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MEDICINE

Active management of the third stage of labour with and without controlled cord traction: a randomised, controlled, non-inferiority trial

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Summary

Background Active management of the third stage of labour reduces the risk of post-partum haemorrhage. We aimed to assess whether controlled cord traction can be omitted from active management of this stage without increasing the risk of severe haemorrhage.

Methods We did a multicentre, non-inferiority, randomised controlled trial in 16 hospitals and two primary health-care centres in Argentina, Egypt, India, Kenya, the Philippines, South Africa, Thailand, and Uganda. Women expecting to deliver singleton babies vaginally (ie, not planned caesarean section) were randomly assigned (in a 1:1 ratio) with a centrally generated allocation sequence, stratified by country, to placental delivery with gravity and maternal effort (simplified package) or controlled cord traction applied immediately after uterine contraction and cord clamping (full package). After randomisation, allocation could not be concealed from investigators, participants, or assessors. Oxytocin 10 IU was administered immediately after birth with cord clamping after 1–3 min. Uterine massage was done after placental delivery according to local policy. The primary (non-inferiority) outcome was blood loss of 1000 mL or more (severe haemorrhage). The non-inferiority margin for the risk ratio was 1·3. Analysis was by modified intention-to-treat, excluding women who had emergency caesarean sections. This trial is registered with the Australian and New Zealand Clinical Trials Registry, ACTRN 12608000434392.

Findings Between June 1, 2009, and Oct 30, 2010, 12 227 women were randomly assigned to the simplified package group and 12 163 to the full package group. After exclusion of women who had emergency caesarean sections, 11 861 were in the simplified package group and 11 820 were in the full package group. The primary outcome of blood loss of 1000 mL or more had a risk ratio of 1·09 (95% CI 0·91–1·31) and the upper 95% CI limit crossed the pre-stated non-inferiority margin. One case of uterine inversion occurred in the full package group. Other adverse events were haemorrhage-related.

Interpretation Although the hypothesis of non-inferiority was not met, omission of controlled cord traction has very little effect on the risk of severe haemorrhage. Scaling up of haemorrhage prevention programmes for non-hospital settings can safely focus on use of oxytocin.

Funding United States Agency for International Development and UN Development Programme/UN Population Fund/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Department of Reproductive Health and Research.

Introduction

Post-partum haemorrhage is a major cause of severe morbidity and maternal death, particularly in Africa and Asia, where nearly a third of pregnancy-related deaths are associated with haemorrhage.[1] Most such deaths occur because of insufficient uterine contraction soon after birth. Two management packages for the third stage of labour are commonly used, known as active management and expectant management.[2] In active management, several prophylactic interventions are applied in combination. WHO recommends administration of oxytocin soon after delivery of the baby, controlled cord traction, and delayed clamping and cutting of the cord until the health-care worker is ready to apply traction.[3] Uterine massage after placental delivery is included in professional society guidelines.[4] In expectant management, the interventions included in active management are withheld unless needed. Randomised trials[5,6] of active versus expectant management have been done in hospital settings and they included early clamping and cutting of the cord in addition to the WHO components. Overall, the risk of post-partum haemorrhage was more than 60% lower with active management than with expectant management. The timing of cord clamping does not seem to play a significant part in blood loss.[7] Side-effects such as increased blood pressure, nausea, vomiting, and increased placental retention are generally attributed to the use of uterotonic ergot alkaloids.

WHO recommendations published in 2007[3] advocated use of the full active management package, while

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acknowledging the absence of evidence for the effectiveness of some individual components. Estimation of the relative contribution of each of the components could help to determine the most effective way to use the intervention at different levels of health care or by health-care workers with different skills.[6] Some evidence suggests that the uterotonic component can be effective on its own.[8,9] However, the contribution of controlled cord traction is largely unknown.

In controlled cord traction[10] the birth attendant pushes the uterine fundus upwards with one hand while the other hand applies continuous traction on the umbilical cord to extract the placenta.[11] Because the procedure requires manual skills, it has been recommended for use by skilled birth attendants only. However, if traction does not have a meaningful effect on blood loss then it could be omitted and a simplified package focusing mainly on the uterotonic could be recommended. Such a recommendation would have important implications for reducing resources required to train and deploy health-care personnel attending childbirth and could expand access to effective care in places where staff shortages and physical barriers to access remain.

