Approaches to understanding and interpreting the risks of red blood cell transfusion in neonates

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SUMMARY

In this review, we explore how to assess potential harm related to neonatal transfusion practice. We consider different sources of information, including passive or active surveillance systems such as registries, observational studies, randomised trials and systematic reviews. Future research directions are discussed.

Key words: adverse effects, haemovigilance, infants.

Transfusions are given therapeutically to treat a clinical problem, such as giving red cells to improve oxygen delivery, or prophylactically to prevent a problem, such as platelets to prevent bleeding. There is uncertain evidence in many cases. Therefore, the balance between perceived benefit and risk of harm needs to be carefully considered. Neonates, especially preterm low-birth-weight (LBW) infants, are an immunologically immature, highly transfused patient population that may receive large transfusion volumes relative to their total blood volume. For this group of patients, it is particularly important to have a clear understanding of both potential immediate harms and long-term consequences given the expectation of their post-transfusion survival over many decades.

Neonatal adverse transfusion reactions remain particularly poorly characterised. They may be difficult to distinguish from non-specific changes or a worsening of concurrent clinical morbidities, such as hypoxia, apnoeic episodes, requirement for increased respiratory support, rash or fever. Oxygen requirements and the degree of respiratory support are important indicators that guide red blood cell (RBC) transfusions in neonates. Yet worsening hypoxia, apnoea or increased respiratory requirements in an extremely preterm infant with chronic lung disease (CLD) receiving an RBC transfusion for anaemia of prematurity (AOP) may be the earliest indicators of an adverse transfusion reaction and may be unrecognised and unreported as a transfusion adverse event. Neonates are at particular risk of metabolic complications such as hypocalcaemia, hyperkalaemia, hypothermia and overload conditions if large-volume transfusions are given rapidly with insufficient monitoring.

This review explores how we can identify and assess harm related to the practice of neonatal transfusion medicine. We will consider different sources of information, including passive or active surveillance systems such as registries, observational studies, randomised trials and systematic reviews.

NEONATAL MEDICINE

There have been major changes in the characteristics and types of admissions to neonatal units over the last few decades. Infants born at 27 or 28 weeks’ gestation, an age that 20 years ago would have been considered to be at the limits of medical care, are now admitted with an expectation of discharge home. The EPICure studies found increases in survival for extremely preterm babies (22–26 weeks’ gestation) from 40% in 1995 to 53% in 2006. Of note, no differences in rates of neonatal morbidities (findings on cerebral ultrasonography, bronchopulmonary dysplasia, retinopathy of prematurity or surgically treated necrotising enterocolitis) were reported, despite advances in neonatal care over this time (Costeloe et al., 2012). This likely reflects
increasing survival at lower gestational ages but with significant long-term health problems.

It remains a clinical and research priority to improve the longer-term outcomes of the increasing numbers of extremely preterm neonates surviving each year, and there are ongoing initiatives aimed at optimising supportive care as reported by the James Lind Association and other priority setting strategies (Duley et al., 2014). Supportive care more broadly includes fluid and nutrition, respiratory support and use of antimicrobials. Transfusion remains a cornerstone of supportive care in neonatal medicine. Neonates are a heavily transfused patient population with high survival rates and the longest potential lifespan of all transfusion recipients (Keir et al., 2015). Therefore, any transfusion-related consequence may have long-term deleterious effects (Gauvin et al., 2008; Morley et al., 2016).

THE PRACTICE OF NEONATAL RBC TRANSFUSION

In neonatal units, RBC transfusions are most often undertaken to manage AOP. AOP is a multifactorial condition defined by early, significant anaemia in the context of phlebotomy blood losses, lower erythropoietin (EPO) production and limited bone marrow response (Strauss, 2010). Recognition of AOP relies on a combination of non-specific clinical symptoms of anaemia and haemoglobin (Hb) or haematocrit (HCT) levels (Gibson et al., 2004; Miller et al., 2007). It would be expected for the Hb threshold for defining anaemia as well as the threshold for RBC transfusion to be well established in neonates. However, although there is increasing evidence in this area (see later discussion) and consensus on the need to stratify thresholds by age and respiratory support requirement as incorporated into recent guidelines (National Blood Authority, 2016; New et al., 2016; Crighton et al., 2018), there remain conflicts between the neonatal RBC Hb transfusion threshold trial results, particularly regarding longer-term outcomes. Therefore, the evidence for RBC transfusion thresholds for neonates currently remains suboptimal (Goel & Josephson, 2018). There is no evidence of a Hb or HCT threshold where inadequate tissue oxygenation (critical anaemic hypoxaemia) definitively occurs in infants of any gestational age (Guillen et al., 2012). However, current transfusion guidelines do incorporate the available evidence (and lack of evidence) and are our best source of expert guidance on practice in this area (National Blood Authority, 2016; New et al., 2016; Crighton et al., 2018).

