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premature cord clamping vs. neonatal venesection:
Randomised controlled trial protocol**

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Impossible, but plausible, research studies

Achieving routine prophylactic red cell reduction via premature cord clamping vs. neonatal venesection: Randomised controlled trial protocol for the PERVERT study

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Contributorship statement: AW has a research interest in the third stage. Both AW and SB have published on the neonatal consequences of maternal interventions. AW conceived the trial, but both authors contributed equally to final study design, writing the protocol and paper, and have approved the final version. AW is the guarantor for the article.

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3 **Declaration of conflicting interests:** AW registered intellectual property rights for a small neonatal
4 resuscitation trolley (The BASICS trolley; Bedside Assessment, Stabilisation and Immediate
5 Cardiorespiratory Support) via the University of Liverpool on behalf of a group of 8 clinicians
6 (including SB) interested in avoiding premature cord clamping (Weeks et al. 2015). The rights were
7 then transferred to LifeStart© in lieu of charitable donations. Such equipment may avoid premature
8 cord clamping, even – or especially – in babies born in a compromised condition. If the proposed
9 RCT does ever take there would still be no financial conflict of interest in the event that Day 1
10 venesection proved superior to premature cord clamping. SB chaired the 2014 NICE Intrapartum
11 Care Guideline Update CG190.
12

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24 we would welcome grant funding suggestions and approaches from private cord stem cell collection
25 companies.
26

27
28 **Proposed referees:**

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Summary

Routine prophylactic neonatal red cell reduction, presently achieved through premature cord clamping, is widely practiced worldwide. ~~It is, and, advocated by some to avoid hyperbilirubinaemia and jaundice.~~ It also provides larger volumes for commercial cord blood stem cell collection. Routine first day umbilical vein venesection is a controlled and visible method of achieving the same effect and may be safer. The rationale and protocol for a randomised comparison to determine which is better is described ~~(the PERVERT Study) and the ethics satirised.~~

Introduction

Our first breath and its relationship to cord clamping literally affects us all. Presently, routine prophylactic neonatal red cell reduction is commonly achieved through premature cord clamping at birth; defined as any time before natural cessation of umbilical cord pulsations. This has two main consequences: firstly, restriction of the transfer of blood from the placenta to the neonate in the first minutes after birth; and secondly, increased blood pressure (BP) fluctuations during the liminal period of transition from fetal to adult circulation. Blood volume reduction typically averages 19mls/kg (21% of the neonate's total blood volume) or 18 mls/kg red cell volume (37% of the neonate's red cell volume).^{1,2} ~~Systematic reviewers examine the apologist claim that Proponents and apologists of premature cord clamping claim this~~ may be beneficial because it reduces the rate of hyperbilirubinaemia and need for exchange transfusion.³ However, it increases the rate of neonatal anaemia and there is evidence that the BP fluctuations can cause or exacerbate cerebral damage.⁴ It is therefore important to explore alternative means of achieving the same end.

Premature Cord Clamping (Control)

First introduced in the 1700s, obstetricians have encouraged premature cord clamping since the 1960s as part of 'active management' of the third stage of labour to prevent postpartum haemorrhage.^{5,6} Formal investigation in the last two decades has demonstrated that whilst neonatal jaundice was lowered, premature cord clamping also had potentially harmful infant side-effects.^{3,7,8} Consequently, in 2006, the cord clamping component of 'active management' was discarded by the World Health Organisation⁹ and the International Federation of Obstetrics and Gynaecology¹⁰. In the UK, NICE initially determined there was insufficient evidence to recommend a change from 'normal practice'.¹¹ The Royal College of Obstetricians and Gynaecologists was also cautious about embracing change in the face of accumulating evidence of harm,^{12,13} but NICE recently updated its guidance to avoid clamping in the first minute.¹⁴ Although premature cord clamping has been abandoned in many countries, it remains entrenched, undocumented and unmonitored in the UK, which had one of the highest rates in Europe.¹⁵ ~~This may be because circular logic advice that -the cord 'should not be clamped earlier than necessary' is unclear and unhelpful.~~¹³ Higher rates are noted by direct observation.¹⁶ More recent work on implementation of 'delayed', 'physiological' or 'wait a minute before' clamping, in countries as far away as Peru,¹⁷ Norway,¹⁸ India¹⁹ and the USA²⁰ has shown the possibilities and difficulties in changing birth practices. We cannot find work auditing recent UK practice. ~~It is unclear whether resistance to change stems from ingrained culture, clinical uncertainty, the wish to rapidly transfer practical (and legal) responsibility for the newborn to the~~

