Author:
Van Der Nelson, Helen A

Title:
Prophylactic uterotonic drugs for prevention of postpartum haemorrhage after vaginal birth

Prophylactic uterotonic drugs for prevention of postpartum haemorrhage after vaginal birth

Helen Anne van der Nelson

A dissertation submitted to the University of Bristol in accordance with the requirements of the degree of Doctor in Medicine in the Faculty of Medicine and Dentistry

School of Translational Health Sciences

August 2021

Word Count: 37, 164

Abstract

Primary postpartum haemorrhage is the loss of ≥ 500ml of blood from the genital tract within 24 hours of childbirth. It remains a leading cause of maternal morbidity and mortality world-wide(1). The risk of postpartum haemorrhage (PPH) can be reduced by administration of a prophylactic uterotonic drug straight after birth. In the United Kingdom, the drug recommended for this purpose after vaginal birth is oxytocin. A telephone survey of 185 hospitals in England, Scotland and Wales which I conducted in 2013 concluded that 70% of all obstetric units were not adhering to this guidance. Syntometrine was the most used prophylactic uterotonic drug after vaginal birth in low-risk women, even though its use is associated with increased maternal side effects(2).

The IMox Study, presented within this thesis, was the first randomised control trial to directly compare intramuscular oxytocin, Syntometrine and carbetocin for prevention of PPH after vaginal birth. 5929 women were randomised in 6 hospitals from February 2015 – August 2018. The primary outcome measure was the use of additional uterotonic drugs. Secondary outcomes included weighed blood loss, blood transfusion, and side effects. Health-related quality of life was measured antenatally and on postnatal days 1 & 14. Participants receiving Syntometrine were significantly less likely to receive additional uterotonics than those receiving oxytocin or carbetocin. Rates of PPH and blood transfusion were not different between arms. Prophylactic uterotonic drug allocation did not affect maternal quality of life at any timepoint. Syntometrine use was associated with increased maternal side effects, and a negative impact on the mother's ability to bond with and care for her baby in the first two postnatal hours. Within this thesis I present the methods and

result of the The IMox Study, as well as a critique of the trial and an exploration of the impact of my work.

Dedication and Acknowledgements

Thank you, Christy Burden and Elsa Marques, for your unwavering support and encouragement during the writing of this thesis. You both stepped in at a time when I could easily have given up on my dreams of completing this body of work and you have been instrumental to me to reaching this point.

Thank you, Tim Draycott for your great ideas, advice, and support over these many years. Thank you, Cathy Winter, for your kindness and your brilliant and practical mind. Thank you, Sara Burnard, for all your help and encouragement over the years – you always knew what a long road this would be and stood by me every step of the way. Thank you, Michelle Mayer, Mary Alvarez, Jade Knowlden and Deb Kendall - without your hard work and dedication IMox would not have launched and flourished like it did. Thank you, Stephen O'Brien, for steering the ship while I was having babies. Your support has been invaluable.

Thank you, Narges Dailami and Erik Lenguerrand, for your precious time and statistical input. An especially big thank you to Paul White – you have gone above and beyond to support and help me and have the patience of a saint.

A final enormous thank you to my wonderful husband, Alex. For the countless hours of parenting while I pulled myself away to work over the years, and for your unwavering support and belief in me. I dedicate this thesis to my precious little family – to Alex, Arthur, Jack (and the growing bump, Lotte!)

Author's declaration

1. I, Helen Anne van der Nelson, declare that I am the author of this work.
2. I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award.
3. Except where indicated by specific reference in the text, the work is my own work. Work done in collaboration with, or with the assistance of, others, is indicated as such:
    a. Chapter 2 (Telephone survey): Ffion Jones helped with data collection. Tim Draycott provided supervision.
    b. Chapter 3 (IMox Study methodology): Tim Draycott, Dimitrios Siassakos, Elsa Marques and Cathy Winter helped to develop the study protocol. Erik Lenguerrand and Narges Dailami gave advice on statistical and methodological matters. Tim Draycott was the Chief Investigator for The IMox Study. Stephen O'Brien took over as Principal Investigator at North Bristol NHS Trust and provided overall study support once I went on maternity leave.
    c. Chapter 4 (Results): Paul White and Narges Dailami performed the statistical analyses. Tim Draycott advised on analyses. Tim Draycott, Dimitrios Siassakos, Stephen O'Brien, Christy Burden, Elsa Marques and Cathy Winter helped in the writing of the final publication.
    d. Chapters 1, 5, 6 and 7: Christy Burden and Elsa Marques supervised writing of these chapters.
4. Any views expressed in the dissertation are those of the author, Helen Anne van der Nelson.
5. Ferring Pharmaceuticals provided part of the funding for The IMox Study but did not influence trial design, implementation or reporting.

SIGNED: .... DATE:..........................

Table of contents

List of tables and figures

Tables

Figures

Chapter 1 :

Introduction

1.1 Definition and nomenclature

Primary post partum haemorrhage (PPH) is traditionally defined as the loss of 500ml or more of blood from the genital tract within 24 hours of the birth of a baby. Secondary PPH is defined as abnormal or excessive bleeding from the genital tract which occurs more than 24 hours and up to 6 weeks after birth.

These definitions were agreed upon by an *"informal meeting of experts"* at a World Health Organisation meeting in Geneva in 1989 and have been internationally accepted and used ever since. It was acknowledged in the report of the Technical Working Group that the choice of 500ml was *"arbitrary"* and *"not always of great clinical significance"*(8). However, because it was recognised that clinical estimation of blood loss was commonly inaccurate, and an underestimate of true loss, it was concluded that the definition should remain at 500ml(8).

In more recent years, there has been a drive to develop definitions with more clinical significance(9). Although there is no universal consensus relating to this, there appears to be a drift towards a threshold of 1000ml. The American College of Obstetricians and Gynaecologists standardised all obstetric definitions in 2014 and now defines "early" (primary) PPH as *"cumulative blood loss of ≥1000ml or blood loss accompanied by sign/symptoms of hypovolemia within 24 hours following the birth process"(10)*. An additional threshold of 1000ml has also been suggested by the Royal College of Obstetricians and Gynaecologists in the United Kingdom, who categorise PPH of 500-1000ml as "minor" and 1000ml or more as "major", with "major" PPH being further subcategorised into "moderate" (1001-2000ml) and "severe" (>2000ml)(11). The World Health Organisation has not revised its definition of PPH in general but has now provided an operational definition of "severe" PPH for *"perceived abnormal bleeding (1000ml or more) or any bleeding with hypotension or blood transfusion"(12)*.

Blood loss ≥500ml is the most common primary outcome used in Randomised Control Trials (RCTs) investigating PPH prevention strategies(13). In a research context, it has been suggested that the poor specificity of 500ml as a marker for maternity morbidity makes it *"almost useless*" as a clinical outcome(9), as many of those with a blood loss of 500ml are entirely well. The selection of any threshold which tries to generically distinguish "normal" from "abnormal" bleeding does not take into account population factors, health care factors or pregnancy factors(9) which may influence the "norm". There is also suggestion that the use of a 500ml threshold in a research context could be misleading; studies showing a treatment benefit at a 500ml may not actually have any benefit at larger more clinically significant volumes, and those negative studies which had been powered to detect change at a threshold of 500ml may have missed treatment effects at greater volumes(9). A core outcome set for the prevention and treatment of postpartum haemorrhage was published in 2018, following an international Delphi consensus study(14). This recommended reporting of blood loss at thresholds of both ≥500ml and ≥1000ml, together with median or mean blood loss in each group, as well as other outcomes relating to maternal morbidity.

1.2 Global burden and incidence of PPH

Obstetric haemorrhage is the most common cause of direct (due to pregnancy itself) maternal death worldwide, accounting for 27% of all global maternal deaths(1). Two thirds of all obstetric haemorrhage deaths occur in the postnatal period(1), equating to one woman dying every 4 minutes. The early postnatal period is therefore known to be one of the most hazardous times during childbirth, and in recent years PPH prevention has been a major focus of global efforts to reduce overall maternal mortality rates by 75% in line with Millenium Development Goal 5. Vast disparities exist between developing and developed countries. 99% of deaths due to postpartum haemorrhage occur in developing countries(1), the majority of which occur in Sub-Saharan Africa

and Southern Asia. Overall risk of death from haemorrhage is 1 in 1,000 deliveries in developing countries(15), compared to just 1 in 100,000 in the UK(16).

The incidence of PPH is typically estimated at 2-10% across all settings(12, 17-19). Quoted incidence of PPH is affected by both the PPH definition used and the way in which blood loss is measured. A systematic review of global PPH datasets found that estimates of severe PPH (≥1000ml) almost doubled when objective methods were used to quantify blood loss, highlighting the inaccuracy and frequent underestimation in visual assessment of blood volume(20). Reliance on visual estimation of blood loss in resource-poor settings makes comparison of incidence rates across settings difficult; a retrospective cohort study in Zimbabwe quoted a PPH rate of just 1.6%, yet 5.4% of these women died as a result of their bleeding(21), suggesting that blood volumes lost may have been greater than those reported, and that PPH of lesser volumes may have gone unreported.

Rate of PPH is known to be increasing in developed countries(18, 22-24), particularly that related to uterine atony(25). While the cause of this is unclear, it may be due to improved estimation and reporting, or increasing rates of intervention(26, 27). One such example is the small but concerning increase in the number of women dying of haemorrhage due to abnormally invasive placentation after previous caesarean section, itself generally consequence of rising caesarean section rates(26, 28).

1.3 Aetiology and risk factors

Causes of PPH can be classified according to “four T’s”; tone, trauma, tissue and thrombin. *Tone* of myometrial smooth muscle is required to constrict blood vessels which supply the placental bed after separation of the placenta. Factors which may hinder postpartum uterine tone include uterine overdistension (multiple pregnancy, polyhydramnios, fetal macrosomia), anatomical factors

(fibroids, congenital uterine anomalies) and oxytocin desensitisation (prolonged second stage of labour, oxytocin use in labour). *Trauma* to maternal tissues causes bleeding (caesarean section, episiotomy and perineal or cervical laceration). Retained *tissue* (placenta, membranes, or blood clot) prevents adequate uterine contraction and can promote eventual infection and breakdown of superficial endometrial vessels. *Thrombin* relates to clotting abnormalities and can include both those which pre-date the pregnancy (e.g. anticoagulant use, thrombocytopaenia) or those caused by the pregnancy itself (e.g. disseminated intravascular coagulation secondary to pre-eclampsia, amniotic fluid embolism or sepsis).

Inadequate uterine tone (atony) is the most common cause of PPH, accounting for up to 70% of episodes(29). However, it is believed to be self-limiting and is not the most dangerous cause, accounting for only 6% of PPH deaths in a Confidential Enquiry based in South Africa, where uterotonics are not universally available (27). By comparison, bleeding during caesarean section in the same setting accounted for 26.2% of deaths, bleeding related to uterine rupture accounted for 17.9% of deaths and that related to placental abruption accounted for 16% of deaths. A Danish cohort study, which formed part of a PhD thesis, investigated the distribution of PPH causes according to volume of blood lost in 43,357 women who gave birth vaginally in two large maternity units in Copenhagen. A single cause was assigned to each case of PPH, and the distribution of these causes was compared across PPH volumes. This study found a decreasing role of atony and increasing role of retained placenta as blood volume increased(30).

Various risk factors for PPH have been identified in published literature, and more can be hypothesised when considering the “4 Ts”. There appears to be notable variation across populations(29), yet some risk factors are common across studies. These include fetal macrosomia, retained placenta, prolonged second stage of labour, caesarean section and genital tract trauma(29). Induction of labour was historically believed to be a risk factor for PPH(11). However, a 2020

Cochrane review of induction of labour from 37 weeks onwards, in those with otherwise normal pregnancies, found that induction probably made little or no difference to rates of PPH. While recommendations exist for women with known PPH risk factors to plan for birth in a hospital with a blood bank(31), it is recognised that many women who experience a PPH have no identifiable clinical or historical risk factors(32). It is therefore imperative that risk reducing measures are taken for all labouring women where possible. Table 1.1 summarises the risk factors for PPH described by the Royal College of Obstetricians and Gynaecologists in the 2009 version of this guideline, which was active when The IMox Study was designed. This version has since been superseded(31).

Table 1.1: Risk factors for PPH (Adapted from RCOG Greentop Guideline 52: Prevention and Management of Postpartum Haemorrhage, May 2009(11))

Historical risk factors

- Previous PPH
- Asian ethnicity
- Obesity (BMI >35)
- Anaemia

Pregnancy related risk factors

- Multiple pregnancy
- Pre-eclampsia/gestational hypertension
- Fetal macrosomia
- Placenta praevia or accreta
- Placental abruption

Intrapartum risk factors

- Prolonged second stage of labour
- Retained placenta
- Episiotomy
- Caesarean section
- Induction of labour
- Operative vaginal birth
- Pyrexia in labour
- Age (>40, not multiparous)

Risk factors which were no longer included in the updated 2016 version of the RCOG guideline (obesity and anaemia) or not included in either guideline (parity and age):

Parity

In the United Kingdom women of grand multiparity (four or more previous births(33)) are considered to be at higher risk of obstetric complication(34) and are often counselled regarding increased PPH risk. However, review of published literature suggests that no firm conclusions have been reached to this effect. Evidence exists both for extremes of parity increasing risk of severe PPH(26, 35), and for grand multiparity not increasing PPH risk in either high(36) or low income settings(37). There is a suggestion that the effect of grand multiparity may be compounded by age; older grand multips are more at risk of obstetric complications than younger grand multips (36, 38).

Age

There is evidence to suggest that PPH is associated with increased maternal age(26). This may be due to an increase in general obstetric intervention and complication, rather than a direct increase in PPH causes such as atony (39).

Obesity

Risk of PPH is known to rise with increasing Body Mass Index (40-42), especially as a result of uterine atony(40). This is in part explained by altered myometrial function in obese women during pregnancy, with higher levels of adipokines which decrease myometrial contractility, and typically higher levels of cholesterol, which inhibits oxytocin receptor function(43). In the obese, a deeper subcutaneous fat layer may also make the routine administration of intramuscular prophylactic uterotonic drugs less effective. Women with a BMI of 40 or more are reported to be 1.23 (95% CI 1.04-1.45) times more likely to experience PPH after normal vaginal birth than normal-weight women, and 1.69 (95% CI 1.22-2.34) more likely to experience PPH after instrumental delivery(40).

Anaemia

Anaemia is common in the developing world and puts women at increased risk of morbidity and mortality due to PPH. Odds of PPH are reported to increase up to 17-fold in women with moderate to severe antenatal anaemia(44). Anaemia impedes myometrial contractility and reduces the woman's systemic tolerance of blood loss, making smaller volumes of blood loss more clinically significant, and easily overlooked.

1.4 Estimation of blood loss

In order to act promptly and appropriately, it is imperative that clinicians recognise the occurrence of PPH at the time of birth in "real-time". This relies on accurate estimation of blood loss, as well as awareness of the speed of blood flow and the cause of the bleeding(45). Visual estimation or the "eye-ball technique" is most frequently used to estimate blood loss. This is quick, low-cost, and can be used by anyone in any setting. However, health professionals are known to be inaccurate when visually estimating blood loss as a volume(45, 46). The most consistently reported observation is a tendency for blood loss to be increasingly underestimated as blood volume increases(47-49). There is conflicting evidence regarding the accuracy of clinicians according to level of seniority, with some evidence to suggest improvement in accuracy with increasing years of experience(50) and other studies reporting no difference between the accuracy of medical students versus experienced clinicians(51). Clinical judgement may be improved by periodic re-estimation of total volume lost throughout the course of an ongoing obstetric haemorrhage(52). Training results in short term improvements in the accuracy of estimation(49), but improved accuracy does not translate to improvements in clinical outcomes(45).

Methods used to try and directly measure blood loss to improve the accuracy of estimation include gravimetric methods (where blood is collected and weighed) and direct calibration (where blood is collected in a volumetric bag, and volume is directly quantified). More invasive methods include

measurement of maternal haemoglobin by venous blood sampling before and after delivery, dye dilution techniques (where a known quantity of dye is intravenously administered before delivery, and its concentration is measured postnatally), nuclear medicine techniques (where a known quantity of a radioactive tracer is intravenously administered before delivery, and its concentration is measured postnatally) and spectrophotometry (where absorption spectrometry is used to directly quantify the amount of haemoglobin within collected blood). Although these more invasive methods would hypothetically provide a more accurate quantification of blood loss, they are more expensive and time consuming, and not available in all settings. With the exception of venous blood sampling for haemoglobin measurement, these invasive methods would probably not be acceptable to women giving birth, outside a research context.

A 2018 Cochrane review concluded that there is insufficient high-quality evidence to support the use of any one method of estimation over another after vaginal birth, and that future trials need to correlate blood loss with relevant clinical maternal and neonatal outcomes(53).

Maternal physiological response and outcomes vary according to the volume of blood lost.
The significance of blood loss is relative to the size of the mother (and thus her total circulating blood volume), her pre-delivery haemoglobin levels, and other co-morbidities. While there is known to be substantial variability in the relationship between blood lost and the clinical signs displayed by individuals (54), there are certain features of shock which are broadly related to the severity of PPH, as shown in Table 1.2. Awareness of these signs can also help clinicians gauge the magnitude of blood lost and the interventions needed.

Table 1.2: Clinical features of shock in pregnancy related to blood loss (Reproduced from Practical Obstetric Multi-Professional Training Course Manual (2nd Ed) RCOG Press 2012)

Blood loss (ml)	Clinical features	Level of shock
500-1000	Normal blood pressure Tachycardia Palpitations, dizziness	Compensated
1000-1500	Hypotension (systolic 90-80mmHg) Tachycardia Tachypnoea (21-30 breaths/min) Pallor, sweating Weakness, faintness, thirst	Mild
1500-2000	Hypotension (systolic 80-60mmHg) Rapid, weak pulse (>110 beats/min) Tachypnoea (>30 breaths/min) Pallor, cold clammy skin Poor urinary output (<30ml/hour) Restlessness, anxiety, confusion	Moderate
2000-3000	Severe hypotension (<50mmHg) Pallor, cold clammy skin, peripheral cyanosis Air hunger Anuria Confusion or unconsciousness, collapse	Severe

1.5 Wider impact of PPH

Pregnancy experiences are known to affect subsequent Quality of Life in both women who give birth and their birth partners (55). There is a paucity of published data relating to the psychological impact of PPH, and the few studies that exist tend to be small or focussed on a limited number of morbidities(56). Emotional sequalae of PPH include anxiety, depression, fatigue and post-traumatic stress disorder(57), with risk of postnatal depression and post-traumatic stress disorder at their highest in the first postnatal year(58). PPH may lead to negative memories of the delivery and intense anxiety in subsequent pregnancies, with a persistent fear of dying reported by some women(59). Interestingly, scores for Health-Related Quality of Life were not as low after PPH as after pregnancies affected by hypertension or intra-uterine growth restriction(60).

A strong correlation is known to exist between levels of fatigue and depression in the first two years after childbirth, as reported by a 2019 systematic review and meta-analysis of 35 studies(61). One randomised trial assessed the effect of red blood cell transfusion on the quality of life of acutely anaemic women after post-partum haemorrhage. This found only a small difference in physical fatigue and no difference in Health-Related Quality of Life and physical complications between groups of women who were, and were not, transfused blood(62). PPH greatly increased physical fatigue when compared with post-partum women who had not experienced PPH. Interestingly, previously published differences in post-natal physical fatigue between modes of delivery(63) were not demonstrated in this study; PPH may have a larger influence than mode of delivery. Another study(64) found a weak correlation between post-natal haemoglobin values and fatigue scores in the first two post-natal days, but no correlation by 3 and 6 weeks post-natal. Of note, women included in this study had not experienced PPH. Another study looking at women with an uncomplicated labour and birth found low haemoglobin in the first postnatal week to be a risk factor for the development of post-natal depression when assessed at 28 days postnatal (65), (61). Surprisingly, emotional and physical health outcomes in one cohort of 206 women experiencing PPH of >1500ml in Australia and New Zealand were found to be similar to those in general post-natal populations(57). The range of blood loss in this cohort was 1500-8000ml, but the study did not analyse outcomes by volume of blood lost or by mode of delivery. The relatively small size of this study might also have influenced this finding, as may the fact that the cohort of 206 women was recruited across a total of 17 different hospitals, in which birth experience may have varied greatly.

PPH is known to affect breastfeeding rates, both due to the practicalities of initiating breastfeeding postnatally (i.e. later opportunity for the newborn to initiate suckling) and due to the physiological impact of large volume PPH (i.e. ischaemia of the pituitary gland with subsequent impact on prolactin production and lactogenesis). As would be expected, those with blood loss ≥3000ml were less likely to fully breastfeed in the first postpartum week than those with PPH <2000ml(66).

1.6 Management of the third stage of labour

1.6.1 Types of management

The third stage of labour is the time between birth of the baby and expulsion of the placenta and membranes. The management of this part of childbirth can take different forms;

Physiological Management

(synonyms “conservative management”, “expectant management”)

With physiological management of the third stage of labour, the placenta and membranes are birthed spontaneously after signs of placental separation. This is sometimes encouraged by maternal pushing or gravity, but not by clamping of or traction on the cord, or the use of uterotonic drugs.

Active Management

This triad of intervention has been described and advocated since the late 1980’s and traditionally(67, 68) involves:

(1) Administration of a prophylactic uterotonic drug with birth of the baby’s anterior shoulder

(2) Immediate clamping of the umbilical cord

(3) Controlled cord traction to deliver the placenta and membranes with the first uterine contraction.

Mixed Management

(synonyms “combined management”, “the piecemeal approach”)

In practice, it has been recognised that women often receive care which does not entirely fall within the definition of either physiological or active management(69-71). This is commonly referred to as mixed management.

1.6.2 Evidence surrounding management

A 2019 Cochrane review of Active versus Physiological Management of the third stage of labour concluded that Active Management of the Third Stage of Labour (AMTSL) probably reduces risk of PPH >500ml, the need for additional uterotonic drugs to treat PPH, mean maternal blood loss and postnatal maternal anaemia(72). It is uncertain whether Active Management reduces risk of PPH >1000ml, due to the low quality of the evidence included.

The three components of Active Management of the Third Stage of Labour have been individually scrutinised:

(1) Use of a uterotonic drug

The use of a uterotonic drug appears to be the most important component of AMTSL(73); a conclusion drawn largely from more in-depth evaluation of cord cutting and clamping, and controlled cord traction, as described below. There are several prophylactic uterotonic drugs which can be used for prevention of PPH during the third stage of labour. A Network Meta-Analysis concluded that three most effective drugs for prevention of PPH >500ml after vaginal birth are oxytocin/ergometrine combination, carbetocin, and misoprostol/oxytocin combination(74). When oxytocin is used, the timing of administration of this (before or after expulsion of the placenta) does not have any significant impact on the incidence PPH, retained placenta, or duration of the third stage of labour(75). There appears to be a benefit of intravenous over intramuscular administration of uterotonic drugs(76-79).

(2) Clamping and cutting of the umbilical cord

The timing of umbilical cord clamping has become a topic of significant interest over the last decade. While early clamping of the cord was initially thought to reduce risk of PPH, more recent evidence

suggests that there is no significant difference in PPH rates when early (immediately after birth) and late cord clamping (one to three minutes after birth) are compared(80). In addition to this, the act of delayed or "deferred" cord clamping appears to benefit the newborn baby, as a result of the increased passage of 83-100ml(81) blood from the placenta to the term newborn's circulation. This process is usually completed within 2 minutes of birth(81). Delayed cord clamping results in increased birth weight, a higher haemoglobin concentration at 24 and 48 hours, and improved iron stores which persist up to 6 months of age(80). There is however an increased need for phototherapy to treat neonatal jaundice when delayed cord clamping is practised(80). Current guidance advocates delayed cord clamping in healthy term infants, especially when phototherapy is available(33, 82). When cord clamping is delayed in the interests of the baby, the practice of administration of an intramuscular uterotonic drug before the cord is clamped does not appear to have any significant effect on placental transfusion of blood to the baby(83).

(3) Controlled cord traction

The omission of controlled cord traction is believed to have very little effect on the risk of PPH >1000ml (84, 85). This is important to know for developing countries, where there may be no skilled birth attendants present.

1.7 Summary of prophylactic uterotonic drugs

Uterotonic drugs increase the tone of the uterus by increasing the frequency and strength of myometrial muscle contraction. Circumstances in which these drugs are used include the induction of labour, prophylaxis against PPH when given immediately after birth, and the treatment of PPH when due to uterine atony. While several different types of uterotonic drug exist, they cannot all be used prophylactically. The use of a prophylactic uterotonic drug does not preclude the use of further uterotonics if PPH occurs.

Oxytocin

Oxytocin is a natural uterotonic peptide hormone which binds to receptors in uterine smooth muscle to stimulate uterine contractions during labour, and promotes lactation by a different pathway. It is produced by the human hypothalamus and released by the posterior pituitary gland. Oxytocin was first discovered by Sir Henry Dale in 1906, when he noted that a human posterior pituitary gland extract contracted the uterus of a pregnant cat(86), and later synthesised by Vincent Du Vigneaud in 1955, winning him a Nobel Prize in Chemistry. Oxytocin is deactivated by the gastrointestinal tract, so is only administered by the intravenous and intramuscular route. When given intravenously it has an almost immediate onset of action, reaching a peak concentration after 30 minutes, whereas intramuscular administration has a slower onset of action (3-7 minutes) but longer lasting effects (up to 1 hour)(87). Oxytoxin is stable at temperatures of 30 degrees Celsius for up to 3 months but requires refrigerated storage at 2-8 degrees Celsius to prolong its shelf life. Inadequate storage reduces its potency, and this is a significant problem in resource-poor settings, where ambient temperatures are often hot, fridges are not always available and supplies of electricity can be inconsistent. In one systematic review, > 60% of oxytocin samples tested in Africa contained <90% of the oxytocin quantity stated on the ampoule(88).

Ergometrine

Ergometrine is an ergot alkaloid derived from the parasitic fungus Claviceps purpurea, which grows on rye and other grains (see Figure 1.1). The ingestion of ergot of rye has been known to induce strong uterine contractions since the 16th Century, and its overdose causes ergotism or “St Anthony’s fire”, characterised by skin rash, convulsion, muscle pain, gangrene and death. Ergometrine was first isolated by Professor John Chassar Moir and Dr Harold Dudley in 1932 (89), and its use as a prophylactic uterotonic was reported in the British Medical Journal in 1936 (90). Ergometrine causes sustained contraction of uterine muscle and has a duration of action of 3 hours when given intramuscularly and 45 minutes when given intravenously. If protected from sunlight, it can be

stored up to 25 degrees Celsius for 2 months, but is ideally refrigerated at 2-8 degrees Celsius to prolong its shelf-life(91). In obstetrics, it is most commonly used in a fixed-drug combination of 500mcg ergometrine/5iU oxytocin, called Syntometrine. Well documented side effects of Ergometrine include hypertension and nausea(2, 89, 91).

Figure 1.1: Ergot growing on rye (Taken from University of Guelf website(92))

Carbetocin

Carbetocin is a long-acting synthetic oxytocin agonist, produced exclusively by Ferring Pharmaceuticals and registered since 1997. It binds to oxytocin receptors in uterine smooth muscle, resulting in sustained muscle contraction within 2 minutes, lasting up to 11 minutes, and rhythmic smooth muscle contraction for up to an hour after intravenous administration and 2 hours after intramuscular administration(93). Its half-life is significantly longer than oxytocin (40 minutes v 6 minutes). A heat-stable version of Carbetocin, which differs from the non-heat stable version only in its excipients, has been available since 2015(94). This has great potential for use in low-resource settings, where cold-chain storage is a significant challenge.

Misoprostol

Misoprostol is a synthetic prostaglandin E1 analogue, first developed in 1973. Its many uses include the induction of labour or abortion and prevention of PPH, as well as treatment and prevention of

stomach ulcers, premature closure of the ductus arteriosus in newborn infants and erectile dysfunction. Misoprostol can be given orally, sublingually, vaginally or rectally, and tablets do not have any specific storage requirements other than needing to be protected from humidity in closed packaging. The side effects of misoprostol include significant nausea, rash, vomiting and gastrointestinal discomfort(95). As a potent uterotonic, it can cause uterine rupture in overdose.

1.7.2 Effectiveness of uterotonic drugs for prevention of PPH

Intravenous versus intramuscular oxytocin

The Cochrane review of intravenous versus intramuscular oxytocin was updated in 2020 and concluded that there is high certainty evidence that intravenous oxytocin reduces risk of both PPH ≥500ml (RR 0.78, 95% CI 0.66 – 0.92) and blood transfusion (RR 0.44, 95% CI 0.26 – 0.77) compared with intramuscular administration(96). This same work also concluded that the use of an intravenous route probably also reduces risk of PPH ≥1000ml. It is highlighted that although the 95% odds ratio for this comparison crosses 1 (RR 0.65, 95% CI 0.39 – 1.08), this was due to only one study which had caused heterogeneity. This one study was small and contributed only 3% of events overall. When this single study was removed, intravenous administration was found to be favourable (RR 0.61, 95% CI 0.42 – 0.88). A further sensitivity analysis which explored risk of bias concluded the same for PPH ≥1000ml, when looking at the two studies at “low” risk of bias (RR 0.64, 95% CI 0.43 to 0.94)(96). No significant difference was found between the two routes for outcomes including the use of additional uterotonic drugs and serious maternal morbidity (97). The intravenous route is not routinely used for the administration of oxytocin in the United Kingdom, because women in labour do not routinely have intravenous access. There have also been historical concerns regarding haemodynamic instability caused by rapid boluses of intravenous oxytocin(98), particularly in those undergoing caesarean section. However, this more recent Cochrane review concluded that there is

probably little or no difference in risk of hypotension (RR 1.01, 95% CI 0.88 to 1.15) when these two routes of administration were compared after vaginal birth(97).

Oxytocin versus no uterotonic

Compared with physiological management or placebo, oxytocin used for active management of the third stage of labour is thought to reduce risk of PPH ≥500ml (RR 0.51, 95% CI 0.37-0.72) and PPH ≥1000ml (RR 0.59, 95% CI 0.42-0.83), and reduce the need for additional uterotonic drugs (RR 0.54, 95% CI 0.36-0.80)(99).

Oxytocin versus oxytocin/ergometrine

Use of oxytocin/ergometrine seems to be associated with a reduced risk of PPH ≥500ml, when compared with oxytocin alone (OR 0.82, 95% CI 0.71-0.95), at a dose of either 5iU or 10iU. There was no difference between oxytocin/ergometrine, and oxytocin (at either dose) for PPH ≥1000ml. Oxytocin/ergometrine is associated with significantly more side effects, including nausea, vomiting and hypertension(100).

Carbetocin

Compared with oxytocin, use of carbetocin has been found to significantly reduce the need for additional uterotonic drugs to treat uterine atony after caesarean section (RR 0.62, 95% CI 0.44-0.88), but not after vaginal birth(101). There was no reduction in risk of PPH of ≥500ml or ≥1000ml for either caesarean or vaginal birth, when carbetocin and oxytocin were compared(101). Since the publication of the aforementioned Cochrane review, additional data has become available regarding the comparison of oxytocin and carbetocin after vaginal birth. The CHAMPION Study, a large multi-national trial of oxytocin versus carbetocin for PPH prophylaxis after vaginal birth involving 29,645 women, demonstrated non-inferiority of carbetocin relative to oxytocin for the prevention of PPH ≥500ml, and no difference in the need for additional uterotonics, or adverse events(102).

When compared with oxytocin/ergometrine, use of carbetocin is associated with no significant difference in the need for additional uterotonic drugs, and a lower mean blood loss(101). However, this mean difference was small (48ml, 95% CI 94.82-2.85) (101), and is not clinically relevant. In keeping with all other studies involving oxytocin/ergometrine, use of carbetocin is associated with fewer maternal side effects than oxytocin/ergometrine(101).

Misoprostol

Because misoprostol does not need to be injected or refrigerated, it is frequently used in low-resource settings, where there may be no skilled birth attendants or access to cold-chain storage. A Cochrane review(103) concluded that use of misoprostol (compared within various populations, at various doses, with differing comparators including placebo) does not reduce maternal mortality. Prophylactic misoprostol administration did reduce incidence of the composite outcome "maternal death or severe mortality" when compared with placebo (RR 1.70, 95% CI 1.02 - 2.81), but not when compared with other uterotonics (RR 1.50, 95% CI 0.50 to 4.52). Use of misoprostol is related with increased maternal side effects including fever and shivering, the severity of which increased with increasing dose(103).

Network Metanalysis

A Cochrane network metanalysis of uterotonic agents for preventing PPH(104) was published in 2018. Carbetocin, oxytocin/ergometrine and the combination of oxytocin plus misoprostol were top three ranked for prevention of PPH ≥500ml. Most included trials were for women having a vaginal birth (140/196 trials). Compared with oxytocin alone, oxytocin/ergometrine was found to reduce risk of PPH ≥500ml (RR 0.70, 95% CI 0.59-0.84) but not PPH ≥1000ml (RR 0.83, 95%CI 0.66-1.03). Compared with oxytocin alone, misoprostol plus oxytocin was found to reduce risk of PPH ≥500ml (RR 0.70, 95% CI 0.58 -0.86) but not PPH ≥1000ml (RR 0.88, 95% CI 0.70-1.11), and use of carbetocin

was found to reduce risk of PPH ≥500ml (RR 0.72, 95% CI 0.56-0.93) but evidence for PPH ≥1000ml was of very low certainty. Higher rates of adverse outcomes including nausea and vomiting following use of oxytocin/ergometrine rather than oxytocin or carbetocin. Misoprostol use increased likelihood of vomiting and fever.

1.8 Current recommendations for use of uterotonic drugs to prevent primary PPH after vaginal birth

Globally concordant recommendations exist regarding the routine use of oxytocin for prevention of PPH after vaginal birth(105). However, guidelines vary regarding the recommended dose and route of administration of oxytocin. In the UK, 10iU by intramuscular injection is recommended after vaginal birth(31, 33) and 5iU by slow intravenous bolus after caesarean birth (31, 106). Fast or higher dosed boluses of oxytocin are known to cause more haemodynamic adverse effects. In countries such as France, where women admitted to a labour ward routinely have an intravenous cannula, 5 or 10iU by intravenous injection is recommended (105). Globally, the avoidance of ergometrine is favoured, due to its increased side effect profile and potential for severe hypertension to contribute to potentially fatal intracranial haemorrhage.

In 2018 the World Health Organisation updated its recommendations(107) to reflect the CHAMPION trial(102) results. Where multiple uterotonics are available, 10 units of oxytocin by intravenous or intramuscular route is recommended for all births. If oxytocin is not available, or its quality cannot be guaranteed, ergometrine or ergometrine/oxytocin or carbetocin or misoprostol are advocated. When skilled birth attendants are not present, misoprostol 400µg or 600µg is recommended. In addition to this, the use of carbetocin is advocated for all births, if its cost is comparable to other uterotonic drugs(107).

Chapter 2 :

Are consultant-led obstetric units following national guidance on selection of prophylactic uterotonic drug for the prevention of PPH after vaginal birth?

2. 1 Background

It is thought that active management of the third stage of labour reduces risk of post partum haemorrhage (PPH) at the time of birth, compared with physiological management(72). In the United Kingdom, The National Institute for Health and Care Excellence states that all women should be advised to have an actively managed third stage of labour as this reduces risk of PPH and blood transfusion(33). It is recommended that 10 international units of oxytocin should be administered by intramuscular injection with the birth of the anterior shoulder, or immediately after birth, and specifies that use of oxytocin over Syntometrine reduces maternal side effects(33, 100). One such side effect is hypertension, severe forms of which can potentially increase maternal risk of cerebrovascular events(108). It is for this reason that oxytocin is the universally recommended prophylactic uterotonic drug for vaginal birth in guidelines internationally, and it has been commented that the "overall high quantity and quality of available evidence" is responsible for this "unequivocal and globally concordant" recommendation(105). A Cochrane network meta-analysis of uterotonic agents to prevent post-partum haemorrhage was published more recently, in 2018. This concluded that Syntometrine, when compared with oxytocin alone, may reduce risk of PPH ≥500ml but that it makes little or no difference to PPH ≥1000ml(104). It therefore seems unlikely that the aforementioned international recommendations would change in light of this new evidence and the known side effects of Syntometrine.

When I first went Out of Programme for Research, I was looking to set up a randomised control trial to investigate the use of carbetocin for prevention of PPH after vaginal birth. The logical comparator seemed at first to be oxytocin, given that this is the prophylactic uterotonic recommended for use after vaginal birth(31, 33). However, I was aware that I had not worked in any obstetric units where oxytocin was used as the first-line prophylactic uterotonic agent in this context, and I therefore questioned the relevance of oxytocin as the single comparator for carbetocin in a randomised control trial of its effectiveness. At the time, there was already some evidence to suggest that a

substantial proportion of obstetric units in the United Kingdom used Syntometrine as their prophylactic uterotonic agent of choice after vaginal birth. A postal survey conducted in 2010 reported that 79% of surveyed obstetricians and 86% of surveyed midwives "usually" used Syntometrine for Active Management of the Third Stage of Labour(109). While this postal survey did include just over 4000 respondents, there was no record of the region or unit in which they practiced, or whether they were based within the NHS or the private sector. To map this more succinctly, I decided to conduct a telephone survey of all obstetric units in England, Wales and Scotland to ascertain what current practice was with regard to prevention of PPH in low-risk women having a vaginal birth.