The majority of the literature around usage patterns of blood products in neonatal units was published in the 1990s and is based primarily on data obtained from practice surveys (Levy et al., 1993; Hume et al., 1997). Several additional contemporary studies are now available. A UK national audit of RBC use in neonates and children (National Comparative Audit of the use of Red Cells in Neonates and Children Project Group, 2010) found that, for the first transfusion episode for neonates in neonatal units, the median (IQR) gestational age at birth was 27 (26 – 30) weeks, n = 1194, and the majority (81%; 971) of the transfusions were given to infants born at <32 weeks’ gestational age. Most first RBC transfusions were given for anaemia, with (60%) or without (21%) clinical signs. The majority of infants (75%) were either mechanically ventilated or on continuous positive airway pressure (CPAP) at the time of the transfusion. Most neonatal RBC transfusions given were between 15 and 20 mL.kg\(^{-1}\), which represents a significant volume load. Standard practice continues to be to transfuse neonates with relatively high doses (e.g. 15 mL.kg\(^{-1}\) recommended by New et al., 2016) compared to those given to adult patients where it is common to give a single unit (approximately 4 mL.kg\(^{-1}\)) in the first instance if the patient is not bleeding. A recent retrospective cohort study of preterm neonates born at <30 weeks’ gestational age and admitted to participating neonatal intensive care units in the Canadian Neonatal Network (CNN) from 2004 to 2012 was conducted to evaluate blood product usage (Keir et al., 2015). It reported that blood component use remained high in preterm infants in this gestational age cohort, with 8252 (56%) receiving RBCs, 2151 (15%) platelets, 1556 (11%) fresh frozen plasma, 915 (6%) albumin and 302 (2%) cryoprecipitate.

ADVERSE TRANSFUSION EVENTS REPORTED IN INFANTS AND CHILDREN

Data published in the UK national haemovigilance systems have been used to explore the relative frequency of adverse events related to transfusions and compare the results between neonates, children and adults. The Serious Hazards of Transfusion (SHOT) haemovigilance scheme has reviewed reports of adverse reactions and errors associated with transfusions in the UK since 1996 (www.shotuk.org). The first years of paediatric SHOT data were analysed by Stainsby and colleagues (Sainsbury et al., 2008), showing a disproportionate number of adverse outcomes of transfusion in children (particularly infants) compared with adults, largely due to transfusion of the ‘incorrect blood component’. Using epidemiological denominator data on RBC transfusion numbers, the rates of an adverse outcome were estimated to be 18 per 100 000 RBCs issued for children younger than 18 years and 37 per 100 000 for infants younger than 12 months, compared with 13 per 100 000 for adults.

Since 2007, SHOT Annual Reports have included a separate paediatric chapter, with detailed analyses of types of adverse events reported for neonates and children (www.shotuk.org). Paediatric reports are disproportionately represented, particularly in the ‘incorrect blood component transfused’ error categories (‘wrong component transfused’ and ‘specific requirements not met’) and ‘avoidable, delayed or under transfusion’ (Bolton-Maggs et al., 2018). The majority of paediatric SHOT adverse event reports are ‘errors’ (68% in 2017) (Bolton-Maggs et al., 2018), reflecting the complexity of paediatric transfusion both for the laboratory and at the bedside. The small proportion of reactions reported is particularly the case for the neonatal/infant group (89% ‘errors’ in 2017), possibly due to under-recognition or more subtle signs of reactions in the neonatal group or fewer reactions due to immunological
immaturity. Nonetheless, there are significant numbers of febrile, allergic and hypotensive reactions reported in children, most commonly following platelet transfusions, in contrast to adults, where such reactions are most commonly reported to SHOT following RBC transfusion. Moreover, as described in the 2017 SHOT report, other cases of adverse reactions following paediatric transfusion are reported, including ‘confirmed’ paediatric reports of transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO). TRALI and TACO continue to be occasionally described as case reports in the broader literature (Gupta et al., 2012; Radhakrishnan et al., 2012; Agrawal et al., 2015).