We aimed to find out whether a simplified approach to management of the third stage of labour without controlled cord traction is not less effective than the full active management package at reduction of severe blood loss (ie, ≥1000 mL).

Methods
Study design and patients
We did a multicentre, non-inferiority, randomised controlled trial in 16 hospitals and two primary health-care centres in Argentina, Egypt, India, Kenya, the Philippines, South Africa, Thailand, and Uganda. Before the trial started we assessed the existing policies at the study sites. With the exception of the two primary-care centres in India, all sites practised controlled cord traction. All sites used intramuscular or intravenous oxytocin 10 IU, although the timing of administration differed. In the Philippines, a policy of concurrent use of intramuscular oxytocin and ergometrine was in place before the trial. In Argentina and Kenya, cord clamping was described as delayed, whereas other sites were practising immediate cord clamping. Uterine massage after placental delivery was part of routine management in the Philippines and Thailand and reported as about 50% in Egypt. It was not part of routine policy in any of the other countries.

All women expecting to deliver vaginally at the participating hospitals were potentially eligible. They were excluded if they were first seen in advanced labour (>6 cm cervical dilatation), were not capable of giving consent because of an obstetric emergency, a mental disorder, or distress, or if they planned to have caesarean section, were minors without a guardian, or had twin pregnancies. The fetus had to be at a gestational age of viability according to local limits. Women were asked for written informed consent either before or early in labour. The trial protocol was approved by the WHO Ethics Review Committee and the local ethics committees of the participating institutions.

Randomisation and masking
Random allocation took place as close to the anticipated vaginal delivery as possible. The random allocation sequence was computer generated centrally at WHO. Randomisation was stratified by country and restricted with randomly varying blocks of six to eight. At each facility, a computer programmed with the random allocation sequence was provided and allocation was made once the woman's details were entered into the computer by local investigators. Each site had one spare computer in case of break-down or theft; if both failed the centre had to revert to sealed opaque envelopes as the back-up option. Centres in Egypt and Kenya had to revert to sealed opaque envelopes because of break-down and theft midway through the trial. Neither the investigators nor participants could be masked to the interventions or outcomes.

Procedures
In both groups of the trial, intramuscular oxytocin 10 IU was administered as soon as possible after birth, preferably within 1 min. If a woman had an intravenous line, oxytocin diluted in 100 mL saline could be administered through the line for 5 min. The cord was clamped and cut after manual or visual observation of a uterine contraction, usually around 1–3 min after delivery of the baby. Collection of lost blood was initiated immediately after birth of the baby by passing a drape under the woman's buttocks.[12] Blood collected in the drape was put in a bucket, weighed on a digital scale together with the drape, and the amount recorded in grams. Trial interventions were administered by the staff who managed the deliveries. For the analysis, the weight of the drape was subtracted and the weights were converted to volumes; the value in grams was divided by 1·06 (blood density in g/mL).[13]

The experimental intervention assessed in the trial was the simplified package, in which placental delivery was allowed to occur with the aid of gravity and maternal effort. The birth attendant was expected to note the signs of placental separation such as a gush of blood, uterine contraction, lengthening of the umbilical cord, and visualisation of the placenta in the vagina, and then encourage the woman to cough or push. The control was the full package, in which controlled cord traction was applied immediately after observation of a uterine contraction. The cord was clamped and cut as described for the simplified package. The full package practised in the trial was applied as in other active management trials except for timing of cord clamping. However, available evidence suggests that the timing of cord clamping is not likely to have a major effect on blood loss.[7] The protocol required that after placental delivery the uterine

fundus was rubbed and any clots expressed. Because policies for uterine massage varied and no evidence to support or refute its role is available, individual sites were allowed to implement it or not according to their existing routine. The protocol stated that, if the procedure was used, the uterus should be massaged gently until it contracted and then every 15 min for up to 2 h. Adherence to allocated treatment was defined as hands-off management of the cord in the simplified package group and application of cord traction within 30 min of delivery in the full package group.

