A phase 2 clinical trial of the PPH Butterfly, a new device to 'turn off the tap' of Post-Partum Hemorrhage.

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Running Title

Clinical testing of the PPH Butterfly device.

ABSTRACT

Objective: To assess the acceptability, safety and efficacy of the PPH Butterfly, a new uterine compression device, in women with postpartum haemorrhage (PPH).

Design: A phase two clinical device trial using matched historical controls, with accompanying grounded theory study.

Setting: UK university consultant obstetric unit.

Population: women with PPH after vaginal birth unresponsive to initial oxytocin therapy. Outcomes were compared to historical controls matched on blood loss, parity and type of birth.

Methods: after oral consent, trained staff used the device in additional to normal care.

Main Outcome Measures: The primary outcome was additional blood loss >1000mls. Qualitative interviews assessed device feasibility and acceptability.

Results: Of the 57 recruits, two-thirds were primiparous and almost half had undergone operative birth. Two percent of recruited women had additional blood loss of over 1000mls compared to 8% of 113 controls (adjusted odds ratio 0.13, 95% CI (0.02 to 1.09)). Women treated with the device received significantly more additional treatments and had higher rates of exclusive breast-feeding at discharge. There were no serious adverse events related to the device.

In 47 interviews, participants, birth partners, clinicians and attending midwives viewed the device positively. Clinicians found it useful to stop blood loss and diagnose the source of bleeding.

Conclusions: the PPH Butterfly is acceptable and may have clinical benefits: it is a promising device for PPH management.

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Keywords: postpartum haemorrhage, childbirth, oxytocin, third stage of labour, uterine compression.

Registration: prospective ISRCTN (15452399); www.isrctn.com/ISRCTN15452399

Tweetable Abstract

In 57 women with unresponsive PPH, the PPH Butterfly functioned well, was safe and well accepted.

INTRODUCTION

It is estimated that 60,000 women die from postpartum haemorrhage (PPH) each year.[1,2] The initial treatment of uterine atony involves discontinuation of causative agents, bladder emptying, uterine massage, uterotonics and bimanual compression (BMC).[3,4] As BMC requires the insertion of a fist into the vagina, an act that is both painful and has overtones of gender-based violence, it is currently only used in extreme situations.

If, however, uterine compression could be performed in a less invasive manner, then it could act as an effective first aid to abruptly 'turn off the tap' of PPH[5] whilst other therapies are administered. Furthermore, where the bleeding continues despite compression, the source is likely to be vaginal lacerations. If correct, then the device would also localize the cause of the PPH.

The PPH Butterfly (PPHB) is a simple intravaginal device that is inserted beneath the uterus in place of the fist, providing a platform against which the abdominal hand can apply pressure to the uterus (Fig 1, video appendix 1).[6] This is the first clinical report of the device use. The objective of the study was to assess its acceptability, safety and efficacy.

METHODS

The study was a prospective cohort study using mixed methods in a UK university consultant obstetric unit. Clinical outcomes were compared to a matched historical cohort. Our objectives were to investigate the device's acceptability, safety and efficacy.

Women at high risk of PPH could also be recruited antenatally with advance informed consent sought in case of PPH. However, most participants were recruited at the time of their PPH. After initial uterotonic treatment, they were briefly informed about the device and verbal consent sought for its use. Women who declined or who were uncertain were not included.

All recruiting doctors underwent training in consent and device use. Women who had a clinical PPH following vaginal birth and placental delivery and who were unresponsive to first line treatment with oxytocin +/- ergometrine were recruited. The device was used within 1 hour of birth (or 15 minutes of manual placental removal). Women with communication difficulties were not approached, nor were those under 16 years old, with clotting disorders, stillbirth, or unreversed female genital mutilation.

The device was inserted vaginally by the obstetrician, and the uterus compressed against it by pushing through the abdominal wall. If the bleeding stopped, the pressure was maintained for 5 minutes before releasing the pressure. If the bleeding restarted after release, then the uterine compression was restarted and continued for further cycles of 5 minutes each, up to a maximum of 25 minutes. If then the bleeding persisted, then the compression was restarted and the woman transferred to theatre for examination under anaesthetic. If the bleeding did not stop with compression, then the device was removed and the genital tract examined for lacerations. During use of the device, medical therapies with oxytocin, ergometrine, carboprost, tranexamic acid and surgical interventions were continued as required according to normal practice. Blood loss at time of insertion and at the end of the bleeding were assessed by the clinicians using weighing of swabs and measuring of blood volume where available.

The day following the birth, a research midwife sought fully informed consent to continue study participation and collect outcome data. Postnatal haemoglobin levels were obtained in non-transfused women and the value obtained closest to 24 hours postnatally used.

An interim safety analysis was carried out after 15 recruits and the Independent Data and Safety Monitoring Committee (ISDMC) deemed the study safe to continue.

The PPHB prototype was made by Protolabs Ltd (Telford, UK) from computer aided designs by Astarcor (High Wycombe, UK) in collaboration with the University of Liverpool. The single use

polypropylene prototypes (PPM H250) underwent ethylene oxide sterilization by Anderson Caledonian Ltd (Bellshill, UK).

Clinical outcomes were based on the PPH Core Outcome Set.[7] The primary outcome was blood loss of over 1000mls after first device use. In the historical controls this was calculated as the total blood loss minus the blood loss at the time of insertion in the matched case (see supplement figure S1). Secondary outcomes included total blood loss, use of additional interventions and organ dysfunction.[8]

The outcomes for cases were compared with those of a matched historical cohort of women with PPH who had given birth at the same hospital two years previously. Each case was matched to two controls on parity (primiparous or multiparous) and mode of birth (spontaneous vaginal or operative vaginal). In addition, each control had to have at least as much blood loss as the blood loss at the time of first device insertion for the case. Controls were selected by searching the hospital database and finding the next two successive women who met the criteria after the same date and time of the PPHB case's birth two years previously.

Audit data from the recruiting hospital suggested that 42.5% of those with a PPH of 500mls at vaginal birth ended with additional blood loss of over 1000mls. It was calculated that 118 recruits and 236 controls would provide 90% power to detect a 40% relative reduction in additional 1000mls blood loss to 25.5%.

