SINGLE VERSUS MULTIPLE RED BLOOD CELL UNIT TRANSFUSION STRATEGIES

SINGLE VERSUS MULTIPLE RED BLOOD CELL UNIT TRANSFUSION STRATEGIES

By ANDREW WEI-YEH SHIH, MD, FRCPC, DRCPSC, BSc

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Science

McMaster University MASTER OF SCIENCE (2017) Hamilton, Ontario (Health Research Methodology)

TITLE: Single Versus Multiple Red Blood Cell Unit Transfusion Strategies

AUTHOR: Andrew Wei-Yeh Shih, MD, FRCPC, DRCPSC, BSc

SUPERVISOR: Professor Nancy M. Heddle

PAGES: xvii, 118

Preface

Transfusion has historically been guided to target a higher hemoglobin level of 100 g/L and thus transfusing multiple units of red blood cells (RBCs) successively has been considered standard of practice. However, transfusions are not without risk and multiple randomized controlled trials now support the use of a restrictive transfusion trigger (target hemoglobin level of 70-80 g/L). Recent recommendations from transfusion experts now also recommend to transfuse a single unit of RBCs and reassess before transfusing another unit rather than transfusing successive RBC units. The research question being addressed in this thesis was: *In hospitalized adult inpatients receiving non-emergent transfusions, does a strategy of transfusing one unit of red blood cells followed by reassessment compared to transfusing multiple units result in significant differences in clinical and utilization outcomes?* I hypothesized that: *a lack of direct evidence would be available to support any recommendation, that "expert" opinion would be variable, and that retrospective studies may provide a starting point to rigorously assess whether single unit transfusion strategies truly have benefit.*

The objectives of this thesis were: 1) to perform two systematic reviews to assess whether current transfusion guidelines and review article recommendations addressed this question and to identify and assess studies that directly provided evidence for benefit of single unit transfusion strategies [Chapters 2A and B]; 2) to survey Canadian transfusion medicine experts on their practice and what "reassessment" entails [Chapter 3]; 3) to develop a conceptual flow diagram that would help address the factors that would affect the decision to use either transfusion strategy and what would constitute important clinical and utilization outcomes [Chapter 4]; and 4) to design a retrospective study to assess the research question, considering both ethical and methodological issues [Chapters 5 and 6].

This work led to design of the retrospective study discussed in Chapter 6 that addresses the research question:

In adult (age ≥18) inpatients at tertiary care hospitals in HHS and SJHH between January 1, 2010 to December 31, 2016 who were transfused RBCs during their first hospitalization, is there a difference in the gap time between the first and second transfusion episode depending on whether the patient was transfused a single unit or multiple units during their first transfusion episode?

In conclusion, performing this retrospective study may help generate hypotheses that may lead to design a prospective randomized controlled trial to assess if either transfusion strategies lead to benefit or harm.

Abstract

Historical practice supported the transfusion of multiple units of red blood cells (RBCs) successively. Recent recommendations from transfusion medicine experts now support transfusion of single units of RBCs with reassessment before transfusing successive units. Two systematic reviews of the literature were performed to determine if A) transfusion guidelines and review articles recommended either strategy and B) if studies directly support the benefit of transfusion. A lack of concordance in recommendations in the published literature was found and in addition to a lack of evidence supporting single unit transfusion strategies.

A survey of transfusion medicine experts demonstrated that while most agreed on single unit transfusion strategies for stable inpatients, variability in practice was seen in outpatients and patients with comorbidities. Common elements were seen in what constitutes reassessment which may be useful to practicing clinicians.

A conceptual flow diagram was developed to outline the factors that might influence the decision to use a single or multiple unit transfusion strategy and outcomes important to assess. The flow diagram was then used to guide an exploratory analysis to determine if defining single and multiple unit cohorts retrospectively, baseline characteristics could be collected, and to determine what outcomes could be assessed. This then led to the design of a retrospective study that would assess: *In adult (age ≥18) inpatients at tertiary care hospitals in HHS and SJHH between January 1, 2010 to December 31, 2016 who were transfused RBCs during their first hospitalization, is there a difference in the gap time between the first and second transfusion episode depending on whether the patient was transfused a single unit or multiple units during their first transfusion episode?*

The findings from this study may be hypothesis generating to develop future prospective studies to determine if single unit transfusion strategies have benefit.

Dedication & Acknowledgements

I am eternally grateful to Professor Nancy Heddle for her guidance and mentorship not only through my masters, but through my transfusion medicine training as well. I'm continually inspired by her drive to further the science in the field, her compassion and kindness to nurture the next generation of scientists and practitioners in the field, and how she continually demonstrates that progress is truly a shared enterprise and not an individual one. I hope one day I can be half the mentor she has been to future trainees and colleagues.

I'd like to thank the rest of my masters committee: Mark Crowther, Richard Cook, and Cyrus Hsia – I appreciate the time and energy you've spent providing input despite having busy lives yourselves. I greatly appreciate the efforts of everyone else who was involved in helping me with my thesis, including: Rebecca Barty, Na Li, Yang Liu, Shannon Lane, Aixin Liu, Radwa Elsharawi, Shadhiya Alkhan, Allahna Elahie, Christopher Hillis, Deborah Siegal, Andrea McLellan, and Ron Movilla.

The McMaster Centre for Transfusion Research has been invaluable for laying the foundation for a lifetime of being inquisitive and for providing a supportive environment – and I would credit the team there for giving me opportunities as well as making my time there such an exciting and productive period of my life. Specifically, I'd like to particularly thank: Donnie Arnold, Madeleine Verhovsek, Ted Warkentin, Erin Jamula, Heather Patterson, Grace Wang, Aicha Traore, Anushka Jaffer, Julie Carruthers, and Joanne Duncan.

I'd like to thank my new colleagues in Vancouver Costal Health and British Columbia for taking a chance on a completely "green" person like me. The opportunity to learn and to collaborate to advance transfusion medicine I don't take for granted, and I don't plan to let you down.

More than anyone else, I'd especially like to thank my family: Alice, Charles, and Francis. My mom and dad built their life as immigrants from humble beginnings to give me an opportunity to work hard, play hard, and pursue my dreams. They really gave me the opportunity that they never had. My brother is someone I've always looked up to and paved the way for who I am now. The bond in our family and the unconditional support means everything to me.

I'd like to dedicate this thesis to my love, Cathy Wang. You more than anyone know the ups and downs during my journey and I'm so grateful to have you by my side. You continually push me to be the best I can be, which is what you deserve. As much as I care about my career goals, my biggest goal in life is to make you happy and fulfilled. I can't wait to spend the rest of my life with you.

Table of Contents

List of Tables and Figures

List of Appendices

List of Abbreviations

2,3-DPG	2,3-Bisphosphoglyceric Acid
ABIM	American Board of Internal Medicine
AHTR	Acute Hemolytic Transfusion Reaction
APACHE II	Acute Physiology and Chronic Health Evaluation II
ATP	Adenosine Triphosphate
CBC	Complete Blood Count
CCC	Chart Completion Code
CCI	Charleston Comorbidity Index
CSU	Computer Services Unit
CI	Confidence Interval
DAD	Discharge Abstract Database
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EPO	Erythropoetin Stimulating Agent
FNHTR	Febrile Non-Hemolytic Transfusion Reactions
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HHS	Hamilton Health Sciences
HIREB	Hamilton Integrated Research Ethics Board
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HSCT	Hematopoetic Stem Cell Transplantation
HTR	Hemolytic Transfusion Reactions
ICD-10	International Statistical Classification of Diseases and Related Health Problems (10th Revision)
ICU	Intensive Care Unit
ID	Identifier
IL	Interleukin
INR	International Normalized Range
LIS	Laboratory Information System
MASCOT	McMaster AccesssS Clinical ROsters and Trust
MCTR	McMaster Centre for Transfusion Research
MRN	Medical Record Number
MRP	Most Responsible Physician
NAC	(Canadian) National Advisory Committee
NOS	Not Otherwise Specified
ORBCoN	Ontario Regional Blood Coordinating Network
PRBC	Packed Red Blood Cell
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
SD	Standard Deviation
SJHH	St. Joseph's Healthcare Hamilton
TACO	Transfusion Associated Circulatory Overload
TAD	Transfusion Associated Dyspnea

TRALI	Transfusion-Related Acute Lung Injury
TRICC	Transfusion Requirements in Critical Care
TRUST	Transfusion Registry for Utilization Statistics and Tracking
TTI	Transfusion-Transmitted Infections
TTISS	Transfusion Transmitted Injury Surveillance System

Declaration of Academic Achievement

The development of the thesis proposal was undertaken by A. Shih with input from N. Heddle (supervisor), R. Cook (second reader), and M. Crowther (third reader).

The systematic reviews were developed by A. Shih with input from N. Heddle. The search strategy was developed by A. Shih, A. Liu, and A. McLellan (librarian). Article review and data collection were performed by A. Liu and R. Elsharawi, with A. Shih acting to resolve discrepancies.

The survey was developed by A. Shih with input from N. Heddle and S. Lane. Data management was performed by A. Shih and S. Lane. Analyses were performed by A. Shih, S. Lane, S. Alkhan, and R. Movilla (research assistant).

The retrospective study research question, design, and ethics proposal were developed by A. Shih with input from N. Heddle, R. Cook (second reviewer), R. Barty (research coordinator), N. Li (biostatistician), and Y. Liu (biostatistician). A. Shih developed the statistical analysis plan and the statistical analyses for the exploratory analyses were performed by N. Li and Y. Liu.

Chapter 1. Introduction

Transfusion of red blood cells is performed in the clinical setting to correct symptoms of anemia and to maintain vital organ function; and was historically guided by the "10/30" rule to transfuse to a hemoglobin level of 10 g/dL (100 g/L in SI units) and a hematocrit of 30%. To maintain this high hemoglobin level, the practice of ordering and transfusing two or more red blood cell units was previously standard of practice.

