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Health outcomes in recipients of blood transfusion – observational studies versus randomized clinical trials.

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Abstract (287 words)

There is good evidence that blood transfusion practice varies by time and geography, and often departs from evidence-based guidelines. On the other hand, interventions to change physician practice around the ordering of blood transfusions can be successful. The challenge is therefore to develop reliable evidence to support rational transfusion practice. Both observational studies and randomized clinical trials have strengths and limitations. Observational studies are cheaper and usually larger with concomitant improved statistical power, and may be more representative by including a wide range of patients and hospitals in the routine setting unaffected by a research protocol. Weakness of observational studies include confounding by unmeasured factors; indication bias, namely overestimation of adverse outcomes by the fact that transfused patients tend to be sicker than similar patients who did not receive transfusion; and the fact that available data may not suit the research question. Randomized clinical trials have the advantage of minimizing the effects of confounding and bias by virtue of the randomization process. Limitations of randomized trials include their expense which limits them to specific research questions and may limit statistical power; and ethical limits to study design such as inability to utilize a placebo by withholding transfusion. Finally, inclusion and exclusion criteria can limit the generalizability of conclusions by restricting enrollment to a set of patients that differ from those seen in general medical practice. In this review, I shall attempt to illustrate the complementary contributions and limitations of observational epidemiological studies and randomized clinical trials in understanding several transfusion-related adverse outcomes: mortality; TRALI; TACO; and the RBC storage lesion. I conclude that evidence for the efficacy and adverse outcomes of blood transfusion needs to be obtained from a balanced combination of observational studies and clinical trials.

Key words: Blood transfusion   Trials, randomized clinical   Epidemiologic studies   Mortality   Pulmonary edema   Lung injury

Introduction

There is good evidence that transfusion practice is highly variable by time and geography, and often departs from evidence-based guidelines.[1-4] On the other hand, critical reviews have shown that interventions to change physician practice around the ordering of blood transfusions can be successful, especially by using computerized physician order entry (CPOE) to track physician decisions, with linkage to objective data laboratory, vital sign and outcomes data.[5-8] The challenge is therefore to synthesize evidence and apply it to educating physicians in practice.

Observational studies versus randomized clinical trials of adverse outcomes in transfusion recipients.

Both observational studies have both strengths and weaknesses in producing evidence for rational transfusion practice. Observational studies are cheaper and usually larger with concomitant improved statistical power. The use of large data sets also allows them to be more representative by including a wide range of patients and hospitals and to capture actual practice in the routine setting unaffected by a research protocol. Weakness of observational studies includes confounding by unmeasured or inadequately controlled influences of patient demographics, diagnoses; and indication bias, namely overestimation of adverse outcomes by the fact that transfused patients tend to be sicker than similar patients who did not receive transfusion. Finally, available data for observational studies may not suit the research question, either due to geography or coverage of electronic databases constructed for administrative purposes, i.e. Medicare data in the USA includes only patients over age 65.

Randomized clinical trials have the advantage of minimizing the effects of confounding and bias by virtue of the randomization process, whereby these effects are balanced in the intervention and control groups. On the other hand, randomized trials are quite expensive and must

therefore be limited to specific research questions in circumscribed patient populations and may have inadequate power to detect small differences in outcomes. It would generally be unethical to utilize a true placebo by withhold transfusion. Finally, inclusion and exclusion criteria can limit the generalizability of conclusions by restricting enrollment to a set of patients that differ from those seen in general medical practice.

In this brief review, I shall give attempt to illustrate the complementary contributions and limitations of observational epidemiological studies and randomized clinical trials directed at understanding outcomes following transfusion.

