Effect of a collector bag for measurement of postpartum blood loss after vaginal delivery: cluster randomised trial in 13 European countries.

Wei-Hong Zhang, Catherine Deneux-Tharaux, Peter Brocklehurst, Edmund Juszczak, Matthew Joslin, Sophie Alexander, Euphrates Group

Effect of a collector bag for measurement of postpartum blood loss after vaginal delivery: a cluster randomised trial in thirteen European countries

Authors

Wei-Hong Zhang (Senior researcher) [*], Catherine Deneux-Tharaux (Senior researcher)†, Peter Brocklehurst (Professor of Perinatal Epidemiology)‡, Edmund Juszczak (Senior Medical Statistician)‡, Matthew Joslin (General Practitioner)[*], Sophie Alexander (Professor of Public Health)[*] and the EUPHRATES Group[§]

[*]Perinatal Epidemiology Research Unit, School of Public Health, Université Libre de Bruxelles (ULB), Belgium.

†INSERM, UMR S953, UPMC, Epidemiological research unit on perinatal health and women's and children's health. Bâtiment de recherche Hôpital Tenon 4, rue de la Chine 75020 Paris, France.

‡National Perinatal Epidemiology Unit, University of Oxford. Old Road Campus, Headington, Oxford OX3 7LF, United Kingdom.

§ EUPHRATES (EUropean Project on obstetric Haemorrhage, Reduction, Attitudes, Trial and Early warning System) collaborators : Sophie Alexander (Project leader, Belgium), Diogo Ayres-de-Campos (Portugal), Istvan Berbik (Hungary), Marie-Hélène Bouvier-Colle (France), Gérard Bréart (France), Peter Brocklehurst (United Kingdom), Vicenç Cararach (Spain), Anna Maria Marconi (Italy), Catherine Deneux-Tharaux (France), Risto Erkkola (Finland), Mathias Klein (Austria), Jens Langhoff-Roos (Denmark), Alison Macfarlane (United Kingdom) , Walter Prendiville (Ireland), Jos van Roosmalen (Nederlands), Babill Stray-Pedersen (Norway), Carolyn Troeger (Switzerland), Clare Winter (United Kingdom), Wei-Hong Zhang (Belgium)

Keywords: severe post-partum haemorrhage, collector bag, cluster-randomised controlled trial, Europe

CORRESPONDING AUTHOR:

Wei-Hong ZHANG, M.D., MPH. PhD

Unité de recherche en Santé Reproductive et Epidémiologie Périnatale, Ecole de Santé Publique, Université Libre de Bruxelles (ULB), Route de Lennik 808, CP 597, B-1070 Bruxelles, Belgium

Tel: ++ 32 2 555 63 68, Fax: ++ 32 2 555 40 49

Email: wzhang@ulb.ac.be

Abstract

Background- Postpartum haemorrhage (PPH) remains a leading cause of maternal morbidity and mortality worldwide. Delay in diagnosis and care for PPH has been reported. The inaccuracy of visual estimation of postpartum blood loss has been demonstrated.

Objectives- To evaluate the effectiveness of the systematic use of a transparent plastic collector bag for measurement of postpartum blood loss after vaginal delivery in reducing the incidence of severe PPH

Design- A cluster randomised trial

Setting- Thirteen European countries

Participants-78 maternity units and 25381 women who had a vaginal delivery

Interventions- Maternity units were randomly assigned to systematically use a collector bag (intervention group), or to continue to visually assess postpartum blood loss after vaginal delivery (control group)

Main outcome measures- The primary outcome was the incidence of severe PPH in vaginal deliveries, defined as a composite of one or more of the following events: blood transfusion, intravenous plasma expansion, arterial embolisation, surgical procedure, admission to intensive care unit, treatment with recombinant factor VII, or death.

Results- The incidence of severe PPH was 189 out of 11037 of vaginal deliveries (1.71%) in the intervention group compared to 295 out of 14344 in the control group (2.06%). The difference was not statistically significant either in individual level analysis (adjusted odds ratio 0.82; 95% CI 0.26 to 2.53) or in cluster level analysis (difference in weighted mean rate adjusted for baseline rate 0.16%; 95 % CI -0.69% to 1.02%).

Conclusion- The use of a collector bag after vaginal delivery did not reduce the rate of severe PPH as compared to visual estimation of postpartum blood loss.

Trial registration: International Standard Randomised Controlled Trial Number (ISRCTN) 66197422.

Introduction

Worldwide, postpartum haemorrhage (PPH) remains one of the leading causes of maternal mortality[1] and the main component of severe morbidity[2-5], jeopardizing the woman's fertility, exposing her to risks of transfusion and intensive care, and incurring costs. From reports in developed countries, about one percent of deliveries are associated with severe PPH[3-6]. Decreasing the prevalence of severe PPH remains challenging. This appears all the more important given the recent increase in the incidence of PPH reported in several developed countries[2, 7, 8]. Individual risk factors have been described but they poorly predict the occurrence of PPH [9, 10]. Interest has focused on care-processes as they are potentially amenable to change. Studies of maternal deaths show that most deaths due to PPH involve delayed and substandard care in the diagnosis and management of haemorrhage[11-13]. Similar findings were drawn from a population-based study of severe non-lethal PPH[14].

Delay in diagnosis and treatment of PPH may result from an underestimation of blood loss at delivery. Assessment of post-partum blood loss, particularly following vaginal birth, is recognised as difficult. Many studies demonstrate that visual estimates of peripartum blood loss are frequently inaccurate[15-21], showing an overestimation of blood loss at low volumes and an underestimation at larger volumes, the magnitude of underestimation typically increasing with the volume of haemorrhage.

The hypothesis of this study was that if blood loss is monitored and objectively measured by collection in a transparent plastic bag, rather than being visually assessed, care-giver response will be triggered more rapidly when excessive blood loss occurs. Specifically when bleeding is excessive but before haemorrhage has become catastrophic, appropriate management will take place without delay, so reducing the incidence of severe PPH. A preliminary study shows that a plastic collector bag constitutes a simple instrument to diagnose haemorrhage in the delivery room[22]. However, the impact of its use on PPH-related health outcomes has never

been tested. Despite lacking evidence, the bag is routinely used in a significant proportion of maternity units in Belgium, France, Italy, and Portugal (Euphrates survey[23], unpublished data). The objective of this trial was to evaluate the effectiveness of the systematic use of a transparent plastic collector bag for measurement of postpartum blood loss after vaginal delivery in reducing the incidence of severe PPH.

Methods

Trial design

A cluster-randomised design with maternity unit was the unit of randomization. Given the logistics of clinical practice on the delivery suite, contamination appeared to be inevitable in an individual-patient randomised trial setting.