The primary (non-inferiority) outcome was severe post-partum haemorrhage defined as measured blood loss of 1000 mL or more at 1 h and up to 2 h for women who continued to bleed after 1 h. The secondary (superiority) outcomes were blood transfusion, use of additional uterotonics, blood loss of 500 mL or more, maternal death, manual placental removal, surgical procedures (hysterectomy, ligation of vessels), the composite outcome of maternal death or severe morbidity (admission to intensive-care unit, hysterectomy, blood loss of 2000 mL or more, uterine inversion), and initiation of breastfeeding.

The Data Safety and Monitoring Committee met three times during the course of the project. The Committee reviewed two interim analyses according to the Haybittle-Peto rule[14] with a superiority criterion on the primary outcome. The committee advised the trial Steering Committee to continue recruitment on both occasions.

Statistical analysis

We aimed to assess non-inferiority of the simplified package compared with the full package in terms of efficacy within a pre-stated non-inferiority margin. We chose the non-inferiority margin by examining the effect of the gold standard, in this case full active management, compared with expectant management (control) in previous trials.[5,15] Estimates of severe post-partum haemorrhage with active and expectant management were taken from published and unpublished data of WHO studies in which post-partum blood loss was measured.[5,9,16] On the basis of those data, we assumed a 1·5% risk of severe haemorrhage with the full package. The severe haemorrhage rate with expectant management was based on data available from earlier trials.[5,15] Values between 3·0% and 4·0% were judged realistic. For sample size estimates, we therefore assumed a 3% risk of severe haemorrhage with expectant management. The simplified package was assumed to preserve 70% of the benefit of the full active management package. With these assumptions, a trial of 22 908 women would have 80% power to show non-inferiority of the simplified package within 0·45% of the severe haemorrhage rate for the full package (ie, $[1·0-0·7] \times [3·0-1·5]$, with a two-sided 95% CI, and an α of 2·5%). In relative terms, this gives a margin of non-inferiority of 1·3 (ie $[1·5+0·45]/1·5 = 1·95/1·5$). The non-inferiority hypothesis was used for the primary outcome. For the

secondary endpoints superiority hypotheses were used. SAS version 9.1 was used for all analyses.

We identified two analysis populations: intention-to-treat population—all enrolled women assessed within groups as randomised, irrespective of adherence—and modified intention-to-treat population—as intention-to-treat population, but excluding women having a caesarean section after randomisation. Our primary analysis and interpretation are based on the modified intention-to-treat population. We chose to focus on this population because for women having a caesarean section (whether elective or emergency), the trial interventions could not be implemented, nor the primary outcome assessed, in the same way as with a vaginal delivery. Elective caesarean section was an exclusion criterion but some emergency caesarean sections occurred after randomisation.

Although some researchers have suggested that in non-inferiority trials per-protocol analysis provides a more conservative interpretation,[17] this notion has been disputed.[18] In this trial, women with much blood loss in the simplified group were more likely to receive cord traction and other interventions to remove the placenta than were women with little blood loss. Because women with great blood loss would be excluded in a per-protocol analysis, the results would favour the simplified package group, and push the results towards erroneous non-inferiority.

