The Rule of THUMB trial

Multi-centre cluster trial evaluating the implementation of a perioperative care complex intervention to improve outcomes following haemorrhage during and after caesarean section in eight hospitals in four countries (Ethiopia, South Africa, Tanzania, and Uganda).

Study

To evaluate whether implementation of the 'Rule of THUMB' perioperative complex intervention increases risk assessment and improves, diagnosis and compliance with proven interventions for haemorrhage during and after caesarean section. A mixed-methods process evaluation of the trial intervention.

Statistical Analysis Plan (SAP)

Version 1.0

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Based on "Rule of THUMB protocol version 1.0 HREC approved"

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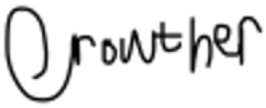
Signature	
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Remit of the SAP

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the paper of the THUMB study documenting the perioperative interventions to improve outcomes related to haemorrhage before and after caesarean section in African hospitals. It is important to set these out and to agree them in advance of inspecting the outcome data for the study, so that data derived decisions in the analysis are avoided. Any exploratory, post hoc, or unplanned analysis will be clearly identified as such in the statistical analysis report.

Timing of the SAP

The SAP version 1.0 was written prior to analysis and prior to those writing the SAP having access to the trial data.

1. Study Summary

Short title	**Rule of THUMB**
Methodology	A multi-centre cluster trial.
Research sites	Maternity units in eight hospitals in four countries (Ethiopia, South Africa, Tanzania, and Uganda).
Primary objective and outcomes	To evaluate whether implementation of the 'Rule of THUMB' perioperative complex intervention increases the number of risk assessment and improves, diagnosis and compliance with proven interventions for haemorrhage during and after caesarean section, by evaluating the following: 1. Number of patients assessed as high-risk for postpartum haemorrhage 2. Number of patients with administration of uterotonics intra- or postoperatively 3. Number of patients with administration of tranexamic acid intra- or postoperatively 4. Number of patients with uterine massage intra- or postoperatively after delivery of the baby 5. Number of high-risk patients who received a postoperative clinician visit within four hours of discharge to the ward
Secondary objective and outcomes	To evaluate the effect of the trial intervention on the following patient outcomes: 1. The number of patients with a diagnosis of postpartum haemorrhage 2. 30 day in-hospital mortality 3. Number of patients with a repeat laparotomy for suspected haemorrhage 4. Duration of hospital stay 5. The number of patients referred to higher level of care for further management of bleeding/resuscitation
Number of patients	Amongst the four participating countries, eight hospitals were included in the study. We intended to sample approximately 800 caesarean sections for the control data collection period, and 800 caesarean sections for the transition period, and 800 for the implementation period. Total data set is expected to include approximately 2400 patients (800 in the control period, 800 in the transition period and 800 in the implementation period).

Inclusion criteria	Hospitals: Hospitals in participating countries that have an established maternity service that routinely perform caesarean section. Patients: Any female patient who requires a caesarean section.
Exclusion criteria	Hospitals: Hospitals that do not consent to be part of the trial; hospitals that do not run a 24-hour caesarean section theatre service. Patients: Patients who opt out of the trial will be excluded.
Trial design	Patients in the control phase received the current standard postoperative care at their hospital. The intervention (a quality improvement programme) was then implemented by the unit for all patients, aimed at delivering care that is already known to be effective in delivering better patient outcomes. This included a transition period, which was then followed by the implementation period. All patients were part of the quality improvement programme, but they were allowed to opt out of data collection.
Patient follow-up	Until hospital discharge or 30 days from surgery, whichever occurs first
Data collection duration	The duration of the entire study was six months from beginning of the control period to the end of the implementation period. All patients were followed until hospital discharge or censored at 30 days
Proposed start date	June 2025
Proposed end date	June 2026

2. Introduction

Obstetric haemorrhage is the leading cause of maternal death worldwide, 99% of which occurs in low- and middle-income countries.[1] A systematic review of studies between 1990 and 2017 reported that women in low- and middle-income countries who had a caesarean section were more likely to die, and one third died from postpartum haemorrhage.[2] Evidence from the recent African Surgical Outcomes Study (ASOS) shows that caesarean section is associated with maternal deaths in Africa, with postpartum haemorrhage contributing up to 25% of cases. Maternal mortality following caesarean section in this African study was 50 times higher than in high-income countries, and mostly driven by peripartum haemorrhage and anaesthesia complications.[3] In 2014, a World Health Organisation survey on global maternal deaths highlighted caesarean section as one of the key factors associated with the diagnosis of postpartum haemorrhage.[4]

