



**UNIVERSITY OF CAPE TOWN**  
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

**TRANSFUSION PRACTICES AMONG CHILDREN UNDERGOING CARDIAC  
SURGERY ADMITTED TO THE RED CROSS WAR MEMORIAL CHILDREN'S  
HOSPITAL PAEDIATRIC INTENSIVE CARE UNIT**

by

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**SUBMITTED TO THE UNIVERSITY OF CAPE TOWN**

**In fulfillment of the requirements for the degree of**

**MASTER OF PHILOSOPHY (MPhil) in**

**PAEDIATRIC CRITICAL CARE**

**SUPERVISORS: DR S SALIE, PROF A ARGENT, PROF B MORROW**

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## Declaration

This research is based on independent work performed by **Dr Kaiser Fitzwanga** for the requirement of the degree - Master of Philosophy in Paediatric Critical Care, and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to any other university. This work has not been reported or published prior to registration for the above-mentioned degree.

Signed: 

Signed by candidate
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Date: October 16, 2018

## Abstract

### **Transfusion Practices Among Children Admitted to a South African PICU Following Cardiac Surgery**

**Objective-** We aimed to describe the use of blood products following cardiac surgery, as well as the outcomes and factors associated with post-operative blood product use

**Design-** Prospective, single centre observational study

**Setting-** Paediatric intensive care unit (PICU) in Cape Town, South Africa

**Patients-** One hundred and twenty-six children <18 years old admitted to the PICU following cardiac surgery between July 2017 and January 2018

**Interventions-** None

**Measurements and Main Results-** The data was prospectively obtained from blood bank charts, intraoperative and PICU observation charts. Demographic data, intraoperative details and post-operative blood product use were extracted from patient records and entered in a standardised case record form. Fifty three percent of children received blood products following cardiac surgery. The blood products transfused included cryoprecipitate (30.9%), packed red cells (22.2%), albumin (18.3%), fresh frozen plasma FFP (15.9%) and platelet concentrate (15.1%). Low haemoglobin level was commonest indication (86%) for red cell use. Bleeding was the commonest indication for FFP (70%) and cryoprecipitate (67%) use. Thrombocytopenia was the commonest indication (84%) for platelet use while hypotension episodes were predominant (95%) in those who received albumin. The standardized mortality ratio was 3.1 vs 0, respectively, among transfused versus non-transfused patients ( $p < 0.0001$ ). The median (IQR) duration of PICU stay was 5 (3-11) vs 2 (2-5) days, respectively in those transfused versus non-transfused ( $p < 0.0001$ ). The median (IQR) ventilation duration was 47

(22-132) hours vs 20 (6-27) hours, respectively among the transfused versus non-transfused ( $p = < 0.0001$ ). The factors associated with blood-product use post cardiac surgery include previous cardiac surgery, younger age, lower weights, and prolonged coagulation parameters ( $p = < 0.05$ ).

**Conclusion-** There is high usage of blood products among children post cardiac surgery. The children transfused had a longer ICU stay, ventilation duration, and higher standardized mortality ratio compared to the non-transfused.

**Key words:** blood product(s); transfusion; practice(s); children; cardiac surgery

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## Abbreviations

ACT- Activated clotting time

ALCAPA- Anomalous left coronary from the pulmonary artery

AR- Aortic regurgitation

ASD- Atrial septal defect

AS- Aortic stenosis

AVSD- Atrioventricular septal defect

BT- Blalock Taussig

DORV- Double outlet right ventricle

HLHS- Hypoplastic left heart syndrome

MR- Mitral regurgitation

MS- Mitral stenosis

OR- Operating room

PA- Pulmonary atresia

PAPVC- Partial anomalous pulmonary venous connection

PDA- Patent ductus arteriosus

PICU- Paediatric intensive care unit

PIM- Paediatric index of mortality

PTT- Partial thromboplastin time

RVOT- Right ventricular outflow tract

TA- Tricuspid atresia

TAPVC- Total anomalous pulmonary venous connection

TET- Tetralogy of fallot

TGA- Transposition of great arteries

TR- Tricuspid regurgitation

VSD- Ventricular septal defect

## Chapter 1: Introduction

### 1.1 Context

Blood products are not identical across the world and may vary considerably in how they are collected, stored, processed and administered. The quality of blood products is hugely variable in various parts of the world. The guidelines for blood transfusion in the cardiac perioperative period are based on relatively small numbers of studies, and the focus of this study was to define the transfusion practice in our unit. This would provide the basis for further focus on quality improvement and optimization of protocols.

#### **Risk Factors Associated With Transfusion Or Bleeding During and After Cardiac Surgery**

The factors that predispose patients undergoing cardiac surgery to bleeding include patient, procedure and drug-related factors. Patient related factors include age, preoperative anaemia, preoperative thrombocytopenia, preoperative coagulopathy and antithrombotic therapy. Procedure related factors include repeated procedures (re-operation), the type and urgency of the operation, cardiopulmonary bypass (CPB); the use of heparin on CPB, residual heparin, reduced thrombin generation, fibrinogen deficiency, thrombocytopenia, platelet dysfunction, hyperfibrinolysis, hypothermia, acidosis during the procedure, dilution of clotting factors with intravenous fluid administration, surgical causes and consumption of clotting factors in active bleeding (1-3).

Drug related factors are related to use of antiplatelet agents such as aspirin, clopidogrel or use of anticoagulant therapy such as warfarin, or use of low molecular weight heparin or unfractionated heparin (3).

The interventions that have been shown to reduce bleeding during cardiac surgery include: anti-fibrinolytic therapy such as tranexamic acid, recombinant factor VIIa and epsilon aminocaproic acid, use of minimized CPB circuits with reduced priming volume, normovolaemic haemodilution, salvage of blood from the CPB circuit, modified ultrafiltration, and microplegia (4-7). The use of pre-operative erythropoietin increases the haemoglobin level prior to surgery, hence reducing blood transfusion requirement.

### **Type of Blood Products Used and Indications during Cardiac Surgery**

The use of haemoglobin level in isolation, as a threshold for red cell transfusion is not sufficient, and additional factors such as markers of oxygen delivery, ongoing bleeding and comorbid disease processes should be considerations factored in the decision to transfuse red blood cells (8).

Red blood cells increase arterial oxygen content by increasing haemoglobin level, therefore increasing tissue oxygen delivery. However, this does not take immediate effect as red cell transfusion increases blood viscosity which can reduce cardiac output in normovolaemic patients whose cardiac function is not impaired. Stored red cells undergo biochemical and biophysiological changes which affects their oxygen affinity and delivery (9).

Fresh frozen plasma is a source of procoagulant factors and fibrinogen, and is indicated in the context of massive bleeding, where it is administered in fixed ratios with platelets and red cells (10, 11). Cryoprecipitate contains high concentrations of factors VIII, XIII and fibrinogen, and is indicated for correcting fibrinogen levels below 1g/l (12).

Platelet transfusion is indicated in significant microvascular bleeding with diffuse oozing without an obvious surgical cause, after correction of clotting factors (1, 13). Platelet dysfunction and thrombocytopenia increase the risk of bleeding and threshold for transfusion

after CPB(14). The factors that influence platelet count and function during CPB include exposure to the bypass circuit and shear stress at different levels of CPB resulting in platelet adhesion and aggregation, inflammatory mediators during CPB, haemodilution, hypothermia, preoperative use of anti-platelet agents (1, 3, 15, 16). Other molecular mechanisms that contribute to platelet dysfunction include loss of cell surface glycoprotein receptors, such as the platelet collagen receptor, glycoprotein GPIb-IX and GPIIb-IIIa (1, 14).

### **Transfusion Practice and Thresholds Used in Paediatric Cardiac Critical Care**

The physiologic threshold at which oxygen consumption decreases due to reduced oxygen delivery in humans is a haemoglobin level of 3-4 g/dl, an oxygen extraction ratio of 0.44 and a mixed venous oxygen of 34 mmHg as demonstrated in studies in Jehovah's witness population who decline blood transfusion (17). The evidence guiding red cell transfusion thresholds in children is scanty. Data obtained from retrospective studies in Kenyan children with severe anemia related to high parasitemia from *P.Falciparum* malaria demonstrated high early mortality rates at haemoglobin levels below 4g/dl (18). Carson and colleagues demonstrated a > 50% mortality rate of in patients with a post operative haemoglobin below levels of 5 g/dl, as well as a two-fold increase in odds of death for every 1g/dl drop in haemoglobin among adults with post-operative haemoglobin concentration below 8g/dl (19).

Patients with ongoing bleeding, who are in haemorrhagic shock should receive red blood cells, with plasma and platelet concentrate in fixed ratios (8). Results from the subanalysis of the Transfusion Requirements in Paediatric Intensive Care Unit (TRIPICU) study suggest that a haemoglobin threshold of 7g/dl and 9 g/dl for haemodynamically stable children >28 days old with non cyanotic heart disease and cyanotic heart disease respectively is reasonable. These thresholds have been adapted for use in children post cardiac surgery (4, 8, 20).

The British Committee for standards in haematology recommends that fresh frozen plasma (FFP) and cryoprecipitate should not be used primarily on the basis of abnormal lab results, but should be restricted to use in patients with signs of bleeding or planned invasive procedures (21). FFP should be given to children with prothrombin time/ activated partial thromboplastin time (PT/APTT) levels >1.5 times the midpoint of the normal range and cryoprecipitate for fibrinogen levels <1.5g/l associated with significant haemorrhage following cardiopulmonary bypass (21). Platelets should be transfused when there is clinically significant haemorrhage and a threshold of  $< 100 \times 10^9/l$  should be used in paediatric cardiac surgery (21).

### **Complications Associated With Blood Product Use**

Blood product transfusion is associated with immune-mediated and non immune-mediated risks. Immune-mediated risks include transfusion-related lung injury, acute haemolytic reactions, allergic and anaphylactic reactions, non haemolytic febrile reactions, and transfusion associated graft versus host disease (2, 22). Non-immune mediated risks of blood transfusion include hyperkalaemia, fluid overload, transmission of infection, hypothermia and iron overload (22).