2.2 Aim

To establish whether prophylactic uterotonic drug use in obstetric units in England, Scotland and Wales followed national guidance, for the prevention of primary postpartum haemorrhage after vaginal birth in low-risk pregnancies.

2.3 Methods

Design

A telephone survey of current practice in obstetric units in England, Scotland and Wales was conducted in October-November 2013.

Population

All consultant-led obstetric units governed by the National Health Service in England, Wales and Scotland were included in the survey.

Inclusion criteria

Obstetric units in different hospitals within the same NHS Trust were surveyed separately. "Alongside" maternity units (midwife-led birthing units located within the grounds of a hospital with an obstetric unit) and "stand-alone" maternity units (midwife-led birthing units not located within the grounds of a hospital with an obstetric unit) were not included in the survey. These units are all part of an NHS Trust, and their corresponding obstetric unit would have been included in the survey. It was felt that guidelines would be common across individual Trusts regarding Active Management of the Third Stage of Labour.

Screening

A contact list was created by first referring to the document "Mapping maternity care: the configuration of maternity care in England"(110). This provided a comprehensive list of all Strategic Health Authorities (SHA) in England, and the number of NHS Trusts in each SHA with a consultant-led obstetric unit. The website of each NHS Trust was then reviewed, to confirm the name and contact telephone number for each obstetric unit providing consultant-led maternity care. Lists were cross-checked by referring to the websites for all Deaneries in England, Scotland and Wales providing training in Obstetrics and Gynaecology, to ensure that no hospitals were missed.

Survey conduct

All obstetric units were contacted during daytime working hours by Helen van der Nelson (Clinical Research Fellow) or Ffion Jones (medical student).

The midwife co-ordinator on duty was asked which prophylactic uterotonic drug their unit routinely used for normal-risk, healthy, normotensive women having an actively managed third stage of labour after a vaginal birth. Midwife co-ordinators were chosen because as a senior member of staff they were likely to know their local hospital policy and because there is a midwife co-ordinator on duty and contactable 24 hours a day.

If the midwife co-ordinator was not available, a senior midwife, practice development midwife or doctor was asked to respond instead. When requested by the respondent, an email was sent from an NHS email account, requesting the same information (to confirm legitimacy of the survey).

Ethics and approvals

This survey was conducted while I was a Clinical Research Fellow employed by the National Health Service, prior to my registration with the University of Bristol as a Postgraduate Student. Approval for this study was therefore not sought from the University of Bristol. The North Bristol NHS Trust Research and Innovation department was approached for advice regarding ethical approval or registration of this study. As a national survey of practice without any direct patient data, this was deemed unnecessary.

2.4 Results

187 hospitals with obstetric units were initially identified in England, Scotland and Wales. Two of these were not included in the survey; the hospital on The Isle of Man was not run by the National Health Service, and Western Isles Hospital in Scotland was not consultant-led.

A total of 185 hospitals were surveyed by telephone in October 2013. 99.5% of units (184/185) participated in the survey. One hospital did not wish to respond to the survey. 87% (161) of responses were given by the midwife coordinator on duty, 10% (19) by a senior labour ward midwife, 1% (2) by a Practice Development Midwife, and 1% (2) by a doctor. Results are presented in Tables 2.1 and 2.2.

Table 2.1: Telephone survey results

East of England	Hospitals with obstetric units (17)	Respondent	Uterotonic used
King's Lynn & Wisbech Hospitals NHS Trust	Queen Elizabeth Hospital, Kings Lynn	Coordinator	oxytocin 10 iU IM
Norfolk & Norwich Univeristy Hospital NHS Trust	Norfolk & Norwich Univeristy Hospital	Midwife on labour ward	oxytocin 10 iU IM
James Paget Healthcare NHS Trust	James Paget University Hospital, Great Yarmouth	Midwife on labour ward	oxytocin 10 iU IM
Peterborough & Stamford Hospitals NHS Foundation Trust	Peterborough City Hospital	Coordinator	oxytocin 10 iU IM
Hinchingbrooke Health Care NHS Trust	Hinchingbrooke Hospital, Huntingdon	Coordinator	oxytocin 10 iU IM
West Suffolk Hospitals NHS Trust	West Suffolk Hospital, Bury St. Edmunds	Midwife on labour ward	Syntometrine
Bedford Hospital NHS Trust	Bedford Hospital	Practice development midwife	Syntometrine
Cambridge University Hospital NHS Foundation Trust	Addenbrooke's Hospital	Coordinator	Syntometrine
The Ipswich Hospital NHS Trust	Ipswich Hospital	Midwife on labour ward	Syntometrine
Colchester Hospital University NHS Foundation Trust	Colchester General Hospital	Coordinator	oxytocin 10 iU IM
East & North Hertfordshire NHS Trust	Lister Hospital, Stevenage	Coordinator	oxytocin 10 iU IM
Luton & Dunstable Hospital NHS Foundation Trust	Luton & Dunstable University Hospital	Coordinator	Syntometrine
West Hertfordshire Hospitals NHS Trust	Watford Hospital	Midwife on labour ward	Syntometrine
Princess Alexandra Hospital NHS Trust	Princess Alexandra Hospital, Harlow	Doctor	oxytocin 10 iU IM
Mid Essex Hospitals NHS Trust	Broomfield Hospital, Chelmsford	Coordinator by email	Syntometrine
Basildon & Thurrock Univeristy Hospitals	Basildon Hospital	Coordinator	Syntometrine
Southend Health Care NHS Trust	Southend University Hospital	Coordinator	Syntometrine
East Midlands	**Hospitals with obstetric units (11)**	**Respondent**	**Uterotonic used**
Nottingham University Hospitals NHS Trust	Nottingham City Hospital	Coordinator	oxytocin 10 iU IM
	Queens Medical Centre	Coordinator	oxytocin 10 iU IM
Derby Hospitals NHS Foundation Trust	Royal Derby Hospital	Coordinator	Syntometrine
Sherwood Forest Hospitals NHS Trust	Kingsmill Hospital	Coordinator	Syntometrine
United Lincolnshire Hospitals NHS Trust	Pilgrim Hospital, Boston	Coordinator	oxytocin 10 iU IM
	Lincoln County Hospital	Coordinator	Syntometrine
Chesterfield & North Derbyshire Hospitals NHS Trust	Chesterfield Royal Hospital	Coordinator	Syntometrine
University Hospitals of Leicester NHS Trust	Leicester Royal Infirmary	Coordinator	Syntometrine
	Leicester General Hospital	Coordinator	Syntometrine
Northampton General Hospital NHS Trust	Northampton General Hospital	Coordinator	oxytocin 10 iU IM
Kettering General Hospital NHS Foundation Trust	Kettering General Hospital	Coordinator	oxytocin 10 iU IM
Severn Deanery	**Hospitals with obstetric units (7)**	**Respondent**	**Uterotonic used**
North Bristol NHS Trust	Southmead Hospital	Coordinator	Syntometrine
University Hospitals Bristol	St Michael's Hospital	Coordinator	Syntometrine
Gloucestershire Hospitals NHS Trust	Gloucestershire Royal Hospital	Coordinator	Syntometrine
Royal United Hospital Bath NHS Trust	Royal United Hospital, Bath	Coordinator	Syntometrine
The Great Western Hospitals NHS Foundation Trust	The Great Western Hospital, Swindon	Coordinator	Syntometrine
Taunton and Somerset NHS Foundation Trust	Musgrove Park Hospital, Taunton	Coordinator	Syntometrine
Yeovil District Hospital NHS Trust	Yeovil District Hospital	Coordinator	Syntometrine

Southwest Peninsular Deanery	Hospitals with obstetric units (5)	Respondent	Uterotonic used
Plymouth Hospitals NHS Trust	Derriford Hospital	Practice development midwife	Syntometrine
Royal Devon & Exeter NHS Foundation Trust	Royal Devon & Exeter Hospital, Wonford, Exeter	Coordinator	Syntometrine
South Devon Healthcare Trust	Torbay Hospital	Coordinator	Syntometrine
Royal Cornwall Hospitals NHS Trust	Royal Cornwall Hospital, Truro	Coordinator	oxytocin 10 iU IM
Northern Devon Healthcare Trust	North Devon District Hospital	Coordinator	Syntometrine
Mersey Deanery	**Hospitals with obstetric units (8)**		
Countess of Chester Hospital NHS Trust	Countess of Chester Hospital, Chester	Coordinator	Syntometrine
Mid Cheshire Hospitals NHS Trust	Leighton Hospital	Coordinator	Syntometrine
East Cheshire NHS Trust	Macclesfield District General Hospital	Coordinator	Syntometrine
Southport and Ormskirk NHS Trust	Ormskirk and District General Hospital	Coordinator	Syntometrine
Warrington and Halton Hospitals NHS Foundation Trust	Warrington Hospital	Coordinator	Syntometrine
St Helen's and Knowsley NHS Trust	Whiston Hospital	Coordinator	oxytocin 10 iU IM
Wirral University Teaching Hospital NHS Foundation Trust	Wirral Women and Children's Hospital, part of Arrowe Park Hospital	Coordinator	Syntometrine
Liverpool Women's NHS Foundation Trust	Liverpool Women's Hospital	Coordinator	oxytocin 10 iU IM
London: North East	**Hospitals with obstetric units (11)**		
Barking, Havering & Redbridge University Hospitals NHS Trust	Queen's Hospital	Coordinator	Syntometrine
Barnet and Chase Farm Hospitals NHS Trust	Barnet General Hospital	Coordinator	oxytocin 10 iU IM
	Chase Farm General Hospital	Coordinator	oxytocin 10 iU IM
Barts and The London NHS Trust	Newham General Hospital	Coordinator	Syntometrine
	Royal London Hospital	Coordinator	oxytocin 10 iU IM
	Whipps Cross University Hospital	Coordinator	Syntometrine
Homerton University Hospital NHS Foundation Trust	Homerton University Hospital	Coordinator	Syntometrine
North Middlesex University Hospital NHS Trust	North Middlesex Hospital	Midwife on labour ward	Syntometrine
Royal Free Hampstead NHS Trust	Royal Free Hospital	Coordinator	Syntometrine
University College London Hospitals NHS Foundation Trust	University College London Hospital	Coordinator	Syntometrine
Whittington Hospital NHS Trust	Whittington Hospital	Midwife on labour ward	Syntometrine
London: North West	**Hospitals with obstetric units (7)**		
Chelsea and Westminster Hospital NHS Foundation Trust	Chelsea & Westminster Hospital	Coordinator	woman's choice (oxytocin 10 iU IM or Syntometrine)
Ealing Hospital NHS Trust	Ealing Hospital	Coordinator	oxytocin 10 iU IM
The Hillingdon Hospital NHS Trust	The Hillingdon Hospital	Coordinator	Syntometrine
Imperial College Healthcare NHS Trust	Queen Charlotte's & Chelsea Hospital	Coordinator	oxytocin 10 iU IM
	St Mary's Hospital	Coordinator	Syntometrine
North West London Hospitals NHS Trust	Northwick Park Hospital	Midwife on labour ward	Syntometrine
West Middlesex University Hospital NHS Trust	West Middlesex University Hospital	Coordinator	oxytocin 10 iU IM
London: South	**Hospitals with obstetric units (10)**		
Guy's & St Thomas' NHS Foundation Trust	St Thomas' Hospital	Coordinator	Syntometrine
King's College Hospital NHS Foundation Trust	Princess Royal University Hospital	Coordinator	Syntometrine
	King's College Hospital	Coordinator	oxytocin 10 iU IM
Lewisham and Greenwich NHS Trust	Lewisham Hospital	Midwife on labour ward	oxytocin 10 iU IM
Lewisham and Greenwich NHS Trust	Queen Elizabeth Hospital, Woolwich	Coordinator	Syntometrine
Epsom & St Helier University Hospital NHS Trust	Epsom General Hospital	Coordinator	Syntometrine
	St Helier Hospital	Coordinator	Syntometrine

St George's Healthcare NHS Trust	St George's Hospital	Coordinator	Syntometrine
Kingston Hospital NHS Trust	Kingston Hospital	Coordinator	Syntometrine
Croydon Health Services NHS Trust	Croydon Hospital	Coordinator	Syntometrine
Kent, Surrey & Sussex	**Hospitals with obstetric units (13)**		
Ashford & St Peters Hospital NHS Trust	St Peter's Hospital	Coordinator	Syntometrine
Brighton & Sussex University Hospitals NHS Trust	Royal Sussex County Hospital	Midwife on labour ward	Syntometrine
	Princess Royal Hospital	Coordinator	Syntometrine
Dartford & Gravesham NHS Trust	Darrent Valley Hospital	Coordinator	Syntometrine
East Kent Hospitals University NHS Foundation Trust	William Harvey Hospital, Ashford	Midwife on labour ward	Syntometrine
	Queen Elizabeth the Queen Mother Hospital	Coordinator	Syntometrine
East Sussex Hospitals NHS Trust	Conquest Hospital	Coordinator	Syntometrine
Maidstone & Tunbridge Wells NHS Trust	Tunbridge Wells Hospital	Coordinator	Syntometrine
Medway NHS Foundation Trust	Medway Maritime Hospital	Coordinator	oxytocin 10 iU IM
Royal Surrey County Hospital NHS Trust	Royal Surrey County Hospital	Coordinator	Syntometrine
Sussex & Surrey Healthcare NHS Trust	East Surrey Hospital	Coordinator	Syntometrine
Western Sussex Hospitals NHS Trust	St Richard's Hospital	Coordinator	Syntometrine
	Worthing Hospital	Coordinator	Syntometrine
Northern	**Hospitals with obstetric units (12)**		
Northumbria Healthcare NHS Foundation Trust	Wansbeck General Hospital	Coordinator	oxytocin 10 iU IM
Newcastle Upon Tyne Hospitals NHS Foundation Trust	Royal Victoria Infirmary, Newcastle	Coordinator	oxytocin 10 iU IM
Gateshead Health NHS Foundation Trust	Queen Elizabeth Hospital, Gateshead	Coordinator	Syntometrine
City Hospitals Sunderland NHS Foundation Trust	Sunderland Royal Hospital	Coordinator	Syntometrine
South Tyneside NHS Foundation Trust	South Tyneside District General Hospital	Coordinator	Syntometrine
North Tees and Hartlepool NHS Foundation Trust	University Hospital North Tees	Coordinator	oxytocin 10 iU IM
South Tees Hospital NHS Foundation Trust	James Cook University Hospital	Coordinator	oxytocin 10 iU IM
	Friarage Hospital, Northallerton	Coordinator	oxytocin 10 iU IM
County Durham & Darlington NHS Foundation Trust	University Hospital North Durham	Coordinator	oxytocin 10 iU IM
	Darlington Memorial Hospital	Midwife on labour ward	oxytocin 10 iU IM
North Cumbria University Hospitals NHS Trust	Cumberland Infirmary, Carlisle	Coordinator	oxytocin 10 iU IM
	West Cumberland Hospital, Whitehaven	Coordinator	oxytocin 10 iU IM
North West	**Hospitals with obstetric units (14)**		
University Hospitals of Morecambe Bay NHS Trust	Furness General Hospital	Coordinator	Syntometrine
	Royal Lancaster Infirmary	Coordinator	Syntometrine
Blackpool Teaching Hospitals NHS Foundation Trust	Blackpool Victoria Hospital	Midwife on labour ward	Syntometrine
Bolton Hospitals NHS Foundation Trust	Royal Bolton Hospital	Coordinator	Syntometrine
Central Manchester University Hospitals NHS Foundation Trust	St Mary's Hospital	Coordinator	Syntometrine
East Cheshire NHS Trust	Macclesfield General Hospital	Coordinator	Syntometrine
East Lancashire Hospitals NHS Trust	Burnley General Hospital	Midwife on labour ward	Syntometrine
Lancashire Teaching Hospitals NHS Foundation Trust	Royal Preston Hospital	Doctor	Syntometrine
Penine Acute Hospitals NHS Trust	Royal Oldham Hospital	Coordinator	Syntometrine
	North Manchester General Hospital	Coordinator	Syntometrine
University Hospital of South Manchester NHS Foundation Trust	Wythenshawe Hospital	Coordinator	Syntometrine
Stockport NHS Foundation Trust	Stepping Hill Hospital	Coordinator	Syntometrine
Tameside & Glossop Acute Services NHS Trust	Tameside General Hospital	Coordinator	oxytocin 10 iU IM
Wrightington, Wigan & Leigh NHS Trust	Royal Albert Edward Infirmary	Coordinator	Syntometrine
Oxford	**Hospitals with obstetric units (6)**		

Milton Keynes Hospital NHS Foundation Trust	Milton Keynes General Hospital	Coordinator	Syntometrine
Oxford University Hospitals NHS Trust	The John Radcliffe Hospital, Oxford	Coordinator	Syntometrine
	Horton General Hospital, Banbury	Coordinator	oxytocin 10 iU IM
Buckinghamshire Healthcare NHS Trust	Stoke Mandeville Hospital, Aylesbury	Coordinator	oxytocin 10 iU IM
Royal Berkshire NHS Foundation Trust	The Royal Berkshire Hospital, Reading	Midwife on labour ward	Syntometrine
Heatherwood & Wexham Park Hospitals NHS Foundation Trust	Wexham Park Hospital	Coordinator	Syntometrine
Yorkshire & The Humber	**Hospitals with obstetric units (18)**		
North Lincolnshire and Goole Hospitals NHS Foundation Trust	Diana Princess of Wales Hospital, Grimsby	Coordinator	Syntometrine
	Scunthorpe General Hospital	Coordinator	Syntometrine
Harrogate and District NHS Foundation Trust	Harrogate District General Hospital	Coordinator	oxytocin 10 iU IM
Hull and East Yorkshire Hospitals NHS Trust	Hull Royal Infirmary	Coordinator	Syntometrine
York Teaching Hospital NHS Foundation Trust	Scarborough Hospital	Coordinator	Syntometrine
	York District General Hospital	Coordinator	Syntometrine
Barnsley Hospital NHS Foundation Trust	Barnsley District General Hospital	Coordinator	Syntometrine
	Doncaster Hospital	Coordinator	oxytocin 10 iU IM
	Jessop Hospital, Sheffield	Coordinator	Syntometrine
	Rotherham District General Hospital	Coordinator	oxytocin 10 iU IM
	Bassetlaw Hospital, Worksop	Coordinator	oxytocin 10 iU IM
Airedale NHS Foundation Trust	Airedale General Hospital	Coordinator	Syntometrine
Bradford Teaching Hospitals NHS Foundation Trust	Bradford Royal Infirmary	Coordinator	oxytocin 10 iU IM
Carderdale & Huddersfield NHS Trust	Calderdale Royal Infirmary, Halifax	Coordinator	oxytocin 10 iU IM
Mid Yorkshire NHS Trust	Dewsbury District General Hospital	Coordinator	Syntometrine
	Pinderfields Hospital	Coordinator	Syntometrine
Leeds Teaching Hospitals NHS Trust	Leeds General Infirmary	Coordinator	Syntometrine
	St James's Univeristy Hospital	Coordinator	Syntometrine
West Midlands	**Hospitals with obstetric units (17)**		
Birmingham Women's NHS Foundation Trust	Birmingham Women's Hospital	Coordinator	Syntometrine
Sandwell & West Birmingham Hospitals NHS Trust	Birmingham City Hospital	Midwife on labour ward	Syntometrine
Heart of England NHS Foundation Trust	Heartlands Hospital (Princess of Wales Womens Unit)	Coordinator	Syntometrine
University Hospitals Birmingham NHS Foundation Trust	Good Hope Hospital	Coordinator	Syntometrine
The Dudley Group NHS Foundation Trust	Russells Hall Hospital	Midwife on labour ward	Syntometrine
Walsall Healthcare NHS Trust	Walsall Manor Hospital	Coordinator	Syntometrine
University Hospital of North Staffordshire NHS Trust	University Hospital of North Staffordshire	Coordinator	Syntometrine
Royal Wolverhampton Hospitals NHS Trust	New Cross Hospital Maternity Unit, Wolverhampton	Coordinator	Syntometrine
Burton Hospitals NHS Foundation Trust	Queen's Hospital	Coordinator	Syntometrine
Mid Staffordshire NHS Foundation Trust	Stafford Hospital	Coordinator	Syntometrine
Royal Shrewsbury and Telford Hospital NHS Foundation Trust	Shrewsbury Hospital	Coordinator	Syntometrine
University Hospitals Coventry and Warwickshire NHS Trust	Walsgrave Hospital	Coordinator	Syntometrine
South Warwickshire NHS Foundation Trust	Warwick Hospital	Coordinator	Syntometrine
George Elliott Hospital NHS Trust	George Elliott Hospital	Coordinator	Syntometrine
Worcester Acute Hospitals NHS Trust	Alexandra Hospital, Redditch	Coordinator	Syntometrine
	Worcester Royal Hospital	Coordinator	Syntometrine
Wye Valley NHS Trust	The County Hospital, Hereford	Coordinator	Syntometrine
Wales	**Hospitals with obstetric units (11)**		
Aneurin Bevan University Health Board	Royal Gwent Hospital	Co-ordinator	Syntometrine
	Nevill Hall	Co-ordinator	Syntometrine
Betsi Cadwaladr University Health Board	Ysbyty Gwynedd	Co-ordinator	Syntometrine
	Wrexham Maelor Hospital	Co-ordinator	Syntometrine
	Glan Clwyd Hospital	Co-ordinator	Syntometrine
Cardiff & Vale University Health Board	University Hospital of Wales	Co-ordinator	Syntometrine

Cwm Taf Health Board	Prince Charles Hospital	Co-ordinator	Syntometrine
	Royal Glamorgan Hospital	Co-ordinator	Syntometrine
Hywel Dda Health Board	Bronglais General Hospital	Co-ordinator	Syntometrine
	Glangwili General Hospital	Co-ordinator	Syntometrine
	Withybush Hospital	Did not wish to answer	No response
Scotland	**Hospitals with obstetric units (18)**		
NHS Dumfries & Galloway	Dumphreys & Galloway Royal Infirmary	Coordinator	oxytocin 10 iU IM
NHS Borders	Borders General Hospital	Coordinator	Syntometrine
NHS Ayrshire & Arran	Ayrshire Central Hospital	Coordinator	oxytocin 10 iU IM
NHS Greater Glasgow & Clyde	Princess Royal Maternity Hospital	Coordinator	oxytocin 10 iU IM
	Southern General Hospital	Coordinator	oxytocin 10 iU IM
	Royal Alexandra Hospital	Coordinator	oxytocin 10 iU IM
NHS Lanarkshire	Wishaw General Hospital	Coordinator	oxytocin 10 iU IM
NHS Lothian	Royal Edinburgh Infirmary	Coordinator	oxytocin 10 iU IM
	St John's Hospital	Midwife on labour ward	oxytocin 10 iU IM
NHS Fife	Forth Park Hospital	Coordinator	Syntometrine
NHS Forth Valley	Forth Valley Royal Hospital	Coordinator	Syntometrine
NHS Tayside	Ninewells Hospital	Coordinator	Syntometrine
NHS Grampian	Aberdeen Maternity Hospital	Coordinator	Syntometrine
	Dr Gray's Hospital	Coordinator	oxytocin 10 iU IM
NHS Highland	Raigmore Hospital	Coordinator	Syntometrine
	Caithness General Hospital	Coordinator	Syntometrine
	Cambelltown Hospital	Midwife on labour ward	Syntometrine
NHS Western Isles	Western Isles Hospital	Coordinator	oxytocin 10 iU IM

Table 2.2: Summary of regional choice of routine prophylactic uterotonic drug for use after vaginal birth

Country	Region (number of hospitals)	Syntometrine (% of region)	Oxytocin 10iu (% of region)	Other
England (156)	East of England (17)	9 (53%)	8 (47%)	
	East Midlands (11)	6 (55%)	5 (45%)	
	Severn (7)	7 (100%)	0	
	Southwest Peninsular (5)	4 (80%)	1 (20%)	
	Mersey (8)	6 (75%)	2 (25%)	
	London: North East (11)	8 (73%)	3 (27%)	
	London: North West (7)	3 (43%)	3 (43%)	1 hospital: patient choice of syntometrine or syntocinon
	London: South (10)	8 (80%)	2 (20%)	
	Kent, Surrey and Sussex (13)	12 (92%)	1 (8%)	
	Northern (12)	3 (25%)	9 (75%)	
	Northwest (14)	13 (93%)	1 (7%)	
	Oxford (6)	4 (67%)	2 (33%)	
	Yorkshire and The Humber (18)	12 (67%)	6 (33%)	
	West Midlands (17)	17 (100%)	0	
Wales (11)	Wales (11)	10 (91%)	0	1 hospital did not wish to respond
Scotland (18)	Scotland (18)	8 (44%)	10 (56%)	
TOTAL	**185 hospitals**	**130 (70%)**	**53 (29%)**	**2 (1%)**

130 hospitals (70%) used Syntometrine as the routine prophylactic uterotonic drug after vaginal birth. 53 (29%) hospitals routinely used 10iu IM oxytocin. One respondent reported that their unit routinely gave the patient a choice of Syntometrine or oxytocin.

There appeared to be a preponderance of routine Syntometrine use in the West and South-west of England (see Figure 2.1).

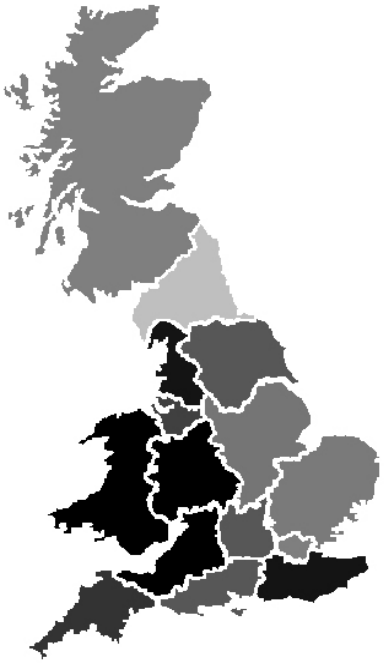


Figure 2.1 Map showing proportion of consultant-led obstetric units in each NHS deanery using Syntometrine routinely for Active Management of the Third Stage of Labour. Shading represents proportion of Syntometrine use (black = 100% Syntometrine® use, white = 0% Syntometrine use)

Table 2.3 Themes drawn from telephone conversations

Theme
1. Uncertainty regarding licensing and responsibility for the administration of intramuscular oxytocin
2. Local audit data superseding Level 1 evidence

2.5 Discussion

Seventy percent of NHS consultant-led obstetric units in England, Scotland and Wales used routine Syntometrine for prevention of primary postpartum haemorrhage after vaginal birth, despite national and international guidelines which advocate use of oxytocin. This suggestion that the majority of units were not adhering to guidelines with respect to prophylactic uterotonic use correlates with both the postal survey of obstetricians and midwives conducted in 2010 and a

subsequent survey of obstetric units published by the British Journal of Midwifery in 2013(71). Further evidence supporting this notion comes from a national obstetrics and gynaecology trainee-led audit relating to the management of post partum haemorrhage, conducted in 2014(5). This national audit spanned one calendar month and looked prospectively at the management of all women who experienced a postpartum haemorrhage after vaginal birth or caesarean birth. This found that 97% of women were offered and received a prophylactic uterotonic drug, and that the most frequently used prophylactic uterotonic drug after vaginal birth was intramuscular Syntometrine(5). Interestingly, oxytocin is used routinely during Active Management of the Third Stage of labour in the majority of other European countries(111). This may in part be because Syntometrine is not licensed for use in most other European countries (although ergometrine alone is).

A strength of this study is its high response rate, with only one of 185 hospitals surveyed declining to respond, increasing the generalisability of results. Telephone surveys of this nature place the onus of time on the person conducting the survey (i.e.: phoning again repeatedly until the respondent has time to answer), in contrast to postal or online surveys which can result in non-response bias and the under representation of certain groups as they rely on the respondent being motivated and interested enough to respond in their own time. Survey "representativeness" refers to how well the sample drawn for the questionnaire compares with the population of interest(112). There is a chance that the individual staff member surveyed at each hospital gave an inaccurate response regarding their local guidelines and routine local practice. The impact of this limitation could have been minimised by phoning all units twice and comparing the responses given. A more accurate picture of national guidelines may have been created by accessing each hospital's local guidelines. However, the process of obtaining these would have been far more time consuming, there may have been more resistance to sharing of whole guidelines, and it is unlikely that the study would have included 184/185 hospitals. It would have been possible to access a small subset of guidelines

(online, or by email request), and to cross-check these with telephone responses. This may have helped to provide some assurance about the methods used in this telephone survey. Even if a small number of respondents were inaccurate in the information which they provided by telephone, this is unlikely to have changed the overall conclusion that most UK obstetric units are still not adhering to national and international guidance, particularly as this corroborates other published surveys conducted at similar points in time.

While this survey did not aim to investigate reasons for deviation from guidance, some themes were identified as shown in Table 2.3:

1. *Uncertainty regarding licensing and responsibility for the administration of intramuscular oxytocin*

The British National Formulary lists "prevention of post partum haemorrhage" as an indication for the use of 10 units oxytocin by intramuscular injection, but also states that administration by intramuscular route is an unlicensed use. Some survey respondents commented that drug licensing for oxytocin was a barrier to its use in their hospital, and that doctors are routinely needed to prescribe oxytocin before it can be administered by a midwife. The Nursing and Midwifery Council states that "*midwives can [also] supply and administer a limited list of prescription only medicines (POMS)*"(113). Oxytocin is included as a midwife exemption in Schedule 17, Part 3, of the Human Medicines Regulations(114). This means that a doctor's prescription should not be needed. It is surprising that this should remain a true barrier to the use of routine oxytocin. This may support the notion that survey responses could have reflected personal preference and practice, rather than local departmental guidelines.

2. Local audit data superseding Level 1 evidence

Several respondents stated they their unit had trialled a period of routine oxytocin, but that this was abandoned in favour of routine Syntometrine when local audit data suggested a rise in PPH rate. This pattern of change and reversion to previous practice has also been reported in other surveys(71). There appears to be a cultural lack of confidence in use of oxytocin, despite Level 1 evidence suggesting that Syntometrine is no more effective than oxytocin at preventing PPH ≥1000ml(100). There is perhaps a belief that individual populations or services are in some way unique, or a lack of understanding of the evidence base surrounding this topic.

2.6 Summary

Seventy percent of all obstetric units in England, Scotland and Wales did not follow guidance regarding the use of prophylactic oxytocin for prevention of postpartum haemorrhage after otherwise low risk vaginal birth, at the time of this telephone survey. Reasons for this may include local barriers to the administration of oxytocin by midwives, a cultural lack of confidence in oxytocin as a prophylactic uterotonic drug, or a lack of understanding regarding the evidence base surrounding this topic. This survey demonstrates that any trial of uterotonic drugs aiming to inform and change practice in the United Kingdom needs to include a Syntometrine arm. In addition to this, the barriers to oxytocin use must be further considered in future.

Chapter 3 :

The IMox Study – Methods

In my role as a Clinical Research Fellow and Postgraduate MD student, I designed The IMox Study and wrote the study protocol and associated Standard Operating Procedures. I coordinated and completed our applications to the ethics committee and the Medicine and Healthcare products Regulatory Agency and attended the ethics committee interview. I established contacts within the Research and Innovation departments and Clinical Trials Pharmacies at participating sites and helped to facilitate roll-out of the study, and trouble-shoot problems, at participating sites. I worked closely with the Head of Production at St Mary's Pharmaceutical Unit in Cardiff to develop a plan for the blinding and randomisation of the study drug and helped to ensure that each participating unit had adequate stock of the Interventional Medicinal Product to match their predicted recruitment within the expiry date of the stock. I was the acting Trial Manager, and Principal Investigator for North Bristol NHS Trust, until my first period of maternity leave in October 2015. When I returned to work after maternity leave I was based in Gloucestershire Hospitals NHS Foundation Trust, and engaged within my local hospital to improve recruitment figures. During a further period of maternity leave the study finished recruiting. Thereafter I took on the role of co-ordinating the project once more towards our final goal of publishing study results. I worked closely with the trial statisticians over a period of months to complete data cleaning and co-ordinate data analysis. I was first author for the results paper and was responsible for making all required revisions to ultimately have this published(7) in June 2021.

3.1 Trial design

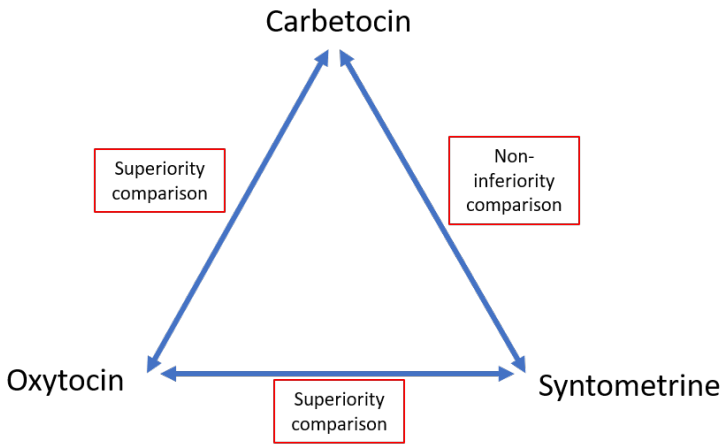
The IMox Study was a multi-centre, blinded, randomised active-controlled trial comparing oxytocin, carbetocin and oxytocin/ergometrine (Syntometrine) for the prevention of primary postpartum haemorrhage after vaginal birth, in which participants were randomised to three parallel arms (oxytocin, carbetocin and Syntometrine). It was a Phase IV drug trial. The trial protocol is publicly available(6).

3.2 Aims

The primary study aims were to determine whether, when given intramuscularly:

- carbetocin is as effective as Syntometrine
- carbetocin is more effective than oxytocin
- Syntometrine is more effective than oxytocin

Figure 3.1: Diagrammatic representation of the comparisons made in the three-armed IMox Study



A non-inferiority comparison was made between carbetocin and Syntometrine because fewer maternal side effects may make carbetocin a better option; if carbetocin were to be at least as good as Syntometrine, with fewer side effects, then carbetocin could be seen to be favourable. Superiority comparisons were made between carbetocin and oxytocin, as well as Syntometrine and oxytocin. (See Figure 3.1)

The secondary study aims were to determine whether, when given intramuscularly:

- Carbetocin is associated with fewer side effects than Syntometrine and oxytocin
- Choice of uterotonic drug affects a mother's subjective ability to bond with and care for her baby in the first two postnatal hours
- Choice of uterotonic drug affects maternal quality of life in the first two postnatal weeks

3.3 Outcomes

Primary outcome measure:

- Proportion of participants receiving additional uterotonic drugs within 24 hours of birth, after administration of the study drug

In this study, the proportion of participants receiving additional uterotonic drugs was used as the primary outcome measure for the following reasons:

1. Estimation of obstetric blood loss is known to be inaccurate regardless of how it is estimated(53), or who estimates it(51). This is largely due to the presence of contaminants such as amniotic fluid and urine etc. and difficulty ensuring that all blood is accounted for.

2. Vaginal or cervical tears also bleed and contribute to the incidence and severity of PPH (introducing further variance). The use of additional uterotonic drugs is therefore more reflective of the ability of the study drug to prevent uterine atony.

3. Additional uterotonic drugs are used to treat an atonic uterus, aiming to prevent or minimise PPH. In some cases, several uterotonic drugs may be used to avoid blood loss of ≥500ml. This would not be captured with a primary outcome of PPH incidence, which would not account for the clinically important (and costly) administration of additional uterotonics.

The decision to give additional uterotonic drugs lies with the individual midwife or doctor caring for the patient at the time of birth. In a routine clinical context, this subjective decision is made based on their professional assessment of the clinical situation at that time. For this reason, indications for the use of additional uterotonic drugs were revised and clarified at the IMox teaching sessions, (attended by all those entered onto the study delegation log) with the aim of standardising care. Members of staff were informed that the decision to give additional uterotonic drugs must be: (i)

made by a qualified midwife or doctor (ii) to improve the tone of a uterus deemed to be inadequately contracted on abdominal palpation (iii) when assessed at the time of abnormally brisk vaginal bleeding.

Secondary outcome measures:

- Number of doses of an additional uterotonic drug received
- Estimated (weighed) blood loss at delivery (millilitres)

Blood loss was routinely weighed for all participants; blood was collected and blood-soaked materials (swabs, pads, drapes, inco-sheets) were weighed with dry weights subtracted to give a gravimetric estimation of volume. This continued from birth until transfer from Delivery Suite, or until normal post-partum lochia was established.

- Postnatal blood transfusion requirements (number of units of red cells or other blood products given)
- Volume of own blood returned to participant if Cell Salvage used (millilitres)
- Perineal tear
- Duration of the third stage of labour (minutes)
- Need for manual removal of placenta
- Need for other "non-drug" methods of PPH management including: examination under anaesthetic in theatre, use of an intrauterine balloon for tamponade, uterine compression suture or interventional radiology (composite outcome)
- Need for peripartum hysterectomy
- Maternal hypertension in first two post-natal hours

Blood pressure was routinely measured (manually) at 1 and 2 hours postnatal for all participants. For the purpose of analysis, hypertension was defined as any episode of post-partum systolic blood pressure >140mmHg or diastolic blood pressure >90mmHg on any occasion in the first two

post-natal hours (not necessarily two consecutive high readings 30 minutes apart, as per exclusion criteria set out later in this chapter.)

