Randomized Trial of Early Detection and Treatment of Postpartum Hemorrhage

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ABSTRACT

BACKGROUND

Delays in detection or treatment of postpartum hemorrhage (PPH) can result in morbidity or death. A blood collection drape can provide objective, accurate and early diagnosis of PPH and delayed or inconsistent use of effective interventions can be addressed by a treatment bundle.

METHODS

We performed a multi-country, cluster randomized trial to assess a multi-component clinical intervention for PPH in women undergoing vaginal delivery. The intervention included: a calibrated blood collection drape for **E**arly PPH detection and a bundle of first-response treatments (uterine **M**assage, **O**xytocic drugs, **T**ranexamic acid, **I**ntra**V**enous fluids and **E**xamination and **e**scalation ["E-MOTIVE"]), supported by an implementation strategy. Control clusters received usual care. The primary outcome was a composite of severe PPH (blood loss ≥1000mL), laparotomy for bleeding, or maternal death from bleeding.

RESULTS

Eighty secondary-level hospitals across Nigeria, Kenya, Tanzania and South Africa, involving 210,132 women with vaginal births, were randomized to E-MOTIVE or usual care. The primary outcome occurred in 1.6% in the E-MOTIVE group vs 4.3% in the control group (risk ratio [RR] 0.40; 95% confidence interval [CI] 0.32 to 0.50; P<0.001). PPH was detected in 93% in the E-MOTIVE group vs 51% in the usual care group (RR 1.58, 95% CI 1.41 to

1.76), and the treatment bundle was used in 91% vs 19%, respectively (RR 4.94, 95% CI 3.88 to 6.28).

CONCLUSIONS

Early PPH detection and bundled treatment reduced severe PPH and associated adverse outcomes in women following vaginal delivery.

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INTRODUCTION

Postpartum hemorrhage (PPH), defined as a blood loss ≥500 mL after birth, accounts for 27% of maternal deaths worldwide.[1,2] The World Health Organization (WHO) has published and updated several evidence-informed recommendations for the prevention and treatment of PPH.[3,4] Despite the best efforts to adopt and scale up the use of these recommendations, PPH remains the leading cause of maternal mortality and morbidity globally.[1,2] Three key challenges contribute to this lack of progress.

The first challenge is that PPH is often undetected or detected late; thus life-saving treatment is not promptly initiated. In a large multi-country randomized trial of PPH prophylaxis (n=29,645),[5] only 53% (of women who developed PPH were diagnosed and treated with a uterotonic drug. The current approach for blood loss assessment at birth is visual estimation, which is widely recognized to be inaccurate and tends to underestimate blood loss.[6]

The second challenge is delayed or inconsistent use of interventions for PPH management. PPH treatments are often administered in a sequential manner; a healthcare provider administers an intervention and waits to see whether it has had an effect, before administering another intervention.[7] However, PPH is a time-critical condition, and delaying the use of life-saving interventions can result in loss of lives. Some effective PPH interventions may not be used at all. For example, a survey of the hospitals in Nigeria, Kenya, Tanzania, and South Africa found that tranexamic acid was used late and most often as a last resort for women requiring surgery for PPH.[8]

The third challenge is that despite the availability of clear PPH recommendations and their wide dissemination, uptake is poor at the point of care.[9] Our previous work identified several barriers to implementation including limited staffing, lack of relevant PPH knowledge and skills, lack of self-efficacy, lack of engagement from healthcare providers, and professional attitudes that discouraged task sharing.[9]

We designed a cluster randomized trial to assess a multi-component strategy for detection and treatment of PPH following vaginal delivery.