Setting

The sites selected for the trial comprised 78 maternity units in 13 European countries (see Table1).

Participants

Maternity units

Maternity units were eligible if they had more than 200 vaginal deliveries annually (excluding water births), and no previous policy of routine use of collector bags. In addition, to ensure that the standard of care for management of the third stage of labour was similar across all participating units, they had to comply with the EUPHRATES consensus statement on the prevention and management of PPH[24]; a minimum standard, not a detailed guideline.

Women

In all maternity units of participating countries (except Denmark), all women undergoing a vaginal delivery during the study period were included. In Denmark, enrolment into the study

in each maternity unit was midwife-dependant; if a midwife agreed to participate, all his/her vaginal deliveries were included.

Randomization

The random allocation was produced centrally by the National Perinatal Epidemiology Unit in Oxford, UK. A stratified design was used to ensure that the two arms of the trial were as similar as possible at baseline with respect to the stratification factors (i) country and (ii) size of maternity unit (median split within country).

Maternity units were randomly allocated to either systematically use a collector bag after vaginal delivery (intervention arm), or not use the bag (control group).

Intervention

The trial was implemented between January 2006 and May 2007, depending on the country. Prior to participation, each centre was visited by the national coordinator. At the visit, staff were reminded of the EUPHRATES consensus statement on the prevention and management of PPH and familiarised with the processes and the data collection instrument.

In the intervention group, a second visit from the national coordinator took place after randomisation, during which, use of the collector bag was explained to birth attendants with standard written instructions and a training video aid. The bag was to be placed under the pelvis of the mother as soon as the baby was born and before delivery of the placenta. It was transparent and graduated, allowing continuous monitoring of blood loss. It did not require sterilization and could be used in dorsal, lateral or lithotomy positions. Women delivering standing or crouching could be offered the opportunity to lie down for the third stage, allowing the bag to be placed under their pelvis. The bag was to be left under the woman's buttocks until the birth attendant was no longer concerned about blood loss e.g. when the

sanitary towel was applied to the vulva. Bags were purchased centrally and provided to each cluster in the intervention arm.

In the control group, no collector bag was used, postpartum blood loss being visually assessed. During the study period, use of collector devices was monitored to assess compliance with allocation.

Outcomes

The primary outcome for the trial was the incidence of severe PPH following vaginal deliveries, defined as a composite of all women who experienced one or more of the following: blood transfusion, intravenous plasma expansion, arterial embolisation, surgical procedure, admission to intensive care unit, treatment with recombinant factor VII and death. Secondary outcomes were each of the components of the primary outcome, manual removal of the placenta and administration of prostaglandins after delivery.

Data collection

Each participating centre was asked to collect data from all women undergoing a vaginal delivery for a period of 4 months.

Data were collected during two time intervals: a 1-month period pre-randomisation (baseline period), and a 3-month period beginning immediately following randomisation in the control group (trial period). In the intervention group, the 3-month period of data collection followed a 2-week training period during which the unit started using the collector bag on women undergoing vaginal delivery.

Data were collected using a form filled in by the birth attendants for each vaginal delivery, and included information on the woman's age, induction of labour, mode of delivery, number of babies and birth weight, prophylactic uterotonics, and outcome data. Additionally, a second

form was used for deliveries where severe PPH occurred, collecting detailed information regarding delivery and PPH management. This form was used to cross-check criteria for the primary outcome.

Sample size

Sample size calculation took into account the cluster-randomised design; the intracluster correlation coefficient was estimated to be 0.01. Assuming an event rate for the primary outcome of 2.5% in the control group, in order to detect a decrease in the event rate to 1.5% (a 40% relative risk reduction) with 80% power, a 2-sided significance level of 5% and an average cluster size of 300 women, 82 clusters (41 in each arm of the trial) were required[25].

Statistical analysis

Participants/maternity units were analysed in the groups to which they were assigned regardless of the management received by individual women or deviation from the protocol. Baseline characteristics of maternity units and individual women were summarized with counts (percentages) for categorical variables, mean (standard deviation [SD]) for normally distributed continuous variables, or median (interquartile [IQR]) for other continuous variables. Comparative statistical analysis was performed at both individual and cluster level and took into account the effect of clustering. All statistical tests were two-sided (5% significance level) and not adjusted for multiple comparisons. Statistical analyses were performed using SPSS version 17 (SPSS) and Stata v10.0 software (Stata Corporation, College Station, Texas, USA).

Individual woman level analysis - primary and secondary outcomes were compared between the two study groups both unadjusted and adjusted for the effect of clustering. In order to determine the magnitude and direction of any differences in outcomes between the two

groups, crude odds ratios and 95% confidence intervals were calculated. Furthermore, logistic regression was used to adjust for clustering and key prognostic factors. The cluster randomised design imparts a data structure that facilitates the calculation of a valid intracluster correlation coefficient, ρ.

Cluster level analysis was only performed on the primary outcome. Some hospitals contributed fewer events than others, and some recruited fewer women. We allowed these hospitals to have less effect on the treatment estimate by weighting the analysis based on the precision, i.e. calculating the weighted mean difference for the treatment comparison. A weighted linear regression model was used to test the effect of the intervention on the rate of severe PPH during the trial period, adjusting for the baseline rate, expressed as the weighted mean difference (plus 95% confidence interval).

Ethical aspects

Ethics approval was obtained in each country from relevant local or national research ethics committees. Consent to participate was taken from the maternity units. Because the procedure being tested was not invasive or different from current clinical practice, and because outcome data were routinely collected at maternity units and anonymously transmitted, no individual consent was sought.

Role of the funding source

The project was funded by the European Union (EU) under Framework 5 (contract QLG4-CT-2001-01352). EU had no role in the design, management, data collection, analyses, or interpretation of the data. EU had no role in the writing of the manuscript or in the decision to submit for publication.

Results

Figure 1 shows the flow of maternity units and women through the study. Of the 84 maternity units meeting the inclusion criteria, two maternity units declined to participate before allocation. Forty one maternity units were randomised to the intervention group and 41 to the control group. Two maternity units in each group opted out before receiving notification of allocation because they lacked the necessary resources. Thirty-nine maternity units in each group completed the trial. Table 1 shows the number of participating maternity units and women included in each country.

One maternity unit did not collect baseline data in the intervention group. Deviating from the protocol, the majority of maternity units (31 of 39) continued collecting data during the 2-week training period in the intervention arm. In these units, trial data collection started after the first month of baseline data collection. Four units in the control group collected trial data for more than 3 months (up to 5 months). Only the 3-month period of data collection specified in the protocol was considered for all units. In some Austrian hospitals, the number of women included was low, given the total expected number of deliveries. The national coordinator confirmed that the missing data were all caesarean deliveries, and that in some hospitals the caesarean rate was very high. Nevertheless, sensitivity analyses were performed, and showed that excluding these hospitals or even the entire Austrian data set did not influence the results.