Because the effects of uterine massage with or without the full package were unknown, we planned stratified analysis according to the policy of use or non-use of uterine massage. Finally, we did sensitivity analyses with and without the data set from the Philippines. We
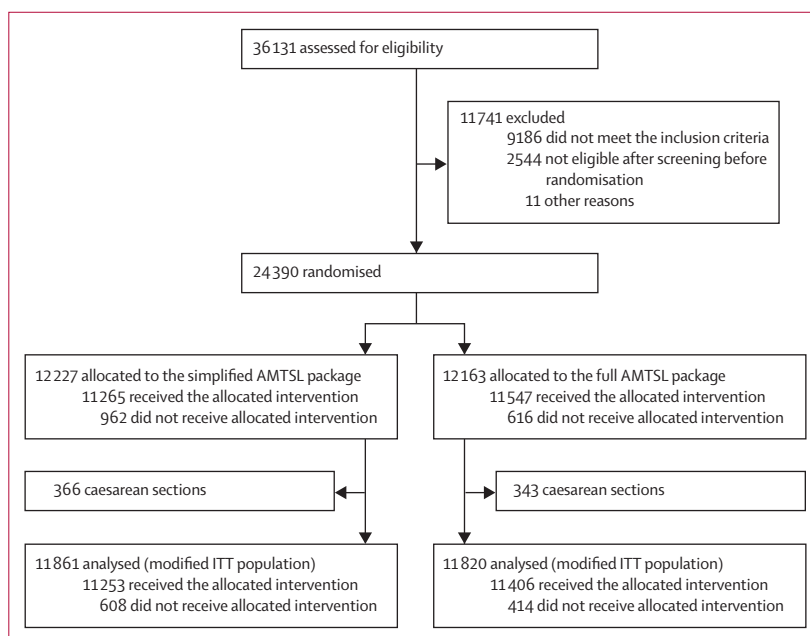

Figure: Trial profile
AMTSL=active management of the third stage of labour. ITT=intention to treat.

	Simplified package	Full package
Age (years)*	25·3 (5·6)	25·3 (5·6)
Primigravidae	5362/11 823 (45%)	5476/11 799 (46%)
Duration of gestation ≥37 weeks	10 713/11 815 (91%)	10 620/11 797 (90%)
Labour induced or augmented	5923/11 815 (50%)	5796/11 795 (49%)
Spontaneous cephalic vaginal delivery	11 266/11 818 (95%)	11 240/11 795 (95%)
Perineal trauma (episiotomy or tear requiring suture)	7667/11 816 (65%)	7616/11 791 (65%)
Birthweight (g)†	3069 (538)	3054 (544)
Baby alive	11 661/11 818 (99%)	11 639/11 797 (99%)

Data are n/N (%) or mean (SD). Denominators vary because of missing data. *N=11 861 for the simplified group, and 11 820 for the full package group. †N=11 818 for the simplified group, and 11 797 for the full package group.

Table 1: Characteristics of women at trial entry and delivery for the modified intention-to-treat population

	Simplified package	Full package
Adherence		
Cord management according to protocol*†	11 253 (95%)	11 406 (97%)
Oxytocin administered†	11 779 (99%)	11 751 (99%)
Delayed cord clamping and cutting†	9321 (79%)	9242 (78%)
Interventions used for final delivery of the placenta‡		
Hands off (maternal effort)§	10 668 (91%)	833 (7%)
Controlled cord traction¶	731 (6%)	11 389 (97%)
Umbilical vein injection‖	10 (<1%)	10 (<1%)
Manual removal ‖	153 (1%)	105 (<1%)
Curettage‖	165 (1%)	98 (<1%)
Hysterectomy‖	2 (<1%)	6 (<1%)
Left in situ because of severe adherence**	2 (<1%)	6 (<1%)
Placenta and baby delivered simultaneously††	29 (<1%)	23 (<1%)

Data are n (%). Denominators vary because of missing data. *Hands-off in the simplified package and controlled cord traction in the first 30 min in the full package. †N=11 861 for the simplified package, and 11 820 for the full package. ‡More than one intervention could be used for any one patient. §N for hands off is 11 776 for the simplified package, and 11 763 for the full package. ¶N for controlled cord traction is 11 777 for the simplified package, and 11 766 for the full package. ‖N for umbilical vein injection, manual removal, curettage, and hysterectomy is 11 814 for the simplified package, and 11 794 for the full package. **N for left in situ is 11 813 for the simplified package and 11 792 for the full package. ††N for delivered simultaneously is 11 814 for the simplified package, and 11 797 for the full package.

