The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 6, 2023 VOL. 389 NO. 1

Randomized Trial of Early Detection and Treatment of Postpartum Hemorrhage

I. Gallos, A. Devall, J. Martin, L. Middleton, L. Beeson, H. Galadanci, F. Alwy Al-beity, Z. Qureshi, G.J. Hofmeyr, N. Moran, S. Fawcus, L. Sheikh, G. Gwako, A. Osoti, A. Aswat, K.-M. Mammoliti, K.N. Sindhu, M. Podesek, I. Horne, R. Timms, I. Yunas, J. Okore, M. Singata-Madliki, E. Arends, A.A. Wakili, A. Mwampashi, S. Nausheen, S. Muhammad, P. Latthe, C. Evans, S. Akter, G. Forbes, D. Lissauer, S. Meher, A. Weeks, A. Shennan, A. Ammerdorffer, E. Williams, T. Roberts, M. Widmer, O.T. Oladapo, F. Lorencatto, M.A. Bohren, S. Miller, F. Althabe, M. Gülmezoglu, J.M. Smith, K. Hemming, and A. Coomarasamy

ABSTRACT

BACKGROUND

Delays in the detection or treatment of postpartum hemorrhage can result in complications or death. A blood-collection drape can help provide objective, accurate, and early diagnosis of postpartum hemorrhage, and delayed or inconsistent use of effective interventions may be able to be addressed by a treatment bundle.

METHODS

We conducted an international, cluster-randomized trial to assess a multicomponent clinical intervention for postpartum hemorrhage in patients having vaginal delivery. The intervention included a calibrated blood-collection drape for early detection of postpartum hemorrhage and a bundle of first-response treatments (uterine massage, oxytocic drugs, tranexamic acid, intravenous fluids, examination, and escalation), supported by an implementation strategy (intervention group). Hospitals in the control group provided usual care. The primary outcome was a composite of severe postpartum hemorrhage (blood loss, ≥1000 ml), laparotomy for bleeding, or maternal death from bleeding. Key secondary implementation outcomes were the detection of postpartum hemorrhage and adherence to the treatment bundle.

RESULTS

A total of 80 secondary-level hospitals across Kenya, Nigeria, South Africa, and Tanzania, in which 210,132 patients underwent vaginal delivery, were randomly assigned to the intervention group or the usual-care group. Among hospitals and patients with data, a primary-outcome event occurred in 1.6% of the patients in the intervention group, as compared with 4.3% of those in the usual-care group (risk ratio, 0.40; 95% confidence interval [CI], 0.32 to 0.50; P<0.001). Postpartum hemorrhage was detected in 93.1% of the patients in the intervention group and in 51.1% of those in the usual-care group (rate ratio, 1.58; 95% CI, 1.41 to 1.76), and the treatment bundle was used in 91.2% and 19.4%, respectively (rate ratio, 4.94; 95% CI, 3.88 to 6.28).

CONCLUSIONS

Early detection of postpartum hemorrhage and use of bundled treatment led to a lower risk of the primary outcome, a composite of severe postpartum hemorrhage, laparotomy for bleeding, or death from bleeding, than usual care among patients having vaginal delivery. (Funded by the Bill and Melinda Gates Foundation; E-MOTIVE ClinicalTrials.gov number, NCT04341662.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Devall can be contacted at a.j.devall@bham.ac.uk or at the Institute of Metabolism and Systems Research, WHO Collaborating Centre on Global Women's Health, College of Medical and Dental Sciences, University of Birmingham, 4th Fl. E., Heritage Bldg., Mindelsohn Way, Edgbaston, Birmingham B15 2TH, United Kingdom.

This article was published on May 9, 2023, at NEJM.org.

This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Accepted Manuscript, which is the author's version after external peer review and before publication in the *Journal*, is available at PubMed Central.

N Engl J Med 2023;389:11-21.
DOI: 10.1056/NEJMoa2303966

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Postpartum hemorrhage, defined as blood loss of at least 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 postpartum hemorrhage.[3,4] Despite strong efforts to adopt and scale up the use of these recommendations, postpartum hemorrhage remains the leading cause of maternal complications and death worldwide.[1,2] Three key challenges contribute to this lack of progress.

The first challenge is that postpartum hemorrhage is often undetected or detected late; thus lifesaving treatment is not promptly initiated. In a large, international, randomized trial of prophylaxis for postpartum hemorrhage in 29,645 participants,[5] only 53% of the participants in whom postpartum hemorrhage developed received a diagnosis and were 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 the management of postpartum hemorrhage. Treatments for postpartum hemorrhage are often administered in a sequential manner; a health care provider administers an intervention and waits to see whether it has had an effect before another intervention is administered.[7] However, postpartum hemorrhage is a time-critical condition, and delays in the use of lifesaving interventions can result in loss of life. Some effective interventions may not be used at all. For example, a survey of hospitals in Kenya, Nigeria, South Africa, and Tanzania showed that tranexamic acid was used late and most often as a last resort in women in whom surgery for postpartum hemorrhage was indicated.[8]

The third challenge is that despite the availability of clear recommendations regarding postpartum hemorrhage and their wide dissemination, uptake is poor at the point of care.[9] In previous work, we identified several barriers to implementation, including limited staffing, lack of relevant knowledge and skills, lack of engagement from health care providers, and professional attitudes that discouraged task sharing.[9] To address these challenges, we designed a cluster-randomized trial to assess a multicomponent strategy for the detection and treatment of postpartum hemorrhage after vaginal delivery.

METHODS

TRIAL DESIGN AND OVERSIGHT

The E-MOTIVE trial was an international, parallel cluster-randomized trial that included a baseline control phase, along with mixed-methods evaluation. A cluster design was necessary because the intervention was delivered at the hospital level, targeting health care providers. The trial was approved by the University of Birmingham, the Ethics Review Committee of the World Health Organization (WHO) (for the formative phase), and the relevant ethics and regulatory review committees in each country.