Characteristics of maternity units and women

Baseline data were collected for 4937 in the intervention group and 4758 vaginal deliveries in the control group and characteristics of maternity units and women (Table 2) were broadly similar in the two groups for all factors, except for manual removal of the placenta and prophylactic uterotonics, which were more common among women in the intervention group.

Primary outcome

Individual level analysis

A total of 25381 women were included in the analysis (11037 in the intervention group and 14344 in the control group). The greater number of women in the control group was due to a larger median cluster size (241 and 284 in the intervention and control groups, respectively).. The incidence of severe PPH was 189 out of 11037 of vaginal deliveries (1.71%) in the intervention group compared to 295 out of 14344 in the control group (2.06%). The difference was not statistically significant (Table 3). The crude odds ratio for the effect of the intervention was 0.83 (95% CI, 0.69 to 1.00). The odds ratio adjusted for clustering was 0.83 (95% CI, 0.27 to 2.60); after further adjustment for age, prophylactic uterotonics in the third stage, mode of delivery and birth weight, the odds ratio was 0.82 (95% CI, 0.26 to 2.53). Sensitivity analyses were conducted to test the robustness of this result excluding units deviating from the protocol, and also by country, and by baseline rate of severe PPH (median split by country); these analyses provided similar results.

Cluster level analysis

The weighted mean severe PPH rate was 1.71% (SD 2.51) in the intervention group and 2.06% (SD 3.52) in the control group. The intracluster correlation coefficient for severe PPH was 0.023. There was no significant difference in the rate of severe PPH between the two groups (weighted mean difference -0.34%, (-2.56% to 1.87%); p=0.75). Adjusting for the baseline rate of severe PPH resulted in a slight change in this result (adjusted weighted mean difference 0.16%, (-0.69% to 1.02%); p=0.70). Rates of severe PPH in the baseline and trial periods for each maternity unit were heterogeneous across units in different countries (Figure 2).

Figure 3 shows the difference in baseline and trial rates of severe PPH for each unit in the intervention group, according to the compliance of bag usage. There was no relationship

between the difference in severe PPH rates (baseline and trial) and the actual proportion of bag use. The analysis of the intervention effect on the primary outcome, including in the intervention arm only maternity units where the bag was used in at least 50% of vaginal deliveries, showed no significant difference between the two groups (individual level analysis adjusting for cluster and individual characteristics; adjusted OR 0.59, 95% CI (0.23-1.53)).

Secondary outcomes *(individual level analysis)*

Analyses were performed to test the effect of the intervention on the main components of the primary outcome (Table 3). The proportion of blood transfusion, surgical procedure or embolisation and of manual removal of placenta, did not substantially differ between the intervention and control groups, whether after adjusting for cluster or after further adjusting for other prognostic factors. There were no maternal deaths.

The proportions of receipt of intravenous plasma expanders and of prostaglandins use were different between intervention and control groups, but the differences were not significant after adjusting for clustering effect.

Discussion

Strengths and limitations of study

In this cluster randomised trial conducted on 25381 vaginal deliveries in 78 maternity units of 13 European countries, the systematic use of a collector bag after vaginal delivery did not modify the rate of severe forms of postpartum haemorrhage. There was no evidence of heterogeneity, the results not differing according to country or size of hospital.

This trial provides new results on an unexplored although controversial aspect of care in the third stage of labour. Although objective measurement has been shown to increase the accuracy of postpartum blood loss assessment compared to visual estimation[15-21], the routine use of a collector

bag is not associated with a significant decrease in severe PPH. This result constitutes an important contribution to the on-going debate on strategies to improve the care of women with PPH and decrease the incidence of severe cases.

Additionally, the cluster-randomised design, the large number of clusters and their diversity provide good external validity to this trial.

There were small deviations from the protocol for data collection, but sensitivity analyses showed that none of these changed the internal validity of the trial.

There was large heterogeneity of baseline rates for the severe event between units (0 to 13.4 %). In theory, such a variation should be an asset, and reflect a broad range of levels of risk in the participating maternity units. However, because these differences were strongly related to the country, there remains some concern regarding the criteria in use for the management of PPH in different parts of Europe. Again sensitivity analysis showed that this aspect did not alter the results.

There was some heterogeneity in baseline data between the intervention and control groups. Heterogeneity in PPH-related practices and PPH rates has been reported across maternity units in Europe, both between and within countries[4, 23]. Although randomization is expected to balance these differences between the two arms, the number of units randomized, although large for a cluster RCT, makes residual imbalance possible although probably very slight. However, analyses were adjusted for the main determinants of PPH (individual level analysis), and baseline rate of severe PPH (cluster-level analysis); in addition, sensitivity analysis indicated that the absence of significant impact of the intervention was similar whether the maternity units had high or low baseline rate of severe PPH. In consequence, any perceived or real imbalance in these characteristics should have little or no impact on the findings.

Hypotheses for the results

Different mechanisms may explain the absence of difference in the rates of severe PPH between maternity units which used the bag and those where blood loss was visually assessed.

This may be due to a lack of compliance to the intervention. However, the persistent absence of difference between the 2 groups when the analysis was restricted to the units where the bag was used in a high proportion of deliveries suggests this is unlikely.

One potential reason for the apparent ineffectiveness of the intervention might be that the bags were actually not used correctly; in particular, there might be concern that the bags were covered most of the time and thus could not be viewed. However, because detailed oral and written instructions were provided and the training video clearly showed the care giver watching the bag and the graduations, such misuse is unlikely to explain the observed lack of effect.

Participation in the study may indicate a particular interest in the management of PPH so that existing management had little room for improvement. However, the variety of baseline rates of severe PPH in these units makes such a selection process unlikely.

It may be hypothesized that the intervention has a double effect, in two opposite directions: increasing the rate of ascertainment through increased vigilance and decreasing the prevalence rate through timely management of excessive bleeding. If these two components were of the same order of magnitude, the global effect would be no effect. However, if this explanation was realistic, one would expect different size of effects with different baseline rates and/or different degrees of compliance. None of this occurred, making it unlikely that a benefit of the intervention in terms of decreased severe outcome was balanced by an equivalent increase in ascertainment. In fact the intervention appeared to increase PPH rates, reflecting possibly, that the intervention was more effective on improving ascertainment than on changing practice.

A concomitant effect in the control group may also have contributed to the absence of difference between the two arms. Contamination of the intervention to control units is

unlikely since participating units were not in contact, and no use of bags was reported in any control unit. Participation in a research study, independently of any specific intervention, has been reported to change behaviors of participants (Hawthorne effect[26]). The hypothesis that the management of PPH would have improved in the control arm is, however, not supported by the absence of change in the rate of severe PPH between the baseline and trial periods in this group.