All data were collected initially on paper, then double entered by two researchers independently into a REDCap database (Vanderbilt University, Tennessee, USA); discrepancies were resolved by ADW. Data were analysed under the intention-to-treat principle. Logistic regression was used to estimate the odds of additional blood loss of over 1000mls, adjusting for the cause of PPH (atonic or other) and blood loss at recruitment (≥1000mls or other). Two sensitivity analyses were undertaken: McNemar's test to account for the matched data, and a logistic regression model adjusting for the matching variables. Logistic regression was used for binary secondary outcomes. Linear regression

was used to compare the number of additional interventions used between the two groups. The Kruskal-Wallis test was used to compare the number of units transfused in women who had received a blood transfusion. Analyses were performed using SAS (v9.4).

QUALITATIVE ASSESSMENT

Qualitative research using grounded theory[9] was undertaken to explore the experience, feasibility, usability and acceptability of the device for women, obstetricians, midwife observers and birth partners. Informed written consent was obtained from each participant; interviews continued until data saturation.[9,10]

Face-to-face semi-structured interviews were conducted within 3 weeks of recruitment; open-ended questions were digitally recorded and transcribed verbatim. Most interviews with women and birth partners were conducted in the home with clinical interviews in the hospital. Data were analysed using framework analysis[11,12]: data from each group were analysed separately before exploring the commonalities and diversity of views.

PATIENT AND PUBLIC ENGAGEMENT

A Public Engagement Panel (PEP) was consulted throughout the original development of the device and its testing; the co-ordinator of this group (EH) was a full member of the Trial Management Group (TMG) that met each month and provided ongoing liaison with the PEP. The PEP provided initial input into the consent and recruitment process, met the PI and research midwives 6-monthly during the study to provide ongoing advice and feedback, and again at the end to discuss conclusions and overall assessment of the outcomes.

The clinical study was approved from the Health Research Authority (HRA) and the North West Liverpool Central Research Ethics Committee (Ref 17/NW/0373). The qualitative study was approved by the Office for Research Ethics Committees Northern Ireland (17/NI/0140). Both studies were sponsored by the University of Liverpool.

FUNDING

Funding for the study was provided by the National Institute for Health Research (NIHR) Invention for Innovation (i4i) program (II-LA-0715-20008) after external peer review. A representative attended trial steering committee meetings, but had no direct involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication

RESULTS

The study aimed to recruit 118 women over a 12-month period. After only 45 women had been recruited over 9 months, the Trial Steering Committee (TSC) and IDSMC reviewed the safety reports and interim outcomes for the participants. Given project timelines and funding limits, as well as the inability of the study design to provide definitive evidence of efficacy, they recommended that recruitment be stopped at the end of pre-planned 12 months of recruitment rather than pursuing the 118 target.

In total, 57 women were recruited (02Jan2018-21Dec2018; Figure 2). Demographics and clinical characteristics are shown in Table 1. The median blood loss at the time of device insertion was 750mls (IQR: 550-1300, range: 400-2600). The device was used was for a median of five minutes (IQR: 4-8) and reinserted a second time in five women when bleeding restarted.

Fifteen adverse events were reported for 13 women (Supplementary Table 1). The 3 serious adverse events were all unrelated to the device. In two women, vaginal grazes were seen after use of the device (one required a single suture) but it was unclear whether these had been caused by use of the device. One woman had an episiotomy breakdown that required outpatient antibiotic treatment.

In three women, proper use of the device was made difficult by the immediately postpartum lax vaginal walls. In one woman, tissue caught in the device causing sudden pain, whilst in the others it

only hindered effective device use.

When questioned about pain during use of the device, 16% had pain on insertion and 34% on uterine compression (Supplementary Table 2). However, all women said that they would want the device to be used again if they bled after a future birth.

Ninety-eight percent of clinicians stated that it was easy to use; they said that it stopped the bleeding in 52% of cases and assisted in making a diagnosis in 52% of cases (Supplementary Table 3). In 86% of cases it was thought that the device assisted with the management overall, and in 93% of cases the doctor wanted it to be available in future for clinical use.

The PPHB cases were similar to the matched historical controls in most respects (Table 1). However, more index cases had atonic PPH than controls, and labor induction and oxytocin augmentation were also more common.

Additional blood loss of over 1000mls occurred in 1 of the 57 women treated with the PPHB, but 9 of the 113 controls (adjusted odds ratio 0.13 (95% CI: 0.02 to 1.09), p=0.06. Table 2). Sensitivity analyses to account for matching did not change the conclusions (Supplementary Tables 4-5). The 'failed' PPHB case had the device inserted at 750mls from an atonic uterus following spontaneous vaginal birth and failed BMC (Table 3); final blood loss was 1955mls. The nine controls with 'additional' blood loss of more than 1000mls had undergone a mixture of spontaneous (44%) and operative (55%) vaginal births; 78% had uterine atony as a cause, and 22% had trauma as a cause.

PPHB cases received more concurrent measures to stop the bleeding than controls (mean (SD) 6.51 (1.60) versus 3.66 (1.85), adjusted mean difference: -2.37, 95% CI (-2.89 to -1.84), Table 4). The increased use of interventions covered medical therapies (e.g. ergometrine and tranexamic acid), manual therapies (e.g. BMC and fundal massage) as well as 'surgical' interventions (e.g. Bakri balloon and repair of complex tears).

Of those treated with the PPHB, 14% received a blood transfusion before hospital discharge compared to 24% of historical controls (Table 5). Those not transfused had a slightly higher postnatal

hemoglobin. A significantly higher number of PPHB women were exclusively breastfeeding at hospital discharge. However, there were no other major differences in clinical outcomes between the PPHB and historical control groups.

QUALITATIVE FINDINGS

Fifty-one interviews were conducted with 12 recruited women, 12 birth partners, 16 users and 11 midwife observers. The interviews took place January - November 2018 and lasted from 7 - 6I minutes. Quotes are provided in Table S7.