Table 2: Adherence to trial interventions and final mode of placental delivery

decided on the sensitivity analysis after the protocol was written but before the analysis. In the Philippines, both study sites were large, high-volume hospitals and frequent closures occurred because of repairs and infections in the neonatal units that led to interruptions in recruitment and loss of study forms (140 of 2527 [5·5%] in the simplified package group and 137 of 2524 [5·4%] in the full package group). When examining the quality of data from the Philippines, we noted that in one of the two sites, the routine policy of oxytocin and ergometrine administration from before initiation of the study continued during the trial. For these reasons, and especially in view of the association of ergometrine with placental retention identified in published work,[5] the trial steering committee decided that the sensitivity analyses were justified. This trial is registered with the Australian and New Zealand Clinical Trials Registry, ACTRN 12608000434392.

Role of the funding source

Results

The figure shows the trial profile. Enrolment took place between June 1, 2009, and Oct 30, 2010. 3455 women were in Argentina, 3527 in Egypt, 2165 in India, 4005 in Kenya, 5051 in the Philippines, 1277 in South Africa, 3181 in Thailand, and 1729 in Uganda. Table 1 shows patient characteristics at trial entry and delivery. Adherence to the oxytocin and controlled cord traction components was high (>90%), with overall package adherence reduced mainly because of the timing of cord clamping and cutting (table 2). Rates of early cord clamping were particularly high in some of the Thai facilities because of hospital policies. Most sites did not practise uterine massage regularly, except Egypt (2507 of 3518 cases, 99·7%), Thailand (2790 of 2976, 93·7%), and Uganda (1715 of 1723 cases, 99·8%). In all other sites uterine massage was used in less than 10% of cases. Some differences between policies before and at the end of the trial are to be expected because the principal investigators attempted to bring their policies in line with trial procedures. About 6% of all women allocated to the simplified package eventually needed controlled cord traction (table 2). We were not able to differentiate whether their placentas were truly retained or whether the total included women whose placentas were already separated but not expelled by maternal efforts.

Table 3 shows primary and secondary outcomes. For the primary endpoint, the upper range of the 95% CI lies slightly above the non-inferiority limit (1·30). The risk of the secondary outcome of post-partum haemorrhage was higher in women given the simplified package than in those given the full package (risk ratio 1·07, 95% CI 1·00–1·14, superiority hypothesis). The rate of manual placental removal was significantly higher in the simplified package group (table 3). Mean blood loss was about 11 mL greater and the third stage about 7 min longer with the simplified package than with the full package. One case of uterine inversion occurred in the full package group. Other adverse events were haemorrhage-related.

In the sensitivity analysis excluding the Philippines (table 4), the summary estimates had slightly larger CIs, and the statistically significant difference in the rate of

	Simplified package	Full package	% risk difference (95% CI)	Risk ratio (95% CI)
Blood loss ≥1000 mL*	239 (2%)	219 (2%)	0·17 (–0·19 to 0·53)	1·09 (0·91 to 1·31)
Blood loss ≥500 mL*	1598 (14%)	1493 (13%)	0·90 (0·03 to 1·78)	1·07 (1·00 to 1·14)
Blood loss in mL†	282	271	10·8 (4·7 to 16·9)	..
Additional uterotonics‡	2434 (21%)	2390 (20%)	0·34 (–0·69 to 1·37)	1·02 (0·97 to 1·07)
Blood transfusion§	62 (<1%)	55 (<1%)	0·06 (–0·12 to 0·24)	1·12 (0·78 to 1·62)
Manual removal of placenta¶	153 (1%)	105 (<1%)	0·40 (0·14 to 0·67)	1·45 (1·14 to 1·86)
Third stage duration in min‖	12·6	6·1	6·5 (6·2 to 6·8)	..
Maternal death**	2 (<1%)	1 (<1%)	0·01 (–0·02 to 0·04)	2·00 (0·18 to 22·0)
Additional surgical procedures††	2 (<1%)	9 (<1%)	–0·06 (–0·11 to 0·00)	0·22 (0·05 to 1·03)
Maternal death or severe morbidity‡‡	20 (<1%)	31 (<1%)	–0·09 (–0·22 to 0·03)	0·65 (0·37 to 1·13)
Baby put to breast within 30 min§§	10 565 (90%)	10 532 (90%)	0·14 (–0·62 to 0·91)	1·00 (0·99 to 1·01)