Transfusions are not without risk. The most direct evidence of this is transfusion reactions, which are common (Figure 1-1).[1] Although the majority of transfusion reactions are of minimal clinical significance, reactions associated with significant morbidity and mortality are not uncommon, especially in the context of transfusion being a ubiquitous therapy. The failure to protect transfusion recipients from transfusion-transmitted infections (TTI) shaped the modern culture of safety in transfusion medicine in Canada with the Krever Report.[2]

Figure 1-1. Transfusion Reactions and Frequencies in Ontario

Reaction Definition[3]	**Frequency Estimates Per Unit Transfused in Sentinel Sites* Ontario TTISS (2008-2012)**	**Etiology**	**Symptoms/ Signs**
Minor allergic Within 4h of transfusion any 1 of: Morbilliform rash with pruritus; Urticaria (hives); Localized angioedema; Edema of lips, tongue and uvula; Periorbital pruritus, erythema and edema; Conjunctival edema	1:1,463	Allergy to transfused donor antigens (protein or carbohydrate)	urticaria, pruritus
TACO Within 6h of transfusion any 4 of: Acute respiratory distress; Tachycardia; Hypertension; acute/worsening pulmonary edema on CXR; Positive fluid balance	1:8,008	Volume overload due to underlying cardiac disease and/or too rapid infusion rate	dyspnea, orthopnea, cough
FNHTR	1:1,641	**Predominate cause:**	fever, chills

An increase in temperature of ≥1˚C over baseline and ≥38˚C within 4h of transfusion		Cytokine accumulation during product storage. **Minor cause:** leukocyte antibody reacting with transfused leukocytes	
TRALI Within 6h of transfusion: Acute onset; Hypoxemia; Bilateral infiltrates on CXR; No circulatory overload; No alternative risk for ALI[4]	Possible 1:61,926 Definite 1:92,889	I) anti-HLA or anti-granulocyte antibodies II) leukocyte priming substances	dyspnea, fever, hypotension
AHTR Clinical or laboratory features of hemolysis within 24h of transfusion.	1:46,444	Transfusion of incompatible blood red cells[5]	fever, pain, dyspnea, vomiting, hypotension
Severe allergy / anaphylaxis Allergic reaction involving respiratory and/or cardiovascular system	1:16,296	Allergy to transfused donor antigens	rash, wheeze, stridor, dyspnea, angioedema, hypotension
Septic	1:77,407*	Bacterial contamination of donor unit	fever, chillis, hypotension, dyspnea
Hypotensive reaction Isolated fall in systolic or diastolic blood pressure of >30mmHg within 1h of transfusion and sBP <80mmHg	1:35,726	Vasodilation and smooth muscle relaxation triggered by bradykinin synthesis[6]	isolated hypotension
TAD Respiratory distress within 24h of transfusion that does not meet the criteria of TRALI, TACO, or allergic reaction	1:58,055	Unknown	dyspnea

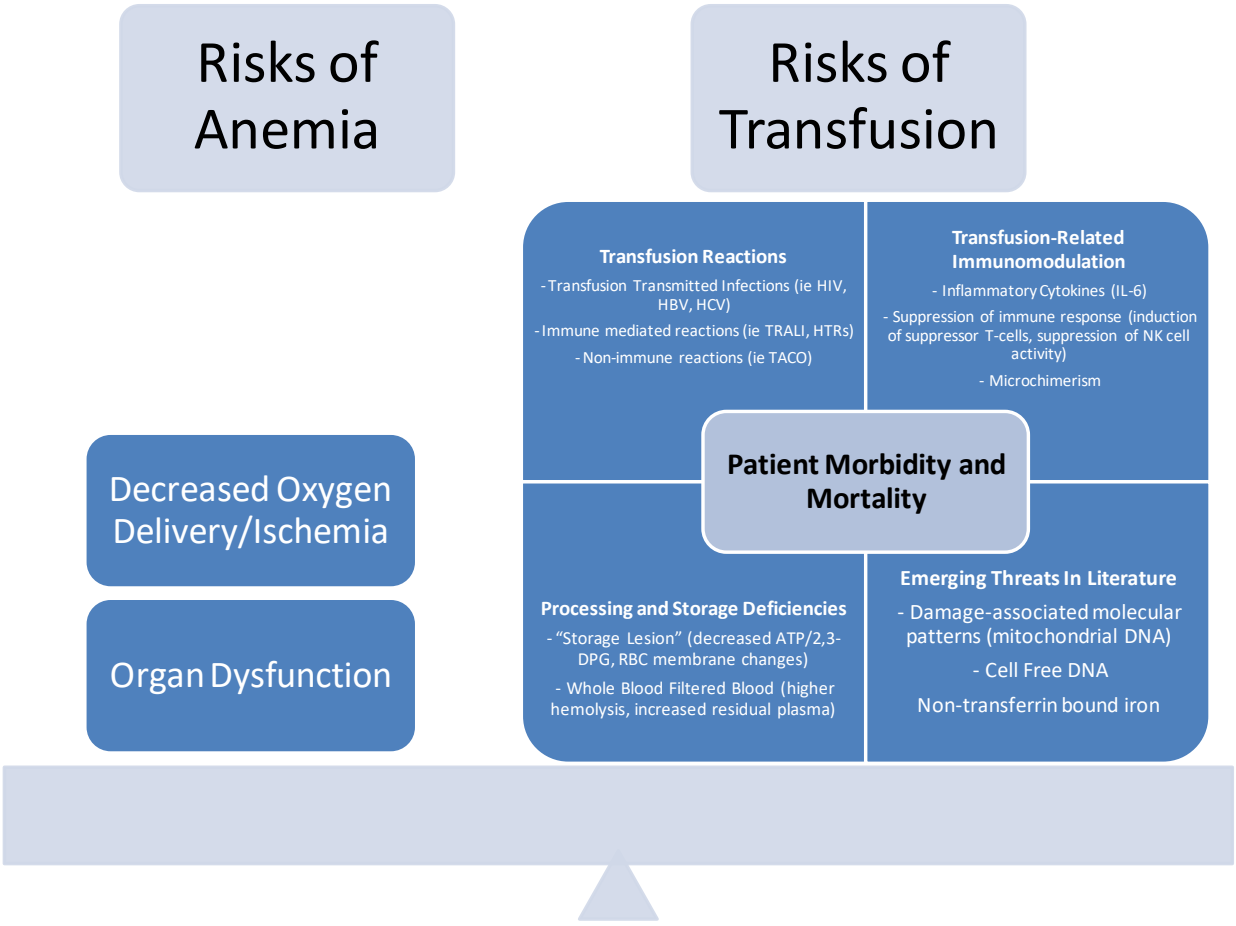
Adapted from Shih AW et al, International Journal of Clinical Transfusion Medicine 2016
**Sentinel sites of the Ontario Transfusion Transmitted Injury Surveillance System (TTISS) (n=25) report all transfusion reactions. The frequency of each acute transfusion reaction was calculated based on 2,021 transfusion related adverse events reported by sentinel sites from 2008-2012.*
h, hours; TACO, transfusion-associated circulatory overload; CXR, chest radiograph; FNHTR, febrile non-hemolytic transfusion reaction; TRALI, transfusion-related acute lung injury; HLA, human leukocyte antigen; AHTR, acute hemolytic transfusion reaction; TAD, transfusion-associated dyspnea

1.1 The Emergence of Restrictive Transfusion Strategies

In addition to risks of transfusion that are direct sequelae, transfusion has indirect risks to patients. Transfusion has been known to cause transfusion-related immunomodulatory effects and microcirculatory complications that may harm patients (Figure 1-2).[7,8] In patients who are critically ill, the additional insult of transfusion may

lead to significant morbidity and mortality. This hypothesis was proven in the TRICC randomized controlled trial, where a restrictive approach to transfusions (maintaining a hemoglobin between 70-90 g/L) was at least equivalent to a liberal approach to transfusions (maintaining a hemoglobin between 100-120 g/L). Subgroup analyses demonstrated the potential superiority of restrictive transfusion strategies, such as in patients who were younger than 55 years old or had an APACHE II score ≤ 20.[9]

Figure 1-2. Diagram Demonstrating Balance of Benefits and Risks of Transfusion

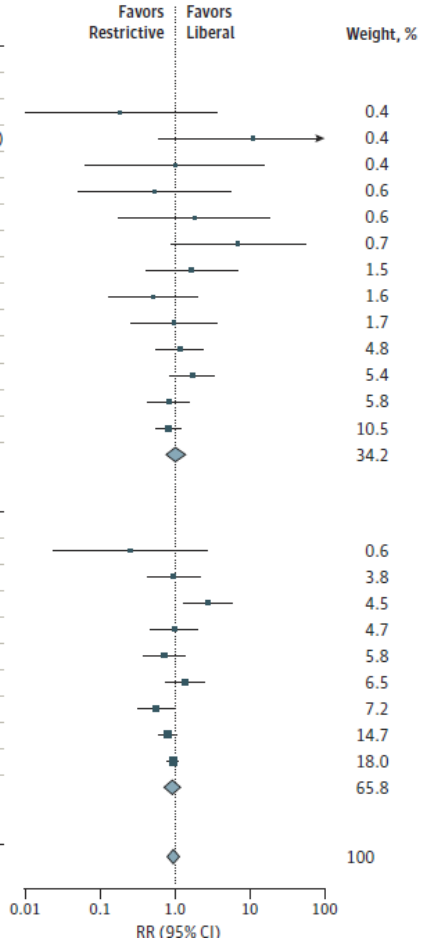


The finding of either non-inferiority or potential superiority in regards to patient safety or mortality of a restrictive transfusion strategy has been duplicated in multiple randomized controlled trials in multiple settings. This is shown in a meta-analysis published as part

of the 2016 AABB guidelines (Figure 1-3).[10,11] The exact mechanisms of harm for transfusion are not well understood, but could include biochemical and membrane structural changes in blood products during storage,[12] transfusion of sex-mismatched transfusions,[13,14] and transfusion of ABO-compatible but not matched products.[15] While transfusion has the great potential to be life-saving, it should be utilized recognizing the balances of risks and benefits similar to other medical interventions.

Figure 1-3. Comparison of 30-Day Mortality Using Restrictive versus Liberal Hemoglobin Transfusion Thresholds in Randomized Clinical Trials (taken from [11])

	Restrictive Transfusion Threshold		Liberal Transfusion Threshold		
Source	No. of Deaths	Total No.	No. of Deaths	Total No.	RR (95% CI)
Restrictive threshold, hemoglobin <8 to 9 g/dL					
Lotke et al,[75] 1999	0	62	0	65	Not estimable
Blair et al,[53] 1986	0	26	2	24	0.19 (0.01-3.67)
Foss et al,[63] 2009	5	60	0	60	11.00 (0.62-194.63)
Carson et al,[58] 1998	1	42	1	42	1.00 (0.06-15.47)
Webert et al,[86] 2008	1	29	2	31	0.53 (0.05-5.58)
Cooper et al,[61] 2011	2	23	1	21	1.83 (0.18-18.70)
Carson et al,[56] 2013	7	55	1	55	7.00 (0.89-55.01)
Parker,[78] 2013	5	100	3	100	1.67 (0.41-6.79)
Bracey et al,[54] 1999	3	215	6	222	0.52 (0.13-2.04)
Bush et al,[55] 1997	4	50	4	49	0.98 (0.26-3.70)
Hajjar et al,[68] 2010	15	249	13	253	1.17 (0.57-2.41)
Gregersen et al,[64] 2015	21	144	12	140	1.70 (0.87-3.32)
Jairath et al,[72] 2015	14	257	25	382	0.83 (0.44-1.57)
Carson et al,[60] 2011	43	1009	52	1007	0.83 (0.56-1.22)
Subtotal	121	2321	122	2451	1.05 (0.78-1.40)
Heterogeneity: $\tau^2=0.02$; $\chi^2_{12}=13.14$; $P=.36$; $I^2=9\%$					
Tests for overall effect: z score = 0.31; $P=.76$					
Restrictive threshold, hemoglobin <7 g/dL					
DeZern et al,[87] 2016	1	59	2	30	0.25 (0.02-2.69)
Hébert et al,[70] 1995	8	33	9	36	0.97 (0.42-2.22)
de Almeida et al,[79] 2015	23	101	8	97	2.76 (1.30-5.87)
Lacroix et al,[74] 2007	14	320	14	317	0.99 (0.48-2.04)
Walsh et al,[85] 2013	12	51	16	49	0.72 (0.38-1.36)
Murphy et al,[76] 2015	26	1000	19	1003	1.37 (0.76-2.46)
Villanueva et al,[84] 2013	19	416	34	417	0.56 (0.32-0.97)
Hébert et al,[69] 1999	78	418	98	420	0.80 (0.61-1.04)
Holst et al,[71] 2014	168	502	175	496	0.95 (0.80-1.13)
Subtotal	349	2900	375	2865	0.94 (0.74-1.19)
Heterogeneity: $\tau^2=0.05$; $\chi^2_8=16.09$; $P=.04$; $I^2=50\%$					
Tests for overall effect: z score = 0.53; $P=.59$					
Overall	470	5221	497	5316	0.97 (0.81-1.16)
Heterogeneity: $\tau^2=0.04$; $\chi^2_{21}=29.75$; $P=.10$; $I^2=29\%$					
Tests for overall effect: z score = 0.29; $P=.77$					
Tests for subgroup differences: $\chi^2_1=0.34$; $P=.56$; $I^2=0\%$					



