion
28
29 ii. Given the short duration of follow up, we will not have any information regarding the long term effects of
30 sodium bicarbonate on maternal and perinatal outcomes.
31
32 iii. Improving maternal and fetal lactate levels may not improve the fetal outcome in OL, as the tocolytic effect
33 of the lactate may be a fetal protective mechanism.
34
35

36
37 **Introduction**

38
39 Globally, the annual number of maternal deaths (MD) has decreased from 532,000 in 1990 to 303,000 in
40 2015.[1,2] But almost all of them (99.6%) occur in Sub Saharan Africa (66.3%) and South Central Asia,[1]
41
42 where it is estimated that the lifetime risk of MD is as high as 1 in 16 and 1 in 46 respectively, compared
43
44 to 1 in 2,800 in developed regions.[1,2] Although, primary postpartum haemorrhage (PPH) and sepsis are
45
46 the leading causes of MD, obstructed labour (OL) indirectly contributes to more than 70% of these deaths.
47
48 [3] Directly, OL causes 8% of all the MD[4,5] and up to 90% of the perinatal deaths due to birth asphyxia.[6]
49
50 In the 2015/16 financial year, of the 246 maternal deaths reported to the Uganda Ministry of Health
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52 (MOH), 9% were due to OL, 39% were due to haemorrhage and 20% were due to sepsis.[7] In addition,
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3 69.3% of 411 perinatal deaths were due to birth asphyxia although the contribution of OL was not
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5 specified.
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8 The prevalence of OL varies from 2– 8 % worldwide. It is highest in low and middle income countries
9
10 (LMICs) and is almost none-existent in developed countries. [4,5] In LMICs many patients experience
11
12 delays in accessing quality emergency obstetric and neonatal care services, so they end up with neglected
13
14 OL which causes significant maternal morbidity (dehydration, uterine rupture, sepsis,
15
16 vesicovaginal/rectovaginal fistulae and postpartum haemorrhage) and neonatal morbidity (asphyxia and
17
18 sepsis).[3,8] Obstructed labour occurs when the fetal presenting part does not descend into the maternal
19
20 pelvis despite adequate uterine contractions. [4] Usually, the obstruction can only be safely relieved by
21
22 an operative delivery.[6] In fact OL is the commonest indication for primary caesarean section and a major
23
24 risk factor for infective morbidity (puerperal and neonatal sepsis) especially in LMICs.[3,9]
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29 Obstructed Labour is associated with higher levels of lactate in blood and amniotic fluid compared to
30
31 normal labour, and this correlates directly with perinatal outcomes.[10] Lactate is a byproduct of
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33 anaerobic respiration that is produced by both the fetus and the myometrium in response to intermittent
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35 hypoxia during labour.[11] In OL, the episodes of hypoxia are prolonged leading to accumulation of lactic
36
37 acid (metabolic acidosis) from anaerobic break down of glucose. Although impaired uterine contractility
38
39 caused by myometrial acidosis increases the risk of primary PPH, it is beneficial to the fetus because it
40
41 increases fetal placental circulation (oxygenation) which is protective against intrapartum birth
42
43 asphyxia.[10,12] The transfer of excess hydrogen ions across the placenta to the fetus is associated with
44
45 low fetal PH, fetal distress and poor APGAR. [13]
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50 Oral bicarbonate is a widely used acid buffer in sports science, to improve physical performance in
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52 vigorous exercises because it can reverse lactic acidosis.[14] Bicarbonate does not cross the placental
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54 barrier,[15] but it plays a key role in regulating the maternal and fetal acid-base chemistry.[13] There are
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3 conflicting reports regarding its benefits in labour. Earlier studies involving the use of Bicarbonate in
4 normal labour showed improvements in pH, base excess and plasma bicarbonate, but none reported
5 APGAR scores. A recent RCT involving the use of oral bicarbonate solution in abnormal (dystocic) labour
6 reported a significant improvement in both maternal and perinatal outcomes. [14] Significantly, none of
7 these studies reported adverse maternal and perinatal effects or included participants with OL. Currently,
8 preoperative intravenous infusion with at least 1.5 L of fluid is recommended as a key element of the
9 standard care. This is adequate to correct the dehydration and electrolyte imbalance but it probably
10 doesn't completely reverse the associated metabolic acidosis.[16,17]