Few complex interventions for perioperative maternal haemorrhage have been tested in caesarean section, and many studies have not given due attention to processes of care, which may have a significant impact on outcomes in low- and middle-income countries. Despite the progress in postpartum haemorrhage research in these areas, there remains an important gap in the clinical evidence to define optimal care for patients at high risk of postpartum haemorrhage following caesarean section. Recent studies have examined a combination of interventions consisting of checklists, care bundles, or interlinked complex interventions. These interventions, mainly tested in patients having vaginal delivery or low-risk caesarean section, have shown positive results in reducing the incidence of complications and deaths due to postpartum haemorrhage.[5] A Delphi consensus study in 2022 found that many health professionals recommended a surgical safety checklist and routine risk assessment.[6]

The E-MOTIVE trial (a cluster randomised trial) showed that early detection of blood loss by objective measurement, combined with bundled care, improved patient outcomes following postpartum haemorrhage.[5] The intervention was developed through a robust process that outlined a “first response to postpartum haemorrhage” bundle, and a “response to refractory postpartum haemorrhage” bundle.[7] The E-MOTIVE trial showed improvement in the primary postpartum haemorrhage outcomes (a composite of severe postpartum haemorrhage, laparotomy, and death), in four sub-Saharan African countries. However, this trial included only patients who had undergone vaginal delivery, who were thought to represent a lower risk group than those undergoing caesarean section.

Anders et al reported a multi-stage intervention to prevent deaths from postpartum haemorrhage in Niger over a period of 72 months.[8] The intervention included prevention of postpartum haemorrhage, followed by staged treatment with misoprostol, intrauterine condom balloon tamponade and the use of non-inflatable anti-shock garment. Importantly, the intervention was based on a strong foundation of health care support with training and distribution of supplies, which are known to contribute to improvement in care. This reduced the rate of postpartum haemorrhage from 32% to 10% over a period of five years (2015 to 2020). It provided evidence that staged-care strategies can improve outcomes if based on a strong health care system that is equipped with resources and a trained workforce. Main et al suggested an “obstetric haemorrhage safety bundle” to standardise the multidisciplinary care for postpartum haemorrhage, through a consensus

statement.[9] This bundle provides a framework for improved care of peri- caesarean section haemorrhage.

We developed a complex intervention to improve maternal outcomes for patients undergoing caesarean section based on early diagnosis of haemorrhage during and after surgery coupled to early treatment through first-responder protocolised treatment using a care bundle of five elements called the rule of THUMB. The intervention is essentially a quality improvement programme aimed at delivering better care, care that is already known to be effective in delivering better patient outcomes.

2.1 Aim

To assess whether there is an improvement in haemorrhage outcomes before and after implementation of a perioperative care bundle package during a multi-centre cluster trial.

2.2.1 Primary objectives

To evaluate whether implementation of the 'Rule of THUMB' perioperative complex intervention increases the number of risk assessment, and improves diagnosis and compliance with proven interventions for haemorrhage during and after caesarean section.

2.2.2 Secondary objectives

To evaluate the effect of the trial intervention on patient outcomes relevant to future trials.

2.3.1 Cohort

The cohort include any patient who requires a caesarean section.

2.3.2 Outcomes

2.3.2.1 Primary outcomes

1. Number of patients assessed as high-risk for postpartum haemorrhage

2. Number of patients with administration of uterotonics intra- or postoperatively

3. Number of patients with administration of tranexamic acid intra- or postoperatively

4. Number of patients with uterine massage intraoperatively after delivery, or postoperatively

5. Number of high-risk patients with postoperative clinician visit within four hours of discharge to the ward

2.3.2.2 Secondary outcomes

1. Number of patients with diagnosis of postpartum haemorrhage

2. 30-day in-hospital mortality

3. Number of patients with a repeat laparotomy for suspected haemorrhage within 30 days

4. Duration of hospital stay (censored at 30 days)

5. Number of patients with a referral to higher level of care for further management of bleeding/resuscitation within 30 days