Between August and October 2021, all the participating hospitals entered a 7-month baseline period during which they provided usual care for postpartum hemorrhage. After this 7-month baseline period, hospitals were randomly assigned, in a 1:1 ratio, in a sequential manner as they approached the end of their assigned baseline phase either to continue providing usual care or to receive the trial intervention for 7 months, with an allowance of 2 months for transition in order to conduct training and to implement and embed the intervention in practice. A minimization algorithm that was generated by an independent statistician was used to ensure balance between the intervention hospitals and usual-care hospitals within each country for key prognostic variables, including the number of vaginal births per hospital (dichotomized with the use of the median value obtained during the baseline phase), the prevalence of primary-outcome events during the baseline phase (dichotomized with the use of the median value obtained during the baseline phase), the quality of oxytocin (dichotomized as high or low quality on the basis of the percent of active ingredient contained in the product),[10] and the number of hospitals per country (count). During the 7-month implementation phase, we conducted mixed-methods process evaluations to assess implementation outcomes.

Trial 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 for the fidelity of the

E	M	O	T	IV	E
Early Detection and Trigger Criteria	**Massage of Uterus**	**Oxytocic Drugs**	**Tranexamic Acid**	**IV Fluids**	**Examination and Escalation**
Calibrated drape for the the collection of blood, with trigger lines at 300 ml and 500 ml for the first hr after birth Observations (blood loss, blood flow, uterine tone) every 15 min documented on the blood-loss monitoring chart Blood pressure and pulse monitored once in the first hr post partum and documented on the blood-loss monitoring chart **Trigger Criteria** Clinical judgment Blood loss ≥500 ml Blood loss ≥300 ml plus one abnormal observation	Massage until uterus has contracted or for 1 min	10 IU IV oxytocin injected or diluted in 200–500 ml crystalloid administered over 10-min period, plus a maintenance dose of 20 IU IV oxytocin diluted in 1000 ml saline administered over 4-hr period (with misoprostol 800 μg if used)	1 g IV tranexamic acid injected or diluted in 200 ml crystalloid administered over 10-min period	IV fluids in addition to the infusion should be given if clinically indicated for resuscitation and will require a second intravenous 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 clinician is unable to identify or manage cause of bleeding

Implementation Strategies

Audit newsletters: Sharing with all staff monthly rates of detection and bundle use, along with rates of PPH, severe PPH, blood transfusion, laparotomy, and death from PPH and giving feedback at monthly departmental meetings

Champions: Midwife and doctor to oversee change, troubleshoot, give feedback on audit newsletters, connect with other champions by means of chats, meetings, and websites for sharing knowledge and lessons learned

Trolley or carry case: Restocking of all medicines and devices used for treatment of PPH after every use and completion of a stocking checklist at the start of every shift

Training: Onsite, simulation-based, and peer-assisted training, lasting from 90 min to an entire workday, facilitated by the use of provider guides, flipcharts, and job aids displayed in labor wards

Figure 1. E-MOTIVE Treatment Bundle.

Early detection and treatment of postpartum hemorrhage (PPH) involved the use of a blood-collection drape and the World Health Organization first-response treatment bundle, which together comprise the E-MOTIVE protocol. Misoprostol may be administered rectally or sublingually. IV denotes intravenous.

trial to the protocol, available with the full text of this article at NEJM.org. Commercial suppliers and contractors had no role in the design of the trial; the collection, analysis, or interpretation of the data; or the writing of the manuscript.

PARTICIPATING HOSPITALS

Hospitals were the randomization unit. We included secondary-level hospitals in Kenya, Nigeria, South Africa, and Tanzania; hospitals in Pakistan were initially included in the baseline phase but could not be included in the randomization process (see below). Hospitals were eligible for inclusion if they were geographically and administratively distinct from each other, had between 1000 and 5000 vaginal births per year, and were able to provide comprehensive obstetrical care with the ability to perform surgery for postpartum hemorrhage. We excluded hospitals that had already implemented a bundle for treatment of postpartum hemorrhage. 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.

E-MOTIVE INTERVENTION AND USUAL CARE

The E-MOTIVE intervention consisted of a calibrated drape for early detection of postpartum hemorrhage and the WHO first-response treatment bundle, which included uterine massage, oxytocic drugs, tranexamic acid, intravenous fluids, and a process for examination and escalation (Fig. 1; and see the Supplementary Appendix, available at NEJM.org). Implementation was supported by several components, including the use of trolleys or carry cases for postpartum hemorrhage; simulation-based, on-site training; local champions (midwives and doctors who lead and support change in participating hospitals); and audit and feedback of actionable data to providers. The implementation strategy was

informed by the findings from our formative research[8,9] and refined during multidisciplinary 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 hospitals, where usual care was provided, estimated blood loss visually and used various interventions for postpartum hemorrhage in accordance with local or national guidelines. These 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 hospitals to quantify blood loss for the purpose of the trial. Drapes were manufactured and supplied by Excellent Fixable Drapes in India.

The medications (oxytocic drugs and tranexamic acid) and intravenous fluids that were used in the trial were obtained by means of existing procurement pathways and sourced from local stocks at the hospitals. Samples of medications from the participating hospitals were analyzed according to the International Pharmacopoeia (oxytocin) and British Pharmacopoeia (tranexamic acid) standards to ensure that they were of adequate quality (see the Supplementary Appendix).[10]

OUTCOME MEASURES

The primary outcome was a composite of three clinical outcomes after vaginal birth: severe postpartum hemorrhage, defined as blood loss of at least 1000 ml after vaginal birth, measured at 1 hour and, if there was continued bleeding, for up to 2 hours post partum; postpartum laparotomy for bleeding at any time up to discharge from the hospital; or maternal death from bleeding at any time up to discharge from the hospital. Blood loss was objectively measured with the use of a blood-collection drape. Uncalibrated drapes were used in the hospitals in the usual-care group to obtain data on blood loss; calibrated drapes were used in the hospitals in the intervention group to enable early and accurate diagnosis of postpartum hemorrhage as well as to obtain data on blood loss. Data on blood loss 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 in the photograph. Only data that had been source-verified were used in the analysis for blood-loss outcomes, according to the recommendation of the independent data monitoring committee and the trial steering committee after data-reliability concerns were raised at an external pilot site. An end-point review committee whose members were unaware of the trial-group assignments assessed case summaries to confirm whether any postpartum laparotomy or maternal death was due to bleeding.