1.2 The Development of Quality Improvement in Health Care

Limiting transfusions may also reduce costs, significant as the cost per RBC unit in Canada is $425 (2011 data). The cost of transfusion would also include hospital activity based costs which would further add to cost. The high costs of RBC transfusion have been observed in multiple jurisdictions outside of Canada.[16-18]

Quality improvement strategies have been utilized successfully in multiple settings to improve resource utilization and delivering quality to the end user.[19] These concepts were translated into health care through organizations such as the Institute for Healthcare Improvement (IHI), which was initially focused on reducing errors through systems and behavioural changes, and evaluating their effect on measurable metrics.[20] Success in this approach led to the expansion of quality improvement in health care to resource utilization.[21]

In 2012, the American Board of Internal Medicine (ABIM) Foundation launched Choosing Wisely based on an editorial by medical ethicist Howard Brody, with the goal of avoiding wasteful or unnecessary medical tests, treatments, and procedures.[22,23] Specialty society partners representing many subspecialties have released recommendations, often with published scientific evidence supporting them.[23] Campaigns supporting the mission of Choosing Wisely have been adopted internationally, such as in Canada with the Choosing Wisely Canada campaign.[24]

1.3 Single Versus Multiple Unit Transfusion Strategies

The rationale for transfusing one unit of packed red blood cells at a time with clinical reassessment before a second unit is transfused rather than transfusing multiple units successively is based on the belief that fewer red blood cell units would be transfused leading to fewer deleterious effects of transfusion and lower costs; with the published literature describing this approach as early as 1972.[25] With restrictive transfusion strategies demonstrating benefit from randomized control trial data, the "10/30" rule falling out of clinical practice, and increasing interest in quality improvement in health care, experts in transfusion medicine have begun to recommend transfusion of one unit of packed red blood with clinical reassessment to determine if a second transfusion is needed. This strategy has now been recommended as part of the Choosing Wisely

Canada recommendations from the Canadian Society of Transfusion Medicine and the Choosing Wisely recommendations from the American Society of Hematology.[26] However, the evidence for this recommendation is extrapolated from the benefit of restrictive transfusion strategies and does not cite any scientific evidence that transfusing one unit at a time is beneficial. Delaying transfusion by using this single unit strategy could potentiate lack of oxygen delivery to vital organs, increase the frequency of errors associated with a higher number of individual transfusion orders, may be more costly, and may not decrease the utilization of RBCs. Therefore, the purpose of this thesis is to explore the question of benefits and practices utilizing single unit transfusion strategies.

1.4 Components of the Proposed Thesis

This thesis contains five components to explore single versus multiple unit transfusion strategies: 1) two systematic reviews: the first of red blood of guidelines/reviews; and the second of studies to support a single unit transfusion approach; 2) a survey of transfusion medicine experts to explore current red blood cell ordering practices and reassessment; 3) a conceptual flow diagram to outline factors affecting to the decision to transfuse single versus multiple units as well as outcomes, 4) methodological considerations of designing a retrospective study to assess local practice, and 5) the design of a retrospective registry study to assess local practice.

Chapter 2A: Systematic Review of Transfusion Guidelines

Two systematic reviews were performed to assess the evidence base around transfusing single units of RBCs at a time compared to transfusion of multiple units successively. The first systematic review was performed to determine if transfusion guidelines or review articles made recommendations for transfusing single versus multiple RBC units. This was performed to assess the range of recommendations in the literature as well as to identify evidence supporting either strategy. A second systematic review was performed to identify studies that had directly compared single versus multiple unit transfusion strategies. The first systematic review will be discussed in this chapter.

2A.1 Methods

2A.1.1 Study Selection

The systematic review of transfusion guidelines included the following eligibility criteria: 1) English language guidelines or systematic reviews relating to transfusion (which did not include those published only in abstract form); and 2) English language treatment guidelines and clinical practice recommendations for anemia and hemorrhage (as transfusion would likely be part of the management). Keywords extracted from articles identified from a previous systematic review of transfusion guidelines to assess best transfusion practices were added to make the search strategy more robust. The search for guidelines included key words and relevant synonyms such as guidelines, strategies, recommendations, erythrocyte, red blood cell, blood, and transfusion. The full search strategy is outlined in Appendix 2A-1, 2A-2, and 2A-3; where search terms were adapted for individual databases.

For the review of the transfusion guidelines, articles that were excluded on review of title and abstract done independently by two reviewers (AL and RE) included: 1) articles that did not include a recommendation for red blood cell transfusion (platelet transfusion guidelines for example), 2) articles that focused solely on comparing restrictive versus liberal transfusion strategies, 3) articles that focused solely on alternatives to transfusion (such as EPO or intravenous iron) and did not contain recommendations regarding

transfusion, 4) guidelines or clinical practice recommendations of diseases that may require transfusion but did not have transfusion as its focus (other than anemia and hemorrhage), 5) articles with cost analyses as the only outcome, 6) articles only mentioning transfusion recommendations for massive hemorrhage protocols (relating to ratio-based component transfusion), 7) articles relating only to exchange transfusion, intrauterine transfusion, or transfusion of apheresis blood products only, 8) audits/practice assessments that were descriptive and did not have a recommendation (ie articles that are not guidelines or reviews), and 9) articles that were only published in abstract form.

The title and abstract screen were done simultaneously as information provided in the title was not often descriptive enough to assess inclusion and exclusion criteria determined *a priori*. A full-text review was then performed for articles that met inclusion criteria based on screening the title and abstract. Multiple databases searched did not include abstract information: if the title was felt to meet inclusion criteria, it was included in the full-text review. All articles included at the end of full-text review that met inclusion criteria had data abstraction performed. Disagreements were resolved after discussion with a third reviewer (AS).

2A.1.2 Data Sources

The databases MEDLINE, EMBASE, CINAHL, Web of Science, National Guideline Clearinghouse, and the Trip Database were searched from inception to June 2016. Reference lists of included studies were also manually searched for potentially relevant articles and articles found during the search for either review that were relevant were included.

2A.1.3 Data Extraction

Two investigators (AL and RE) extracted data independently using a standardized data extraction spreadsheet, with discrepancies resolved by consensus with a third reviewer (AS). Agreement in data abstraction and articles excluded were assessed by kappa score.

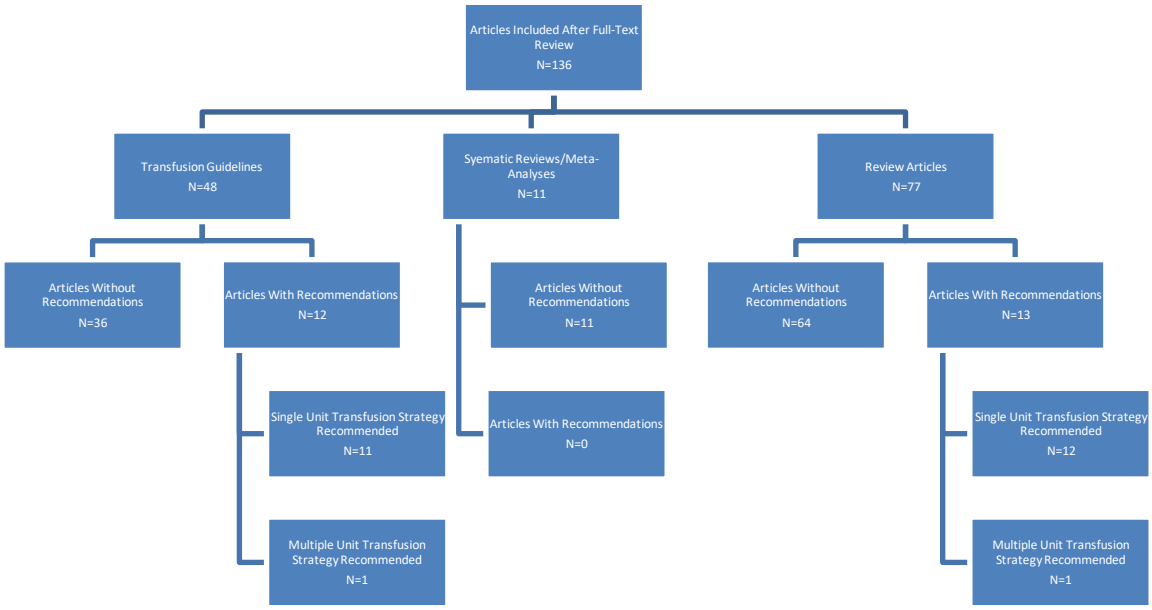
Extracted data for the review of guidelines included year of publication, article type (guideline, systematic review/meta-analysis, or other review articles), patient population (adult [default if age not mentioned], pediatric, critical illness, perioperative, peripartum, conditions predisposing to anemia [cancer, chronic kidney disease, iron deficiency, or sickle cell anemia], or bleeding/hemorrhage), whether there was a recommendation for single versus multiple unit transfusions, and the strategy the article recommended (single or multiple).

Articles categorized as guidelines contained the words “guideline”, “practice recommendations”, “consensus”, or “management” in the title of the article and clinical practice recommendations were observed in the full text review. The quality of individual guidelines was not assessed as the purpose of this review was to determine if guidelines made recommendations regarding single or multiple unit transfusions. Systematic reviews and meta-analyses were categorized as such unless they made clinical practice recommendations and/or were developed by an institution/professional society, where they were instead categorized as guidelines.

2A.1.4 Analysis

The proportion of eligible articles with any recommendation regarding single versus multiple unit transfusion strategies was determined. This analysis was stratified for articles that were guidelines or other types of articles with recommendations. For the articles with a recommendation, the proportion of articles recommending single unit transfusion strategies and multiple unit transfusion strategies were determined respectively. The analysis strategy is outlined in Figure 2A-1.