neonatologist,²¹ or because it has never been demonstrated that the same ends can be achieved in another way.

In term infants, the blood volume reduction achieved through premature cord clamping amounts to around 60-75mls (a fifth of the total on average, although it can be substantially more)^{1,2} which shifts the 'normal' curve of neonatal haemoglobin concentration to the left by about 2.2 g/dl (95% CI -0.28 to -4.06).³ This results in clinical effects at both ends of the distribution (Figure 1). The benefit of premature cord clamping is a reduction in hyperbilirubinaemia and phototherapy, set against increased rates of anaemia and iron deficiency in the term infant, and higher blood transfusion requirements in the preterm. Increased rates of hypotension are also seen in the preterm infant who undergoes premature cord clamping.⁸ -These changes are thought to result from the combination of volume depletion and abrupt haemodynamic changes.²² In fetal life, the majority of blood flows from the heart, down the aorta and directly into the umbilical arteries and placenta, before returning oxygenated to the right side of the heart through the umbilical vein. Immediate cord clamping not only blocks the umbilical arteries, leading to an abrupt increase in cardiac afterload, but also blocks the umbilical vein leading to an immediate decrease in cardiac pre-load. [The implications of this are not clear, but cerebral vascular damage may be responsible. Indeed, randomised trials have found that deferred cord clamping in term babies improves fine motor skills and social functioning at 4 years of age²³ \(Andersson O, Lindquist B, Lindgren M, Stjernqvist K, Domellöf M, Hellström-Westas L. Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age: A Randomized Clinical Trial. JAMA Pediatr. 2015 Jul;169\(7\):631-8\), whilst randomised trials of premature babies show a reduction in](#) [These disturbances may be the source of the increased periventricular haemorrhages⁸ and neonatal mortality excess deaths seen in clinical trials.^{23,24,25,26}](#)

Routine prophylactic red cell depletion through premature cord clamping is entrenched in the birthing culture of many maternity units despite the lack of evidence base and newer recommendations.¹⁴ -Fortuitously, - it enhances the volume of cord blood for stem cell collection, thus providing a strong commercial and potential future interest. [This has led some to persist with premature cord clamping, and the reduction in neonatal hyperbilirubinaemia is commonly given as a reason for this. A reduction in inpatient neonatal surveillance is also claimed to be increase the importance of this, as some parents, and NHS managers, aim for postnatal discharge even before collection of the 10 minute APGAR score. However, r](#) Rather than berate the evidence laggards or blame 'vampire capitalism', we have applied 'realist' and 'harm reduction' theory to explore a safer and more controlled way to achieve the same end; a tailored neonatal blood volume reduction without associated haemodynamic fluctuations.

Routine day 1 umbilical vein venesection (Innovation)

This pioneering, gentle method of venesection aims to achieve precise red cell volume reduction slowly, visibly and safely without significant adverse effects. As traditional cord clamps require special cutters to be removed, we propose using a sterilized freezer bag clip at birth that can be released a few hours later. An umbilical vein catheter will be inserted, followed by blood drainage over half an hour. This will also make routine collection of neonatal stem cells simpler as the blood can be stored directly in a sterile blood bag with anticoagulant (Figure 2). Despite the theoretical advantages [of this controlled neonatal volume depletion](#), it is unclear whether [replacing premature cord clamping with a policy of the benefits of routine](#) umbilical vein venesection [will reduce the rate](#)

of cerebral damage and thus improve cognitive function. We will also seek to determine whether the policy change is clinically and cost-effective, and, crucially, whether the procedure would be acceptable to parents. A randomised trial will compare the two interventions.