Prespecified key secondary implementation outcomes were the detection of postpartum hemorrhage (assessed in patients with a diagnosis of postpartum hemorrhage recorded by the birth attendants, out of the total number of patients who had a postpartum hemorrhage as objectively measured in the blood-collection drape), and adherence to the treatment bundle (assessed in patients treated with the bundle after a diagnosis of postpartum hemorrhage recorded by the birth attendants, out of the total number of patients in whom postpartum hemorrhage was objectively measured). Adherence to the treatment bundle was defined as adherence to at least three core bundle elements: administration of oxytocic drugs, tranexamic acid, and intravenous fluids.

Other secondary outcomes included the individual components of the primary composite outcome, postpartum hemorrhage (defined as blood loss of ≥500 ml), death from any cause, blood transfusion for any cause, blood transfusion for postpartum hemorrhage, blood loss as a continuous variable, uterine tamponade use, intensive care unit (ICU) admission or higher-level hospital transfer, newborn death, implementation outcomes, and resource-use outcomes. The independent data monitoring committee monitored maternal deaths and ICU admissions as markers of serious adverse events. A detailed list of all the secondary outcomes is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

In order for the trial to have 90% power at 5% significance to detect a change from 4% to 3% (a 25% relative reduction) in the risk of a primary-outcome event, with allowance for clustering and for varying cluster sizes across most realistic scenarios, we calculated that at least 72 clusters would be required (inflated to 80 clusters to

allow for withdrawal of 10% of the clusters). All the analyses were performed according to a modified intention-to-treat principle (including all the hospitals that underwent randomization and had available data). A full sample-size justification is provided in the trial protocol.

The primary comparison was between the hospitals (clusters) that had been randomly assigned to the intervention group and those randomly assigned to the usual-care group. 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 the analyses were adjusted for clustering with the use of random cluster and cluster-by-period effects and used robust standard errors. The primary analysis was unadjusted, except for the factors used in the randomization method (number of vaginal births per hospital, country, proportion of patients with a primary-outcome event at each hospital, and the quality of oxytocin at each hospital during the baseline phase). A sensitivity analysis was additionally adjusted for prespecified clinically important prognostic factors at the patient level (age, newborn birth weight, parity, multiple pregnancy, and mode of delivery [spontaneous or instrumentally assisted delivery]). Finally, we allowed for missing covariate data by 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 prespecified subgroups (Table S1 in the Supplementary Appendix). Summaries of data (numbers and percentages according to randomized group) about the primary outcome, maternal death, and ICU admission were provided to the independent data monitoring committee by the trial statistician (who remained unaware of the trial-group assignments) once after randomization. Because the interim analyses were performed with the use of the Peto principle,[12] no adjustment was made in the final P value to determine statistical significance. Because the statistical analysis plan did not include a provision for correcting for multiplicity for tests of secondary or other outcomes, those results are reported as point estimates with 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 the analyses were carried out with the use of Stata software, version 17 (StataCorp).

RESULTS

HOSPITAL AND PATIENT CHARACTERISTICS

A total of 104 secondary-level hospitals were assessed for eligibility. Fourteen hospitals were excluded because they had already implemented an early-detection protocol or treatment bundle for postpartum hemorrhage. A total of 90 hospitals in Kenya, Nigeria, Pakistan, South Africa, and Tanzania started the baseline prerandomization period (Fig. 2). These facilities were representative of our target population (Table S2). The independent data monitoring committee recommended completion of the trial before the hospitals in Pakistan could undergo randomization, 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; these hospitals were excluded before randomization. The remaining hospitals stayed in the baseline phase and provided usual care for 7 to 8 months.

A total of 80 hospitals in Kenya, Nigeria, South Africa, and Tanzania underwent randomization, with 40 assigned to the intervention group and the remaining 40 to continue providing usual care. Two hospitals in Tanzania, 1 in each group, did not receive the assigned intervention because of participation in a conflicting program (Fig. 2). After randomization, a 2-month transition period was implemented so that the intervention could be embedded into clinical practice in the intervention sites. Data that were collected in the trial groups during this transition period did not contribute to the analysis. Data for analysis were available from 78 hospitals (from 14 in Kenya, 38 in Nigeria, 14 in South Africa, and 12 in Tanzania), with a total of 210,132 patients (110,473 in the baseline phase and 99,659 in the implementation phase) giving birth in the hospitals during the trial period (Table 1). Source-verified data regarding blood loss were available for 206,455 patients