- Maternal hypotension in first two post-natal hours

Hypotension was defined as any post-partum systolic blood pressure <90mmHg in the first two post-natal hours.

- Post-partum nausea and vomiting in the first two post-natal hours
- Vomiting in labour

This data was collected to allow identification of those who vomited postnatally, who were not already vomiting in labour (in whom vomiting was more likely to be directly attributable to the uterotonic given).

- Time from delivery to discharge from Delivery Suite (either to post-natal ward or home)
- Proportion of participants going to recovery, and time spent there (hours)
- Proportion of participants requiring High Dependency Care on labour ward, and length of time (hours)
- Proportion of participants requiring admission to the Intensive Care Unit, and time spent there (hours)
- Side effects experienced by participants in the first two post-natal hours (none/mild/moderate/severe);
    - Nausea
    - Vomiting
    - Headache
    - Dizziness
    - Abdominal pain

    - The effect which the above symptoms had on the participants' ability to bond with and care for their baby in the first two postnatal hours
- Maternally reported health-related quality of life using EQ-5D-5L questionnaire
- Length of postnatal hospital stay (days)

Data was also collected for the following, to allow for multivariable logistic regression;

- Pyrexia in labour
- Baby birth weight (kg)
- Mode of vaginal birth (spontaneous/instrumentally assisted/breech)

3.4 Outcome assessment

Case Report Form (see Appendix)

Case report forms were completed by the midwife or doctor caring for the participant in labour, before the participant was discharged from labour ward. To minimise the amount of time which the on-shift clinician had to spend performing research related tasks, some demographic and birth related details (routinely entered onto a maternity database for each delivery in clinical practice) were collated on the back page of the Case Report Form and collected by research staff at a later timepoint.

Reporting boxes were placed on the postnatal wards, and clinical staff were encouraged to use these to flag up any postnatal participants who had been transferred back to labour ward, participants who they believed might have experienced any adverse events, or any participants who had required a postnatal blood transfusion. Participants completing their day 1 and day 14 postnatal EQ-5D-5L questionnaires were also asked again whether they had received a blood transfusion since the birth of their baby, to ensure that this important postnatal outcome was not missed.

Maternal postnatal experience questionnaire (see Appendix)

Participants were invited to complete the maternal postnatal experience questionnaire at approximately 2 hours postnatal, or at the next most appropriate time if necessary (i.e.: if the participant was drowsy after a general anaesthetic, if the participant was particularly distressed for any reason). If completed at a later timepoint, the participant was specifically requested to relate their responses to their experiences in the first two postnatal hours. Participants were given the option of a member of staff reading out the questionnaire and recording their responses, if they felt unable to complete the paper form themselves. An evaluation of this type of questionnaire is provided in Chapter 6.

EQ-5D-5L IMox Health Questionnaire (see Appendix)

In the absence of maternity-specific validated instruments for the measurement of quality of life in pregnant and postnatal women, studies often use more generic tools. The EQ-5D-5L was chosen for use in The IMox Study because it is the tool preferred for measurement of health-related quality of life in adults by the National Institute for Health and Care Excellence (NICE), and because it is short and simple to complete. Limitations of this tool will be discussed further in Chapter 6. The EQ5D covers five domains; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The "5 level" questionnaire was chosen over the "3 level" version, for its improved sensitivity and precision.

Participants were asked to complete an EQ-5D-5L questionnaire antenatally at the time when written consent was taken, and on postnatal day 1 and postnatal day 14. Antenatal questionnaires were not completed by those already in the latent phase of labour when written consent was taken, as this would bias the "pain/discomfort" domain. Day 1 postnatal questionnaires were completed using a paper version if the participant was still in hospital, or by telephone if the participant had

already been discharged. Day 14 postnatal questionnaires were completed by telephone. If after 3 attempts at telephone contact the patient did not respond, the questionnaire was sent by post together with a covering letter and a stamp addressed return envelope.

3.5 Interventions

A single intramuscular injection of the allocated uterotonic drug (10 IU oxytocin or 500µg/5IU Syntometrine or 100µg carbetocin) was administered to the participant immediately after clamping of her newborn baby's umbilical cord following birth. The intervention was withheld if the participant was no longer eligible after randomisation (e.g. emergency caesarean section or hypertension), or if the participant withdrew consent. Clamping of the umbilical cord is routinely performed after 1 minute in the UK. This could be performed later than 1 minute as per parental wishes.

3.6 Setting

Women were recruited from six consultant-led obstetric units in Southwest and Central England (See Figure 3.2).

Figure 3.2: Location of maternity units participating in The IMox Study

Map reference	Hospital	Trust	City
1	Southmead Hospital	North Bristol NHS Trust	Bristol
2	St Michael's Hospital	University Hospitals Bristol NHS Foundation Trust	Bristol
3	Royal United Hospital	Royal United Hospitals Bath NHS Foundation Trust	Bath
4	Gloucestershire Royal Hospital	Gloucestershire Hospitals NHS Foundation Trust	Gloucester
5	Great Western Hospital	Great Western Hospitals NHS Foundation Trust	Swindon
6	Nottingham City Hospital	Nottingham University Hospitals NHS Foundation Trust	Nottingham

The hospitals in Bristol, Bath, Gloucester and Swindon were selected first, due to their geographical proximity and links through the West of England NIHR Clinical Research Network. The study was later also rolled out to Nottingham University Hospitals NHS Trust (Nottingham).

Many hospitals have both a consultant-led labour ward, and an "alongside" (co-located) midwife-led birthing centre. Women giving birth in consultant-led labour ward do so due to obstetric risk factors or patient choice. Women who are "low risk" can choose to give birth in a birth centre. This study recruited participants giving birth on the consultant-led labour ward or birth centre at Southmead Hospital, but from consultant-led labour wards alone at the other sites. It was logistically more difficult to manage and monitor recruitment, staff training, study fridge compliance, and protocol adherence from two areas within one hospital. This was only deemed feasible at Southmead Hospital, the study base, because of the proximity of the Birth Centre to the labour ward, the on-site Clinical Research Fellow/Trial Manager and the greater number of IMox-specific research midwives present per day.

Start dates of recruiting centres staggered by approximately 2 months to facilitate robust study roll out.

3.7 Blinding, randomisation, allocation

A computer-generated drug allocation sequence was created by an independent statistician, with an assignment ratio of 1:1:1 and block size of nine. Blocked randomisation allowed us to stratify by site; participating sites were allocated consecutively numbered doses of the randomised and blinded Interventional Medicinal Product (IMP), and the randomised sequence was only ever cut at the end of a block.

Several factors influenced the way in which the IMP was ultimately blinded:

(1) All three uterotonics are commercially available in one millilitre ampoules, but the Syntometrine ampoule is 5mm shorter than the other two ampoules, and the ampoules tops vary in the colour of their rings and break point dots (see Figure 3.3). It was therefore not possible to blind by direct over-labelling alone.

Figure 3.3: Comparative sizes of ampoules containing the three IMox Study drugs

(2) The Summary of Product Characteristics for carbetocin states that once drawn up from the ampoule, carbetocin should be administered immediately. It was therefore not possible to blind through use of pre-drawn up syringes.

(3) While it would have been possible for a separate unblinded member of staff to draw up the randomised IMP and pass this unlabelled syringe on to the blinded clinical members of staff for use, this was deemed impracticable. The study budget did not allow for research staff presence 24 hours/day, and we wanted research staff (even those not directly involved in this study) to remain blinded. We did not want any clinical staff members on-shift to be unblinded, as anyone could become involved in the care of a participant in the case of an obstetric emergency.

Drug blinding and labelling according to the randomisation sequence was carried out by St Mary's Pharmaceutical Unit (SMPU), Cardiff. Ampoules were ultimately blinded by use of snapper tops and over labelling. Original labels were removed, and the ampoules were labelled with a Good Manufacturing Practice-compliant IMP label which featured an arrow aligning with the original break-dot of the ampoule. The ampoule snapper was also covered with an opaque white label, to obscure the coloured rings (see Figures 3.4 and 3.5). Each ampoule was placed centrally in an individual ampoule box (see Figure 3.6), and the box was labelled in accordance with the randomisation list. The label featured a detachable section containing details of the batch number, randomisation number and trial identifier. This was stuck onto the drug chart next to the prescription, once administered, and became part of the accountability trail.

Figure 3.4: Snapper tops used to obscure the IMox Interventional Medicinal Product ampoule height difference, ring colour, and prevent the occurrence of sharps injury

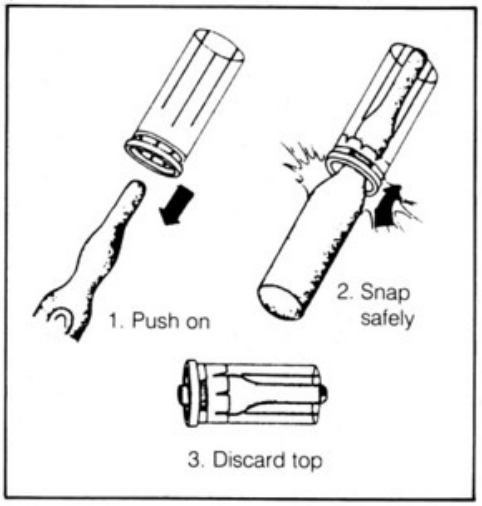


Figure 3.5: Photo of blinded IMox Interventional Medicinal Product ampoule with labelling explained

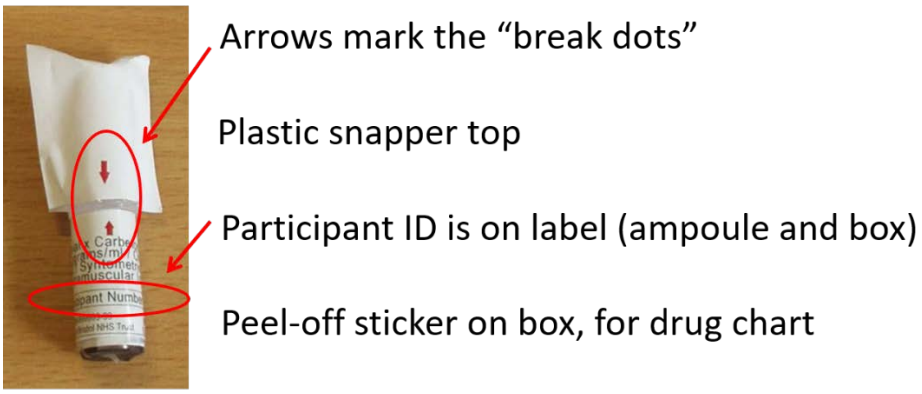


Figure 3.6: Photo of blinded IMox Interventional Medicinal Product presented in storage box

.

All study drugs were stored in refrigerators to maintain blinding. Oxytocin requires storage between 2-8 degrees Celsius, as did the carbetocin used in this study. Syntometrine can be stored up to 25 degrees Celsius for up to 2 months when protected by light. The study carbetocin was not of heat stable formulation, because this was not widely available at the time when recruitment commenced.

Although this became commercially available part way through the recruitment period, a decision was made not to change the formulation used, so as not to introduce any potential source of bias. Heat stable carbetocin varies from non-heat stable carbetocin only in its excipients(94).

Drugs were stored in IMox Study refrigerators in consecutive order, according to the computer-generated randomisation sequence (see Figure 3.7). Women were randomised when vaginal birth was imminent, with assignment to the next consecutively numbered box by the midwife caring for the participant at the time of birth. This method of randomisation was chosen over the use of a telephone randomisation service, to maximise efficiency at a time when clinical staff are already very busy, to minimise cost and to maintain blinding of clinical staff (outcome assessors) as well as researchers and participants. This method of randomisation was similar to that used in a randomised control trial of carbetocin versus oxytocin after caesarean section, conducted at Southmead Hospital in 2006(115). All groups remained blinded until data lock after study closure.

Figure 3.7: IMox IMP stored in consecutive numbered boxes in IMox research fridge. Arrow on the box indicating which end the next consecutively numbered box should be taken from

3.8 Handling and accountability of the Interventional Medicinal Product

3.8.1 Manufacturing and distribution

The oxytocin and Syntometrine used in this study were bought in by SMPU, and carbetocin was supplied to SMPU directly by Ferring Pharmaceuticals. Carbetocin was supplied in batches through the course of the study, to ensure maximal shelf-life while it was waiting to be blinded, randomised, and administered.

SMPU blinded and randomised the IMP in batches of ~600 doses. The expiry of the individual boxes of IMP corresponded to the shortest shelf life of the oxytocin/Syntometrine/carbetocin used in that batch. SMPU required a 3-month lead-in period to the supply of the next batch of IMP. Recruitment targets and recruitment rates at each site were constantly monitored by the IMox Trial Manager. This enabled pre-emptive ordering of IMP for each site, and minimised situations in which the recruiting site ran out of IMP, or IMP passed its expiry date. The IMP was dispatched from SMPU directly to participating sites. The randomisation sequence was only ever split at the end of a block of 9, to ensure the equal distribution of the three drugs to the participating centres. The block size was only known to research staff, so as not to compromise the quality of the blinding.

There were occasions when the transfer of IMP between sites was required, to avoid drug wastage when approaching IMP expiry dates. This occurred with oversight and sign off from the Qualified Person (QP) at SMPU, in line with the standards of Good Manufacturing Practices. All IMP transfers were made using thermoregulated couriers.

3.8.2 In-house management of IMP

Once dispatched from SMP, IMP was sent directly to the Clinical Trials Pharmacy at each participating site. The stock held in the Pharmacy was used to restock the clinical areas. All IMP was

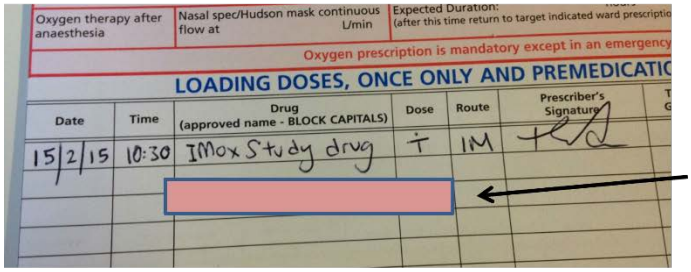
stored at 2-8 degrees Celsius in a locked study-specific fridge on or near the labour ward at each participating site. Each fridge was set up with two thermometers. A standalone minimum/maximum thermometer was checked and logged by research staff daily, and by clinical staff each time the fridge was opened. Daily checks by research staff also confirmed that the IMP was being stored in consecutive order, to honour the randomisation sequence. If ever the temperature was found to have deviated from the required range, the fridge was placed into "quarantine". During times of quarantine, the fridge key was removed from the clinical area (by research staff in-hours, or the co-ordinating midwife out-of-hours) and randomisation at that site was temporarily halted. Any eligible and previously consented participants giving birth during this period were withdrawn from the study and treated as per standard local clinical practice during the third stage of their labour. At the next available opportunity, the second thermometer (with capacity for constant recording and storing of fridge temperature) was interrogated by the local Clinical Trials Pharmacist, or Clinical Trials Pharmacy Technician. If it was confirmed that the fridge had gone out of temperature range for any period of time, the IMP held in the fridge during that period was destroyed, after written confirmation from the Sponsor (North Bristol NHS Trust Research & Innovation Department). If it was confirmed that the fridge had not gone out of temperature range, the quarantine was lifted and randomisation resumed.

3.8.3 Drug Accountability

An Accountability Log was kept to account for each dose of the study drug. Every time a participant was randomised, their details were entered alongside the date, time, and the person performing the randomisation. Any drugs wasted (i.e.: vial accidentally smashed, participant no longer eligible after drug removed from fridge for reasons including hypertension or caesarean section) were documented in the log, alongside the reasons for drug wastage. The peel-off sticker detailing the participant number, from the front of the study drug storage box, was attached to the participant's drug chart alongside the prescription for the "IMox drug" (see Figure 3.8). This served as another

part of the accountability trail. The prescription for the “IMox drug” could be made by any GCP trained doctor who had also undergone the IMox-specific training and had been allocated the role of prescribing in the delegation log.

Figure 3.8: Example of IMox IMP prescription on a drug chart



“IMox Study drug, ONE, intramuscularly”

Detachable sticker to go underneath, once administered

3.9 Participants

Women ≥18 years old with a spontaneous or assisted vaginal birth of a live singleton baby ≥24 weeks gestation were eligible to participate. Women were recruited in the antenatal period and were not eligible for recruitment once they were in established labour (diagnosed at 3-4cm or more cervical dilatation).

Exclusion criteria, with reasons for exclusion, are described below:

- Known or suspected hypertensive disorders (i.e.: essential hypertension, pregnancy induced hypertension, pre-eclampsia); it would not be appropriate to randomise these women to receive Syntometrine.
- Intrapartum hypertension, defined as any single intrapartum systolic blood pressure ≥160mmHg, or any two consecutive intrapartum blood pressures with a systolic value ≥140mmHg or diastolic value of ≥90mmHg, taken thirty minutes part; it would not be appropriate to randomise these women to receive Syntometrine.

- Women who laboured quickly and did not have their blood pressure checked in labour; it would not be appropriate to randomise these women to receive Syntometrine, in case new onset hypertension had not been detected.
- Antepartum haemorrhage ≥50ml or suspected placental abruption; antepartum haemorrhage is a significant risk factor for post-partum haemorrhage. In case of concealed haemorrhage with a placental abruption, overall blood loss would not be directly attributable to the study drugs.
- Maternal coagulation disorder; this is relatively rare in the study population, but could significantly affect blood loss, thus having potential to unbalance groups.
- Significant hepatic, cardiac of peripheral vascular disease; these are contraindications to the use of Syntometrine and carbetocin(91, 93).
- Intrauterine fetal death in this pregnancy; the ethics committee advised that it would not be appropriate to approach these women for participation in this study.
- Women who would decline blood products if required; clinicians are likely to have a lower threshold for administering additional uterotonic drugs to these women.
- Women with epilepsy; this is a listed contraindication to the use of carbetocin(93).

Regarding eligibility to consent, one further exclusion criteria was applied:

- Women who received parenteral opiates (i.e.: pethidine, diamorphine) less than 6 hours before consent took place; as the effects of these opiates are believed to be apparent for up to 6 hours, this was felt to potentially affect a woman's ability to give informed consent to participate.

3.10 Staff preparation

All midwives, maternity care assistants and doctors working in the participating maternity departments underwent IMox-specific training, taught by local research midwives. This training covered study aims, interventions, eligibility criteria, study outcomes, use of data collection tools (Case Report Form and participant questionnaires) and correct use of the study fridge. There was also an overview of the principles of Good Clinical Practice.

All midwives and doctors taking written consent, and all doctors prescribing the study drug or signing off participant eligibility, were required to be Good Clinical Practice trained. Additional face-to-face Good Clinical Practice training sessions were organised in Bristol to help ensure that all doctors were GCP trained across the Severn Deanery, and training was also accessible through each hospital's Research and Innovation department.

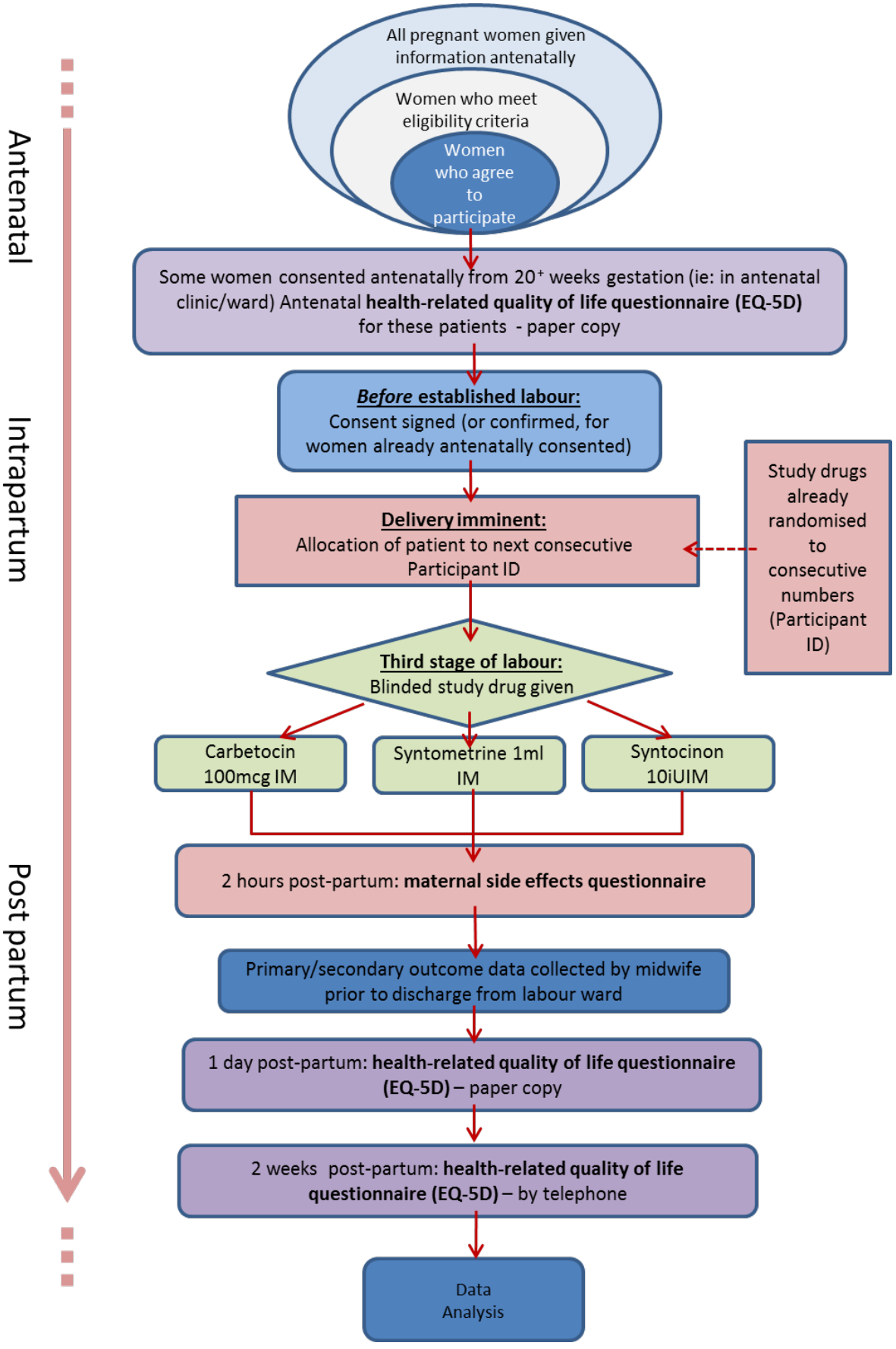
3.11 Recruitment

3.11.1 The ethics of consent for The IMox Study

Labouring women can be a vulnerable population, due to the pain and fatigue which they may experience in labour and the heightened emotion surrounding the birth of their child. There is often debate about the amount of information which you can burden an otherwise uncomplicated pregnant woman with when recruiting to intrapartum research, especially that involving emergency obstetric complications. Participants need to have been given enough time to consider information in advance of giving consent, but ultimately the information given may place undue psychological burden on the pregnant woman, regarding complications which may not ultimately affect her. The recruitment process for this study was developed in line with national guidance(116) and with help from the North Bristol NHS Trust lay Maternity Service User Panel, a group of volunteer lay women who had previously been maternity service users. The RCOG Guideline "Obtaining Valid Consent to

participate in Perinatal Research Where Consent is Time Critical" was published in 2010 (the version referred to when writing this protocol) and updated in 2016(116). The Maternity Service User Panel reviewed the study recruitment process, Participant Information Leaflets and Participant Questionnaires, and provided feedback. The recruitment process was carefully considered by the Research Ethics Committee prior to approval being granted. A pictorial representation of the flow of each participant is given in Figure 3.9.

Figure 3.9: The flow of participants through The IMox Study



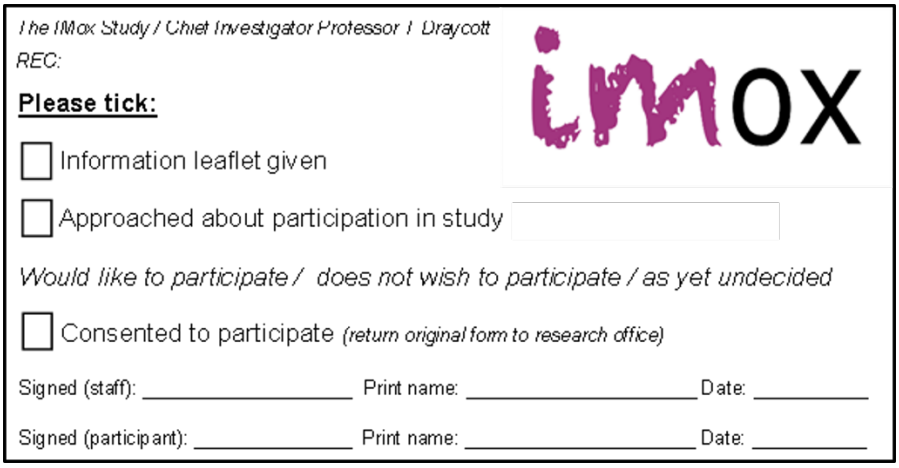
3.11.2 Distribution of Patient Information Leaflets

We deemed it appropriate to provide all pregnant women with an IMox Study Patient Information Leaflet, because >70% of women do go on to have a vaginal birth(117), and approximately 10% of women are believed to experience a postpartum haemorrhage(18, 118). National guidelines state that Active Management of the Third Stage of Labour should be recommended for all women, and so discussions surrounding the prevention of PPH should already be happening during each pregnancy(33). We aimed to provide all pregnant women, booked to give birth at a participating site during its recruitment period, a study information leaflet antenatally. Patient information leaflets were available in English, Arabic, Polish and Urdu. Leaflets were given to all women who attended their routine 18-21 week anomaly ultrasound scan throughout the study period, and opportunistically where possible, to those attending a Day Assessment Unit, Antenatal Ward or Antenatal Clinic who had not yet received a leaflet. Posters providing study information and contact details were displayed in antenatal clinical areas both in hospital and community sittings.

3.11.3 Obtaining consent

Women seeing a doctor or midwife from 20 weeks gestation, were asked whether they had received a Patient Information Leaflet, and whether they wished to participate in the study. The woman's preference was indicated using an IMox specific sticker placed on the front of her hand-held maternity notes (see Figure 3.10). This helped to ensure that women who did not wish to participate were not repeatedly approached about participation. Written consent was then taken by an IMox and GCP trained member of staff at the next available opportunity. Women were not expected to schedule an extra hospital visit solely for the purpose of being consented to the study, unless they wished to do so.

Figure 3.10: IMox Study Sticker, placed on the front of the hand-held maternity notes of all women passing through the antenatal clinic during the study recruitment period



At the time when written consent was taken, eligibility was reconfirmed, and a copy of the consent form was stored in the woman's hand-held maternity records. Women attending the hospital in early labour, who had received an antenatal Patient Information Leaflet but had not yet been consented, could be approached to participate if they were not yet in established labour (diagnosed when vaginal examination confirmed the cervix to be 3-4cm dilated, with regular painful contractions). This restriction was placed by the Research Ethics Committee, due to concerns about the vulnerabilities of labouring women, and the thought that consent taken in active labour may not be truly informed. Women who had received parenteral opiates (i.e. intramuscular pethidine or diamorphine) within 6 hours were also deemed inappropriate to newly consent to participate (but were able to reconfirm their wish to participate, if previously consented).

3.12 Sample size

The sample size calculation was based on rates of need for additional uterotonic drugs (our primary outcome measure), reported by other randomised control trials of intramuscular prophylactic

uterotonics after vaginal birth, with each individual study comparing two of our three study drugs(119-124). Data from these trials was pooled and weighted for study size, to derive the weighted mean prevalence on which our sample size was based. Previously published data was broadly pooled to give the estimates shown in table 3.1; differences in drugs equate to approximately 4 points.

Table 3.1: Broadly pooled weighted (for study size) estimates of the primary outcome measure from available published data

Uterotonic drug	Proportion requiring additional uterotonic drugs
Oxytocin	19.1%
Syntometrine	15.2%
Carbetocin	11.5%

Superiority comparison

To identify a 4-point (15/19 = 0.8 or 20%) difference between Oxytocin and Syntometrine, a sample size of 1904 participants per arm would provide at least 88% power for this comparison with an α of 0.05 (two-sided comparison).

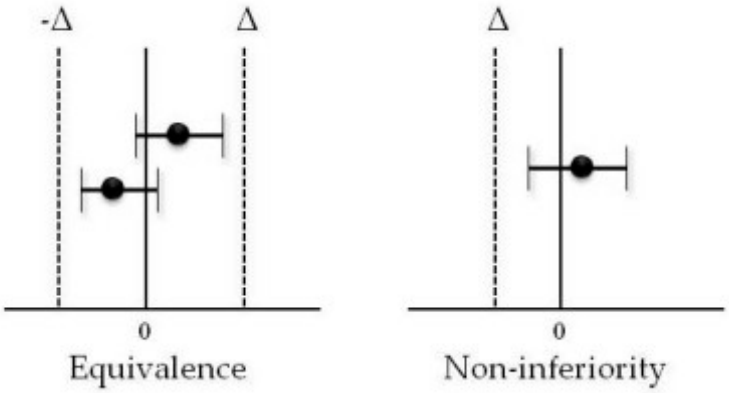
To identify an 8-point difference (11/19 = 0.6 or 40%) difference between Oxytocin and Carbetocin, the proposed sample size of 1904 participants per arm would have at least 99% power for this comparison with an α of 0.05 (two-sided comparison).

Non-inferiority comparison

A non-inferiority comparison was made between Carbetocin and Syntometrine, because if Carbetocin is “not unacceptably worse”(125) than Syntometrine, with a better side effect profile, it may be a more favourable prophylactic uterotonic drug.

Non-inferiority was assessed using a two-sided 95% confidence interval for the difference in proportions, with significance declared if the confidence interval lay entirely on the correct side of the non-inferiority margin (Δ). The differences between outcome assessments in equivalence and non-inferiority trials are illustrated in Figure 3.11. The non-inferiority margin chosen for this study was 1%, in favour of Carbetocin. This margin was chosen based on clinical judgement, while taking the broadly pooled pre-study data shown in Table 3.1 into consideration. In Figure 3.11, the non-inferiority margin is a negative value (depicted by the dotted line and Δ to the left of the y axis). In this study we are looking at the proportion of participants requiring an additional uterotonic drug. Negative values favour a good outcome for carbetocin; the need for fewer *additional* uterotonic drugs equates to a more effective *prophylactic* uterotonic drug. To demonstrate non-inferiority of carbetocin to Syntometrine we are therefore using a non-inferiority margin to the right of the y axis; we would need the upper limit of the 95% CI for the carbetocin versus Syntometrine comparison to be less than +1. Please see Figure 4.2 for further illustration of this in the Results section (Chapter 4). A sample size of 1904 per arm has 95% power for the non-inferiority margin of 1%.

Figure 3.11: The role of Δ in equivalence and non-inferiority trials. Reproduced from Schumi & Wittes; "Through the looking glass: understanding non-inferiority"(125)



Based on the above, a sample size of 5712 (1904 participants per arm) was decided upon for The IMox Study. In early protocols, the rate of attrition was predicted to be 10%, and the sample size was inflated to 6285 to reflect this. Once the study was underway, it was realised that there was actually very little time for participants to drop out of the study between randomisation (when birth is imminent) and administration of the study drug (immediately after birth). When actual attrition was found to be less than 0.5% during the study, the inflation was removed, and the required sample remained at 5712.

3.13 Statistical analysis

This section is adapted from the IMox Statistical Analysis Plan and the description of the statistical analysis presented in *"Intramuscular oxytocin versus oxytocin/ergometrine versus carbetocin for prevention of primary postpartum haemorrhage after vaginal birth: study protocol for a randomised controlled trial (the IMox study)"* by van der Nelson et al, 2019(6).

Primary, secondary and safety outcome results will be reported by randomised arm. Analyses will be performed for both the modified intention to treat population (mITT) and the per protocol population. Sensitivity analyses will use the Intention to Treat Population. See Table 3.2 for descriptions of these populations. Substantive conclusions are drawn from the mITT population and not the Intention to Treat (ITT) population, because the ITT group included those who underwent caesarean section and those who did not receive a prophylactic uterotonic drug as part of the study.

Table 3.2: Study populations used in analysis of The IMox Study

Population	Definition
Intention to Treat	All those randomised.
Modified Intention to Treat	Participants who were randomised, remained eligible and received a study uterotonic. Analysed according to their original randomisation.
Per Protocol	Participants who were randomised, remained eligible, had no protocol deviations, and received the uterotonic drug which they were first randomised to. Analysed according to uterotonic received.

For the primary outcome, an omnibus test for difference in proportions needing additional uterotonic drugs will use the chi-squared test of association. Statistical significance will be two-sided p <0·05. The chi-square test of association will be used to examine superiority of Syntometrine versus oxytocin, and carbetocin versus oxytocin. In the comparison between carbetocin and Syntometrine, non-inferiority will be declared if the upper limit of the two-sided 95% CI for the proportion receiving additional uterotonics excludes the non-inferiority margin of 1%.

Analyses for all secondary outcomes will be conducted only for superiority, using an appropriate omnibus test. The secondary outcome "weighed estimated blood loss (ml)" will be categorised (<500ml, ≥500ml, ≥1000ml, ≥2000ml) for analysis.

A sensitivity analysis will be performed using the ITT group. Missing primary outcome data will be substituted with an assumption that additional uterotonic drugs were required at increments of 1% between 10 – 25% of missing data.

The primary outcome will be adjusted for known PPH risk factors including induction of labour, BMI and previous PPH using multivariable logistic regression. The same will be done for the outcome of PPH ≥500ml.

Health states generated from the EQ-5D-5L will be valued from the EQ-5D-3L preference utility weights for the UK population using Van Hout's crosswalk method(126).

3.14 Withdrawal

Participants were free to withdraw from the study at any point, and it was highlighted to them that this would not affect their ongoing care in any way. Any data which had already been collected from a participant before she was withdrawn from the study was still analysed, unless she specifically withdrew consent for this as well. This was explained in the Patient Information Leaflet and the consent form.

3.15 Adverse Event reporting and recording

Suspected Adverse Events were recorded as a part of the Case Report Form (see Appendix to Chapter 3). To ensure that any Serious Adverse Events which occurred within the first 12 postnatal hours were captured even after discharge from the labour ward, units were encouraged to have an additional "IMox postbox" on the postnatal wards in which staff could document any other events believed to be important. Adverse events were assessed and reported in line with the flowchart given in Figure 3.12.

The symptoms listed in Table 3.3 are known side effects of the study drugs, as listed in their respective Summary of Product Characteristics(87, 91, 93). These were already routinely collected through the Case Report Form and Maternal Postnatal Experience Questionnaire and were considered not to be "serious" for purposes of adverse event reporting.

Table 3.3: Known side effects of study drugs, considered to be a "non-serious" Adverse Event for purposes of Adverse Event reporting

Drug	Known side effects which were not "serious" and not "unexpected"
Oxytocin	Rash, headache, dizziness, nausea, vomiting, tachycardia, bradycardia
Syntometrine	Rash, headache, dizziness, hypertension, nausea, vomiting, abdominal pain
Carbetocin	Headache, dizziness, feeling of warmth, tremor, hypotension, flushing, chills, nausea, vomiting, metallic taste, abdominal pain, itching, shortness of breath

The side effects listed in Table 3.4 are known side effects of the study drugs, as listed in their respective Summary of Product Characteristics. These were considered to be serious but not "unexpected". These were recorded, assessed, and reported to the Sponsor and Chief Investigator within 24 hours.