The majority of the participants interviewed had some form of analgesia at the time of birth, primarily epidural. Most gave birth in lithotomy position; more than half were vacuum or forceps births on delivery suite. A small number who gave birth on the midwifery-led unit had the device used with minimal or no analgesia.

Women

Most of the women reported no pain with device use. Several mentioned they were aware of insertion and/or removal but that it was not painful. Those who had already received BMC perceived the device to be more comfortable. Those who had not, thought that BMC sounded more invasive and more uncomfortable, and believed the PPHB would be preferable.

The removal of the need to go to theatre was important to several women as it meant they could remain with their newborn and birth partner, and this played a part in consenting to device use.

Many were affected by exhaustion, blood loss, drugs, pain, or fear. However, they were also aware that the situation was serious and wanted this resolved. The requirement to stop the bleeding quickly was their priority, and they were satisfied that the device had helped to stop or reduce the bleeding. Some were less aware of the urgency, but described that they would prefer not to know

what was happening at the time. One indicated a preference for the health professionals to take control of the situation.

Obstetricians

All doctors interviewed had at least 3 years of obstetric training; the majority had extensive experience and used BMC frequently.

The quality of the PPHB training was commended, especially the benefits of repeated mannequin insertions. The majority found the device easy to use and thought it more comfortable for the woman than BMC. They also believed it enabled better maintenance and sustenance of uterine compression. Some felt the device enabled better management of the emergency than BMC, as they had a better command of the room due to their elevated position.

Ease of use was emphasized, but some had concerns about the risk of vaginal wall entrapment. Vaginal wall laxity was considered especially a problem due to the recruits being within 1 hour of birth. A few queried whether the device could cause trauma, especially if they had caught tissue themselves.

The majority were unable to say whether the device reduced bleeding because participants had also received standard PPH treatment. However, some believed it was a useful adjunct tool for performing compression whilst waiting for the drugs to take effect. Several suggested that a randomized controlled trial would be necessary to assess effectiveness. Some also felt that the device was useful in assessing blood loss.

In addition to its role in managing bleeding, obstetricians also commented upon the benefits of using the device as a diagnostic tool to locate bleeding source. Most would recommend the device, saw the experience as positive, thought it was a useful addition to standard treatment, and would be happy to use the device again.

Midwife Observers

Most of interviewed midwives were busy providing care and so struggled to recall accurate details of the device use. Furthermore, the hemostatic benefits of the device were unclear due to concurrent administration of uterotonic drugs. Despite this, they believed the device to be a positive addition to standard treatment, even though they struggled to see where it fitted into the PPH protocol.

It was generally believed that the device was less invasive, less painful, less traumatic, less aggressive and preferable to BMC, even by those who had been skeptical prior to use. Several midwives stated that they would prefer the device used on them to BMC if they personally experienced a PPH because it was less intimate and appeared more comfortable. They felt that effective BMC was usually difficult to perform due to both maternal discomfort and clinician effort, and the device would make the task less tiring and more effective.

Midwives were confident in the clinician's ability to use the device. A few stated that they would not have allowed the clinician to use the device if they were unsure as to their capabilities.

Birth Partners

The quantity of blood, the number of people in the room and a rapidly changing situation left some partners feeling panic, fear and confusion. However, praise for the team caring for the woman was reiterated throughout interviews with birth partners citing confidence in the clinicians and the rapport that had already developed between clinician and the woman.

The majority of birth partners thought the device was a quick, effective, straightforward process that was better than the alternatives (BMC or surgical intervention). The comfort of their partner was also important to birth partners.

Overall, birth partners considered the device useful and were pleased that it was available. Several saw the device and remarked on its appearance. However, they accepted the device as a medical aid

and did not feel it was unusual in the setting. They echoed the views of women that it was worth trying the device in order to resolve the emergency.

DISCUSSION

Main Findings

The main message of this study is that the PPHB is both safe and acceptable in the hands of well-trained clinicians. Currently, mechanical devices are used as a last resort in PPH as they are so invasive. The PPHB is less invasive and so can be used early in PPH care as a tool for both diagnosis and treatment. Clinicians, participants and observers all found it acceptable. As it was used alongside standard therapies, most were unsure whether it was responsible for the cessation of blood loss. However, most felt that it provided a useful management tool, both to stop the bleeding, and to determine the source of the blood loss. Virtually all who experienced its use would want to use it again.

Strengths and limitations

The main strength of this study is the detailed 360° assessment conducted of the device use. This included clinical outcomes, acceptability, historical control group and a detailed qualitative assessment, giving a holistic view of the device from multiple perspectives. The use of the device in a normal practice setting by trainees working on a busy hospital delivery suite gives insight into how it might function in routine practice. However, the cases and users may not be completely representative of all women with PPH. It is likely that only competent and confident trainees were prepared to recruit to the study, and this may be a factor in the observation that far more concurrent therapies were used in the PPHB cases than in controls. However, some of the increase may also be accounted for by changes in practice (e.g. introduction of tranexamic acid),

ascertainment bias (as some therapies like fundal massage may not be recorded routinely in the case notes), and the preponderance of atonic uteri in the PPHB cases lading to more uterotonic therapies. All these demonstrate that, despite the careful matching for parity, mode of birth and multiple pregnancy, it was not possible to sufficiently control for aetiology and practitioner. The validity of the comparison is therefore in question, and this, along with the small sample size, are the obvious weaknesses of the study. Furthermore, it is conceivable that those interviewed provided positive narratives as a response to good outcomes from a perceived life-threatening situation rather than because of the device itself. These issues will only be resolved through a randomised controlled trial.

Interpretation

The main messages of this assessment of the new PPHB device are that it appears to be both safe and acceptable in the hands of well-trained clinicians. Currently mechanical methods are very invasive and so are generally used as a last resort. The PPHB is different in that it is designed to be less invasive and to be used early in the PPH pathway as a tool for both diagnosis and treatment. Despite this early use, clinicians, participants, observing midwives and birth partners all found it acceptable. Given that the device was used alongside concurrent standard therapies, most clinicians and midwives could understandably not be confident that it alone was responsible for the cessation of blood loss. However, most felt that it provided a useful management tool, both to stop the bleeding, and to determine the source of the blood loss. Virtually all who experienced its use would want it used again in a future pregnancy in the event of a PPH.