11
12 Various formulations and doses of sodium bicarbonate have been safely used for both clinical indications
13 and research purposes with no reported adverse clinical reactions. A single preoperative infusion of 4.2 g
14 of sodium bicarbonate solution (50 mls of 50 mmol/L) will be given as a single dose at enrolment, since
15 OL is an obstetric emergency that requires urgent intervention. [18] The same dose was used orally in the
16 recent trial in which bicarbonate solution was administered to women with dystocia in labour. [14] The
17 main outcome of this study will be to assess whether bicarbonate changes the maternal and fetal lactate
18 levels among patients with OL. Lactate is easier to measure than full blood gas analysis using maintenance
19 free, battery operated pocket size devices like the lactate Pro2 (Arkray). This device produces accurate
20 results in a short time with a high intraclass correlation coefficient (ICC) which is comparable to that of
21 gold standard in a given population i.e. 0.90 versus 0.92.[18] Lactate is comparable to pH and base deficit
22 with respect to sensitivity, specificity and predictive values of various perinatal complications.[13]

23
24 We hypothesize that supplementation with preoperative sodium bicarbonate infusion as an acid buffer
25 among patients with OL can reduce maternal acidosis at one hour after administration, while their
26 newborns in the bicarbonate group will have less acidosis in cord blood at birth. Bicarbonate is safe,
27 effective, cheap and already widely used.[19] Establishing its effect on maternal and fetal outcomes
28 following OL is necessary because it could be added to the standard preoperative care package as a form

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3 of tertiary prevention. This study aims to establish the effect of a single dose preoperative infusion of
4 sodium bicarbonate on maternal and fetal lactate levels and clinical outcomes among patients with OL.
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8 **Methods/Design**

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10 **Study design**

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12 This will be a superiority, double blind, randomised controlled clinical phase IIb trial. Half of the 478
13 patients with OL will receive the intervention (sodium bicarbonate infusion) with preoperative normal
14 saline infusion, and the other half will receive the standard of care (preoperative saline infusion) alone.
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21 **Study setting**

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23 We will conduct this study in Mbale Regional Referral Hospital located at the heart of Mbale Municipality,
24 214 km to the East of the capital city, Kampala. It is the main referral hospital, serving 14 districts in the
25 Elgon zone, bordering western Kenya. This is a government run, not-for-profit, charge-free, 470-bed
26 hospital with 52 maternity beds. The Department of Obstetrics and Gynaecology has one consultant, two
27 specialists, three medical officers and 21 Midwives. In terms of outputs, the labour and delivery suite is
28 only second to the Mulago National Referral Hospital labour suite. Annually, about 12,000 childbirths
29 occur in this hospital with a caesarean section rate of 35% and nearly 500 mothers have OL. The Ministry
30 of Health has ranked it as the best performing Regional Referral Hospital in Uganda for the last four years.
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43 **Participants**

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45 This study will be carried out among patients with OL admitted to the labour suite in Mbale Regional
46 Referral Hospital for emergency cesarean section during the period of the study. Either a Medical Officer
47 or specialist on duty using the ACOG definition will make the diagnosis of OL. In the first stage of labour
48 she should have cervical dilatation >6cm with ruptured membranes, adequate contractions lasting > 4hrs
49 with no change in cervical dilatation, OR, delay in the second active stage of labour (nullipara > 2hrs,
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3 multipara > 1 hr.) with adequate uterine contractions. IN ADDITION, ANY TWO OF: the obvious signs of
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5 severe obstruction such as caput formation, severe moulding, Bandl's ring, sub-conjunctival hemorrhages,
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7 or an oedematous vulva.
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10 We will include patients with OL carrying singleton, term pregnancies (≥ 37 weeks of gestation) in cephalic
11
12 presentation. We will exclude patients with other obstetric emergencies such as (ante partum
13
14 haemorrhage, Pre-eclampsia and eclampsia (defined as elevated blood pressure of at least 140/90 mmHg,
15
16 urine protein of at least 2+, any of the danger signs and fits), premature rupture of membranes and
17
18 intrauterine fetal death. Patients with comorbidities such as diabetes mellitus, Sickle cell disease, renal
19
20 disease, liver disease & heart disease. We will also exclude those patients with hypokalemia (<3.3
21
22 mmol/L), hypocalcaemia (<8.2 mmol/L), hypernatraemia (> 148 mmol/L) and alkalosis (bicarbonate > 22
23
24 mmol/L) because they are more likely to develop adverse drug reactions.
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29 **Randomization**