METHODS

STUDY DESIGN AND OVERSIGHT

The E-MOTIVE trial was a multi-country, parallel-cluster randomized trial with a baseline control phase, along with mixed-methods evaluation. A cluster design was necessary as the intervention was delivered at the hospital level, targeting healthcare providers. The trial was approved by the University of Birmingham, the WHO Ethics Review Committee (formative phase), and the relevant ethics and regulatory review committees in each country. Between August and October 2021, all participating hospitals entered a 7-month baseline period in which they followed usual care for PPH. After this 7-month baseline period, hospitals were randomized sequentially as they approached the end of their allocated baseline phase (1:1 ratio) to continue usual care or to receive the E-MOTIVE intervention for seven months, allowing two months for transition to train, implement and embed the intervention in practice. A minimization algorithm generated by an independent statistician was used to ensure balance between the intervention and usual care hospitals within each country for key prognostic variables including 1) number of vaginal births per hospital (dichotomized using median during baseline phase), 2) prevalence of the primary outcome during baseline phase (dichotomized using median during baseline phase), 3) quality of oxytocin (dichotomized as high or low quality based on percentage of active ingredient contained in the product)[10] and 4) number of hospitals per country (count). During the 7-month intervention phase, we conducted mixed-methods process evaluations to assess implementation outcomes. Study oversight and monitoring were provided by a Trial Steering Committee and an Independent Data Monitoring Committee . The first two and last two authors vouch for the accuracy and

completeness of the data and analyses and for the compliance of the trial to the protocol, available with the full text of this article at NEJM.org.

STUDY PARTICIPANTS

Hospitals were the randomization unit. We included secondary-level hospitals in Kenya, Nigeria, Tanzania, and South Africa. Hospitals were eligible for inclusion if they were geographically and administratively distinct from each other, had between 1000 and 5000 vaginal births a year, and were able to provide comprehensive obstetric care with the ability to perform surgery for PPH. We excluded hospitals that already implemented a bundle for treatment of PPH. Written permission was granted by each participating hospital for clinical staff employed in that hospital to extract anonymized clinical outcome data for each vaginal birth.

THE E-MOTIVE INTERVENTION AND USUAL CARE

The intervention consisted of a calibrated drape for early detection of PPH, which triggered the 'first response' treatment bundle (Figure 1 and Supplementary Appendix) ("MOTIVE"), based on the WHO recommendations, including uterine Massage, Oxytocic drugs, Tranexamic acid, IV fluids and Examination and Escalation (Figure 1 and Supplementary Appendix). Implementation was supported by several components, including the use of PPH trolleys or carry cases; simulation-based, on-site training; local champions, and audit and feedback of actionable data to providers (Supplementary Appendix). The implementation strategy was informed by the findings from our formative research,[8,9] and refined during multi-professional workshops in each of the participating countries. The intervention was piloted and refined in three hospitals in each country that did not participate in the main trial.

The control facilities, where usual care was provided, estimated blood loss visually and used PPH interventions in accordance with local or national guidelines. The interventions were often administered sequentially, with oxytocic drugs given as first-line treatment, and tranexamic acid reserved for refractory bleeding. Uncalibrated drapes, without alert or action lines, were used in the control facilities to quantify blood loss for the purpose of the trial.

The medications (oxytocic drugs, tranexamic acid) and IV fluids used in the trial were obtained using existing procurement pathways and sourced from local stocks at the hospitals. Samples of medications from the participating hospitals were analyzed according to the International (oxytocin) and British Pharmacopeia (tranexamic acid) standards to ensure they were of adequate quality (Supplementary Appendix).[10] The drapes were manufactured and supplied by Excellent Fixable Drapes, India. Commercial suppliers and contractors had no role in the design of the study, the collection, analysis, or interpretation of the data or the writing of the report.

OUTCOME MEASURES

The primary outcome was a composite of three clinical outcomes following vaginal birth: 1) primary severe PPH defined as blood loss ≥1000 mL following vaginal birth, measured at 1 hour, and if there was continued bleeding, for up to two hours postpartum; 2) postpartum laparotomy for bleeding at any time up to discharge from hospital; or 3) maternal death from bleeding at any time up to discharge from the hospital. Blood loss was objectively measured using a blood collection drape. *Uncalibrated* drapes were used in the usual care facilities to collect blood loss data; *Calibrated* drapes were used in the intervention facilities to enable early and accurate diagnosis of PPH as well as collect blood loss data. Blood loss data were source-verified by capturing a photograph of the drape with collected blood inside it, positioned on a digital weighing scale, with the weight visible on the photograph. Only data with source data verification were used in the analysis for blood loss outcomes following the

recommendation of the Independent Data Monitoring Committee and Trial Steering Committee after data reliability concerns were raised at an external pilot site. A Blinded Endpoint Review Committee (BERC) assessed case summaries to confirm if any postpartum laparotomy or maternal death was due to bleeding.