Data are n (%) or mean (SD) unless otherwise specified. *N=11 621 for both packages. †Denominator is 11 621 for both groups. ‡N= 11 802 for the simplified package, and 11 783 for the full package. §N=11 814 for the simplified package, and 11 790 for the full package. ¶N=11 814 for the simplified package, and 11 794 for the full package. ‖Denominator is 11 662 for simplified package, and 11 648 for full package. **N=11 818 for the simplified package, and 11 798 for the full package. ††N=11 814 for the simplified package, and 11 790 for the full package. ‡‡N=11 616 for both packages. §§N=11 711 for the simplified package, and 11 693 for the full package.

Table 3: **Trial outcomes for the modified intention-to-treat population**

	Simplified package	Full package	% risk difference (95% CI)	Risk ratio (95% CI)
Blood loss ≥1000 mL*	153 (2%)	140 (2%)	0·14 (–0·21 to 0·49)	1·09 (0·87 to 1·37)
Blood loss ≥500 mL*	987 (11%)	927 (10%)	0·65 (–0·22 to 1·51)	1·07 (0·98 to 1·16)
Blood loss (mL)†	266	256	10·2 (3·9 to 16·4)	..
Additional uterotonics‡	1026 (11%)	962 (10%)	0·66 (–0·21 to 1·54)	1·07 (0·98 to 1·16)
Blood transfusion§	50 (<1%)	34 (<1%)	0·17 (–0·02 to 0·36)	1·47 (0·95 to 2·27)
Manual removal of placenta¶	62 (<1%)	64 (<1%)	–0·02 (–0·25 to 0·21)	0·97 (0·68 to 1·37)
Third stage duration (min)‖	11·4	6·2	5·2 (4·9 to 5·5)	..
Maternal death**	1 (<1%)	1 (<1%)	0·00 (–0·03 to 0·03)	1·00 (0·06 to 16·0)
Additional surgical procedures§	0	3 (<1%)	–0·03 (–0·07 to 0·00)	..
Maternal death or severe morbidity††	12 (<1%)	15 (<1%)	–0·03 (–0·14 to 0·08)	0·80 (0·37 to 1·71)
Baby put to breast within 30 min‡‡	8571 (91%)	8566 (91%)	–0·01 (–0·85 to 0·82)	1·00 (0·99 to 1·01)

Data are n (%) unless otherwise specified. N=9411 for the simplified package, and 9420 for the full package. †Denominator is 9403 for the simplified package, and 9409 for the full package. ‡N=9472 for the full package, and 9459 for the full package. §N=9484 for the simplified package, and 9463 for the full package. ¶N=9483 for the simplified package, and 9470 for the full package. ‖Denominator is 9391 for the simplified package, and 9378 for the full package. **N=9487 for the simplified package, and 9471 for the full package. ††N=9407 for the simplified package, and 9415 for the full package. ‡‡N=9468 for the simplified package, and 9461 for the full package.

Table 4: **Sensitivity analysis for the trial outcomes excluding Philippines sites, for the modified intention-to-treat population**

manual placental removal was no longer apparent. Mean blood loss was still greater and the third stage longer with the simplified package than with the full package. We recorded uterine massage after placental delivery and did a pre-specified subgroup analysis of the primary and secondary outcomes with or without uterine massage (data not shown). The interaction test did not suggest that the outcomes differed according to this policy (p=0·61).

Discussion

Our findings suggest that omission of cord traction results in very little, if any, increased risk of severe haemorrhage. The primary outcome of blood loss of 1000 mL or more has a risk ratio of 1·09 (95% CI 0·91 to 1·31) and the upper 95% CI limit crosses the pre-stated non-inferiority margin of 1·30 (appendix). If the upper

limit had been below 1·30 we would have declared the simplified package non-inferior to the full package.[19] The estimated number needed to harm (the reciprocal of the risk difference 0·17%) is 581 (one-sided 97·5% CI 189 to ∞), indicating that for every 581 women receiving the simplified package, one additional woman would have a severe haemorrhage than if all received the full package. We draw two inferences from these results: first, controlled cord traction is safe and its use can be continued in settings in which it is routinely practised; and second, the main component of active management is the uterotonic and in settings in which the full package cannot be used safely, focus should be on the uterotonic component (panel).