2.3.2.3 Baseline characteristics of the cohort

Patient-specific covariates include:

- Age
- ASA status
- Gravidity
- Parity
- Height (cm)
- Weight (kg)
- Body mass index (derived from height and weight)
- Preoperative haemoglobin
- Preoperative platelet count
- Emergency or elective caesarean section
- Anaesthesia provider
- Obstetric provider
- Type of Anaesthesia
- Administration of vasopressor
- Systolic blood pressure
- Duration of caesarean section
- Estimated blood loss
- Monitoring in recovery
- Recovery needs

Hospital-specific covariates include:

- Hospital level
- Number of hospital beds
- Number of theatres
- Number of critical care beds
- Number of high care beds
- Dedicated caesarean section theatre
- Overall number of caesarean sections per month
- Number of elective caesarean sections per month
- Number of emergency caesarean sections per month
- 24-hour staffed emergency theatre
- Regular education training for staff
- Simulation training for treatment of PPH
- Protocols in place to prevent and treat PPH
- Protocols to refer women to higher level of care
- Ambulance transport to and from centres
- Preoperative risk assessment for PPH
- Critical incident reviews of PPH cases (>1,5L blood loss)
- WHO surgical checklist perioperatively

- Details about the reimbursement status of the hospital.

2.3.3 Definitions

2.3.3.1 Definitions for patient level Primary outcomes

Patient assessment of risk for postpartum haemorrhage (yes/no - binary): Risk assessment performed using a preoperative PPH risk assessment tool in the control period and the mandated risk assessment tool in the transition and implementation periods, and the patient documented to have one or more risk factors prior to commencement of caesarean section.

Administration of uterotonics intra- or postoperatively (yes/no - binary): Uterotonics were administered following delivery of the fetus in accordance with local policy.

Administration of tranexamic acid intra- or postoperatively (yes/no - binary): Tranexamic acid was administered following a diagnosis of postpartum haemorrhage.

Uterine massage intraoperatively after delivery, or postoperatively (yes/no - binary): Uterine massage following delivery of the fetus or diagnosis of postpartum haemorrhage in accordance with local policy.

Postoperative clinician visit within four hours of discharge to the ward (yes/no - binary): A documented postoperative visit for high-risk patients by a clinician (designation of clinician as per local hospital capacity) within four hours of discharge to the ward.

2.3.3.2 Definitions for secondary outcomes

A diagnosis of postpartum haemorrhage (yes/no - binary): Postpartum haemorrhage following caesarean section is defined as blood loss of >500 mL. The diagnostic criteria for estimating that this threshold has been exceeded will be decided at each hospital during the co-design phase.

Some of the options that may be considered are: soaking of swabs (e.g., ≥ 3 soaked tape swabs), suction bottle >500 ml blood, haemodynamic instability (low SBP/high HR) as diagnosed by direct observation of significant/rapid bleeding by the anaesthetist and obstetric surgeon.

30 day in-hospital mortality (alive/dead - binary): Death in-hospital, measured within 30 days following caesarean section. The day of the caesarean section shall be Day 0. Patients discharged prior to Day 30 will be marked as ‘Alive’.

Repeat laparotomy for suspected haemorrhage (yes/no - binary): Did the patient undergo a laparotomy to obtain surgical control of bleeding following caesarean section?

Duration of hospital stay (censored at 30 days) (continuous count): How long did the patient stay in hospital following caesarean section? The day of the caesarean section will be defined as day 0.

Higher level of care (yes/no - binary): whether women were referred to higher level of care for further management of bleeding/resuscitation.

3. Trial design

Control data are collected at all hospitals over a two-week period (usual care period). Thereafter, all hospitals are trained for 2-6 weeks, as required, on the intervention (transition period): comprising two mandatory risk assessments (preoperatively in theatre and postoperatively prior to discharge from the recovery area) which are linked to hospital-specific responses. Assessments for bleeding occurs intraoperatively (through direct vision, haemodynamic changes and/or measurement of blood loss) and postoperatively (with the use of the rapid assessment tool). If bleeding was diagnosed at any point, the THUMB checklist is used to activate bundled care. On discharge from recovery, high-risk patients are scheduled to receive a postoperative ward visit within four hours, where a further assessment for bleeding occurs.