Pre-specified key secondary implementation outcomes were PPH detection rate (women diagnosed as having a PPH by the birth attendants out of the total number of women who had a PPH as objectively measured in the blood collection drape), and compliance with the MOTIVE bundle (women treated with the bundle following a diagnosis of PPH by the birth attendants out of the total number of women who had objectively measured PPH). Compliance with the bundle was defined as adherence to at least three core bundle elements: administration of oxytocic drugs, tranexamic acid and IV fluids.

Other secondary outcomes included the individual components of the composite outcome, blood loss as a continuous variable, PPH (defined as blood loss ≥500 mL), all-cause mortality, overall blood transfusion and blood transfusion for PPH, uterine tamponade use, intensive care unit admissions or higher-level hospital transfers, newborn deaths, implementation outcomes and resource use outcomes. The independent data monitoring committee monitored maternal deaths and intensive care admissions as markers of serious adverse events.

A detailed list of all secondary outcomes is provided in the Supplementary Appendix, available at NEJM.org.

STATISTICAL ANALYSIS

For 90% power at 5% significance to detect a change from 4% to 3% (25% relative reduction) in the primary outcome, allowing for clustering, and for varying cluster sizes across most realistic scenarios, at least 72 clusters were required (inflated to 80 clusters to

allow for 10% dropout). All analyses were performed according to the intention to treat principle. A full sample size justification is provided in the study protocol.

The primary comparison was between those clusters randomized to E-MOTIVE versus those randomized to usual care. For the primary outcome, we fitted a generalized linear mixed model incorporating a constrained baseline analysis.[11] We used the binomial distribution and logit link, followed by marginal standardization to estimate risk differences and risk ratios. All analyses are adjusted for clustering using random cluster and cluster by period effects, and used robust standard errors. The primary analysis was unadjusted, except for factors used in the randomization method (number of vaginal births per hospital, country, hospital primary outcome proportion and quality of oxytocin per hospital during the baseline phase). A sensitivity analysis additionally adjusted for pre-specified clinically important prognostic factors at the patient level (age, birthweight, parity, multiple pregnancy, and mode of birth. Finally, we allowed for missing covariate data using multiple imputation and an evaluation of none missing at random patterns under a tipping point analysis (all allowing for clustering and a number of auxiliary covariates).

We analyzed the treatment effect on the primary outcome in pre-specified subgroups (Table S1). Summaries of data (numbers and percentages by allocated arm) on the primary outcome, maternal deaths and intensive unit admissions were provided to the IDMC by the trial statistician (who remained unaware of the allocations) once after randomization. Because the interim analyses were performed using the Peto principle,[12] no adjustment was made in the final P value to determine significance. Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, those results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes. All analyses were carried out using STATA v17.

RESULTS

HOSPITAL AND WOMEN'S CHARACTERISTICS

One hundred and four secondary-level hospitals were assessed for eligibility. Fourteen hospitals were excluded because they already implemented early detection or a PPH bundle. Ninety hospitals started the baseline pre-randomization in Nigeria, Kenya, Tanzania, South Africa and Pakistan (Figure 2). These facilities were representative of our target population (Table S2). The independent DMC recommended completion of the trial before hospitals in Pakistan could be randomized, since the required sample size had been achieved in the other four countries. Two hospitals in Kenya could not implement the full trial protocol including source data verification requirements for blood loss measurements, so were excluded prior to randomization. The remaining hospitals stayed in the baseline phase providing usual care for 7 to 8 months (Figure 2). Eighty hospitals in Nigeria, Kenya, Tanzania, and South Africa were randomized, with 40 allocated to E-MOTIVE, and the remaining 40 continuing with usual care. Two hospitals in Tanzania, one in each group, did not receive the allocated intervention because of participation in a conflicting program (Figure 2). Following randomization, a two-month transition period was implemented so that the E-MOTIVE intervention could be embedded into clinical practice in the intervention sites. Data collected in both groups during this transition period did not contribute to the analysis. Data for analysis were available from 78 hospitals: 38 from Nigeria, 14 from Kenya, 12 from Tanzania and 14 from South Africa, with a total of 210,132 women (110,473 in the baseline phase, and 99,659 in the intervention phase) giving birth in the hospitals during the study period (Table 1). Source-verified blood loss data were available for 206,455 women (98% follow-up rate), and laparotomy and maternal mortality data were available for all women.