Moving forward, it will be important to determine how much training each clinician needs before use. In this study, each practitioner had around 10 minutes of training on a custom-made mannequin with repeated insertions to ensure ‘muscle memory’. However, once available outside of a study setting, care will be needed to ensure that users are appropriately trained. This is especially important given the potential for entrapped tissue or vaginal wall grazes. Since this study, the PPHB has been modified to reduce the risk of trauma, but some risk remains, and monitoring will be

needed when introduced into clinical practice.

CONCLUSIONS

This trial of the PPH Butterfly has demonstrated its acceptability, as well as initial safety and efficacy. However, the numbers tested were small and the historical control group provides an imperfect comparator group. To demonstrate efficacy requires a randomised trial, and this study provides evidence of the required clinical equipoise, and gives confidence that recruitment is ethical.

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INDEPENDENT TRIAL STEERING COMMITTEE: Professor Jim Thornton (Chair), Dr Annette Briley, Dr Graham Tydeman.

INDEPENDENT SAFETY and DATA MANAGEMENT COMMITTEE: Dr Shireen Meher (Chair), Professor Alex Heazell, Dr Chris Sutton.

Disclosure of Interests

ADW and PW are co-inventors of the PPH Butterfly. The patent is held by the University of Liverpool, but ADW and PW could in future receive a share of any profits generated from commercialization. No other authors declare any relationships or activities that could appear to have influenced the submitted work.

Contributions to authorship

Contributors: ADW conceived of the device and study, is co-inventor of the device, drafted the protocol, led the trial management group and drafted and revised the paper. He is the guarantor. CC conducted the postnatal data collection, managed the data and revised the paper. WT devised the training programme and trained the clinician recruiters, led the qualitative study, conducted interviews, analysed the qualitative date and drafted and revised the qualitative sections of the paper. AR-H was the study statistician, managed the data management, designed the case report

forms and online database, analysed the data, produced the tables and revised the paper. PW co-invented the device, sat on the trial management group, developed training tools and revised the paper. LB developed the health economics evaluation, conducted the analysis and revised the paper. VE conducted the health economics analysis, drafted and revised the health economics sections of the paper. LC conducted postnatal data collection, managed the data and revised the paper. EH was the 'expert through experience' on the trial management group and assisted with conceptualisation and design of the project, trouble-shooting, interpretation of the results, and revising the paper. DL assisted with the grant application, was on the trial management group, managed the project and supported editing of the paper. CB supervised the staff training in device use and the qualitative aspects of the study, assisted with the data management and analysis and revision of the paper. SL provided methodological advice and statistical support for the grant application, study design and supervised the study statistician during data collection, analysis and write-up. TF supported the conceptualisation of the project and obtaining funding, provided resources for device design and modification, and approved the paper. RTE led the health economics analysis, working throughout on conceptualisation, grant application, supervision of data collection and analysis and revision of the paper. TL led on the staff device training and qualitative analysis, working throughout on conceptualisation, grant application, supervision of training, data collection and analysis, and the revision of the paper.

Details of Ethics Approval

Approvals for the clinical study were obtained from the Health Research Authority (HRA), the North West - Liverpool Central Research Ethics Committee (11th August 2017; Ref 17/NW/0373). Ethical approval for the qualitative study came from the Office for Research Ethics Committees Northern Ireland (9th August 2017; 17/NI/0140). Both the clinical and qualitative studies were sponsored by

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Table / Figure Caption List

Figure 1. Mechanism of action of the PPH Butterfly

Figure 2. CONSORT flowchart

Supplementary Figure S1. Primary outcome assessment. *Hypothetical outline of study outcomes in those in the PPH group and controls, designed to mimic a randomised trial where randomisation occurs at the time of device insertion. In the index case above, the total blood loss was 1100mls. Blood loss on insertion of the PPH Butterfly device was 550mls and therefore additional blood loss was 1100 – 550 = 550mls. Since this is lower than 1000mls the primary outcome value would be 'No'. The two controls are selected from 2 years prior to the index case, progressing forward from exactly 2 years previously until 2 matches are found who had at least the amount of blood loss at which the device was used in the index case (550mls in this case). The comparable outcome in the controls is the blood loss beyond the amount at which the device was inserted in the index case. For control 1, 'additional blood loss' is calculated as 800 – 550 = 250mls. For control 2 the 'additional blood loss' is calculated as 1600 – 550mls = 1050mls. Control 1 would therefore have primary outcome value as 'No' and control 2 would have a 'Yes'.*

Table 1: Baseline characteristics

Table 2: Primary outcome analysis: Logistic Regression

Table 3: Further details on participants who had additional blood loss >1000mls

Table 4: Interventions used within 24 hours of birth to stop the bleeding

Table 5: Secondary Outcomes

Supplementary Table S1: Adverse Events and Serious Adverse Events

Supplementary Table S2: Participant questionnaire results

461 **Supplementary Table S3:** Clinician questionnaire results

462 **Supplementary Table S4:** Primary Outcome Sensitivity Analysis: McNemar's test for matched data

463 **Supplementary Table S5:** Primary Outcome Sensitivity Analysis: Logistic regression adjusting for
464 matching factors

465 **Supplementary Table S6:** CONSORT flow diagram reasons

466 **Supplementary Table S7:** Quotes from participants, birth partners, recruiting doctors and midwives

467 **Supplementary video 1 (V1):** PPH Butterfly video of correct use (V1)

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469 ***Table 1. Baseline characteristics***