Transfusion-transmitted infections are uncommon, although in the paediatric literature, some of these complications do occur and include bacteria and parasites, such as babesiosis (Tonnetti et al., 2009; Glanternik et al., 2018). Haemolytic transfusion reactions and alloimmunisation as a consequence of RBC transfusion appear to be less common in neonates, which may reflect relative immunological immaturity (Floss et al., 1986). Finally, reports to SHOT of paediatric adverse events have also highlighted specific areas of risk in complex specialised situations, including fatal transfusion-associated graft versus host disease (TAGvHD) following intrauterine transfusion with maternal blood, morbidity from delays in neonatal exchange transfusions and unusually high supranatant potassium levels in RBCs from donors with a mutation that increases potassium leakage during cold storage (Bawazir et al., 2014). In 2015, key messages related to neonates and children included noting increased reporting of TA-NEC and use of adult emergency group O, RhD-negative RBCs despite availability of neonatal emergency packs (Bolton-Maggs, 2015).

Other countries also collect paediatric haemovigilance data, although it is currently difficult to compare rates of adverse events between countries due to differences in reporting and analysis. A single-centre study from the United States reported a recent analysis of the comparative incidence of transfusion reactions, with an incidence of 6-2 reactions per 1000 transfusions within the paediatric (age < 21 years) population compared to an incidence of 2-4 reactions per 1000 transfusions within the adult population (Oakley et al., 2015). Within this paediatric population, the authors reported an increased incidence of allergic transfusion reactions (2/7/1000 vs. 1/1/1000), febrile non-haemolytic transfusion reactions (FNHTR) (1/9/1000 vs. 0/47/1000) and hypotensive transfusion reactions (0/29/1000 vs. 0/078/1000) compared to the adult population (Oakley et al., 2015). These findings again demonstrate that there may be a disproportionate number of transfusion adverse events in the neonatal and paediatric age groups. A multi-centre study from the United States found that paediatric patients had an overall higher adverse transfusion reaction rate compared to adults: 538 versus 252 per 100 000 transfusions, notably higher for RBC (577 vs. 278 per 100 000; P < 0.001) and platelet (833 vs. 358 per 100 000; P < 0.001) transfusions (Vossoughi et al., 2018).

In 2005 to 2015, the Québec Hemovigilance System also found that the incidence of adverse reactions was more frequent in the paediatric age group compared to adults (1:84 vs. 1:201 blood components transfused). FNHTR, allergic reactions and acute haemolytic transfusion reactions were more common in paediatric recipients, whereas circulatory overload was less common. However, it should be recognised that differences between these and other estimates are likely to be influenced by different reporting and categorisation by the haemovigilance systems. There may also be under-reporting, given a lack of recognition of many adverse transfusion effects and associations in sick neonates with inter-current illness or a lack of awareness of clinicians given uncertainties about definitions.

REGISTRIES AND HAEMOVIGILANCE

A first approach to understanding the risks of neonatal transfusion is to interrogate and compare findings from different registries, including haemovigilance systems. In 2015, a group of interested clinicians met at the Regional Congress of the International Society for Blood Transfusion (ISBT) in London, UK, to start to consider better ways of evaluating risk of transfusions in children. Many countries support haemovigilance systems to promote and monitor safety and other transfusion-related issues, but there is little understanding of how these are adapted internationally for children and neonates. In 2016, a survey was distributed through ISBT networks seeking information about neonatal and paediatric adverse transfusion events. Specific information was sought on neonatal and paediatric adverse transfusion event reporting, including definitions used, whether data was routinely collected and the approach to analysis of these events. The overarching aim of this survey was to develop consensus age-appropriate definitions to improve standardisation of future haemovigilance reporting. Twenty-seven responses were received from around the world, including Denmark, Colombia, Norway, Australia, Finland, Cameroon, Morocco, Brazil, United States, Netherlands, South Africa, Argentina, Malta, France, Croatia, Portugal, Japan, the UK, Canada and India (Table 1).