The presence of leucocytes in blood has been linked to the febrile reactions and immune-mediated reactions observed after blood transfusion, therefore leucoreduction and filtration is performed in most centres prior to blood storage (23-25). Leukoreduction has been further shown to increase packed red cell viability prior to storage (23). Although transfusion-associated graft versus host disease (TA-GVHD) is an uncommon complication of blood transfusion, it is a fatal complication especially for patients with congenital immune deficiency, therefore gamma-irradiation of blood products prior to transfusion impairs the proliferation of lymphocytes, and prevents TA-GVHD (23, 25).

High income countries which are also quite well resourced, have adopted a universal policy of leucocyte depletion of stored blood products, which is a costly affair that low and middle-income countries may not afford routinely. In South Africa, infants routinely receive leucodepleted blood as a standard, and the blood packs are leucodepleted during preparation and storage. Adult units are generally used to prime the bypass circuit for infants undergoing cardiac surgery. The adult blood packs are not routinely leucodepleted, unless there is a clinical indication to warrant the use of leucocyte depleted blood products, in this case the clinician will put in a specific request to the blood bank for leucocyte depleted blood (26, 27).

Bacterial infections that occur post transfusion may happen because of bacterial contamination of blood products during venipuncture or collection of blood from an asymptomatic bacteremic donor. Gram negative bacteria such as *Yersinia enterocolitica* and *Pseudomonas* rapidly proliferate at storage temperatures of 4°C, whereas gram positive bacteria such as *Staphylococcus epidermidis*, *Staphylococcus aureus* and *Bacillus species* proliferate rapidly at room temperature (22).

In the well-resourced countries, donor blood is routinely screened for hepatitis B and C, human immunodeficient virus (HIV) 1 and 2, cytomegalovirus (CMV), human T cell lymphotropic virus and syphilis, and the incidence of viral transmission through blood transfusion has greatly reduced (22, 24, 28). In South Africa, donor blood is routinely screened for hepatitis B and C, HIV 1 and 2, and Syphilis. (South African National Blood Service) The variant Creutzfeldt-Jakob disease is a human prion disease that can also be transmitted by contaminated blood products (22, 28). The following are agents that can also be transmitted by transmission of contaminated blood, however they are not routinely screened in donor blood; hepatitis A virus, parvo B19 virus, *Babesia leishmania*, plasmodium, and *Brucella species* (28). Transfusion of blood products (red cells, fresh frozen plasma, platelet concentrate) intra and post operatively has also been found to be a potential risk factor to development of health care

associated infections in cardiac surgery (29-31).

Several studies have been done and demonstrated an association between red cell transfusion and length of stay in post-operative paediatric cardiac patients (32-35). The use of lower haemoglobin thresholds for red cells transfusion and leucocyte reduced blood products are factors that have been shown to reduce morbidity related to paediatric cardiac surgery (36, 37). Transfusion-mediated immune suppression has been described in transfusion medicine and thought to pose an increased risk in postoperative infections and activation of latent viral infections (22, 24, 38).

Complications such as transfusion related lung injury (TRALI), transfusion- associated cardiac overload, nosocomial infections, multi-organ organ dysfunction will result in increased ventilator days and hence increased ICU length of stay and have also been in implicated in associated mortality (24, 28, 39, 40).

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## 1.2 Ethical Considerations

### **Potential risks and benefits**

This was a minimal- risk observational study of routinely collected data related to standard clinical practice and no study- related interventions or investigations were performed.

Patients did not directly benefit from study participation. The findings of this study will form the baseline for future studies and inform practice- improvement initiatives, which has a potential societal benefit for improved practice and outcomes for future children admitted for cardiac surgery.

### **Ethical compliance**

The study was undertaken after approval from the Department of Paediatrics and Child Departmental Research Committee (DRC) and the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC ref: 437/2017), and carried out as guided by the Declaration of Helsinki, 2013, Ethical Principles for Medical Research involving Human Subjects (see appendices). Permission was also obtained from the hospital CEO before the study was commenced (see appendices). The investigators requested and obtained a waiver of the need for full informed consent due the non-interventional and minimal risk nature of this study. The information obtained from the study was kept confidential by recording data in questionnaires with assigned study numbers, avoiding the use of patient names.

## Chapter 2: Publication-ready manuscript

### **Transfusion Practices Among Children Admitted to a South African PICU Following Cardiac Surgery**

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**Objective-** We aimed to describe the use of blood products following cardiac surgery, as well as the outcomes and factors associated with post-operative blood product use

**Design-** Prospective, single centre observational study

**Setting-** Paediatric intensive care unit (PICU) in Cape Town, South Africa

**Patients-** One hundred and twenty-six children <18 years old admitted to the PICU following cardiac surgery between July 2017 and January 2018

**Interventions-** None

**Measurements and Main Results-** The data was prospectively obtained from blood bank charts, intraoperative and PICU observation charts. Demographic data, intraoperative details and post-operative blood product use were extracted from patient records and entered in a standardised case record form. Fifty three percent of children received blood products following cardiac surgery. The blood products transfused included cryoprecipitate (30.9%), packed red cells (22.2%), albumin (18.3%), fresh frozen plasma FFP (15.9%) and platelet concentrate (15.1%). Low haemoglobin level was commonest indication (86%) for red cell use.

Bleeding was the commonest indication for FFP (70%) and cryoprecipitate (67%) use. Thrombocytopenia was the commonest indication (84%) for platelet use while hypotension episodes were predominant (95%) in those who received albumin. The standardized mortality ratio was 3.1 vs 0, respectively, among transfused versus non-transfused patients ( $p < 0.0001$ ). The median (IQR) duration of PICU stay was 5 (3-11) vs 2 (2-5) days, respectively in those transfused versus non-transfused ( $p < 0.0001$ ). The median (IQR) ventilation duration was 47 (22-132) hours vs 20 (6-27) hours, respectively among the transfused versus non-transfused ( $p = < 0.0001$ ). The factors associated with blood-product use post cardiac surgery include previous cardiac surgery, younger age, lower weights, and prolonged coagulation parameters ( $p = < 0.05$ ).

**Conclusion-** There is high usage of blood products among children post cardiac surgery. The children transfused had a longer ICU stay, ventilation duration, and higher standardized mortality ratio compared to the non-transfused.

**Key words:** blood product(s); transfusion; practice(s); children; cardiac surgery

## Introduction

Blood products are frequently given to patients undergoing cardiac surgery. Recently, there has been increasing focus on the complications associated with blood transfusion. Some of those complications relate primarily to the volumes of blood used, but many relate to the blood products themselves (1, 2). The initial focus of adverse event review was on issues such as compatibility, bacterial and increasingly viral infections. There is now increasing focus on the associations between use of blood products and respiratory problems, duration of PICU stay, morbidity and mortality (1, 2). Blood products are not identical across the world and may vary

considerably in how they are collected, stored, processed, administered and overall quality. The guidelines for blood transfusion in the cardiac perioperative period are based on relatively small numbers of studies, primarily from countries with high quality blood products. The primary objectives of this observational study were to describe the use of blood products and their indications during the 72-hour period following cardiac surgery. The secondary objectives were to describe the PICU mortality, PICU length of stay, duration of ventilation and the factors associated with post-operative blood use.

## Materials and Methods

### **Study site**

This study was conducted in the intensive care unit of the Red Cross War Memorial Children's Hospital, South Africa, which is a 22-bedded multi-disciplinary unit that serves the Western Cape province. It is a closed PICU which serves both medical and surgical specialties, and approximately 1300 admissions are recorded annually.

### **Study Population**

We prospectively, consecutively recruited all children less than 18 years admitted to the PICU following cardiac surgery, during the period 13 July 2017 to 13 January 2018. Children admitted to PICU with medical and surgical conditions other than cardiac surgery were excluded from the study.

### **Data Collection and Management**

The data was obtained from blood bank records, intra operative charts and patient folders (including PICU observation charts). The definition of blood products included the following; red blood cells, fresh frozen plasma (FFP), platelets, cryoprecipitate and human albumin. The information regarding the type and characteristics of the different blood products used was

obtained from the blood bank records. Chest drain losses was used as the surrogate marker for active bleeding, with losses  $\geq 4\text{ml/kg/hr}$  considered as significant bleeding in our unit. Previous blood transfusion was defined as recent blood product administration within 14 days preceeding the current cardiac surgery. Hypotension episodes were defined as the systolic blood pressure or mean blood pressure below the low limit as set by the intensivist.

The intra operative charts provided the following information: preoperative cardiac diagnosis, surgical procedure performed, the type and characteristics of the different blood products used, haemoglobin level pre and post surgery, details on cardiopulmonary bypass (CPB) and the use of pharmacotherapy (tranexamic acid, Vitamin K, activated factor VII) to prevent bleeding. Demographic data (age, sex, weight, date of PICU admission and discharge) was obtained from the patient folders. In addition, data regarding haemoglobin levels, oxygen saturations, hypotension episodes, clotting profile, chest drain losses, duration of mechanical ventilation, length of stay and mortality (including PIM 3 scores (3, 4)) in the PICU, previous cardiac surgery, previous blood transfusion, previous ICU admission was obtained from the patient folders and PICU observation charts.

Data on the different blood products used intraoperatively and their characteristics was recorded. Details of the blood products used in the PICU, indications and volume (in ml/kg) of each blood product prescribed during the first 72 hours following cardiac surgery was recorded. Daily data collection captured the chest drain losses (in ml/kg/hr) during the first 72 hours following cardiac surgery. The outcomes recorded included length of stay in the PICU, total duration of ventilation and mortality.

All the data obtained was filled into a standardised case record form before transferring it into an excel data base (Excel 2016). We requested and received a waiver of the need for full

informed consent from the parents/guardians of the study participants, owing to the low risk, observational study design.

The study was undertaken after approval from the Department of Paediatrics and Child Departmental Research Committee and the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC 437/2017), and carried out as guided by the Declaration of Helsinki, 2013, Ethical Principles for Medical Research involving Human Subjects. We also obtained permission from the hospital medical superintendent before commencing the study.