Proposed Trial Protocol

Participants: All pregnant women at 2 large university teaching hospitals will be invited to participate at booking.

Exclusion criteria: Mothers who are not prepared to be randomised before birth, or who insist on “natural/physiological” third stage or deferred cord clamping. Neonates with cardiac complications (who may be put at risk by the marked blood pressure fluctuations or hypovolaemia associated with premature cord clamping volume depletion, possibly more so during transition immediately following birth). No exclusions for place of birth, gestation, multiple pregnancy or condition at birth.

Study Procedures

1. Premature cord clamping (control): Routine cord clamping within 30 seconds of birth. No umbilical venesection permitted except for indicated tests. All volumes of blood (including from peripheral vessels and ‘heel prick’ tests) to be recorded.

2. Controlled umbilical vein venesection (intervention): The cord will only be clamped once it has stopped pulsating or at least 5 minutes after birth, irrespective of mode of delivery. Those babies appearing to need immediate care will be assessed, stabilised and resuscitated at the bedside with the cord intact using the LifeStart Trolley, a portable BASICS bedside resuscitation trolley²⁷⁶ (see competing interest statement). All neonates will subsequently have their umbilical cord clamp released between 4 and 24 hours postpartum, an umbilical vein catheter inserted and 19mls/kg of blood will be gradually drained over 60 minutes with cardiovascular monitoring. The blood will be discarded hygienically unless required for clinical tests or retained as part of a stem cell collection programme. Venesection might be associated with some maternal emotional distress, and this will be minimised by completing the intervention “out of sight” in an examination room on the postnatal ward or on the neonatal unit.

Outcomes: Primary outcome: Mild developmental delay and/or behaviour problem at 18 months as determined by the Bayley III Cognitive Scale. Secondary outcomes: Rates of postnatal hypotension, periventricular haemorrhage, cerebral infarcts, hyperbilirubinaemia, phototherapy, exchange transfusion, anaemia and need for special care admission or transfusion in the first week of life, iron storage at 3 and 6 months. Alongside death, other adverse effects will be collected: need for resuscitation or oxygen, hypotension, periventricular haemorrhage, hypothermia and respiratory distress syndrome relating to premature cord clamping; and bleeding, hypotension, umbilical vein occlusion, vessel puncture or sepsis relating to umbilical vein venesection. Volume of blood retrieved for commercial stem cell collection. At 1, 3 and 12 months, parents will be asked to fill in questionnaires about baby behaviour and feeding as well as standard modified Edinburgh post-natal depression and post-traumatic stress scores. Rates of parental distress, hyperventilation and collapse during the venesection procedure will also be monitored as a secondary safety outcome.

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3 **Reporting:** Once funded, the trial will be registered in a WHO-approved public trial registry.
4 EQUATOR reporting guidelines²⁸ will be followed for publication. Dissemination will include
5 becoming a WHO approved standard of care for safety.²⁹
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7 Randomisation: Women will be recruited antenatally and randomised online after participant
8 registration. Randomisation lists, stratified by gestation will be generated electronically at the
9 clinical trials unit.
10