The most plausible explanation of the negative result of this trial is that having a more accurate assessment of postpartum blood loss is not, by itself, sufficient to change behaviors of care givers and improve PPH management**.** Lack of identification of women with excessive postpartum bleeding is a considerable problem, potentially leading to higher levels of medical intervention if the bleeding progresses to severe haemorrhage. We designed a strategy to increase care-givers awareness. The fact that this has not translated into a change in clinical outcomes probably reflects the complexity of management decisions, which are influenced by multiple factors such as organization of the delivery ward, and how care givers perceive and cope with emergencies.

Comparison with other studies

We did not find any other published study assessing the effectiveness of the collector bag. However we have identified other large multicentre randomised trials in the field of maternal and child health where a diagnostic or screening test was evaluated without any associated instructions about the management of abnormal results[27-29]. None of these trials showed benefit with the introduction of the test. In addition Althabe et al have shown that simple information is not sufficient to impact birth attendants readiness to change[30]. These various reports suggest that the effect of enhanced diagnostic methods should include an accompanying protocol of management, and maybe a specific behavioral intervention, which in effect becomes a "complex intervention".

Conclusions and policy implications

The practical implication of these results for high income countries, is that those units which are using a collector bag (at a cost between 1 and 11 € per bag in Europe) need to reconsider their practice, and maybe reallocate the resources to other aspects of care. Units which are not routinely using the bag should keep the same policy. For resource poor countries positive results of the use of the "kanga collector" have been reported[31]. This needs to be tested in a randomised design. In the current context of reported on-going increase in the prevalence of PPH, further research is needed to develop and test effective strategies to decrease the prevalence of severe PPH through improvement of management. These will probably be multifaceted interventions, and in this context, the collector bag may warrant further investigation.

« What this paper adds » box

What is already known on this subject

Delay in diagnosis and initial care for postpartum hemorrhage (PPH) has been reported, and may result from an underestimation of postpartum blood loss, due to the inaccuracy of visual assessment. A collector bag has been proposed as a useful tool to objectively measure postpartum blood loss. However, the impact of its use has never been tested. Despite lacking evidence, the bag is routinely used in a significant proportion of maternity units in Europe.

What this study adds

Our study suggests that, for western countries, the routine use of a collector bag to objectively assess postpartum blood loss after vaginal delivery, without specific guideline regarding threshold and action, does not reduce the incidence of severe PPH.

Acknowledgements

The project was funded by the European Union (EU) under Framework 5 (contract QLG4-CT-2001-01352).

We are grateful to Professors Allan Donner (Canada) and Pierre Buekens (USA) for their scientific advice; to Stéphane Freze and Myriam Loubriat for their contribution to data collection and cleaning.

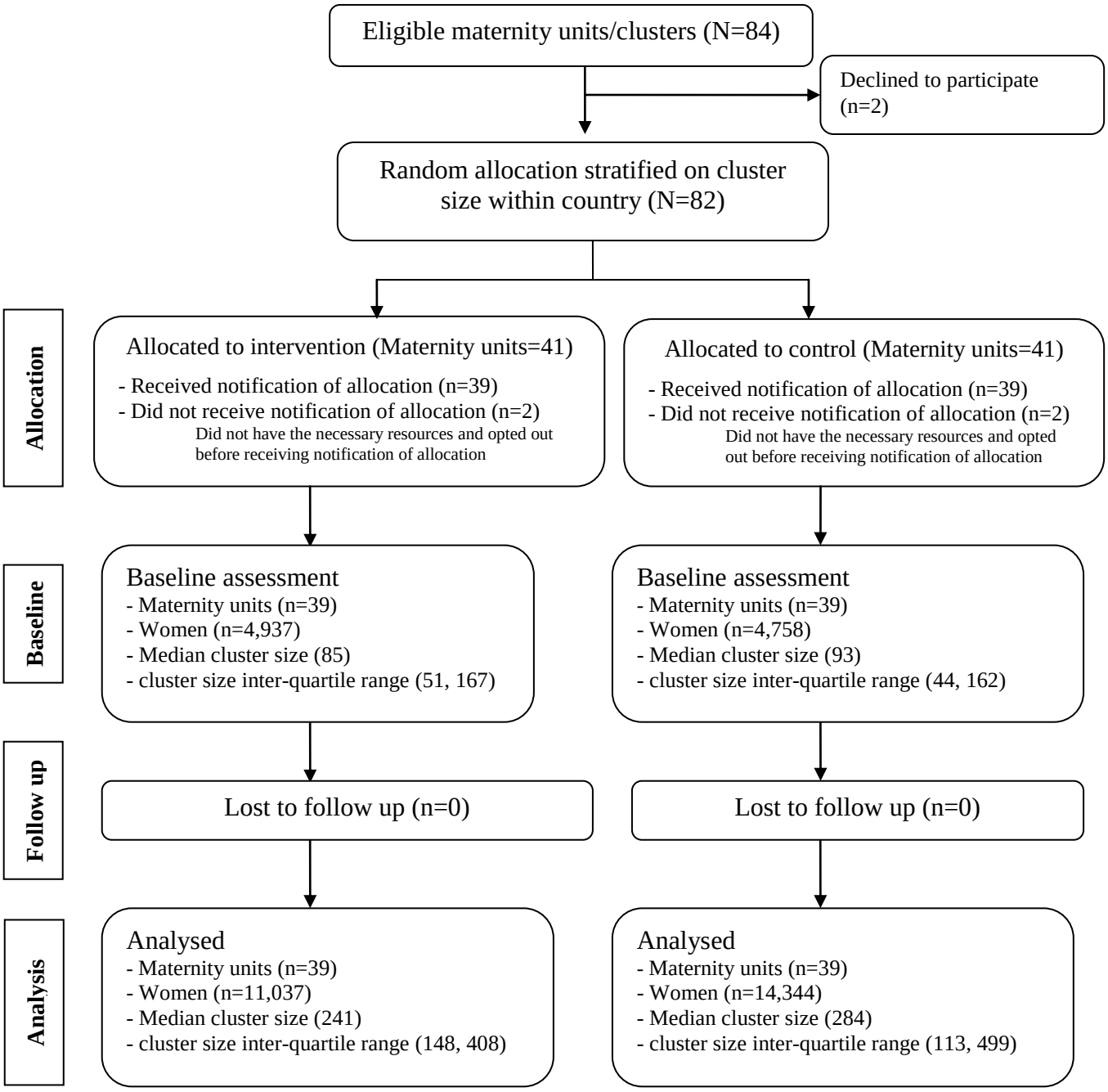
The following people played an essential part in running the trial in their own country and units: ***Austria:*** Co-ordination –Sylvia Artner-Matuschek, Adolf Beck, Daniela Meger David; KH Ried- Penzinger Monika; LKH Bad Ischl – Carola Fuschlberger-Traxler; LKH Heinz Klagenfurt- Leipold; Hanusch KH- Daniela Meger David; AKH Univ- Hans Helmer, Katharina Klein; LKH Kufstein- Andrea Ehm. ***Belgium:*** Ambroise Paré (Mons)- Gilles Ceysens, Annick Nouls, Yaacoub Salame, Linda Van Lierde; Ath- Françoise Clerquin, Pierre Delvoye, Jean Piret; UZ Gent- Paul Defoort, Marleen Temmerman; AZ VUB (Brussels)- Maria Breugelmans, Lieve Devalckeneer, Monika Laubach; Baudour- Joël Annet, Renaud Paquay, Valérie Vandenbosch; Brugmann (Brussels)- Thomas Pezin, Alain Vokaer; Erasme (Brussels)- Christine Kirkpatrick, Anne Maas; Hopital St Pierre (Brussels)- Patricia Barlow, Julie Belhomme, Nordine Ben Ali, Daniel Murillo; Ieper- Colette Berten, Geert Page; Ixelles (Brussels)- Véronique Ziereisen; KUL (Leuven)- Bernadette Bijnens, Bernard Spitz, Joske Timmermans; St Jean (Brussels)- Xavier de Muylder, Christine Stoop; Ste Anne & St Remi (Brussels)- Paul Befahy, Anne Fostier; Tivoli –Maria Fabbricattore , Jacques Francotte, Sylvie Hollemaert; Tournai IMC- Viviane Gadenne; Vésale (Charleroi)- Patrick De Nayer, Didier Oberweiss. ***Denmark***: Co-ordination –Ane Rom, Birgitte Rode Diness; Gentofte Hospital- Anne Barfoed; Glostrup- Ambika Ravn; Hillerød- Gitte Ulriksen; Slagelse- Karen Marie Wigh Felsen; Holbæk- Marianne Brandstrup Larsen; Frederiksberg- Ane Rom.