### **Statistical Analysis**

Descriptive statistics were tested for normality using the Shapiro Wilks W test, and the data are summarized using median (interquartile range) for continuous variables and n (%) for categorical variables. Inferential statistics were conducted with the primary and secondary outcomes of blood transfusion and mortality using Mann-Whitney u and Chi Square tests as appropriate. Continuous data were compared using Spearman rank order correlation tests. Variables found to be significantly associated with blood product use were entered into stepwise binary logistic regression models to determine independent predictive factors. Results were considered statistically significant when the p-value was less than 0.05. Statistical analyses were conducted using Statistica (Version 13, StatSoft Inc, USA).

## Results

The characteristics of the 126 patients admitted to PICU following cardiac surgery are summarized in Table 1. Twenty-two (17.5%) patients had undergone previous cardiac surgery, of which 15.1% were median sternotomies. The commonest single lesion pre-operative cardiac diagnoses were: atrioventricular septal defect-17 (13.5%), tetralogy of fallot-12 (9.5%), ventricular septal defect-11 (8.7%), mitral regurgitation-7 (5.6%), aortic stenosis-6 (4.8%), total anomalous pulmonary venous connection- 6 (4.8%), patent ductus arteriosus- 6 (4.8%), atrial septal defect-5 (3.9%).

The commonest single cardiac surgical repairs included: total correction of tetralogy of fallot-13 (10.3%), ventricular septal defect repair-11 (8.7%), atrial septal defect repair-11 (8.7%), fontan operation-7 (5.6%), patent ductus ligation- 7 (5.6%), mitral valve repair-6 (4.8%), total anomalous pulmonary venous connection repair-6 (4.8%). The commonest two lesion cardiac surgical repair was atrial and ventricular septal defect repair-12 (9.5%).

Sixty-nine patients admitted to the PICU had received pharmacotherapy to prevent bleeding in theatre, of which 68 patients received tranexamic acid and one patient received both tranexamic acid and activated factor VII. Six (4.8%) patients received pharmacotherapy to prevent bleeding in ICU, which included Vitamin K (33.3%), tranexamic acid (33.3%) and activated factor VII (33.3%). Sixty-eight (53.9%) patients received blood products in theatre, and 50% of the patients received red blood cells as a single blood product, followed by 25% who received red blood cells in combination with platelets and cryoprecipitate. The length of stay (LOS) was 5 (2-11) versus 3 (2-5) days ( $p=0.002$ ) in those who received versus those who did not receive transfusion intraoperatively.

**Table 1: Characteristics of the study group**

<i>Variable</i>	<i>Total (N)</i>	<i>Median</i>	<i>IQR</i>
Weight (kg)	126	7.6	4.1-16.0
Age (months)	126	14.3	3.8-66.4
Risk of mortality (PIM 3)	126	0.01	0.01-0.02
PICU duration (days)	126	3.5	2.0-7.0
Haemoglobin post-surgery (g/dl)	126	10.4	9.3-12.2
ACT pre-bypass (sec)	113	113.0	104.0-122.0
ACT post-bypass (sec)	113	141.0	126.0-162.0
Haemoglobin at PICU admission (g/dl)	126	12.7	11.1-14.2
PTT at PICU admission (sec)	117	32.0	25.6-42.7
Fibrinogen at PICU admission (g/L)	118	1.4	1.1-1.9
Platelet count at PICU admission (*10 <sup>9</sup> /L)	126	197.5	127.0-253.0
Ventilation duration (hours)	112	23.6	17.5-90.5
<b><i>Variable</i></b>	<b><i>Frequency (%) N=126</i></b>		
Female	58 (46.0%)		
Previous cardiac surgery	22 (17.5%)		
Recent transfusion	4 (3.2%)		
Pharmacotherapy to prevent bleeding post-surgery	69 (54.8%)		
Blood product use during surgery	68(53.9%)		
Repeat cardiopulmonary bypass in theatre	14 (11.1%)		
Pharmacotherapy to prevent bleeding in PICU	6 (4.8%)		
Pre-operative cardiac diagnosis			
1 lesion	83 (65.9%)		
2 lesions	31 (24.6%)		
≥ 3 lesions	12 (9.5%)		
Cardiac surgical procedure			
1 lesion repair	85 (67.5%)		
2 lesion repairs	32 (25.4%)		
≥ 3 lesion repairs	9 (7.1%)		

The different blood products used during cardiac surgery are summarised in table 2 below. Sixty-eight (53.9%) patients received blood products intraoperatively, with packed red cells being the predominant single blood product received. Ten (7.9%) patients received a combination of two different blood products, nineteen (15.1%) patients received a combination of three different blood products and one (0.8%) patient received a combination of four different blood products.

**Table 2: Blood products used in children during cardiac surgery in the OR**

<i>Blood product</i>	<i>Frequency (% , N=126)</i>
<b>Packed red cells</b>	34 (26.9%)
<b>Cryoprecipitate</b>	3 (2.4%)
<b>Platelet concentrate</b>	1 (0.8%)

The different blood products and the median volumes used post cardiac surgery are summarised in Table 3. A total of 67 (53.2%) children received blood products in PICU following cardiac surgery. Cryoprecipitate was the commonest blood product used (30.9%) post cardiac surgery, followed by packed red cells (22.2%), 18.3% of the patients received albumin, 15.9% received FFPs and 15.1% were transfused platelet concentrate. There was an overlap of 41 (32.5%) patients, who received blood products in both the operating room and the PICU.

**Table 3: Blood products used in children post cardiac surgery in the PICU**

<i>Blood product</i>	<i>Frequency (% , N=126)</i>	<i>Median volume transfused (ml/kg)</i>
<b>Cryoprecipitate</b>	39 (30.9%)	1.9 (IQR 1.6-3.0)
<b>Packed red cells</b>	28 (22.2%)	16.1 (IQR 14.2-20.1)
<b>Albumin</b>	23 (18.3%)	10.1 (IQR 5.2-22.2)
<b>Fresh frozen plasma</b>	20 (15.9%)	12.1 (IQR 10.1- 17.6)
<b>Platelet concentrate</b>	19 (15.1%)	14.2 (IQR 10.0-20.2)

**Table 4: Indications for blood product use in children post cardiac surgery**

The indications for the different blood products that were used have been summarised below.

<b>Blood product</b>	<b>Indications for use</b>
<b>1.Cryoprecipitate</b>	Bleeding (67%). Median chest drain loss threshold 4.5 ml/kg/hr (IQR 2.3-5.9) Low fibrinogen level (64%). Median fibrinogen level threshold 0.9g/l (IQR 0.7-1.1) Hypotension episodes (23%) Consultant orders (10%)
<b>2.Packed red cells</b>	Low haemoglobin level (86%). Median haemoglobin threshold 7.9g/dl (IQR7.3-8.7) Hypotension episodes (32%) Bleeding (25%). Median chest drain loss threshold 8.5m/kg/hr (IQR 5.9-18.0) Consultant orders (25%)
<b>3.Albumin</b>	Hypotension episodes (95%) Consultant orders (4%)

<b>4.Fresh frozen plasma (FFP)</b>	Bleeding (70%). Median chest drain loss threshold 5.6 ml/kg/hr (IQR 2.3-7.0) Partial thromboplastin time level (45%); $\geq$ *2 control (35%) Hypotension episodes (35%) Consultant orders (25%)
<b>5.Platelet concentrate</b>	Thrombocytopenia (84%). Median platelet count threshold $67 \times 10^9/l$ (IQR 46.5-93.5) Bleeding (63%). Median chest drain loss threshold 5.9 ml/kg/hr (IQR 4.3-10.0) Hypotension episodes (42%) Consultant orders (10%)

Other indications for blood product use following cardiac surgery included: during resuscitation in the presence of generalised oozing, oozing from the sternal wound and central line insertion site (packed red cells, FFPs and cryoprecipitate), for partial exchange transfusion (FFPs) and elevated INR (cryoprecipitate).

**Table 5: Outcomes associated with post-operative blood product use**

<b>Variable</b>	<b>PICU transfusion (n=67)</b>	<b>No PICU transfusion (n=59)</b>	<b>P value</b>
<b>Death n(%)</b>	4 (5.9)	0 (0.0)	0.2
<b>Risk of mortality</b>	0.015 (0.010-0.034)	0.012 (0.009-0.017)	0.10
<b>Standardized mortality ratio (actual/mean predicted mortality)</b>	3.1	0	<0.0001
<b>PICU duration (days)</b>	5.0 (3.0-11.0)	2.0 (2.0-5.0)	<0.0001
<b>Ventilation duration (hours)</b>	47.0 (21.8-131.5)	19.9 (6.0-26.5)	<0.0001

*Continuous data are median (interquartile range)*

The duration of PICU stay and mechanical ventilation was longer in the patients who received blood products post-cardiac surgery, compared to their counterparts who did not (both  $p < 0.0001$ ; Table 5). There was a significant difference in the standardized mortality ratio between the transfused and non-transfused group of children ( $p < 0.0001$ ).

**Table 6: Factors associated with post-operative blood product use**

<b>Variable</b>	<b>PICU transfusion (n=67)</b>	<b>No PICU transfusion (n=59)</b>	<b>P value</b>
<b>Previous cardiac surgery n (%)</b>	15 (22.4)	7 (11.9)	0.03
<b>Age (months)</b>	6.4 (2.2-43.0)	31.6 (6.4-82.1)	0.003
<b>Weight (kg)</b>	4.8 (3.5-13.0)	11.4 (5.6-18.2)	0.001
<b>Pharmacotherapy use post-surgery n (%)</b>	37 (55.2)	32 (54.2)	0.9
<b>ACT post bypass/surgery (sec)</b>	150.5 (131.0-174.5)	133.0 (120.0-148.0)	0.002
<b>Haemoglobin level at PICU admission (g/dl)</b>	13.1 (11.3-14.8)	12.4 (10.6-13.5)	0.06
<b>PTT level at PICU admission (sec)</b>	39.0 (29.0-50.9)	27.6 (24.5-36.0)	<0.0001
<b>Fibrinogen level at PICU admission (g/l)</b>	1.3 (0.9-1.9)	1.5 (1.3-1.9)	0.05
<b>Platelet count at PICU admission (*10<sup>9</sup>/l)</b>	161.0 (102.0-226.0)	224.0 (160.0-269.0)	0.0006

*Continuous data are median (interquartile range)*

On univariate analysis, the children who received blood products post cardiac surgery were younger, smaller in size, had undergone previous cardiac surgery, and had worse clotting parameters as compared to their counterparts who did not receive blood products ( $p < 0.005$ ; Table 6). The use of pharmacotherapy post-surgery was similar in both the transfused and non-transfused group of children and was not associated with a difference in post-operative blood product utilisation ( $p = 0.9$ ). On multiple regression analysis, no independent predictors of blood product use post-surgery were identified.