The results of this survey suggested that the majority of haemovigilance systems (17/26; 65%) used haemovigilance definitions as defined by ISBT in collaboration with the International Haemovigilance Network, and only two systems modified definitions specifically for neonates and children. The Hemovigilance Module of the US Biovigilance System of the NHSN has a modified definition for hypotensive transfusion reaction in neonates and infants as well as for children and teenagers. As an example, hypotension in neonates and in infants younger than 1 year old OR any age at <12 kg body weight is defined as a drop greater than 25% in baseline value using whichever measurement is being recorded (e.g. mean blood pressure (Centers for Disease Control, 2018)). Since 2016, the Québec Hemovigilance System has a similar definition for hypotensive transfusion reactions in children. However, neither haemovigilance system has modified definitions for other paediatric transfusion adverse events. The majority (17/27; 63%) of systems in our survey managed uncertainty around classifications of events in neonates and
Children through individual case review by a delegated expert(s). Several haemovigilance systems (9/27; 33%) undertook regular separate analysis of neonatal/paediatric adverse events, with 5 of 27 (19%) presenting findings in an annual haemovigilance report, e.g. the UK SHOT report. The development of more precise definitions of adverse effects of transfusion in neonates and children is required if we are to better report, understand and prevent them.

ASSOCIATIONS OF CLINICAL OUTCOMES WITH NEONATAL RBC TRANSFUSION

A further approach to understanding risk is to evaluate the broader literature of any harmful outcomes in transfused neonates and infants. Associations between neonatal RBC transfusions and increased range of outcomes, including mortality (Valieva et al., 2009; dos Santos et al., 2011), as well as significant morbidities such as necrotising enterocolitis (Mohamed & Shah, 2012) intraventricular haemorrhage (IVH), (Baer et al., 2011) and retinopathy of prematurity (ROP) (Giannantonio et al., 2012) and CLD (Cure et al., 2017) have all been raised and discussed. Many of the ‘associations’ between morbidity and transfusion will inevitably be more commonly described in the sickest patient populations, such as neonates. It is challenging to differentiate the perceived need for and consequent receipt of RBC transfusion, together with a possible transfusion reaction in the context of an evolving critical illness.

Additional work should address potential mechanisms, including the associations between RBC transfusion and the development of NEC, ROP and CLD (Cure et al., 2017). Transfusion may modulate a recipient’s immune system, termed transfusion-related immunomodulation (TRIM) (Muszynski et al., 2016). In the clinical setting of an underlying inflammatory state priming the recipient’s immune system, transfusion of allogeneic RBC may trigger immune cell activation and related immunomodulation, resulting in clinical manifestations of inflammation. Increases in interleukin (IL) 1β, IL-8, tumour necrosis factor (TNF) α and monocyte chemoattractant protein-1 have been observed after allogeneic RBC transfusion in transfused recipients, including preterm infants (Keir et al., 2013). These increases also appear to correlate with increases in markers of endothelial activation, which may be one possible mechanism explaining the association between neonatal RBC transfusion and adverse outcomes (Keir et al., 2013).

RANDOMISED TRIALS: RISKS AND ADVERSE EVENTS

Insights into the nature of transfusion risks may also be explored by considering randomised trials in more detail. Two major transfusion RBC thresholds studies have been undertaken in preterm/LBW infants (Table 2). The first was the Premature Infants in Need of Transfusion (PINT) study (Kirpalani et al., 2006), including 451 very LBW (VLBW) infants. This was designed to assess the composite primary outcome of death before hospital discharge or survival with any of the following: severe ROP, CLD or brain injury on cranial ultrasound. No differences in the composite primary outcome were found between low and high RBC transfusion threshold groups in the PINT study. Although this study was of high quality, the mean Hb difference between the two arms was small. The second trial, by Bell and colleagues (Bell et al., 2005), included infants <1000 g and was designed to examine numbers of RBC transfusions and donor exposures per infant. The Bell study (Kirpalani et al., 2006) reported no differences in the length of time of ventilator

Table 1. Haemovigilance systems around the world

| Haemovigilance system | Location |
|-----------------------|----------|
| SHOT                  | Manchester, UK |
| SABRE                 | London, UK |
| Portuguese Haemovigilance System | Lisbon, Portugal |
| Haemovigilance Programme of India – National Institute of Biologicals (NIB) | Mumbai, India |
| Haemovigilance Malta | Malta |
| South African National | Johannesburg, South Africa |
| Norwegian Haemovigilance System (Troll) | Oslo, Norway |
| Japanese Red Cross Society Blood Service | Japan |
| US Biovigilance System of the National Healthcare Safety Network (NHSN), Hemovigilance Module | USA |
| TRIP                  | Netherlands |
| Serious Transfusion Incident Reporting (STIR) | Melbourne, Australia |
| Brazilian Haemovigilance System | Brazil |
| Systematic Surveillance of Transfusion Treatment | Zagreb, Croatia |
| Finnish Red Cross Blood Service | Helsinki, Finland |
| Colombian Haemovigilance Programme | Bogota, Colombia |
| Danish Registration of Transfusion Risks | Copenhagen, Denmark |
| The Québec Hemovigilance System | Québec, Canada |