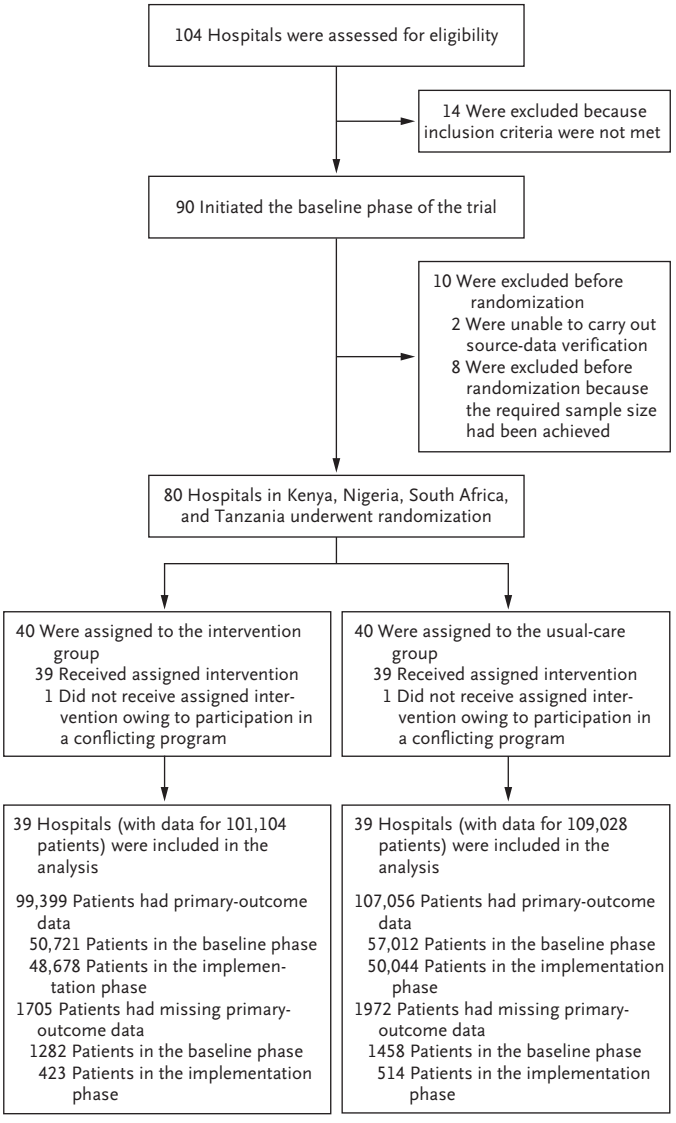

Figure 2. Randomization of Hospitals in the Cluster-Randomized Trial.

All the participating hospitals entered a 7-month baseline period in which they provided usual care for postpartum hemorrhage. After the baseline period, hospitals were randomly assigned, in a 1:1 ratio, in a sequential manner as they approached the end of the baseline phase to either the intervention group (in which hospitals implemented the E-MOTIVE protocol) or the usual-care group (in which hospitals continued to provide usual care). The 80 hospitals that underwent randomization were in Kenya, Nigeria, South Africa, and Tanzania. Two hospitals in Tanzania, 1 in each trial group, did not receive the assigned intervention because of participation in a conflicting program and were not included in the analyses.

(98% follow-up), and data on laparotomy and maternal death were available for all the patients. The hospital characteristics, patient characteristics, and the availability of essential drugs for postpartum hemorrhage (oxytocin and tranexamic acid) were similar in the two groups (Table 1).

OUTCOMES

A primary-outcome event occurred in 794 of 48,678 patients (1.6%) in the intervention group and in 2139 of 50,044 (4.3%) in the usual-care group (risk ratio, 0.40; 95% confidence interval [CI], 0.32 to 0.50; P<0.001) (Table 2). Postpartum hemorrhage was detected in 93.1% of the patients in the intervention group and in 51.1% of those in the usual-care group (rate ratio, 1.58; 95% CI, 1.41 to 1.76), and adherence to the treatment bundle was 91.2% and 19.4%, respectively (rate ratio, 4.94; 95% CI, 3.88 to 6.28). The risk of the primary outcome in the intervention group progressively decreased with time after randomization, from a mean of 3.8% during the baseline prerandomization phase to 1.1% by the last month of the implementation phase (Fig. 3).

The median blood loss was 160 ml (interquartile range, 100 to 280) in the intervention group and 220 ml (interquartile range, 120 to 380) in the usual-care group (Fig. S1). Postpartum hemorrhage (defined as blood loss of ≥500 ml) was diagnosed in 8.5% of the patients in the intervention group and in 16.7% of those in the usual-care group (risk ratio, 0.51; 95% CI, 0.44 to 0.60), and severe postpartum hemorrhage (defined as blood loss of ≥1000 ml) in 1.6% and 4.3%, respectively (risk ratio, 0.39; 95% CI, 0.31 to 0.49). Postpartum blood transfusion for bleeding was used in 1.2% of the patients in the intervention group and in 1.9% of those in the usual-care group (risk ratio, 0.71; 95% CI, 0.55 to 0.90).

There were 17 maternal deaths in the intervention group and 28 deaths in the usual-care group (risk ratio, 0.73; 95% CI, 0.40 to 1.31). A total of 12 and 18 of these deaths, respectively, were attributed to postpartum bleeding.

There were few cases of laparotomy, compression sutures, uterine-artery ligation or hysterectomy, a situation that limited meaningful comparisons between the trial groups. The results for all the secondary outcomes are shown in Table 2 and Tables S3 and S4.

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

Table 1. Characteristics of Participating Hospitals and Clinical Characteristics of the Patients.*

Characteristic	Intervention (N=49,101)	Usual Care (N=50,558)
Hospital characteristics		
Median no. of vaginal births per hospital (IQR)	1136 (775–1881)	1263 (787–1854)
Median availability of bundle components (IQR) — % of time available		
Oxytocin	100 (100–100)	100 (100–100)
Tranexamic acid	100 (100–100)	100 (100–100)
Intravenous fluid	100 (100–100)	100 (100–100)
Clinical characteristics of the patients		
Country — no. (%)		
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)
Median age (IQR) — yr	26 (21–31)	26 (21–30)
No. of previous births†		
Median (IQR)	1 (0–2)	1 (0–3)
Distribution — no./total no. (%)		
0	17,719/47,575 (37.2)	17,642/48,228 (36.6)
1–4	25,477/47,575 (53.6)	25,805/48,228 (53.5)
≥5	4,379/47,575 (9.2)	4,781/48,228 (9.9)
Previous cesarean section — no./total no. (%)	1456/48,911 (3.0)	1281/50,364 (2.5)
Postpartum hemorrhage in previous pregnancy — no./total no. (%)	487/47,869 (1.0)	405/48,925 (0.8)
Multiple pregnancy — no. (%)	804 (1.6)	960 (1.9)
Delivery with forceps or vacuum — no./total no. (%)	358/49,100 (0.7)	278/50,558 (0.5)
Birth weight — g	3033±559	3044±552
Median gestational age (IQR) — wk	39 (37–40)	38 (37–39)
Gestational age <37 wk — no./total no. (%)	6,877/44,389 (15.5)	8,565/48,844 (17.5)
Antepartum hemorrhage — no./total no. (%)	372/48,000 (0.8)	275/48,692 (0.6)
Preeclampsia — no./total no. (%)	1,038/48,280 (2.1)	1,182/50,171 (2.4)
Labor augmented or induced — no. (%)	6,811 (13.9)	9,323 (18.4)
Retained placenta or manual removal of placenta — no. (%)	566 (1.2)	1,072 (2.1)