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	PPHB Cases (n=57)	Historical Controls (n=113)
Primiparous, n (%)*	38 (67%)	76 (67%)
Operative vaginal birth, n (%)*	27 (47%)	52 (46%)
Multiple Pregnancy, n (%)*	3 (5%)	1 (1%)
Maternal age at booking (years); mean (SD)	28.79 (5.87)	29.23 (5.48)
BMI at booking (kg/m^2); mean (SD)	26.40 (6.38)	26.87 (6.98)
PPH in a previous pregnancy	5 (9%)	15 (13%)
Induced birth, n (%)	38 (67%)	66 (58%)
Received oxytocin (as treatment for slow labour); n (%)	7 (13%)	7 (6%)
Length of third stage (mins); median (IQR)	9.00 (6.00, 16.00)	8.00 (5.00, 21.00)
Birth weight (g); mean (SD)	3482.12 (506.47)	3499.51 (521.95)
Intact perineum / vagina [i.e. no episiotomy, vaginal or perineal lacerations]; n (%)	7 (12%)	15 (13%)
Cause of PPH†		
Atony	55 (97%)	57 (50%)
Retained placenta or tissue	6 (11%)	31 (27%)
Coagulopathy	0 (0%)	1 (1%)
Trauma	17 (30%)	54 (48%)
Blood loss at time of device insertion (mls); median (IQR)	750 (550, 1300)	-

471 *matching characteristics

472 †multiple options possible

473 SD = Standard Deviation

474 IQR = Interquartile range

475

476 ***Table 2. Primary outcome analysis: Logistic Regression***

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478 Frequency of instances with blood loss >1000mls, above blood loss at which the device was first

479 inserted in the matched index case.

Group	N	Additional blood loss >1000mls N (%)	Unadjusted Odds Ratio (95% CI) P-value	Adjusted[1] Odds Ratio (95% CI) P-value
Control	113	9 (8%)	0.21 (0.03, 1.67) P=0.1391	0.13 (0.02, 1.09) P=0.0601
Index	57	1 (2%)		

480 [1]Predefined baseline covariates: cause of PPH (atonic or other) and blood loss prior to intervention (≥1000mls or other).

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Table 3: Further details on participants who had additional blood loss >1000mls

Index/Control	Mode of birth	Blood loss on device insertion (mls) *(or at point device inserted in matched case)*	Total blood loss (mls)	Cause of PPH *(see key[1] below)*	Surgical interventions *(see key[2] below)*
Index	Spontaneous vaginal	750	1955	A	F; Bi; Ep[3]
Control	Forceps	1000	2080	A; T	F; R
Control	Ventouse	600	3000	A; R	F; M; R
Control	Spontaneous vaginal	750	2200	T	R
Control	Spontaneous vaginal	1300	2500	A; R	M
Control	Ventouse	700	2500	R	M
Control	Spontaneous vaginal	600	2400	A	F
Control	Ventouse	500	2150	A	Ep
Control	Spontaneous vaginal	1300	2500	A; R	M; Ba
Control	Forceps	800	2000	A	Ep; Bi

[1]A=Atonic; R=Retained placenta or tissue; T=Trauma.

[2]F=Fundal massage; Ep=Episiotomy repair; Bi=Bimanual compression; Ex=Examination under anaesthetic; M=Manual uterine exploration (inc. for retained placenta); Ba=Bakri balloon; R=Repair of vaginal or cervical tears.

[3]Episiotomy repair was also performed after device insertion; all other interventions were prior to device insertion.

491 ***Table 4: Interventions used within 24 hours of birth to stop the bleeding[1]***

Measures to stop the bleeding	Control N=113	Index		
		Before insertion N=57	After insertion N=57	At least once *(before or after insertion)*
Oxytocin bolus	93 (82%)	55 (96%)	3 (5%)	55 (96%)
Oxytocin infusion	78 (69%)	39 (68%)	17 (30%)	53 (93%)
Ergometrine	54 (48%)	30 (53%)	15 (26%)	44 (77%)
Carboprost	18 (16%)	6 (11%)	12 (21%)	17 (30%)
Tranexamic acid	3 (3%)	19 (33%)	25 (44%)	42 (74%)
Misoprostol	1 (1%)	1 (2%)	1 (2%)	1 (2%)
Fundal massage	35 (31%)	54 (95%)	24 (42%)	54 (95%)
Episiotomy repair	53 (47%)	24 (42%)	16 (28%)	32 (56%)
Bimanual compression	9 (8%)	31 (54%)	1 (2%)	31 (54%)
Examination under anaesthetic	10 (9%)	5 (9%)	4 (7%)	8 (14%)
Manual uterine exploration (inc. for retained placenta)	19 (17%)	9 (16%)	3 (5%)	12 (21%)
Bakri balloon	1 (1%)	0 (0%)	3 (5%)	3 (5%)
Repair of vaginal or cervical tears	40 (35%)	5 (9%)	14 (25%)	19 (33%)
TOTAL	**414**	**278**	**138**	**416**

492 [1]More than one intervention could be used for each participant.

493 ***Table 5. Secondary Outcomes***

	Index Cases N=57	Historical Controls N=113	Unadjusted Odds Ratio (95% CI)	Adjusted[1] Odds Ratio (95% CI)
Total estimated blood loss, mls (median (IQR))	1110 (700, 1600)	1175 (750, 2000)	N/A	N/A
Blood transfusion, N (%)	8 (14%)	27 (24%)	0.52 (0.22, 1.23)	0.50 (0.19, 1.35)
Number of units transfused				
1	4 (50%)	9 (33%)		
2	3 (38%)	15 (56%)		
3	1 (13%)	3 (11%)	Kruskal-Wallis Test[3]: P=0.5131	
Day 1 haemoglobin level in non-transfused women[2] (mean, SD)	N=47 97.02 (15.12)	N=86 93.00 (13.49)	-	-
Number of women transferred to a higher level of care, N (%)	24 (42%)	46 (41%)	1.06 (0.56, 2.02)	1.21 (0.51, 2.86)
Number of women examined under anaesthetic to investigate the cause of bleeding, N (%)	6 (11%)	10 (9%)	1.21 (0.42, 3.52)	2.38 (0.59, 9.60)
Number of women exclusively breastfeeding at time of hospital discharge, N (%)	26 (46%)	32 (28%)	2.12 (1.09, 4.12)	2.53 (1.17, 5.49)
Coagulopathy	0 (0%)	3 (3%)	-5.72 (-246.1, 234.6)	-5.46 (-227.5, 216.6)
Cardiovascular shock	0	0	-	-
Organ dysfunction (WHO criteria)	0	0	-	-
Hysterectomy	0	0	-	-
Maternal Death	0	0	-	-

494 [1]Adjusted for predefined baseline covariates: cause of PPH (atonic or other) and blood loss prior to intervention (≥1000mls or other).