The hospital characteristics, patient characteristics and the availability of essential PPH drugs (oxytocin and tranexamic acid) were similar between groups (Table 1).

OUTCOMES

The primary outcome occurred in 794/48,687 women (1.6%) in the intervention group and 2139/50,044 (4.3%) in the usual care group (risk ratio [RR] 0.40; 95% confidence interval [CI] 0.32 to 0.50; P<0.001; Table 2). The PPH detection rate was 93% in the intervention group vs 51% in the usual care group (RR 1.58, 95% CI 1.41 to 1.76) and bundle use rate 91% vs 19%, respectively (RR 4.94, 95% CI 3.88 to 6.28). The primary outcome rate in the intervention group progressively declined with time after randomization from 3.8% to 1.1% over the 7 months of the intervention phase (Figure 3).

The median blood loss was 160 mL (interquartile range [IQR] 100 – 280 mL) in the intervention group vs 220 mL (IQR 120 – 380 mL) in the usual care group. PPH (blood loss ≥ 500 mL) was diagnosed in 8.5% vs 16.7%, respectively (RR 0.51, 95% CI, 0.44 to 0.60) and severe PPH (blood loss ≥ 1000 mL blood) in 1.6% vs 4.3%, respectively (RR 0.39, 95% CI 0.31 to 0.49). Postpartum blood transfusion for bleeding was used in 1.2% vs 1.9%, respectively (RR 0.71, 95% CI 0.55 to 0.90).

There were 17 maternal deaths in the intervention group vs 28 in the usual care group (RR 0.73, 95% CI 0.40 – 1.31). Twelve and 18 of these deaths, respectively, were attributed to postpartum bleeding.

There were few cases of laparotomy, compression sutures, uterine artery ligation or hysterectomy limiting meaningful inter-group comparisons. The results for all the secondary outcomes are shown in Table 2 and Table S3 and S4.

Exploratory analyses indicated consistent effects across subgroups (Table S5). Results of sensitivity analyses, including analyses with full adjustment for co-variates and with multiple imputation for missing data, were consistent with the primary analysis (Tables S6, S7 and S8).

DISCUSSION

The E-MOTIVE intervention resulted in a 60% reduction in the composite outcome of severe PPH, laparotomy for PPH and maternal death from PPH following vaginal birth across secondary-level hospitals in Nigeria, Kenya, Tanzania, and South Africa. This benefit is presumably attributable to observed improvements in the detection of PPH and use of the WHO 'first response' bundle in the E-MOTIVE facilities.

An important finding is that there was a reduction in the rate of PPH ≥500 mL with the E-MOTIVE intervention. The E-MOTIVE protocol allowed for triggering of the treatment bundle at ≥300 mL of blood loss, if there was an accompanying abnormality in the vital signs or clinical observations. This trigger criterion was commonly used in the E-MOTIVE facilities, resulting in a reduction in the rate of PPH ≥500 mL.

We minimized identification and recruitment bias by using broad inclusion criteria to include all women with vaginal births in the trial hospitals. The analysis approach adjusted for the slight residual imbalance in the baseline phase across treatment arms in proportion with the primary outcome.[11] We took care to avoid contamination between trial groups by ensuring the study hospitals were geographically dispersed and in different administrative areas to the best extent possible. The control hospitals continued with usual care, and had the same access to bundle components and quality-checked medicines as the intervention facilities.