Table 2. Lower limits for capillary haemoglobin thresholds evaluated in the Cochrane review (Whyte & Kirpalani, 2011)

| Hb (g.L⁻¹) | Post-natal week | No respiratory support | Respiratory support (any kind) |
|-----------|----------------|------------------------|-------------------------------|
|           |                |                        |                               |
| 1         |                | 100                    | 115                           |
| 2         |                | 85                     | 100                           |
| ≥3        |                | 75                     | 85                            |
or oxygen support, length of hospitalisation, rate of severe ROP or CLD or mortality between the two groups. Interestingly, a post hoc analysis of a composite outcome of IVH and periventricular leucomalacia performed favoured the liberal group. However, it should be acknowledged that this study was primarily designed to examine differences in transfusion numbers between groups. The main similarity between these two trials was the volume for each transfusion (15 mL kg\(^{-1}\)), but there were considerable differences in most other areas, including the study’s primary outcomes, as well as participant birth weights, and the transfusion thresholds and transfusion algorithms used in the trials (Bell et al., 2005; Kirpalani et al., 2006).

Longer-term follow-up of these studies (Nopoulos et al., 2011; Whyte, 2012) found conflicting results with regard to neurodevelopmental outcome. The longer-term follow up to the PINT study suggested that higher Hb thresholds may benefit longer-term neurodevelopmental outcomes assessed at 18–24 months of age (Whyte, 2012). The longer-term follow up to the Bell study found that more liberal RBC transfusions were associated with reduced brain volumes at 12 years of age; however, only 44 of the original 100 trial participants were followed (Nopoulos et al., 2011), limiting the value of the findings. It is important to note that neither study was designed nor statistically powered to assess long-term neurodevelopmental outcomes.

For term infants, there is even less evidence to guide the safety of thresholds for RBC transfusion. Only one study provides very limited guidance, the Transfusion Strategies for Patients in Pediatric Intensive Care Units (TRIPICU) study (Lacroix et al., 2007). This study showed no difference in oxygenation markers, duration of ventilation, cardiac dysfunction and length of hospital stay when critically ill infants and children were transfused at thresholds of Hb of 70 g L\(^{-1}\) compared to 95 g L\(^{-1}\). However, this study included only 11 neonates (<28 days) in the restrictive arm and 8 in the liberal arm of a total study population of 637. The study had relatively broad exclusion criteria, and many potentially eligible children and infants were excluded, including neonates <40 weeks’ gestational age or <3 kg, <3 days of age, with uncorrected cyanotic heart disease, severe thrombocytopenia, acute blood loss, hypoxaemia; on dialysis; a decision to withhold or withdraw critical care; a predicted survival of less than 24 h; or needing extracorporeal membrane oxygenation. In view of the small numbers of neonates included in this study and the broad exclusion criteria, the optimal Hb threshold at which to transfuse term neonates remains unclear.

Two clinical trials, the Thresholds on Neurocognitive Outcome of extremely LBW infants (birthweight <1000 g) (ETTNO Investigators, 2012) and the Transfusion of Prematures trial (TOP) (U.S. National Institutes of Health, 2014), examining the short- and longer-term neurodevelopmental outcomes to 24 months’ corrected age in extremely LBW infants randomised to liberal or restrictive RBC transfusion thresholds are well underway. These trials should provide valuable additional information to guide neonatal transfusion practice and longer-term outcomes related to transfusion.

**SYSTEMATIC REVIEWS**

The safety and efficacy of RBC transfusions in neonates was summarised in a broad review that identified a total of 27 randomised controlled trials (Venkatesh et al., 2012). The majority of included trials were small and compared different schedules, doses or products for RBC transfusion. The authors noted that, although it might appear that the total number of identified trials represents a substantial evidence base to inform the safety of neonatal transfusion practice, this is substantially limited by methodological limitations of the included trials (Venkatesh et al., 2012). Only 3 of the included 27 trials compared RBC transfusion with no transfusion (or placebo) and enrolled fewer than 100 patients. The authors found that the other potential risks for neonatal transfusion, e.g. TRALI or TACO, were generally very poorly reported in the identified trials, again also noting that these risks for neonatal transfusion are not well captured in current haemovigilance schemes (Venkatesh et al., 2012).