The higher rate of manual removal with the simplified package is probably attributable to the high use of ergometrine as prophylaxis in one of the Philippines

See **Online** for appendix

Panel: **Research in context**

Systematic review
We searched PubMed and the Cochrane Library with the terms "postpartum hemorrhage" and "randomised controlled trial" for trials and systematic reviews assessing controlled cord traction. We indentified one review[20] at protocol stage and one pilot randomised trial,[13] which included 200 women and suggested a potential protective effect of controlled cord traction on blood loss. The date of the last search was Feb 7, 2012.

Interpretation
Our study provides the largest evidence so far of the effect of controlled cord traction as part of active management. Controlled cord traction adds only marginally to the beneficial effect of the full package. Because the main component of the management package is oxytocin, in settings in which no skilled birth attendants are present to give the full package, efforts should focus on the uterotonic (primarily oxytocin) to reduce post-partum haemorrhage.

sites as suggested by the sensitivity analysis and earlier systematic review.[5]

Our findings challenge the concept of active management of the third stage of labour as a package of interventions. Effective prevention of post-partum haemorrhage can be accomplished by an intramuscular injection of oxytocin 10 IU after delivery of the baby and present evidence suggests that the uterotonic component of the active management package is the essential component.

The strengths of our study were its size and the diversity of settings of the study sites. We used a secure method of allocation concealment that allocated the women only after specific data were entered. Furthermore, the large number of participants allowed us to implement the study at a realistic scale in line with the prevalence of severe postpartum haemorrhage recorded in other work. The data for measured blood loss were collected consistently across the trial sites. The adherence to trial intervention in terms of cord management was high—in previous trials of active versus expectant management, adherence with cord management was between 46% and 99%.[5] Because of the nature of the intervention we could not do the trial in a double-blind manner. We acknowledged the potential for bias and attempted to minimise this risk by providing standard training for staff who were going to implement the trial interventions. However, we could not make blind outcome assessments.

Our study is relevant both to health-facility settings and to those in which health-care personnel do not have the skills to apply controlled cord traction safely. However, we could not have done the trial in a non-facility setting precisely because such personnel are not available. The issue investigated is also relevant to settings in which skilled attendants are available but women prefer a hands-off mode of placental delivery. Our findings suggest such placental delivery can be safely offered in those circumstances.

Recruitment interruptions and the high number of deliveries in the Philippines resulted in loss of about 5% of forms. However, those losses were similar in both groups of the trial. The high rates of ergometrine use in one of the Philippine hospitals was another justification for the sensitivity analysis, which supported the hypothesis that the overall increase in manual removal could be attributable to ergometrine use. However, this analysis was post hoc and the increase in manual removal could be attributable to other unknown factors.

Our findings have several implications for clinical practice. Simplification of the active management of third stage of labour is possible: an intramuscular injection of oxytocin 10 IU after delivery of the baby should be regarded as the primary intervention for prevention of haemorrhage. Injections are increasingly being used in settings in which skilled birth attendants are not available but a trained health worker is present. In such settings, oxytocin should be used as the routine uterotonic for prevention of post-partum haemorrhage even if controlled cord traction cannot be implemented. Such a policy could also result in cost savings by eliminating the need for training in cord traction skills. In settings in which skilled birth attendants are available, the full package of oxytocin and controlled cord traction should be preferred especially if the shortest possible third-stage duration is desirable. Because a few women will eventually require controlled cord traction with the simplified package and it is the first procedure to be attempted in case of retained placenta, we believe that teaching of controlled cord traction in medical and midwifery curricula should continue.