Study limitations warrant consideration. Owing to the pragmatic design, we did not collect information on some clinical outcomes such as post-natal hemoglobin level and anemia rates, or on women's experience of care. Our study was not powered for maternal mortality, but findings for this outcome, albeit uncommon, were in the direction of those for the primary outcome. The uncalibrated drapes used in the control facilities for the purpose of gathering trial outcome data were transparent, and therefore providers would have been able to see

the blood collecting in the drape. To the extent this may have influenced their actions, it would be expected to attenuate the observed effect of the intervention.

Blood loss following birth is currently visually estimated, resulting in underestimation of blood loss and delays in initiating life-saving treatment. A Cochrane review concluded that calibrated drape use improved PPH detection rate when compared with visual estimation (RR 1.86, 95% CI 1.11 to 3.11, high certainty) but had no clear impact on health outcomes.[13]

Results of this large multicenter trial show that the use of a calibrated drape for detection of PPH and a bundle of treatments, supported by a multifaceted implementation strategy, substantially reduces the risk of severe PPH and associated adverse outcomes.

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Table 1. Comparison of hospital and clinical characteristics for E-MOTIVE and usual care groups.

Characteristics	E-MOTIVE (N = 49,101, Clusters = 39)*	Usual Care (N = 50,558, Clusters = 39)*
Hospital		
Number of vaginal births per hospital, median [IQR]	1,136 [775 to 1,881]	1,263 [787 to 1,854]
Availability of bundle components (percentage of time available), median [IQR]		
Oxytocin	100 [100 to 100]	100 [100 to 100]
Tranexamic acid	100 [100 to 100]	100 [100 to 100]
IV Fluid	100 [100 to 100]	100 [100 to 100]
Clinical		
Location of births		
- Kenya	11,475 (23.4)	9,992 (19.8)
- Nigeria	17,300 (35.2)	20,909 (41.4)
- South Africa	9,668 (19.7)	9,030 (17.9)
- Tanzania	10,658 (21.7)	10,627 (21.0)
Age (years), median [IQR]	26 [21, 31]	26 [21, 30]
Previous births		
- 0	17,719 (37.2)	17,642 (36.6)
- 1-4	25,477 (51.9)	25,805 (51.0)
- 5 or greater	4,379 (9.2)	4,781 (9.9)
- Median [IQR]	1 [0, 2]	1 [0, 3]
Previous caesarean section	1456/48,911 (3.0%)	1281/50,364 (2.5%)
Postpartum haemorrhage in previous pregnancy	487/47,869 (1.0%)	405/48,925 (0.8%)
Multiple pregnancy	804 (1.6)	960 (1.9)
Instrumental birth	358 (0.7)	278 (0.5)
Birthweight (g), mean (SD)	3,033 (559)	3,044 (552)
Gestational age (weeks), median [IQR]	39 [37, 40]	38 [37, 39]
Gestational age <37 weeks	6,877 (15.5)	8,565 (17.5)
Antepartum haemorrhage	372 (0.8)	275 (0.6)
Preeclampsia	1,038 (2.2)	1,182 (2.4)
Labour augmented or induced	6,811 (13.9)	9,323 (18.4)

Retained placenta or manual removal of placenta	566 (1.2)	1,072 (2.1)

* Values are number (percentage) unless otherwise stated. N = Number of participants. Clusters = Number of Facilities.