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32 An independent biostatistician will generate a sequence of random numbers using the online randomisation
33
34 service of www.sealedenvelope.com in permuted block sizes of four, six and eight. Based on this
35
36 sequence, OL patients will be randomly allocated to either intervention or control arms in a 1:1 ratio. An
37
38 independent pharmacist who is not involved in the recruitment of study participants, will conceal the
39
40 randomization sequence by preparing new labels with sequential numbers to be placed on identical study
41
42 drug packages each containing five similar 10 ml glass vials without the original labels. After consent for
43
44 inclusion is confirmed, a study nurse will take the next study drug package and administer its contents to
45
46 the participant.
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50 **Intervention;**

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53 The intervention will be a preoperative infusion of 50 mls of sodium bicarbonate 8.4% solution equivalent
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55 to 4.2 g or 50 mmol/L of bicarbonate (Martindale Pharma, Essex) in 10 ml glass vials. The sodium
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3 bicarbonate will be administered intravenously as a bolus immediately after recruitment by trained
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5 research assistants who are all experienced midwives working in the labour suite, followed by 1.5 L of
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7 Normal Saline over the next hour.
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10 **Comparator;**

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13 Participants in the control arm will receive a preoperative infusion of Normal Saline, which is part of the
14
15 current standard of care. Fifty mls of sodium chloride 0.9% in identical 10 ml glass vials (AccuHealth Care,
16
17 Gujarat) will be administered intravenously as a bolus immediately after recruitment by trained research
18
19 assistants, who are all experienced midwives working in the labour suite, followed by 1.5 L Normal Saline
20
21 over the next hour.
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24
25 In addition, recruits will receive the standard pre-operative care which includes pre-operative antibiotic
26
27 prophylaxis, at least 1.5 L of intravenous fluids pre-operatively, bladder emptying, administration of
28
29 oxygen, and lying in left lateral position.[16]
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32 **Measurements;**

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35 The primary outcomes in this study will be the mean lactate levels in maternal capillary blood at one hour
36
37 after the onset of study drug administration and in arterial cord blood within 1 minute of birth. We will
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39 measure Lactate at the bedside using a hand-held Lactate Pro 2 device (Arkray Factory Inc. Shiga).
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43 The Secondary maternal outcomes will include myometrial lactate levels at caesarean section, maternal
44
45 mortality up to 14 days postpartum. Other morbidities such as primary PPH, birth canal injuries, duration
46
47 of admission, puerperal sepsis (Persistent fever $>38^{\circ}\text{C}$, Chills and general malaise, Pain in the lower
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49 abdomen, Persistent bloody/pus discharge (lochia) from genital tract, which may have an unpleasant
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51 smell, Tenderness on palpating the uterus Uterine sub-involution, wound dehiscence/ burst
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53 abdomen),[16] fistulae and readmissions. Secondary perinatal outcomes will include mean lactate in
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3 venous cord blood, Apgar score, admission to the NICU, asphyxia, neonatal sepsis (irritability, poorly
4 breastfeeding, bulging anterior fontanelle)[16] and perinatal death up to 7 days postpartum.
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8 For the secondary safety outcomes, we will monitor for the following drug reactions throughout the
9 period of the study. Frequent urge to urinate, continuing headache, continuing loss of appetite, mood or
10 mental changes, muscle pain or twitching, nausea or vomiting, stomach cramps, slow breathing, swelling
11 of feet or lower limbs, unpleasant taste, increased thirst, unusual tiredness or weakness, venous irritation,
12 cellulitis and IV site pain.[20–22]
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19 20 **Sociodemographic, clinical and laboratory characteristics;** 21