## Discussion

This prospective observational study demonstrated an overall blood product usage prevalence of 53.2% in children following cardiac surgery, in line with previously published rates of between 14% and 79% in different contexts (2, 5, 6). The majority of epidemiological studies on blood product use in children have focussed on the general PICU population, and have mostly described indications and outcomes associated with red blood cell usage (1, 7). This study looked at all the different blood products used in the post-cardiac surgery cohort in

contrast with majority of previously published epidemiological studies that focussed on red blood cell usage.

Cryoprecipitate was the most common blood product used in this study, demonstrating a difference in practice in blood product utilisation compared to studies done in North America, which report that red cells are the commonest blood product used among critically ill children and following paediatric cardiac surgery in PICUs in North America (8-11). The main indications for the use of cryoprecipitate in this study was active bleeding and low fibrinogen level, which complies with the recommended guidelines for use of cryoprecipitate (12, 13).

Low haemoglobin level was the indication for packed red cell transfusion in 86% of occasions in this study, which complied with recommendations of Lacroix and colleagues (14). On the contrary, data from 30 North American PICUs showed that low haemoglobin level was the primary indication for red cell transfusion in 17% of cases (2). Mazine and colleagues stratified the patients into cyanotic and acyanotic cardiac lesions, and 56% of the cohort comprising cyanotic congenital heart disease, with higher pre-transfusion haemoglobin levels compared to the acyanotic patients (mean values  $11.8 \pm 2.1$  vs  $11.1 \pm 2.2$  g/dl respectively)(2). The difference in the proportion of red cell transfusion due to anaemia between Mazine's study and our study could possibly be because their study had a high proportion of patients with cyanotic cardiac lesions with generally higher haemoglobin levels, however, we did not stratify our patients into cyanotic and acyanotic cardiac lesions in our study.

Carson and colleagues demonstrated a two-fold increase in odds of death for every 1g/dl drop in haemoglobin among adults with post-operative haemoglobin concentration below 8g/dl (15). Loor and colleagues described the "safety zone", which is a U-shaped relationship between the deleterious effects of worsening anaemia to the left of the X-axis and aggressive interventions to correct anaemia to the right of the X-axis, and reported increased morbidity and mortality

when operating outside this “safety zone”(16). Durandy recommended the safety zone haemoglobin range of 8-10g/dl, based on an expert review by Loo et al(16, 17).

Albumin was used mainly for hypotension episodes in this study. The use of albumin for hypotension episodes in cardiac surgery in our unit has been extrapolated from the current recommendations by the 2016 surviving sepsis campaign guidelines for fluid management of septic shock (18). The landmark Fluid Expansion as Supportive Therapy (FEAST) trial conducted in East Africa among children with febrile illness, compared the use of saline and albumin fluid boluses versus no fluid boluses for impaired perfusion, and there was reported similar mortality rates among the saline and albumin group(19). There is limited literature on the use of albumin for fluid resuscitation in paediatric cardiac surgery, however it is the policy in our unit to alternate ringer’s lactate and 4.5% albumin boluses for children who are clinically assessed as being hypovolaemic.

Haemorrhage was the main indication (70% of patients) for the use of FFPs in this study, followed by deranged partial thromboplastin time. The British Committee for Standards in haematology recommends that FFPs should be used in bleeding patients, with caution, avoiding volume overload and clinical outcome should be monitored (12) . The indications for use of platelet concentrate in this study also complied with the current recommendation of significant bleeding and platelet count  $<100 \times 10^9/l$  following cardiopulmonary bypass surgery by the British Committee for Standards in haematology (12).

The use of antifibrinolytic agent, tranexamic acid intraoperatively was similar in both the transfused and non-transfused group of children ( $p=0.9$ ), and no patients required re-exploration surgery due to major haemorrhage during the study period. A study by Chauhan and colleagues among children with cyanotic heart disease undergoing corrective heart surgery, randomised children into two groups and looked at the effect of tranexamic acid on post-

operative blood loss and blood and blood product usage. The children who did not receive tranexamic acid intraoperatively had a re-exploration rate of 16.6% compared to 7.3% in those who received tranexamic acid due to high mediastinal chest tube drainage loss ( $p < 0.05$ ). The patients who received tranexamic acid had higher fibrinogen levels and reduced blood product usage compared to their counterparts who did not receive tranexamic acid (20).

We observed an increase in PICU stay, ventilation duration and standardized mortality ratio among the children who received blood products in ICU compared to those who did not. We also observed that children who received blood products in theatre had a significant increase in PICU stay compared to those who did not. The causal relationship between blood product use and increased PICU stay, ventilation duration and standardized mortality ratio cannot be determined based on this study, as there are other possible factors that may have contributed to these findings such as the severity of illness related to the correction of the primary cardiac lesion and the complexity of the cardiac surgery, age of the blood products used, concurrent infections including those acquired because of being in PICU.

A prospective, multicentre study done by Mazine and colleagues among children transfused post cardiac surgery demonstrated increased PICU length of stay in the transfused group, but no difference in ventilation duration and mortality between the transfused and non-transfused children(2) . Salvin and colleagues demonstrated a significantly increased length of PICU stay and ventilation duration among children transfused post-cardiac surgery compared to their counterparts who were not transfused(6). A large, prospective multicentre study by Bateman and colleagues in 30 PICUs in North America, among critically ill children reported increased risk of death, a higher rate of nosocomial infections, more cardiac or respiratory dysfunction, longer duration of mechanical ventilation and PICU stay in the transfused group compared to their non-transfused counterparts (21).

Despotis and colleagues highlighted the “two-hit hypothesis” as an explanation for the transfusion-related morbidity (22). The first hit involves a primary precipitating event such as systemic inflammatory response syndrome (SIRS) response from surgery or the underlying illness, which primes the pulmonary endothelium leading to neutrophil sequestration, because of endothelial activation. The second hit is from the blood products used, as a result of biological modifiers such as human leucocyte antigen (HLA) and white cell antibodies, as well as neutrophil-activating mediators present in the blood products transfused, which lead to complement activation and pulmonary injury (22). The two-hit theory has also been hypothesised as an explanation for the development of transfusion-related acute lung injury, which is a leading cause of mortality following allogeneic blood transfusion in the United States (23).

The storage lesion has also been well described as a significant factor associated with transfusion morbidity. Red cells undergo changes as they age under refrigerated conditions, resulting in an increase in free iron and pro-inflammatory markers, biochemical changes and loss of nitric oxide bioactivity, causing vasoconstriction and further vascular damage (24). Our blood bank issues pre-storage leucocyte-reduced blood for all infants as a policy, however the older children only get leuco-depleted blood products if specifically requested by the prescribing clinician.

The factors associated with blood product use on univariate analysis in this study were previous cardiac surgery, younger age, smaller size and worse coagulation parameters. The previous cardiac surgery and worse coagulation parameters put these children at a higher risk of bleeding due to adhesions with prolonged re-exploration and ineffective haemostasis respectively, hence the need for blood products use. The multiple regression analysis however did not identify independent predictors of blood product use in this study.

Our study had strengths and limitations. The strength of this study was that the study was performed prospectively, therefore we could minimize information bias. The first limitation of this study was that it was a single centre study and therefore not generalizable to other populations in different contexts. We did not measure possible confounding variables that may have influenced the associated outcomes we found with associated blood product use such as severity of illness score at admission (Paediatric Risk of Mortality; PRISM score), organ dysfunction score; Paediatric Logistic Organ Dysfunction (PELOD) score, storage duration of blood products. We do not routinely calculate scores that measure the complexity of the surgical repair, such as the Risk Adjustment for Congenital Heart Surgery (RACHS-1) score, which has a bearing on outcomes following congenital heart surgeries. Thus, we cannot accurately conclude the causal relationship between blood product use and our observed outcomes. The data collected on blood product use intra-operatively was scarce, hence a lack of link between intra-operative and post-operative transfusion events and the correlation with outcomes investigated.

## Conclusions

The results of our study have demonstrated a high usage of blood products in the PICU among children following cardiac surgery. There is a difference in blood product use practice in our centre, with more cryoprecipitate being used in comparison to other centres in published literature, that predominantly use red blood cells. Children who received blood products following cardiac surgery had a longer duration of PICU stay, mechanical ventilation and a higher standardized mortality ratio, compared to their counterparts who did not. The results of this study can be used to guide the use of blood products in paediatric cardiac surgery at our centre, however they may not be generalizable in other centres. Larger multi-centre studies will be needed in the future to analyse the relationship between intra-operative factors and

utilization of blood products post cardiac surgery and generate results that can be generalised to develop protocols for the use of blood products in paediatric cardiac surgery.

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## Appendix 1: Protocol

### **TRANSFUSION PRACTICES AMONG CHILDREN UNDERGOING CARDIAC SURGERY ADMITTED TO THE RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL PAEDIATRIC INTENSIVE CARE UNIT**

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#### **Background**

Blood products are frequently given to patients undergoing cardiac surgery. Recently there has been increasing focus on the complications associated with blood transfusion. Some of those complications relate primarily to the volumes of blood used, but many relate to the blood products themselves(1, 2). The initial focus of adverse event review was on issues such as compatibility, infection (bacterial and increasingly viral). However, there is now increasing focus on the associations between use of blood products and respiratory problems, duration of paediatric intensive care unit (PICU) stay, morbidity and mortality(1, 2). There are new recommendations for the use of blood products in the perioperative period for children undergoing cardiac surgery, and the focus of this study is really on defining the transfusion practice in our unit(3, 4). This would provide the basis for further focus on quality improvement and optimization of protocols.

Blood products are not identical across the world and may vary considerably in how they are collected, stored, processed and administered. The quality of blood products is hugely variable in different parts of the world. The guidelines for blood transfusion in the cardiac perioperative period are based on relatively small numbers of studies.