Our study likewise has implications for future research. A substantial proportion of maternal deaths from haemorrhage take place in settings in which skilled birth attendants and facility-based care are not available. Our findings strengthen the need to focus on strategies to scale up the use of oxytocin in peripheral health-care settings as the primary component of active management of the third stage of labour. In this context, the use of task-shifting strategies to expand access should be considered and assessed. Such scaling-up efforts could be aided by use of prophylactic oxytocin in a pre-filled, compact, auto-disabled device system. A cluster-randomised trial to investigate the effects of this system on post-partum haemorrhage at community level in Ghana is under way (NCT01108289). In settings in which no injection is possible, the role of misoprostol should be assessed with similarly rigorous research.

We were not able to examine any possible role of uterine massage in reducing blood loss in this trial. Uterine massage remains one component of third-stage management that can be implemented without any need for technology or skilled birth attendants. However, it has

not been rigorously assessed so far.[21] The variation in use of uterine massage across study sites suggests that uncertainty remains among practitioners and a thorough investigation of the preventive and therapeutic use of this intervention would be timely.

References
1 Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006; **367:** 1066–74.
2 Festin MR, Lumbiganon P, Tolosa JE, et al. International survey on variations in practice of the management of the third stage of labour. *Bull World Health Organ* 2003; **81:** 286–91.
3 WHO. WHO Recommendations for the prevention of postpartum haemorrhage. Geneva: World Health Organization, 2007.
4 Clinical Practice Obstetrics Committee. Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage: No. 235 October 2009 (Replaces No. 88, April 2000). *Int J Gynecol Obstet* 2010; **108:** 258–67.
5 Begley CM, Gyte GML, Murphy DJ, Devane D, McDonald SJ, McGuire W. Active versus expectant management for women in the third stage of labour. *Cochrane Database of Syst Rev* 2010; **7:** CD007412.
6 Keirse MJC. What does prevent postpartum haemorrhage? *Lancet* 1998; **351:** 690–92.
7 McDonald SJ, Middleton P. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Syst Rev* 2008; **2:** CD004074.
8 Cotter A, Ness A, Tolosa JE. Prophylactic oxytocin for the third stage of labour. *Cochrane Database Syst Rev* 2001; **4:** CD001808.
9 Gulmezoglu AM, Forna F, Villar J, Hofmeyr GJ. Prostaglandins for preventing postpartum haemorrhage. *Cochrane Database Syst Rev* 2007; **3:** CD000494.
10 Spencer PM. Controlled cord traction in management of the third stage of labour. *BMJ* 1962; **1:** 1728–32.
11 WHO. Managing complications in pregnancy and childbirth. World Health Organization, 2007. http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9241545879/en/index.html (accessed Feb 19, 2011).
12 Patel A, Goudar SS, Geller SE, et al. Drape estimation vs. visual assessment for estimating postpartum haemorrhage. *Int J Gynaecol Obstet* 2006; **93:** 220–24.
13 Althabe F, Aleman A, Tomasso G, et al. A pilot randomized controlled trial of controlled cord traction to reduce postpartum blood loss. *Int J Gynecol Obstet* 2009; **107:** 4–7.
14 Piantadosi S. Clinical trials: a methodological perspective. 2nd edn. Hoboken, NJ: John Wiley & Sons, 1997.
15 Gülmezoglu AM, Widmer M, Merialdi M, et al. Active management of the third stage of labour without controlled cord traction: a randomized non-inferiority controlled trial. *Reprod Health* 2009; **6:** 2.
16 Widmer M, Blum J, Hofmeyr GJ, et al. Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial. *Lancet* 2010; **375:** 1808–13.
17 ICH Steering Committee. Statistical Principles for Clinical Trials (E9). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. International Conference on Harmonisation 1998. http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html (accessed Feb 19, 2011).
18 Garrett A. Therapeutic equivalence: fallacies and falsification. *Stat Med* 2003; **22:** 741–62.
19 Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006; **295:** 1152–60.
20 Mshweshwe NT, Hofmeyr GJ, Gülmezoglu AM. Controlled cord traction for the third stage of labour. *Cochrane Database Syst Rev* 2009; **4:** CD008020.
21 Hofmeyr GJ, Abdel-Aleem H, Abdel-Aleem MA. Uterine massage for preventing postpartum haemorrhage. *Cochrane Database Syst Rev* 2008; **3:** CD006431.