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23 Using an interviewer administered questionnaire and available records (antenatal cards, facility registers
24 and case report files), sociodemographic and clinical characteristics will be collected by trained research
25 assistants. At baseline, five mls of blood will be collected in the appropriate vacutainers for a complete
26 blood count, renal function tests, liver function tests and electrolytes. Ten mls of fresh urine will be
27 collected in a sterile container for analysis. All these specimens will be delivered to MBN clinical
28 laboratories within 1 hour of collection for analysis. Figure 1 shows the CONSORT flow diagram for this
29 study. We will follow up patients for up to 14 days postpartum either by phone call if they are discharged
30 or by direct visits if they are still admitted according to the current standard of care for patients with OL
31 in Uganda.
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44 **Sample size and power calculation;** 45

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47 Since the multiple testing in this study will be corrected for at analysis, we estimated the sample size to
48 cater for that. The testing will take place $c=two$ times, the final analysis will use a Bonferroni-Holm
49 correction to adjust for multiplicity and the critical value will divide the α level by c .
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To detect a $\Delta = 15\%$ difference in mean lactate levels between the intervention and control arms. Assuming an equal number of participants in each group, a two-sided significance level α of 0.05 for a 95% confidence interval, a power $(1 - \beta)$ of 90%, an allowance of $c =$ two multiple comparisons and a Bonferroni-Holm method for comparison of means, we used the formula, $n \geq (Z_{1 - \frac{\alpha}{2c}} + Z_{1 - \beta})^2 2 \left(\frac{SD}{\Delta}\right)^2$ [23] and Open Epi [24] to determine the sample size. Where $Z_{1 - \frac{\alpha}{2c}} = Z_{1 - \frac{0.05}{2*2}} = Z_{1 - 0.0125} = 2.24$ and $Z_{1 - \beta} = Z_{1 - 0.1} = Z_{0.9} = 1.28$ using standard normal tables.

The mean and standard deviation (SD) of the maternal venous lactate at the end of second stage of labour is 2.6 ± 1.0 mmol/L[25] without any use of bicarbonate. To detect a difference of 15% (0.39 mmol/L) at one hour and assuming the same S.D. of ± 1 in both arms, 326 participants will be required. Correcting for an attrition rate of 10%, [14] gives a total sample size of 364.

The mean arterial umbilical cord blood lactate at 37 weeks of gestation is 4.3 ± 1.9 mmol/L[26] without any use of bicarbonate. In order to detect a difference of 15% (0.645 mmol/L) at birth and assuming the same S.D of ± 1.9 in both groups, 432 participants will be recruited. Correcting for an attrition rate of 10%, [14] gives a total sample size of 478. We therefore, chose a sample size of 478 to provide adequate power for both hypotheses.

Data collection and management;

Well trained RAs will collect data using a pretested interviewer administered electronic questionnaire on password protected smart phones using the Open Data Kit software.[27] To increase accuracy, the data will be triangulated with a review of relevant health facility records such as the antenatal cards, the maternity and theatre registers, and the participants' case notes. The questionnaire will be coded with checks for internal consistency. Data on sociodemographic, clinical and laboratory parameters will be collected at baseline, at one hour after onset of study drug administration for the primary maternal

outcome, at the time of childbirth for the primary neonatal outcome, and at 7 and 14 days postpartum for the secondary perinatal and maternal outcomes as summarised in table 1. The PI will review the entries from the Google aggregate server every 24 hours to ensure data quality and completeness.

Table 1; Summary of the study procedures and timelines

Procedure	At admission (Baseline)	1 hour after onset of study drug administration	At birth	At 7 days postpartum	At 14 days postpartum
Assessment of eligibility	x				
Randomisation	x				
Data collection for baseline parameters	x				
Study drug administration	x				
Questionnaire administration	x	x	x	x	x
Data collection for primary outcome		x	x		
Data collection for secondary outcome			x	x	x

Statistical analysis;

This will be conducted using STATA version 14 software or higher using the principle of 'intention to treat'. Descriptive statistics will be used to summarise baseline characteristics of the study participants and assess if randomisation was successful. The primary maternal outcome will be the difference in capillary blood lactate levels at one hour after onset of study drug administration. The Bonferroni-Holm method[28,29] will be used to compare the difference in means at baseline and one hour after onset of study drug administration both within and between each of the two arms.

For the primary fetal outcome of mean arterial cord blood lactate at birth, The Bonferroni-Holm method will be used to compare the mean lactate levels in the two arms within 1 minute of childbirth.