11 **Statistics:** The number of babies with primary outcome will be compared between groups using chi-
12 square tests. Multivariable logistic regression models will be used to adjust for stratification factors
13 used at randomisation and any other baseline clinical covariates (e.g. gestational age, mode of
14 delivery, weight and condition at birth.). Covariates to be used will be pre-specified prior to analysis
15 in a detailed statistical analysis plan.
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18 **Power calculation:** To demonstrate a 10% reduction in the relative risk of mild developmental delay
19 and/or mild behaviour problems from 30% to 27% at 18 months would require 7,242 children (alpha
20 0.05, power 80%). With a conservative anticipated 12% recruitment rate from the two units
21 (combined 16,000 deliveries per annum), recruitment is expected to take 4 years.
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24 **Ethics:** Parents currently receive reassurance from a variety of sources that premature cord clamping
25 and cord blood collection is entirely safe (e.g. maternity professionals, government agencies, stem
26 cell collection companies). Presently, no formal consent is required or obtained for premature cord
27 clamping, its timing is rarely recorded. Nevertheless, a detailed information sheet will be prepared
28 explaining that the practices of premature cord clamping and umbilical vein venesection both carry
29 similar theoretical risks, although these are likely to be less with slower, controlled venesection
30 based on confirmed birth weight. We see no ethical objections to this trial, and research ethics
31 approval is awaited.
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34 **Qualitative analysis:** Face-to-face interviews will be conducted by study specific research nurses,
35 audio-taped (with permission) and field notes taken. These will focus on mothers' views of the two
36 procedures, and the perceived effect on the child, bonding and feeding, as well as the involvement
37 and view of the partner. Any parental concerns about safety compared to 'normal' or 'natural' will
38 be considered 'cultish' and not explored further.²⁸
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41 **Economic analysis:** The economic case will be examined by comparing the cost of setting up and
42 running a service with the outcomes and profits it achieves. Estimates will be made for lifelong costs
43 of different infant outcomes. Costs of pain and suffering, plus costs to various public sector agencies
44 are derived using Hospital Inpatient Episode data and notional reference data. The medium to long-
45 term consequences of red cell reduction are unknown (due to lack of routine data collection of
46 clamping time and minimal research). The process necessarily rests on assumptions whose accuracy
47 cannot be audited. The resulting uncertainty will be recognised in a Monte Carlo simulation. Because
48 analysis is dependent upon plausible assumptions not founded on data, a policy of optimistic
49 guesstimates will be adopted throughout. Costs of equipment, professional time, monitoring and
50 cots will be offset by the commercial exploitation of resultant blood products. Given the epigenetic
51 implications, we will apply for a 50 year follow up study.
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55 **Future Policy and Research**

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3 Having described the rationale and details of the routine prophylactic PrEmature cord clamping vs
4 Routine umbilical vein VEnesection blood volume ReducTion study (or 'PERVERT'), we invite
5 researchers worldwide to join this exciting collaboration. In the event that the trial shows umbilical
6 vein venesection is superior to premature cord clamping but causes more maternal anxiety, then
7 future research might concentrate on modifications; e.g. night-time venesection whilst parents are
8 asleep might be used to allay worries, or listening to reassuring music or watching videos. It is
9 postulated that routine venesection would become less traumatic to parents with time and
10 familiarity, and could even be incorporated into popular culture. New rituals might be developed
11 whereby the father is encouraged to participate in the 'releasing of tension' through the draining of
12 blood. These might build on recent fashions in high income countries for paternal cord cutting as a
13 rite of passage to separate the mother from her baby. Alternatively, Hospital Chaplaincy Services
14 might conduct a short ceremony on the newborn relevant to religion and denomination (e.g.
15 removing the baby's blood as 'penitence for original sin' for Christians). [The Blood Transfusion
16 Service might use 'baby's first blood donation' to encourage ~~the~~ blood donation amongst adults.](#)
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20 **Conclusion**