Table 3.4: Known side effects of study drugs, considered to be a "serious" Adverse Event for purposes of Adverse Event reporting

Drug	Known side effects which were considered to be "serious" but not "unexpected"
Oxytocin	Anaphylactoid reaction, coronary arteriospasm, myocardial infarction
Syntometrine	Anaphylactoid reaction, coronary arteriospasm, myocardial infarction
Carbetocin	Anaphylactoid reaction, coronary arteriospasm, myocardial infarction

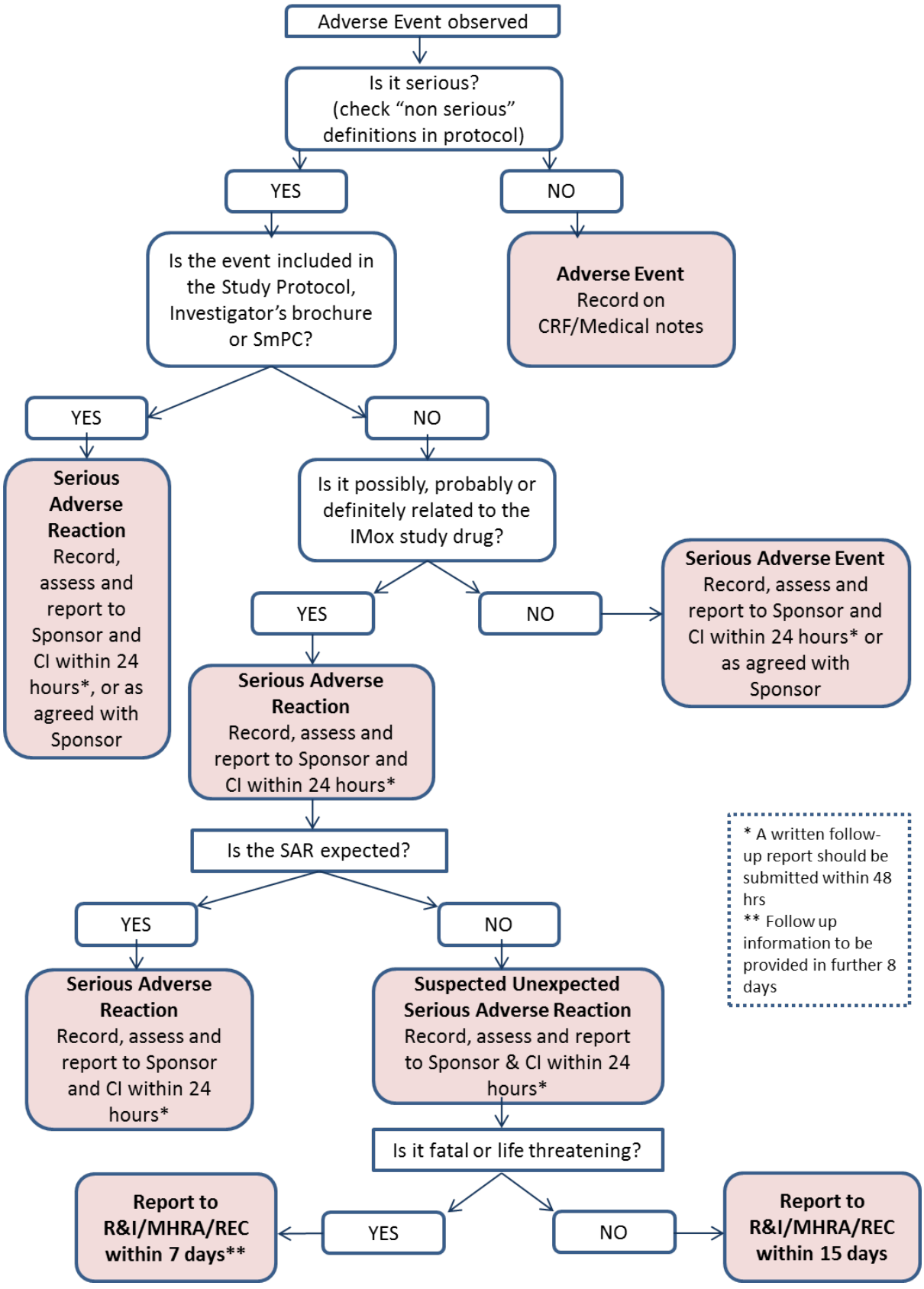
A Serious Adverse Event, Serious Adverse Reaction or Unexpected Serious Adverse Reaction was defined as something which resulted in death, was life-threatening, resulted in persistent or significant disability or incapacity, or required hospitalisation or prolongation of hospital stay beyond that which would usually be anticipated for a woman having an uncomplicated birth (e.g.: undergoing an additional surgical procedure). Even though PPH is a known complication of

childbirth, it was decided that severe PPH ≥2000ml could be life threatening, and that this should be reported as a Serious Adverse Event. These events were recorded to the Chief Investigator within 24 hours, with a follow up report (i.e.: faxed SAE report) submitted within 48 hours.

Outcomes which did not need reporting included those relating to the participant's baby (because the umbilical cord would already have been clamped by the time the IMP is given) and those relating to the participant >12 hours after vaginal birth (because the effects of the single intramuscular dose of the IMP was not expected to last beyond this time). Prolongation of hospital stay for purposes of blood transfusion alone also did not require reporting as an SAE (blood transfusions are a recognised complication of pregnancy and this data was already recorded as part of the Case Report Form).

Figure 3.12: Flowchart demonstrating the assessment and reporting of Adverse Events in

The IMox Study



3.16 Unblinding

The University Hospitals Bristol Clinical Trials Pharmacy held a master list of the randomisation schedule and provided a 24-hour telephone unblinding service via the on-call pharmacist. Instructions were that the blind should only ever be broken for the specific participant in question. The consultant obstetrician on duty for labour ward was to act as the lead physician for a woman's intrapartum care and was thus deemed responsible for the individual intrapartum clinical care of any clinical trial participants. The decision to unblind was at the discretion of the consultant obstetrician on duty for labour ward at that recruiting site, in accordance with the situations listed below;

1. A Serious Adverse Event in which the unblinding of the study drug would alter the management of the patient (i.e.: a need to know). This was believed to be a possible but presumed rare occurrence, as all three study drugs were already well known in routine clinical practice, and because the three study drugs are similar in their modes of action and side effects. Unblinding in this situation would involve the participant, clinical staff and investigators.

2. A Suspected Unexpected Serious Adverse Reaction, where a report to the MHRA would need to include information about the unblinded study drug. In this situation it was anticipated that clinical staff would remain blinded, where possible.

3.17 Trial oversight and governance

Approvals

The trial was approved by the South Central – Oxford B Research Ethics Committee (28th October 2014) and the Medicines and Healthcare products Regulatory Agency (30th October 2014) in the United Kingdom. The Research Ethics Committee were approached for approval of any substantial amendments to the study protocol which became necessary during the study.

Trial oversight

North Bristol NHS Trust Research and Innovation Department acted as the Sponsor and provided trial oversight. This role included review and approval of any amendments to study documents or the study protocol prior to submission to the Research and Ethics Committee, site initiation and monitoring visits, and review of Adverse Events and Protocol Breaches.

Monitoring plan

Monitoring took place both remotely and on-site and was conducted by in-house Sponsor representatives (see Table 3.5 for the study monitoring plan).

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (DMC) convened mid-way through the trial. This meeting comprised an open session where no data was presented, and a closed session to consider standard DMC responsibilities including safety, recruitment, and the health of databases. The DMC report was produced and presented by an independent statistician.

Table 3.5: Monitoring plan for The IMox Study

On-site monitoring			Remote monitoring
Site Initiation visits	Progress visits	Site close-down visits	
Timing: • 6-8 weeks before site start date Purpose: • Meet research staff and lead clinical staff • Review site files and all other documentation • Review plans for pharmacy • Discuss training plans and progress.	Timing: • 3 months into recruitment • 9 months into recruitment • Additional visits as required Purpose: • Meet research staff • Review site files • Review storage arrangements for CRFs and consent forms • Review accountability and storage of study drugs • Review appropriateness of consent and recruitment processes • Review SAE reporting processes • Report back to team about ongoing remote monitoring	Timing: • After last participant randomised Purpose: • Review completeness of filing/archiving arrangements • Provide support for closure of site	Timing: • Ongoing Purpose: • Spot check audits of Case Report Form data against data entered onto database • Spot check of consent forms and related documentation • Review of actual and projected recruitment rates at each site

3.18 Patient and Public Involvement

The North Bristol NHS Trust "Maternity Service User Panel" (MSUP) is composed of a small group of women who have previously given birth at Southmead hospital, and who volunteer to act as lay representatives for research-related tasks when needed. They kindly helped to review early versions of the protocol, Patient Information Sheet and Maternal Postnatal Experience Questionnaire, to help optimise study conduct for patient experience and patient relevance. They were very positive about the inclusion of maternal bonding data and felt that this was particularly important due to the known side effects of Syntometrine. They helped to highlight that some new mothers may not feel well enough to read and handwrite their own responses to the Maternal Postnatal Experience Questionnaire in the first two post-natal hours. The MSUP recommended that women should be given the option of midwives reading questions out loud, and for the midwife to act as a scribe for the new mother. This advice was subsequently incorporated into the protocol. We had intended to involve lay-members in the Trial Steering Committee, but this did not ultimately happen.

Chapter 4 :

The IMox Study – Results

The results of The IMox Study have been published in the British Journal of Obstetrics and Gynaecology(7). These results are presented in more detail within this thesis chapter. Results and tables presented within this chapter are for modified Intention To Treat (mITT) analyses, unless stated otherwise. Per Protocol (PP) results tables are presented within the Appendix to Chapter 4. There were no differences in any conclusions drawn between mITT and PP results.

4. 1 Participants

5929 women were recruited and randomised from six maternity units between February 2015 and August 2018: 2709 participants at Southmead Hospital, Bristol; 1249 participants at Royal United Hospital, Bath; 495 participants at Gloucester Royal Hospital, Gloucester; 540 participants at St Michael's Hospital, Bristol; 824 at Great Western Hospital, Swindon; 112 at Nottingham University Hospitals, Nottingham (see Table 4.1). We do not have a record of the number of women approached to participate in the study.

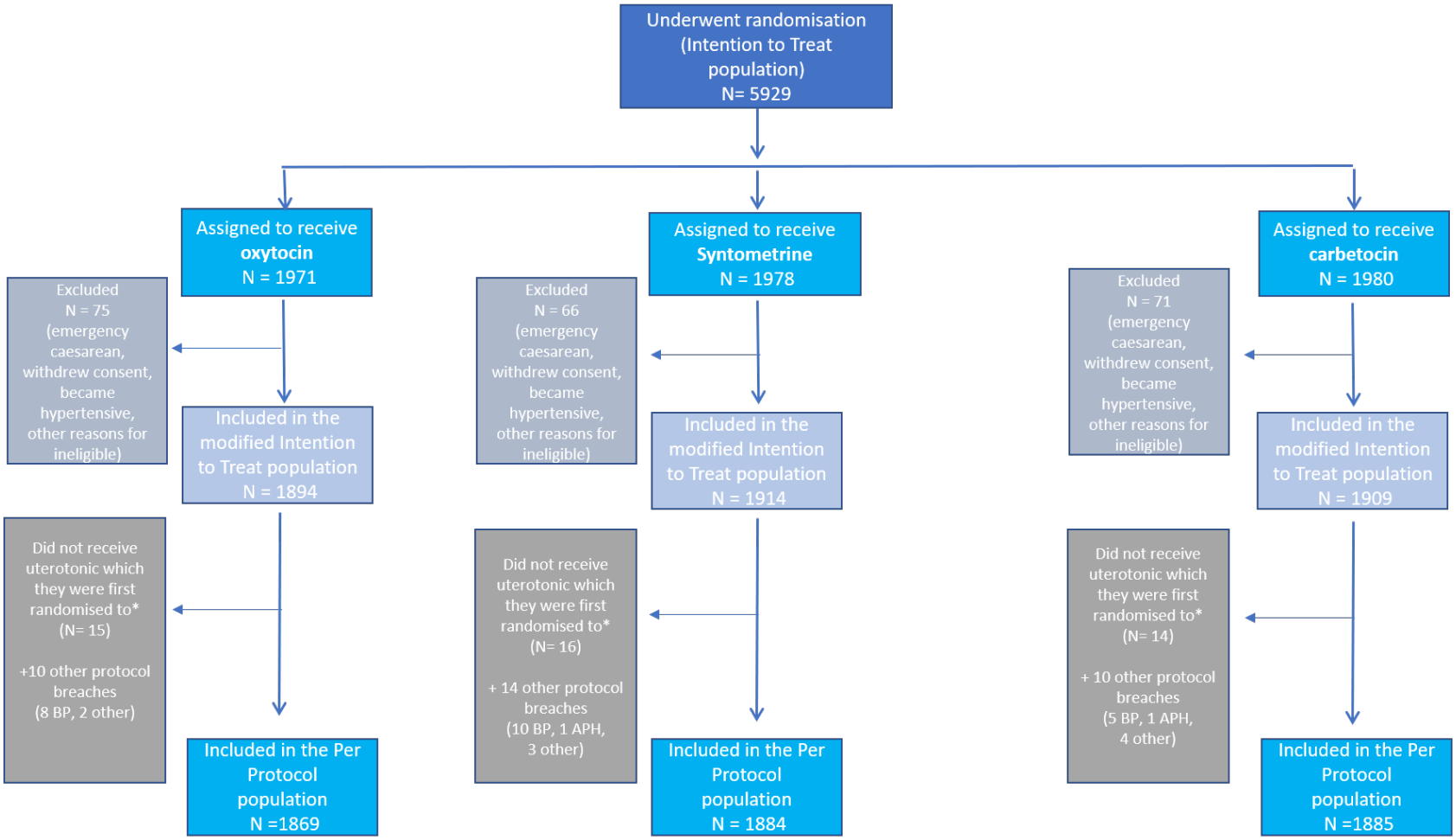
Table 4.1: Participants recruited and randomised at each site

Site	Recruitment period (first and last randomised participant)	Number of participants randomised (ITT)	Participants who were randomised, remained eligible and received a study drug (mITT)	Participants who were randomised, remained eligible and received the uterotonic drug which they were first randomised to (PP)
Southmead Hospital, Bristol	17/02/2015 – 22/07/2018	2709	2644	2624
Royal United Hospital, Bath	13/4/2015 – 23/7/2018	1249	1209	1196
Gloucestershire Royal Hospital, Gloucester	05/06/2015 – 18/07/2018	495	468	445
St Michael's Hospital, Bristol	04/12/2015 – 26/10/2017	540	511	501
Great Western Hospital, Swindon	14/08/2016 – 22/07/2018	824	777	764
Nottingham University Hospitals, Nottingham	26/10/2016 – 10/01/2018	112	108	108

212 of these participants became ineligible after the point of randomisation and did not receive a study drug (see Table 4.1 and Figure 4.1). Reasons for this included: emergency caesarean section occurring after the point of randomisation (e.g. after an attempted but unsuccessful instrumental delivery), participants withdrawing consent before administration of the study drug, hypertension and antepartum haemorrhage.

A total of 5717 participants did receive a study drug and were included in the modified Intentional to Treat (mITT) analyses. 45 of these participants (15 oxytocin, 16 Syntometrine, 14 carbetocin) did not receive the drug they were first randomised to, due to erroneous premature randomisation when birth was believed to be imminent (i.e: second stage of labour was longer than first anticipated, or participant actually found to not yet be fully dilated). The protocol mandated that drugs should be administered "immediately" after removal from the fridge, as per the summary of Product Characteristics for carbetocin. In cases of erroneous premature randomisation, the drug was discarded by the member of staff as it was "out of the fridge too long" [to comply with the protocol]. For these 45 participants, the next consecutive numbered drug was taken from the fridge at the appropriate time, and this next randomised drug was administered after vaginal birth. These 45 participants were analysed according to their original randomised arm for the mITT analyses but were not included in the Per Protocol (PP) analyses. A further 34 participants were excluded from the PP analyses due to other protocol breaches (e.g.: blood pressure not having been checked prior to delivery in cases of precipitate labour, antepartum haemorrhage discovered in notes retrospectively meaning participant should have been excluded). A total of 5638 participants were included in the PP analyses.

Figure 4.1: CONSORT diagram showing flow of participants through The IMox Study



*Uterotonic which participants originally randomised to discarded as out of fridge too long (birth believed to be imminent when randomised but took longer). Next consecutively numbered drug administered.
Abbreviations: BP (blood pressure), APH (antepartum haemorrhage)

4.2 Baseline characteristics

Maternal characteristics at baseline and characteristics of babies at birth are presented in Table 4.2. Maternal age, BMI, gestational age at birth and baseline antenatal EQ5D utility score were nearly identical between arms. History of PPH, median birth weight, mode of birth and Asian ethnicity were similar between arms. Parity and onset of labour by induction differed slightly between arms. These were among the PPH risk factor variables which were included in the logistic regression analysis (Table 4.5).

Table 4.2: Characteristics of women at trial entry and babies at birth (mITT)

Characteristic	Baseline Characteristics Oxytocin (N = 1894)	 Syntometrine (N = 1914)	 Carbetocin (N = 1909)
Median age, *years* (IQR)	30 (26-33)	30 (26-34)	30 (26-34)
Median BMI (IQR)	25 (22-30)	25 (22-30)	25 (22-30)
Parity:			
Nulliparous, *number* (%)	814 (42.9)	852 (44.6)	780 (40.9)
Parity 1-4, *number* (%)	1061 (56.0)	1032 (54.0)	1095 (57.3)
Parity 5+, *number* (%)	20 (1.1)	25 (1.4)	33 (1.8)
History of previous PPH, *number* (% of parous women)	155 (14.3)	127 (12.0)	147 (13.0)
Asian ethnicity, number (%)	66 (3.5)	60 (3.2)	66 (3.5)
Onset of labour induced, *number* (%)	1339 (70.7)	1340 (70.3)	1391 (73.1)
Baseline antenatal utility score from EQ-5D-5L questionnaire	0.81	0.81	0.81
	Intrapartum characteristics		
Prolonged labour, number (%)	244 (12.9)	256 (13.4)	219 (11.5)
Pyrexia in labour, number (%)	66 (3.5)	89 (4.7)	76 (4.0)
Mode of birth:			
Spontaneous, *number* (%)	1492 (78.8)	1453 (76.2)	1486 (78.0)
Instrumental, *number* (%)	401 (21.2)	454 (23.8)	420 (22.0)
Median gestational age at birth, *completed weeks* (IQR)	39 (38-41)	39 (38-40)	40 (38-41)
Median gestational age at birth for those with an induced labour, *completed weeks (IQR)*	39 (38-41)	39 (38-41)	39 (38-41)
Median birth weight (kg) (IQR)	3.43 (3.08-3.77)	3.42 (3.07-3.77)	3.44 (3.11-3.79)

Table 4.3: Primary and Secondary Outcomes (mITT)

Table 2: Primary and Secondary Outcomes by arm

Outcome	Oxytocin (N =1894)	Syntometrine (N = 1914)	Carbetocin (N = 1909)	Missing data for outcome
Primary outcome				
Use of additional uterotonics	368 (19.5%)	298 (15.6%)	364 (19.1%)	8 participants (4 oxytocin, 2 Syntometrine 2 carbetocin)
Secondary outcomes				
Median blood loss (ml), (IQ range)	500 (290-834)	483 (288-820)	500 (298-837)	
Weighed blood loss ≥500ml	949 (50.5%)	920 (48.2%)	961 (50.4%)	Data for weighed blood loss was missing for 8 participants (0
Weighed blood loss ≥1000ml	355 (18.7%)	352 (18.4%)	330 (17.3%)	oxytocin, 3 Syntometrine, 5 carbetocin)
Weighed blood loss ≥2000ml	74 (3.9%)	59 (3.1%)	56 (2.9%)	
Perineal tear	1398 (73.9%)	1451 (76.0%)	1404 (73.5%)	
Duration of third stage of labour (minutes), (IQ range)	10 (7-14)	9 (6-14)	10 (7-14)	21 participants (3 oxytocin, 9 Syntometrine, 9 carbetocin)
Blood transfusion	58 (3.1%)	51 (2.7%)	54 (2.8%)	4 participants (2 Syntometrine, 2 carbetocin)
Manual removal of placenta	43 (2.3%)	49 (2.6%)	57 (3.0%)	4 participants (1 oxytocin, 3 Syntometrine, 1 carbetocin)
Other surgical/mechanical ("non-drug") methods to treat PPH ϕ	58 (3.1%)	38 (2.0%)	42 (2.2%)	6 participants (1 oxytocin, 2 Syntometrine, 3 carbetocin)
Peripartum hysterectomy	0 (0%)	0 (0%)	0 (0%)	No missing data
Blood pressure: hypertension in first 2 postnatal hours*	134 (7.1%)	233 (12.3%)	132 (7.0%)	21 participants (1 oxytocin, 10 Syntometrine, 10 carbetocin)
Blood pressure: hypotension in first 2 postnatal hours**	47 (2.5%)	30 (1.6%)	31 (1.6%)	
Nausea	169 (8.9%)	458 (24.0%)	153 (8.0%)	Maternal side effects questionnaires not completed for 3
Vomiting ¤	92 (4.9%)	337 (17.6%)	91 (4.8%)	participants (0 oxytocin, 2 Syntometrine, 1 carbetocin)
Headache	26 (1.4%)	65 (3.4%)	28 (1.5%)	
Dizziness	163 (8.6%)	188 (9.8%)	123 (6.4%)	
Abdominal pain	129 (6.8%)	162 (8.5%)	99 (5.2%)	
Answer "yes" to question "Have any of the above symptoms affected your ability to bond with and/or care for your baby in these first two hours?"	83 (4.4%)	160 (8.4%)	56 (2.9%)	188 participants (64 oxytocin, 63 Syntometrine, 61 carbetocin)
Mean EQ-5D utility score: all returned antenatal questionnaires, (SD)	0.8107 (0.17524)	0.8104 (0.17745)	0.8115 (0.16954)	638 participants (217 oxytocin, 210 Syntometrine, 211 carbetocin)
Mean EQ-5D utility score: all returned day 1 postnatal questionnaires, (SD)	0.7553 (0.17460)	0.7470 (0.18497)	0.7578 (0.17879)	359 participants (135 oxytocin, 113 Syntometrine, 111 carbetocin)
Mean EQ-5D utility score: all returned day 14 postnatal questionnaires, (SD)	0.9031 (0.12520)	0.8910 (0.12556)	0.8998 (0.12520)	783 participants (264 oxytocin, 262 Syntometrine, 257 carbetocin)
Mean EQ-5D utility score for participants with all EQ-5D questionnaires completed: day 14 postnatal ¶, (SD)	0.9034 (0.12652)	0.8918 (0.12524)	0.8995 (0.12607)	1544 participants did not have a complete EQ-5D dataset (528 oxytocin, 513 Syntometrine, 503 carbetocin)

- ϕ Composite outcome of examination under anaesthetic/intrauterine balloon/uterine compression suture/interventional radiology
- * Defined as SBP ≥140mmHg or DBP ≥90mmHg in the first two postnatal hours ** Defined as DBP <90mmHg in the first two postnatal hours
- ¤ Vomiting in those not already vomiting in labour
- ¶ "Complete" defined as those participants who returned EQ-5D questionnaires antenatally, on day 1 and on day 14

Table 4.4: Pairwise comparison of study arms (mITT)

	Carbetocin v Syntometrine	Syntometrine v Oxytocin	Carbetocin vs Oxytocin
Primary outcome Use of additional uterotonics	Percentage difference 3.54% 95% CI 1.14% to 5.93% OR 1.28, 95% CI 1.08 – 1.51, P = 0.004 (For non-inferiority comparison see text)	Percentage difference -3.90% 95% CI -6.31% to -1.49% OR 0.75, 95% CI 0.65 - 0.91, P = 0.002	Percentage difference -0.36% 95% CI -2.87% to 2.15% OR 0.98, 95% CI 0.83 - 1.15, P = 0.78
Secondary outcomes			
Weighed blood loss ≥ 500ml	OR 1.10, 95% CI 0.96 – 1.24, P = 0.16	OR 0.93, 95% CI 0.82 – 1.05, P = 0.25	OR 1.02, 95% CI 0.90 – 1.15, P = 0.80
Weighed blood loss ≥ 1000ml	OR 0.93, 95% CI 0.79 – 1.09, P = 0.37	OR 0.91, 95% CI 0.83 – 1.16, P = 0.82	OR 0.91, 95% CI 0.77 – 1.07, P = 0.26
Weighed blood loss ≥ 2000ml	OR 0.95, 95% CI 0.66 – 1.38, P = 0.79	OR 0.78, 95% CI 0.55 – 1.11, P = 0.17	OR 0.75, 95% CI 0.52 – 1.06, P = 0.10
Perineal tear	OR 0.88, 95% CI 0.76 – 1.02, P = 0.08	OR 1.124, 95% CI 0.99 – 1.30, P = 0.12	OR 1.01, 95% CI 0.85 – 1.15, P = 0.87
Duration of third stage of labour	Md* 0, 95% CI 0, 0 , P = 0.573	Md* 0, 95% CI -1, 0 , P = 0.096	Md* 0, 95% CI -1, 0 , P = 0.269
Blood transfusion	OR 1.06, 95% CI 0.72 – 1.57, P = 0.76	OR 0.87, 95% CI 0.59 – 1.27, P = 0.52	OR 0.92, 95% CI 0.63 – 1.35, P = 0.68
Manual removal of placenta	OR 1.17, 95% CI 0.79 – 1.72, P = 0.43	OR 1.14, 95% CI 0.75 – 1.72, P = 0.36	OR 1.33, 95% CI 0.89 – 1.98, P = 0.17
Other surgical/mechanical ("non-drug") methods to treat PPH	OR 1.11, 95% CI 0.71 – 1.72, P = 0.64	OR 0.64, 95% CI 0.42 – 0.97, P = 0.04	OR 0.71, 95% CI 0.48 – 1.06, P = 0.10
Hypertension in first two postnatal hours	OR 0.53, 95% CI 0.42 – 0.66, P < 0.001	OR 1.85, 95% CI 1.48 – 2.32, P <0.001	OR 0.98, 95% CI 0.76 – 1.26, P = 0.88
Hypotension in first two postnatal hours	OR 0.97, 95% CI 0.59 – 1.60, P = 0.91	OR 0.67, 95% CI 0.43 – 1.06, P = 0.83	OR 0.65, 95% CI 0.41 – 1.03, P = 0.07
Nausea	OR 0.28, 95% CI 0.23 – 0.34, P < 0.001	OR 3.22, 95% CI 2.67 - 3.90, P < 0.001	OR 0.89, 95% CI 0.71 – 1.12, P = 0.32
Vomiting	OR 0.23, 95% CI 0.18 – 0.30, P < 0.001	OR 4.20, 95% CI 3.30 - 5.35, P < 0.001	OR 0.98, 95% CI 0.73 – 1.32, P = 0.91
Headache	OR 0.42, 95% CI 0.27 – 0.66, P < 0.001	OR 2.53, 95% CI 1.60 - 4.02, P < 0.001	OR 1.07, 95% CI 0.63 – 1.83, P = 0.80
Dizziness	OR 0.63, 95% CI 0.50 – 0.80, P < 0.001	OR 1.16, 95% CI 0.93 - 1.45, P = 0.18	OR 0.73, 95% CI 0.57 – 0.93, P = 0.01
Abdominal pain	OR 0.59, 95% CI 0.46 – 0.76, P < 0.001	OR 1.27, 95% CI 1.00 - 1.62, P = 0.05	OR 0.75, 95% CI 0.57 – 0.98, P = 0.04
Answer "yes" to question "Have any of the above symptoms affected your ability to bond with and/or care for your baby in these first two hours?"	OR 0.33, 95% CI 0.24 – 0.45, P < 0.001	OR 2.00, 95% CI 1.52-2.62, P < 0.001	OR 0.66, 95% CI 0.47 – 0.93, P = 0.02

*Md = difference of medians (continuous data)

4.3 Primary outcome

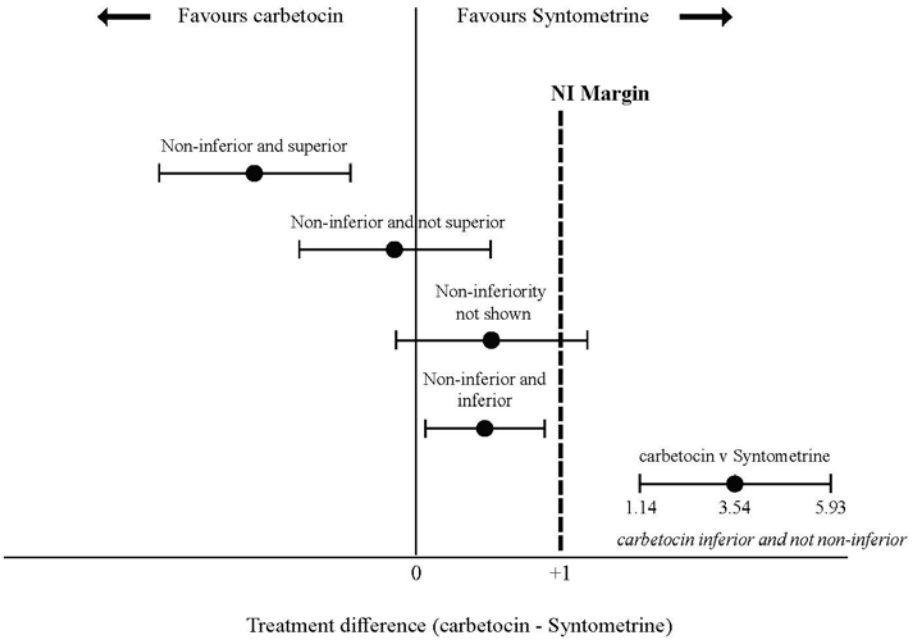
In the modified Intention to Treat population, primary outcome data was missing for a total of 8 participants: 4 participants (0.2%) in the oxytocin arm and 2 participants (0.1%) each in the carbetocin and Syntometrine arms (Table 4.3).

Carbetocin versus Syntometrine

The use of additional uterotonics differed by 3.54 percentage points between the carbetocin and Syntometrine arms (95% CI 1.14% to 5.93%), depicted in Figure 4.2. In this diagram, a negative treatment difference in the "carbetocin versus Syntometrine" comparison would favour carbetocin, as this would mean that fewer additional uterotonic drugs are needed (suggesting that carbetocin would be more effective). With our pre-specified non-inferiority margin of 1%, non-inferiority of carbetocin to Syntometrine was therefore not shown, as both the upper and lower limit of the confidence interval are > +1 (see Figure 4.2). With our 95% confidence intervals for treatment difference, there is evidence to suggest that carbetocin is inferior to Syntometrine in the need for additional uterotonic drugs.

Figure 4.2: Interpretation of non-inferiority comparison Carbetocin v Syntometrine, relating to the need for additional uterotonic drugs.

(adapted from Schumi and Wittes, *Trials* 2011(125)).



In a pairwise superiority comparison, women in the carbetocin arm of this study were more likely to receive additional uterotonics than those in the Syntometrine arm (OR 1.28, 95% CI 1.08–1.51).

Syntometrine versus oxytocin

There was a 3.90% difference in use of additional uterotonics between the Syntometrine and oxytocin arms (95% CI -6.31 to -1.49%). Women randomised to Syntometrine were less likely to receive additional uterotonics than those randomised to oxytocin (OR 0.75, 95% CI 0.65-0.91).

Carbetocin versus oxytocin

There was a very small, non-significant, difference of 0.36% in the use of additional uterotonic drugs between the oxytocin and carbetocin arms (95% CI -2.87% to 2.15%). Women in the carbetocin arm were no more likely to receive additional uterotonic drugs than those in the oxytocin arm of this study (OR 0.98, 95% CI 0.83 - 1.15).

Sensitivity analysis

In a sensitivity analysis, we included the primary outcome data for all women in the ITT but excluded in the mITT analyses and per protocol analyses. The data was systematically imputed with an assumed need for additional uterotonic drugs in the range of 10% to 25%, covering any rate likely to be needed in clinical practice. Acrosss all of these combinations, the same overarching conclusions was of no significant difference between Oxytocin and Carbetocin, and the proportion requiring an additional uterotonic drug was consistently significantly lower in the Syntometrine arm compared to either of the other two.

Logistic regression

The primary outcome was adjusted for PPH risk factors (those which were described by the RCOG at the time of protocol development(11)), as shown in Table 4.5. In the logistic regression model, women who received carbetocin or oxytocin remained more likely to receive additional uterotonic drugs than those who received Syntometrine after adjusting for risk factors and recruiting site.

Table 4.5: Logistic regression model results relating use of additional uterotonic drugs and PPH ≥500ml (mITT)

	Outcome: Additional uterotonics		Outcome: PPH ≥500ml	
	Odds ratio (95% CI)	Significance (p)	Odds ratio (95% CI)	Significance (p)
Study arm (relative to Syntometrine)				
Carbetocin	1.33 (1.11 - 1.60)	0.002	1.16 (1.01 – 1.33)	0.04
Oxytocin	1.35 (1.13 – 1.61)	0.001	1.15 (1.00 – 1.32)	0.05
*Risk factors (*BMI relative to normal)*				
Previous PPH	3.58 (2.83 – 4.54)	<0.001	3.09 (2.47 – 3.87)	<0.001
Asian ethnicity	1.12 (0.75 – 1.67)	0.58	1.31 (0.94 – 1.81)	0.11
BMI: Underweight *	0.50 (0.26 – 0.95)	0.04	0.74 (0.50 – 1.09)	0.13
BMI: Overweight*	1.08 (0.90 – 1.28)	0.41	1.16 (1.01 – 1.33)	0.03
BMI: Obese*	1.31 (1.09 – 1.56)	0.003	1.31 (1.13 – 1.51)	<0.001
Induced labour	1.40 (1.18 – 1.67)	0.002	1.22 (1.07 – 1.39)	0.002
Prolonged labour	2.22 (1.83 – 2.69)	<0.001	2.06 (1.70 – 2.51)	<0.001
Big Baby (>4kg)	1.57 (1.28 – 1.92)	<0.001	2.42 (2.02 – 2.89)	<0.001
Nulli-Parous	1.43 (1.21 – 1.70)	<0.001	2.21 (1.95 – 2.51)	<0.001
Pyrexia in labour	2.14 (1.60 – 2.88)	<0.001	1.85 (1.34 – 2.56)	<0.001
Operative birth	2.26 (1.90 – 2.69)	<0.001	2.33 (2.00 – 2.72)	<0.001
Hospital (relative to Southmead)				
Bath	1.11 (0.92 – 1.34)	0.29	0.70 (0.60 – 0.82)	<0.001
Gloucester	1.06 (0.81 – 1.40)	0.66	0.89 (0.71 – 1.11)	0.50
Nottingham	2.38 (1.52 – 3.73)	<0.001	0.66 (0.44 – 1.01)	0.08
St Michael's	1.36 (1.06 – 1.75)	0.02	0.50 (0.40 – 0.62)	<0.001
Swindon	1.09 (0.87 – 1.37)	0.46	0.78 (0.66 – 0.93)	0.005

Participants in Nottingham and St Michael's hospitals were more likely to receive additional uterotonic drugs than those at Southmead, when all other risk factors were accounted for. Bath, Gloucester and Swindon were not different to Southmead. In this model, the following were risk factors associated with a participant requiring additional uterotonic drugs; previous PPH, raised BMI, having an induced or prolonged labour, baby weight >4kg, nulliparity, pyrexia in labour and having an operative vaginal birth.

As per protocol, Multiple Imputation using Chained Equations was used to impute missing data for the Intention to Treat and Per Protocol analyses, on all predictors and outcome variables, to

examine the stability of the logistic regression model. This was done 100 times and did not alter any conclusions.

Secondary outcomes and side effects

4.4 Number of additional uterotonic drugs required

Table 4.6: Number of doses of an additional uterotonic drug given by arm

	Number of additional uterotonic drugs given								
	0	1	2	3	4	5	6	7	Total
Oxytocin	1524	190	130	43	6	1	0	0	1894
Syntometrine	1610	173	99	22	5	2	0	1	1912*
Carbetocin	1541	221	107	25	12	2	0	0	1908**
Total	4675	584	336	90	23	5	0	1	5714
*data regarding number of additional uterotonics missing for 1 participant **data regarding number of additional uterotonics missing for 2 participants									

As seen in Table 4.6, the majority of participants who received additional uterotonic drugs received only one. As the number of additional uterotonics per participant increased, the frequency of participants receiving that many additional uterotonics decreased, and this trend was seen across all arms. Data regarding the number of additional uterotonic drugs received was missing for 3 participants (1 Syntometrine, 2 carbetocin).

4.5 Weighed blood loss

In the modified Intention to Treat population, data for weighed blood loss was missing for a total of eight participants (zero in the oxytocin arm, three in the Syntometrine arm and five in the carbetocin arm) (see Table 4.3). Median blood loss across the arms ranged from 483ml – 500ml. Weighed blood

loss was categorised into blood loss ≥500ml, ≥1000ml, ≥2000ml for analysis. There was no difference in blood loss of any volume category in any pairwise comparison of arms in this study (see Table 4.4). The proportion of participants experiencing blood loss of ≥500ml ranged from 48.2 - 50.5%, ≥1000ml ranged from 17.3 - 8.7% and ≥2000ml ranged from 2.9 - 3.9%.

In the regression model, the following known risk factors(11) for PPH were shown to be risk factors for PPH ≥500ml in this study: previous PPH, obesity, induction of labour, prolonged labour, big baby (>4kg), pyrexia and operative vaginal birth. The relevance of parity as a risk factor for PPH has long been debated. In this dataset, nulliparous women were more likely to experience PPH ≥500ml than multiparous women (OR 2.21, 95% CI 1.95 – 2.51). Asian ethnicity has previously been documented as a risk factor for PPH (11). This was not supported by the results of our study, nor was it a risk factor for needing additional uterotonic drugs.

When PPH risk factors and recruiting site were accounted for (see Table 4.5), women randomised to carbetocin or oxytocin were more likely to experience PPH ≥500ml than those randomised to Syntometrine, but this difference was marginal for both carbetocin (95% CI 1.01-1.33) and oxytocin (95% CI 1.00-1.32). Participants giving birth in Bath (OR 0.70, 95% CI 0.60 – 0.82), St Michael's (OR 0.50, 95% CI 0.40 – 0.62) and Swindon (OR 0.78, 95% CI 0.66 – 0.93) were less likely to experience PPH ≥500ml than those giving birth in Southmead.

4.6 Blood transfusion requirements

Rates of blood transfusion were evenly distributed across the three arms (range 2.7-3.1%), with a mean transfusion rate of 2·9% (see Tables 4.3 and 4.7). A total of 100 participants received a transfusion of additional blood products (platelets, plasma and cryoprecipitate): 35 oxytocin, 29 Syntometrine and 36 carbetocin.