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3 The secondary outcomes will be reported as proportions in each of the two arms. Categorical variables
4 will be compared using the Chi-square and Fishers exact tests. Potential confounders and effect modifiers
5 unbalanced at baseline and associated with the outcome ($p < 0.05$) will be adjusted for using multivariable
6 linear or/and logistic regression. Proportions and the number needed to treat/harm (NNT/NNH) will be
7 reported for the secondary maternal and fetal outcomes.
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10 We will do a sub-group analysis of patients admitted as referrals with a diagnosis of OL (to represent
11 patients most likely to have neglected OL) to compare them with those that are diagnosed with OL within
12 the referral hospital. A second sub-group analysis will be for those patients that give birth more than two
13 hours after administration of the study drug, when we expect the effect of the intervention to have worn
14 off.
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17 **Quality control;**

18 We will conduct a dry run for a period of one month before introducing the intervention. To facilitate the
19 training of all the research assistants in the study protocol procedures, filling of study questionnaires using
20 the ODK software,[27] accurate measurement of lactate at the bedside using the Lactate Pro 2 device and
21 the ideal technique for collection of samples especially blood to avoid haemolysis. The MBN clinical
22 laboratories are internationally accredited and they are involved in regular internal and external quality
23 control checks.
24
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26 The sponsor of this study (Makerere University) does not formally monitor studies to ensure compliance
27 and adherence to the standard operating procedures (SOP's) of the study protocol. The PI will check each
28 case report form (CRF) on submission for completeness and undertake regular interviews with study staff
29 and a sample of the study participants to check on the adherence. In addition, the regulatory bodies such
30 as the IRB, UNCST and National Drug Authority (NDA) also carry out regular scheduled and unscheduled
31 spot checks to monitor adherence of the study to the approved protocol.
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Ethics and dissemination;

The protocol is approved by the Makerere University School of Medicine Research and Ethics Committee (#REC REF 2017-103), the Uganda National Council for Science and Technology (HS217ES) and the Mbale Regional Referral Research and Ethics Committee(MRRH-REC IN-COM 00/2018). Participant safety;

During the study, all the serious adverse events will be actively identified and reported to the IRB within 24 hours of occurrence. We will adopt and use the School of Medicine Research Ethics Committee reporting form. Only qualified health workers will be recruited and trained in the protocol to work as Research Assistants on this trial. The independent data monitoring committee will review unblinded data when 1/3 of the participants have been enrolled and followed up to completion and report to the sponsor of the study. If need arises such as patient safety, the study Steering Committee and the IDMC will request the independent study biostatistician to unblind the treatment allocation for a specific patient or group of patients without compromising the allocation concealment for the rest of the participants.

Dissemination plan;

Results will be disseminated to the study participants through the local radio stations and local council community meeting at the village level. Findings will be shared with colleagues and administrators in Mbale Regional Referral Hospital/Busitema University Faculty of Health Sciences and the Uganda Ministry of Health through workshops and seminars. To reach the wider scientific community, the findings will be published in open access peer reviewed journals and presented at both local and international conferences. The data sets will be provided free of charge by the primary author on request.

Patient and Public involvement;

The patients and public were not involved in the design and conceptualisation of this study.

Discussion;