Finland: Helsinki University Central Hospital- Vedran Stefanovic; Midwifery Institute of Helsinki- Veli-Matti Ulander; University central hospital of Turku- Risto Erkkola; University Hospital of Tampere-Jukka Uotila. ***France:*** Moulin Hospital- Michel Beytout, Catherine Damouret; University Hospital (Nancy)- Brigitte Guillemain; Antoine Béclère; University Hospital (Clamart)-Aurélia Chauveaud; Tenon University Hospital (Paris)- Nadia Berkane, Marie-Christine Chaux; University Hospital (Rouen)- Loic Marpeau, Sabine Sionville; Villleneuve St Georges Hospital- Patricia Tran van. ***Hungary:*** Co-ordination – István Szabó; Baranya County Hospital (Pécs)-József Bódis; City Hospital (Mosonmagyaróvár)- István Barcza; Erzsébet Hospital (Sopron)- Károly Péter Csécsei; Petz Aladár Teaching Hospital (Győr)- Sándor Gardó; Selye János Hospital (Komárom)- László Rokay; Szent Borbála Hospital (Tatabánya)- Mihály Molnár; University Hospital (Sci. Univ. Pécs)- István Szabó, Tamás Csermely; Vaszary Kolos Teaching Hospital (Esztergom)- István Berbik. ***Ireland:*** Co-ordination –Reem Akkawi, Fidelma Cavanagh; Coombe Women's Hospital (Dublin)- Suzanne Kelly; Our Lady of Lourdes (Drogheda)- Dalia Sikafi, Ann Keating; Cavan General Hospital- Iram Basit, Marie McCusker; Midland Regional Hospital Mullingar- Mary Corbet. ***Italy:*** Az. SS. Antonio e Biagio e C Arrigo- Enrico Rovetta; Osp di Bassano del Grappa- Yoram Meir; Osp Civile San Paolo- Antonio Castellano; Osp Civile S Liberatore- Claudio Angeloni; Osp San Massimo di Penne- Quirino Di Nisio; Pres Osp Di Piove Di Sacco- Antonino Oro. ***Netherlands:*** Co-ordination – Marlies Rijnders, Esteriek de Miranda; St Lucas Hospital; Bronovo Hospital. ***Norway:*** Co-ordination –Bente Rønnes; Sykehuset Innlandet; Gjovik- Anne Kari Gjestvang, Elham Mahjoob; Sykehuset Innlandet Elverum- Agneta Stramrud. ***Portugal:*** Co-ordination – Maria Fatima Oliveira, Cristina Ferreirinha; Maternidade Bissaya Barreto (Coimbra)- Ascenção Baía ; Maternidade Daniel de Matos (Coimbra) - José Portugal; H. S. Marcos (Braga) - Lucília Guerra Sousa: H. S. Joao (Porto)- Cristina Ferreirinha; Senhora da Oliveira (Guimaraes) - Alice Santos .***Spain:*** Co-ordination -

Sonia Pisa, Sara Herrero; H. Clínic- Enrique Barrau, Jordi Bellart, Isabel Salgado; H. Vall d'Hebró- Anna Suy; H. Sabadell- Jordi Costa, Maria Grimau; H. Joan XXIII- Ramón Mª Miralles; H. del Mar- Antoni Payà; H. San Joan de Deu- Sergi Cabré; H. Sant Pau- Marta Simó; H. Germans Trias- José Lecumberri. ***Switzerland:*** Co-ordination -Irene Hösli, Gideon Sartorius; Aarau-Monya Todesco; Basel- Gideon Sartorius; Frauenfeld- Verena Geissbühler; Fribourg- David Stucki, Heidrun Schönberger; Solothurn- Suzanne Zakher; St Gallen- Gero Drack, Anika Hey-Moonen.