Table 2. Primary, key implementation and secondary outcomes

Outcomes	E-MOTIVE (N = 49,101, Clusters = 39)	Usual Care (N = 50,558, Clusters = 39)	Risk Ratio[1] (95% CI)	P value	Risk Difference[1] (95% CI)	P value
Primary outcome						
Composite of severe postpartum haemorrhage (blood loss ≥ 1000 ml); laparotomy for bleeding; and maternal mortality from bleeding [2]	794/48,678 (1.6)	2,139/50,044 (4.3)	0.40 (0.32 to 0.50)	<0.001	-2.53 (-3.04 to -2.02)	<0.001
Key Secondary Implementation Outcomes						
Postpartum haemorrhage detection [3]	3,870/4,158 (93.1)	4,244/8,299 (51.1)	1.58 (1.41 to 1.76)		33.3 (26.9 to 39.8)	
Compliance with MOTIVE bundle [4]	3,791/4,158 (91.2)	1,623/8,351 (19.4)	4.94 (3.88 to 6.28)		70.2 (64.6 to 75.7)	
Secondary Outcomes						
Postpartum haemorrhage (blood loss ≥ 500 ml) [5]	4,158/48,678 (8.5)	8,351/50,043 (16.7)	0.51 (0.44 to 0.60)	-	-8.15 (-9.74 to -6.56)	-
Severe postpartum haemorrhage (blood loss ≥ 1000 ml) [6]	786/48,678 (1.6)	2,129/50,043 (4.3)	0.39 (0.31 to 0.49)	-	-2.57 (-3.09 to -2.05)	-
Laparotomy for bleeding [7]	12/49,101 (0.02)	7/50,558 (0.01)	1.72 (0.57 to 5.16)	-	0.01 (-0.02 to 0.04)	-
Maternal mortality from bleeding [8]	12/49,101 (0.02)	18/50,558 (0.04)	0.80 (0.38 to 1.68)	-	-0.01 (-0.03 to 0.02)	-
All cause maternal mortality	17/49,101 (0.03)	28/50,558 (0.06)	0.73 (0.40 to 1.31)	-	-0.02 (-0.04 to 0.01)	-
Blood transfusion	1,074/49,101 (2.2)	1,296/50,558 (2.6)	0.87 (0.69 to 1.10)	-	-0.36 (-0.93 to 0.21)	-
Blood transfusion for bleeding [9]	580/49,101 (1.2)	944/50,558 (1.9)	0.71 (0.55 to 0.90)	-	-0.57 (-0.95 to -0.19)	-
Blood loss up to 2 hours postpartum as a continuous variable (mL) [10]	160 [100 to 280]	220 [120 to 380]		-	-84.4 (-103.0 to -64.5)	
Blood loss up to 24 hours postpartum as a continuous variable (mL) [10]	160 [100 to 280]	220 [120 to 380]		-	-84.6 (-103.5 to -62.0)	-

Values are number (percentage) unless otherwise stated. N = Number of participants. C = Number of Facilities (clusters). The widths of the confidence intervals for secondary outcomes have not been adjusted for multiplicity and cannot be used to infer treatment effects.

The intracluster correlation coefficient (ICC) for the primary outcome on the latent scale was 0.011 (95% CI: 0.008 to 0.014). The cluster autocorrelation (CAC) for the primary outcome was 0.61. The ICC and CAC were estimated by fitting a mixed-effects linear model to the data with random effect for cluster and for a cluster-period interaction.

[1] Differences between risks are presented in percentage points, and differences between mean values are presented in the unit of the mean values. Adjusted for cluster-level covariates used in the randomisation (number of vaginal births, postpartum haemorrhage rate, country, and the primary outcome rate) and for imbalances during the baseline period. Baseline data before implementation of the intervention (N = 110,473, Clusters = 78) disaggregated for interventional and usual care sites for each outcome: *Composite primary*: intervention: 1,931/50,721 (3.8), usual care: 2,546/57,012 (4.5); *Postpartum haemorrhage detection*: intervention: 5,097/8,179 (62.3), usual care: 4,971/9,717 (51.2); *Compliance with MOTIVE bundle*: intervention: 1,682/8,194 (20.5), usual care: 1,038/9,779 (10.6); *Postpartum haemorrhage:* intervention: 8,194/50,720 (16.2), usual care: 9,779/57,010 (17.2); *Severe postpartum haemorrhage:* intervention: 1,920/50,720 (3.8), usual care: 2,535/57,010 (4.4); *Laparotomy for bleeding:* intervention: 10/52,003 (0.02), usual care: 12/58,470 (0.02); *Maternal mortality from bleeding:* intervention: 16/52,003 (0.03), usual care: 24/58,470 (0.04); *All cause maternal mortality;* intervention: 29/52,003 (0.06), usual care: 34/58,470 (0.06); *Blood transfusion:* intervention: 1,507/52,003 (2.9), usual care: 1,700/58,470 (2.9); *Blood transfusion for bleeding:* intervention: 991/52,003 (1.9), usual care: 1,176/58,470 (2.0); *Blood loss up to 2 hours postpartum:* intervention: 220 [120 to 380], usual care: 220 [120 to 380]; *Blood loss up to 24 hours postpartum:* intervention: 220 [120 to 380], usual care: 220 [120 to 380].