A Cochrane review further summarised the more specific data examining liberal (high) compared to restrictive (low) RBC transfusion thresholds and found no evidence that either strategy had an effect on mortality, major neonatal morbidities or on survival without major morbidity in preterm infants ≤1500 g. It included three published studies (Blank et al., 1984; Bell et al., 2005; Kirpalani et al., 2006) and one unpublished study (Whyte & Kirpalani, 2011). Similar restrictive transfusion thresholds were used for all included studies and are shown in Table 2. Safety at Hb levels below these limits in Table 2 has not been evaluated, and therefore, it is not recommended to allow levels to fall below these outlined limits. The Cochrane review included, as secondary outcomes, post-natal acquisition of viral infection (cytomegalovirus, human immunodeficiency virus or hepatitis C) and number of donor exposures per infant but did not include other transfusion adverse events as an outcome of interest for the review (Whyte & Kirpalani, 2011).

In an attempt to more systematically review this literature, Keir and colleagues described a broad synthesis of all reported risks to better understand the clinical associations attributed to neonatal RBC transfusions (Keir et al., 2016). Eligible studies were observational studies with or without comparator groups and randomised trials. Studies were classified into two groups, in which there was a difference in transfusion numbers and/or volume between groups to compare liberal versus restrictive RBC transfusion practices. Liberal transfusion practice was defined as one group receiving a greater volume and/or number of RBC transfusions compared with the comparison group (restrictive transfusion practice). This allowed a comparison between the outcomes of infants who were exposed to restrictive or liberal RBC transfusion practices. The study examined a total of 61 studies (16 randomised trials and 45 non-randomised studies) and demonstrated no evidence of difference in rates of mortality between restrictive and liberal strategies for transfusion (8 randomised controlled trials: risk ratio 1·24; 95% confidence interval 0·89–1·67, heterogeneity = 0%) (Keir et al., 2016). Similarly, no difference was seen between transfusion strategies for
important neonatal morbidity outcomes, including NEC, ROP, CLD or IVH (Goel & Josephson, 2018). These findings are contrary to the views of some neonatologists and transfusion experts about the risks of transfusion in the neonatal population (Christensen et al., 2012; Christensen & Ilstrup, 2013). Reasons may include differences in study identification between reviews and limitations of primary study evidence. Systematic reviews such as this report should have clear definitions of study inclusion criteria and outcomes of interest and may only capture a small number of studies with definitions of the different potential adverse effects related to RBC transfusion (Keir et al., 2016).

Kirpalani and Zupancic undertook a meta-analysis (Kirpalani & Zupancic, 2012) focusing on the specific association between RBC transfusions and the occurrence of NEC. Necrotising enterocolitis is a rare but devastating disease that affects preterm infants and is associated with high rates of morbidity and mortality. Again, the majority of identified studies were observational. The authors found that the direction of effect of RBC transfusions on NEC (more transfusions showed lower NEC), as demonstrated in randomised trials, was opposite of that seen in observational studies (transfusions were associated with NEC). A recent study by Patel et al. (2016a) found that severe anaemia, not RBC transfusion, was associated with an increased risk of NEC. The authors suggest that prevention of severe anaemia may be more important than minimising RBC transfusion alone (Patel et al., 2016a).

RESEARCH PRIORITIES AND CONCLUSIONS

As recently highlighted by Goel and Josephson (Goel & Josephson, 2018), one of the main current impediments to advancement of neonatal transfusion research is a lack of registries or networks that include neonatal RBC transfusion-relevant data with outcome or donor linkage to recipients in sufficient detail. Use of and expansion of existing databases and registries could be utilised, e.g. the Vermont Oxford Network, American Academic of Pediatrics Section on Neonatal-Perinatal Medicine Task Force for Neonatal Perinatal Therapeutic Development (NeoPeritD), Pediatric Clinical Data Warehouse, the CNN and the International Network for Evaluation of Outcomes (iNeo). Multicentre international research collaborations are also required to definitively determine the risk of RBC transfusion in neonates, and planned work in this area has been clearly outlined previously by Patel and colleagues (Patel et al., 2016b). Alongside these initiatives is the need for the standardisation of definitions of adverse effects through international consensus, which is being supported by ISBT via the Haemovigilance Working Party and the Paediatric subgroup of the Clinical Transfusion Working Party, and working with other national international partners such as national haemovigilance systems and the International Haemovigilance Network.

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CONFLICT OF INTEREST

The authors have no competing interests.

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