1 Figure 1

2
3



4

Table 1- Number of maternity units and women in baseline and trial periods by allocation and by country*

	Maternity units		Women							
Country	**Intervention**	**Control**	**Total**	**% total**	**Baseline period**			**Trial period**		
	N	**N**	**N**	**(%)**	**Total**	**Intervention**	**Control**	**Total**	**Intervention**	**Control**
Austria	3	3	1067	3.0	371	219	152	696	359	337
Belgium	8	8	6013	17.1	1552	728	824	4461	1867	2594
Denmark	3	3	1657	4.7	507	272	235	1150	562	588
Finland	2	2	4805	13.7	1347	656	691	3458	1551	1907
France	3	3	3702	10.6	972	544	428	2730	1351	1379
Hungary	4	4	2230	6.4	562	268	294	1668	784	884
Ireland	2	2	3971	11.3	950	300	650	3021	946	2075
Italy	3	3	926	2.6	196	138	58	730	491	239
Netherlands	1	1	1084	3.1	301	130	171	783	322	461
Norway	1	1	668	1.9	143	72	71	525	241	284
Portugal	2	3	3274	9.3	810	338	472	2464	901	1563
Spain	4	3	4351	12.4	1595	1097	498	2756	1239	1517
Switzerland	3	3	1328	3.8	389	175	214	939	423	516
Total	**39**	**39**	**35076**	**100.0**	**9695**	**4937**	**4758**	**25381**	**11037**	**14344**

* Baseline data were unavailable in one maternity unit in the intervention group

Table 2- Baseline characteristics of maternity units and individual women by allocation*

	Intervention group	**Control group**
Maternity units	N=38†	N=39
Rate of caesarean delivery − (%)		
Median	21.1	21.7
Interquartile range	17.4-26.6	14.6-26.0
>1600 deliveries/yr − no. (%)	20 (52.6)	19 (48.7)
Women	N=4937	N=4758
Age − yr		
Mean	29.6±5.4	29.7± 5.5
Median	30.0	30.0
Interquartile range	26-33	26- 33
Missing data − no.	31	23
Mode of delivery − no. (%)		
Spontaneous vaginal delivery	4104 (83.1)	4062 (85.4)
Operative vaginal delivery	833 (16.9)	696 (14.6)
Induction − no. (%)	1080 (21.9)	1043 (21.9)
Number of babies − no. (%)		
Single	4833 (98.5)	4645 (98.6)
Multiple	76 (1.5)	68 (1.4)
Missing data − no.	28	45
Birth weight − grams		
Mean	3315±566.4	3349±549.1
Median	3330	3370
Interquartile range	3020-3660	3050-3690
Missing data − no.	26	29
Prophylactic uterotonics in 3rd stage − no. (%)	3527 (71.4)	3153 (66.3)
Missing data – no.	0	5
Prostaglandin used after birth − no. (%)	212 (4.3)	218 (4.6)
Missing data – no.	0	5
Manual removal of the placenta − no. (%)	204 (4.1)	121 (2.5)
Missing data – no.	0	5
Severe PPH − no. (%)	60 (1.22)	90 (1.89)

* Plus-minus values are mean ±SD. Severe PPH denotes severe Post-Partum Haemorrhage defined by one of the following: maternal death, transfusion, plasma expansion, surgery/embolisation, ICU, recombinant factor VII.

† Baseline data were unavailable in one maternity unit.

Table 3- Main outcomes*

	Intervention N=11037 no. (%)	Control N=14344 no. (%)	ICC (ρ)	Crude odds ratio (95% CI)	Adjusted OR (95% CI)†	Adjusted OR (95% CI)‡
Primary outcome						
Severe PPH	189 (1.71)	295 (2.06)	0.023	0.83 (0.69-1.00) P=0.05	0.83 (0.27-2.60) P=0.8	0.82 (0.26-2.53) P=0.7
Secondary outcomes						
Blood transfusion	86 (0.78)	135 (0.94)	0.011	0.83 (0.63-1.68) P=0.2	0.83 (0.35-1.96) P=0.8	0.80 (0.33-1.90) P=0.6
Plasma expander	127 (1.15)	222 (1.55)	0.022	0.74 (0.59-0.92) P=0.007	0.74 (0.20-2.72) P=0.7	0.95 (0.62-1.46) P=1.0
Surgical procedure or embolisation	50 (0.45)	76 (0.53)	0.012	0.85 (0.60-1.22) P=0.9	0.85 (0.20-3.63) P=0.9	0.78 (0.18-3.40) P=0.7
Manual removal of placental	326 (2.95)	366 (2.55)	0.016	1.16 (1.00-1.35) P=0.05	1.16 (0.76-1.77) P=0.5	1.09 (0.72-1.67) P=0.7
Prostaglandins use	501 (4.54)	766 (5.34)	0.129	0.84 (0.75-0.95) P=0.004	0.84 (0.40-1.77) P=0.7	0.85 (0.40-1.80) P=0.7

* Severe PPH denotes severe Post-Partum Haemorrhage defined by one of the following: maternal death, transfusion, plasma expansion, surgery/embolisation, ICU, recombinant factor VII. ICC denotes Intracluster Correlation Coefficient (ρ)
† Adjusted for clustering (maternity unit)
‡ Adjusted for clustering (maternity unit), age of mother, prophylactic uterotonics using in the third stage, mode of delivery and birth weight