[2] For severe postpartum haemorrhage, only women with source-verified blood loss data are included. Laparotomy and maternal mortality related to bleeding was determined by a Blinded Endpoint Review Committee (BERC).

[3] Defined as recording of diagnosis of postpartum haemorrhage by birth attendant. Denominator is women with objectively measured postpartum haemorrhage (blood loss ≥ 500 ml).

[4] Defined as adherence with three core elements of the bundle: administration of oxytocic drugs, TXA, and IV fluids. Denominator is women with objectively measured postpartum haemorrhage (blood loss ≥ 500 ml).
[5] For postpartum haemorrhage, only women with source-verified blood loss data are included.
[6] For severe postpartum haemorrhage, only women with source-verified blood loss data are included.
[7] Laparotomy related to bleeding was determined by a Blinded Endpoint Review Committee (BERC).
[8] Maternal mortality related to bleeding was determined by a Blinded Endpoint Review Committee (BERC).
[9] Defined as blood transfusion in women that suffered postpartum haemorrhage (blood loss ≥ 500 ml).
[10] Outcomes were analysed with permutation tests and confidence intervals have been constructed using permutation tests, by finding the upper and lower boundaries of the intervention effect that leads to a two-sided p-values that is less than the 5% level.

Figure 1. The Early detection and treatment of postpartum hemorrhage using the World Health Organization 'first response' bundle intervention (E-MOTIVE)

Early detection & trigger criteria	Massage of uterus	Oxytocic drugs	Tranexamic acid	IV fluids	Examination & escalation
					
■ Calibrated drape for blood loss collection with trigger lines at 300ml and 500ml for the first hour after birth ■ Observations (blood loss, blood flow, uterine tone) every 15 minutes documented on the blood loss monitoring chart ■ Blood pressure and pulse carried out once in the 1st hour postpartum and documented on the blood loss monitoring chart **Trigger criteria** 1) Clinical judgment 2) Blood loss 500ml or more 3) Blood loss 300ml or more plus one abnormal observation	■ Massage until uterus has contracted or for one minute	■ 10 IU IV oxytocin injection or diluted in 200-500ml crystalloid over 10 minutes plus a maintenance dose of 20 IU IV oxytocin diluted in 1000ml saline over 4 hours (± misoprostol 800mcg PR/SL if used)	■ 1g IV injection of tranexamic acid or diluted in 200ml crystalloid over 10 minutes	■ IV fluids in addition to the infusion should be given if clinically indicated for resuscitation and will require a 2nd IV access	■ Ensure bladder is empty, evacuate clots, check for tears with an internal examination and placenta for completeness ■ Escalate if bleeding does not stop after first response or you are unable to identify or manage cause of bleeding
	Implementation strategies **Audit newsletters:** sharing with all staff monthly detection and bundle use rates along with PPH, severe PPH, blood transfusion, laparotomy and death from PPH rates and given feedback at monthly departmental meetings **Champions:** Midwife and doctor to oversee change, troubleshoot, give feedback on audit newsletters, connect with other champions through chats, meetings and websites for sharing knowledge and lessons learnt **Trolley and/or carry case:** including all medicines and devices required for the treatment of PPH restocked after every use and complete a stocking checklist at the start of every shift **Training:** on-site, simulation-based, and peer-assisted training of 90 minutes to a whole day facilitated by the use of provider guides, flipcharts and job aids displayed in labour wards				