* Plus–minus values are means ±SD. Hospitals in the intervention group implemented a protocol for the early detection and treatment of postpartum hemorrhage that included a calibrated blood-collection drape and a bundle of first-response treatments; hospitals in the control group provided usual care. Each trial group in this cluster-randomized trial included 39 clusters (i.e., hospitals). The numbers in the column heads are the numbers of patients. Percentages may not total 100 because of rounding. IQR denotes interquartile range.

† Data on the number of previous births were missing for 1526 patients in the intervention group and for 2330 in the usual-care group.

DISCUSSION

The E-MOTIVE intervention resulted in a 60% lower risk of the primary outcome — a composite of severe postpartum hemorrhage, laparotomy for postpartum hemorrhage, or maternal death from postpartum hemorrhage — after vaginal birth across secondary-level hospitals in Kenya, Nigeria, South Africa, and Tanzania. This benefit was presumably attributable to observed

Table 2. Primary Outcomes, Key Secondary Implementation Outcomes, and Secondary Outcomes.*

Outcome	Intervention (N=49,101)	Usual Care (N=50,558)	Risk or Rate Ratio (95% CI)†	Difference (95% CI)†
Primary outcome				
Composite of severe postpartum hemorrhage, laparotomy for bleeding, or maternal death from bleeding — no./total no. (%)‡	794/48,678 (1.6)	2139/50,044 (4.3)	0.40 (0.32 to 0.50)§	−2.5 (−3.0 to −2.0)§
Key secondary implementation outcomes				
Detection of postpartum hemorrhage — no./total no. (%)¶	3870/4158 (93.1)	4244/8299 (51.1)	1.58 (1.41 to 1.76)	33.3 (26.9 to 39.8)
Adherence to treatment bundle — no./total no. (%)‖	3791/4158 (91.2)	1623/8351 (19.4)	4.94 (3.88 to 6.28)	70.2 (64.6 to 75.7)
Secondary outcomes				
Postpartum hemorrhage — no./total no. (%)**	4158/48,678 (8.5)	8351/50,043 (16.7)	0.51 (0.44 to 0.60)	−8.2 (−9.7 to −6.6)
Severe postpartum hemorrhage — no./total no. (%)**	786/48,678 (1.6)	2129/50,043 (4.3)	0.39 (0.31 to 0.49)	−2.6 (−3.1 to −2.0)
Laparotomy for bleeding — no. (%)	12 (<0.1)	7 (<0.1)	1.72 (0.57 to 5.16)	0.01 (−0.02 to 0.04)
Maternal death — no. (%)				
From bleeding	12 (<0.1)	18 (<0.1)	0.80 (0.38 to 1.68)	−0.01 (−0.03 to 0.02)
From any cause	17 (<0.1)	28 (0.1)	0.73 (0.40 to 1.31)	−0.02 (−0.04 to 0.01)
Blood transfusion — no. (%)				
For any cause	1074 (2.2)	1296 (2.6)	0.87 (0.69 to 1.10)	−0.4 (−0.9 to 0.2)
For bleeding††	580 (1.2)	944 (1.9)	0.71 (0.55 to 0.90)	−0.6 (−1.0 to −0.2)
Blood loss at ≤2 hr post partum — ml‡‡				
Median (IQR)	160 (100 to 280)	220 (120 to 380)	—	—
Mean	225±229	318±321	—	−84 (−103 to −64)

* Plus–minus values are means ±SD. Laparotomy related to bleeding and maternal death from bleeding were determined by the end-point review committee, whose members were unaware of the trial-group assignments. The widths of the confidence intervals for secondary outcomes have not been adjusted for multiplicity and cannot be used to infer treatment effects.

† Rate ratios are reported for the outcomes of detection of postpartum hemorrhage and use of treatment bundle; risk ratios are reported for other outcomes. Differences between percents are presented in percentage points, and differences between mean values are presented in the unit of the values. Analyses were adjusted for the cluster-level covariates that were used in the randomization (number of vaginal births, prevalence of postpartum hemorrhage, country, and prevalence of primary-outcome events) and for imbalances during the baseline period. Baseline data before implementation of the intervention (involving 110,473 patients in 78 clusters) were disaggregated for the interventional and usual-care sites for each outcome as follows: for the composite primary outcome, 1931 of 50,721 patients (3.8%) in the intervention group and 2546 of 57,012 (4.5%) in the usual-care group; for the detection of postpartum hemorrhage, 5097 of 8179 (62.3%) and 4971 of 9717 (51.2%), respectively; for adherence to the treatment bundle, 1682 of 8194 (20.5%) and 1038 of 9779 (10.6%), respectively; for postpartum hemorrhage, 8194 of 50,720 (16.2%) and 9779 of 57,010 (17.2%), respectively; for severe postpartum hemorrhage, 1920 of 50,720 (3.8%) and 2535 of 57,010 (4.4%), respectively; for laparotomy for bleeding, 10 of 52,003 (<0.1%) and 12 of 58,470 (<0.1%), respectively; for maternal death from bleeding, 16 of 52,003 (<0.1%) and 24 of 58,470 (<0.1%), respectively; for maternal death from any cause, 29 of 52,003 (0.1%) and 34 of 58,470 (0.1%), respectively; for blood transfusion for any cause, 1507 of 52,003 (2.9%) and 1700 of 58,470 (2.9%), respectively; for blood transfusion for bleeding, 991 of 52,003 (1.9%) and 1176 of 58,470 (2.0%), respectively; for median blood loss up to 2 hours post partum, 220 ml (IQR, 120 to 380) and 220 ml (IQR, 120 to 380), respectively; and for median blood loss up to 24 hours post partum, 220 ml (IQR, 120 to 380) and 220 ml (IQR, 120 to 380).