Table 4.7: Additional transfusion data for mITT population

	Oxytocin (N = 1894)	Syntometrine (N = 1914)	Carbetocin (N = 1909)
Red blood cells transfused	58 (3.1%)	51 (2.7%)	54 (2.8%)
Platelets transfused	35 (1.8%)	29 (1.5%)	36 (1.9%)
Plasma transfused	35 (1.8%)	29 (1.5%)	36 (1.9%)
Cryoprecipitate transfused	35 (1.8%)	29 (1.5%)	36 (1.9%)
Cell salvaged blood	0 (0%)	0 (0%)	0 (0%)

Identical number of participants received transfusion of these individual blood products within each arm, suggesting that the products were likely to have been given as one "bundle" in the event of a major obstetric haemorrhage. It is also possible that there may have been inaccuracy in the recording of transfused blood products on the Case Report Forms. Cell salvage after vaginal birth was not used in any of the participating sites during the time when this study was recruiting, as reflected in the fact that no participants received cell salvaged blood (Table 4.7).

4.7 Perineal tears

Perineal tears were common and occurred in 74.5% (4250/5709) of all births (see Table 4.3). A greater proportion of nulliparous than multiparous participants sustained a perineal tear (see Table 4.9). More women with a tear experienced PPH ≥500ml than those without a tear, regardless of parity or whether an additional uterotonic drug was used or not. As volume of blood loss increased from <500ml to 1000-1999ml, so did of the proportion of women receiving additional uterotonic drugs (see Table 4.8). This was true, regardless of whether there was a tear or not. Interestingly, this trend did not continue for blood loss ≥2000ml. It is possible that an effect was missed due to smaller numbers in this blood loss category. It might also reflect inaccuracy in detection of large volume blood loss(47-49); perhaps in these large volume losses the extent of blood loss was only recognised in retrospect when it was weighed, and the bleeding had already settled.

Table 4.8: Relationship between perineal tears, PPH and additional uterotonic drugs

		Estimated blood loss category				
		<500ml	**500-999ml**	**1000-1999ml**	**≥2000ml**	**Total of additional uterotonic drug group**
No additional uterotonics used	**No tear (% of no additional uterotonics group)**	1013 (21.7%)	242 (5.2%)	20 (0.4%)	0 (0.0%)	1275 (27.3%)
	Perineal tear (% of no additional uterotonics group)	1783 (38.2%)	1218 (25.1%)	355 (7.6%)	42 (0.9%)	3398 (72.7%)
Additional uterotonics used	**No tear (% of additional uterotonics group)_**	28 (2.7%)	60 (5.8%)	69 (6.7%)	22 (2.1%)	179 (17.4%)
	Perineal tear (% of additional uterotonics group)	50 (4.9%)	271 (26.4%)	403 (39.2%)	124 (12.1%)	848 (82.6%)

Table 4.9: Relationship between perineal tears, PPH and parity

		Estimated blood loss category				
		<500ml	**500-999ml**	**1000-1999ml**	**≥2000ml**	**Total of parity group**
Nulliparous women	**No tear (% of nulliparous)**	135 (5.5%)	59 (2.4%)	15 (0.6%)	4 (0.2%)	213 (8.7%)
	Perineal tear (% of nulliparous)	781 (32.0%)	852 (34.8%)	490 (20.0%)	107 (4.4%)	2230 (91.3%)
Multiparous women	**No tear (% of multiparous)**	907 (27.8%)	243 (7.4%)	74 (2.3%)	18 (0.6%)	1242 (38.1%)
	Perineal tear (% of multiparous)	1055 (32.3%)	638 (19.5%)	268 (8.2%)	59 (1.8%)	2020 (61.9%)

4.8 Third stage of labour

The median duration of the third stage of labour was 9-10 minutes, with an interquartile range of 6-14 minutes (see Table 4.3). The duration of the third stage of labour did not differ between arms (see Table 4.4). The rate of manual removal of placenta was 2.3-3% across the arms. The use of Syntometrine did reduce the rate of "non-drug" PPH treatment methods (examination under

anaesthetic/intrauterine balloon/uterine compression suture/interventional radiology), when compared with oxytocin (OR 0.64, 95% CI 0.42–0.97) but not carbetocin (carbetocin v Syntometrine OR 1.11, 95% CI 0.71 – 1.72). There was no difference in the rate of "non-drug" PPH treatments between carbetocin and oxytocin (OR 0.71, 95% CI 0.48 – 1.06, p = 0.10). No participants required a peripartum hysterectomy in this study.

4.9 Blood pressure

Carbetocin and oxytocin were associated with less hypertension in the first two postnatal hours than Syntometrine: carbetocin versus Syntometrine OR 0.53, 95% CI 0.42–0.66; Syntometrine versus oxytocin OR 1.85, 95% CI 1.48–2.32. There was no difference in the rate of hypertension in those receiving carbetocin versus oxytocin (OR 0.98, 95% CI 0.76 – 1.26). No difference was found between arms for hypotension, in any pairwise comparison.

4.10 Maternal side effects

Some data regarding maternal side effects (nausea, vomiting, dizziness, headache, abdominal pain) were collected through both the Case Report Form and the Maternal Postnatal Experience Questionnaire. In the Case Report Form, clinicians were required to document whether the participant had voluntarily reported any of the listed side effects postnatally. In the Maternal Postnatal Experience Questionnaire, participants documented whether they had personally experienced any of the symptoms postnatally ("none"/"mild"/"moderate"/"severe"). Results presented here represent the Maternal Postnatal Experience Questionnaire data; subjective maternal experience is of primary importance (and women may experience unpleasant side effects without vocalising their symptoms to their care giver). Please see "Appendix to Chapter 3" for a copy of the Maternal Postnatal Experience Questionnaire. Raw data for this questionnaire is presented in

Table 4.10. Data were used to create a binary outcome for these subjective symptoms ("none" or mild/moderate/severe"), and these are the results presented in Tables 4.3 and 4.4.

Table 4.10: Breakdown of Maternal Postnatal Experience Questionnaire

Part 1: "Please indicate whether you have experienced any of the following in the first two hours since the birth of your baby, and how severe you feel this has been"												
	Oxytocin				Syntometrine				Carbetocin			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Nausea	1466	239	98	29	1087	390	258	121	1523	214	81	36
Vomiting	1724	36	52	17	1441	128	193	89	1733	37	58	21
Headache	1701	29	29	1	1631	153	46	13	1716	94	33	3
Dizziness	1336	133	133	38	1246	419	136	38	1444	287	88	21
Abdominal pain	1134	193	193	32	1122	441	236	50	1211	451	159	30
Have any of the above affected your ability to bond with/care for baby in these first 2 hours?	No	Yes	(64 no response)		No	Yes	(63 no response)		No	Yes	(61 no response)	
	1747	83			1690	160			1792	56		

Part 2: "If YES, has the effect of each of these symptoms on your ability to bond with and/or care for your baby been…"												
	Oxytocin				Syntometrine				Carbetocin			
	*N/A**	Mild	Moderate	Severe	*N/A**	Mild	Moderate	Severe	*N/A**	Mild	Moderate	Severe
Nausea	*48*	11	19	5	*48*	38	35	39	*19*	13	11	13
Vomiting	*60*	4	13	6	*62*	31	39	28	*36*	7	4	9
Headache	*68*	9	4	2	*112*	38	3	7	*36*	15	4	1
Dizziness	*36*	18	19	10	*65*	38	38	19	*24*	9	15	8
Abdominal pain	*45*	16	11	11	*106*	28	14	12	*29*	11	9	7
*N/A = this symptom not responsible												

Nausea

Nausea was the most frequently reported maternal side effect. Participants randomised to receive Syntometrine experienced more nausea (24.0%) than those randomised to receive either oxytocin (8.9%) or carbetocin (8.0%). The evidence for this increase in nausea was strong for both comparisons (carbetocin versus Syntometrine OR 0.28, 95% CI 0.23 – 0.34; Syntometrine versus oxytocin OR 3.22, 95% CI 2.67 - 3.90). The difference in reported nausea between carbetocin and oxytocin was not found to be significant (P = 0.32).

Vomiting

Vomiting data represents those not already vomiting in labour. Participants randomised to receive Syntometrine experienced more vomiting (17.6%) than those randomised to receive either oxytocin (4.9%) or carbetocin (4.8%). The evidence for this increase in vomiting was also strong for both comparisons (carbetocin versus Syntometrine OR 0.23, 95% CI 0.18 – 0.30; Syntometrine versus oxytocin OR 4.20, 95% CI 3.30 - 5.35). The difference between carbetocin and oxytocin was not found to be significant (P =0.91).

Headache

Participants randomised to receive Syntometrine experienced more headache (3.4%) than those randomised to receive either oxytocin (1.4%) or carbetocin (1.5%). The evidence for this increase in headache was stronger for the carbetocin versus Syntometrine comparison (OR 0.42, 95% CI 0.27 – 0.66) than the Syntometrine versus oxytocin comparison, which had a wider confidence interval (OR 2.53, 95% CI 1.60 - 4.02). No difference was found between the occurrence of postnatal headache in the carbetocin and oxytocin arms.

Dizziness

Participants randomised to receive Syntometrine experienced more dizziness (9.8%) than those randomised to receive either oxytocin (8.6%) or carbetocin (6.4%). For pairwise comparisons,

carbetocin versus Syntometrine OR 0.63, 95% CI 0.50 – 0.80, and carbetocin versus oxytocin OR 0.73, 95% CI 0.57 – 0.93. No difference was found in reports of dizziness after receiving Syntometrine versus oxytocin.

Abdominal pain

Participants receiving Syntometrine reported more abdominal pain (8.5%) than those receiving either oxytocin (6.8%) or carbetocin (5.2%). In the pairwise comparisons, this evidence of a difference was upheld for the carbetocin versus Syntometrine comparison (OR 0.59, 95% CI 0.46 – 0.76) but less so for the Syntometrine versus oxytocin comparison in which the 95% confidence interval included unity (OR 1.27, 95% CI 1.00 – 1.62). Those receiving carbetocin reported less abdominal pain than those receiving oxytocin (OR 0.75, 95% CI 0.57 – 0.98).

4.11 Ability to bond with and care for her new baby

A total of 299/5717 participants (5.2%) reported that the symptoms which they experienced in the first two postnatal hours affected their ability to bond with and care for their baby in this time frame (see Table 4.10 Part 1). Dizziness was the side effect most attributed to this by participants receiving prophylactic oxytocin, and nausea was the side effects most commonly attributed to this by participants receiving prophylactic Syntometrine or carbetocin (see Table 4.10 Part 2).

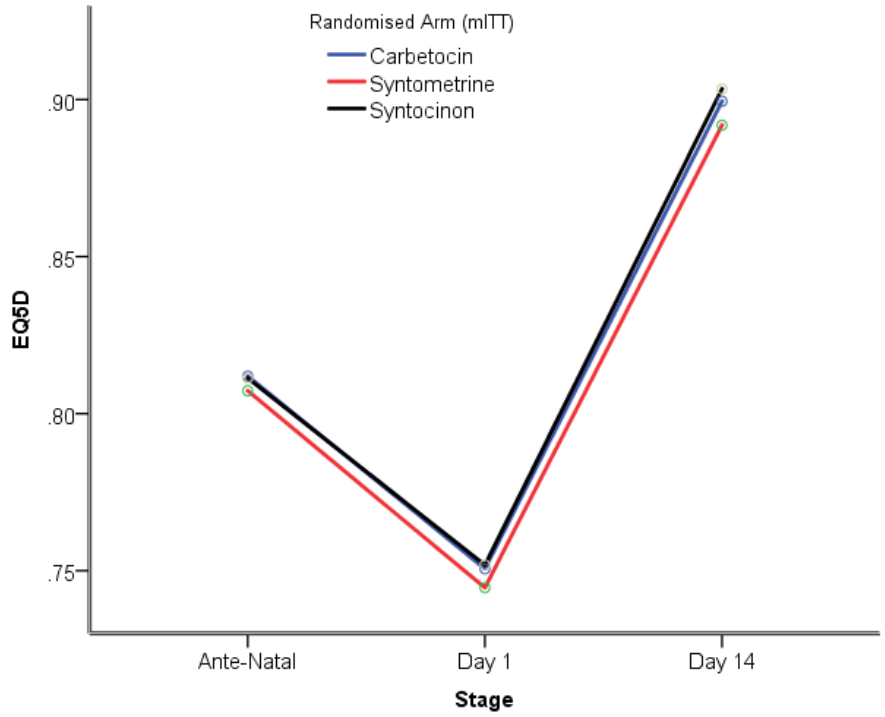
Overall, 160/1914 (8.4%) participants who received prophylactic Syntometrine reported that their postnatal symptoms affected their ability to bond with and care for their baby in the first two postnatal hours, compared with 83/1894 (4.4%) of participants who received prophylactic oxytocin, and 56/1909 (2.9%) of participants who received prophylactic carbetocin. Women receiving prophylactic Syntometrine were twice as likely to report this negative effect of side effects when compared with women receiving oxytocin (OR 2.00, 95% CI 1.52-2.62, P <0.001). The bonding of

women receiving carbetocin was less likely to be affected than that of those receiving oxytocin (OR 0.66, 95% CI 0.47 – 0.93) or Syntometrine (OR 0.33, 95% CI 0.24–0.45).

4.12 Health-Related Quality of Life

5079 (89%) of participants provided antenatal EQ-5D-5L data at the time of consent. 5358 (94%) completed EQ-5D-5L questionnaires on the first postnatal day, and 4923 (85%) on day 14 postnatal. 4173 participants (73%) completed the questionnaire at all three time points. When mean utility scores were compared between randomised arms at all timepoints, no significant differences were found. Generally, there was a fall in health utility score on day 1 compared with baselines scores, and mean utility score then improved to exceed antenatal utility scores by day 14 postnatal (see Figure 4.3). Scores at 14 days postnatal for all available data and for patients who completed the EQ-5D at all three time points are very similar, suggesting any missing data would have been at random.

Figure 4.3: Mean utility scores antenatally and on Day 1 and Day 14 postnatal



4.13 Postnatal care required

Time from delivery to discharge from labour ward

Median time from birth to discharge from labour ward (either to the postnatal ward or home) was similar across arms; 11 hours 45 minutes for oxytocin (IQR 5 hours 30 minutes – 18 hours), 11 hours 30 minutes for Syntometrine (IQR 5 hours 15 minutes – 18 hours) and 12 hours for carbetocin (IQR 5 hours 30 minutes to 18 hours 30 minutes).

Postnatal care in recovery area

Those requiring postnatal care in the recovery area on labour ward were similar across arms; 142/1894 (7.5%) participants randomised to receive oxytocin, 140/1914 (7.3%) participants randomised to receive Syntometrine and 144/1909 (7.5%) participants randomised to receive carbetocin. The median time spent in recovery was 2 hours for all study arms (IQR 2-3 hours for oxytocin and Syntometrine and IQR 1-3 hours for carbetocin).

Care in High Dependency Care on labour ward

192/1894 (10.1%) participants randomised to receive oxytocin, 161/1914 (8.4%) participants randomised to receive Syntometrine and 192/1909 (10.1%) participants randomised to receive carbetocin required High Dependency level of care (with increased frequency of observations and 1:1 midwifery support) on labour ward postnatally. The difference in this proportions was not significant ($p = 0.131$). The median time spent in High Dependency Care was 9 hours for all arms (IQR 7-12 hours for oxytocin and Syntometrine, and 6-13 hours for carbetocin).

Care in Intensive Care Unit

One study participant required admission to the Intensive Care Unit. She had been randomised to receive Syntometrine and spent 34 hours in the Intensive Care Unit.

4.14 Serious Adverse Events (SAE)

As described in the study protocol, a Serious Adverse Event was one which resulted in death, was life threatening, required hospitalisation/a prolongation of hospital stay or resulted in permanent disability or incapacity. Only outcomes <12 hours postnatal and related to the participant (not her baby) required reporting. As per the protocol, PPH ≥2000ml was reportable as an SAE.

A total of 187 SAE forms were submitted by clinical staff members or research teams through the course of the study. The breakdown of these by randomised arm is given in Table 4.11.

Table 4.11: Summary of SAE forms submitted

	Oxytocin	Syntometrine	Carbetocin	*Total*
SAE category				
PPH ≥2000ml	65	50	52	*167*
Anaemia	1	2	2	*5*
Sepsis	1	1	1	*3*
Stroke-type symptoms	1	0	2	*3*
Miscellaneous	2	3	4	*9*
Total	*70*	*56*	*61*	

167 (89%) related to PPH ≥2000ml. Of note, the actual number of PPH events ≥2000ml totalled 189 (see Table 4.3) suggesting that 22 had not been reported as an SAE. 5 (2.7%) SAEs related to anaemia (patients very symptomatic due to anaemia despite total blood loss <2000ml). 3 (1.6%) SAEs related to sepsis (patients unwell with extended stay on labour ward with High Dependency Unit level of care). 3 (1.6%) related to patients with symptoms of potential stroke (tingling, limb

numbness, difficulty word-finding). 9 (4.8%) SAE forms were submitted for miscellaneous reasons (localised injection site numbness; a large vulval haematoma; tachycardia requiring admission to the Coronary Care Unit; a laparotomy performed in a postnatal patient; a suspected allergic reaction to an unknown allergen; a numb leg immediately postnatal; 3 cases of prolonged hospital stay with unspecified reason.) No maternal deaths occurred, and no hysterectomies were performed in this study population.

Chapter 5 :

Discussion Part A - Study findings

5.1 Study Aims: Overall summary of findings

We directly compared the use of prophylactic intramuscular oxytocin, Syntometrine and carbetocin in the third stage of labour after vaginal birth, to determine whether:

- carbetocin is as effective as Syntometrine
- carbetocin is more effective than oxytocin
- Syntometrine is more effective than oxytocin

For the primary outcome of the need for additional uterotonic drugs, non-inferiority of carbetocin to Syntometrine was not shown; carbetocin was inferior to Syntometrine and is therefore considered not to be as effective. There was no significant difference between carbetocin and oxytocin; carbetocin was not more effective than oxytocin. Syntometrine use significantly reduced the need for additional uterotonics when compared with oxytocin; Syntometrine was more effective than oxytocin.

The secondary study aims were to determine whether, when given intramuscularly:

- Carbetocin is associated with fewer side effects than Syntometrine and oxytocin
- Choice of uterotonic drug affects a mother's subjective ability to bond with and care for her baby in the first two postnatal hours
- Choice of uterotonic drug affects maternal quality of life in the first two postnatal weeks

We found that carbetocin was associated with significantly fewer side effects (nausea, vomiting, headache, dizziness and abdominal pain) than Syntometrine. Carbetocin was associated with less dizziness and abdominal pain than oxytocin, but rates of nausea, vomiting and headache were not different. Allocation of uterotonic drug did affect a mother's subjective ability to bond with and care for her baby in the first two postnatal hours; mothers receiving Syntometrine were most likely to

report that their side effects affected their early bonding experience. This could be explained by the increased frequency of undesirable side effects following use of Syntometrine. Those receiving carbetocin were least likely to report this effect on bonding specific to the first two postnatal hours. Uterotonic drug allocation did not affect maternal quality of life in the first two postnatal weeks; there was no difference in utility scores between the three drugs in any pairwise comparisons.

5.2 Interpretation of results

5.2.1 Participating site

Participating sites each had a monthly recruitment target, which was used to calculate the overall recruitment period for the study. These targets were used only as a guide; recruitment continued at all sites, until the site either withdrew from the study or the overall required sample size was reached. Southmead Hospital recruited and randomised nearly half of all randomised participants (45.7%, 2709/5929 in ITT group). A higher proportion of recruits from Southmead Hospital was expected as the study originated from Southmead Hospital, it had more IMox-specific research staff, it opened as a recruiting site first and had the longest overall recruitment period. The populations of Bristol, Bath, Gloucester, Swindon and Nottingham do vary from a socioeconomic perspective. The English Index of Multiple Deprivation ranked Nottingham 10th (of 326) in the country for deprivation in 2015, Bristol 77th, Gloucester 139th, Swindon 189th and Bath 268th(127). Clinical practice is unlikely to have been identical across sites. While we know which prophylactic uterotonic drug was routinely used as a part of routine clinical care for normotensive labouring women in each maternity unit just before commencement of this trial (see Chapter 2), we do not have any specific details of ways in which intrapartum care or departmental culture (i.e.: for the transfusion of blood products) may have varied across sites during the study. However, all UK maternity units practice according to the same national guidelines, and participating units (except for Nottingham) were already linked through the Southwest Obstetric Network, which shared general clinical learning and experiences.

As this trial was large and block randomisation was used to ensure an equal spread of participants in each of the study arms across sites, the fact that recruitment figures differed across sites should not have significantly affected results.

When all other risk factors were accounted for in this study (Table 4.5: Logistic regression model results relating use of additional uterotonic drugs and PPH ≥500ml), those giving birth in Bath, St Michael's and Swindon hospitals were less likely to experience PPH ≥500ml than those giving birth in Southmead Hospital. In this study, those giving birth in St Michael's Hospital and Nottingham were more likely to receive additional uterotonic drugs than those giving birth at Southmead Hospital.

5.2.2 High PPH rate in this study

The mean rate of PPH ≥500ml in this study was 49.7%. This is one of the highest PPH rates ever reported, and is much higher than the 15.9% incidence of PPH presented in NHS Maternity Statistics for England in 2015-2016(128), or the typically quoted incidence of 2-10% across all settings(17-19). The PPH rate in our study was also higher than that reported by two other randomised control trials of prophylactic intramuscular uterotonic drugs after vaginal birth which took place around the same time; the rate of PPH ≥500ml was approximately three-fold higher in The IMox Study than the global CHAMPION Study(102) and two-fold higher in The IMox Study than the intramuscular oxytocin arm of a trial which took place in Dublin(78).

An exploration of the possible factors contributing to this difference is set out below:

(1) Protocol factors

There were no major differences between the practice laid out in this study's protocol, and usual clinical care(33). This was a trial centred around Active Management of the Third Stage of Labour (AMTSL). The practice of AMTSL is known to reduce incidence of PPH(129) and is recommended for

all women giving birth(33), although not all women choose this type of management for their third stage of labour. This protocol would in theory therefore have driven the PPH rate down compared with population averages, not up. Traditionally, prophylactic uterotonic drugs are administered at the time of the birth of the baby's anterior shoulder. Within this study protocol the prophylactic uterotonic drug was administered after clamping of the umbilical cord. Cord clamping is routinely performed after 60 seconds(33), or later if requested by parents and clinically appropriate. This is unlikely to have contributed to the higher PPH rate as the timing of umbilical cord clamping is not thought to affect PPH risk; a 2013 Cochrane Systematic Review which included 3911 women in 15 randomised trials compared "early" (within 60 seconds) with "late" (mostly 1-3 minutes) cord clamping, and found no significant difference for the occurrence of PPH ≥1000ml(80). The included trials were generally at a moderate risk of bias(130). The broader external validity of The IMox Study is evaluated in more depth in Chapter 6.

(2) Participant factors

Induction of labour

There was a high rate of women with an induced labour in this study. At 70.3 – 73.1% across arms, this was higher than the background UK rate at the time (32.6% for all women giving birth(131)) and higher than the induction of labour rate at participating sites during the course of the study (Table 5.1).

Table 5.1: Induction of labour rate at IMox Study participating sites during the course of the study

Site	Induction of labour rate 2015-2018 (%)
Southmead Hospital, Bristol	27.7 - 34.9
Royal United Hospital, Bath	22.5 – 29.1
Gloucestershire Royal Hospital, Gloucester	15.8 - 28.7
St Michael's Hospital, Bristol	31.9 – 37.8
Great Western Hospital, Swindon	26.9 – 36.8
Nottingham University Hospitals, Nottingham	33.0 – 42.1

The induction of labour rate in this study was also higher than both the CHAMPION Study (14%)(102) and the Dublin Study (53.1%)(78). This difference is likely to be in part due to the difference in denominator (all women having a vaginal birth in this study versus all pregnant women in the UK), and moreover the fact that the women having a vaginal birth in this study were recruited after attending a hospital. Women attending hospital are more likely to have some antenatal risk factors and require induction of labour (132), and patients in hospital (including those being induced) are more easily approached by hospital-based research teams. Induction of labour is a known risk factor for PPH(29), but only when induction is indicated for medical reasons(130, 133). Regression analysis of the results of our study did confirm the link between IOL and PPH, with a positive association between induction of labour and both PPH ≥500ml and the use of additional uterotonic drugs (Table 4.5). Interestingly, there is some evidence to suggest that elective induction without medical indication beyond 38 weeks gestation decreases risk of PPH compared with expectant management(134). Data regarding the reason for induction was not collected as part of The IMox Study, but generally inductions for medical reasons tend to outnumber those for "maternal request" alone.

Instrumental birth rate

Instrumental vaginal birth is an important risk factor for PPH(135). The instrumental birth rate in this study was high (21.2-23.%) when compared with the national rates quoted by the RCOG (10-15%)(136), and those presented in the CHAMPION Study (~4%)(102). It should be recognised however that the CHAMPION Study was a multi-national trial and that instrumental births occur less commonly in developing countries. It has been suggested that complex births may be underrepresented in trials of interventions used to prevent PPH, and that instrumental births are often even excluded from such trials(137). The higher proportion of instrumental births may be contributing to the higher PPH rate seen in this study.

(3) Measurement inaccuracy

The diagnosis of PPH, and comparison of results from different studies, is hindered by the lack of a standardised approach to the estimation of blood loss. There is insufficient evidence to support one method of blood loss estimation over another(53), including acceptability to women.

In The IMox Study, efforts were made to exclude liquor, and to ensure that all blood and blood-soaked materials were weighed. Dry weights of sheets, pads, drapes etc were subtracted to give a gravimetric estimation of blood loss. It remains possible that estimates of blood loss could have been artificially increased by the inadvertent inclusion of some liquor in weighed estimates. The study protocol did not mandate the use of an under-buttock drape following the birth and clamping of the umbilical cord, as seen in the CHAMPION Study. The use of such drapes may have increased assurance that liquor contamination did not artificially elevate blood loss estimates. Under buttock drapes were not used in this study due to a lack of evidence surrounding their use, and due to cost implication and the very limited budget of this study.

It seems that the importance of accurate blood loss estimation is two-fold: (1) clinically, to allow for appropriate triggering of additional interventions and the escalation of care, and (2) for research purposes, and the comparison of data from different studies.

It is likely that no method of blood loss measurement will ever truly capture the exact volume of blood lost by an individual woman giving birth. In reality, measured blood loss is one of many factors which are considered when making treatment decisions. Other factors may include background risk, the rate of blood flow, clinician personality and the availability of other treatments(27) (including the acceptability of treatments such as blood transfusion to that particular patient). While it seems logical that improved diagnosis of PPH would lead to improved maternal outcomes, there is little actual evidence to support this notion(45). From a clinical perspective it is interesting to note that despite the three-fold increase in PPH rate between our study and CHAMPION, the rate of blood transfusion was only twice that in IMox compared with CHAMPION (mean 2.9% versus 1.45%)(7, 102). This suggests that women in our study were not proportionally more haemodynamically unwell or symptomatic of anaemia, despite the increased rate of PPH in our study population. This adds strength to the idea that a blood loss of 500ml may in fact be physiologically “normal” and that our rates of PPH, albeit high, may not be due to over estimation of blood loss volume. Of note, the reported transfusion rate in CHAMPION was the same as the reported rate of PPH ≥1000ml. While it seems unusual for potentially all those with PPH ≥1000ml to need transfusion, the prevalence of antenatal anaemia in developing countries be a contributing factor. It is also possible that blood loss was underestimated in the CHAMPION study.

From a research perspective, more important than accurate assessment of blood loss alone is the collection and reporting of data according to a Core Outcome Set, to enable comparison and pooling of data from different studies. A Core Outcome Set for studies evaluating interventions for preventing PPH was published after our study had finished recruiting(138). Of these ten

recommended outcomes, two (shock and breastfeeding) have not been reported in our study. In any future study it would be important to include all these outcomes.

(4) Previously under-estimation of the true incidence of PPH

It is possible that the previously accepted PPH incidence of 5-10% underestimated the true burden of PPH across settings. Higher reported rates in more recent years may result from blood loss being more commonly considered and measured, with more accurate diagnosis of PPH when it has occurred; fewer cases are now missed. It is also known that PPH rates in developing countries are rising(22-24, 139); there are more cases occurring. The high PPH rate that we report may act as further evidence of this. Data published recently by other groups also reflects a PPH rate much higher than that previously accepted; the incidence of PPH ≥500 mL for all maternities in Wales in 2017 was 34.0%(140), and 57.7% after vaginal birth in one large Chinese centre in 2018(141). Changing patient demographics and an increase in rates of intervention may be contributing to this.

It may be time to re-evaluate the threshold of blood loss which defines a “post partum haemorrhage”. The use of a threshold of 500ml for the definition of PPH dates back to 1989 and the “informal meeting of experts” at a World Health Organisation meeting(8), as described in my introductory chapter. The acceptance of and reliance on this threshold seems to be evolving. The Core Outcome Set for studies evaluating PPH prophylaxis specifies that both PPH ≥500ml and PPH ≥1000ml should be reported in studies evaluating interventions for the prevention of PPH(14). The RCOG guideline for Prevention and Management of PPH now divides PPH into “minor” (500-1000ml) and “major” (>1000ml), with “minor” PPH in an otherwise haemodynamically stable patient prompting a series of intervention which mostly increase readiness for the development of more “major” PPH (cannulation, venepuncture and increased frequency of observations) (31).

5.2.3 Risk factors for PPH

Our results have validated PPH risk factors documented in the RCOG Greentop Guideline published in 2009(11), including: previous PPH, obesity, induction of labour, prolonged labour, big baby, pyrexia in labour and operative birth (Table 5.2). A history of previous PPH was the most significant risk factor for developing PPH in this study.

Table 5.2: Risk factors for PPH expressed in RCOG Greentop Guideline (2009) compared with findings of The IMox Study

Risk factor	RCOG Greentop Guideline, 2009(11) approximate Odds ratio (99% CI)	Odds ratio from The IMox Study (95% CI)
Previous PPH	3	3.09 (2.47 – 3.87)
Obesity (BMI >35)	2 (1.24 – 2.17)	1.31 (1.13 – 1.51)
Induction of labour	2 (1.67 – 2.96)	1.22 (1.07 – 1.39)
Prolonged labour	2	2.06 (1.70 – 2.51)
Big baby	2 (1.38 – 2.60)	2.42 (2.02 – 2.89)
Pyrexia in labour	2	1.85 (1.34 – 2.56)
Operative vaginal birth	2 (1.56 – 2.07)	2.33 (2.00 – 2.72)
Asian ethnicity	2 (1.48 – 2.12)	1.31 (0.94 – 1.81)
Nulliparity	-	2.21 (1.95 – 2.51)

While Asian and Hispanic race is a documented risk factor for atonic PPH when compared with Caucasian race (142, 143), this was not found to be true for PPH ≥500ml in our dataset (OR 1.31, 95% CI 0.94 – 1.81). This may be because we had relatively few women of Asian ethnicity within our sample (192/5717 participants, 3.4%) resulting in a lower power for the comparison of the Asian ethnicity subgroup. Asian ethnicity was removed as a risk factor in an update of the RCOG PPH guideline published in 2017, while our study was underway.

The role of parity as a risk factor for PPH has long been debated and parity was not listed as a risk factor in the RCOG guideline. We found nulliparity to be an independent risk factor for PPH ≥500ml (OR 2.21, 95% CI 1.95 – 2.51), when all other risks were accounted for.

5.2.4 Blood loss versus need for additional uterotonics

While there was a significant difference between Syntometrine and carbetocin or oxytocin in the use of additional uterotonic drugs, there was no difference between any two arms for estimated blood loss. This is interesting, as additional uterotonics are used to treat uterine atony, and uterine atony is the most common cause of PPH (20, 29). It would therefore seem logical to have assumed that in arms where additional uterotonic drugs are needed more commonly, estimated blood loss would have been greater. The process whereby any clinician decides to give an additional uterotonic drug is very subjective, and is likely to be influenced by a multitude of factors including seniority, personality, rate of blood loss(27) as well as the location of birth and availability of help, the current clinical presentation of the patient in front of them and the clinician's own prior and recent experience of cases of PPH. Data relating to tears may also offer some explanation. Tears of the perineum, vagina and cervix can also contribute to overall blood loss and can be the cause of PPH, although not all tears bleed or require suturing. While it is not possible to deduce what the cause of PPH was from our dataset, some trends were observed as shown in Tables 4.8 and 4.9 in Chapter 4. Perineal tears were common and occurred in 74.5% of all births in this study, a rate in keeping with previously published literature(144, 145). The finding that nulliparous women were more affected than multiparous women is also in keeping with the literature(144, 145). It is perhaps surprising that rates of perineal tear were not higher than previous studies, given the high rate of instrumentally assisted vaginal births in this study. Women with a tear were more likely to experience PPH ≥500ml and to receive additional uterotonic drugs. This could be because uterine atony was also thought to be contributing to the PPH but may also reflect a "knee jerk" reaction in the face of ongoing blood loss, regardless of its origin.

The above observations relating to tears provide some insight into the relationship between PPH, parity, perineal tears and the use of additional uterotonic drugs, but do not fully explain why there was a reduction in the use of additional uterotonic drugs with Syntometrine, but no difference in estimated blood loss between the arms.

5.2.5 Hypertension with Syntometrine

Our results are in keeping with the wealth of previously published evidence regarding the increase in maternal side effects with use of prophylactic Syntometrine(2). From a patient safety perspective, hypertension has long been the most concerning adverse effect caused by drugs containing ergometrine; intracranial haemorrhage is the single most common cause of death relating to maternal hypertensive disorder in the 65 years since Confidential Enquiries into maternal deaths have been conducted(146). Our study has highlighted some difficult aspects of intrapartum care relating to hypertension, which are also relevant to usual clinical practice:

(1) At what threshold of blood pressure is Syntometrine considered not to be safe?

After the point of randomisation, a total of 212 women (3.6%) were excluded from the study as they became ineligible to participate (Figure 4.1). One of the most common reasons for this was the development of hypertension, which in our study was considered to be a single systolic blood pressure of 160mmHg, or two consecutive systolic readings of 140mmHg or diastolic readings of 90mmHg, taken 30 minutes apart. During the course of our study, general awareness and discussions surrounding intrapartum hypertension within the participating units seemed to increase. National guidelines recommend 4-hourly measurement of blood pressure in the first stage of labour, and hourly measurement in the second stage(33). Although the study protocol did not mandate any additional blood pressure monitoring in labour, it is possible that blood pressure was checked more frequently in labour for study participants due to staff awareness of the eligibility criteria, and their intrinsic desire to keep patients safe (and honour the protocol) by returning participants to "usual clinical care" if exclusion criteria were met. Prophylactic Syntometrine was routinely used in the third stage of labour for normotensive women in all participating units except Nottingham, in "usual clinical care", during this study. It is hoped that on return to "usual clinical care", those participants excluded for hypertension went on to receive prophylactic oxytocin, not Syntometrine. While it is accepted in clinical practice that Syntometrine should not be administered to anyone with a

preceding history of hypertension, the threshold at which individual intrapartum blood pressure readings become significant may be prone to inter-clinician variability (e.g. if a patient had one diastolic blood pressure reading of 90mmHg in labour, one person may consider this to be too high to receive Syntometrine, while others may accept this on the basis of other completely normal readings). This study has highlighted that in routine clinical practice, there may be some subjectivity to the diagnosis of intrapartum hypertension. Hypertension can only be diagnosed if recordings are taken accurately and frequently enough. Increased vigilance due to research protocols may have increased the safety of participants in this study.

(2) The difficulties of blood pressure measurement in precipitate labour

Syntometrine should only be given to women who are known to be normotensive. Blood pressure measurement can easily be overlooked when one midwife is caring for a woman who is labouring very quickly, and the midwife has both the mother and fetus to attend to. There were 23 participants who received a study drug but were then excluded from the Per Protocol Analysis (Figure 4.1), as it was found on retrospective review of the notes that the participant had not had a blood pressure checked in what turned out to be a rapid labour. The fact that this happened at least 23 times despite the increased vigilance associated with study participation and repeated checks of eligibility, highlights that this is likely to also be a continued problem in routine clinical practice (where notes will not be retrospectively scrutinised in this way).

5.2.6 Third stage of labour

We have shown that the duration of the third stage of labour and the need for manual removal of placenta did not differ between participants receiving prophylactic oxytocin, Syntometrine or carbetocin. This sheds important light on a query regarding the use of Syntometrine which has been only partially answered over the last 30 years. In 1990, Begley et al published results of a study

comparing physiological management of the third stage of labour with active management, using an intravenous dose of 500μg ergometrine (147). This reported a significant ($p<0.0005$) increase in manual removal of placenta with use of IV ergometrine. Concerns have since remained that this may also apply to IM Syntometrine. A 2011 Cochrane review of Active versus Expectant Management of the Third Stage of Labour(129) included the 1990 Begley study, as well as three other studies featuring Syntometrine, conducted between 1988-1998. The Cochrane review concluded that there was little or no difference to the duration of the third stage of labour with active management, and uncertain evidence regarding the need for manual removal of placenta. It deemed the included evidence to be of "very low" to "low" quality for these comparisons. An earlier 2004 Cochrane review of oxytocin versus Syntometrine found no difference in duration of the third stage of labour or need for manual removal, and our findings corroborate this.

5.2.7 Number of additional uterotonics used as an outcome

The number of additional uterotonic drugs administered is perhaps less clinically important than whether any or none were required. This outcome was included in part for health economic evaluation, if this had been required (see section 5.3). During a larger PPH the volume of blood loss becomes more important from a patient perspective, than the number of additional uterotonic drugs used. As highlighted previously (section 5.2.4), the decision to give additional uterotonic drugs is subjective and likely to be influenced by a multitude of factors.