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22 Within minutes of birth, around 20% of a newborn's final blood volume is transferred from the
23 placenta into the neonate. We are advocates of leaving the cord alone to allow the neonate to
24 receive its total allocation of blood. However, many birth attendants still practice immediate cord
25 clamping, with some arguing it reduces the amount of red cells in the neonate and prevents
26 hyperbilirubinaemia. For those who believe routine prophylactic red cell depletion is necessary, we
27 have designed a more controlled method of achieving the same objective. The PERVERT study will
28 establish its safety and effects on parental anxiety. Those who question the [satarised](#) ethics of this
29 RCT should also examine the ethics of inaction whilst premature cord clamping continues.
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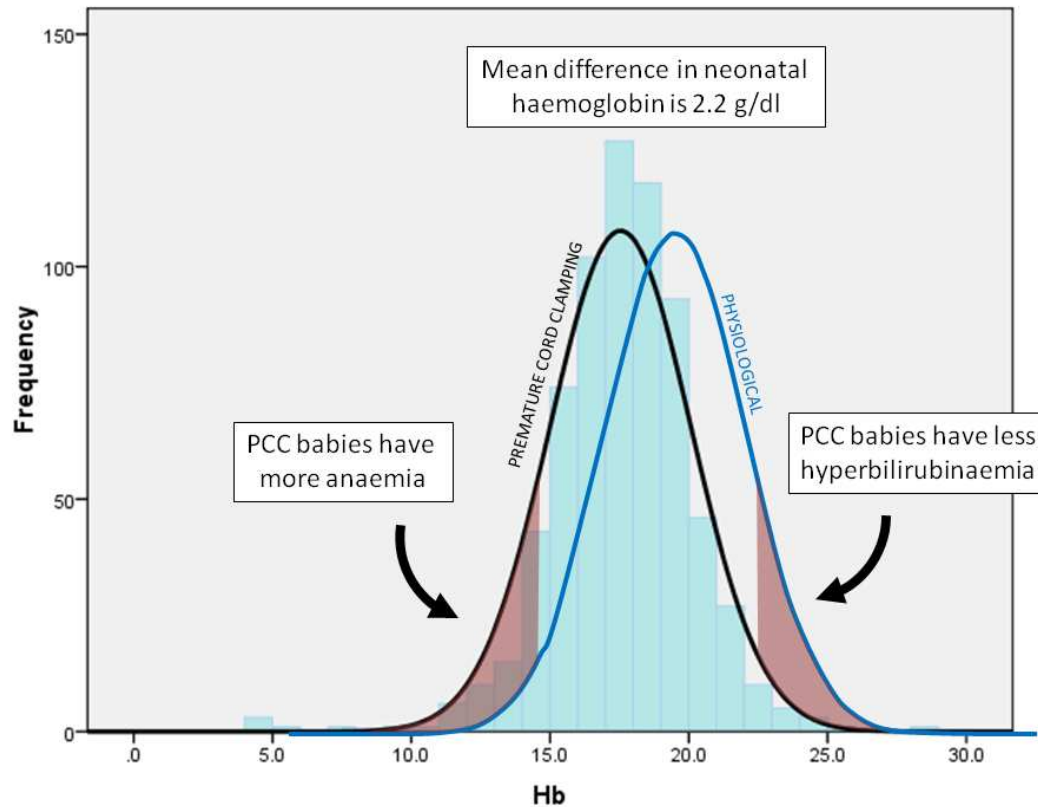
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Figure 1. Histogram showing difference in neonatal haemoglobin with and without premature cord clamping. * Derived from MacDonald (2008).



* The light blue histogram data is derived from Liverpool Women's Hospital statistics of all term babies admitted to neonatal intensive care unit 2005-10 [at a time when routine premature cord clamping was practiced](#). The graph shows the spread of values of term babies in a unit where routine prophylactic neonatal volume depletion is practiced via premature cord clamping (black line) vs physiological cord management (dark blue line shows the expected Haemoglobin levels derived from Cochrane meta-analysis showing a mean difference of 2.2 g/dl Hb in term babies; MacDonald 2008).

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Figure 2. Newborn baby receiving visible venesection on first day of life (Intervention group) aiming to remove a controlled and calculated fifth of the total blood volume based on birth weight