Figure 2

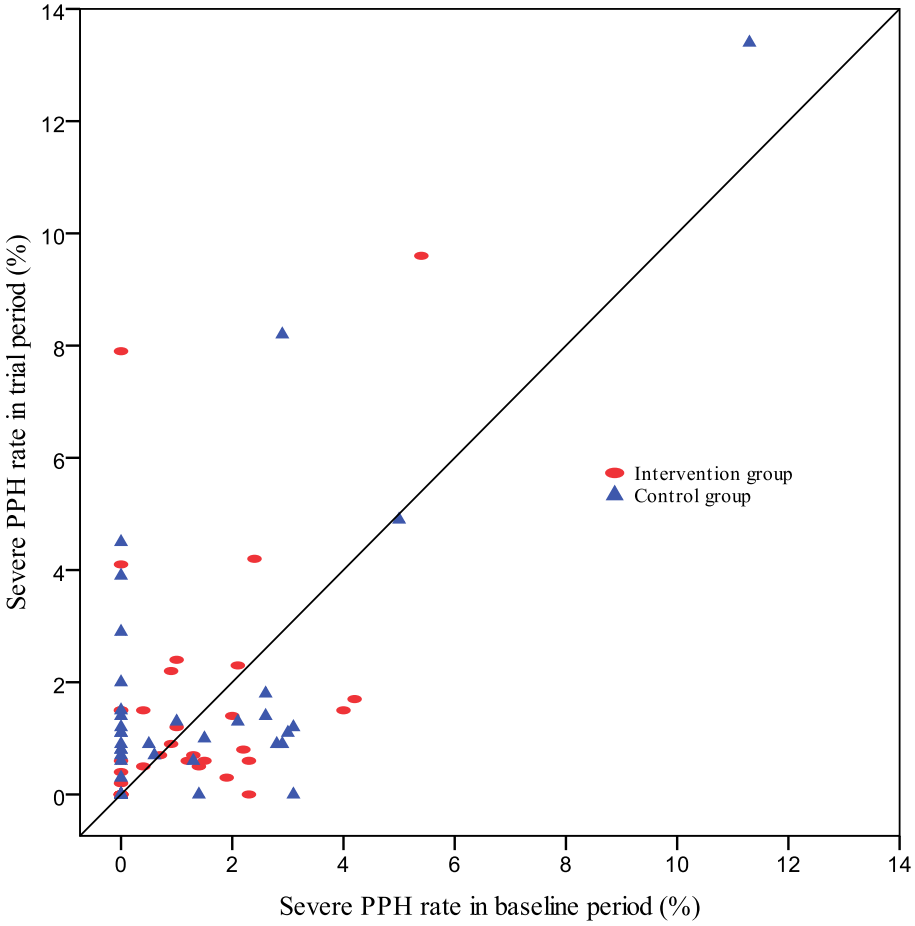
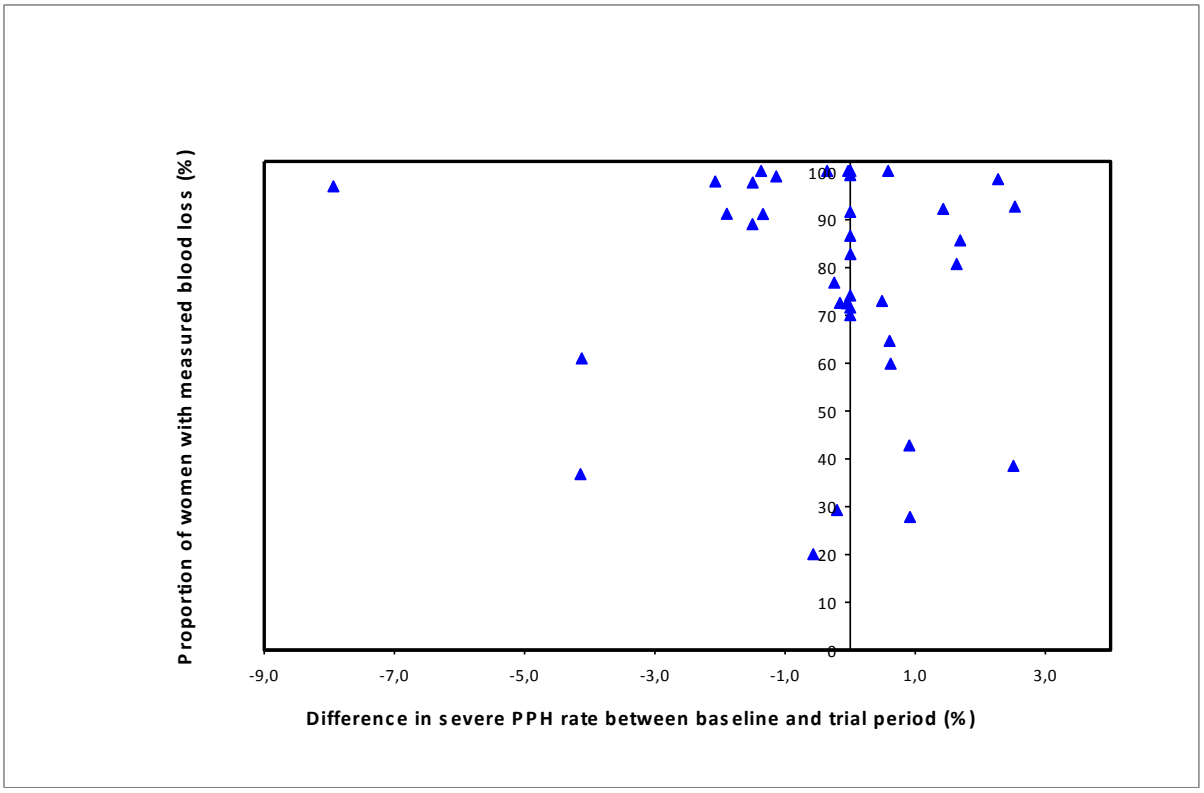

Severe PPH rate in trial period (%)
Severe PPH rate in baseline period (%)
Intervention group
Control group
0
2
4
6
8
10
12
14

Figure 3


Proportion of women with measured blood loss (%)
100
90
80
70
60
50
40
30
20
10
0
-9,0
-7,0
-5,0
-3,0
-1,0
1,0
3,0
Difference in severe PPH rate between baseline and trial period (%)

Legends for figures

Figure 1: Trial flow diagram

Figure 2: Rate of severe post-partum haemorrhage during baseline and trial periods for each maternity unit (Each dot represents one maternity unit. The diagonal line means no change in the PPH rate from baseline to trial period)

Figure 3: Difference in rate of severe post-partum haemorrhage (baseline rate- intervention rate) according to compliance with intervention (% of women with measured blood loss) in the 38 units in the intervention group during the trial period

References

1. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet 2006;367:1066-74.
2. Callaghan WM, Mackay AP, Berg CJ. Identification of severe maternal morbidity during delivery hospitalizations, United States, 1991-2003. Am J Obstet Gynecol 2008;199:133 e1-8.
3. Wen SW, Huang L, Liston R, et al. Severe maternal morbidity in Canada, 1991-2001. Cmaj 2005;173:759-64.
4. Zhang WH, Alexander S, Bouvier-Colle MH, Macfarlane A. Incidence of severe pre-eclampsia, postpartum haemorrhage and sepsis as a surrogate marker for severe maternal morbidity in a European population-based study: the MOMS-B survey. Bjog 2005;112:89-96.
5. Zwart J, Richters J, Öry F, de Vries J, Bloermenkamp K, van Roosmalen J. Severe maternal morbidity during pregnancy, delivery and puerperium in the Netherlands: a natiowide populayion-based study of 371 000 pregnancies. BJOG 2008;115:842-50.
6. Al-Zirqi I, Vangen S, Forsen L, Stray-Pedersen B. Prevalence and risk factors of severe obstetric haemorrhage. Bjog 2008;115:1265-72.
7. Joseph KS, Rouleau J, Kramer MS, Young DC, Liston RM, Baskett TF. Investigation of an increase in postpartum haemorrhage in Canada. Bjog 2007;114:751-9.
8. Roberts CL, Ford JB, Algert CS, Bell JC, Simpson JM, Morris JM. Trends in adverse maternal outcomes during childbirth: a population-based study of severe maternal morbidity. BMC Pregnancy Childbirth 2009;9:7.
9. Sherman SJ, Greenspoon JS, Nelson JM, Paul RH. Identifying the obstetric patient at high risk of multiple-unit blood transfusions. J Reprod Med 1992;37:649-52.
10. Mathai M, Gulmezoglu AM, Hill S. Saving womens lives: evidence-based recommendations for the prevention of postpartum haemorrhage. Bull World Health Organ 2007;85:322-3.
11. Rapport du Comité National d'Experts sur la Mortalité Maternelle (CNEMM). France 2006:http://www.invs.sante.fr/publications/2006/mortalite_maternelle/rapport.pdf.
12. Berg CJ, Harper MA, Atkinson SM, et al. Preventability of pregnancy-related deaths: results of a state-wide review. Obstet Gynecol 2005;106:1228-34.
13. Lewis G. Saving mother's lives: reviewing maternal deaths to make motherhood safer-2003-2005. the seventh report of the Confidential Enquiries into maternal deaths in the United Kingdom. London: CEMACH; 2007.
14. Bouvier-Colle MH, Ould El Joud D, Varnoux N, et al. Evaluation of the quality of care for severe obstetrical haemorrhage in three French regions. Bjog 2001;108:898-903.
15. Bose P, Regan F, Paterson-Brown S. Improving the accuracy of estimated blood loss at obstetric haemorrhage using clinical reconstructions. Bjog 2006;113:919-24.
16. Dildy GA, 3rd, Paine AR, George NC, Velasco C. Estimating blood loss: can teaching significantly improve visual estimation? Obstet Gynecol 2004;104:601-6.
17. Duthie SJ, Ven D, Yung GL, Guang DZ, Chan SY, Ma HK. Discrepancy between laboratory determination and visual estimation of blood loss during normal delivery. Eur J Obstet Gynecol Reprod Biol 1991;38:119-24.
18. Newton M, Mosey LM, Egli GE, Gifford WB, Hull CT. Blood loss during and immediately after delivery. Obstet Gynecol 1961;17:9-18.
19. Prasertcharoensuk W, Swadpanich U, Lumbiganon P. Accuracy of the blood loss estimation in the third stage of labor. Int J Gynaecol Obstet 2000;71:69-70.
20. Razvi K, Chua S, Arulkumaran S, Ratnam SS. A comparison between visual estimation and laboratory determination of blood loss during the third stage of labour. Aust N Z J Obstet Gynaecol 1996;36:152-4.