In South Africa, donated blood is collected and stored in a solution containing sodium citrate as the anticoagulant. Red cells are preserved and stored at a temperature of 1°- 6°C for a duration of up to 42 days, fresh frozen plasma (FFP) is separated from anticoagulated whole blood within 18 hours of donation, frozen and stored at a temperature of < -18°C. Platelets are prepared from the buffy layers of whole blood donation within 8 hours of donation and stored at a temperature of 22°C for a duration of 5 days. Cryoprecipitate is prepared from FFP by thawing FFP at temperatures of 0-4° C, and then the cold fraction is stored at temperatures < -18° C for a duration of up to 1 year. (South African National Blood Service).

### **Risk Factors Associated With Transfusion Or Bleeding During Or After Cardiac Surgery**

The factors that predispose patients undergoing cardiac surgery to bleeding include patient, procedure and drug-related factors. Patient related factors include age, preoperative anaemia, preoperative thrombocytopenia, preoperative coagulopathy and antithrombotic therapy. Procedure related factors include repeated procedures (re-operation), the type and urgency of the operation, cardiopulmonary bypass (CPB); the use of heparin on CPB, residual heparin, reduced thrombin generation, fibrinogen deficiency, thrombocytopenia, platelet dysfunction, hyperfibrinolysis, hypothermia, acidosis during the procedure, dilution of clotting factors with intravenous fluid administration, surgical causes and consumption of clotting factors in active bleeding(5-7).

Drug related factors are related to use of antiplatelet agents such as aspirin, clopidogrel or use of anticoagulant therapy such as warfarin, or use of low molecular weight heparin or unfractionated heparin (7).

The interventions that have been shown to reduce bleeding during cardiac surgery include: anti-fibrinolytic therapy such as tranexamic acid, recombinant factor VIIa and epsilon aminocaproic acid, use of minimized CPB circuits with reduced priming volume,

normovolaemic haemodilution, salvage of blood from the CPB circuit, modified ultrafiltration, and microplegia(8-11). The use of pre-operative erythropoietin increases the haemoglobin level prior to surgery, hence reducing blood transfusion requirement.

Refrigerated stored blood undergoes biochemical and biophysiological changes that include changes in rheology and shape, cellular metabolism, oxidative stress and changes induced from the additive solution (12). There are discrepancies in the evidence in paediatric studies looking at the association between the effects of transfused stored blood and post cardiac surgery morbidity and mortality. Some of the studies have shown no difference in mortality and morbidity with transfusion of old versus fresh blood, while other studies have described increased bleeding risk, mortality and morbidity with use of old blood (13-16). There are six large RCTs ongoing currently, to look at the effects of transfusion of stored versus fresh blood on the development of multiorgan dysfunction syndrome (MODS) and mortality in children and adults in USA, Canada, Finland, New Zealand and Australia.

### **Type Of Blood Products Used And Indications In Cardiac Surgery**

Multiple factors need to be taken into account before transfusion of red blood cells in cardiac surgery. The use of haemoglobin level in isolation, as a threshold for red cell transfusion is not sufficient, and additional factors such as markers of oxygen delivery, ongoing bleeding and comorbid disease processes should be considerations factored in the decision to transfuse red blood cells (4).

Red blood cells increase arterial oxygen content by increasing haemoglobin level, therefore increasing tissue oxygen delivery. However, this does not take immediate effect as red cell transfusion increases blood viscosity which can reduce cardiac output in normovolaemic patients whose cardiac function is not impaired. Stored red cells undergo biochemical and biophysiological changes which affects their oxygen affinity and delivery (12).

Transfusion in neonates and young children is most likely to be equivalent to a massive transfusion leading to dilution of clotting factors(17). Massive transfusion is defined as a situation in which transfusion needs result in replacement of 80 ml/kg in 24 hours, or 40 ml/kg in 3 hours or blood loss of 2-3 ml/kg/min (18). Fresh frozen plasma is a source of procoagulant factors and fibrinogen, and is indicated in the context of massive bleeding, where it is administered in fixed ratios with platelets and red cells (19, 20). Cryoprecipitate contains high concentrations of factors VIII,XIII and fibrinogen, and is indicated for correcting hypofibrinogenemia at levels below 1g litre<sup>-1</sup>(21).

Platelet transfusion is indicated in significant microvascular bleeding with diffuse oozing without an obvious surgical cause, after correction of clotting factors(5, 22). Platelet dysfunction and thrombocytopenia increase the risk of bleeding and threshold for transfusion after CPB(23). The factors that influence platelet count and function during CPB include exposure to the bypass circuit and shear stress at different levels of CPB resulting in platelet adhesion and aggregation, inflammatory mediators during CPB, haemodilution, hypothermia, preoperative use of anti-platelet agents(5, 7, 24, 25). Other molecular mechanisms that contribute to platelet dysfunction include loss of cell surface glycoprotein receptors, such as the platelet collagen receptor, glycoprotein GPIb-IX and GPIIb-IIIa (5, 23).

### **Transfusion Practice And Thresholds Used In Paediatric Cardiac Critical Care**

The physiologic threshold at which oxygen consumption decreases due to reduced oxygen delivery in humans is a haemoglobin level of 3-4 g/dl, an oxygen extraction ratio of 0.44 and a mixed venous oxygen of 34 mmHg as demonstrated in studies in Jehovah's witness population who decline blood transfusion(26). The evidence guiding red cell transfusion thresholds in children is scanty . Data obtained from retrospective studies in Kenyan children with severe anemia related to high parasitemia from *P.Falciparum* malaria demonstrated high

early mortality rates at haemoglobin levels below 4g/dl(27). Carson and colleagues demonstrated a > 50% mortality rate of in patients with a post operative haemoglobin below levels of 5 g/dl, as well as a two-fold increase in odds of death for every 1g/dl drop in haemoglobin among adults with post-operative haemoglobin concentration below 8g/dl (28).

Patients with ongoing bleeding, who are in haemorrhagic shock should receive red blood cells, with plasma and platelet concentrate in fixed ratios (4). Results from the subanalysis of the Transfusion Requirements in Paediatric Intensive Care Unit (TRIPICU) study suggest that a haemoglobin threshold of 7g/dl and 9 g/dl for haemodynamically stable children >28 days old with non cyanotic heart disease and cyanotic heart disease respectively is reasonable. These thresholds have been adapted for use in children post cardiac surgery (3, 4, 8).

The British Committee for standards in haematology recommends that fresh frozen plasma (FFP) and cryoprecipitate should not be used primarily on the basis of abnormal lab results, but should be restricted to use in patients with signs of bleeding or planned invasive procedures (18). FFP should be given to children with prothrombin time/ activated partial thromboplastin time (PT/APTT) levels >1.5 times the midpoint of the normal range and cryoprecipitate for fibrinogen levels <1.5g/l associated with significant haemorrhage following cardiopulmonary bypass (18). Platelets should be transfused when there is clinically significant haemorrhage and a threshold of  $< 100 \times 10^9/l$  should be used in paediatric cardiac surgery (18).

### **Complications Associated With Blood Product Use**

In general, PICU patients who receive blood products have a worse outcome than those who are not transfused (1).

Blood product transfusion is associated with immune-mediated and non immune-mediated risks. Immune-mediated risks include transfusion-related lung injury, acute haemolytic

reactions, allergic and anaphylactic reactions, non haemolytic febrile reactions, and transfusion associated graft versus host disease(6, 29). Non-immune mediated risks of blood transfusion include hyperkalaemia, fluid overload, transmission of infection, hypothermia and iron overload (29).

The presence of leucocytes in blood has been linked to the febrile reactions and immune-mediated reactions observed after blood transfusion, therefore leucoreduction and filtration is performed in most centres prior to blood storage (30-32). Leukoreduction has been further shown to increase packed red cell viability prior to storage(30). Although transfusion-associated graft versus host disease (TA-GVHD) is an uncommon complication of blood transfusion, it is a fatal complication especially for patients with congenital immune deficiency, therefore gamma-irradiation of blood products prior to transfusion impairs the proliferation of lymphocytes, and prevents TA-GVHD (30, 32).

High income countries which are also quite well resourced, have adopted a universal policy of leucocyte depletion of stored blood products, which is a costly affair that low and middle-income countries may not afford routinely. In South Africa, infants routinely receive leucodepleted blood as a standard, and the blood packs are leucodepleted during preparation and storage. Adult units are generally used to prime the bypass circuit for infants undergoing cardiac surgery. The adult blood packs are not routinely leucodepleted, unless there is a clinical indication to warrant the use of leucocyte depleted blood products, in this case the clinician will put in a specific request to the blood bank for leucocyte depleted blood (33, 34).

Bacterial infections that occur post transfusion may happen because of bacterial contamination of blood products. This is because of bacterial contamination during venipuncture or collection of blood from an asymptomatic bacteremic donor. The symptoms of bacterial infection as a result of transfusion can occur during or immediately after transfusion of a contaminated blood

product bag, and include fever, rigors, erythema and cardiovascular collapse(29). Gram negative bacteria such as *Yersinia enterocolitica* and *Pseudomonas* rapidly proliferate at storage temperatures of 4°C, whereas gram positive bacteria such as *Staphylococcus epidermidis*, *Staphylococcus aureus* and *Bacillus species* proliferate rapidly at room temperature(29).

In the well-resourced countries, donor blood is routinely screened for hepatitis B and C, HIV 1 and 2, CMV and human T cell lymphotropic virus, the incidence of viral transmission through blood transfusion has greatly reduced(29, 31, 35). Donor blood is also routinely screened for Syphilis. In South Africa, donor blood is routinely screened for hepatitis B and C, HIV 1 and 2, and Syphilis. (South African National Blood Service) The variant Creutzfeldt-Jakob disease is a human prion disease that can also be transmitted by contaminated blood products (29, 35). The following are agents that can also be transmitted by transmission of contaminated blood, however they are not routinely screened in donor blood; hepatitis A virus, parvo B19 virus, *Babesia leishmania*, plasmodium, and *Brucella species*(35).

Transfusion of blood products (red cells, fresh frozen plasma, platelet concentrate) intra and post operatively has also been found to be a potential risk factor to development of health care associated infections in cardiac surgery(36-38).