Mortality and blood transfusion

Hebert et al. pioneered the use of the randomized clinical trial to study transfusion thresholds with their randomized controlled trial of 838 critically ill patients with initial hemoglobin values below 9.0 g/dL.[9]   Patients were randomized either to a restrictive (hemoglobin < 7.0 g/dL) or liberal (hemoglobin < 10 g/dL) transfusion strategy. Overall 30 day mortality was not significantly decreased, but there was significantly lower mortality in patients with APACHE score <= 20 or age less than 55 years. There was no decrease in mortality in patients with clinically significant cardiac disease. A similar trial restricted to cardiac surgery patients in 2009-2010 reported no difference in 30 day mortality or significant complications (cardiogenic shock, adult respiratory distress syndrome or renal failure) in patients randomized to maintain hematocrit at 24 versus hematocrit of 30 (actual mean hemoglobins were 10.5 and 9.1, respectively).[10] Most recently, Carson et al. randomized 2016 hip surgery patients aged over 50 years and history of our risk factors for cardiovascular disease to a transfusion threshold of 8 g/dL versus 10 g/dl.[11] There was no difference in death or inability to walk across room at 60 days. These studies provide good evidence that more conservative transfusion strategies do not increase mortality or other adverse outcomes in the populations studied.

Vincent et al. reported a large observational study of blood transfusion in intensive care units in Europe during 1999.[12] They reported that patients receiving blood transfusion has significantly increased mortality rate both in the intensive care unit and after 28 days. Corwin et al. reported a similar study from the United States, indicating that 44% of patients in intensive care units receive blood transfusion, with associated increase in mortality, ICU stay, and hospital stay.[13] However these conclusions are limited by probable indication bias.

Pattakos et al. studied 322 Jehovah's Witnesses and 87,453 non-Witnesses who underwent cardiac surgery 1983 to 2011; 56% of non-Witnesses received transfusions.[14] Compared to a subgroup of 322 propensity-matched transfused patients, the non-transfused Jehovah's Witnesses had lower one-year mortality and lower rates of several complications including myocardial infarction, re-operation, and prolonged ventilation. Although propensity score matching has been used to compensate for indication bias, there is controversy as to whether it can account for potential biases other than those included in the propensity score. It is also interesting that the authors did not include a propensity score matched group of non-transfused non-Witnesses - that would have been an interesting way to assess whether confounding by healthier lifestyle may have been responsible for lower mortality and complications among the Jehovah's Witnesses.

Transfusion related acute lung injury (TRALI)

TRALI is a rare complication of blood transfusion but a leading cause of transfusion-related mortality. Because of its rarity, observational studies, and specifically the case-control design, are ideally suited to its study. Toy et al conducted a multicenter study to determine TRALI incidence by prospective, active surveillance and to identify risk factors by a case-control study. [15] Two academic medical centers enrolled 89 cases and 164 transfused controls stratum-

matched by number of blood products received. Recipient risk factors identified by multivariate analysis included higher interleukin-8 levels, liver surgery, chronic alcohol abuse, shock, higher peak airway pressure while being mechanically ventilated, current smoking and positive fluid balance. Transfusion related risk factors included receipt of plasma or whole blood from female donors, volume of human leukocyte antigen (HLA) Class II antibody with NBG > 27.5 and volume of anti-HNA positive plasma.

By chance, the study covered the period during which "plasma mitigation", namely avoidance of female plasma and HLA antibody testing of female platelet donors, was introduced in the United States. The study was able to document a reduction in the incidence of TRALI from 2006 (2.57 per 10,000 transfused units) to 2009 (0.81 per 10,000 transfused units in 2009; p = 0.002). Thus, using an observational design, the study was able to provide supporting evidence for the theory that transfused HLA antibodies cause at least a proportion of TRALI cases. However the residual TRALI cases after mitigation measures suggests that additional research will be needed to identify other causes.

Transfusion associated circulatory overload (TACO)

TACO is characterized by new respiratory distress and hydrostatic pulmonary edema within 6 hours after blood transfusion, but its risk factors and outcomes are poorly characterized. Using an observational case control design, the author and colleagues enrolled 83 patients with severe TACO identified by active surveillance for hypoxemia and 163 transfused controls without hypoxemia at two large tertiary care hospitals.[16] TACO was associated with chronic renal failure, a past history of heart failure, hemorrhagic shock, the number of blood products transfused and a positive fluid balance. Patients with TACO had significantly increased in-hospital mortality after controlling for Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score (Figure 1), and longer hospital and intensive care unit lengths of stay.

These data, if replicated, could be used to construct predictive algorithms for transfusion-associated circulatory overload, and subsequent modifications of transfusion practice might prevent morbidity and mortality associated with this complication. The U.S. National Heart, Lung and Blood Institute (NHLBI) Recipient Epidemiology and Donor evaluation Study-III (REDS-III) is planning additional studies of this common complication.