Figure 2A-1. Systematic Review of Transfusion Guidelines Analysis Strategy and Outcomes

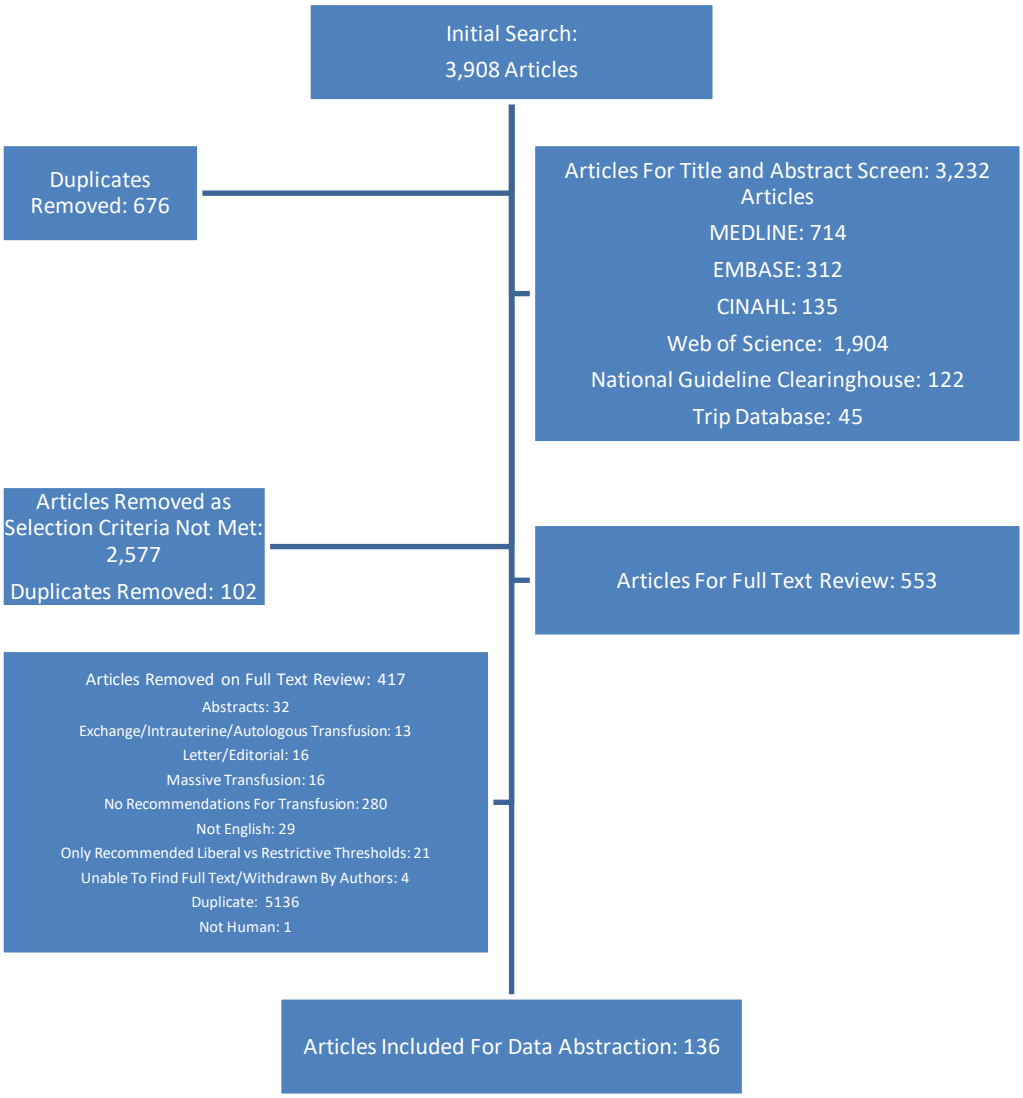


2A.2 Results

2A.2.1 Study Characteristics

The literature search yielded 3,908 studies. After removal of duplicates, we screened 3,232 studies for eligibility and identified 634 articles for full-text review. After full-text review, 136 articles were included for data abstraction (Figure 2A-2). We identified 48 transfusion guideline articles, 77 review articles, and 11 systematic reviews (Figure 2A-1). A kappa agreement for study selection for full text review was 0.648 (95% CI 0.605-0.690), which is indicative of moderate agreement. To improve investigator concordance, we instituted written guidelines and a calibration exercise for data abstraction and study selection. The kappa agreement for selection of articles after full text review was 0.892 (95% CI 0.85 to 0.94), indicative of very good agreement.

Figure 2A-2. Flow Diagram of Summary of Evidence Searching and Final Manuscript Selection



Of the eligible articles, 114 (83.8%) related to red blood cell transfusion in adults (or did not specify a patient population) and 22 (16.2%) related to paediatrics. Articles chosen that related to specific patient populations included: critical illness (12 articles), the perioperative setting (7 articles), peripartum (7 articles), patients with bleeding/hemorrhage (5 articles), other conditions predisposing to anemia (such as cancer, renal disease, iron deficiency anemia, and sickle cell disease) (42 articles), and cardiovascular patients (1 article).

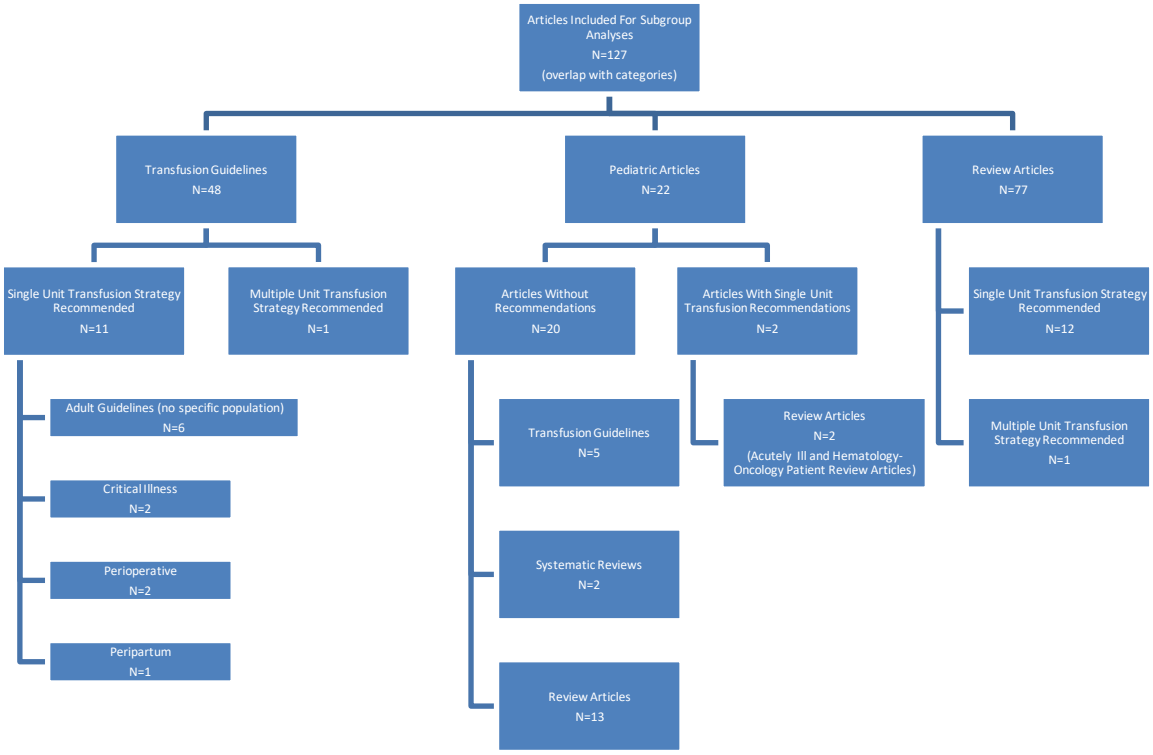
2A.2.2 Study Recommendations

Of the 136 articles included in our review, only 25 (11%) articles made a recommendation regarding transfusing a single unit or multiple units at a time. Of those

articles, 13 were review articles and 12 were guidelines. Of the 25 articles recommending a strategy, 23 articles (92%) recommended transfusing single units then reassessing for the next transfusion; except for one guideline (published in 1998)[27] and one review article (published in 2015)[28] which recommended multiple unit transfusions. Both articles related to transfusion in adults without recommendations for any specific patient population. Patient populations where single unit transfusion strategies were recommended in articles included: critical illness,[29-33] autoimmune hemolytic anemia,[34] the perioperative setting,[35-37] inflammatory bowel disease,[38] patients with malignancies,[39] and pediatric patients.[40,41]All articles that recommended either a single unit transfusion strategy or a multiple unit transfusion strategy either did not have literature to support the recommendation or cited studies supporting restrictive transfusion strategies. The earliest study to recommend a single unit transfusion strategy was recommended in 1992,[42] 9 (39.1%) of these articles were published before 2010,[32,33,37,38,41,43-45] and the remainder (14/23; 60.1%) were published in 2010 or after.[29-31,34-36,39,40,46-51]

Subgroup analyses were performed on all articles (adult and pediatric) that were guidelines, review articles, and pediatric-only articles separately (Figure 2A-3). In the 48 articles that were included in the subgroup of articles categorized as guidelines, only 12 (25%) contained a recommendation regarding single or multiple unit transfusions.[27,29,33,35,36,42,44,47-51]Of those guidelines containing a recommendation, 11 guidelines (92%) recommended a single unit transfusion strategy.[29,33,35,36,42,44,47-51] These guidelines encompassed adult patients in (6 guidelines),[42,44,47-49,51] adult patients with critical illness (2 guidelines),[29,33] adult perioperative patients (2 guidelines),[35,36]and peripartum patients (1 guideline).[50] Of the 77 review articles, only 13 (16.9%) contained a recommendation for a single or multiple unit transfusion strategy.[28,30-32,34,37-41,43,45,46]Of those 13 articles, 12 (92.3%) recommended transfusing one unit at a time.[30-32,34,37-41,43,45,46]In articles relating to pediatrics, 5 articles were guidelines, 2 articles were systematic reviews, and 15 were review articles pertaining to RBC transfusion. Two of these review articles contained a recommendation for single unit transfusions in acutely ill pediatric patients and pediatric hematology-oncology patients.[40,41]

Figure 2A-3. Subgroup Analyses of Guidelines, Review Articles, and Pediatric Articles



2A.3 Discussion

The purpose of performing this systematic review was to determine the frequency and range of recommendations in the scientific literature supporting transfusing one unit at a time or transfusing multiple units at a time. This was also done to identify literature cited for these recommendations that would help inform the evidence base for these recommendations. Our literature search strategy included a wide range of databases other than MEDLINE and EMBASE. Keywords from target articles were utilized in addition to multiple synonyms to ensure all relevant literature was captured. Our search found that the majority of guidelines and other manuscripts relating to RBC transfusion did not specifically recommend either single or multiple unit transfusion strategies. Of those that did, literature cited for supporting evidence were studies supporting restrictive transfusion strategies or expert opinion, not trials directly comparing one strategy to another.