‡ The intracluster correlation coefficient for the primary outcome on the latent scale was 0.011 (95% CI, 0.008 to 0.014). The cluster autocorrelation for the primary outcome was 0.61. The intracluster correlation coefficient and cluster autocorrelation were estimated by fitting a mixed-effects linear model to the data with random effect for cluster and for a cluster–period interaction. In the analysis of severe postpartum hemorrhage, only women with source-verified data on blood loss were included.

§ P<0.001.

¶ The detection of postpartum hemorrhage was defined as the recording of a diagnosis of postpartum hemorrhage by the birth attendant. The denominator is the number of patients with objectively measured postpartum hemorrhage (defined as blood loss of ≥500 ml).

‖ Adherence to the treatment bundle was defined as adherence to three core elements of the bundle: the administration of oxytocic drugs, tranexamic acid, and intravenous fluids. The denominator is the number of patients with objectively measured postpartum hemorrhage.

** Only patients with source-verified data on blood loss were included in this analysis.

†† Blood transfusion for bleeding was defined as blood transfusion in patients with postpartum hemorrhage.

‡‡ For the analysis of blood loss as a continuous variable, mean differences are reported. Outcomes were analyzed by permutation tests, and confidence intervals were constructed with the use of permutation tests, by finding the upper and lower boundaries of the intervention effect that would lead to a two-sided P value at less than the 5% level.

improvements in the detection of postpartum hemorrhage and the use of the WHO first-response bundle in the hospitals in the intervention group.

Findings regarding postpartum hemorrhage (blood loss, ≥500 ml) were consistent with those for the primary outcome. The E-MOTIVE protocol allowed for triggering of the treatment bundle at blood loss of 300 ml or more if there was an accompanying abnormality in the vital signs or clinical observations. This trigger criterion was commonly used in the hospitals in the intervention group, and this trigger criterion probably underlies the apparent benefit of the intervention for less-severe postpartum hemorrhage.

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

Several limitations of this trial warrant consideration. First, owing to the pragmatic design, we did not collect information on some clinical outcomes, such as the postnatal hemoglobin level and anemia, or on patients' experience of care. Second, our trial was not powered to assess maternal death, but findings for this outcome, albeit uncommon, were in the direction of those for the primary outcome. Third, the trial was conducted in low- and middle-income countries; further implementation research is needed in high-income settings, focusing on process outcomes such as postpartum hemorrhage detection and bundle use to ensure broader generalizability. Finally, the uncalibrated drapes that were used in the control hospitals 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 that this situation may have influenced their actions, it would be expected to attenuate the observed effect of the intervention.

Blood loss after birth is currently visually estimated, which results in underestimation of blood loss and delays in the initiation of lifesaving treatment. A Cochrane review showed that use of a calibrated drape improved the detection of postpartum blood loss as compared with visual estimation (rate ratio, 1.86; 95% CI, 1.11 to 3.11 [high certainty]) but had no clear effect on health outcomes.[13]

This large, international trial showed that the use of a calibrated drape for detection of postpartum hemorrhage and a bundle of treatments, supported by a multifaceted implementation strategy, resulted in a substantially lower risk of the primary outcome, a composite of severe postpartum hemorrhage, laparotomy for bleeding, or death from bleeding than usual care.

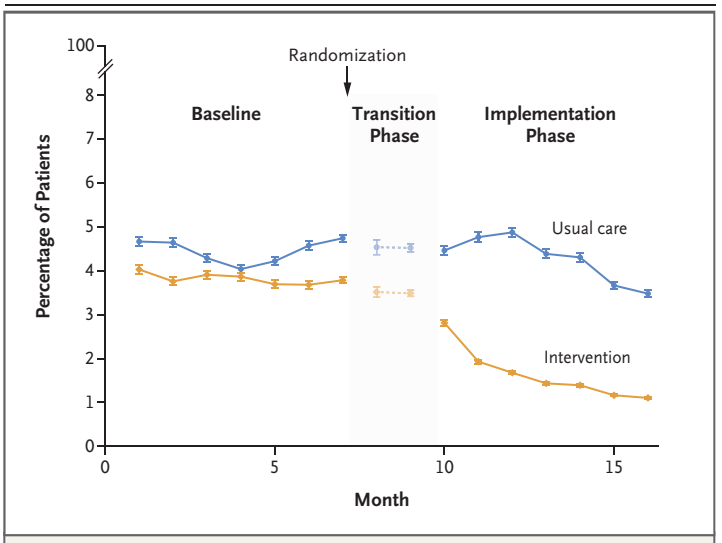

Figure 3. Patients with Primary-Outcome Event during the Baseline, Transition, and Implementation Phases.

The primary outcome was a composite of severe postpartum hemorrhage, laparotomy for bleeding, or maternal death from bleeding. After the 7-month baseline period, hospitals had an allowance of 2 months for transition in order to conduct training and to implement and embed the intervention in practice before beginning the 7-month implementation phase. I bars indicate the 95% confidence interval.

The views and opinions in this article are those of the authors and do not necessarily reflect those of their respective institutions or the World Health Organization.