The red blood cell (RBC) storage lesion

Another area of current controversy in transfusion outcomes research includes the topic of the RBC storage lesion, namely whether longer RBC storage is associated with more frequent adverse outcomes in transfusion recipients. Observational studies on this topic have yielded conflicting results; one randomized clinical trial has shown null results and at least two others are in progress.

Koch et al. performed a retrospective observational study in cardiac surgery patients including 2872 patients who received 8802 units of blood that had been stored for 14 days or less and 3130 patients who received 10,782 units of blood that had been stored for more than 14 days. [17] Using logistic regression and propensity score methods to control for bias and confounding, they found that patients who were given older units had higher rates of in-hospital mortality, intubation beyond 72 hours, renal failure and sepsis or septicemia. The probability of a composite outcome measure comprised of these bad outcomes in relation to storage duration was increased with older blood. At one year, mortality was significantly lower in patients given newer blood.

Edgren et al. also performed an observational study using the very large database of transfusion and health outcomes data covering Sweden and Denmark, and including 404,959

transfusion episodes.[18] The 7-day risk of death was similar in all storage duration groups, but a 5 percent higher risk emerged among recipients of blood stored for 30 to 42 days compared to recipients of blood stored for 10 to 19 days (Figure 2). With 2-year follow-up, this excess remained at the same level. No dose-response pattern was revealed and no differential effect was seen when the analyses were restricted to recipients of leukoreduced units only. The authors concluded that although a small excess mortality was possible in recipients of the oldest RBCs, the risk pattern was more consistent with weak confounding than with an effect of exposure to older RBCs.

The recently reported Age of Red cells In Premature Infants (ARIPI) randomized clinical trial showed no effect of RBC storage duration in critically ill pediatric patients in Canada.[19] A total of 377 premature infants with birth weights less than 1250 g were randomized to receive RBCs stored for less than seven days (mean 5.1 days) versus standard practice (mean 14.6 days). There was no difference in the composite primary outcome of necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, and intraventricular hemorrhage, as well as death.

Other randomized clinical trials of the RBC storage lesion are underway, including the ABLE trial in Canada, which will examine ICU patients randomized to receive RBCs stored for less than seven days versus standard practice (15 to 20 days), with a primary outcome of 90 day all-cause mortality.[20] Finally, the Red Cell Storage Duration Study (RECESS) in the U.S. will compare the effects of transfusing red blood cell units stored <= 10 days vs. red blood cell units stored >= 21 days, in patients who are undergoing complex cardiac surgery and are likely to need a red blood cell transfusion.[21] The primary outcome is change in the composite multiple organ dysfunction score (MODS) from the pre-operative baseline and secondary outcomes include 28-day mortality.

Future directions for database research

Large administrative databases will have increasing promise for outcomes research in transfusion medicine, spurred by the growing utilization of electronic medical records in the U.S. First, the NHLBI REDS-III study is currently building a linked research database which will include donor and donation data from the blood center, blood product information, and transfused patient data from hospital electronic medical records. The Kaiser Permanente Division of Research is pursuing similar efforts within their network of 21 Northern California Kaiser Permanente hospitals. Finally, trade groups and commercial enterprises are pursuing strategies whereby customer hospitals would release data on blood transfusions to third-party databases which would link these data to donor and donation data obtained from blood centers.

In parallel with the formation of these databases, advances in analytic and statistical approaches will be required to allow optimal modeling of the transfusion process and to avoid pitfalls of indication bias and confounding. Additionally, imaginative approaches to translating evidence to interventions to improve in medical practice need to be developed. As mentioned above, CPOE systems could be improved with the creation of real-time decision support algorithms. In conclusion, evidence for the efficacy and adverse outcomes of blood transfusion needs to be obtained from a balanced combination of observational studies and clinical trials.

Figure 1. In-hospital mortality in patients with TACO compared to controls without hypoxemia.