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3 If the preoperative infusion of sodium bicarbonate is safe and effective in reducing maternal and fetal
4 lactatemia (acidosis) among patients with OL, then the data from this trial will inform the design of future
5 trials that will facilitate the inclusion of sodium bicarbonate infusion in the standard preoperative care for
6 patients with OL in low resource settings. Its adoption will help to mitigate adverse maternal and perinatal
7 outcomes associated with OL as a tertiary preventive measure for intrauterine maternal and fetal
8 resuscitation. Obstructed labour is still an important clinical and public health problem in low resource
9 settings because of the associated maternal and perinatal morbidity and mortality caused by the
10 accompanying electrolyte and metabolic changes. Therefore, identifying an effective, cheap, safe and
11 readily available acid buffer like sodium bicarbonate might offer immense health benefits.
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15 In obstructed labour, lactatemia might be a protective mechanism to prevent uterine rupture especially
16 in the multiparous patients and fetal hypoxia by causing relaxation of the myometrium in order to improve
17 fetal placental circulation.[10–12] Therefore, reversal of lactic acidosis might result in stronger uterine
18 contractions and increase the degree of fetal hypoxia or risk of uterine rupture especially if the surgical
19 intervention is delayed. Thus, although this study will help us to understand whether 50 mmol of
20 bicarbonate is effective at reversing lactic acidosis; further studies will be required to ascertain its effects
21 on maternal and fetal morbidity.
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25 In the body, sodium bicarbonate (NaHCO_3) rapidly disintegrates into sodium and bicarbonate ions and its
26 effects wear off in 60-90 minutes. It does not cross the placenta, it is unknown if NaHCO_3 is excreted in
27 breast milk and its effects on lactation are unknown. Since we are administering a single low dose
28 preoperatively, we believe that it will have no effect on lactation. This will need further study in the future
29 even if past studies have not reported any adverse effects.[20–22]
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51 **Acknowledgements;**

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3 We thank the PI of the Survival Pluss Project and all his Co-Investigators for funding this work through a
4
5 PhD fellowship awarded to me under Busitema University.
6
7

8 We thank Felix Wamono from the School of Statistics and planning for providing the statistical support on
9
10 this study.
11
12

13 **Author contributions;**

14
15
16 Musaba Milton Wamboko (MMW) conceptualised, designed, developed the protocol and drafted the
17
18 manuscript. Justus K Barageine (JKB), Julius N Wandabwa (JNW), Grace Ndeezi (GN) and Andrew Weeks
19
20 (AW) all participated in the conceptualization, design, development of the protocol and writing of the
21
22 manuscript by providing critical review and refinement of the research idea as supervisors of my PhD
23
24 studies. All the authors reviewed and approved the final draft of the manuscript for submission.
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27

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29
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32
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34
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36
37 (NORAD).
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41 Competing interests statement; None declared
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43 Patients consent; Required
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46 **Ethics approval;**

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49 Provenance and peer review; Not commissioned; externally peer reviewed.
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52 **Open Access;**

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3 Figure1 Flow diagram of study participants in the trial
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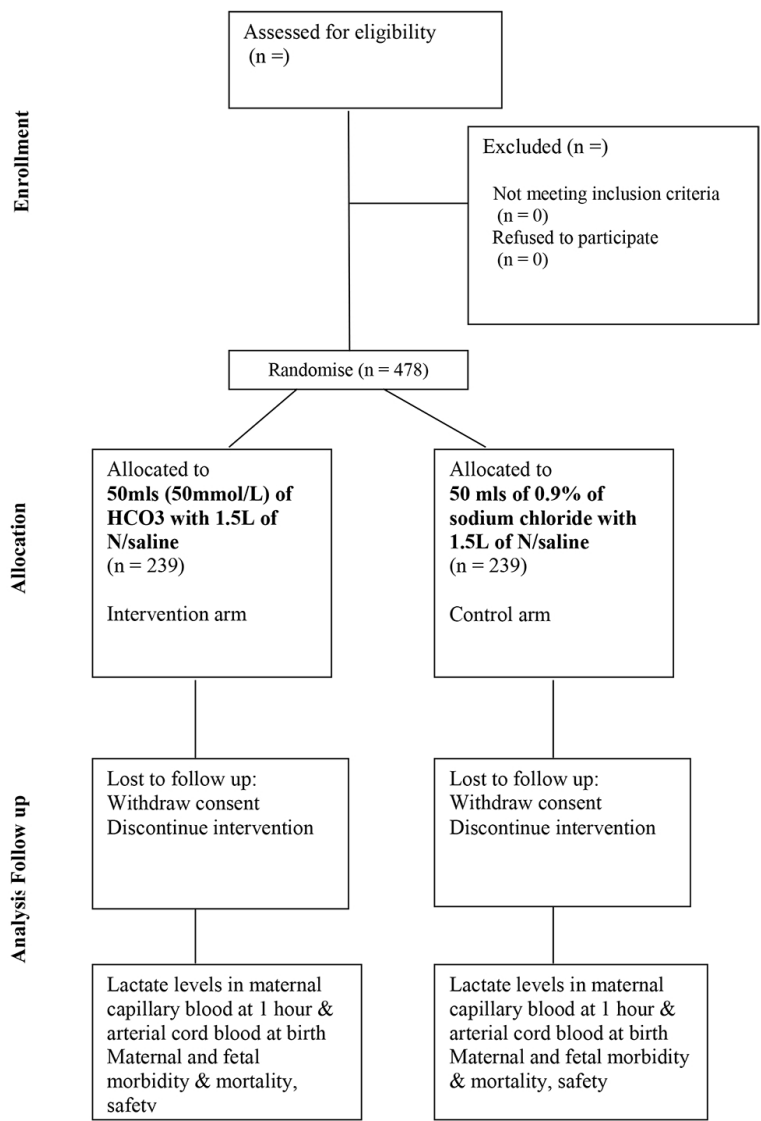