495 [2]*12-36 hours post birth or at discharge, whichever is soonest*

496 [3]*Post-hoc test*

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498 ***Supplementary Table S1: Adverse Events and Serious Adverse Events***

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	Description (Free-text)	CI assessment of severity	CI assessment of causality	Serious
1	Episiotomy, forceps delivery. Sutures in rectum removed and re-sutured. Treated as a 3rd degree tear (laxatives, antibiotics and follow up)	Mild	Unrelated	No
2	Vaginal Graze[1]	Mild	Possibly	No
3	Patient attendance post discharge with perineal breakdown and infection.[1]	Moderate	Unlikely	No
4	Labia minora caught by the PPH Butterfly device causing pain.	Mild	Almost certainly	No
5	Labia minora caught on insertion of the PPH Butterfly.	Mild	Almost certainly	No
6	Urticarial rash onset thought to be due to Fragmin. Not admitted, treated as outpatient.	Moderate	Unrelated	No
7	Had to be re-catheterised when catheter removed post-delivery[2].	Mild	Unlikely	No
8	Episiotomy breakdown/infection P/N. Treated as outpatient, reviewed later and discharged from hospital care[2].	Moderate	Possibly	No
9	Noted something protruding from vagina, diagnosis of prolapse. Advised to do pelvic floor exercises.	Mild	Unrelated	No
10	Small right vaginal wall graze noted after examination under anaesthetic and removal of clots. Required 1 suture.	Mild	Possibly	No
11	Broken down perineum	Mild	Unlikely	No
12	Infected Episiotomy.	Mild	Unlikely	No
13	Post epidural Dural Tap requiring blood patch	Severe	Unrelated	Yes: Hospitalisation/ prolongation of existing hospitalisation
14	Attended P/N with heavy lochia, seen on MAU and discharged. Re-attended with infection/sepsis. USS revealed retained products, had uterine evacuation. Due to be followed up on but DNA; no response to phone calls-discharged.	Moderate	Unrelated	Yes: Hospitalisation/ prolongation of

				existing hospitalisation
15	Returned to Liverpool Women's Hospital 12 days P/N with signs and symptoms of pelvic infection. Admitted as an inpatient and treated with IV antibiotics.	Severe	Unlikely	Yes: Hospitalisation/ prolongation of existing hospitalisation

[1]AEs 2 and 3 relate to the same woman.

[2]AEs 7 and 8 relate to the same woman

502 ***Supplementary Table S2: Participant questionnaire results (N=57)***

503

Response	It was painful when the PPH Butterfly was inserted	It was painful when the PPH Butterfly was squeezing the womb	I was happy with the way that I was recruited to this study	If I bled after a future birth, I would want the PPH Butterfly to be used
Completely disagree	10 (18%)	10 (18%)	0 (0%)	0 (0%)
Disagree	18 (33%)	13 (24%)	2 (4%)	0 (0%)
Neither agree nor disagree	18 (33%)	13 (24%)	4 (7%)	0 (0%)
Agree	9 (16%)	16 (29%)	33 (59%)	25 (63%)
Completely agree	0 (0%)	3 (5%)	17 (30%)	21 (38%)
Unobtainable	2	2	1	1

504 ***Supplementary Table S3: Clinician questionnaire results***

505

Question	Number of individual responses (% of 57)	Number of clinicians (% of 23)
Did the PPH Butterfly device assist with the management of the PPH overall?		
Definitely no	1 (2%)	1 (4%)
Possibly no	4 (7%)	3 (13%)
Undecided	3 (5%)	3 (13%)
Possibly yes	26 (46%)	16 (70%)
Definitely yes	22 (39%)	11 (48%)
Unobtainable	1	1
Was the PPH Butterfly easy to use?		
Definitely no	0 (0%)	0 (0%)
Possibly no	0 (0%)	0 (0%)
Undecided	1 (2%)	1 (4%)
Possibly yes	10 (18%)	7 (30%)
Definitely yes	45 (80%)	18 (78%)
Unobtainable	1	1
Did the PPH Butterfly stop the bleeding?		
Definitely no	5 (9%)	4 (17%)
Possibly no	4 (7%)	4 (17%)
Undecided	18 (32%)	11 (48%)
Possibly yes	20 (36%)	12 (52%)
Definitely yes	9 (16%)	5 (22%)
Unobtainable	1	1

Did the PPH Butterfly assist in making a diagnosis of the cause of the bleeding?		
Definitely no	7 (13%)	4 (17%)
Possibly no	13 (23%)	8 (35%)
Undecided	7 (13%)	4 (17%)
Possibly yes	20 (36%)	12 (52%)
Definitely yes	9 (16%)	7 (30%)
Unobtainable	1	1
Would you like the PPH Butterfly to be available to use as a treatment for PPH?		
Definitely no	0 (0%)	0 (0%)
Possibly no	0 (0%)	0 (0%)
Undecided	4 (7%)	4 (17%)
Possibly yes	18 (32%)	9 (39%)
Definitely yes	34 (61%)	17 (74%)
Unobtainable	1	1

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Supplementary Table S4: Primary Outcome Sensitivity Analysis: McNemar's test for matched data

Each index case was matched, where possible, to an historical control. McNemar's test was performed for both control groups separately.

Additional blood loss	Control 1 N (%)	Control 2 N (%)	Index N (%)	McNemar's Test for matched data
≤1000mls	54 (95%)	50 (89%)	56 (98%)	Control 1: p=0.6250 Control 2: p=0.0625
>1000mls	3 (5%)	6 (11%)	1 (2%)	
Total	**57**	**56**	**57**	

Supplementary Table S5: Primary Outcome Sensitivity Analysis: Logistic regression adjusting for matching factors

Frequency of instances with blood loss >1000mls, above blood loss at which the device was first inserted in the matched index case.