Supported by an investment grant (INV-001393) from the Bill and Melinda Gates Foundation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Mark Misiko, Jim Kelly, Polycarp Oyoo, Hilal Mukhtar, Stephen Abu, Ahmad Danjuma Suleiman, Muhammed Shittu, Muftahu Dahiru Mahmoud, Lolade Arigbede, Baba Mai Yaki, Faisal Dankishiya, Fatima Abubakar, Adeosun Love Funmi,

Rahamtu Yusuf, Sadiq Abubakar, Taiwo Amole, Elani Muller, Sara Willemse, Fawzia Samuels, Sibongile Doris Khambule, Juma Makungu, Andrea Pembe, David Sando, Amani Kikula, Mohamed Bakari, Sambusa Masumbuko, Beatrice Erastus Mwilike, Akwinata Banda, Christina Myalla, Roy Kaberia, Purity Kagendo, Henry Atsewa, Mary Otuku, Augustine Khaemba, Hassan Mwachome, Halima Kaka, Damaris Wambui, Virginia Wangeci Irungu, Lydia Mwihaki Wanjiku, Noreen Nangira Were, Getrude Baya, Janet Munyanzi, Protus Wafula Nyongesa, Jennifer Jennis Saru, Debra Chepchirchir, Flora Tanui, Grace Limo, John Karani Kimani, Mary Njuguna, Maureen Adundo Okango, Rita Yumbe, Mary Njoroge, Salome Waweru, Ndungu Muchiri, Nalika Robai, Binta Garba Bello, Mahmoud Kawu Magashi, Stephen Bature, Binta Mohammed, Lewis Lebara, Nonye Enyidah Esther, Emmanuel Agbogo, Hapsat Farouk, Ismail Saad Ayuba, Fatima Adamu Yunusa, Aisha Shehu Satatima, Hajara Sani, Ibrahim Shehu, Hauwa Yakubu, Eigbadon Ambrose Odianosen, Osunde Faith Enifome, Aisha Nana Adamu, Maryam Muhammad, Asma'u Abdullahi, Innocent Ogbonnaya Michael, Ajiboye Ruth Tayo, Olowogbayi Tope, Khadija Muhammad Kanoma, Rashida Badaru, Saadatu Abubakar Tanimu, Habiba Muhammad Idris, Aminu Ibrahim Haruna, Maikudu Sulaiman, Chritiana Omuwa Ikhane, Salima Muhammad, Akpofure Harriet Ese, Ikem Christiana Nwanne, Sunday Pius, Maryam Halilu Mohammed, Olorunfemi Ajibola John, Rebecca Solomon Elisha, Abigail Gwimi, Ejura Ochala, Ehigha Enabudoso, Lawal Oyeneyi, Hadiza Usman, Muhammad Jamil Shuaibu, Collins Agbeze Kalu, Ahmad Tijjani Ibrahim, Muhammad Umar, Nura Mainasara, Zaki Abubakar, Amaka Ngozi Ocheke, Nasiru Abdullahi Gada, Adebayo Adedokun, Aminu Magaji, Fatima Rasheed, Hussaina Adamu, Amy Ivori, Umma Bawa, Constance Shehu, Jombo Sunday, Ishaku Musa, Buyiswa Euginia Pongwana, Khokhela Mba, Annelize Barnard, Gwendolene Booys, Tracey Hinkel, Ronel Faro, Liaquat Parker, Nompumelelo Seyisana, Monique Mieke Amira, Thea Williams, Thandiwe Mabusha, Bongekile Ethel Mbewana, Mangola Daniel Kabongo, Dhanabagium Gramoney, Katrin Middleton, Eze Collins, Emile Manefeldt, Tessa McMillan, Jessica Westwood, Mziwohlanga Mdondolo, Sibonile Zitha, Knowledge Chipango, Robert James Bwire, Shoma Guyela, Edward Philemon, Yasintha Elifather, Bijengo Zakaria Mabiba, Helenestina Anatory Chizzery, Consolata Reuben Kyengu, Isack Mwongera Kyagari, Uddy Kyula, Happiness Braison Munisi, Paschal Gerald Kalinga, Immaculatha Mewama Samuel, Peter Nachiwa, Jacqueline Amani, Mbaraka Hussein, Fatuma Mono, Lulu Boniventure, Baltazary M. Joseph, and Balima Itambu; the members of the trial steering committee (Sabaratnam Arulkumaran [chair], Deborah Armbruster, Pierre Buekens, and Monica Taljaard); the members of the independent data monitoring committee (Zarko Alfirevic [chair], Pisake Lumbiganon, and Andrew Copas); the members of the end-point review committee (Harry Gee, Amie Wilson, Raffaele Napolitano, Irshad Ahmed, and Margarita Bariou); and all those not otherwise mentioned above who contributed to this trial.

APPENDIX

The authors' full names and academic degrees are as follows: Ioannis Gallos, D.M.S., M.D., Adam Devall, B.Med.Sci., Ph.D., James Martin, Ph.D., Lee Middleton, M.Sc., Leanne Beeson, B.Sc., Hadiza Galadanci, F.R.C.O.G., Fadhlun Alwy Al-beity, M.D., Ph.D., Zahida Qureshi, M.B., B.S., M.Med., G. Justus Hofmeyr, M.B., B.Ch., D.Sc., Neil Moran, B.M., B.Ch., Sue Fawcus, M.B., B.S., Lumaan Sheikh, F.C.P.S., M.R.C.O.G., George Gwako, M.B., Ch.B., Ph.D., Alfred Osoti, M.B., Ch.B., Ph.D., Ashraf Aswat, B.Sc., Kristie-Marie Mammoliti, M.Sc., Kulandaipalayam N. Sindhu, M.B., B.S., M.D., Marcelina Podesek, M.Sc., Isobelle Horne, B.A., Rebecca Timms, M.Res., Idnan Yunas, M.B., B.Chir., D.C.H., Jenipher Okore, B.Sc., Mandisa Singata-Madliki, Ph.D., Edna Arends, B.A., Aminu A. Wakili, M.B., B.S., Ard Mwampashi, B.A.P.S&P.A., Sidrah Nausheen, M.B., B.S., Shah Muhammad, M.B., B.S., M.P.H., Pallavi Latthe, M.B., Ch.B., M.D., Cherrie Evans, Dr.P.H., C.N.M., Shahinoor Akter, Ph.D., Gillian Forbes, Ph.D., David Lissauer, M.B., Ch.B., Ph.D., Shireen Meher, M.B., B.S., M.D., Andrew Weeks, M.B., Ch.B., M.D., Andrew Shennan, M.B., B.S., M.D., Anne Ammerdorffer, Ph.D., Eleanor Williams, M.Sc., M.A., Tracy Roberts, Ph.D., Mariana Widmer, M.Sc., Olufemi T. Oladapo, M.D., M.P.H., Fabiana Lorencatto, Ph.D., Meghan A. Bohren, Ph.D., M.S.P.H., Suellen Miller, Ph.D., M.H.A., Fernando Althabe, M.D., Metin Gülmezoglu, M.D., Ph.D., Jeffrey M. Smith, M.D., M.P.H., Karla Hemming, Ph.D., and Arri Coomarasamy, M.B., Ch.B., M.D.