The initial intervention is modified in accordance with data collected during the usual care period. This initial intervention is then used in the transition period. Further intervention refinement occurs after the transition period of data recruitment and will be used in the implementation period. All clusters did not have to commence this process on the same date.

4. Statistical Analysis Plan

4.1 Recruitment / Sample size

This is an international trial in four African countries. We included consecutive patients admitted to eight participating hospitals and undergoing caesarean section. The basis for participation in this trial was opt out i.e., patients were included unless they asked not to be included. All adult patients undergoing caesarean section were eligible for inclusion in the trial.

For the eight hospitals, the expected delivery rate per month is between 500 – 1000. Given an average caesarean section rate of 30%, this will yield 150-300 caesarean sections per month, or 75-150 caesarean sections per two-week period. We therefore expect approximately 100 caesarean sections per hospital per two-week period. This will result in 800 caesarean sections for the control data collection period, and 800 caesarean sections for the transition period, and 800 for the implementation period. Total data set is expected to include approximately 2400 patients (800 in the control period, 800 in the transition period and 800 in the implementation period).

One-level clustering by hospital has been assumed, not accounting for clustering by countries separately. As no intra-cluster correlation (ICC) estimates are available, the resulting power for a range of ICCs is calculated. An ICC in the 0.01-0.1 range seems most likely.

All sample size calculations are for a one-sample proportion tests, testing against a fixed value and accounting for clustering. The fixed values are based on baseline estimates, however, choosing target values might be preferable. System optimisation step rates assumed not used in analyses.

Participation in the study, and completeness of follow-up will be illustrated by a STROBE flow diagram.

Patient recruitment and description will be presented as follows:

- STROBE flow diagram including i) countries, ii) number of eligible patients, iii) patients included and excluded.
- The number of participating hospitals, hospital characteristics and patients at each hospital level will be reported in a table. Detailed hospital characteristics will be provided in a Supplementary Table.
- The patient characteristics of the cohort will be presented in the table.

4.2 Analysis

Outcomes will be presented for the whole cohort. Categorical variables will be described as the number (n/N) and proportions and will be compared using chi-square tests. We will describe continuous variables as either mean and standard deviation or median and inter-quartile range (IQR) based on the data distribution. Comparisons of continuous variables between groups will be performed using t-tests, one-way ANOVA or equivalent non-parametric tests as appropriate.

Basic statistical analyses will be performed using the Statistical Package for the Social Sciences (SPSS) version 28.0.1.1 (SPSS Inc., Chicago, IL, USA) and R statistical software: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing (2024) using Studio: Integrated Development Environment for R. Boston, MA: RStudio, Inc. (2024).

4.2.1 Tables

Table 1. Patient characteristics

	All patient (n=?)	**Control period (n=?)**	**Transition period (n=?)**	**Implementation period (n=?)**	**P-value**
Age (mean (SD)/median (IQR))					
ASA status - I - II - II - IV - V					
Gravidity (mean (SD)/median (IQR))					
Parity (mean (SD)/median (IQR))					
Height (mean (SD)/median (IQR))					
Weight (mean (SD)/median (IQR))					

BMI (mean (SD)/median (IQR))					
Preoperative Hb (mean (SD)/median (IQR))					
Preoperative platelet count (mean (SD)/median (IQR))					
Urgency of caesarean section - Emergency - Elective					
Anaesthesia provider - Non-specialist - Specialist - Non- doctor					
Obstetric provider - Non-specialist - Specialist - Non- doctor					
Type of anaesthesia - General - Spinal - Epidural - Sedation					
Vasopressor administered - Phenylephrine Ephedrine - Adrenaline or noradrenaline - Other - None					
Systolic blood pressure ≤ 80 mmHg (mean (SD)/median (IQR))					

Caesarean section duration (mean (SD)/median (IQR))					
Estimated blood loss (mean (SD)/median (IQR))					
Monitoring in recovery - Heart rate - Blood pressure - Saturation - Respiratory rate - Bleeding - Spinal level					
Recovery needs - Vasopressors needed in recovery - Oxygen dependent in recovery - Rapid assessment tool used					