5.2.8 Transfusion of blood products

We found no difference in rates of blood transfusion between the three arms. The rate of blood transfusion (mean 2.9% across arms) was lower than the IM arm of the Dublin study of IV versus IM oxytocin (4.4%), but higher than that presented in the CHAMPION Study (1.3% and 1.6% for

carbetocin and oxytocin arms, respectively). A previous randomised trial of carbetocin versus oxytocin at caesarean section, also based in Bristol's Southmead Hospital in 2010, found a similar transfusion rate as the IMox Study(115). This could in part by influenced by departmental culture towards blood transfusion and the thresholds at which transfusion are considered. Although the rate of PPH of The IMox Study was three times higher than that of the CHAMPION Study, the rate of blood transfusion was only twice as high. A lower prevalence of antenatal anaemia in the UK compared with developing countries may have contributed to this relatively lower rate of blood transfusion-per PPH event in our study.

It is surprising to see (Table 4.7) that more than half of those who received red blood cells also received other blood products in addition to this, and that these seemed to also have been given as a "bundle". Point of care testing for haemoglobin level was widely available in participating units at the time when the study was conducted but point of care testing for coagulopathy (using machines such as ROTEM or TEG) were not widely used in routine management of PPH. If a cohort of PPH events reported in this study had taken place now, it is likely that there would be less of a "bundle" approach to the administration of additional blood products. No participants received cell savaged blood in this study, as cell salvage is not yet used after vaginal birth, and those undergoing caesarean section were no longer eligible to participate. The use of cell salvage at vaginal birth is a current topic of anaesthetic and obstetric interest(148, 149).

5.2.7 Aiding a patient's autonomous decision making

Pivotal to the quality of the care which we provide women in labour, is the quality of the conversation which we have with them regarding their choices. This is especially important when the choices which we make for them contravene national and international guidance, as with the frequent routine use of prophylactic Syntometrine rather than oxytocin during the third stage of labour in the UK (presented in Chapter 2). In my own experience, having worked in 6 different

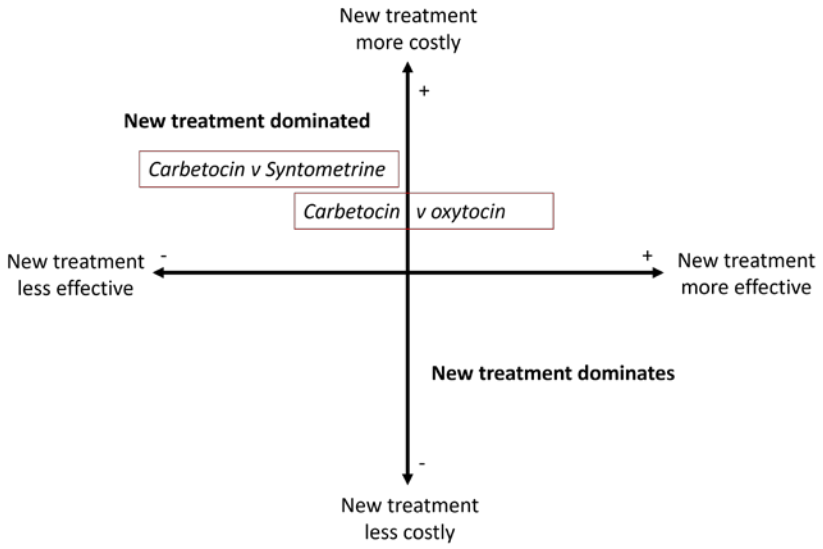
maternity departments over the last 12 years, these are not conversations which I have seen happen frequently. Our study was the first to ask women how much their side effects affected their ability to bond with and care for their baby in the first two postnatal hours, and we concluded that women receiving Syntometrine were twice as likely to report a negative impact of these side effects when compared with women receiving oxytocin. Routine prophylactic Syntometrine use is advocated by the RCOG specifically only for normotensive women at increased risk of PPH(31), based on a Cochrane review which showed a small reduction in PPH ≥500ml (OR 0.82, 95% CI 0.71 – 0.95)(2) with Syntometrine compared to oxytocin. There was no significant difference for PPH ≥1000ml. This 2004 Cochrane metanalysis included 6 trials, totalling 9332 women, and preceded the publication of results from The IMox Study(7) or The CHAMPION Trial(102). The first "Golden Hour"(150) after birth is a well-recognised and reported time, in which skin to skin contact between mother and baby helps to prevent neonatal hypothermia, promotes early breastfeeding, enables colonisation of the baby's skin with the mother's healthy bacterial flora, and improves mother-newborn bonding(151). The question which we asked regarding postnatal experience *("Have any of the above symptoms [nausea, vomiting, dizziness, abdominal pain, other] affected your ability to bond with and/or care for your baby in these first few hours?")* was very specific to our study, and by no means covers the huge breadth of factors which are likely to contribute to a mothers' early postnatal experience, or their ongoing ability to bond with their baby. However, it does serve to highlight that the side effects which prophylactic uterotonics can cause are important to women, and that they could feasibly interfere with a woman's ability to optimise her experience of her first "Golden Hour" with her newborn. To improve the frequency and quality of conversations which midwives or doctors have with women regarding their third stage of labour, information needs to be available in an up to date, succinct and accessible format. Clinicians caring for women in labour need to make time available to have these discussions when requested, to aid the autonomous decision making of the women in our care.

5.3 Health economic evaluation

Carbetocin is significantly more expensive at £17.64 per dose, compared with £0.80 per dose of prophylactic oxytocin and £1.57 per dose of Syntometrine(152). With this in mind, we collected some resource use data in the Case Report Form, including the length of stay in higher dependency areas, total length of postnatal stay, and the number and type of additional uterotonics, and blood products transfused. A health economic evaluation is beyond the remit of this dissertation, but these data were collected to aid any such evaluation conducted in the future. The cost of delivering treatment in each arm would include the cost of the intervention drug and any additional drugs required, as well as need for a longer hospital stay. In a cost-consequences table we could compare the costs of the intervention drugs, with the costs of additional drugs required and hospital stay, as well as other outcomes, such as blood loss and complications.

We found that carbetocin is less effective and more expensive than Syntometrine, and it is as effective but more expensive than oxytocin; it is therefore the dominated treatment compared with both Syntometrine and oxytocin (see Figure 5.1). Carbetocin has an improved side effect profile, which may warrant investigation as to whether it reduces length of hospital stay compared with Syntometrine or oxytocin, and whether it saves on average health care resources. There is uncertainty in the comparison between Syntometrine and oxytocin; Syntometrine is both more effective and more expensive than oxytocin, but the difference in costs of these two treatments is very small. A future economic evaluation would also be able to quantify the differences in total costs and determine whether Syntometrine is cost-effective compared with oxytocin.

Figure 5.1: Cost effectiveness plane for comparison of carbetocin with Syntometrine or oxytocin



5.4 Overall message and conclusions in context of other studies

Our study findings corroborate conclusions from other recently published literature comparing prophylactic oxytocin, Syntometrine and carbetocin after vaginal birth. In keeping with the CHAMPION Study(94), and a Meta-Analysis of carbetocin versus oxytocin for prevention of primary PPH after vaginal birth(153) which was published before the CHAMPION Study, we did not find a significant difference between oxytocin and carbetocin for use of additional uterotonic drugs, or maternal side effects. The CHAMPION Study was based on a non-inferiority comparison and concluded non-inferiority of carbetocin to oxytocin for PPH ≥500ml at a margin of 1·16, but no significant difference for PPH ≥1000ml. We also found no difference between carbetocin and oxytocin for rates of PPH, but based conclusions on a superiority, instead of non-inferiority, comparison of these two uterotonics. The similarity in side effects profile of carbetocin and oxytocin was also echoed by the Cochrane Network Meta Analysis (NMA), which identified and ranked the most effective uterotonic drugs, based on all published literature.

Other NMA conclusions which support our own include: Syntometrine use does not reduce PPH ≥1000ml compared with oxytocin and there are higher rates of adverse outcomes(104). Like the NMA, we found that Syntometrine reduces the need for additional uterotonics compared to oxytocin and carbetocin, although the certainty of the evidence for this in the NMA was low. However, our results differ from NMA conclusions when Syntometrine or carbetocin are compared with oxytocin for the outcome of PPH ≥500ml. The NMA concluded that use of Syntometrine and carbetocin probably reduce PPH ≥500ml compared with oxytocin(104), but we did not find this to be true.

There is increasing interest in the mode of prophylactic uterotonic administration after vaginal birth. In the UK, prophylactic uterotonics are routinely given intramuscularly after vaginal birth, but strong evidence is now emerging to suggest that intravenous administration of oxytocin further reduces risk of PPH and blood transfusion, as well as moderate evidence that it reduces admission to Intensive Care Units(97). This may explain why carbetocin has previously been found to be more effective than oxytocin at caesarean section(101), as it is then given intravenously; there is a higher peak level of carbetocin after intravenous administration than after intramuscular use(154).

In conclusion and looking back at the initial study aims, The IMox Study has not found carbetocin to be as effective as Syntometrine or more effective than oxytocin, for either the use of additional uterotonic drugs, or risk of PPH. This study did find Syntometrine to be more effective than oxytocin for the use of additional uterotonic drugs, but not for risk of PPH. However, the frequency of maternal side effects and negative impact of these on maternal ability to bond with and care for her baby in the first two postnatal hours does call into question the frequent routine use of prophylactic Syntometrine in hospitals in England, Scotland and Wales, as documented by the telephone survey reported in Chapter 2. There does not seem to be compelling reason to go against national and international guidance through continued use of routine Syntometrine; the small reduction in need

for additional uterotonic drugs comes at a large cost for maternal birth experience, without PPH benefit. If Syntometrine continues to be used routinely, I feel that there needs to be an increase in the frequency of good quality conversations between clinicians and women regarding this choice, and the pros and cons of options available, with women empowered to make this choice for themselves given overall advice about their risk factors for PPH.

There is no clear benefit of carbetocin use after vaginal birth in a UK context, especially given its cost. From a global perspective, the development of heat-stable carbetocin could in future profoundly change the landscape of PPH prophylaxis after vaginal birth. There has previously been concern about the quality of oxytocin in Low and Middle Income Countries, both due to low manufacturing quality as well as inadequate storage and transportation conditions(88). The arrival of heat stable carbetocin, which has now repeatedly been shown to be comparable to oxytocin in terms of PPH prevention and the need for additional uterotonic drugs, adds an important alternative. The World Health Organisation has now included carbetocin in its list of prophylactic uterotonics recommended for use in all births, with the context-specific recommendation that its use is advised where its cost is comparable to other effective uterotonics(155). Carbetocin has also been added to the WHO List of Essential Medicines, and Ferring Pharmaceuticals have pledged to make it available at an oxytocin-equivalent price to low and lower-middle income countries(156). While this could all change the availability of high quality, effective prophylactic uterotonics in developing settings, there is still concern that uterotonics alone are no “magic bullet”(157). Maternal PPH-related deaths are commonly due to placental issues including retained placenta, placenta praevia and placental abruption, and the availability of blood transfusion and skilled surgeons are thought to be more important(157).

The findings of our study inform the choices for prevention of PPH at vaginal birth for clinicians, policy makers and women, both in the UK and abroad. I am proud to have been instrumental to the design, implementation, analysis, and publication of this multi-centre randomised control trial.

Chapter 6 :

Discussion Part B - Critique of trial and future learning points

Within this chapter I aim to assess the strengths and limitations of this study, through detailed evaluation of its internal and external validity. I will also highlight some of the practical problems encountered throughout the duration of this project and describe what I would do differently next time if planning a similar study again.

6.1 Strengths and limitations of this study

6.1.2 Internal validity

Selection bias

Selection bias is the biased allocation to comparison groups. Selection bias was minimised by use of a randomisation list with an unpredictable sequence, within the block size of 9. The randomisation sequence was generated by a statistician who was not otherwise involved in the trial, and the sequence was known to only that statistician and St Mary's Pharmaceutical Unit, who blinded and labelled the IMP. The blocked randomisation allowed us to stratify by centre, by only cutting the randomisation list at the end of a block when deciding which IMP numbers to distribute to each participating maternity unit. Any potential regional population differences and differences in local practice between centres were therefore balanced between randomised arms. A block size of 9 was chosen (instead of 3 or 6) to reduce the chance of the next allocation being guessed (Syntometrine is well known to cause more nausea and vomiting, and if this led an outcome assessor to correctly guess this allocation in a block size of 3, they would have had 50% chance of guessing the next allocation correctly). Allocation was concealed by over-labelling, and the use of "snapper tops" to cover the coloured rings at the top of the ampoules and to make the ampoules identical in height (see Figure 6.1).

Figure 6.1: Blinding to conceal differences in height and coloured rings on ampoules

As we were not able to remove the coloured rings, it is possible that outcome assessors may have looked up the bottom of the snapper tops, once snapped, to see the rings and thus unblind the IMP. A torch or bright light would have been needed to do this, and I feel it is unlikely that this would have happened. We considered stratification by other confounding PPH risk factors (such as parity, history of PPH and BMI), but concluded that this would over-complicate the randomisation process and risk allocation error. This was especially so as clinical staff were relied on to collect the next consecutively numbered box from the study fridge (by day or night) without the help of research staff, in a situation when birth was imminent, and time was pressured. As the total sample size was large, these confounding PPH risk factors were naturally balanced across the arms (see Table 4.2).

Performance bias

Performance bias is the unequal provision of care, other than the treatment under evaluation. All clinical staff, research staff and patients remained blinded to allocation; the provision of care or assessment of outcomes should not have been affected by awareness of group allocation. Side effects of nausea and vomiting were already known to be more associated with Syntometrine than oxytocin or carbetocin, based on previous evidence, and this fact is well known to clinicians. It is

possible that care providers may have suspected allocation to the Syntometrine arm for participants experiencing postnatal nausea or vomiting, but this suspicion could not have been proven. This was unavoidable but should not have affected results, particularly as outcomes relating to subjective maternal side effects were taken from maternal postnatal experience questionnaires (completed by participants) rather than the Case Report Forms (completed by clinical staff).

Detection bias

Detection bias is the biased assessment of outcomes. It is possible that clinicians had pre-established beliefs relating to the trial uterotonics. Given the fact that many maternity units continued to use routine prophylactic Syntometrine despite national guidance advocating routine use of oxytocin, it is possible that clinicians believed, either subconsciously or not, that Syntometrine was in some way superior to oxytocin. Anecdotally, I do recall conversations with midwives about the study, in which they were concerned that women with particular risk factors for PPH should be receiving Syntometrine rather than participating in this trial and possibly being allocated to receive oxytocin. However, as outcome assessors remained blinded to allocation for the duration of the study, these pre-established beliefs should not have caused detection bias.

Attrition bias

Attrition bias occurs due to biased handling of protocol deviations, withdrawals, and losses to follow up. Due to the short time frame between the point of randomisation (when birth was imminent) and the administration of the study drug (within minutes of birth), attrition rates were very low (<0.5%). As participants and clinical staff were blinded to allocation, knowledge of allocation should not have affected attrition which did occur. There were a small number of participants who reportedly withdrew consent after the point of randomisation and were thus removed from the study and did

not go on to receive the drug which they had been allocated. This mostly occurred on the low-risk midwifery led Birth Centre. The most frequently stated reason for this was the wish of the participant to have physiological management of the third stage of their labour, rather than active management with a study drug. This is acceptable from a patient choice perspective, and plausible given the frequency with which physiological management is encouraged and chosen in the low-risk Birth Centre. It is however disappointing from a protocol perspective, as the participants had been fully counselled about active versus physiological management during the consenting process and may have been encouraged to go back on these choices by the members of staff tending to them in labour. Any bias caused by staff favouring physiological management over active management of the third stage in an otherwise low risk labour, should not have affected the balance between arms, and was also minimised using modified Intention to Treat analyses. As these withdrawals mostly occurred in low-risk women, they would have reduced the generalisability of results to low risk populations, by reducing the overall number of low risk women participating in the trial.

We know that we were not able to approach all eligible women and that higher risk women were over-represented within our study population; those with low-risk pregnancies would not have attended the hospital routinely other than for ultrasound scans, and we did not have many community midwives able to consent to this study. We do not have accurate records of the number of women who were eligible to participate at each site, how many were approached, and the proportion of these who were ultimately recruited. This is a recommendation in Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines, and the absence of this data makes it difficult to evaluate our recruitment process and difficulties which we faced with this.

Handling of missing data

The amount of missing data for key outcomes was small (8/5717 participants for the primary outcome measure in mITT, 8/5717 participants for weighed blood loss in mITT). A sensitivity analysis

was performed, as per the a-priori Statistical Analysis Plan, to assess the impact of missing data (for those included in the ITT and not mITT population) on the primary outcome conclusions. This did not affect conclusions drawn for superiority comparisons. The non-inferiority comparison would have been on the cusp of showing non-inferiority, if up to 20% of those with missing data had required additional uterotonic drugs. Multiple Imputation using Chained Equations was used to account for missing data and assess the stability of the logistical regression model. The amount of missing data was most substantial for EQ-5D-5L questionnaires, especially as these were completed at 3 different times points. The Day 14 questionnaire required telephone follow up, and this was the timepoint with the most missing data (14% participants with missing data). 27% of participants did not have a complete EQ-5D-5L dataset. Each timepoint was treated independently (with a mean utility score created for each arm at each timepoint, from all available data for that timepoint). Mean utility scores at day 14 were similar between those with complete datasets, and those for Day 14 alone, suggesting that any missing data were at random. The use of an a-priori Statistical Analysis Plan which specified the non-inferiority margin and the rounding of decimal places, and the publication of the study protocol, helped to minimise attrition bias due to the handling of missing data.

Reporting bias

Reporting bias includes selective reporting and biased publication. The details of the study and its outcomes were registered at clinicaltrials.gov from 15th August 2014, prior to the commencement of recruitment in February 2015. The protocol(6) and results(7) of this study have been published separately, in peer reviewed journals. The protocol paper was published in January 2019. This could be criticised, as it does not predate the completion of study recruitment in August 2018. Some amendments were made to the online registry in July 2018 while the study was still underway, and this was questioned by the reviewers of the final paper. Amendments included clarifications of the inclusion and exclusion criteria (e.g. “Singleton live pregnancy” was already in inclusion criteria,

therefore “multiple pregnancy (twins or higher order)” was removed from exclusions, and “intrauterine fetal death” was removed from exclusions because “singleton live” pregnancy was already in the inclusions). Other clarifications were made on advice of the independent Data Monitoring and Ethics Committee, which sat in October 2017. The DMEC made a request for the addition of a time scale to the primary outcome measure, and therefore this was updated to be the “requirement for additional uterotonic drugs within 24 hours of birth”. All pre-specified outcomes have been reported in the final paper(7) and in this thesis. The number of secondary outcomes pre-specified and reported for this study was large. For each outcome, three separate pair-wise comparisons have been made. It is likely that one or more of these tests have accidentally found a significant association by chance, due to the number of overall tests performed. It should be remembered that these comparisons were not the main hypothesis being tested, and that comparisons may not be adequately powered to enable conclusions to be drawn from all the data presented here.

6.1.3 External validity

For the results of any trial to be clinically useful, we must be able to generalise our findings to other populations. Set out below is an evaluation of The IMox Study’s external validity, categorised as per Rothwell (2006)(158).

Setting of trial

Five of the six participating sites were selected based on their geographical location within both the Severn Deanery and the West of England Clinical Research Network. Hospitals and members of staff within the Severn Deanery were familiar to me due to the rotational training programme which I am in, and these units were also linked through the Southwest Obstetric Network. The rotational nature of training across the Severn Deanery also helped to maximise the output from the Good Clinical

Practice training sessions which we set up; we eventually had a whole cohort of GCP-trained junior doctors who were able to help facilitate eligibility assessment and prescribing of the IMP for this study across the region. Geographical location was also felt to be important from a Sponsor point of view (North Bristol NHS Trust Research & Innovation Department). The cost and time related to Site Visits were directly related to the geographical distance travelled, and the responsibility for Site Visits fell to the Sponsor as we did not have the funds to run the study through a Clinical Trials Unit. Towards the end of recruitment, one additional recruiting site (Nottingham University Hospitals NHS Trust) was added, based on their interest in the study and their previously good record of recruitment to intrapartum studies.

These participating units are socioeconomically diverse (e.g. higher migrant population in Bristol than elsewhere(159)). They are likely to be representative of UK practice and be easily generalisable to other UK populations. While healthcare systems across developed countries are likely to have many similarities, differences which exist may affect the generalisability of our findings. Our study focussed on intramuscular prophylactic uterotonics, but all labouring women in France(105) and most labouring women in the United States(160) undergo intravenous cannulation on admission to hospital and are likely to receive intravenous rather than intramuscular prophylactic uterotonic agents after birth. There is already good evidence of the benefit of intravenous over intramuscular administration of prophylactic oxytocin(97). While oxytocin and carbetocin can be administered intravenously, this is not recommended for Syntometrine.

We did not collect any data regarding ante or postnatal anaemia. Rates of antenatal anaemia are typically higher in developing countries, and anaemia is known to increase risk of PPH due to uterine atony(44). The direct generalisability of our results is also limited to settings where a skilled birth attendant is present (to administer the uterotonic drug, as a minimum), and cold chain storage facilities exist (to store and transport the uterotonic drugs in their optimum condition). However, carbetocin is now of heat-stable formulation, and therefore no longer relies on cold chain storage.

An additional barrier to the use of carbetocin has historically been its cost, but Ferring Pharmaceuticals have now pledged to make it available at an oxytocin-equivalent price to low and lower-middle income countries(156). Carbetocin has also been added to the World Health Organisation List of Essential Medicines. Given these developments, our findings which suggest no significant difference in PPH rates between carbetocin and the cold-chain storage dependent prophylactic uterotonics, are still of use in a global context.

Selection and exclusion of participants

The eligibility criteria were generally broad, strengthening the external validity of the study findings. In hindsight, the exclusion of "antepartum haemorrhage or suspected placental abruption" was unnecessary. Antepartum haemorrhage is not rare, and in the context of this large sample size, its occurrence would have been balanced between arms. Antepartum haemorrhage is an important risk factor for PPH and is not represented within this population. However, as the mechanisms underlying PPH due to antepartum haemorrhage or placental abruption are the same as those due to other risk factors ("The 4 H's and 4 T's"), our findings are still relevant to those who experience antepartum haemorrhage or placental abruption. Due to the inclusion of the Syntometrine arm, those with hypertension were excluded from the study. This therefore meant that women who would otherwise have been safe to receive oxytocin or carbetocin were not able to do so. However, our findings for the oxytocin versus carbetocin comparison corroborate those from other recently published studies, which were able to include those with hypertension, suggesting that this exclusion has not altered conclusions for this comparison.

Due to the mainly hospital-based recruitment strategies employed, our study did not include many women at the lowest risk of bleeding. However, previous metanalyses of data comparing active and expectant management of the third stage of labour found no substantial differences between women with risk factors and those at the lowest risk of bleeding(72), which may suggest that our

results would also be applicable to those at low risk of bleeding. Arguably, those at highest risk of bleeding are most in need of the most effective uterotonics. It must however be remembered that PPH can happen in any setting, and in the absence of risk factors. It could be also argued that those who are most remote (e.g. home births) are most in need of the most effective prophylactic uterotonics due to the time delay for accessing further help if needed. This subset of the maternity population is not represented within our study population.

Characteristics of randomised participants

We collected data on ethnicity, as Asian ethnicity was listed as a risk factor for PPH by the Royal College of Obstetricians and Gynaecologists(11) at the time when the study protocol was developed. We ultimately found race not to be an independent risk factor for PPH. However, only 3.4% of our participants were of Asian ethnicity, so conclusions drawn regarding Asian ethnicity as a PPH risk factor are probably not generalisable to other populations, as the power to detect a difference would have been reduced by the small sample of participants with this characteristic. Southmead Hospital randomised almost half of all study participants (46% of total participants in mITT population, see Table 4.1). This should not have affected internal validity; block randomisation would have ensured that population differences or local practice would have been balanced between arms. Having many participants from one centre increases the chance that the participants sampled in this study could be different from wider populations (such as those in other countries, or in future generations) in ways which we have not identified, thus potentially limiting the study's external or ecological validity. However, this is still less so than it would have been, had this been a single not multi-centre trial.

Differences between trial protocol and routine practice

The trial protocol differed from usual clinical care only in the timing of the uterotonic drug administration. In the United Kingdom, prophylactic uterotonic drugs are traditionally given with birth of the baby's anterior shoulder(33), although in actual practice this is known to vary(109).

Within the protocol for the present study, the prophylactic uterotonic was given after clamping of the umbilical cord; either after 1 minute of routine delayed cord clamping, or after a longer period of delayed cord clamping if requested by the participant and her partner. There is already evidence to suggest that the practice of early versus late clamping of the cord(80), or administration of the prophylactic uterotonic drug before or after delivery of the placenta(75), do not affect PPH rate. This would suggest that the timing of uterotonic drug administration in our protocol should not be a factor which significantly limits the generalisability of conclusions drawn.

Outcomes measures and follow up

The sample size calculation for this study was based on the primary outcome of the need for additional uterotonic drugs. While this was selected as a surrogate marker for the uterotonic "power" of the study drugs, a more important outcome from a patient care or patient experience perspective might have been weighed blood loss. This seems to be the most frequently used primary outcome measure in trials of prophylactic uterotonic drugs.

The Maternal Postnatal Experience Questionnaire was completed by participants at 2 hours postnatal. An advantage of this approach, compared to a scenario in which participants are asked to complete the questionnaire later with reference to the first two postnatal hours, is that it may have helped to reduce recall error. A notable disadvantage is that participants were still in the care of the maternity team at the time when they completed the questionnaire. Participants may have felt pressured to respond in a certain way so as not to jeopardise the care they were receiving, or to please their care givers. However, this questionnaire related only to the participants' own experience of any side effects, and not the care which was received. It is therefore likely that any such bias was minimal.

Euroqol's EQ-5D (EQ-5D-5L)(161) was the instrument chosen for assessment of Health-Related Quality of Life, whereby you can assign societal preference-based utility scores to health-states produced by the responses to the EQ-5D-5L. This is the tool preferred by the National Institute for

Health and Care Excellence for the calculation of Quality Adjusted Life Years (QALYs). While we found no difference in utility scores of participants in each arm at any time point, this does not mean that no differences existed. The EQ-5D-5L is a generic tool that weights time spent in a health-state by its quality of life. It may therefore not be sensitive enough to capture differences in quality of life in the postnatal health state of women after their unique pregnancy experiences. This may be due to the timing of our questionnaires, or due to the questionnaire which was used. It could also be compounded by the relatively short period of time over which quality of life was assessed. The EQ-5D-5L does not cover many of the domains which have been found to be important to new mothers, including psychological and baby-related concerns, relationships with partner/friends/family, and health & functioning, as set out in the Maternal Postpartum Quality of Life Questionnaire(162). As each woman's journey to motherhood is so unique, a tool named the Mother Generated Index has also been developed, in which women identify and score 8 aspects of postnatal life which are most important to her since having a baby, without pre-set domains(163). The mother then scores each area out of 10 ("worst" to "best" that it could be), and finally allocates 20 "spending points" to signify the importance of each domain to her. Thematic analysis is then required of the responses. Use of a maternity-specific tool alongside the EQ-5D-5L may have helped to capture a difference in postnatal experience, if one did exist.

Adverse effects of treatment

Maternal Postnatal Experience questionnaire data was missing for only 3 of 5717 participants (0.5%), suggesting that the occurrence of side effects did not affect completion of the questionnaire and that results relating to side effects are generalisable to other similar populations, as described above.

6.2 Practical problems encountered

Protocol/training issues

We found that randomisation repeatedly occurred too early; by protocol, randomisation was meant to occur when delivery was believed to be imminent (i.e. when the head was crowning), but in reality it often occurred when the woman was fully dilated and in the latter stages of pushing. This seemed to happen due to the clinical demands on midwives during the second stage of labour and the fact that labour wards are often short-staffed. Randomisation when the fetal head is crowning and delivery is truly imminent would require an additional member of staff to be summoned to collect the study drug, as the midwife looking after the patient would not be able to leave the labouring woman at that time. When developing the protocol, I felt that a Midwifery Care Assistant, a free doctor, or the shift midwife co-ordinator would be able to perform this role. In reality this was often not practical. "Early" randomisation should not have been a problem from a drug stability perspective; oxytocin can be stored up to 30°C for 3 months, Syntometrine can be stored up to 25°C for 2 months when protected from light, and carbetocin should be used "as soon as possible" when removed from the fridge (with no defined time period). However, "early" randomisation did result in occasional drug wastage and disturbance of the randomisation sequence. This occurred when participants were ultimately found not to be fully dilated, and the drug was therefore discarded and the next consecutively numbered drug retrieved when birth *was* imminent, as the protocol mandated that study drugs could not be put back in the fridge. This situation was particularly prevalent in the low-risk Birth Centre, where women are not always examined to confirm full dilatation before pushing is commenced. There were also times when "early" randomisation led to drug wastage if participants required a second stage caesarean section and were therefore no longer eligible to participate. We gained the support of senior shift co-ordinating midwives and Midwifery Care Assistants and appointed enthusiastic "IMox Champions" to try and facilitate the collecting of the study drug when delivery was imminent, and to promote the study protocol and Standard

Operating Procedures. We also used staff newsletters, training sessions and IMox noticeboards in labour ward staff coffee rooms to try and highlight the practical challenges which we were facing.

Another hurdle more frequently encountered in low-risk Birth Centres was the last-minute exclusion of participants, perhaps when staff perceived that Active Management of the Third Stage of Labour was no longer necessary after an otherwise uncomplicated labour. It seemed that participants were at times opting instead for physiological management of the third stage of their labour (resulting in withdrawal from the study), despite having previously voiced that they wanted an actively managed third stage as part of the trial. This was a difficult scenario to overcome as we were never truly able to pinpoint the origin of this deviation. It is possible that the "seed" for this scenario was sown during the consenting process (i.e. prospective participants were told that they could participate in the study if they still opted for active management after the birth of their baby, with these conversations occurring in an attempt to maximise participation in the study), or that this idea was suggested by the midwife caring for the participant in labour, or indeed that this idea was entirely due to the beliefs and wishes of the participant herself. This scenario also highlighted the real-life variation in clinical practice regarding management of the third stage of labour, and the reality of the "blurred line" between prophylaxis and treatment with uterotonic drugs. In low risk settings, there seems to sometimes be a tendency to opt for active management when the placenta takes longer than anticipated to deliver, or if unexpected bleeding occurs during physiological management. In clinical practice this is probably of little consequence, as oxytocin and Syntometrine can be used for both prophylaxis and treatment of PPH, and the timing of uterotonic administration (before or after delivery of the placenta) is not thought to influence the incidence of PPH(75). From a research perspective, the distinction between "prophylaxis" and "treatment" is important, when reporting outcomes. The potential blurring of this distinction in lower risk settings may have reduced the number of low-risk women included in the study and increased the risk of the "low-risk" women who did participate.

There was occasional confusion regarding the purpose of prophylactic uterotonic drugs. In clinical practice, I often hear staff describing prophylactic uterotonics as drugs "to help deliver the placenta", rather than drugs which optimise uterine tone and reduce overall risk of haemorrhage. As such, there were times when study participants were not randomised because birth and delivery of the placenta happened spontaneously in quick succession, and it was felt by the staff caring for the participant that the study drug was therefore no longer relevant. We were quick to pick up on this and were able to disseminate education through newsletters and inclusion of study "red flags" during the safety briefing report at the shift change meeting each morning. We also found that this trend, and other protocol deviations, were minimised when IMox research staff were present at these meetings to provide support and generally promote study awareness.

There was a higher than anticipated proportion of participants with a weighed blood loss totalling a multiple of 100ml (i.e. 500ml), and the mean blood loss in two arms was 500ml. While it is possible that these were all weighed estimates drawn from the meticulous weighing of all blood-soaked materials with subtraction of dry weights, it was perhaps more likely that there was an element of estimation involved in some of these cases. We worked hard to promote the importance of accurate weighing and the Standard Operating Procedure corresponding to this, throughout the study. We made money available for the purchase of additional weighing scales for each unit and found that the appointed IMox Champions often enjoyed taking on the role of "weighing-support".

Availability of the Interventional Medicinal Product

It was challenging to facilitate the constant availability of Interventional Medicinal Product at each participating unit. St Mary's Pharmaceutical Unit took an average of 2-3 months to blind, randomise and sign off each batch of ~1000 doses of the IMP, ready for dispatch to participating units. Each batch of IMP had the same expiry date printed on box label and ampoule label, and this matched the shortest expiry date of all the oxytocin, Syntometrine or carbetocin stock which had been blinded within that batch. I needed to ensure that participating units had enough IMP stock to last them

until the next batch was ready for dispatch, while also ensuring that stock at each site was allocated to participants before the stock expired. This required constant careful monitoring of recruitment rates and IMP stock levels at each participating site. When expiry dates drew near, and these were not matched by recruitment rates at a particular site, the temperature-controlled transfer of stock between sites was arranged. This was kept to a minimum due to the associated logistics and cost.

St Mary's Pharmaceutical Unit directly sourced oxytocin and Syntometrine from their own suppliers and charged us for this as part of their overall costs. Carbetocin was supplied by Ferring Pharmaceuticals and sent directly to St Mary's Pharmaceutical Unit when requested, up to an agreed total of 2095 doses (as per initial sample size calculation and agreed with Ferring Pharmaceuticals). This was complicated by a change in the formulation of all global carbetocin production, to a heat-stable version, from August 2015. Plans for this were not known when this study was first conceived and when I wrote the protocol and sought ethical and MHRA approval for the study. Although heat-stable carbetocin only differed from non-heat stable carbetocin only in its excipients(94), we did not want to change the formulation of the carbetocin used in the study. Possible differences in the shape and colour of the new heat-stable carbetocin ampoule would potentially jeopardise the process of IMP blinding, and a change in formulation could have introduced bias and affected the integrity of the trial (and future systematic reviews in which trial results would be included) and provoked criticism from trial reviewers. The latest expiry date of non-heat stable carbetocin was initially projected to be July 2016. I projected that the trial could not finish recruiting by this deadline. This then meant that carbetocin stock which had initially been sent to St Mary's Pharmaceutical Unit had to be returned to Ferring (alongside stringent documentation to declare that temperature monitoring had been consistent) and swapped for stock with a later expiry date. This process was then required again when the study did not meet its first anticipated recruitment end date. Ultimately we were able to roll the study out to an additional participating site (Nottingham University Hospitals) and increase recruitment rates across all sites, to conclude the

study before the end-August 2018 expiry date of the last batch of non-heat stable carbetocin which was available to us.

The 2-8°C cold-storage requirements of the IMP also proved challenging. Each fridge had an integrated minimum/maximum reading thermometer which was checked daily by the research team and each time the fridge was opened by clinical staff, and a data logging thermometer which kept a constant record of internal fridge temperatures. The fridges were occasionally sent into "quarantine" (during which time participants could not be randomised) when the integrated fridge thermometer showed the temperature to have gone out of temperature range, and this quarantine lasted until fridge data logger readings could be downloaded and reviewed by the Clinical Trials Pharmacy team at the corresponding site. There were times when all the IMP stock held within the labour ward fridges needed to be destroyed due to temperature deviations. We were able to troubleshoot this by holding most of the stock within the Clinical Trials Pharmacy of each hospital, and restocking labour ward study fridges only when necessary. One site also needed to change the location of their fridge several times as the ambient temperature in the room where the fridge was kept was too high, and this was causing the fridge to go out of range due to frequent opening of the fridge door throughout the day. A further 251 doses of IMP needed to be destroyed at one site, after the delivery of this stock from St Mary's Pharmaceutical Unit did not occur at the time anticipated, and the doses were not immediately stored in the fridge on arrival.

Women wanting to participate in two consecutive pregnancies

As the study was open for recruitment for 3.5 years, we found that there was a small number of women who had given birth and participated in the study, who had a subsequent pregnancy and wished to participate again. Women seemed to strongly support the aims of the study, gain personal satisfaction from participating in research which would help women in future, and benefit from the additional time which the research midwives had to provide care and answer clinical queries. We debated this at length due to the potential for clustering and dependency within our sample. We

decided that these women could participate twice because they would comprise an exceedingly small proportion of the overall sample size, and because previous uterotonic use does not impact on the effectiveness of drugs or management of PPH in subsequent pregnancies. Demographics such as ethnicity and age (if she had not passed another birthday) may have been double counted, but others such as BMI, parity, gestational age and baby birth weight would most likely have been different, although not entirely independent of previous values.

6.3 What I would do differently in future similar studies

Protocol

If I were to repeat this study, I would consider changing the primary outcome measure to PPH >500ml. This is potentially more clinically relevant than the use of additional uterotonic drugs and has a greater impact on the woman giving birth and her subsequent clinical care. The use of additional uterotonic drugs was chosen as the primary outcome measure as it is more directly reflective of the uterotonic power of the prophylactic uterotonic drug. However, as >70% PPH results from uterine atony(29), the effectiveness of the uterotonic drug would still be captured.

The inclusion of antepartum haemorrhage as an exclusion criterion was probably unnecessary. The occurrence of antepartum haemorrhage is not infrequent, and the sample size was large enough to have balanced this PPH risk factor between arms. In retrospect, it seems unjust to have excluded women who had experienced an intrauterine fetal death in their current pregnancy. This decision was made on advice of the ethics committee, but in future I would dispute this view. These women may still go on to experience PPH, and should be given equal opportunity to participate in research.