TACO was associated with significantly increased mortality after controlling for APACHE-2 and

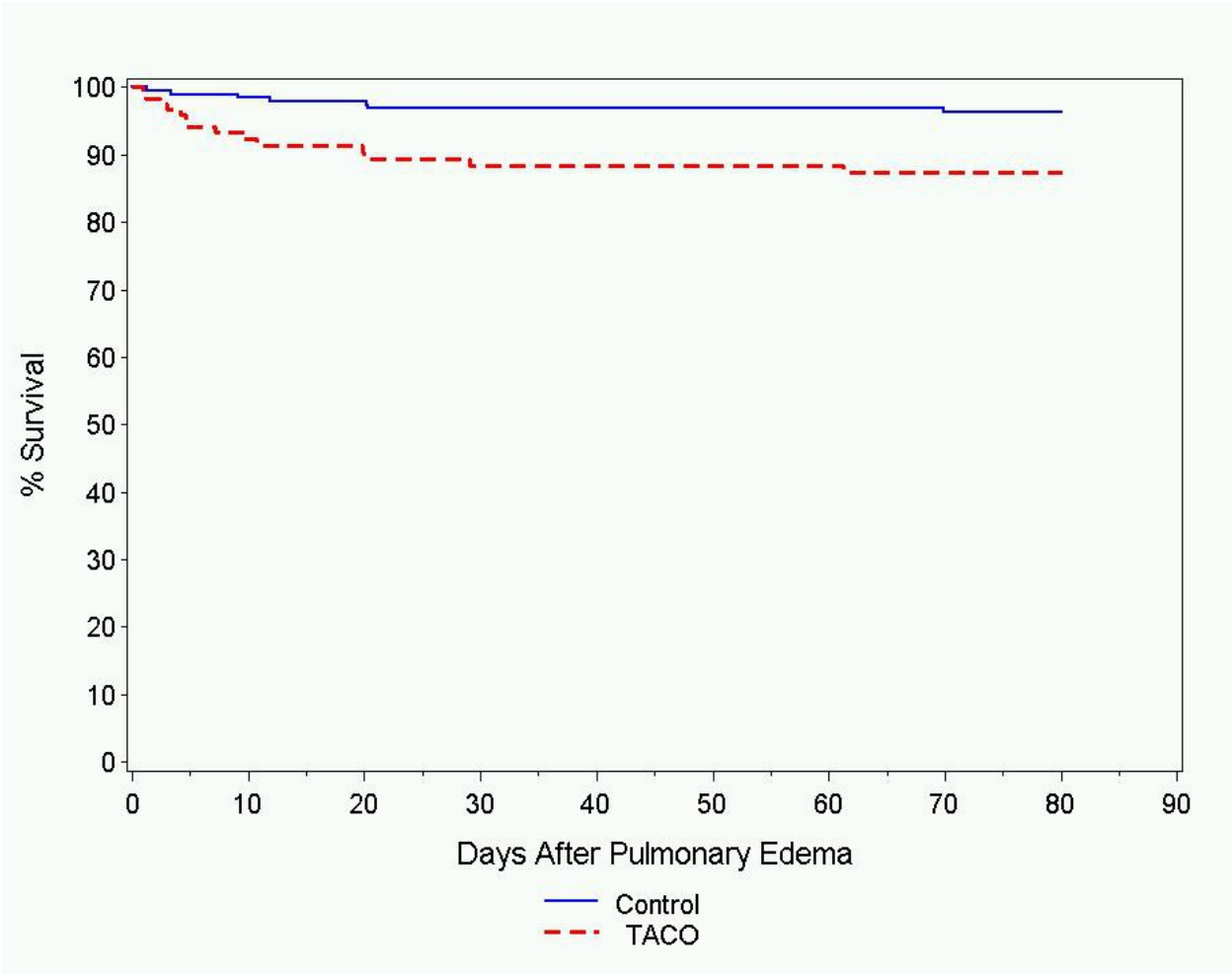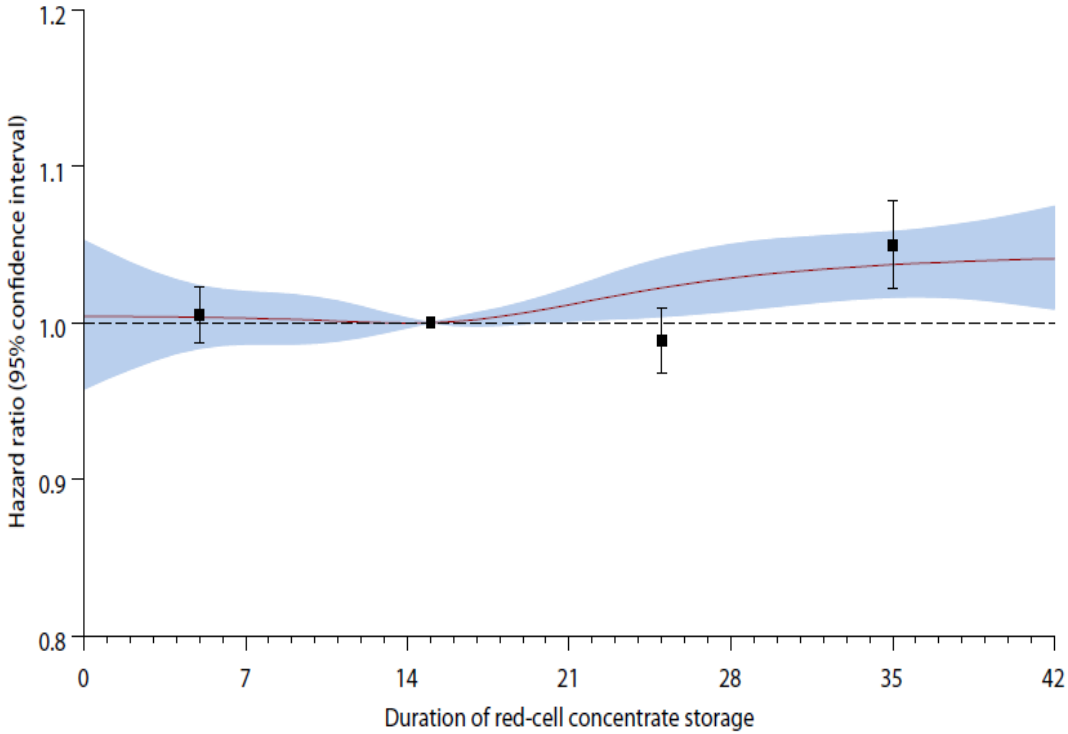ICU enrollment (HR = 3.20, 95% CI 1.23 - 8.10).[16]