Table S1: Hospital characteristics

	Resources and activities
Hospital level - Primary - Secondary - Tertiary	
Number of hospital beds (mean (SD)/median (IQR))	
Number of theatres (mean (SD)/median (IQR))	
Number of critical care beds (mean (SD)/median (IQR))	
Number of high care beds (mean (SD)/median (IQR))	

Dedicated caesarean section theatre - Yes - No	
Total number of caesarean sections per month (mean (SD)/median (IQR))	
Number of elective caesarean sections per month (mean (SD)/median (IQR))	
Number of emergency caesarean sections per month (mean (SD)/median (IQR))	
24 hour staffed emergency theatre - Yes - No	
Regular education training for staff - Yes - No	
Simulation training for treatment of PPH - Yes - No	
Protocols for prevention and treatment for PPH - Yes - No	
Protocols to refer women to higher level of care - Yes - No	
Ambulance transport to and from centres - Yes - No	
Preoperative risk assessment for PPH - Yes - No	
Critical incident reviews of PPH cases (>1,5L blood loss) - Yes - No	

WHO surgical checklist perioperatively - Yes - No	
Details of reimbursement status of the hospital - Government - Private - Non-profit	

Table 2: Primary and secondary outcome characteristics

	All patients (n=?)	Control period (n=?)	Implementation period (n=?)	P-value
Primary outcomes				
Identified as high risk for PPH - Yes - No				
Uterotonics administered - Yes - No				
Tranexamic acid given - Yes - No				
Uterine massage performed - Yes - No				
Postoperative visit done - Yes - No				
Secondary outcomes				
Postpartum haemorrhage diagnosed - Yes - No				

30-day in-hospital mortality - Dead - Alive				
Repeat laparotomy - Yes - No				
Duration of hospital stay (mean (SD)/median (IQR))				
Referral to higher level of care - Yes - No				

Table S2: Patient characteristics stratified by country

	All patients (n=?)	Country 1 (n=?)	Country 2 (n=?)	Country 3 (n=?)	Country 4 (n=?)	P-value
Age (mean (SD)/median (IQR))						
ASA status - I - II - II - IV - V						
Gravidity (mean (SD)/median (IQR))						
Parity (mean (SD)/median (IQR))						
Height (mean (SD)/median (IQR))						
Weight (mean (SD)/median (IQR))						
BMI (mean (SD)/median (IQR))						
Preoperative Hb (mean (SD)/median (IQR))						
Preoperative platelet count (mean (SD)/median (IQR))						
Urgency of caesarean section - Emergency - Elective						
Anaesthesia provider - Non-specialist - Specialist - Non- doctor						

Obstetric provider - Non-specialist - Specialist - Non- doctor						
Type of anaesthesia - General - Spinal - Epidural - Sedation						
Vasopressor administered - Phenylephrine Ephedrine - Adrenaline or noradrenaline - Other - None						
Systolic blood pressure ≤ 80 mmHg (mean (SD)/median (IQR))						
Caesarean section duration (mean (SD)/median (IQR))						
Estimated blood loss (mean (SD)/median (IQR))						
Monitoring in recovery - Heart rate - Blood pressure - Saturation - Respiratory rate - Bleeding - Spinal level						
Recovery needs - Vasopressors needed in recovery						

- Oxygen dependent in recovery - Rapid assessment tool used						

Table 3: Characteristics of patients with a peripartum or postpartum haemorrhage

	Intraoperative (n=?)	**Postoperative recovery (n=?)**	**Postoperative ward (n=?)**	**P-value**
Cause of bleeding - Tone - Tissue - Thrombin - Trauma				
Abnormal placentation at caesarean section - Yes - No				
Relook laparotomy - Yes - No				
Uterine trauma - B-Lynch - Artery ligations - Hysterectomy - Tear repaired - Balloon tamponade - Haemostatic sutures				
Transfusion required - Yes - No				
Haemoglobin measurement (mean (SD)/median (IQR))				
Colloid given - Yes				

- No - Not available				
Temperature <35.5° C - Yes - No - Not done				
Called for help - Yes - No				
Uterine massage performed - Yes - No				
Uterotonics given - ≥1 - Long acting - ≥2 boluses				
Monitoring considered - Yes - No				
Bedside visit - Yes - No				

5. References

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