21. Stafford I, Dildy GA, Clark SL, Belfort MA. Visually estimated and calculated blood loss in vaginal and cesarean delivery. Am J Obstet Gynecol 2008;199:519 e1-7.
22. Tourne G, Collet F, Lasnier P, Seffert P. [Usefulness of a collecting bag for the diagnosis of post-partum hemorrhage]. J Gynecol Obstet Biol Reprod (Paris) 2004;33:229-34.
23. Winter C, Macfarlane A, Deneux-Tharaux C, et al. Variations in policies for management of the third stage of labour and the immediate management of postpartum haemorrhage in Europe. Bjog 2007;114:845-54.
24. European consensus on prevention and management of postpartum haemorrhage, 2005. (Accessed at http://www.euphrates.inserm.fr/inserm/euphrates.nsf/AllDocumentsByUNID/95A14F46F31A5246C125707400485AED?OpenDocument&l=3.1.)
25. Donner A, Klar N. Design and analysis of cluster randomized trials in health research. London: Arnold; 2000.
26. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". J Clin Epidemiol 2001;54:217-24.
27. Cheyne H, Hundley V, Dowding D, et al. Effects of algorithm for diagnosis of active labour: cluster randomised trial. Bmj 2008;337:a2396.
28. Buekens P, Alexander S, Boutsen M, Blondel B, Kaminski M, Reid M. Randomised controlled trial of routine cervical examinations in pregnancy. European Community Collaborative Study Group on Prenatal Screening. Lancet 1994;344:841-4.
29. Grant A, Elbourne D, Valentin L, Alexander S. Routine formal fetal movement counting and risk of antepartum late death in normally formed singletons. Lancet 1989;2:345-9.
30. Althabe F, Buekens P, Bergel E, et al. A behavioral intervention to improve obstetrical care. N Engl J Med 2008;358:1929-40.
31. Prata N, Mbaruku G, Campbell M. Using the kanga to measure postpartum blood loss. Int J Gynaecol Obstet 2005;89:49-50.

Authors' statements

Competing interest statement
All authors declare that the answer to the questions on your competing interest form are all No and therefore have nothing to declare.

Copyright statement
The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in BMJ editions and any other BMJPGL products and sublicences such use and exploit all subsidiary rights

Contribution statements
I declare that I participated in the design of the trial, the implementation of the trial in my country, the central monitoring of data collection, writing the statistical analysis plan, the cleaning and analysis of the data and the drafting and revision of the paper and that I have seen and approved the final version. I had full access to all the data in the study and had final responsibility for the decision to submit for publication. I have no conflicts of interest.
Wei-Hong Zhang

I declare that I participated in the design of the trial, the implementation of the trial in my country, the analysis of the data and the drafting and revision of the paper and that I have seen and approved the final version. I have no conflicts of interest.
Catherine Deneux-Tharaux

I declare that I participated in the design of the trial, the analysis of the data and the drafting and revision of the paper and that I have seen and approved the final version. I have no conflicts of interest.
Peter Brocklehurst

I declare that I participated in the conduct of the trial, writing the statistical analysis plan, the central monitoring of data collection and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Edmund Juszczak

I declare that I participated in the design of the trial, the implementation of the trial in my country, the central monitoring of data collection and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Matthew Joslin

I declare that I initiated the collaborative project, participated in the design of the trial, the implementation of the trial in my country, the central monitoring of data collection, the analysis of the data and the drafting and revision of the paper and that I have seen and approved the final version. I have no conflicts of interest.
Sophie Alexander

I declare that I participated in the design of the trial, the implementation of the trial in my country and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.

Diogo Ayres-de-Campos

I declare that I participated in the design of the trial, the implementation of the trial in my country and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Istvan Berbik

I declare that I participated in the design of the trial, the implementation of the trial in my country and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Marie-Hélène Bouvier-Colle

I declare that I participated in the design of the trial, the analysis of the data and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Gérard Bréart

I declare that I participated in the design of the trial, the implementation of the trial in my country and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Vicenç Cararach

I declare that I participated in the design of the trial, the implementation of the trial in my country and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Risto Erkkola

I declare that I participated in the design of the trial, the implementation of the trial in my country and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Mathias Klein

I declare that I participated in the design of the trial, the implementation of the trial in my country and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Jens Langhoff-Roos

I declare that I participated in the design of the trial and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Alison Macfarlane

I declare that I participated in the design of the trial, the implementation of the trial in my country and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Walter Prendiville

I declare that I participated in the design of the trial, the implementation of the trial in my country and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Jos van Roosmalen

I declare that I participated in the design of the trial, the implementation of the trial in my country and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Babill Stray-Pedersen

I declare that I participated in the design of the trial, the implementation of the trial in my country and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Carolyn Troeger

I declare that I participated in the design of the trial and the revision of the draft paper and that I have seen and approved the final version. I have no conflicts of interest.
Clare Winter