Group	N	Additional blood loss >1000mls N (%)	Unadjusted Odds Ratio (95% CI) P-value	Adjusted[1] Odds Ratio (95% CI) P-value
Control	113	9 (8%)	0.21 (0.03, 1.67) P=0.1391	0.22 (0.03, 1.76) P=0.1526
Index	57	1 (2%)		

[1]Matching factors: parity, multiple pregnancy, operative birth

519 ***Supplementary Table S6: CONSORT flow diagram reasons***

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Reason for non-approach in antenatal wards	**2**
Cannot read or understand the level of English used in the study documentation	2 (100%)
Reason for non-consent in antenatal wards	**8**
Needed more information/time to decide	6 (60%)
Not interested	2 (20%)
Reason for non-approach for consent at time of PPH	**82**
Clinician in attendance not trained	26 (32%)
Birth by caesarean section	9 (11%)
PPH occurred more than 1 hour following birth	6 (7%)
Managed by midwives	6 (7%)
Woman fainted or was unconscious (including those under anaesthetic) during the PPH	5 (6%)
PPH due to Trauma	4 (5%)
Third stage of labour was not complete (placenta remains in situ) or who had a retained placenta	3 (4%)
Bleeding stopped	3 (4%)
Women could not read or understand the level of English used in the study documentation	2 (2%)
Woman/partner distressed	2 (2%)
Had undergone Female Genital Mutilation/vaginal surgery which is unreversed (assessed antenatally)	1 (1%)
Woman had clotting disorders (either longstanding or following intrapartum events)	1 (1%)
Bi-manual compression due to rapid, heavy blood loss and was unable to remove hand to insert device.	1 (1%)
Had not completed first line medical treatment for PPH	1 (1%)
Unknown	12 (15%)
Reason for non-consent at time of PPH	**6**
Woman not interested	4 (67%)
Didn't like the idea of a 'new' treatment	1 (33%)
Insufficient analgesia	1 (33%)
Reason for PPHB not being used in women who gave consent	**8**
Woman stopped bleeding	5 (63%)

PPH >1 hour	2 (25%)
In theatre awaiting a MROP, Bi Manual Compression in place	1 (13%)

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526 ***Supplementary Table S7: Quotes from participants, birth partners, recruiting doctors and***

527 ***midwives***

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Codes	**Quote**
	<u>Women</u>
Pain Comparison with BMC	*'They started talking to me about using this and then so when I said 'Yes, go for it', she went round that end of the table and put it in. And that was it. Definitely more comfortable with the device than the lady's hand.'* (W05)
Preventing trip to theatre Comparison with BMC	*'I would never have said 'no' to going to theatre but to know there was another option er yeah definitely it did help. She also said that they would have had what they quite often have to do is put their hand in and then keep it there on the way to theatre as well and that sounds awful. Yeah. The fact that that had to happen all the time and they've actually a device that does that instead is a lot better.'* (W12)
Agreeing to treatment	*'I was just happy to get anything used that would stop the bleeding. I felt if something was going to work, just use it.'* (W04)
Success in stopping bleeding	*'It does the job, I would recommend it. Er well I'm happy with the experience overall and it did the job and it wasn't er particularly painful'* (W07)
Depersonalisation	*'It wasn't somebody with their hand inside of me, it was an*

	ordained product that was going inside of me, doing its' job and then coming out.' (W02)
Agreeing to treatment	*'As the time was passing I was thinking and they couldn't find where the blood was, I was thinking, there's something wrong or, you know, they need to be finding where the blood is 'cos it looks like I'm losing a lot now.'* (W01)
Agreeing to treatment	*'The amount of people at the bottom of the bed suggested it was quite a heavy bleed. I've bled previously with my first child.'* (W04)
Trust in clinicians Seeing the device	*'I didn't want to see the device because it'd probably frighten me so it's better me not knowing. I didn't know I'd haemorrhaged so if I did know, I would have probably gone into a bit of a meltdown. 'Cos I do know how bad it can be. But not knowing at the time, is the best thing for me not to know. I just wanted to be fixed basically.' (W06)*
<u>Obstetricians</u>	
Importance of training	*'I think the training identifies really well the angle that you put it in…that bit of training clicked in straight away. That that that there was a lot of reinforcement about putting that in. It was worthwhile just getting that bit right.'* (O12)
Importance of training	*'It was very easy to use, 'cos you know, I know we've gone through the demonstrations and I have gone back to it and tried it again on the model, erm, it did feel quite natural, you know, the*

	way that you do it.' (O03)
Positive response Well tolerated Ease of use Less tiring	*'And the Butterfly's quite a good option erm so people find it, women find it more less distressing than a normal bimanual compression. Because they can't tolerate bimanual compression erm and having the Butterfly, I guess I presume it's been less difficult than a bimanual compression. It's er more able to carry on with compression for longer. I've not had a problem with it.''* (O15)
Constant pressure	*'There's more constant pressure with the device than bimanual compression so yeah I I I think certainly I was happy that it had stopped.'* (O16)
Importance of pain relief	*'Normally it depends on what your patient's erm pain relief is that's onboard at that time. A patient like this where she has er a very well working epidural erm bimanual compression is normally quite straightforward. You normally have to do that to evacuate the clots anyway….In patients that have less pain relief, bimanual compression would obviously be a lot more uncomfortable for them.'* (O14)
Ease of use	*'I think that any obstetric registrar would feel happy inserting it. Erm I think anyone used to doing vaginal examinations would feel happy inserting it. I think er I think junior er I think senior midwives would certainly be happy inserting it. Erm I'm not so sure that junior midwives would be happy inserting it.'* (O05)