In future, I would consider using a second tool such as the Mother-Generated-Index to assess health-related quality of life, alongside the EQ-5D-5L. Although this may be more burdensome for the participant, the tool itself is short and quick to complete, and its feasibility and acceptability in the

context of a RCT has previously been assessed(164). Such a tool may also be more appropriate for capturing health-related quality of life over such a short period of time. Use of the Mother-Generated-Index would allow for subjective evaluation of the individual's experience, while also generating a single Quality of Life score which could be compared across groups. This tool does, however, have the drawback of not being valued by society's preferences. As such, it would not be possible to generate QALYs to allow comparison across treatments and conditions not measured by the Mother-Generated-Index.

I would also consider integrating the collection of costs, to allow for a more succinct health economic evaluation if this were to be required. These could be captured as part of the Case Report Form (direct medical costs; equipment use, staffing, drug use) and as part of a postnatal follow up log kept by participants for the first two weeks (number of community midwife and health visitor visits and time taken, interactions with GP, re-attendances or communications with the hospital). The value of this would need to be balanced against the additional burden of time which it would place on those completing the Case Report Forms and logs.

As a Core Outcome Set for use in trials assessing prevention and treatment of PPH has now been published(14) it would be important to ensure the inclusion of all recommended outcomes in any similar study in future. This trial would therefore need to collect additional data regarding shock and breastfeeding rates.

Resources

This study was run on a small budget. With more funding we could have made some noteworthy improvements. The use of calibrated under-buttock drapes, placed after the birth of the baby, may have helped to reduce the potential inadvertent contamination of blood-soaked materials with liquor. Although the use of these has not been shown to improve clinical outcomes(53), there is some evidence of improved accuracy with their use(165). The inclusion of an additional study fridge in the Birth Centre at Southmead Hospital may have reduced the number of "early" randomisations;

staff would not have had as far to travel to collect the study drug and they may have felt more able to wait until birth was truly imminent. An additional fridge in this location may also have allowed Birth Centre staff to feel more ownership of the study.

We GCP trained a cohort of research-enthusiastic community midwives, who then tried to consent women alongside conducting their routine clinical work. The impact of this was limited by the time pressures which community midwives are already under in their community clinics. Ideally, we would have had research-specific midwives based in the community at each participating site, who could have attended routine 36-week antenatal clinic appointments to consent interested patients. This together with the inclusion of more low-risk birth centres would have helped to reduce the proportion of higher risk participants with an induced labour and may have helped to further increase the external validity of our study.

Other

In future I would aim to increase Patient and Public Involvement further. Lay members of the Southmead Hospital Maternity Service User Panel were involved in the development of early protocols, but the study would have benefited further from their inclusion in the Trial Steering Committee.

We do not have any data relating to the numbers of patients approached for participation. When participants were withdrawn from the study, reasons for withdrawal were kept within site files at each hospital, but not uploaded to the main database. Better record keeping of each prospective participant's journey in future would help the construction of CONSORT diagrams and inform recruitment strategies in future work.

Chapter 7 :

Impact of this thesis

This concluding chapter summarises the impact of this thesis both in a wider context, and on me personally.

7.1 Wider impact of this thesis

The IMox Study is the first three-armed randomised control trial to directly compare the use of prophylactic intramuscular oxytocin, Syntometrine and carbetocin after vaginal birth. It is also one of the biggest trials of prophylactic uterotonic drugs to have taken place to date. PPH prevention is currently an active area of research and The IMox Study complements other recently published works focussing on this topic, including The CHAMPION Study(102) and the Cochrane Network Meta-Analysis(104). As carbetocin is now of heat-stable in formulation, it is becoming increasingly relevant in a developing world context. The IMox Study results were not yet published when the World Health Organisation updated its guideline "Uterotonics for the Prevention of Post Partum Haemorrhage" in December 2018, but conclusions from The IMox Study do support the updated recommendation that carbetocin is a suitable uterotonic for PPH prevention (in contexts where its cost is comparable to other effective uterotonics)(155). The IMox Study findings will be included in future meta-analyses of prophylactic uterotonics for the prevention of PPH. It will most likely also feature in evidence considered when the Royal College of Obstetricians and Gynaecologists soon starts work on an update of its Greentop Guideline "Prevention and Management of Postpartum Haemorrhage", and I am especially proud to have been invited to join this working party.

Regionally, there has been a lasting impact from this body of work. The weighing of blood loss is now more commonplace in obstetric settings. It seems that doing so routinely for the IMox Study may have highlighted the inaccuracy of visually estimated blood loss, and acted in effect as a "pilot" for the introduction of the routine weighing of blood loss; visual aids which were created for the study

to list dry weights of locally used swabs and drapes are still in use, staff have become quick at performing these calculations and seem more comfortable doing so, and the task of weighing blood loss now seems to have been routinely adopted by Operating Department Practitioners in theatre and midwives/midwifery care assistants in delivery rooms.

This was the first multi-centre Clinical Trial of an Investigational Medicinal Product in obstetrics within our region. I believe it will have strengthened our Southwest Obstetric Network and demonstrated the power of our collective working. New working relationships have been forged, and this study will hopefully pave the way for more multi-centre research in future. There is now also a cohort of Good Clinical Practice-trained Obstetrics and Gynaecology doctors working across the Deanery, who have benefited from their first-hand exposure to a randomised control trial, and who may be able to help facilitate the delivery of further research. The IMox Study also helped to create more roles for midwives working in research across participating hospitals, partly because it was an NIHR Portfolio study and it had the support of the West of England Clinical Research Network. Many of these midwives have continued to work in research alongside their clinical work. This has helped to bring research knowledge and opportunity to the "shop floor" more, with the ultimate benefit of increasing patient access to research participation.

7.2 Personal impact and learning

Before taking time "Out of Programme for Research", I had not taken a leading role in any project of this scale before. I've learnt a great deal about leadership having built our team from the outset and by acting as the trial co-ordinator until I went off on my first period of maternity leave. Part of my learning, which is relevant to the rest of my career and life generally, is that one person can't do everything. As my first period of maternity leave approached I realised that I was taking on responsibility for the writing of all documentation, the management of stock and expiry dates across

sites, the organisation of training and the liaising and set-up of new recruiting sites. I was quite methodical and particular about the way in which I was co-ordinating these activities and took great pride in the study and its progress; it truly felt like my "first baby". As the date of my first maternity leave approached, it struck me that I soon needed to hand these tasks over and that it was important to have everything clearly documented to facilitate this. It also later struck me later once I was on maternity leave and everything was continuing without me, that different people might manage projects in different ways, and that this is ok. This learning is pertinent to my future career as a consultant too; no clinical service should be reliant on just one person, as any individual's time away from work (for illness, injury, maternity leave or any other reasons) should not affect service provision.

I now also have a much greater appreciation of the work that goes into every shred of evidence on which we base our clinical practice. Looking back at my initial interview for my research post with the intention of splitting my two years of research between Bristol and Zimbabwe, I realise how naïve these plans were. I now appreciate how many hurdles are involved in the development and running of a randomised control trial including the creation of protocols and Standard Operating Procedures, grant applications, ethical and MHRA approvals, online registries, staffing appointments and lead in times for contracts starting, the complex logistics of blinding/randomising/distributing an Interventional Medicinal Product, and the nuances of departmental set up in different units meaning that one model may need to be applied differently in different settings. I now also appreciate how long it can take for new drugs to be evaluated; the original paper regarding the pharmacological properties of carbetocin dates back to 1992!

I feel that my research experience has allowed me to mature as a clinician. My experiences dealing with cold-chain storage, expiry dates and stock levels have given me more of an appreciation of the challenges which other professionals face "behind the scenes" in my daily NHS work. The quantity

and meticulousness of paperwork which is required in the Pharmaceutical Industry for a Qualified Person to be able to sign off a batch of drugs for use in clinical trials or clinical practice, is something which I may never have otherwise encountered. I now also feel more driven to understand the evidence behind the medicine that I practice, both out of a sense of duty to the patients in my care, and out of respect for the researchers who invested their time and energy searching for answers to the clinical questions which remain. I previously, perhaps subconsciously, felt that the reading of papers and interpretation of evidence was for only for "true" academics, but now feel much more equipped and confident when critiquing and applying evidence. I've come to understand that research questions are very specific, and that the application of evidence to real-life scenarios requires careful consideration of the exact hypothesis which was tested and the external validity of that work.

As researchers, we probably all aspire to create the perfect study which categorically answers the question before us and discovers the "truth" with the greatest possible degree of certainty. I now realise that practical matters often shape what is actually possible; finances, resources, time constraints and setting amongst other factors. Having nurtured one randomised control trial from conception to completion, I also realise that every methodological decision which is made along the way has potential implications for the way in which the research is ultimately reviewed and received. Finally, I've learnt what a collaborative effort research is. I have been able to draw many parallels between my clinical and research "lives" over the last eight years. I was always drawn to Obstetrics and Gynaecology for its culture of close multi-professional teamworking and the importance which is placed on good communication and collaboration. The same can be said for my experience of research so far. The IMox Study would never have happened without the amazing individuals who created and shared the journey with me – to them I say a final humble "thank you".

References

1. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323-33.

2. McDonald S, Abbott JM, Higgins SP. Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour. Cochrane Database Syst Rev. 2004;2004(1):Cd000201.

3. van der Nelson HA, Draycott T, Siassakos D, Yau CWH, Hatswell AJ. Carbetocin versus oxytocin for prevention of post-partum haemorrhage at caesarean section in the United Kingdom: An economic impact analysis. Eur J Obstet Gynecol Reprod Biol. 2017;210:286-91.

4. Merriel A, van der Nelson H, Merriel S, Bennett J, Donald F, Draycott T, et al. Identifying Deteriorating Patients Through Multidisciplinary Team Training. Am J Med Qual. 2016;31(6):589-95.

5. Al Wattar BH, Tamblyn JA, Parry-Smith W, Prior M, Van Der Nelson H. Management of obstetric postpartum hemorrhage: a national service evaluation of current practice in the UK. Risk Manag Healthc Policy. 2017;10:1-6.

6. van der Nelson H, O'Brien S, Lenguerrand E, Marques E, Alvarez M, Mayer M, et al. Intramuscular oxytocin versus oxytocin/ergometrine versus carbetocin for prevention of primary postpartum haemorrhage after vaginal birth: study protocol for a randomised controlled trial (the IMox study). Trials. 2019;20(1):4.

7. van der Nelson H, O'Brien S, Burnard S, Mayer M, Alvarez M, Knowlden J, et al. Intramuscular oxytocin versus Syntometrine(®) versus carbetocin for prevention of primary postpartum haemorrhage after vaginal birth: a randomised double-blinded clinical trial of effectiveness, side effects and quality of life. BJOG. 2021;128(7):1236-46.

8. World Health Organization. The Prevention and management of postpartum haemorrhage : report of a technical working group, Geneva, 3-6 July, 1989 [internet]. Geneva: World Health Organization; 1990. Available from: http://apps.who.int/iris/handle/10665/61409

9. Kerr RS, Weeks AD. Postpartum haemorrhage: a single definition is no longer enough. BJOG. 2017;124(5):723-6.

10. Hamm RF, Wang EY, Bastek JA, Srinivas SK. Assessing reVITALize: Should the Definition of Postpartum Hemorrhage Differ by Mode of Delivery? Am J Perinatol. 2017;34(5):503-7.

11. Royal College of Obstetricians and Gynaecologists. Greentop Guideline No. 52: Prevention and Management of Post Partum Haemorrhage [internet]. London: RCOG; 2009. Now archived but available upon request via archives@rcog.org.uk

12. World Health Organisation. WHO recommendations for the prevention and treatment of postpartum haemorrhage [internet]. Geneva: World Health Organization; 2012. Available from: https://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548502/en/

13. Alfaifel N. Postpartum haemorrhage: new insights from published trials and the development of novel management options [PhD thesiss accessed online] University of Liverpool; 2015. Available from: https://livrepository.liverpool.ac.uk/2015019/2/AflaifelNas.April%202015.2015019.pdf

14. Meher S, Cuthbert A, Kirkham JJ, Williamson P, Abalos E, Aflaifel N, et al. Core outcome sets for prevention and treatment of postpartum haemorrhage: an international Delphi consensus study. BJOG. 2019;126(1):83-93.

15. World Health Organisation. Chapter 6.16 Post Partum Haemorrhage [internet] Available from: https://www.who.int/medicines/areas/priority_medicines/Ch6_16PPH.pdf?ua=1.

16. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. Bjog. 2011;118 Suppl 1:1-203.

17. Fukami T, Koga H, Goto M, Ando M, Matsuoka S, Tohyama A, et al. Incidence and risk factors for postpartum hemorrhage among transvaginal deliveries at a tertiary perinatal medical facility in Japan. PLoS One. 2019;14(1):e0208873.

18. Ford JB, Patterson JA, Seeho SKM, Roberts CL. Trends and outcomes of postpartum haemorrhage, 2003-2011. BMC Pregnancy and Childbirth. 2015;15(1):334.

19. Sosa CG, Althabe F, Belizán JM, Buekens P. Risk factors for postpartum hemorrhage in vaginal deliveries in a Latin-American population. Obstet Gynecol. 2009;113(6):1313-9.

20. Carroli G, Cuesta C, Abalos E, Gulmezoglu AM. Epidemiology of postpartum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynaecol. 2008;22(6):999-1012.

21. Ngwenya S. Postpartum hemorrhage: incidence, risk factors, and outcomes in a low-resource setting. Int J Womens Health. 2016;8:647-50.

22. Knight M, Callaghan WM, Berg C, Alexander S, Bouvier-Colle M-H, Ford JB, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. BMC Pregnancy and Childbirth. 2009;9(1):55.

23. Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. Anesth Analg. 2010;110(5):1368-73.

24. Cameron CA, Roberts CL, Olive EC, Ford JB, Fischer WE. Trends in postpartum haemorrhage. Aust N Z J Public Health. 2006;30(2):151-6.

25. Lutomski JE, Byrne BM, Devane D, Greene RA. Increasing trends in atonic postpartum haemorrhage in Ireland: an 11-year population-based cohort study. Bjog. 2012;119(3):306-14.

26. Kramer MS, Dahhou M, Vallerand D, Liston R, Joseph KS. Risk Factors for Postpartum Hemorrhage: Can We Explain the Recent Temporal Increase? Journal of Obstetrics and Gynaecology Canada. 2011;33(8):810-9.

27. Weeks A. The prevention and treatment of postpartum haemorrhage: what do we know, and where do we go to next? BJOG. 2015;122(2):202-10.

28. Knight M. Peripartum hysterectomy in the UK: management and outcomes of the associated haemorrhage. BJOG. 2007;114(11):1380-7.

29. Oyelese Y, Ananth CV. Postpartum hemorrhage: epidemiology, risk factors, and causes. Clin Obstet Gynecol. 2010;53(1):147-56.

30. Edwards HM. Aetiology and treatment of severe postpartum haemorrhage. Dan Med J. 2018;65(3).

31. Royal College of Obstetricians and Gynaecologists. Greentop Guideline No. 52: Prevention and Management of Postpartum Haemorrhage [internet]. London: RCOG; 2016. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg52/

32. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 76, October 2006: postpartum hemorrhage. Obstet Gynecol. 2006;108(4):1039-47.

33. National Institute for Health and Care Excellence. Clinical Guideline CG190: Intrapartum Care for healthy women and babies [internet]. Published December 2014, last updated February 2017. Available from: https://www.nice.org.uk/guidance/cg190

34. National Collaborating Centre for Women's and Children's Health (UK). Antenatal care: Routine Care for the Healthy Pregnant Women. London: RCOG Press; 2008 Mar. PMID: 21370514

35. Fuchs K, Peretz BA, Marcovici R, Paldi E, Timor-Tritsh I. The "grand multipara"--is it a problem? A review of 5785 cases. Int J Gynaecol Obstet. 1985;23(4):321-6.

36. Al-Shaikh GK, Ibrahim GH, Fayed AA, Al-Mandeel H. Grand multiparity and the possible risk of adverse maternal and neonatal outcomes: a dilemma to be deciphered. BMC Pregnancy and Childbirth. 2017;17(1):310.

37. Tsu VD. Postpartum haemorrhage in Zimbabwe: a risk factor analysis. Br J Obstet Gynaecol. 1993;100(4):327-33.

38. Alsammani MA, Jafer AM, Khieri SA, Ali AO, Shaaeldin MA. Effect of Grand Multiparity on Pregnancy Outcomes in Women Under 35 Years of Age: a Comparative Study. Med Arch. 2019;73(2):92-6.

39. Lao TT, Sahota DS, Cheng YK, Law LW, Leung TY. Advanced maternal age and postpartum hemorrhage - risk factor or red herring? J Matern Fetal Neonatal Med. 2014;27(3):243-6.

40. Blomberg M. Maternal obesity and risk of postpartum hemorrhage. Obstet Gynecol. 2011;118(3):561-8.

41. Fyfe EM, Thompson JM, Anderson NH, Groom KM, McCowan LM. Maternal obesity and postpartum haemorrhage after vaginal and caesarean delivery among nulliparous women at term: a retrospective cohort study. BMC Pregnancy Childbirth. 2012;12:112.

42. Scott-Pillai R, Spence D, Cardwell CR, Hunter A, Holmes VA. The impact of body mass index on maternal and neonatal outcomes: a retrospective study in a UK obstetric population, 2004-2011. BJOG. 2013;120(8):932-9.

43. Carvajal JA, Oporto JI. The Myometrium in Pregnant Women with Obesity. Curr Vasc Pharmacol. 2021;19(2):193-200.

44. Nair M, Choudhury MK, Choudhury SS, Kakoty SD, Sarma UC, Webster P, et al. Association between maternal anaemia and pregnancy outcomes: a cohort study in Assam, India. BMJ global health. 2016;1(1):e000026-e.

45. Hancock A, Weeks AD, Lavender DT. Is accurate and reliable blood loss estimation the 'crucial step' in early detection of postpartum haemorrhage: an integrative review of the literature. BMC Pregnancy Childbirth. 2015;15:230.

46. Bose P, Regan F, Paterson-Brown S. Improving the accuracy of estimated blood loss at obstetric haemorrhage using clinical reconstructions. BJOG. 2006;113(8):919-24.

47. Duthie SJ, Ghosh A, Ng A, Ho PC. Intra-operative blood loss during elective lower segment caesarean section. Br J Obstet Gynaecol. 1992;99(5):364-7.

48. Glover P. Blood loss at delivery: how accurate is your estimation? Aust J Midwifery. 2003;16(2):21-4.

49. Al-Kadri HM, Dahlawi H, Al Airan M, Elsherif E, Tawfeeq N, Mokhele Y, et al. Effect of education and clinical assessment on the accuracy of post partum blood loss estimation. BMC Pregnancy and Childbirth. 2014;14(1):110.

50. Dunlop K, Eckler R, Rosen A, Komorowski A, Murphy K, D'Souza R. Reliability of Visual Estimation of Intrapartum Blood Loss [10Q]. Obstetrics & Gynecology. 2017;129(5):175S-6S.

51. Dildy GA, 3rd, Paine AR, George NC, Velasco C. Estimating blood loss: can teaching significantly improve visual estimation? Obstet Gynecol. 2004;104(3):601-6.

52. Maslovitz S, Barkai G, Lessing JB, Ziv A, Many A. Improved accuracy of postpartum blood loss estimation as assessed by simulation. Acta Obstet Gynecol Scand. 2008;87(9):929-34.

53. Diaz V, Abalos E, Carroli G. Methods for blood loss estimation after vaginal birth. Cochrane Database Syst Rev. 2018;9(9):Cd010980.

54. Pacagnella RC, Souza JP, Durocher J, Perel P, Blum J, Winikoff B, et al. A systematic review of the relationship between blood loss and clinical signs. PLoS One. 2013;8(3):e57594.

55. Kim P, Swain JE. Sad dads: paternal postpartum depression. Psychiatry (Edgmont). 2007;4(2):35-47.

56. Carroll M, Daly D, Begley CM. The prevalence of women's emotional and physical health problems following a postpartum haemorrhage: a systematic review. BMC Pregnancy and Childbirth. 2016;16(1):261.

57. Thompson JF, Roberts CL, Ellwood DA. Emotional and physical health outcomes after significant primary post-partum haemorrhage (PPH): a multicentre cohort study. Aust N Z J Obstet Gynaecol. 2011;51(4):365-71.

58. Parry-Smith W, Okoth K, Subramanian A, Gokhale KM, Chandan JS, Humpston C, et al. Postpartum haemorrhage and risk of mental ill health: A population-based longitudinal study using linked primary and secondary care databases. J Psychiatr Res. 2021;137:419-25.

59. Sentilhes L, Gromez A, Clavier E, Resch B, Descamps P, Marpeau L. Long-term psychological impact of severe postpartum hemorrhage. Acta Obstet Gynecol Scand. 2011;90(6):615-20.

60. Prick BW, Bijlenga D, Jansen AJ, Boers KE, Scherjon SA, Koopmans CM, et al. Determinants of health-related quality of life in the postpartum period after obstetric complications. Eur J Obstet Gynecol Reprod Biol. 2015;185:88-95.

61. Wilson N, Lee JJ, Bei B. Postpartum fatigue and depression: A systematic review and meta-analysis. J Affect Disord. 2019;246:224-33.

62. Prick BW, Jansen AJ, Steegers EA, Hop WC, Essink-Bot ML, Uyl-de Groot CA, et al. Transfusion policy after severe postpartum haemorrhage: a randomised non-inferiority trial. BJOG. 2014;121(8):1005-14.

63. Jansen AJ, Duvekot JJ, Hop WC, Essink-Bot ML, Beckers EA, Karsdorp VH, et al. New insights into fatigue and health-related quality of life after delivery. Acta Obstet Gynecol Scand. 2007;86(5):579-84.

64. Jansen AJ, Essink-Bot ML, Duvekot JJ, van Rhenen DJ. Psychometric evaluation of health-related quality of life measures in women after different types of delivery. J Psychosom Res. 2007;63(3):275-81.

65. Corwin EJ, Murray-Kolb LE, Beard JL. Low hemoglobin level is a risk factor for postpartum depression. J Nutr. 2003;133(12):4139-42.

66. Thompson JF, Heal LJ, Roberts CL, Ellwood DA. Women's breastfeeding experiences following a significant primary postpartum haemorrhage: A multicentre cohort study. Int Breastfeed J. 2010;5:5.

67. Prendiville WJ, Harding JE, Elbourne DR, Stirrat GM. The Bristol third stage trial: active versus physiological management of third stage of labour. BMJ (Clinical research ed). 1988;297(6659):1295-300.

68. Rogers J, Wood J, McCandlish R, Ayers S, Truesdale A, Elbourne D. Active versus expectant management of third stage of labour: the Hinchingbrooke randomised controlled trial. Lancet. 1998;351(9104):693-9.

69. Bimbashi A, Ndoni E, Dokle A, Duley L. Care during the third stage of labour: obstetricians views and practice in an Albanian maternity hospital. BMC Pregnancy and Childbirth. 2010;10(1):4.

70. Oladapo OT, Akinola OI, Fawole AO, Adeyemi AS, Adegbola O, Loto OM, et al. Active management of third stage of labor: evidence versus practice. Acta Obstet Gynecol Scand. 2009;88(11):1252-60.

71. Rogers C, Harman J, Selo-Ojeme D. The management of the third stage of labour—A national survey of current practice. British Journal of Midwifery. 2012;20(12):850-7.

72. Begley CM, Gyte GML, Devane D, McGuire W, Weeks A, Biesty LM. Active versus expectant management for women in the third stage of labour. Cochrane Database of Systematic Reviews. 2019(2).

73. Aflaifel N, Weeks AD. Active management of the third stage of labour. Bmj. 2012;345:e4546.

74. Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. 2018;12(12):Cd011689.

75. Soltani H, Hutchon DR, Poulose TA. Timing of prophylactic uterotonics for the third stage of labour after vaginal birth. Cochrane Database Syst Rev. 2010(8):Cd006173.

76. Westhoff G, Cotter AM, Tolosa JE. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev. 2013(10):Cd001808.

77. Sheldon WR, Durocher J, Winikoff B, Blum J, Trussell J. How effective are the components of active management of the third stage of labor? BMC Pregnancy Childbirth. 2013;13:46.

78. Adnan N, Conlan-Trant R, McCormick C, Boland F, Murphy DJ. Intramuscular versus intravenous oxytocin to prevent postpartum haemorrhage at vaginal delivery: randomised controlled trial. BMJ. 2018;362:k3546.

79. Oladapo OT, Okusanya BO, Abalos E, Gallos ID, Papadopoulou A. Intravenous versus intramuscular prophylactic oxytocin for the third stage of labour. Cochrane Database Syst Rev. 2020;11:Cd009332.

80. McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database Syst Rev. 2013;2013(7):Cd004074.

81. Farrar D, Airey R, Law GR, Tuffnell D, Cattle B, Duley L. Measuring placental transfusion for term births: weighing babies with cord intact. BJOG. 2011;118(1):70-5.

82. World Health Organization. Guideline: Delayed umbilical cord clamping for improved maternal and infant health and nutrition outcomes [internet]. Geneva: WHO; 2014. Available from: https://apps.who.int/nutrition/publications/guidelines/cord_clamping/en/index.html

83. Royal College of Obstetricians and Gynaecologists. Scientific Impact Paper No. 14: Clamping of the Umbilical Cord and Placental Transfusion [internet]. London: RCOG; 2015. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/sip14/

84. Gülmezoglu AM, Lumbiganon P, Landoulsi S, Widmer M, Abdel-Aleem H, Festin M, et al. Active management of the third stage of labour with and without controlled cord traction: a randomised, controlled, non-inferiority trial. Lancet. 2012;379(9827):1721-7.

85. Hofmeyr GJ, Mshweshwe NT, Gülmezoglu AM. Controlled cord traction for the third stage of labour. Cochrane Database Syst Rev. 2015;1(1):Cd008020.

86. Dale HH. On some physiological actions of ergot. J Physiol. 1906;34(3):163-206.

87. Intrapharm. Summary of Product Characteristics for Oxytocin 10IU/ml Solution. updated 06/07/2018. Available from: ttps://www.medicines.org.uk/emc/medicine/30427#gref.

88. Torloni MR, Gomes Freitas C, Kartoglu UH, Metin Gülmezoglu A, Widmer M. Quality of oxytocin available in low- and middle-income countries: a systematic review of the literature. BJOG. 2016;123(13):2076-86.

89. Dunn PM. John Chassar Moir (1900–1977) and the discovery of ergometrine. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2002;87(2):F152.

90. Moir C. Clinical Experiences with the new alkaloid, ergometrine. Br Med J. 1936;2(3955):799-801.

91. Alliance. Summary of Product Characteristics for Syntometrine 500micrograms/5 IU Solution for Injection (Ampoules) [updated 06/12/2021]. Available from: https://www.medicines.org.uk/emc/product/865/smpc#gref.

92. Barron G. Claviceps purpurea - cause of Ergot of Rye 2013 Available from University of Guelph website at: http://hdl.handle.net/10214/5725.

93. Ferring Pharmaceuticals Ltd. Summary of Product Characteristics for Pabal 100 micrograms in 1ml solution for injection [updated 20/12/2019]. Available from: https://www.medicines.org.uk/emc/product/172/smpc#gref.

94. Widmer M, Piaggio G, Abdel-Aleem H, Carroli G, Chong Y-S, Coomarasamy A, et al. Room temperature stable carbetocin for the prevention of postpartum haemorrhage during the third stage of labour in women delivering vaginally: study protocol for a randomized controlled trial. Trials. 2016;17(1):143-.

95. Pfizer Limited. Summary of Product Characteristics for Cytotec 200mcg Tablets [updated 26/04/2021]. Available from: https://www.medicines.org.uk/emc/product/1642/smpc#gref.

96. Oladapo OT, Okusanya BO, Abalos E, Gallos ID, Papadopoulou A. Intravenous versus intramuscular prophylactic oxytocin for the third stage of labour. Cochrane Database Syst Rev. 2020;11(11):Cd009332.

97. Oladapo OT, Okusanya BO, Abalos E, Gallos ID, Papadopoulou A. Intravenous versus intramuscular prophylactic oxytocin for reducing blood loss in the third stage of labour. Cochrane Database of Systematic Reviews. 2020(11).

98. Pinder AJ, Dresner M, Calow C, Shorten GD, O'Riordan J, Johnson R. Haemodynamic changes caused by oxytocin during caesarean section under spinal anaesthesia. Int J Obstet Anesth. 2002;11(3):156-9.

99. Salati JA, Leathersich SJ, Williams MJ, Cuthbert A, Tolosa JE. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. The Cochrane database of systematic reviews. 2019;4(4):CD001808-CD.

100. McDonald S, Abbott JM, Higgins SP. Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour. The Cochrane database of systematic reviews. 2004;2004(1):CD000201-CD.

101. Su LL, Chong YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012(2):Cd005457.

102. Widmer M, Piaggio G, Nguyen TMH, Osoti A, Owa OO, Misra S, et al. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. N Engl J Med. 2018;379(8):743-52.

103. Hofmeyr GJ, Gülmezoglu AM, Novikova N, Lawrie TA. Postpartum misoprostol for preventing maternal mortality and morbidity. Cochrane Database Syst Rev. 2013(7):Cd008982.

104. Gallos ID, Williams HM, Price MJ, Merriel A, Gee H, Lissauer D, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. 2018;4(4):Cd011689.

105. Sentilhes L, Goffinet F, Vayssière C, Deneux-Tharaux C. Comparison of postpartum haemorrhage guidelines: discrepancies underline our lack of knowledge. BJOG: An International Journal of Obstetrics & Gynaecology. 2017;124(5):718-22.

106. National Institute for Health and Care Excellence. NICE Guideline [NG192]: Caesarean Birth. Published March 20021. Available from: https://www.nice.org.uk/guidance/ng192.

107. Vogel JP, Williams M, Gallos I, Althabe F, Oladapo OT. WHO recommendations on uterotonics for postpartum haemorrhage prevention: what works, and which one? BMJ Glob Health. 2019;4(2):e001466.

108. Scott CA, Bewley S, Rudd A, Spark P, Kurinczuk JJ, Brocklehurst P, et al. Incidence, Risk Factors, Management, and Outcomes of Stroke in Pregnancy. Obstetrics & Gynecology. 2012;120(2 Part 1).

109. Farrar D, Tuffnell D, Airey R, Duley L. Care during the third stage of labour: A postal survey of UK midwives and obstetricians. BMC Pregnancy and Childbirth. 2010;10(1):23.

110. Redshaw M RR, Schroeder L, Puddicombe D, Macfarlane A, Newburn M, McCourt C, Sandall J, Silverton L and Marlow N. Mapping maternity care: the configuration of maternity care in England Birthplace in England research programme. Final report part 3: NIHR Service Delivery and Organisation programme; 2011 [Available from: https://www.researchgate.net/publication/241687293_Mapping_maternity_care_the_configuration_of_maternity_care_in_England_Birthplace_in_England_research_programme_Final_report_part_3.

111. Winter C, Macfarlane A, Deneux-Tharaux C, Zhang WH, Alexander S, Brocklehurst P, et al. Variations in policies for management of the third stage of labour and the immediate management of postpartum haemorrhage in Europe. BJOG : an international journal of obstetrics and gynaecology. 2007;114(7):845-54.

112. Fincham JE. Response rates and responsiveness for surveys, standards, and the Journal. Am J Pharm Educ. 2008;72(2):43-.

113. Nursing and Midwifery Council. Practising as a midwife in the UK: An overview of midwifery regulation [internet]. Updated February 2021. Available from: https://nmc.org.uk/news/news-and-updates/practising-midwife/

114. Legislation.gov.uk. The Human Medicines Regulations 2012. Schedule 17, Part 3: Exemptions from the restriction on administration of prescription only medicines [internet]/ Available from https://www.legislation.gov.uk/uksi/2012/1916/schedule/17/made

115. Attilakos G, Psaroudakis D, Ash J, Buchanan R, Winter C, Donald F, et al. Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomised trial. BJOG. 2010;117(8):929-36.

116. Royal College of Obstetricians and Gynaecologists. Clinical Governance Advice No. 6a: Obtaining Valid Consent to Participate in Perinatal Research Where Consent is Time Critical [internet]. London: RCOG; 2016. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/clinical-governance-advice-6a/

117. Bragg F, Cromwell D, Edozien L, Gurol-Urganci I, Mahmood T, Templeton A, et al. Variation in Rates of Cesarean Section Among English NHS Trusts After Accounting for Maternal and Clinical Risk: Cross-sectional Study. BMJ (Clinical research ed). 2010;341:c5065.

118. Fullerton G, Danielian PJ, Bhattacharya S. Outcomes of pregnancy following postpartum haemorrhage. BJOG. 2013;120(5):621-7.

119. Askar AA, Ismail MT, El-Ezz AA, Rabie NH. Carbetocin versus syntometrine in the management of third stage of labor following vaginal delivery. Arch Gynecol Obstet. 2011;284(6):1359-65.

120. Leung SW, Ng PS, Wong WY, Cheung TH. A randomised trial of carbetocin versus syntometrine in the management of the third stage of labour. Bjog. 2006;113(12):1459-64.

121. Nirmala K, Zainuddin AA, Ghani NA, Zulkifli S, Jamil MA. Carbetocin versus syntometrine in prevention of post-partum hemorrhage following vaginal delivery. J Obstet Gynaecol Res. 2009;35(1):48-54.

122. Su LL, Rauff M, Chan YH, Mohamad Suphan N, Lau TP, Biswas A, et al. Carbetocin versus syntometrine for the third stage of labour following vaginal delivery--a double-blind randomised controlled trial. Bjog. 2009;116(11):1461-6.

123. McDonald SJ, Prendiville WJ, Blair E. Randomised controlled trial of oxytocin alone versus oxytocin and ergometrine in active management of third stage of labour. Bmj. 1993;307(6913):1167-71.

124. Yuen PM, Chan NS, Yim SF, Chang AM. A randomised double blind comparison of Syntometrine and Syntocinon in the management of the third stage of labour. Br J Obstet Gynaecol. 1995;102(5):377-80.

125. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. Trials. 2011;12(1):106.

126. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.

127.Gov.uk Ministry of Housing, Communities and Local Government. National Statistics: English Indices of deprivation in 2015 [internet] Published 30 Septemnber 2015. Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015.

128. NHS Digital. NHS Maternity Statistics Hospital Maternity Activity, 2015-2016 [internet] Published 9 November 2016. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2015-16#:~:text=Key%20Facts,-%E2%80%A2&text=There%20were%20648%2C107%20deliveries%20in,per%20cent%20from%202014%2D15.&text=The%20number%20of%20deliveries%20for,to%2022%2C032%20in%202015%2D16.

129. Begley CM, Gyte GM, Devane D, McGuire W, Weeks A. Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev. 2011(11):Cd007412.

130. Middleton P, Shepherd E, Crowther CA. Induction of labour for improving birth outcomes for women at or beyond term. Cochrane Database of Systematic Reviews. 2018(5).

131. NHS Digital. NHS Maternity Statistics, England 2017-18 [internet]. Published 25 October 2018. Available from: https://digital/nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2017-18

132. Royal College of Obstetricians and Gynaecologists. Greentop Guideline Noo. 57: Reduced Fetal Movements [internet]. London:RCOG; 2011. Available from https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg57/

133. Khireddine I, Le Ray C, Dupont C, Rudigoz RC, Bouvier-Colle MH, Deneux-Tharaux C. Induction of labor and risk of postpartum hemorrhage in low risk parturients. PLoS One. 2013;8(1):e54858.

134. Stock SJ, Ferguson E, Duffy A, Ford I, Chalmers J, Norman JE. Outcomes of elective induction of labour compared with expectant management: population based study. BMJ : British Medical Journal. 2012;344:e2838.

135. Briley A, Seed PT, Tydeman G, Ballard H, Waterstone M, Sandall J, et al. Reporting errors, incidence and risk factors for postpartum haemorrhage and progression to severe PPH: a prospective observational study. BJOG. 2014;121(7):876-88.

136. Royal College of Obstetricians and Gynaecologists. Greentop Guideline No. 26: Assisted Vaginal Birth [internet]. London: RCOG; 2020. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg26/

137. Hawker L, Weeks A. Postpartum haemorrhage (PPH) rates in randomized trials of PPH prophylactic interventions and the effect of underlying participant PPH risk: a meta-analysis. BMC Pregnancy and Childbirth. 2020;20(1):107.

138. Meher S. How should we diagnose and assess the severity of PPH in clinical trials? Best Pract Res Clin Obstet Gynaecol. 2019;61:41-54.

139. Ahmadzia HK, Grotegut CA, James AH. A national update on rates of postpartum haemorrhage and related interventions. Blood Transfus. 2020;18(4):247-53.

140. Bell SF, Watkins A, John M, Macgillivray E, Kitchen TL, James D, et al. Incidence of postpartum haemorrhage defined by quantitative blood loss measurement: a national cohort. BMC Pregnancy and Childbirth. 2020;20(1):271.

141. Wei Q, Xu Y, Zhang L. Towards a universal definition of postpartum hemorrhage: retrospective analysis of Chinese women after vaginal delivery or cesarean section: A case-control study. Medicine (Baltimore). 2020;99(33):e21714.