Figure 2. Relative hazard of death following transfusion of RBC units stored for various durations compared to 10-19 days, among patients in the SCANDAT database covering Sweden and Denmark.[18]

REFERENCES

1.   Wass CT, Long TR, Faust RJ, Yaszemski MJ, and Joyner MJ. Changes in red blood cell

        transfusion practice during the past two decades: a retrospective analysis, with the Mayo

        database, of adult patients undergoing major spine surgery. *Transfusion*, 2007;47:1022-

        7.

2.   Ibrahim HN, Ishani A, Foley RN, Guo H, Liu J, and Collins AJ. Temporal trends in red

        blood transfusion among US dialysis patients, 1992-2005. *Am J Kidney Dis*,

        2008;52:1115-21.

3.   Bennett-Guerrero E, Zhao Y, O'Brien SM, Ferguson TB, Jr., Peterson ED, Gammie JS,

        and Song HK. Variation in use of blood transfusion in coronary artery bypass graft

        surgery. *JAMA*, 2010;304:1568-75.

4.   Qureshi H, Lowe D, Dobson P, Grant-Casey J, Parris E, Dalton D, Hickling K, Waller F,

        Howell C, and Murphy MF. National comparative audit of the use of platelet transfusions

        in the UK. *Transfus Clin Biol*, 2007;14:509-13.

5.   Wilson K, MacDougall L, Fergusson D, Graham I, Tinmouth A, and Hebert PC. The

        effectiveness of interventions to reduce physician's levels of inappropriate transfusion:

        what can be learned from a systematic review of the literature. *Transfusion*,

        2002;42:1224-9.

6.   Rana R, Vlahakis NE, Daniels CE, Jaffe AS, Klee GG, Hubmayr RD, and Gajic O. B-type

        natriuretic peptide in the assessment of acute lung injury and cardiogenic pulmonary

        edema. *Crit Care Med*, 2006;34:1941-6.