Our systematic review demonstrates that there may be a shift in recommendations found in modern guidelines to recommend single unit transfusion strategies. If it is thought that single unit transfusion strategies are a natural extension of restrictive transfusion strategies, then future guidelines should explicitly recommend single unit transfusion strategies to guide clinicians to reduce unnecessary transfusions to patients. However, as guidelines become focused on deriving evidence from high quality evidence rather than extrapolating from studies or using expert opinion, this demonstrates the need for studies to demonstrate the benefit of single unit transfusion strategies in a broad variety of patient populations.

Pediatric articles were included in our study; however, weight-based transfusion is often considered the standard of care in pediatrics, hence, transfusion of a single unit or multiple units at a time is often not a consideration in this patient population. As 15% of the articles included pertained to pediatrics and most did not have a recommendation similar to adults pertaining to adult patients, it is unlikely that inclusion of these articles skewed our results.

Our systematic review does have some limitations. The quality of literature was not assessed for these articles and low quality articles may dilute the strength of recommendations of higher quality evidence. However, our review of guidelines and other relevant articles relating to guidance of RBC transfusions did not reveal any use of specific evidence to make recommendations on transfusing either single or multiple units at a time. The scope of our review would have made use of a tool to assess quality of guidelines impracticable. Furthermore, the purpose of our literature review was also not to assess the quality of evidence, but to assess the range of recommendations for RBC transfusion in the literature. During the title and abstract screen as well as the full-text review, disagreements were resolved by consensus. This has the potential to introduce bias into the selection process, but improved the agreement in study selection through the study and allowed the independent reviewers to discuss their rationale after thorough review.

In summary, our systematic review demonstrated a lack of recommendations amongst guidelines and other review articles pertaining to the use of single or multiple unit RBC

transfusion strategies. While the articles that did provide a recommendation did support single unit transfusion strategies, the supportive evidence was extrapolations from literature on restrictive transfusion strategies or were simply expert opinion. Future guidelines should either explicitly state support for single unit transfusion strategies or if it is felt that evidence is lacking in this area, high quality studies need to be performed to prove the benefit of single unit transfusion strategies. In the next systematic review, we determine if any studies in the literature have been performed to compare single and multiple unit transfusion strategies to support the contention of the articles reviewed in this chapter.

Chapter 2B: Systematic Review of Studies Comparing Single Versus Multiple Unit Transfusion Strategies

The systematic review presented in the previous chapter demonstrated that most transfusion guidelines and reviews do not make recommendations a strategy of transfusing one unit at a time or multiple units at a time. The recommendations that did occur supported a single unit transfusion strategy, but most did not cite specific studies to support this recommendation. Therefore, a second systematic review was performed to identify studies that had directly compared single versus multiple unit transfusion strategies to establish the evidence for transfusing single units then reassessing that is not extrapolated from evidence favoring restrictive transfusion strategies.

2B.1 Methods

2B.1.1 Study Selection

The systematic review of studies included English language articles comparing the transfusion of single RBC units compared to multiple RBC units. All studies irrespective of study design were included. The search for studies included key words and relevant synonyms such as "one unit at a time", "single unit", "double unit", erythrocyte, red blood cell, blood, and transfusion. The full search strategy is outlined in Appendix 2B-1 and 2B-2; where search terms were adapted for individual databases.

The title and abstract screen were done in a similar fashion to the systematic review of guidelines in the last chapter and was performed independently by 2 reviewers (AL and RE). For this systematic review of studies, articles were excluded based on criteria defined *a priori* and included:1) exchange transfusion, 2) intrauterine transfusion, 3) apheresis blood products only, 4) did not include RBC transfusion, 5) did not include outcome data, or 6) if the study only had descriptive data (ie assessing the number of single and multiple unit transfusions within a time period without a comparison). Studies that compared outcomes before and after a multifaceted intervention that contained single unit transfusion strategies as a main focus to a cohort transfused prior to the intervention were included. Relevant keywords from the systematic review of transfusion guidelines were added to make the search strategy more robust.

A full-text review was then performed for articles that met inclusion criteria based on screening the title and abstract (or if abstract information was not provided, based on the title).All articles included at the end of full-text review that met inclusion criteria had data abstraction performed. Disagreements were resolved by consensus with a third reviewer (AS).

2B.1.2 Data Sources

The databases MEDLINE, EMBASE, CINAHL, and Web of Science were searched from inception to June 2016. The National Guideline Clearinghouse and Trip Database were omitted as they are databases of guidelines. Reference lists of included studies were also manually searched for potentially relevant articles and articles found during the search of the systematic review discussed in the last chapter that were relevant were included for full-text review.

2B.1.3 Data Extraction

Two investigators (AL and RE) extracted data independently using a standardized data extraction spreadsheet, with discrepancies resolved by consensus with a third reviewer (AS). Agreement in data abstraction and articles further excluded were assessed by calculating a kappa score.

Extracted data for the studies included: year of publication, study design (retrospective cohort, prospective cohort, or randomized control trial), intervention type (introduction of single unit transfusion strategy or multifaceted), time period of study, and outcomes. Outcomes considered *a priori* included red blood cell utilization, number of units transfused using a single unit transfusion strategy versus a multiple unit strategy, length of stay, and mortality if present in the studies included. Other outcomes from studies collected after full-text review were also included in a post-hoc analysis.

For the review of studies, the methodological quality of the included studies was evaluated independently by two investigators (AL and RE). The quality of randomized control trials was assessed using the Cochrane Collaboration's Risk of Bias tool and the

quality of observational studies was assessed using the Newcastle-Ottawa scale.[52,53] Disagreements were resolved by an independent third reviewer (AS).

2B.1.4 Statistical Analysis

To determine the difference in outcomes between the single and multiple unit transfusion strategies, the relative risk reduction of single unit RBC transfusion strategies in each included study was calculated (increases are denoted as a negative percentage) with 95% confidence intervals for each of the outcomes of red blood cell utilization, number of units transfused using a single unit transfusion strategy versus a multiple unit strategy, length of stay, and mortality if present in the studies included. A pooled estimate was also calculated for each of the outcomes with corresponding 95% confidence intervals using the Mantel-Haenszel random effects model. A random effects model was utilized as it was hypothesized strategies would have heterogenous effects in different patient populations and settings. We performed these analyses on all studies and subgroup analyses depending on intervention type. A p-value of less than 0.05 was considered significant for all statistical testing.

For all outcomes, heterogeneity was calculated between studies using the I^2 statistic, where an I^2 value of greater than 50% indicated significant heterogeneity. Funnel plots were also generated, where asymmetrical funnel plots were indicative of publication bias. These analyses were performed using Review Manager (RevMan, version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

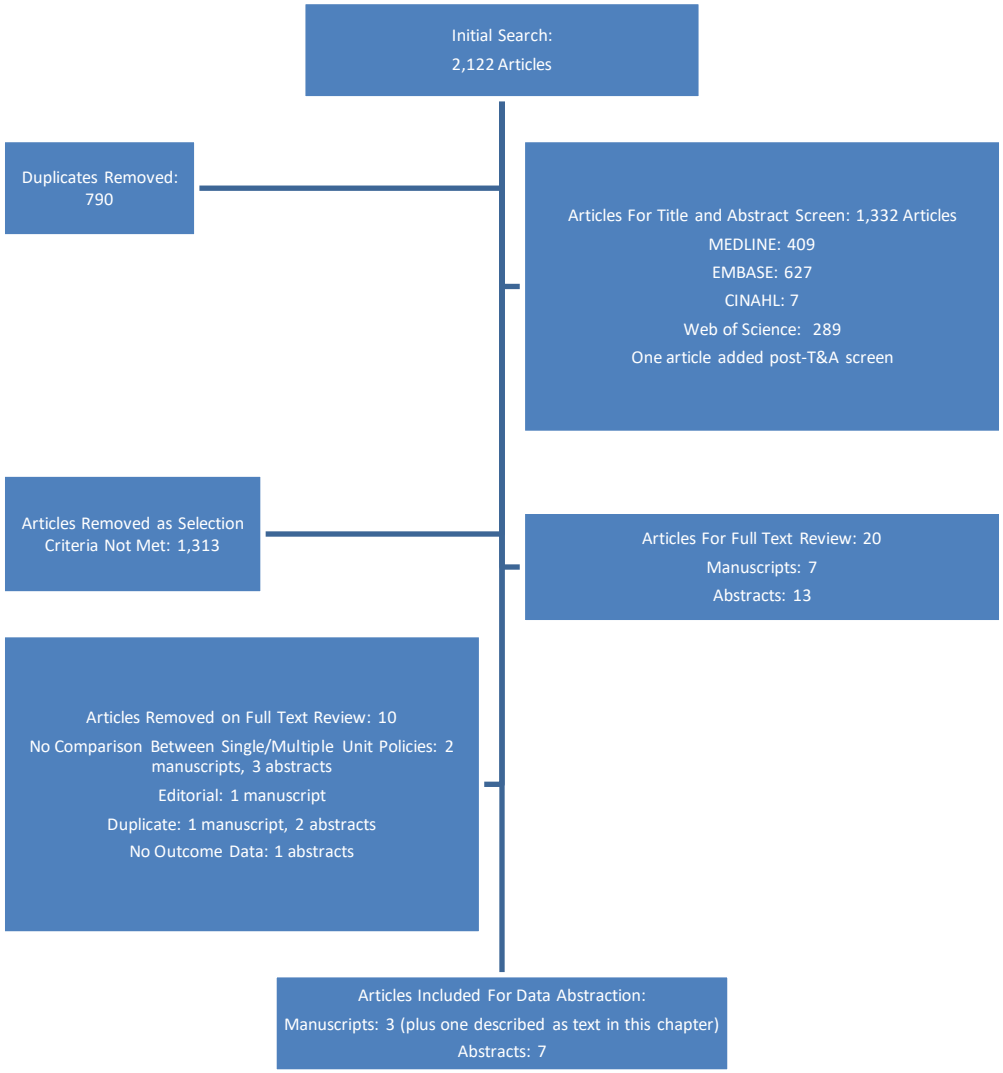
2B.2 Results

2B.2.1 Study Characteristics

The literature search yielded 2,122 studies. After removal of duplicates, we screened 1,332 studies for eligibility and identified 19 articles for full-text review. Before full text review, we were informed of another article that met eligibility criteria that was not found on our original search strategy.[54] After full-text review, 4 articles[54-57] and 7 abstracts[58-64] were included (Figure 2B-1). Reasons for exclusion included: no comparison between single and multiple unit transfusion strategies (2 manuscripts, 3 abstracts), 3 duplicates

(1 article and 2 abstracts; where one abstract had data later published in a manuscript), one article was an editorial with no outcome data, and one abstract discussed a theoretical study design comparing single versus multiple unit transfusion strategies without outcome data. One of the excluded articles contained a theoretical retrospective comparison between single and multiple unit transfusion strategies, summarized in the results of this chapter.[56] A kappa agreement for study selection was 0.95 (95% CI 0.87-1), indicative of excellent agreement.