142. Bryant A, Mhyre JM, Leffert LR, Hoban RA, Yakoob MY, Bateman BT. The association of maternal race and ethnicity and the risk of postpartum hemorrhage. Anesth Analg. 2012;115(5):1127-36.

143. Harvey SA, Lim E, Gandhi KR, Miyamura J, Nakagawa K. Racial-ethnic Disparities in Postpartum Hemorrhage in Native Hawaiians, Pacific Islanders, and Asians. Hawaii J Med Public Health. 2017;76(5):128-32.

144. Smith LA, Price N, Simonite V, Burns EE. Incidence of and risk factors for perineal trauma: a prospective observational study. BMC Pregnancy Childbirth. 2013;13:59.

145. Samuelsson E, Ladfors L, Lindblom BG, Hagberg H. A prospective observational study on tears during vaginal delivery: occurrences and risk factors. Acta Obstet Gynecol Scand. 2002;81(1):44-9.

146. Conti-Ramsden F, Knight M, Green M, Shennan AH, Chappell LC. Reducing maternal deaths from hypertensive disorders: learning from confidential inquiries. Bmj. 2019;364:l230.

147. Begley CM. A comparison of 'active' and 'physiological' management of the third stage of labour. Midwifery. 1990;6(1):3-17.

148. Wilson MJ, Wrench IJ. Cell salvage for vaginal delivery - is it time we considered it? Int J Obstet Anesth. 2015;24(2):97-9.

149. Lim G, Kotsis E, Zorn JM, Dalby PL, Ralph CJ, Waters JH. Cell salvage for postpartum haemorrhage during vaginal delivery: a case series. Blood transfusion = Trasfusione del sangue. 2018;16(6):498-501.

150. Sharma D. Golden hour of neonatal life: Need of the hour. Maternal Health, Neonatology and Perinatology. 2017;3(1):16.

151. Neczypor JL, Holley SL. Providing Evidence-Based Care During the Golden Hour. Nurs Womens Health. 2017;21(6):462-72.

152. British National Formulary (online): London: BMJ Group and Pharmaceutical Press; 2021. Available from: https://bnf.nice.org.uk/.

153. Jin X-H, Li D, Li X. Carbetocin vs oxytocin for prevention of postpartum hemorrhage after vaginal delivery: A meta-analysis. Medicine. 2019;98(47):e17911.

154. Hunter DJ, Schulz P, Wassenaar W. Effect of carbetocin, a long-acting oxytocin analog on the postpartum uterus. Clin Pharmacol Ther. 1992;52(1):60-7.

155. World Health Organization.. Uterotonics for the prevention of postpartum haemorrhage 2018 [internet] Available from: http://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1.

156. Ferring Pharmaceuticals. Ferring statement on subsidised pricing of heat-stable carbetocin for the prevention of postpartum haemorrhage in low- and lower-middle income countries [press release]. Published 18 March 2019. Available from: https://www.ferring.com/ferring-statement-on-subsidised-pricing-of-heat-stable-carbetocin-for-the-prevention-of-postpartum-haemorrhage-in-lower-middle-income-countries/

157. Weeks AD. Oxytocin is needed, but it is no magic bullet. Bjog. 2016;123(13):2086.

158. Rothwell PM. Factors that can affect the external validity of randomised controlled trials. PLoS Clin Trials. 2006;1(1):e9-e.

159. McNeil R. Changes to the migrant population of the South West of England 2013 [Available from: https://migrationobservatory.ox.ac.uk/press/changes-to-the-migrant-population-of-the-south-west-of-england/.

160. Bailey JM, Bell C, Zielinski R. Timing and Outcomes of an Indication-Only Use of Intravenous Cannulation During Spontaneous Labor. J Midwifery Womens Health. 2020;65(3):309-15.

161. Euroqol. EQ-5D-5L [Available from: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/.

162. Hill PD, Aldag JC, Hekel B, Riner G, Bloomfield P. Maternal Postpartum Quality of Life Questionnaire. J Nurs Meas. 2006;14(3):205-20.

163. Symon A, MacDonald A, Ruta D. Postnatal quality of life assessment: introducing the mother-generated index. Birth. 2002;29(1):40-6.

164. Symon A, Downe S, Finlayson KW, Knapp R, Diggle P, team St. The feasibility and acceptability of using the Mother-Generated Index (MGI) as a Patient Reported Outcome Measure in a randomised controlled trial of maternity care. BMC Medical Research Methodology. 2015;15(1):100.

165. Ambardekar S, Shochet T, Bracken H, Coyaji K, Winikoff B. Calibrated delivery drape versus indirect gravimetric technique for the measurement of blood loss after delivery: a randomized trial. BMC Pregnancy and Childbirth. 2014;14(1):276.

Appendices

Please stick hospital identification label here

CASE REPORT FORM

Participant ID: ___ ___ ___ ___

PART 1: Clinical staff to complete on admission to labour ward

Eligibility criteria (please tick) Note: women are only eligible for inclusion if all answers fall within unshaded boxes		
	YES	**NO**
At least 18 years of age at the time of baby's birth?		
Is the patient known to have epilepsy?		
Planned vaginal birth?		
Participant wishing to have active management of third stage of labour?		
Significant APH >50ml, or suspected or proven placental abruption?		
Platelet count known to be < 100 x 10^9/L? (Does not specifically have to be checked on admission, if previously normal)		
Intrauterine fetal death in this pregnancy?		
Would this woman accept blood products if required?		
Is there a known or suspected hypertensive disorder (essential hypertension, pregnancy induced hypertension, pre-eclampsia)?		
• Any single intrapartum systolic blood pressure ≥160mmHg • Any two consecutive intrapartum blood pressures of ≥140mmHg (systolic) or ≥90mmHg (diastolic) taken 30 minutes apart • Any participant who has not had their blood pressure checked in labour Note: if any doubt as to whether this woman should receive Syntometrine, she is not eligible to participate		
Any significant peripheral vascular disease, hepatic or cardiac disease?		
Any allergy or hypersensitivity to any of the active ingredients or excipients in Syntocinon, Syntometrine or Carbetocin, as listed in the Summary of Product Characteristics?		

Midwife sign when eligibility checked	**GCP trained doctor sign to confirm eligibility**
Name (PRINT): **Signature:** **Date:**	**Name (PRINT):** **Signature:** **Date:**

PART 2: Clinical staff to complete before participant leaves labour ward

DATE TODAY		
FORM COMPLETED BY	**NAME:** **DESIGNATION:**	**SIGNATURE:**
PARTICIPANT PHONE NR (for 2 week EQ-5D questionnaire follow up)		
Alternative phone number		

MATERNAL HISTORY		
Past history of PPH ≥500ml?	Yes	No

THIRD STAGE DETAILS		
Date and time IMox Study drug given	DATE:	TIME:
Time placenta delivered	TIME:	
Need for manual removal of placenta?	Yes	No

INTRAPARTUM EVENTS						
BLOOD LOSS						
Estimated (weighed) blood loss (EBL)	(ml)					
Was this a pool birth?	Yes	No				
(Blood loss associated with birth episode. If there is excessively heavy lochia within 24 hours of birth (ie: PPH on post natal ward), this should be weighed and added by research team in retrospect.)						
If >500ml, what was believed to be the main cause of this? (circle most appropriate)	Uterine atony	Perineal tear	Cervical tear	Uterine atony + tear	Not defined	
Any additional uterotonic drugs given?	Yes	No				
If yes, decision made by:	*Midwife*	*Midwife co-ordinator*	*SHO*	*ST3-5*	*ST6-7*	*Cons*

If yes, please list each additional uterotonic drug given and the order in which these were given (list multiple doses of the same drug, such as Hemobate, separately)	*Example: 40 unit Syntocinon infusion IV over 4hrs* 1. 2. 3. 4. 5. 6.		
Was tranexamic acid given?	Yes	No	
Were additional procedures needed to control bleeding?	Yes	No	
If yes, which additional procedures were needed to control bleeding (please circle all that apply)	Intrauterine balloon tamponade	Uterine compression suture (ie: B-Lynch)	Interventional radiology
	Hysterectomy	Other:	
Examination under anaesthetic required?	Yes	No	Required and already in theatre
TRANSFUSION REQUIREMENTS			
Did this participant receive any blood products?	Yes	No	
If yes, the number of units transfused, where appropriate			
Red blood cells	Number of units:		
Volume of cell salvaged blood returned to patient, if used	Volume (ml):		
Platelets	Number of units:		
Fresh Frozen Plasma	Number of units:		
Cryoprecipitate	Number of units:		

MATERNAL WELLBEING			
Any intrapartum vomiting?	Yes	No	
Any vomiting in the first two post natal hours?	Yes	No	
Any anti-emetic drugs given in the first two post natal hours?	Yes	No	
The following relate to blood pressure in the first two post natal hours:			
1 hour PN blood pressure: / mmHg	***2 hours PN blood pressure: / mmHg***		
Any *systolic* BP of 140mmHg or more in the first two post natal hours?	Yes	No	
If yes, what was the highest *systolic* BP recorded in this time?	mmHg		
Any *diastolic* BP of 90mmHg or more in the first two post natal hours?	Yes	No	
If yes, what was the highest diastolic BP recorded in this time?	mmHg		
Any systolic blood pressure under 90mmHg in the first two post natal hours?	Yes	No	
If yes, what was the lowest systolic BP recorded in this time?	mmHg		
OTHER INTRAPARTUM EVENTS			
Any intrapartum pyrexia >38.0 degrees Celsius?	Yes	No	
Any time spent in HDU/Recovery/ITU?	Yes	No	
If yes, document amount of time spent in each	Type of setting	Time spent there **(or write "N/A")**	
	HDU care on Labour Ward	(hours)	
	Recovery	(hours)	
	Intensive Care Unit	(days)	(hours)

SIDE EFFECTS REPORTED BY PARTICIPANT		
Have any of the following been voluntarily reported (do not specifically ask) by the participant anytime between birth and discharge from labour ward? **Please circle all which are relevant:**		
Nausea	Vomiting	Headache
Rash	Dizziness	Abdominal pain
Flushing	Chills	Feeling of warmth
Tremor	Metallic taste	Itching
Shortness of breath		

Time ready for discharge from Labour Ward (ie: ready but postnatal ward not able to accept)	**:**
Time actually discharged from Labour Ward	**:**

Has anything happened which you think might potentially be an adverse event? (ie: other medical occurrence or side effect etc)	
Yes	No
Brief description:	

PART 3: Demographics

<table>
<tr><th colspan="6">MATERNAL DEMOGRAPHICS</th></tr>
<tr><td>Maternal age</td><td colspan="5">(years)</td></tr>
<tr><td>BMI (booking)</td><td colspan="5"></td></tr>
<tr><td rowspan="3">Maternal ethnicity
(please circle)</td><td>White British</td><td>Black African</td><td>Bangladeshi</td><td colspan="2">Chinese</td></tr>
<tr><td>White Irish</td><td>Black Caribbean</td><td>Indian</td><td colspan="2">Any other Asian background</td></tr>
<tr><td>Any other white background</td><td>Any other black background</td><td>Pakistani</td><td colspan="2">Variety of mixed backgrounds</td></tr>
<tr><td>Gravidity and parity
(parity <u>before</u> current birth)</td><td colspan="2">Gravidity:</td><td colspan="3">Parity:</td></tr>
<tr><td>Onset of labour</td><td colspan="3">Spontaneous</td><td colspan="2">Induced</td></tr>
<tr><td rowspan="4">Length of labour</td><td>Stage of labour</td><td colspan="2">Hours</td><td colspan="2">Minutes</td></tr>
<tr><td>1st stage</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>2nd stage</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>3rd stage</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Gestation at birth</td><td colspan="5">Weeks: Days:</td></tr>
<tr><td>Date of baby’s birth</td><td colspan="5">__ __ / __ __ / __ __</td></tr>
<tr><td>Time of baby’s birth</td><td colspan="5">:</td></tr>
<tr><td>Birth weight
<u>(this should be documented in kilograms)</u></td><td colspan="5">__ . __ __ __ kg</td></tr>
<tr><td>Mode of birth (circle)</td><td colspan="5">Spontaneous vaginal birth
Instrumental birth
Spontaneous breech birth
Assisted breech birth</td></tr>
<tr><td rowspan="2">Perineal tears?</td><td>No tear</td><td colspan="2">Episiotomy</td><td colspan="2">1st degree</td></tr>
<tr><td>2nd degree</td><td colspan="2">3rd degree</td><td colspan="2">4th degree</td></tr>
<tr><td>Total length of post natal stay</td><td colspan="5">days</td></tr>
</table>

Maternal post-natal experience questionnaire

Please complete this questionnaire approximately 2 hours after your baby was born. If not possible, please make your answers relate to those first two hours. Thank you!

The date today is: _____

My baby was born at (time): _____

The time now is: _____

Participant ID (your midwife will fill this out for you): _____

Using a tick in the appropriate box, please indicate whether you have experienced any of the following in the first two hours since the birth of your baby, and how severe you feel this has been:

	NONE	MILD	MODERATE	SEVERE
Nausea (feeling sick)				
Vomiting (being sick)				
Headache				
Dizziness				
Abdominal pain (pain in your tummy)				
Other (please write in this box)				
Have any of the above symptoms affected your ability to bond with and/or care for your baby in	**YES / NO**			

these first few hours?			
IF YES, has the effect of each of these symptoms on your ability to bond with and/or care for your baby been:	**MILD**	**MODERATE**	**SEVERE**
Nausea (feeling sick)			
Vomiting (being sick)			
Headache			
Dizziness			
Abdominal pain (pain in your tummy)			
Other (please write in this box)			

Thank you very much for taking the time to fill this out.

Congratulations on the birth of your baby!

Health Questionnaire

English version for the UK

Participant Name	
Participant ID	
Timing (circle)	Antenatal / Day 1 / Day 14
Dear participant: If completing this questionnaire by post, please also fill in the two boxes below:	
Date of completion:	
Did you receive a blood transfusion after the birth of your baby?	Yes / No

IMox EQ-5D-5L_version 2_16/7/15

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

We would like to know how good or bad your health is TODAY.

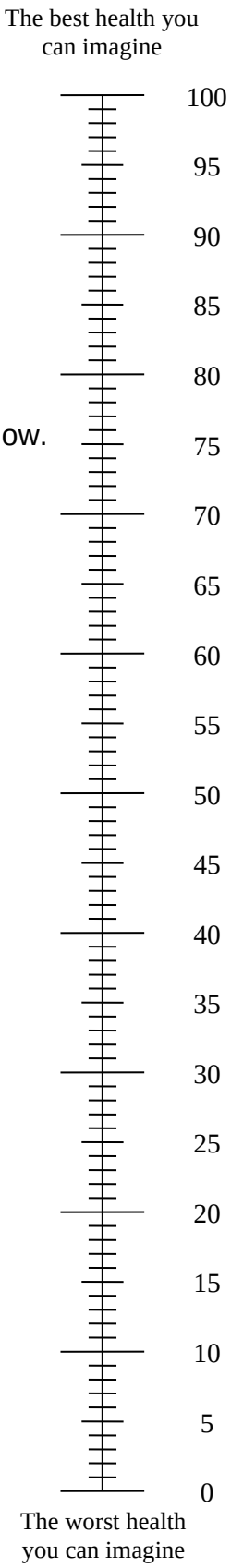
This scale is numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



A comparison study of third stage IM Carbetocin, Syntocinon or Syntometrine for vaginal births

Patient information sheet

IMox: A study comparing three medicines used for the "active management of the third stage of labour" (to help deliver the placenta after your baby has been born).

We would like to invite you to take part in our research study. Before you decide whether you would like to participate, we would like you to understand why this research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have.

Firstly, some information about your labour…

The third stage of labour is the period of time between the birth of your baby and the delivery of your placenta. You have a choice about whether you would like to have a natural or "physiological" delivery of your placenta, or whether you would like "active management" of this stage of labour, which is called the "third stage of labour" Our study would only apply to women wishing to have an "active management" of the third stage of their labour.

"Active management" of the third stage of labour

This involves a one-off injection in your leg just after your baby is born and the umbilical cord has been clamped, and before the placenta being gently delivered by the midwife or doctor. The medicine is given to reduce the risk of you experiencing heavy bleeding (haemorrhage), reduce the need for extra medicines to make your womb contract well, and reduce your need for a blood transfusion after your baby has been born. Having this injection also makes the "third stage of labour" shorter.

Women may choose "active management" if they want to reduce the risk of heavy bleeding. In certain situations your doctor or midwife might advise that you have the third stage of labour managed "actively" in this way, for your safety.

Choosing "active management" does not harm your baby in any way. Previous studies comparing "physiological" and "active" management of the third stage of labour have found that babies born after an actively managed third stage of labour are no more likely to need admission to the baby hospital, and are no more likely to experience jaundice or require treatment for this.

What is the purpose of the study?

We want to find out which of three medicines is best for the "active management" of the third stage of labour for women having a vaginal birth. These medicines are **Syntocinon**, **Syntometrine** and **Carbetocin**. All of these medicines are safe to use and are already being given to women for delivery of their placenta. Our study will find out which medicine is best at reducing blood loss and which allows women to feel as well as possible in the first hours after birth. We also want to compare the

overall cost of these three medicines, to help the NHS spend its money most effectively. Knowing all of this information will help midwives and doctors to provide the best possible care for mothers giving birth.

Syntometrine	• Syntometrine is routinely used for active management of the third stage of labour after vaginal birth in all hospitals participating in this study, and in the majority of maternity units in the UK • When compared with Syntocinon, Syntometrine is slightly more effective at preventing "mild" bleeding • Syntometrine and Syntocinon are equally effective at preventing "major" bleeding • Syntometrine can sometimes make you feel or be sick – this affects less than a quarter of women, and it can sometimes raise your blood pressure for a short time after birth
Syntocinon	• This medicine is usually used instead of Syntometrine, when a woman has high blood pressure • Syntometrine and Syntocinon are equally effective at preventing "major" bleeding • Syntocinon is less likely to make you feel or be sick – this affects less than one in ten women
Carbetocin	• This medicine is currently only used after caesarean section, where it has been found to be better than other medicines at preventing heavy bleeding. This is why we want to carry out this study – to see whether it is also better after vaginal birth. • Some small studies comparing Carbetocin with Syntometrine, and Carbetocin with Syntocinon have already been conducted. These studies have found that Carbetocin may be associated with less bleeding after birth, and less women feeling or being sick.

No studies have compared all three medicines for effectiveness and side effects and this is what we would like to do, with your help.

Why have I been invited?

All pregnant women who are pregnant with a single baby and are planning for a vaginal birth, and active management of the third stage of labour, are being invited to take part in this study. However, if your baby is born by caesarean section then you will no longer be able to take part in this study. Also, if you have high blood pressure, you will not be able to participate. Your midwife or doctor will be able to answer any questions you might have about whether you are able to take part in this study.

Do I have to take part?

It is entirely up to you whether you join this study or not. If you agree to take part, you will be able to change your mind at any time.

What will happen to me if I take part?

If you decide to take part in this study, the clinical care you receive up to the time of this injection, and afterwards, will be almost exactly the same as it would be if you were not taking part in this study. The only slight difference to routine care may be the timing of when this one injection is given. Some hospitals routinely give this injection as soon as the baby's shoulders are born, while other hospitals wait until the whole of the baby has been born, or until after the cord has been

clamped. In this study we routinely wait until whenever the cord has been clamped. Your midwife or doctor will be able to advise you about what happens routinely at your hospital. All of these options are safe for you and your baby.

If you decide to take part in this study, you will be given one of either Syntocinon, Syntometrine or Carbetocin as a one-off injection in your leg. Whether you receive Syntocinon, Syntometrine or Carbetocin will be decided by a computer. The computer will allocate treatment randomly. This means by chance, like tossing a coin. You will not know which you have received, and neither will the doctors or midwives looking after you. (Although they will be able to find out if they ever need to know.) After you have received the injection your placenta will be delivered by the midwife or doctor in the usual way, by gently pulling on the umbilical cord once your womb has started to contract.

Skin to skin contact, cord clamping and hospital stay

You will be able to have skin-to-skin contact with your baby as soon as they are born, and you will also be able to ask that the cord is not clamped straight away after birth. However, there may be some situations in which it is medically necessary to clamp and cut the cord quickly after birth (i.e. if there were concerns about your baby's wellbeing immediately before or after birth)

Participating in this study will not mean that you have to stay longer in hospital after the birth of your baby. However there may be other medical reasons why you have to stay in hospital.

Will there be extra paper work for you to fill in?

The midwife or doctor looking after you will collect information on any bleeding after birth, how well your womb has contracted, whether you needed any extra medicines, and your blood pressure measurements.

You will be asked to complete a simple "maternal experience" questionnaire approximately two hours after your baby is born. This will ask you how you have felt, and bonded with your baby, in the first two hours after your baby's birth. The questionnaire should only take about 5-10 minutes to complete, and the midwife can read the questions out to you if you would prefer.

You will also be asked to fill out a "health-related quality of life" questionnaire. This only contains 5 questions and should only take 5 minutes to answer. You will be given a paper copy of the questionnaire 1 day after your baby's birth. You will also be phoned by one of the study researchers 2 weeks after your baby is born, and asked the same 5 questions on the phone.

What will happen to me if I decide not to take part?

If you decide not to take part, this will not affect the standard of care you receive. If you decide not to take part and would still like active management of the third stage of labour, you would receive the standard medicine used in the hospital where you are giving birth.

What are the side effects of any treatment received when I take part?

All three medicines being compared in this study are safe to use and are already being given to women for delivery of their placenta. The side effects of Carbetocin and Syntocinon are similar. Between one and four out of every ten women may experience feelings of sickness, tummy pain, itching, feeling flushed, feeling of warmth, lower blood pressure, headache or tremor. Between one and five out of a hundred women may experience back pain, dizziness, metallic taste, anaemia, sweating, chest pain, breathlessness, chills or fast heartbeat.

Syntometrine is similar in its side effects, but is slightly more likely to make you feel or be sick. This happens to less than one in four women. Occasionally, it can also give you temporarily high blood pressure. If your midwife or doctor have concerns about your blood pressure being high at any time after you have consented to participate, you would be withdrawn from this study as we would not want you to have Syntometrine.

The primary concern of your doctors and your midwife is the safety of both you and your baby at all times.

Will it affect my baby?

Taking part in this trial will not affect your baby in any way.

What are the possible benefits of taking part?

The information we gain from this study will help to ensure that women are given the best care during the third stage of labour. We will also collect vital information from mothers about their experience of birth. This will help us to provide the right information and choices, and to ensure an even more positive birth experience for new mothers in the future.

What happens when the study stops?

Once this study finishes, we will analyse all of our results to try and find out which is the best medicine. We will then aim to publish our results nationally and internationally, so that other hospitals and countries can learn from our results too.

What if there are any problems?

In the very unlikely event that you are harmed by taking part in this research project, there are no special compensation arrangements. NHS-sponsored research studies such as this one are covered by NHS indemnity (the same indemnity that applies to any NHS patient). If you want to complain about any aspect of the way you have been approached or treated during the course of this study, then the normal NHS complaints mechanisms will be available to you. Please visit www.XXXXXXX.com (hospital website complaints page) for further information about how to make a complaint, or contact the XXX Hospital Patient Advice and Liaison Service (PALS) on XXXX(telephone)XXX. PALS can also provide confidential advice and support to patients, families and their carers. Further contact details for PALS are listed below under “Further information and contact details”.

Who has reviewed the study?

The South Central – Oxford B Research Ethics Committee has reviewed and agreed this study (Ref 14/SC/1312)

What do I do now?

If you are interested in taking part in the study, inform your midwife or doctor when you next come to the hospital, or tell your community midwife when you next see her.

Further information and contact details

If you would like more information about this study, please contact the midwife or doctor providing your care, the research team at your local hospital (XXXXXXXX) or the North Bristol Trust Maternity research team (XXXXXXXXX).

Please email XXXXXXX if you wish to be informed of the results of this study once it has been completed.

The XXX Hospital Patient Advice and Liaison Service (PALS) can be contacted on XXXX(telephone, email, postal address, website for details about complaint procedure).

Please stick hospital identification label here

Participant ID: __ __ __ __

PATIENT CONSENT FORM

The IMox Study: A comparison study of intramuscular Carbetocin, Syntocinon and Syntometrine for the third stage of labour following vaginal birth

1. I confirm that I have read the information sheet (dated __ __ / __ __ / __ __) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that even if I withdraw from the study, the data collected from me until that point will be used in analysing the results from the study, unless I specifically withdraw consent for this. ☐

4. I understand that relevant sections of my medical notes, and data collected during the study, may be looked at by individuals from the research team, the regulatory authorities or staff at University Hospitals Bristol NHS Foundation Trust overseeing the research. I give permission for these individuals to have access to the relevant parts of my medical records. ☐

5. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix to Chapter 4, Table 4.2: Characteristics of women at trial entry and babies at birth (Per Protocol results)

Baseline Characteristics			
Characteristic	**Oxytocin (N = 1896)**	**Syntometrine (N = 1912)**	**Carbetocin (N = 1884)**
Median age, *years* (IQ range)	29 (26-33)	30 (26-34)	30 (26-34)
Median BMI (IQ range)	25 (22-30)	25 (22-30)	25 (22-30)
Parity: Nulliparous, *number* (%) Parity 1-4, *number* (%) Parity 5+, *number* (%)	 802 (42.9) 1046 (56.0) 20 (1.1)	 843 (44.8) 1015 (53.9) 24 (1.3)	 769 (40.8) 1082 (57.4) 33 (1.8)
History of previous PPH, *number (% of parous women)*	152 (8.1)	124 (6.6)	146 (7.7)
Asian ethnicity, *number (%)*	64 (3.4)	59 (3.1)	58 (3.0)
Onset of labour induced, number (%)	1321 (70.8)	1322 (70.3)	1374 (73.1)
Baseline antenatal utility score from EQ-5D-5L questionnaire	0.811	0.811	0.811
Intrapartum characteristics			
Prolonged labour, number (%)	121 (6.5)	115 (6.2)	97 (5.2)
Pyrexia in labour, number (%)	65 (3.5)	85 (4.6)	76 (4.1)
Mode of birth: Spontaneous, *number* (%) Instrumental, *number* (%)	 1472 (78.9) 394 (21.1)	 1433 (76.2) 447 (23.8)	 1469 (78.1) 413 (21.9)
Median gestational age at birth, *completed weeks* (IQR)	39 (38-41)	39 (38-40)	40 (38-41)
Median gestation age at birth for those with an induced birth, completed weeks (IQR)	39 (38-41)	39 (38-40)	39 (38-41)
Median birth weight (kg)	3.43 (3.08-3.77)	3.42 (3.07-3.77)	3.44 (3.11 – 3.79)
*The Per Protocol Population were randomised, remained eligible, received a study drug, analysed without protocol deviation			

Appendix to Chapter 4, Table 4.3: Primary and Secondary outcomes for Per Protocol Population

Outcome	Oxytocin (N =1869)	Syntometrine (N = 1884)	Carbetocin (N = 1885)	Missing data for outcome
Primary outcome				
Use of additional uterotonic drugs	(N = 1869) 359 (19.2%)	(N = 1884) 293 (15.6%)	(N = 1885) 359 (19.1%)	7 participants (4 oxytocin, 1 Syntometrine, 2 carbetocin)
Secondary outcomes (PP)				
Median blood loss (ml), IQR	498 (289-835)	483 (289-819)	500 (296-834)	Data for weighed blood loss was missing for 7 participants (0 oxytocin, 2 Syntometrine, 5 carbetocin)
Weighed blood loss ≥500ml	934 (50.0%)	907 (48.2%)	946 (50.3%)	
Weighed blood loss ≥1000ml	351 (18.8%)	347 (18.4%)	326 (17.3%)	
Weighed blood loss ≥2000ml	74 (4.0%)	57 (3.0%)	56 (3.0%)	
Perineal tear	1377 (73.8%)	1429 (75.9%)	1386 (73.6%)	6 participants (3 oxytocin, 2 Syntometrine, 1 carbetocin)
Duration of third stage of labour (minutes), IQR	17 (12-23)	15 (10-23)	15 (10-23)	23 participants (5 oxytocin, 9 Syntometrine, 9 carbetocin)
Blood transfusion	57 (3.0%)	50 (2.7%)	52 (2.8%)	3 participants (0 oxytocin, 1 Syntometrine, 2 carbetocin)
Manual removal of placenta	43 (2.3%)	48 (2.6%)	56 (3.0%)	4 participants (1 oxytocin, 2 Syntometrine, 1 carbetocin)
Other surgical/mechanical methods to treat PPH ϕ	56 (3.0%)	37 (2.0%)	42 (2.2%)	5 participants (1 oxytocin, 1 Syntometrine, 3 carbetocin)
Peripartum hysterectomy	0 (0%)	0 (0%)	0 (0%)	No missing data
Blood pressure: hypertension in first 2 postnatal hours*	131 (7.0%)	230 (12.3%)	131 (7.0%)	25 participants (5 oxytocin, 8 Syntometrine, 12 carbetocin)
Blood pressure: hypotension in first 2 postnatal hours**	47 (2.5%)	32 (1.7%)	31 (1.7%)	26 participants (5 oxytocin, 9 Syntometrine, 12 carbetocin)
Nausea	167 (8.9%)	453 (24.1%)	149 (7.9%)	Maternal side effects questionnaires not completed for 2 participants (0 oxytocin, 1 Syntometrine, 1 carbetocin)
Vomiting ¤	91 (4.9%)	333 (17.7%)	91 (4.8%)	
Headache	26 (1.4%)	64 (3.4%)	27 (1.4%)	
Dizziness	161 (8.6%)	184 (9.8%)	123 (6.5%)	
Abdominal pain	128 (6.8%)	159 (8.4%)	97 (5.1%)	
Answer “yes” to question…. “Have any of the above symptoms affected your ability to bond with and/or care for your baby in these first two hours?”	81 (4.5%)	157 (8.6%)	56 (3.1%)	184 participants (63 oxytocin, 61 Syntometrine , 60 carbetocin)
Mean EQ-5D utility score: all returned antenatal questionnaires, SD	0.8114 (0.1753)	0.8112 (0.1756)	0.8111 (0.1699)	629 participants (215 oxytocin, 205 Syntometrine, 209 carbetocin)
Mean EQ-5D utility score: all returned day 1 postnatal questionnaires, SD	0.7552 (0.1739)	0.7474 (0.1850)	0.7574 (0.1794)	354 participants (132 oxytocin, 112 Syntometrine, 110 carbetocin)
Mean EQ-5D utility score: all returned day 14 postnatal questionnaires, SD	0.9040 (0.1250)	0.8912 (0.1255)	0.9002 (0.1241)	769 participants (259 oxytocin, 255 Syntometrine, 255 carbetocin)
Mean EQ-5D utility score for participants with a “complete” EQ-5D dataset: day 14 postnatal, SD ¶	0.9042 (0.1263)	0.8920 (0.1252)	0.8997 (0.1259)	1512 participants did not have a complete EQ-5D dataset (519 oxytocin, 503 Syntometrine, 499 carbetocin)

- ϕ Composite outcome of examination under anaesthetic/intrauterine balloon/uterine compression suture/interventional radiology
- * Defined as SBP ≥140mmHg or DBP ≥90mmHg in the first two postnatal hours ** Defined as DBP <90mmHg in the first two postnatal hours
- ¤ Vomiting in those not already vomiting in labour
- ¶ “Complete” defined as those participants who returned EQ-5D questionnaires antenatally, on day 1 and on day 14

Appendix to Chapter 4, Table 4.3: Pairwise comparisons of primary and secondary outcomes for Per Protocol Population

	Carbetocin v Syntometrine	Syntometrine v oxytocin	Carbetocin v Oxytocin
Primary outcome			
Primary outcome (PP population)	Percentage difference 3.5% 95% CI 1.08, 5.92 OR 1.28, 95% CI 1.08 – 1.51	Percentage difference -3.6 95% CI -6.03, -1.17 OR 0.77, 95% CI 0.65 - 0.92	Percentage difference -0.1% 95% CI -2.62, 2.42 OR 0.99, 95% CI 0.84 – 1.16
Secondary outcomes			
Weighed blood loss ≥ 500ml	OR 1.09, 95% CI 0.96 – 1.24, P = 0.19	OR 0.93, 95% CI 0.82–1.06, P = 0.28	OR 1.01, 95% CI 0.89 – 1.15, P =0.83
Weighed blood loss ≥ 1000ml	OR 0.93, 95% CI 0.79 – 1.10, P = 0.38	OR 0.98, 95% CI 0.829–1.15, P = 0.79	OR 0.91, 95% CI 0.77 – 1.07. P = 0.25
Weighed blood loss ≥ 2000ml	OR 0.98, 95% CI 0.68 – 1.43, P = 0.93	OR 0.75, 95% CI 0.53 – 1.08, P = 0.12	OR 0.74, 95% CI 0.52 – 1.06, P = 0.10
Perineal tear	OR 1.13, 95% CI 0.98–1.31, P = 0.10	OR 1.12, 95% CI 0.97–1.30, P= 0.013	OR 1.01, 95% CI 0.88 – 1.17, P = 0.87
Duration of third stage of labour	Md* 0, 95% CI 0, 0, P = 0.96	Md* 0, 95% CI -2, 0, P = 0.57	Md* 0, 95% CI -2, 0, P = 0.78
Blood transfusion	OR 1.04, 95% CI 0.70 – 1.54, P = 0.84	OR 0.87, 95% CI 0.59 – 1.28, P = 0.47	OR 0.90, 95% CI 0.62 – 1.32, P = 0.60
Manual removal of placenta	OR 1.17, 95% CI 0.79 – 1.73, P = 0.43	OR 1.10, 95% CI 0.73 – 1.68, P = 0.62	OR 1.30, 95% CI 0.87 – 1.94, P = 0.20
Other surgical/mechanical methods to treat PPH	OR 1.14, 95% CI 0.73 – 1.79, P = 0.57	OR 0.65, 95% CI 0.43 – 0.99, P = 0.04	OR 0.74, 95% CI 0.49 – 1.11, P = 0.14
Hypertension in first two postnatal hours	OR 0.54, 95% CI 0.43 – 0.67, P <0.001	OR 1.85, 95% CI 1.48– 2.31, P <0.001	OR 0.99, 95% CI 0.77 – 1.28, P = 0.97
Hypotension in first two postnatal hours	OR 0.97, 95% CI 0.59 – 1.59, P = 0.90	OR 0.67, 95% CI 0.43 – 1.06, P = 0.83	OR 0.65, 95% CI 0.41 – 1.03, P = 0.06
Nausea	OR 0.27, 95% CI 0.22 – 0.33, P <0.001	OR 3.23, 95% CI 2.67 - 3.91, P <0.001	OR 0.88, 95% CI 0.69 – 1.10, P = 0.26
Vomiting	OR 0.24, 95% CI 0.19 – 0.30, P <0.001	OR 4.20, 95% CI 3.30 - 5.35, P <0.001	OR 0.99, 95% CI 0.74 – 1.34, P = 0.96

Headache	OR 0.41, 95% CI 0.26 – 0.65, P <0.001	OR 2.49, 95% CI 1.57– 3.95, P <0.001	OR 1.03, 95% CI 0.60 – 1.77, P = 0.91
Dizziness	OR 0.64, 95% CI 0.51 – 0.82, P <0.001	OR 1.15, 95% CI 0.92 - 1.43, P = 0.22	OR 0.74, 95% CI 0.58 – 0.95, P = 0.02
Abdominal pain	OR 0.59, 95% CI 0.45 – 0.76, P <0.001	OR 1.25, 95% CI 0.98 - 1.60, P = 0.07	OR 0.74, 95% CI 0.56 – 0.97, P = 0.03
Answer "yes" to question "Have any of the above symptoms affected your ability to bond with and/or care for your baby in these first two hours?"	OR 0.34, 95% CI 0.25 – 0.46, P <0.001	OR 2.01, 95% CI 1.52-2.65, P <0.001	OR 0.67, 95% CI 0.48 – 0.95, P = 0.03

Appendix to Chapter 4, Table 4.5: Logistic regression model results relating use of additional uterotonic drugs and PPH ≥500ml (Per Protocol Population)

	Outcome: Additional uterotonic drugs		Outcome: PPH ≥500ml	
	Odds ratio	**Significance (p)**	**Odds ratio**	**Significance (p)**
Study arm (relative to Syntometrine)				
Carbetocin	1.335	0.002	1.146	0.056
Oxytocin	1.331	0.002	1.146	0.057
*Risk factors (*BMI relative to Normal weight)*				
Previous PPH	3.520	<0.001	3.057	<0.001
Asian ethnicity	1.148	0.503	1.329	0.088
BMI: Underweight*	0.504	0.037	0.741	0.134
BMI: Overweight*	1.084	0.369	1.171	0.026
BMI: Obese*	1.301	0.004	1.321	<0.001
Induced labour	1.402	<0.001	1.221	0.003
Prolonged labour	2.217	<0.001	2.091	<0.001
Big Baby (>4kg)	1.583	<0.001	2.405	<0.001
Parous	1.440	<0.001	2.222	<0.001
Pyrexia in labour	2.152	<0.001	1.845	<0.001
Operative birth	2.209	<0.001	2.314	<0.001
Hospital (relative to Southmead)				
Bath	1.105	0.313	0.713	<0.001
Gloucester	1.025	0.866	0.874	0.240
Nottingham	2.389	<0.001	0.664	0.054
St Michael's	1.387	0.011	0.498	<0.001
Swindon	1.106	0.389	0.769	0.003