Several studies have been done and demonstrated an association between red cell transfusion and length of stay in post-operative paediatric cardiac patients (39-42). The impact of changing transfusion practices in paediatric cardiac critical care has also been shown to have an effect in morbidity post cardiac surgery and reduced hospital costs (43, 44). Use of lower haemoglobin thresholds for red cells transfusion and leucocyte reduced blood products are factors that have been shown to reduce morbidity related to paediatric cardiac surgery (43, 45).

The morbidity related to blood product use in paediatric cardiac surgery is as a consequence of immune and non-immune mediated mechanisms(31). Transfusion-mediated immune suppression has been described in transfusion medicine and thought to pose an increased risk

in postoperative infections and activation of latent viral infections. It is thought that these effects are a result of the donor leucocytes in transfused blood which express class I and class II Human leucocyte antigens (29, 31, 46).

Complications such as transfusion related lung injury (TRALI), transfusion- associated cardiac overload, nosocomial infections, multi-organ organ dysfunction will result in increased ventilator days and hence increased PICU length of stay and have also been in implicated in associated mortality (31, 35, 47, 48).

### **Study Objectives**

#### **Primary Objectives:**

1. To describe the use of blood products in the 72 hour period following cardiac surgery in children at the Red Cross War Memorial Children's Hospital
2. To describe the indications for blood product use in children post cardiac surgery used by clinicians

#### **Secondary Objectives:**

1. To describe the outcomes associated with post-operative blood product use (ventilator hours, PICU length of stay, PICU mortality)
2. To describe the factors associated with post-operative blood product use

### **Methodology**

#### ***Study design***

This study will be a prospective observational study

### ***Study population***

The study population will comprise all children under 18 years of age who are admitted to the Red Cross War Memorial Children's Hospital (RCWMCH) paediatric intensive care unit (PICU) following cardiac surgery during the study period.

### ***Exclusion criteria***

Children admitted to PICU with other medical and surgical conditions other than cardiac surgery

### ***Recruitment and enrollment***

The patients will be recruited consecutively into the study upon admission to the PICU post cardiac surgery and will be identified by study numbers on the case record form (CRF). Consent for cardiac surgery and use of blood products is routinely taken by the cardiac surgical team, however, additional verbal consent will be taken by the cardiothoracic surgeon from the parents/guardians, to give permission for the routinely recorded data regarding the patient's surgery to be used for the purpose of this study. The parents/guardians will be informed that they have an option to "opt out", should they feel uncomfortable with the study clinician using data about their children's surgery for the purpose of this study. This will not compromise the care offered to their children while admitted to the intensive care unit in any way.

### ***Data collection methods***

The study data will be obtained from blood bank records, intra operative charts and patient folders (including PICU observation charts). The definition of blood products includes the following; red blood cells, fresh frozen plasma, platelets, cryoprecipitate and human albumin. Variables which will be obtained from blood bank records includes type and characteristics of the different blood products used. The intra operative charts will provide the following

information: preoperative cardiac diagnosis, surgical procedure performed, the type, characteristics, age and volumes of different blood products used, haemoglobin level pre and post surgery, details on CPB and details of the use of pharmacotherapy to prevent bleeding. Demographic data will be obtained from the patient folders, and includes; age, sex, weight, date of PICU admission and discharge. Additional information which will be obtained from the patient folders (including the PICU observation charts) includes the following; haemoglobin levels, oxygen saturations, clotting screen, chest drain losses, duration of mechanical ventilation, length of stay and mortality (including PIM 3 scores) in the PICU, previous cardiac surgery, previous blood transfusion, previous PICU admission. The investigator will provide a form ( Appendix 2) to be filled by the PICU clinician, indicating the blood products used, quantities and indications for transfusion of blood products. Chest drain losses will be recorded for the 72 hours post cardiac surgery. Data will be collected on transfusion of each blood product used per patient over a period of 72 hrs post cardiac surgery. The data obtained will then be entered in a standardised CRF (Appendix 2). Data will be collected prospectively over a 6 month period.

### ***Data analysis***

The data collected will be entered into an excel spread sheet and exported to and analysed using Statistica (version 13, StatSoft Inc, USA). Continuous variables will be expressed as a mean ( $\pm$ standard deviation) or median( $\pm$ inter-quartile range). Categorical variables will be expressed as a frequency percentage (%). Primary outcome measures will be the blood product use and indications of blood products used in children admitted to the PICU after cardiac surgery. The secondary outcome measures will be the total ventilation hours, PICU length of stay, mortality in PICU. Statistical significance will be set at  $\alpha$  of 0.05. The data will be presented in tables.

## **Ethical Considerations**

### **Potential Risks**

This is a minimal- risk observational study of routinely collected data related to standard clinical practice. No study- related interventions or investigations will be performed.

### **Potential Benefits**

Patients will not directly benefit from study participation. The results of the study will be used to measure current practices involving the use of blood products in children undergoing cardiac surgery. Findings could form the baseline for future studies and inform practice- improvement initiatives. The study therefore has potential societal benefit, and although individual participants do not stand to benefit, there is the potential for improved practice and outcomes for future children admitted for cardiac surgery.

### **Vulnerability**

This is a particularly vulnerable population of critically ill infants and children following cardiac surgical procedures. However, this study does not impose any additional risk to participants beyond that of standard PICU care. The study could not be done on a less vulnerable group, given the particular pathophysiology of postoperative children with congenital cardiac disease.

### **Privacy And Confidentiality**

Information obtained from the study will be kept confidential by recording data in questionnaires with assigned study numbers, avoiding the use of patient names. Hard copies will be stored in a locked cupboard.

## **Independent Review And Ethical Compliance**

The study will be undertaken after approval from the Department of Paediatrics and Child Departmental Research Committee (DRC) and the University of Cape Town's Faculty of health Sciences Human Research Ethics Committee (HREC), and carried out as guided by the Declaration of Helsinki, 2013, Ethical Principles for Medical Research involving Human Subjects. Furthermore, permission will be sought from the hospital medical superintendent before the study is commenced.

## **Informed Consent**

On admission to the PICU parents/guardians are given a pamphlet describing the PICU, and stating that during their child's stay routine information may be collected for research purposes, but that no research will be done that impacts on their child's experience or treatment in PICU. The parents/guardians will be verbally provided an "opt-out" option should they feel uncomfortable with this process. We believe this process respects parental autonomy, in addition, they will not be penalised in any way for choosing to "opt-out".

We request a waiver of the need for full informed consent given that:

- 1) This is a purely observational study of routinely collected data, and will not affect patient care or the experience the child has in PICU in any way;
- 2) Parents/legal guardians may be situationally incapacitated by the stress and trauma of their child undergoing serious invasive surgical procedures and the subsequent admission to the daunting technological environment of the PICU, and therefore unable to fully understand the request for research involvement;(49)

- 3) Parents/legal guardians will already have signed consent for the surgery, and potentially for receipt of blood products, investigations, placement of lines etc. Another form to fill in may add unnecessary burden to the parents/legal guardians.

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## Appendix 2: Case Record Form

### **TRANSFUSION PRACTICES AMONG CHILDREN POST CARDIAC SURGERY ADMITTED TO RCWMCH PICU STUDY BY DR KAISER FITZWANGA**

#### **SECTION A: PATIENT DEMOGRAPHICS**

Folder No:  Date of birth:  Study Number :   
Sex: Male:  Female:  Weight(kg) :   
Date of PICU admission:  Date of ICU discharge:   
PIM 3 score at admission:

#### **SECTION B: PERI OPERATIVE CHECKLIST**

- 1.Recent admission to PICU within 14 days prior to cardiac surgery: Yes  No
- 2.Currently admitted to PICU at the time of cardiac operation: Yes  No
- 3.Recent mechanical ventilation within 14 days prior to cardiac surgery: Yes  No
- 4.Currently mechanically ventilated in the PICU at the time of the cardiac operation: Yes   
No
- 5.Previous cardiac surgery prior to the current cardiac operation: Yes  No

***If Yes, please select all that applies by placing check mark in the box:***

Median sternotomy  Lateral thoracotomy  Other:

- 6.Recent blood transfusion prior to current cardiac surgery: Yes  No

#### **SECTION C: INTRA OPERATIVE CHECKLIST**

7.Preoperative cardiac diagnosis: *(Please select by placing a check mark in the box)*

VSD <input type="checkbox"/>	HLHS <input type="checkbox"/>	AS <input type="checkbox"/>
ASD <input type="checkbox"/>	TAPVC <input type="checkbox"/>	TR <input type="checkbox"/>
AVSD <input type="checkbox"/>	PAPVC <input type="checkbox"/>	Interrupted Aortic arch <input type="checkbox"/>

TET  MR  Aortopulmonary window   
 TA  AR  Cotriatrum   
 TGA  PA  PDA   
 DORV  MS  ALCAPA

Other:

8.Surgical procedure done: *(Please select by placing a check mark in the box)*

VSD closure  TV annuloplasty  Arterial switch   
 ASD closure  AV repair  TAPVC repair   
 Total correction of TET  AV replacement  PAPAVC repair   
 MV repair  Pulmonary valvuloplasty  Aortic arch repair   
 MV replacement  Glenn shunt procedure  Norwood procedure   
 Ross procedure  Fontan procedure  PDA ligation   
 Sub aortic ridge resection  Central shunt procedure  ALCAPA repair   
 Konno procedure  BT shunt procedure  RVOT patch

Other:

9.Use of blood products during surgery and/ on bypass: Yes  No

10.Blood products used during surgery and/on bypass: *(Please select all that applies by placing a check mark in the box)*

Packed red blood cells   
 Whole blood   
 Fresh frozen plasma   
 Platelet concentrate   
 Cryoprecipitate   
 Albumin

11.Use of colloids intraoperatively: Yes  No

12.Characteristics of blood products used. *(Please select all that applies by placing check mark in the box)*

Irradiated Yes  No

Leucocyte depleted Yes  No

Washed cells Yes  No

Emergency O- negative blood Yes  No

Cell saved blood Yes  No

Pump blood Yes  No

13. Haemoglobin level post cardiac surgery and/ or bypass (g/dl):

14. ACT before bypass ( seconds):

15. ACT after bypass ( seconds):

16. Pharmacotherapy used to prevent bleeding post cardiac surgery and/ or bypass: Yes   
No

*If Yes, please select all that applies by pacing check mark in the box:*

Aprotinin  Activated factor VII  Tranexamic acid  Desmopressin

Other:

17. Underwent repeat bypass in the OR: Yes  No

#### **SECTION D: ICU ADMISSION CHECKLIST**

18. Haemoglobin level at admission (g/dl):

19. Clotting screen at admission:

PTT (s)  Fibrinogen (g/l)  Platelet count (\*10<sup>9</sup>/l)

20. Received mechanical ventilation: Yes  No

21. Date and time of initiation of mechanical ventilation:

22. Date and time of extubation:

23. Re intubated within current post-operative period: Yes  No

*If Yes, in Q23, go to Q24. If No, skip and go to Q26*

24. Date and time of re intubation:

25. Date and time of extubation after re intubation:

26. Total length of mechanical ventilation (hours):

27. Underwent re do surgery: Yes  No

28. Blood product use in PICU: Yes  No

29. Chest drain losses post cardiac surgery(ml/kg/hr):

6 hours post-op  24 hours post-op  72 hours post-op   
12 hours post-op  48 hours post-op

30. Blood products transfused in PICU: *(Please select all that applies by placing a check mark in the box)*

Packed red blood cells  Volume transfused (ml/kg)

Whole blood  Volume transfused (ml/kg)

Fresh frozen plasma  Volume transfused (ml/kg)

Platelet concentrate  Volume transfused (ml/kg)

Cryoprecipitate  Volume transfused (ml/kg)

Albumin  Volume transfused (ml/kg)

31. Characteristics of blood products used. *(Please select all that applies by placing check mark in the box)*

Irradiated Yes  No

Leucocyte depleted Yes  No

Washed cells Yes  No

Emergency O- negative blood Yes  No

Cell saved blood Yes  No

Pump blood Yes  No

32. Indications for blood product use in PICU *(Will refer to a separate form filled by prescribing doctor)*

33. Pharmacotherapy used to control bleeding in PICU: Yes  No

***If Yes, please select all that applies by placing check mark in the box:***

Tranexamic acid  Activated factor VII  Vitamin K  Other:

34. Mortality in PICU: Yes  No  ***If Yes, date of death:***

35. Duration of PICU stay (days):

**INDICATIONS FOR BLOOD PRODUCT USE IN POST OPERATIVE CARDIAC PATIENTS** *(To be filled by the prescribing doctor at the bed side for each transfusion event. Please select all that applies )*

Patient Sticker

**1. Red blood cells** *(Please select the type prescribed):* Whole blood  Packed red cells

Bleeding: Yes  No

*If yes, please indicate the chest drain loss threshold used in ml/kg/hr:*

Low haemoglobin level: Yes  No

*If yes, please indicate the haemoglobin threshold used in g/dl:*

Hypotension episodes: Yes  No

*(Hypotension will be defined as the systolic blood pressure or mean blood pressure (mmHg) below the low limit as set by the intensivist)*

Hypoxemia: Yes  No

*(Hypoxemia will be defined as oxygen saturation below the low limit as set by the intensivist)*

Consultant orders: Yes  No

Other indications by prescribing doctor:

Volume prescribed (ml/kg):

**2. Fresh frozen plasma**

Bleeding: Yes  No

*If yes, please indicate the chest drain loss threshold used in ml/kg/hr*

Partial prothrombin time level: Yes  No

*If yes, please indicate the PTT(s) threshold level used: <\*2 PTT control  >\*2 PTT control*

Hypotension episodes: Yes  No

*(Hypotension will be defined as the systolic blood pressure or mean blood pressure (mmHg) below the low limit as set by the intensivist)*

Consultant orders: Yes  No

Other indications by prescribing doctor:

Volume prescribed (ml/kg):

### 3. Platelet concentrate

Bleeding: Yes  No

*If yes, please indicate the chest drain loss threshold used in ml/kg/hr:*

Low platelet count: Yes  No

*If yes, indicate the platelet count threshold used(\*10<sup>9</sup>/l):*

Hypotension episodes: Yes  No

*(Hypotension will be defined as the systolic blood pressure or mean blood pressure (mmHg) below the low limit as set by the intensivist)*

Consultant orders: Yes  No

Other indications by prescribing doctor:

Volume prescribed (ml/kg):

### 4. Cryoprecipitate

Bleeding: Yes  No

*If yes, please indicate the chest drain loss threshold used in ml/kg/hr:*

Low fibrinogen level: Yes  No

*If yes, please indicate the threshold level(g/l) used:*

Hypotension episodes: Yes  No

*(Hypotension will be defined as the systolic blood pressure or mean blood pressure(mmHg) below the low limit as set by the intensivist)*

Consultant orders: Yes  No

Other indications by prescribing doctor:

Volume prescribed (units):

### 5.Albumin

Hypotension episodes: Yes  No

*(Hypotension will be defined as the systolic blood pressure or mean blood pressure (mmHg) below the low limit as set by the intensivist)*

Consultant orders: Yes  No

Other indications by prescribing doctor:

Volume prescribed (ml/kg):

## Appendix 3: Parents/ Guardians PICU Welcome Pamphlet

### Food

Children may have special dietary requirements or may be 'nil by mouth'. Remember not to feed other children. Ask the nurses.

Food kept at the bedside attracts cockroaches and smells unpleasant to children who are feeling sick.

Where to eat: Waiting area or cafeteria

Where to heat/ store food: a microwave and fridge is available in the ward kitchen. Label any items in the fridge with your child's name. Please ask the nurses to store the food in the fridge for you.

Where to buy food: There is a visitor's cafeteria on the B floor, a shop on the premises & across the road

### Support for Parents

It is very important for you to take care of yourself too. You won't be able to help your child if you are worn out.

- Take care to eat correctly
- Rest regularly
- Have a good sleep at night (or at any other time)
- If you need to talk or wish to use a quiet area for prayer please ask the sister or social worker to assist.

You may be asked to wait outside during: certain procedures, during a medical round (to respect confidentiality of information) or an emergency.

If your child is having surgery or a procedure, you may be asked to sign a consent form (this gives the medical team permission to perform the procedure). Read through the form before signing. Feel free to ask about anything you may be unsure of.



### Telephone Numbers:

The ICU has direct telephone numbers that can be used to received calls.

Beds 6 -14: (021) 658-5317 / 5103

Beds 1-5 & 15-18: (021) 658-5126 / 5113

Beds 19-22: (021) 658-5329

PARENTS MAY TELEPHONE THE UNIT  
AT ANY TIME.

- Staff members do not give information about patients to callers other than parents.
- Please discourage family and friends from phoning the unit.

### Research in the PICU

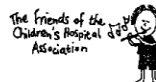
The PICU team do collect information on patients that is used to make sure that the quality of care is the best possible. That information is kept confidential. It may be used for research, but no-one outside the PICU will be able to identify your child in that information

### Friends of Red Cross Hospital

Friends run a Family Resource Centre, on the ground floor of the hospital, where you may be able to find out more information about your child's condition. Please ask the staff to direct you there.

© Children's artwork courtesy of Red Cross War Memorial Children's Hospital school. Photographs used with permission.

Please talk to the Sister if you have any  
compliments or complaints



Welcome to  
Red Cross War  
Memorial Children's  
Hospital

Ward C1  
Intensive Care Unit  
(ICU)



We'd like to make sure your child gets  
the best possible care.

This pamphlet will serve as a guide  
giving you all sorts of helpful  
information.

Of course... we're also here to  
help so feel free to ask!

## Appendix 4: Ethics approval letter



**UNIVERSITY OF CAPE TOWN**  
**Faculty of Health Sciences**  
**Human Research Ethics Committee**



Room E53-46 Old Main Building  
Groote Schuur Hospital  
Observatory 7925  
Telephone (021) 406 6625  
Email: shucette.thomas@uct.ac.za  
Website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms)

13 July 2017

**HREC REF: 437/2017**

**Dr S Salle**  
Paediatrics  
Red Cross Hospital

Dear Dr Salle

**PROJECT TITLE: TRANSFUSION PRACTICES AMONG CHILDREN UNDERGOING CARDIAC SURGERY ADMITTED TO THE RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL PAEDIATRIC INTENSIVE CARE UNIT. (MPhil candidate- Dr K Fitzwanga)**

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee dated 11 July 2017.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

**Approval is granted for one year until the 30 July 2018.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms))

**Please quote the HREC REF in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

**The HREC acknowledge that the student, Dr Kaiser Fitzwanga will also be involved in this study.**

*Yours sincerely*

**PROFESSOR M. BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**  
Federal Wide Assurance Number: FWA00001637.  
Institutional Review Board (IRB) number: IRB00001938

HREC 437/2017

## Appendix 5: Hospital approval letter



Dr Jane Kawadza  
Manager: Medical Services  
Email: Jane.Kawadza@Westerncape.gov.za  
Tel: +27 21 658 5788 fax: +27 21 658 5166  
RXH: RCC85

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Dr K Fitzwanga  
Red Cross War Memorial Children's Hospital

Dear Dr K Fitzwanga

**APPROVAL OF RESEARCH**

**PROJECT TITLE: RANSFUSION PRACTICES AMONG CHILDREN UNDERGOING CARDIAC SURGERY ADMITTED TO THE RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL PAEDIATRIC INTENSIVE CARE UNIT**

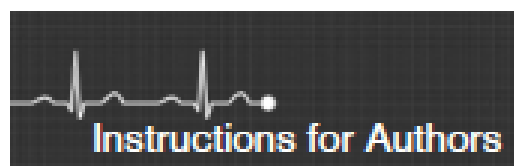
It is a pleasure to inform you that approval is hereby granted to conduct the above-mentioned study at Red Cross War Memorial Children's Hospital.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Jane Kawadza', with the initials 'MMS' written to the right of the signature.

Dr J Kawadza  
Manager: Medical Services  
Date: 22.08.17

## Appendix 6: Instructions to authors



*Pediatric Critical Care Medicine* is an international, peer-reviewed journal that is interested in publishing the highest quality scientific studies in the field of pediatric critical care medicine.