Figure 2B-1. Flow Diagram of Summary of Evidence Searching and Final Manuscript Selection



2B.2.2 Study Results

Overall, the studies included in our systematic review demonstrated that implementation of single unit transfusion strategies decreased the overall utilization of RBCs and increased the proportion of transfusion episodes where a single unit was transfused. Only one of the studies included had outcomes regarding length of stay and mortality, where there was no difference between before and after implementing a single unit transfusion policy. Assessment of bias using the Newcastle-Ottawa Scale demonstrated that studies were, in general, of reasonable methodological quality. Descriptive summaries of the included three manuscripts are described below; and characteristics of these studies and risk of bias assessments are summarized in Table 2B-1.

Table 2B-1. Summary of Studies Included in Full Text Review

Study	Study Design	Definition of Groups	Outcomes: Red Blood Cell Utilization	Proportion of Transfusions Using Single Unit Strategy	Length of Stay	Mortality	Assessment of Bias (Newcastle-Ottawa Scale) Selection	Comparability	Outcome
Berger et al. (2012)[55]	Retrospective Cohort	**Experimental**: Patients with hematological malignancies receiving intensive chemotherapy or HSCT, receiving transfusions as part of a single unit policy	970 units transfused Median 6 IQR 3-10	84% (815 units)	N/A	N/A	Total Score: 4/4 Representativeness of Exposed: 1 Selection of non-exposed: 1 Ascertainment of exposure: 1 Outcome of interest not present at start: 1	Total Score: 2/2 Controls for factors: 2/2	Total Score: 3/3 Assessment of outcome: 1 Adequate Follow Up Length: 1 Adequacy of Follow Up: 1
		Control: Patients with hematological malignancies receiving intensive chemotherapy or HSCT, receiving transfusions as part of previous policy	1242 units transfused Median 8, IQR 4-13	25% (311 units)	N/A	N/A			
Yerrabothala et al. (2014)[57]	Retrospective Cohort	**Experimental**: Transfusion events in inpatients on medical and surgical units, adult critical care units, hematlogy and oncology unit, obestetric unit, emergency department in postimplementation period (Oct 2012-Mar 2013)	1925 units transfused	85% (1363 units)	Mean: 4.69	3% (282)	Total Score: 4/4 Representativeness of Exposed: 1 Selection of non-exposed: 1 Ascertainment of exposure: 1 Outcome of interest not present at start: 1	Total Score: 0/2 Controls for factors: 0/2	Total Score: 3/3 Assessment of outcome: 1 Adequate Follow Up Length: 1 Adequacy of Follow Up: 1
		Control: Transfusion events in inpatients on medical and surgical units, adult critical care units, hematlogy and oncology unit, obestetric unit, emergency department in preimplementation period (Oct 2011-Mar 2012)	2649 units transfused	53% (1404 units)	Mean: 4.76	3.1% (282)			

Covello et al. (2016)[54]	Retrospective Cohort	**Experimental**:Haematology, surgery and internal medicine inpatients in 'Period 3' (Period 2 was a transition period in the study) (Nov 2013 - Aug 2014) receiving transfusions in accordance to a single-unit policy [No patient denominator provided]	Hematology (Absolute: 952; Median: 2 units/patient) Medicine (Absolute: 169; Median 1 units/patient) Surgery (Absolute: 917; Median: 1 units/patient)	Hematology (89%) Medicine (94%) Surgery (88%)	N/A	N/A	Total Score: 4/4 Representativeness of Exposed: 1 Selection of non-exposed: 1 Ascertainment of exposure: 1 Outcome of interest not present at start: 1	Total Score: 0/2 Controls for factors: 0/2	Total Score: 2/3 Assessment of outcome: 1 Adequate Follow Up Length: 0 Adequacy of Follow Up: 1
		Control:Haematology, surgery and internal medicine inpatients in 'Period 1' (March 2012-Jan 2013) receiving transfusions before implementation of a single-unit policy [No patient denominator provided]	Hematology (Absolute: 1064; Median: 2 units/patient) Medicine (Absolute: 192; Median 2 units/patient) Surgery (Absolute: 998; Median: 2 units/patient)	Hematology (17%) Medicine (57%) Surgery (63%)	N/A	N/A			

Berger et al - 2012[55]

A retrospective cohort study in patients with hematological malignancies assessed transfusions at a single centre comparing single to double unit transfusion strategies. The study was performed from July 2007 to December 2009, where in 2008 the RBC transfusion policy changed to allow dispensing one unit at a time. This time period encompassed 139 patients with 2,212 red blood cell units. The study found that there was a 25% relative reduction of transfused RBC units per therapy cycle. The time-to-next transfusion was shorter in the single-unit period (3.25 versus 4.05 days). After adjusting for confounding factors and clustering of multiple transfusions through regression modelling, a single unit transfusion policy was associated with a significant reduction of 2.7 units (95% CI -4.3 to -1.1 units) per therapy cycle. The shift in this strategy did not affect RBC transfusions as outpatients, RBC recovery, severe bleeding rates, or survival rates.

Yerrabothala et al - 2014[57]

This retrospective study compared transfusions in a single centre from a 6-month period before an intervention to enhance single unit transfusion strategies to a 6-month period after its implementation. The computerized provider order entry was reconfigured to remove single-click ordering for 2-unit RBC transfusions. This study was performed from October 2011-March 2012 for the pre-implementation period and October 2012-March 2013 for the post-implementation period, encompassing 3,658 transfusions. The manuscript did not include information on the number of patients in the study. The study found that there was a relative decrease in total RBC units transfused by 27%. When transfusions were normalized to patient-days in each cohort, there was a significant decrease after implementation (60.8 units transfused/1,000 patient-days versus 44.2 transfused/1,000 patient-days). The post-implementation period was not associated with any significant differences in transfusion reactions, length of hospital stay, or mortality. The authors note that a 25% relative decrease in hospital-wide RBC utilization has persisted beyond the study period.

Covello et al - 2016[54]

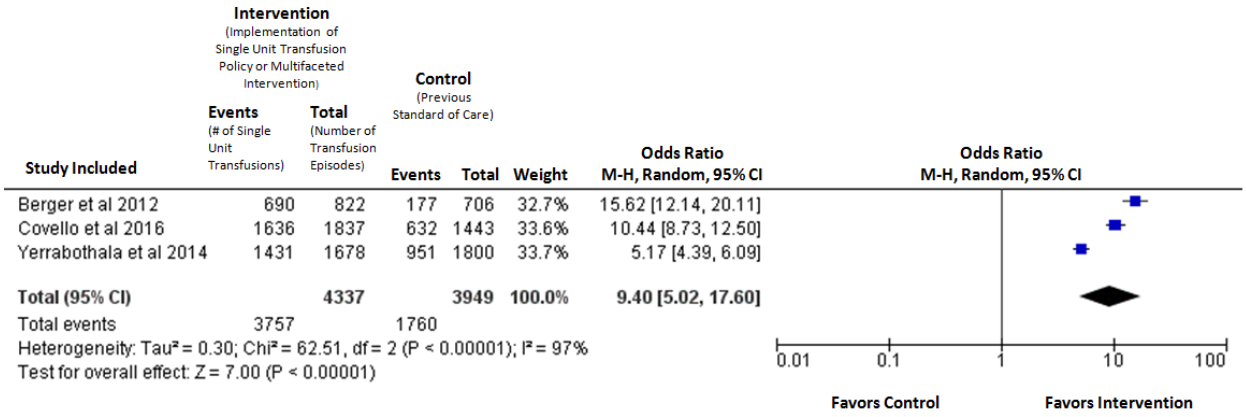
This retrospective study analyzed transfusions that occurred in the Central Zone of the Nova Scotia Health Authority. They instituted a single unit transfusion policy in a staggered fashion, with enforcement in medical/surgical inpatients from January 2013 onwards and enforcement in hematology/bone marrow transplantation patients from November 2013 on. Therefore, the pre-implementation period of March 2012-January 2013 (Period 1) was compared to two similar 10-month periods of time where the policy was rolled out to medical/surgical inpatients (Period 2) and hematology/bone marrow transplantation patients (Period 3). Overall, the proportion of double unit transfusions decreased significantly when comparing Period 3 to Period 1. The proportion of double unit transfusions dropped from 43% (59/134 events) to 6% (8/145 events) for medical inpatients and from 37% (269/729 events) to 13% (111/826 events from Period 1 to Period 2. The proportion of double unit transfusions dropped from 78% (443/567 events) to 11% (93/859 events) from Period 2 to Period 3. When comparing Period 2 to Period 1, a significant decrease in units transfused occurred in surgical patients (approximately a 6% decrease, median number of units decreased from 2 to 1). When comparing the median number of units per patient, there was a significant decrease between Period 3 and Period 1. The hemoglobin trigger for transfusion did not change over the study period.

2B.2.3 Meta-analysis of Outcomes

Meta-analysis was possible for the number of RBC transfusions transfused as a single unit strategy when comparing the implementation of a single unit transfusion policy compared to previous standard of care (or a multiple unit transfusion strategy). Across the three studies, the odds ratio of a single unit transfusion being given was 9.4 (95% CI 5.02-17.60). A forest plot of the findings of this meta-analysis are displayed in Figure 2B-2. An odds ratio was calculated rather than a relative risk given the retrospective nature of the studies included. However, heterogeneity between the studies was high with an I^2 of 97%. This heterogeneity is likely explained by different effect sizes of the intervention in different study populations as all three studies show that implementing a single unit transfusion policy or multifaceted intervention leads to increased odds of transfusion of single units for every transfusion episode. Meta-analysis was not

possible for red blood cell utilization (due to lack of a common denominator), length of stay, or mortality.

Figure 2B-2. Forest Plot of Odds of Proportion of Single Unit Transfusions Comparing Single Unit Transfusion Policies to Previous Standard of Care



2B.2.4 Summary of Abstracts

Based on the seven abstracts included in the systematic review of transfusion studies, there was insufficient information to produce a meta-analysis (Table 2B-2). The three studies that compared a single unit transfusion strategy to previous standard of care (which usually included multiple unit transfusions) demonstrated an absolute reduction in RBC transfusion by approximately 20%. Other initiatives that included promotion of single unit transfusion strategies lead to reductions in RBC transfusion from 11% to 32%. The excluded article that contained a theoretical retrospective comparison between single and multiple unit transfusion strategies is also described below.