Figure 2. Flowchart of recruited hospitals for the E-MOTIVE cluster randomized trial

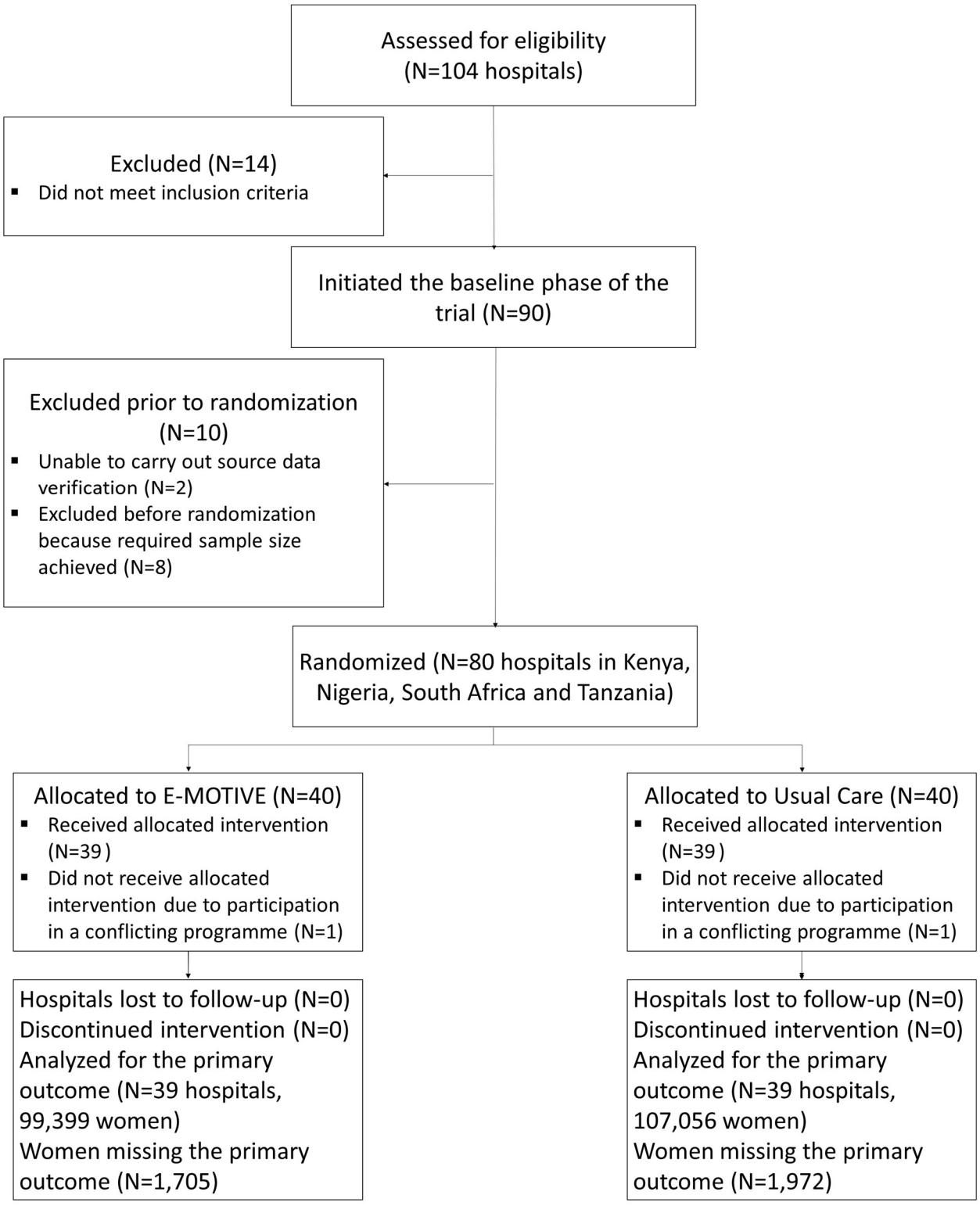

Figure 3. Primary outcome over time for E-MOTIVE and usual care groups