7.   Rothschild JM, McGurk S, Honour M, Lu L, McClendon AA, Srivastava P, Churchill WH,

        Kaufman RM, Avorn J, Cook EF, and Bates DW. Assessment of education and

        computerized decision support interventions for improving transfusion practice.

        Transfusion, 2007;47:228-39.

8.   Lin YC, Chang CS, Yeh CJ, and Wu YC. The appropriateness and physician compliance of platelet usage by a computerized transfusion decision support system in a medical center. *Transfusion*, 2010;50:2565-70.

9.   Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, and Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*, 1999;340:409-17.

10.   Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, Fukushima J, Kalil Filho R, Sierra DB, Lopes NH, Mauad T, Roquim AC, Sundin MR, Leao WC, Almeida JP, Pomerantzeff PM, Dallan LO, Jatene FB, Stolf NA, and Auler JO, Jr. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA*, 2010;304:1559-67.

11.   Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, Nemo G, Dragert K, Beaupre L, Hildebrand K, Macaulay W, Lewis C, Cook DR, Dobbin G, Zakriya KJ, Apple FS, Horney RA, and Magaziner J. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med*, 2011;365:2453-62.

12.   Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, and Peres-Bota D. Anemia and blood transfusion in critically ill patients. *JAMA*, 2002;288:1499-507.

13.   Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot MM, Duh MS, and Shapiro MJ. The CRIT Study: Anemia and blood transfusion in the critically ill--current clinical practice in the United States. *Crit Care Med*, 2004;32:39-52.

14.   Pattakos G, Koch CG, Brizzio ME, Batizy LH, Sabik JF, 3rd, Blackstone EH, and Lauer MS. Outcome of patients who refuse transfusion after cardiac surgery: a natural experiment with severe blood conservation. *Arch Intern Med*, 2012;172:1154-60.

15.   Toy P, Gajic O, Bacchetti P, Looney MR, Gropper MA, Hubmayr R, Lowell CA, Norris PJ, Murphy EL, Weiskopf RB, Wilson G, Koenigsberg M, Lee D, Schuller R, Wu P, Grimes B, Gandhi MJ, Winters JL, Mair D, Hirschler N, Sanchez Rosen R, and Matthay MA. Transfusion-related acute lung injury: incidence and risk factors. *Blood*, 2012;119:1757-67.

16.   Murphy EL, Kwaan N, Looney MR, Gajic O, Hubmayr RD, Gropper MA, Koenigsberg M, Wilson G, Matthay MA, Bacchetti P, and Toy P. Risk factors and outcomes in transfusion-associated circulatory overload (TACO). *Amer J Med*, 2013;126:357.e29-357.e38.

17.   Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, and Blackstone EH. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med*, 2008;358:1229-39.

18.   Edgren G, Kamper-Jorgensen M, Eloranta S, Rostgaard K, Custer B, Ullum H, Murphy EL, Busch MP, Reilly M, Melbye M, Hjalgrim H, and Nyren O. Duration of red blood cell storage and survival of transfused patients (CME). *Transfusion*, 2010;50:1185-95.

19.   Fergusson DA, Hebert P, Hogan DL, LeBel L, Rouvinez-Bouali N, Smyth JA, Sankaran K, Tinmouth A, Blajchman MA, Kovacs L, Lachance C, Lee S, Walker CR, Hutton B, Ducharme R, Balchin K, Ramsay T, Ford JC, Kakadekar A, Ramesh K, and Shapiro S. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: the ARIPI randomized trial. *JAMA*, 2012;308:1443-51.

20.   Lacroix J, Hebert P, Fergusson D, Tinmouth A, Blajchman MA, Callum J, Cook D, Marshall JC, McIntyre L, and Turgeon AF. The Age of Blood Evaluation (ABLE) randomized controlled trial: study design. *Transfus Med Rev*, 2011;25:197-205.

21.   Trial registered on the U.S. Clinical Trials website with identifier: NCT00991341, http://clinicaltrials.gov/show/NCT00991341 last updated March 11, 2013; accessed 26 March 2013.