Table 2B-2. Summary of Abstracts Included After Full Text Review

Study	Year of Publication	Intervention	Number of Patients/ Transfusions	Results
AllameddineA et al[58]	2015	Single Unit Transfusion Strategy	Not stated	1) Increase in compliance to single unit strategies from 10% to 31% (from 2013 to 2014) 2) Reduction of RBC units transfused per patient from 3.71 to 3.03 (18% decrease)
Aronson CA et al[59]	2013	Inpatient Blood Management Program (promotion of Hb trigger	Not stated	1) 20% decrease in RBC transfusions from 2011-2012

		from 10 g/dL to 7 g/dL and transfusion of single units)		2) Average number of RBCs per patient decreased from 2.58 to 2.25 3) Blood cost savings at $5.6 million per year
Evans R et al[60]	2014	Single Unit Transfusion Strategy	200 patients pre-implementation and 200 post-implementation	1) Reduction in RBC utilization by 1.3 units per hospital stay 2) Extrapolating from this: $1300 savings per month, 13 hours of nursing time per month,
Olan I et al[61]	2012	Inpatient Blood Management Program (promotion of restrictive Hb trigger and transfusion of single units)	Not stated	1) 2,080 RBC units saved (from October 2010 to July 2011) 2) Red blood cells used per patient from 0.51 to 0.46 3) Including interventions for plasma: 2,401 hours of nursing time saved, $1.65 million saved
Sutton BC et al[62]	2013	Physician order set and education on appropriate blood utilization	Not stated	1) Single unit transfusions increased from 21% in 2012 prior to the order set to 34% in the last 6 months of 2012 2) Hemoglobin assessment between units increased from 17.4% to 30% by November 2012
Tavares M et al[63]	2013	Single Unit Transfusion Strategy (introduced in 2004)	Not stated	~20% reduction in RBC transfusion: in the 6 years before implementation, 509 ± 45 units transfused/1000 discharges per year compared to 396 ± 50 units transfused/1000 discharges per year ($p<0.01$)
Whitten KL et al[64]	2015	Patient Blood Management Initiative	Not stated	1) 32% decrease in RBC usage from October 2013-December 2014, increase in 1 unit RBC orders 2) $1.46 million decrease in acquisition costs in the time period (including all blood products where 33% reduction seen)

Ma et al - 2005[56]

This study was excluded from our systematic review given there was only a theoretical comparison between single and multiple unit transfusion strategies but is summarized here. Based on a retrospective study of transfusions from January to April 2003, patients with both single and multiple unit transfusion strategies were assessed. Of 302 included patients, 65 received a single unit transfusion. Cardiac surgery patients were excluded given the majority received intraoperative transfusions and would have inadequate documentation of pre and post-hemoglobin levels. At a threshold of <70 g/L, a single unit would have been sufficient for 98% of transfusions (50/51 patients). Adherence to a 70 g/L threshold and transfusion of single units would have led to a savings of 0.82 mean RBC units per patient. In the subgroup of orthopedic patients, a mean of 1 unit would have been saved per patient.

2B.3 Discussion

In the last systematic review presented, recommendations were absent in most RBC transfusion guidelines in regards to transfusing single unit transfusion strategies. Guidelines and review articles did not reference any specific studies supporting single unit transfusion strategies; therefore we performed a systematic review to determine if such studies exist.

Overall, this systematic review demonstrated that promotion of single unit transfusion strategies or multifaceted interventions which may include promotion of single unit transfusion strategies leads to an increase in the proportion of transfusions that are single unit. The studies also suggest a trend towards decreased red blood cell utilization, but one study noted a decreased time to next transfusion with promotion of a single unit transfusion strategy. Patient outcomes were not found to be significantly different, but were not the primary outcomes in these studies. Higher quality studies need to be done as all studies were single center (except one), small, and retrospective. Meta-analyses are considered to be the evidence having the highest methodological quality to establish the link between cause and effect if the studies included are also of high methodological quality. We did not find any systematic reviews supporting single unit transfusion strategies nor was there enough data in the literature to perform meta-analyses to demonstrate the benefit of single unit transfusion strategies other than policies supporting single unit transfusions increasing the proportion of transfusions that are single unit. Most importantly, the contributing studies *made the assumption* that a single unit strategy was preferable despite, as noted, no evidence to confirm this hypothesis. Our analysis provides no reassurance that a single unit strategy does not cause harm, for the reasons identified earlier in this work.

This systematic review does have limitations. Although there is a paucity of studies, meta-analysis was not performed for many outcomes due to lack of data. We did not contact each of the individual authors for the manuscripts and abstracts to determine if more complete data could be used for meta-analysis. Studies included in our review were difficult to assess for methodological quality as the Newcastle-Ottawa score used does not use its elements to determine an “overall” methodological assessment.[52] This is a known limitation of the tool, but currently it remains one of the best tools according

to a systematic review for the evaluation of non-randomized intervention studies.[65] The other tool recommended, the Downs and Black instrument, is difficult to use and its results difficult to summarize with 29 different items of assessment.[65] The main methodological flaws observed with the studies included were the fact that the number of patients and follow up time were based on convenience samples, lack of controlling for confounders/co-interventions, and potential selection bias (which explains the heterogeneous effect of the interventions across different studies).

The two systematic reviews presented show little evidence exists that single unit transfusion strategies have clear benefit. Guidelines that address a single unit transfusion strategy are not based on high quality evidence specifically supporting single unit transfusion strategies but appear to be based on expert opinion extrapolated from studies that support restrictive transfusion threshold studies. While it is likely that policies that support single unit transfusions increase the proportion of single unit transfusions and potentially reduce RBC utilization, there are few studies to show effectiveness and generalizability; studies to date have been grossly underpowered to exclude harm from single unit strategies. Further studies should be performed with larger sample sizes and powered to examine clinical outcomes with parsimonious transfusion strategies.

To better understand the rationale for single unit transfusions and how they are utilized in daily clinical practice, we sought to survey transfusion medicine experts about their practice and rationale regarding single unit transfusion strategies. This information would also help us potentially design a study to better assess the benefits of single unit transfusion strategies.

Chapter 3: Determining Practice Regarding Single Versus Multiple Transfusion Strategies and the Factors For Reassessment After Transfusion From Transfusion Experts

The majority of guidelines and review articles on red blood cell transfusion did not address the issue of "transfusing a single unit of RBCs then reassessing" rather than "transfusing multiple units". There is limited evidence that promotion of single unit transfusion strategies translates into improving appropriate transfusion practice and reducing red blood cell utilization. The recommendation of single unit transfusion strategies is largely based on expert opinion and extrapolation from studies favoring restrictive transfusion triggers. However, it is possible that quality of life may not be improved for all patients, it may not be cost effective for certain patient populations, and it may even be potentially harmful to patients. There is also a paucity of literature on what is the optimal reassessment strategy that should be used. To assess the practice variation amongst transfusion medicine experts, the rationale behind patterns of practice, and the components for reassessment of patients after transfusion which may help guide practice, we developed a survey with the following specific objectives:

3.1 Specific Objectives

1. To assess current practices of transfusion medicine experts in Canada related to transfusion of a single versus multiple units of RBCs at a time.
2. To determine how physicians would transfuse and reassess patients post transfusion using specific clinical scenarios:
    a. A stable medical inpatient that is anemic;
    b. A medical patient discharged from hospital and followed as an outpatient;
    c. A patient with a post-operative drop in hemoglobin

3.2 Research Plan

3.2.1 Development of the Survey - Rationale for Using a Survey with Open Ended Questions

A survey was chosen as the method to address our specific objectives. Surveys are advantageous as a systematic method of collecting data and are able to sample a large population with ease compared to qualitative methods such as interviews. Close-ended questions utilized in surveys have been described in the literature as useful for selecting priorities among issues or policy alternatives.[66]

However, gathering the experience and opinions of content experts in utilizing RBC transfusions and how to perform a reassessment after RBC transfusion would not be captured appropriately using close-ended questions alone. Given the lack of evidence surrounding single unit transfusion strategies and the lack of agreement amongst clinical practitioners and guidelines based on the results of our review, open-ended questioning of our subjects to elicit information produces answers that are richer, more explanatory, and are unanticipated by the researcher.[67] Partially close-ended questions were also used where respondents can specify a response (such as adding the use of an option for "other", where the respondent can type in their answer) if the choices given for close-ended questions are inadequate.

3.2.2 Development of the Survey - Rationale for Not Using a Qualitative Approach

Qualitative methods such as interviews or focus groups were considered as the data gathered by these approaches can have rich content; however, it is a more costly approach and time consuming strategy for gathering information. Qualitative methods are also influenced heavily by the frame of reference, inherent biases, and expectations of the research team.[68] Accurate answers are difficult to obtain in interviews due to the increased likelihood of social desirability bias, interviewer distortion, and subversion.[66] Survey methodology was considered as a better approach, as we wished to sample transfusion medicine experts across Canada and we recognized that practice patterns could be varied across jurisdictions; hence, a survey would be less costly and would minimize selection bias. Surveys are also better suited for maximizing response rate in a large cohort.[66] Including scenarios and open ended questions in an anonymous survey would allow respondents to provide honest answers around their practice patterns.

3.2.3 Development of the Survey - Construction of the Survey

A draft survey was developed to fulfill the objectives as stated above. The survey was initially conceived as being divided into four different sections: 1) demographics, 2) a stable medical inpatient that is anemic, 3) a medical patient discharged from hospital, and 4) a patient a post-operative drop in hemoglobin. The choice of using clinical scenarios was to collect information from experts that could be generalized to real-world practice.

While surveys have advantages of reaching a large cohort in a wide geographic area, there are also disadvantages. They may only provide limited insight into the problem and responses may vary depending on the interpretation of the question. Missing data and low response rates are also concerns, where response rates to online surveys are often worse compared to paper-based response rates. Adequate response rates are difficult to determine from the literature, but range from 50-70%.[69-71] Response rates when surveying physicians tends to be decreased compared to non-physicians.[72,73] A web-based survey of physicians suggested even lower response rates in specialists, which was as low as 27%.[74]

To maximize the response rate, we designed the survey utilizing Dillman's Principles for Internet, mail, and mixed-mode surveys.[75] Recommendations include minimizing the amount of re-reading the respondent has to do, asking one question at a time, using consistent language, and using navigational guides within the survey to minimize reading of non-relevant sections. The original survey consisted of four sections which took approximately 30 minutes. After feedback from an investigator with qualitative expertise and piloting the survey internally within the research team, we shortened the survey to be completed in 15-20 minutes. However due to further concerns of a high non-response rate, ways to shorten the survey were further explored. The option of sending out each section of the survey per week would have shortened the survey to 5 minutes per week, but respondents would likely be lost to attrition and survey fatigue. Thus, after piloting the survey with transfusion experts at our centre, the survey was further shortened and presented in two sections that would take approximately 10-15 minutes total to complete. The demographics section was kept but shortened and the

clinical scenarios were consolidated together into one section. Language used in the survey was clarified to minimize confusion regarding the information requested from respondents.

The protocol and survey were submitted for Hamilton Integrated Research Ethics Board (HIREB) approval and then uploaded to LimeSurvey.[24] LimeSurvey is a free and open source on-line survey application, which allowed for the survey and responses to be stored on MCTR's secure server at McMaster University ensuring that responses by participants remain confidential and the data secure.