The authors' affiliations are as follows: the United Nations (UN) Development Program–UN Population Fund–UN Children's Fund–World Health Organization (WHO)–World Bank Special Program of Research, Development, and Research Training in Human Reproduction, the Department of Sexual and Reproductive Health and Research, WHO (I.G., M.W., O.T.O., F.A.), and the Concept Foundation (A. Ammerdorffer, M.G.) — both in Geneva; the College of Medical and Dental Sciences, University of Birmingham (A.D., J.M., L.M., L.B., A. Aswat, K.-M.M., K.N.S., M.P., I.H., R.T., E.W., T.R., K.H., A.C.), Health Education England (I.Y.), and the Department of Obstetrics and Gynaecology, Birmingham Women's and Children's NHS Foundation Trust (P.L., S.M.), Birmingham, the Centre for Behaviour Change, University College London (G.F., F.L.), and the Department of Women and Children's Health, School of Life Course Sciences, King's College London (A.S.), London, and the Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool (D.L., A.W.) — all in the United Kingdom; the African Center of Excellence for Population Health and Policy, College of Health Sciences, Bayero University, Kano, Nigeria (H.G., A.A.W.); the Department of Obstetrics and Gynecology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania (F.A.A., A.M.); the Department of Obstetrics and Gynecology, University of Nairobi, Nairobi, Kenya (Z.Q., G.G., A.O., J.O.); the Department of Obstetrics and Gynecology, University of Botswana, Gaborone (G.J.H.); the KwaZulu–Natal Department of Health, Pietermaritzburg (N.M.), the Department of Obstetrics and Gynaecology, University of Cape Town, Cape Town (S.F., E.A.), and the Effective Care Research Unit, University of the Witwatersrand, Johannesburg (G.J.H., M.S.-M.) — all in South Africa; the Department of Obstetrics and Gynecology, Aga Khan University, Karachi, Pakistan (L.S., S.N., S.M.); the Maternal and Newborn Health Unit, Technical Leadership and Innovation, Jhpiego, and Johns Hopkins University, Baltimore (C.E.); the Gender and Women's Health Unit, Centre for Health Equity, School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia (S.A., M.A.B.); the Department of Obstetrics and Reproductive Sciences, School of Medicine, University of California, San Francisco, San Francisco (S.M.); and the Maternal, Newborn, and Child Health Team, Bill and Melinda Gates Foundation, Seattle (J.M.S).

REFERENCES

1. Trends in maternal mortality 2000 to 2020: estimates by WHO, UNICEF, UNFPA, World Bank Group and UNDESA/Population Division. Geneva: World Health Organization, 2023.
2. Sheldon WR, Blum J, Vogel JP, Souza JP, Gülmezoglu AM, Winikoff B. Postpartum haemorrhage management, risks, and maternal outcomes: findings from

the World Health Organization multicountry survey on maternal and newborn health. BJOG 2014;121:Suppl 1:5-13.
3. Recommendations WHO for the prevention and treatment of postpartum haemorrhage. Geneva: World Health Organization, 2012.
4. World Health Organization. Updated WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage. October 2017 (https://apps.who.int/iris/bitstream/handle/10665/259379/WHO-RHR-17.21-eng.pdf;sequence=1).
5. Widmer M, Piaggio G, Nguyen TMH, et al. Heat-stable carbetocin versus oxytocin to prevent hemorrhage after vaginal birth. N Engl J Med 2018;379:743-52.
6. Hancock A, Weeks AD, Lavender DT. Is accurate and reliable blood loss estimation the 'crucial step' in early detection of postpartum haemorrhage: an integrative review of the literature. BMC Pregnancy Childbirth 2015;15:230.
7. Althabe F, Therrien MNS, Pingray V, et al. Postpartum hemorrhage care bundles to improve adherence to guidelines: a WHO technical consultation. Int J Gynaecol Obstet 2020;148:290-9.
8. Forbes G, Akter S, Miller S, et al. Factors influencing postpartum haemorrhage detection and management and the implementation of a new postpartum haemorrhage care bundle (E-MOTIVE) in Kenya, Nigeria, and South Africa. Implement Sci 2023;18:1.
9. Akter S, Forbes G, Miller S, et al. Detection and management of postpartum haemorrhage: qualitative evidence on healthcare providers' knowledge and practices in Kenya, Nigeria, and South Africa. Front Glob Womens Health 2022;3:1020163.
10. Ammerdorffer A, Rushwan S, Timms R, et al. Quality of oxytocin and tranexamic acid for the prevention and treatment of postpartum hemorrhage in Kenya, Nigeria, South Africa, and Tanzania. Int J Gynaecol Obstet 2022;158:Suppl 1:46-55.
11. Hooper R, Forbes A, Hemming K, Takeda A, Beresford L. Analysis of cluster randomised trials with an assessment of outcome at baseline. BMJ 2018;360:k1121.
12. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol 1971;44:793-7.
13. Diaz V, Abalos E, Carroli G. Methods for blood loss estimation after vaginal birth. Cochrane Database Syst Rev 2018;9(9):CD010980.