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**Financial Disclosure and Conflicts of Interest.** Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional, and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading "Conflicts of Interest and Source of Funding." For example:

Conflicts of Interest and Source of Funding: "Author A" has received honoraria from "Company 1." "Author B" is currently receiving a grant (#12345) from "Organization Y," and is on the speaker's bureau for "Organization X" — the CME organizers for Company 1. For the remaining authors none were declared.

**Human and Animal Subjects.** All studies of human subjects must contain a statement within the Materials and Methods section indicating approval of the study by the Insti-

tutional Review Board (or institutional review body) that subjects have signed written informed consent, or that the Institutional Review Board waived the need for informed consent. Before your submission can be sent out for peer review, it is necessary that you address this issue of institutional review approval. This is in accordance with the International Committee of Journal Editors uniform requirements for manuscripts submitted to biomedical journals. Please see <http://www.icmje.org> for more details. All animal studies must contain a statement within the Materials and Methods section confirming approval by the Institutional Animal Care and Use Committee and that the care and handling of the animals were in accord with National Institutes of Health guidelines or other internationally recognized guideline for ethical animal treatment.

**Statistical Review.** Any study containing quantitative data and statistical inference should be reviewed by a consultant with formal statistical training and experience.

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## MANUSCRIPT CONTENT

**Title Page.** The title page should contain 1) the title; 2) first name, middle initial, and last name of each author; 3) highest academic degree, fellowship designations, and institutional affiliation for each author; 4) name of the institution(s) where the work was performed; 5) the address for reprints and a statement regarding whether reprints will be ordered; and 6) financial support used for the study, including any institutional departmental funds. The authors should also provide six key words for indexing, using terms from the Medical Subject Headings list of Index Medicus. Structured abstracts are required for all manuscripts (except editorials, letters, and book reviews) submitted to *Pediatric Critical Care Medicine*.

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**Article Tweet.** Each manuscript will be required have a tweet entered on the manuscript submission page that can be used for dissemination on social media if the manuscript is accepted. Tweets are limited to 140 characters and should reflect the overall message of the manuscript. Examples of preferred tweet formats can be found at <https://twitter.com/pedcritcaremed>.

**Text Material.** The text should be organized into the following sections: Introduction, Materials and Methods, Results, Discussion, and Conclusions followed by Acknowledgments, References, Figure Legends, and Tables. Secretarial and editorial assistance are not acknowledged. Results may be presented in the text, in the figures, or in the tables. The Discussion section should interpret the results without unnecessary repetition. References to related studies should be included in the text section.

In addition, the following should be observed:

- The full term for which an abbreviation stands should be used at its first occurrence in the text unless it is a standard unit of measure. The abbreviation should appear in parentheses after the full term. Abbreviations should not be in the title, figure legends or table titles.
- For standard American units, do not use values that are more significant than your analysis is capable of accurately measuring (e.g., Pa<sub>c</sub>, 34 torr [11.2 kPa], not 83.7 torr).
- Hemodynamic measurements for pressure (e.g., MAP) should appear in mm Hg and gas tension measurements (e.g., Pa<sub>o</sub>) should appear in torr with SI units in parentheses. The units of vascular resistance are dynes·sec/cm<sup>5</sup>.
- Please provide r<sup>2</sup> values for parametric data.

**References.** All references should be cited in sequential order in the text and typed on a separate sheet of paper. References should be identified in text, tables, and legends by full-size Arabic numerals on the line and in parentheses. Do not use wordprocessing footnote, endnote, or paragraph numbering functions to make a list of references. Titles of journals should be set in italics and abbreviated according to the style used in Index Medicus. If journal titles are not listed in Index Medicus they should be spelled out. Unpublished data or personal communications should be noted parenthetically within the text but not in the References section. Inclusive page numbers (e.g., p. 1-10) should be used for all references. Listed below are samples of standard references; however, a complete listing of references can be found on the International Committee of Medical Journal Editors Web site, [www.icmje.org](http://www.icmje.org).

**Standard Journal Article:** Bone RC, Fisher CJ, Gemmer TP, et al: Sepsis syndrome: A valid clinical entity. *Crit Care Med* 1989; 17:389-393

**Standard Book with Authors:** Civetta JM, Taylor RW, Kirby RR. *Critical Care*. Third Edition. Philadelphia, Lippincott, Williams & Wilkins, 1996

**Standard Book with Editors:** Norman II, Reform SI (Eds): *Mental Health Care for Elderly People*. New York, Churchill Livingstone, 1996

**Standard Chapter in a Book:** Phillips SJ, Whisnart JP: Hypertension and stroke. In: *Hypertension: Pathophysiology, Diagnosis and Management*. Lough IH, Brenner RM (Eds). Second Edition. New York, Raven Press, 1995, pp 465-478

**Standard Web Site/Electronic Format:** Marion DW, Dornier R, Dunham CM, et al: Practice management guidelines for identifying cervi-

cal spine injuries following trauma. Available at: <http://www.aunt.org>. Accessed July 1, 2000

**Equations.** Equations should be created as normal text or as images. The use of equation editors or utilities may not convert correctly during the manuscript submission process and their use is discouraged.

**Tables and Figures.** The number of figures and tables should be appropriate for the length of the manuscript; do not use superfluous illustrations. Materials reproduced from another published source must be labeled "Reproduced with permission from..." In addition, a letter granting permission to reproduce the materials from the copyright holder must be received by SCCM when the manuscript is submitted for review. If the manuscript is accepted for publication, it will not be able to be printed unless this permission letter has been submitted. Adapted figure or table materials must be labeled "Adapted with permission from..." Letters of permission are also required for adapted materials. A sample of a permission request can be found on Editorial Manager® in the instruction section.

**Tables.** Do not use tabs to create tables and do not use table editors. Table building utilities will convert, providing that no special images were inserted. Do not minimize tabular data in the text. Do not use abbreviations in table titles. Do not use all capital letters in table headings and text. Do not use center, decimal tab, and justification commands. Do not use spaces to separate columns. Use a single tab, not a space, on either side of the t symbol. Do not underline or draw lines within tables. Footnoted information should be referenced using italicized, superscript, lower case letters (i.e., <sup>a</sup>) in alphabetical order (reading from left to right). Avoid lengthy footnotes and insert descriptive narratives in the text.

### Figures.

#### A) Creating Digital Artwork

1. Learn about the publication requirements for Digital Artwork: <http://links.lww.com/ES/A42>
2. Create, scan, and save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).
3. Upload each figure to Editorial Manager® in conjunction with your manuscript text and tables.

#### B) Digital Artwork Guideline Checklist

Here are the basics to have in place before submitting your digital art:

- Artwork should be saved as .tif or .eps files.
- Artwork is created as the actual size (or slightly larger) it will appear in the journal. (To get an idea of the size images should be when they print, study a copy of the journal to which you wish to submit. Measure the artwork typically shown and scale your image to match.)
- Crop out any white or black space surrounding the image.

- Diagrams, drawings, graphs, and other line art must be vector or saved at a resolution of at least 1200 dpi.
- Photographs, radiographs, and other half-tone images must be saved at a resolution of at least 300 dpi.
- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript text file.

**Remember:**

- Cite figures consecutively in your manuscript.
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For captions and variables within a figure, use Helvetica (or Arial) font, if possible, in upper and lower case letters. Radiographic prints must have arrows (if applicable) for clarity. Color photographs will occasionally be published in the journal if use of color is vital to making the point; authors will be charged the cost of color reproduction. Figures that do not conform to these specifications will be sent back to the corresponding author for correction.

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**Manufacturer.** Provide in parentheses the model number, name of manufacturer, their city, and state or country, for all equipment described in the paper.

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Guidelines for the most frequent types of articles submitted to the journal are summarized below.

**Clinical Investigations.** These include randomized controlled trials, case-control series, and retrospective studies, among others. Within this category, we also feature four subspecialty categories including: Cardiac Intensive Care, Neonatal Intensive Care, Neurocritical Care, and Quality and Safety. This category of manuscript

has a word limit of 2000 to 4000 words (8-16 typed double-spaced pages) which includes an abstract of no more than 300 words; the Discussion section of the manuscript should be limited to no more than 1500 words; a maximum of 40 references; and no more than 7 Figures and/or Tables.

**Laboratory Investigations.** These include laboratory and animal research. This category of manuscript has a word limit of 2000 to 4000 words (8-16 typed double-spaced pages) which includes an abstract of no more than 300 words; the Discussion section of the manuscript should be limited to no more than 1500 words; a maximum of 40 references; and no more than 7 Figures and/or Tables.

**Review Articles.** These consist of critical assessment of literature and data pertaining to clinical topics. In review articles, emphasis should be placed on cause, diagnosis, therapy, prognosis, and prevention. Information concerning the type of study or analysis, population, intervention, and outcome should be included for all data used. The selection process used for all data should be described. Meta-analysis will be considered as review papers. The recommended length of review articles is 2000 to 3000 words (8-12 typed double-spaced pages) which includes an abstract of no more than 300 words; a maximum of 100 references; and no more than 10 Figures and/or Tables.

**Brief Reports.** These should be short reports of original studies or evaluations. The recommended length of brief reports is no more than 1500 words (6 typed double-spaced pages) which includes an abstract of no more than 300 words; a maximum of 25 references; and no more than 2 Figures and/or Tables.

**PCCM Perspectives.** These include articles that may fall outside the realm of formal clinical or basic science research, such as social policy, professional education, ethical dilemmas, and delivery of compassionate care. The recommended length is no more than 1500 words (6 typed double-spaced pages) which includes an abstract of no more than 300 words; a maximum of 25 references; and no more than 4 Figures and/or Tables.

**Evidence-Based Journal Club.** These articles provide an evidence-based critique of a recent important paper in the field of pediatric critical care medicine. The recommended length is no more than 1500 words (6 typed double-spaced pages) which includes an abstract of no more than 300 words; a maximum of 25 references; and no more than 4 Figures and/or Tables.

**Letters to the Editor.** Letters to the Editor are encouraged. Letters must specifically address a recent article published in *Pediatric Critical Care Medicine*. They should be no more than 500 words (2 typed double-spaced pages) with a maximum of 5 references.

**Invited Editorial.** These represent commentaries addressing newly published articles in the journal and are by invitation only. Invited editorials should be no more than 1200 words (5 typed double-spaced pages) with a maximum of 15 references and a maximum of 2 Figures and/ or Tables.

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