Tissue entrapment Vaginal tissue	*'I opened the wings of the device that didn't reveal any further bleeding but there was limited view because the erm anterior vaginal wall blocked my view. It sort of came down into the device if you like…after 3 minutes, I started to remove the device and noticed that the anterior vaginal wall was still in the device, not allowing it to be removed easily. Erm, the patient was completely comfortable, at this point, she hadn't noticed, so I reduced the anterior vaginal wall with one hand while removing the Butterfly with the other hand erm and the patient was comfortable during this period.'* (O07)
Situational awareness Intimacy	*'I felt as I could be aware of what was going on around the room a little bit more easily, it probably felt less intimate with the woman so you had a bit more manoeuvre but you were able to maintain eye contact a little bit better.'* (O02)
Effect on blood loss	*'I believe uterotonics would have worked anyway.'* (O13)
Effect on blood loss Well tolerated	*'Erm yeah it's because you're giving those first line uterotonics first, you're never quite know what the impact has been. You know, and there's the question of, you know, would the bleeding have stopped anyway erm and the question I don't really know the answer to but what I would say is that I certainly didn't feel there was any significant discomfort or any I didn't have any concerns about using it and certainly would try it again.'* (O16)
Effect on blood loss	*'Certainly manages the bleeding whilst establishing iv access or*

	waiting for drugs to work.' (O06)
Effect on blood loss	*'You're aware of the blood loss and I could see that the blood loss was diminishing. It was very straightforward to use and I could see the blood loss diminishing.'* (O02)
Diagnosis of PPH cause	*'I think as a diagnostic tool, the good thing was that I could feel the uterus hard against the platform and I could tell for definite that it was well contracted.'* (O01)
Diagnosis of PPH cause	*'Erm I provided pressure with the device, the er bleeding continued and erm and there was no decrease in the bleeding and therefore it was very obvious that it was actually coming from erm vaginal trauma…erm the midwife had already told me that she suspected that it em that it was from trauma because the uterus felt well contracted but this confirmed that that was the case erm therefore I removed the Butterfly. I didn't require to give any further uterotonics because we knew it was from trauma so gave tranexamic acid and completed the er suturing. Erm the woman was very happy with the device erm and it's erm helped to know definitely where the bleeding was coming from.'* (O11)
Positive response	*'I was quite impressed with the device. It was a positive experience. Worth using.'* (O12)
Positive response	*'I was really impressed and the patient herself said afterwards, when she'd stopped, she said 'I would recommend that'.* (O02)

Midwife Observers	
Too busy to notice	*'I was too busy writing the notes, sorting the baby out.'* (MW04)
Too busy to notice	*'I was busy doing the drugs so didn't really see it. The only thing I can probably say is that I wouldn't have known that it was being used as such. I always find when other people have used bimanual compression you've known straight away, you don't even need to be looking at the woman, you know what they're doing and my lady never made a sound.'* (MW09)
Effect on blood loss Well tolerated	*'Erm the only thing about the Butterfly is you don't know whether it was the Butterfly or not if it was the drugs that actually stopped the bleeding. Erm but I mean the woman didn't look in discomfort and the partner didn't look erm he didn't look scared at all. It would be difficult to tell whether, when you're using the drugs you would normally use, if it's the drugs or the Butterfly or a combination of the two.'* (MW06)
Uncertainty about device role	*'Erm but usually erm the protocol you know, the two lots of synto, ergometrine, the tranexamic acid and the 40 units erm that is usually always like our first line so I'm not quite sure really where this Butterfly fits in…in the end, who will be able to actually insert the Butterfly? Is it still gonna be doctors only?'* (MW06)
Intimacy	*'I think an instrument is better than a hand. That's my impression. I think if it was me, and even for my husband, I think I think he'd*

	be traumatised if he'd seen a male or female doctor with their hand right inside my private parts but with an instrument, it seems more, I don't know, legitimate, medicalised.' (MW08)
Positive response Comparison with BMC	*'Although it still is vaginal, it seems less invasive which sounds stupid because it's a device which is inserted but I think it does seem less invasive to watch as well…but now that I've seen it, I think it's good.'* (MW10)
Well tolerated	*'More comfortable experience for the women and clinicians.'* (MW11)
Comparison with BMC	*'Probably more effective as [the clinician] can't do bimanual compression for long.'* (MW10)
<u>Birth Partners</u>	
Intimacy Comparison with BMC Preventing trip to theatre	*'So to use that (the device) instead of manhandling her and the pain I think was better. She was given an option. They said 'I could use my hands or it could ultimately lead to you going to theatre but there's other things we can try'* (P04)
Trust in clinicians	*'I saw it being used and it looked quite straightforward and basically they [the clinician] knew what they were doing.'* (P08)
Less tiring	*'Device looks like it would be less strain on the person using it and pressure would be difficult to sustain, like CPR.'* (P09)
Preventing trip to theatre	*'I'm so glad that she didn't have a caesarean but I'm so glad that*

	she didn't end up in theatre and if it wasn't for that device and him [the clinician] I said anyone else would have probably rushed you to theatre.' (P02)
Well tolerated	*'He [the clinician] couldn't believe that he was able to get done what he got done without any anaesthetic…but she [woman] said the using of the device was pain free.'* (P01)
Trust in clinicians	*'I had full faith in the medical team…from what I saw, from what I was paying attention to, they were acting swiftly, professionally, erm…doing their job to the fullest and couldn't commend them more for it.'* (P03)
Trust in clinicians	*'But the fact that it was him, the fact that the rapport was there, I think, made a lot of difference.'* (P01)
Speed of onset	*'Everything happened in a split second, one minute she was fine and the next she was unconscious.'* (P12)
Speed of onset Anxiety	*'With the amount of blood that was gushing out, I was sitting there thinking, honestly, 'bloody hell, I'm gonna lose you here'.'* (P01)
Positive response	*'I have no qualms about the machine itself or the procedure, you know, I don't have any sort of bad feeling towards it, it was great.'* (P10)
Effect on blood loss	*'It's really useful, reduced the need for blood transfusion, longer*

	hospital stay.' (P09)
Seeing the device	*'It was nothing different to like anything else you would have seen that he had there.'* (P05)
Seeing the device Effect on blood loss	*'I mean, it was obviously plastic and it looked like something maybe you'd knocked up at school, it looked pretty basic yeah. But obviously it does the job.'* (P08)
Seeing the device Agreeing to treatment	*'I was probably a bit more aware of the fact that she was bleeding because I could see sort of under the bed and I could see the device itself em so I think the thing is that if someone tells you that your wife's bleeding, you're not gonna say 'oh no, don't use that.' You know, you're always gonna say 'absolutely, let's give it a go.' Erm 'cos that's what you do in the hope that the bleeding should stop.'* (P06)

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