Figure 1; Flow chart of study participants



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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym YES on the title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry YES at the end of the abstract
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier Yes
Funding	4	Sources and types of financial, material, and other support Yes on page 14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Yes on the title page
	5b	Name and contact information for the trial sponsor Yes page 14
	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 Yes page 14
	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) NA
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 Yes page 3 to 5
	6b	Explanation for choice of comparators Yes 6&7
Objectives	7	Specific objectives or hypotheses Yes page 5

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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) Yes page 6
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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 Yes page 6
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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) Yes Page 6&7
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Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Yes page 7 & 8
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	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) NA
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	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) NA
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	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial NA
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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 Yes page 8
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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 2)
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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 Yes page 11&10
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Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size NA
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Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions Yes see page 7 under randomisation
8			
9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
11	mechanism		describing any steps to conceal the sequence until interventions are
12			assigned Yes see page 7 under randomisation
13			
14	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
15			and who will assign participants to interventions Yes see page 7
16			under randomisation
17			
18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20			how Yes see page 7 under randomisation
21			
22		17b	If blinded, circumstances under which unblinding is permissible, and
23			procedure for revealing a participant's allocated intervention during
24			the trial Yes see page 7 under randomisation
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Methods: Data collection, management, and analysis

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29	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
30	methods		trial data, including any related processes to promote data quality (eg,
31			duplicate measurements, training of assessors) and a description of
32			study instruments (eg, questionnaires, laboratory tests) along with
33			their reliability and validity, if known. Reference to where data
34			collection forms can be found, if not in the protocol Yes see page 11
35			
36		18b	Plans to promote participant retention and complete follow-up,
37			including list of any outcome data to be collected for participants who
38			discontinue or deviate from intervention protocols NA
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41	Data	19	Plans for data entry, coding, security, and storage, including any
42	management		related processes to promote data quality (eg, double data entry;
43			range checks for data values). Reference to where details of data
44			management procedures can be found, if not in the protocol Yes see
45			page 11
46			
47	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
48	methods		Reference to where other details of the statistical analysis plan can be
49			found, if not in the protocol Yes see page 12
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51		20b	Methods for any additional analyses (eg, subgroup and adjusted
52			analyses) NA
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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) **NA**

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 **Yes see page 13**

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 **Yes see page 13**

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 **Yes see page 13**

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Yes see page 13**

Ethics and dissemination

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Yes see page 11**

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) **NA**

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (**see attached consent**)

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **NA**

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 **Yes see page 11**

Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site **see page 14**

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 **NA**

1			
2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation (see
4			attached consent form)
5			
6	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
7	policy		participants, healthcare professionals, the public, and other relevant
8			groups (eg, via publication, reporting in results databases, or other
9			data sharing arrangements), including any publication restrictions Yes
10			see page 13
11			
12		31b	Authorship eligibility guidelines and any intended use of professional
13			writers NA
14			
15		31c	Plans, if any, for granting public access to the full protocol, participant-
16			level dataset, and statistical code NA
17			
18	Appendices		
19			
20	Informed consent	32	Model consent form and other related documentation given to
21	materials		participants and authorised surrogates (Attached to submission)
22			
23	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
24	specimens		specimens for genetic or molecular analysis in the current trial and for
25			future use in ancillary studies, if applicable (Yes see attached
26			consent)
27			

28 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
 29 Explanation & Elaboration for important clarification on the items. Amendments to the
 30 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
 31 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)"
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