3.2.4 Identifying Respondents

Choosing Wisely Canada has the specific recommendation of transfusing single units with reassessment rather than transfusing multiple units at a time, therefore we aimed to consult transfusion medicine experts solely in Canada.[76] Canada has a publically funded health care system and has a national blood supplier, and a relatively small transfusion community providing a readily accessible sample. A number of strategies were used to identify and recruit participants for the survey. Transfusion medicine experts were initially identified using lists of physicians from the Ontario Regional Blood Coordinating Network (ORBCoN) and the Canadian National Advisory Committee (NAC) on Blood and Blood Products. Additional experts from each province were identified by contacting at least one individual from each province by email to identify further experts in the transfusion medicine community within their province. The final contact list was then approved by local transfusion medicine experts. After the final list of potential respondents was identified, their contact information collected and each potential respondent was assigned a unique study ID.

The rationale behind this strategy for identifying respondents was 1) the transfusion medicine community within Canada is relatively small (but large enough to not be amenable to individual interviews), 2) it would allow tracking of those who did not respond to the survey to attempt other methods of contact to increase the response rate, and 3) utilizing a "snowball strategy", where potential respondents may recruit

other respondents, would potentially contaminate our expert respondent pool with practitioners who were not transfusion medicine experts.

Although potentially valuable in future surveys, surveying transfusing clinicians that are not transfusion medicine experts was not done. The objective of this survey was to determine what expert opinion (and practice where applicable) was, given the lack of guidance in the literature. Eliciting responses from frequent users of transfusion would elucidate the practice gap between transfusion medicine experts and users, but was not the objective of this survey.

3.2.5 Distribution of the Survey and Follow-up

Five unique and varied contact methods were considered for the survey: 1) an advance notification letter to mention the purpose of the study and why they have been asked to participate, 2) a link to the survey with a unique token to complete the survey associated with their study ID, 3) a repeat email with the link to the survey after the initial survey contact if not completed, 4) a thank you message for those completing the survey and a reminder message via a different medium other than email (such as contacting a secretary) for non-responders, and 5) special contact for non-respondents such as a phone call or meeting.[77] The pre-notification letter was used to maximize the response rate. Its effectiveness depends on individual studies,[78,79] but based on a meta-analysis is an effective strategy.[80] The reminder message using a different medium than email depended on the contact information available. Meetings with non-respondents were only considered with suboptimal response rates, as they may introduce bias into data collection.[66] Using all five contact methods was only done when deemed necessary for a proper response rate for non-responders.

3.3 Data Analysis

Survey data were analyzed using descriptive statistics summarizing proportions for dichotomous or categorical responses. Assessments of responses to open-ended questions were then coded into themes by the investigator. These themes and a random selection of 25% of the coding were validated by another physician (SA). Subgroup analyses were performed by respondents who were clinicians (including

physicians whose primary place of practice was at a tertiary care ward, operating room, outpatient clinic) or laboratory-based (including physicians whose primary place of practice was at a blood supplier, transfusion medicine laboratory, or research department). The full survey is included in Appendix 3-1.

3.4 Results

3.4.1 Demographics

We identified 67 transfusion medicine experts from our search strategy that were contacted, of which 48 (71.6%) provided a response to the survey. Nineteen responded after the initial survey link and another 29 responded after personalized emails as outlined in the Methods section. As we had reached an adequate sample size, we elected not to use special contacts such as a phone call or meeting. All respondents were sent a thank you email.

The majority of our respondents were highly experienced, having practiced over 10 years (24/48; 50%); there was a small proportion who were within their first 3 years of practice (7/48; 14.6%). The primary place of practice for most respondents was in a laboratory setting (38/48; 79.2%) while 10 respondents stated their primary practice setting was in a clinical setting (5 outpatient clinic, 5 tertiary care ward/operating room). At least 5 RBC units per month were authorized or ordered by 19/48 respondents (62.5%) and 11/48 (22.9%) respondents authorized or ordered at least 10 RBC units per month.

3.4.2 General Transfusion Practice

For a stable, non-bleeding, anemic inpatient requiring transfusion, most respondents (42/48; 87.5%) recommended transfusing one RBC unit, then reassessing. One respondent recommended transfusing two RBC units then reassessing and five respondents stated their practice was variable or did not give an answer as their practice was laboratory based.

Practice and recommendations were much more variable in outpatient settings. Single unit transfusion strategies were recommended by 21/48 respondents (43.8%), 15/48

(31.2%) respondents stated they generally recommended transfusing two units of RBCs then reassessing, and 12/48 (25%) said transfusion was dependent on the clinical circumstance (usually symptoms and when the patient could come back to clinic) or did not give an answer as their practice was laboratory based. Of respondents who were primarily clinicians, 3/10 recommended transfusing two units then reassessing in an outpatient setting and 4/10 said transfusion was dependent on the clinical circumstance.

Respondents were asked to describe what information they would use to reassess if a patient requires further transfusion after a transfusion of RBCs. The format of this question was open-ended. There were 47 complete responses with one laboratory practitioner who did not provide specifics as clinical transfusion was not part of their practice. The vast majority of responses from both lab practitioners and clinicians included: repeating a hemoglobin level; and, reassessing functional status and symptoms (usually symptoms of anemia such as shortness of breath, chest pain, and syncope), and changes in vital signs. Ten and eight respondents (mostly lab practitioners) respectively stated that consideration of the underlying diagnosis contributing to anemia (including bleeding and hemolysis) and volume status would be included in their reassessment. Some other themes in responses included: consideration of comorbidities such as cardiac disease (3/47; 6.4%); history of a transfusion reaction (2/47; 4.3%); patient availability/compliance (2/47; 4.3%); availability of RBCs (1/47; 2.1%); and, laboratory results suggesting organ dysfunction such as creatinine (1/47; 2.1%).

We asked if guidelines and/or evidence informed these practices, for which 33/48 (68.8%) stated "yes" and 14/48 (29.2%) stated "no"; one respondent did not give an answer. Only one respondent who stated "no" has a primarily clinical practice. Of those who responded "yes": the majority of respondents indicated that "Choosing Wisely" recommendations (26/33; 78.8%), societal/organizational recommendations (25/33; 75.8%), and studies demonstrating benefits of restrictive transfusion strategies (26/33; 78.8%) informed them regarding single unit transfusions and reassessment. Local guidelines informed 16/33 (48.4%) of the respondents.

3.4.3 Scenario 1: Stable Anemic Inpatient

You are managing a 65-year old man who presented to the emergency room with shortness of breath on exertion and was admitted to the medicine ward for treatment of pneumonia. His admission hemoglobin is 65 g/L (normal range: 135-175 g/L in men) with a MCV of 82 fL (normal range: 80-100 fL). You call his family physician and she notes that the patient is a new patient in her practice and his baseline hemoglobin is in the low 80s. The cause of this chronic anemia is currently being investigated. The patient otherwise has no significant past medical history.

He is somewhat dyspneic with a respiratory rate of 26 breaths per minute (normal: 12-20 breaths per minute) on 2 litres nasal prong (oxygen saturation at 95%) and feels tired. The patient has no signs or symptoms of bleeding. Physical exam demonstrates crackles on the right side consistent with consolidation in the right lung in a chest x-ray and the patient appears euvolemic. Laboratory work shows that the remainder of the CBC, electrolytes, creatinine, and coagulation screen are within normal limits.

In this scenario, 43 complete responses were recorded. Of those respondents, 31/43 (72.1%) elected to transfuse this patient, with 29 (67.4%) electing to transfuse one unit then reassess. Both respondents that elected to transfuse two units were laboratory-based. Of the 12 respondents that elected to observe the patient, a change in patient vitals, a subjective change in the patient's status, or decrease in hemoglobin/evidence of bleeding/hemolysis would need to be considered together to trigger transfusion on reassessment.

Following either observation or transfusion of another RBC unit, respondents were asked for the physical assessments and laboratory tests they would use for the reassessment of this patient to decide on transfusing a RBC unit. For physical assessments, the majority of both clinicians and laboratory practitioners stated that the patient's symptoms and changes in vital signs would be part of the reassessment to decide on transfusion (Table 3-1). Lab practitioners also emphasized volume status (19 responses from lab practitioners, 1 from a clinician) and auscultation (10 responses from lab practitioners, none from clinicians). Other responses included a cardiac exam (11 responses) and medication review (1 response). For laboratory tests, nearly all respondents would order a repeat CBC/hemoglobin in this scenario. Otherwise, the most common responses were workup for an underlying cause (including iron studies, vitamin B12 levels, and blood film review), cardiac workup (ECG, troponin), and

bleeding/hemolysis workup. Other responses included brain natriuretic peptide, blood gas, chest x-ray, and group and screen; each with one response.

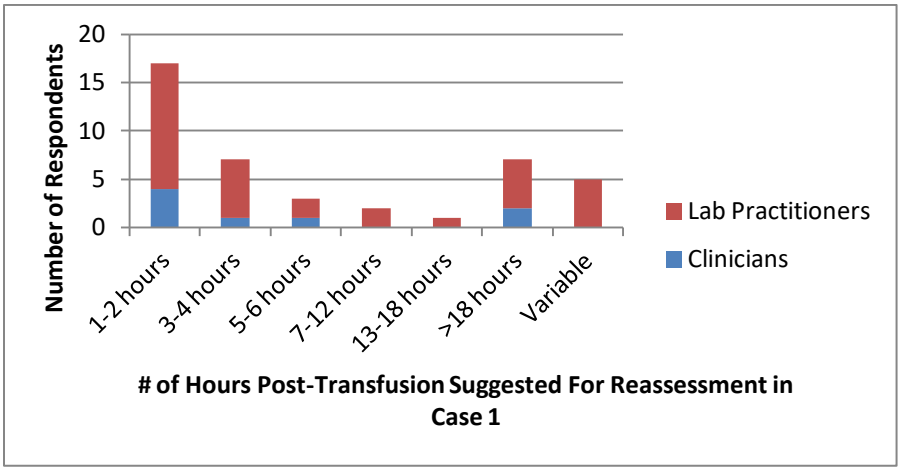
Table 3-1. Summary of Responses to Scenario 1 For Physical Assessments and Laboratory Tests Used In Reassessment

	Lab Practitioners (n=35)	Clinicians (n=8)	Total (n=43)
Physical Assessments	Responses (%)		
• Changes in Vital Signs	29 (82.9%)	6 (75%)	35 (81.4%)
• Functional Status/Symptoms	18 (51.4%)	5 (62.5%)	23 (53.5%)
• Volume Status	19 (54.3%)	1 (12.5%)	20 (46.5%)
• Cardiac Exam	8 (22.9%)	3 (37.5%)	11 (25.6%)
• Auscultation	10 (28.6%)	0	10 (23.3%)
• Medications	1 (2.9%)	0	1 (2.3%)
• Reduction in Urine Output	1 (2.9%)	0	1 (2.3%)
Laboratory Testing	Responses		
• CBC	33 (94.3%)	7 (87.5%)	40 (93.0%)
• Determining Underlying Cause For Anemia	6 (17.1%)	3 (37.5%)	9 (20.9%)
• Cardiac Workup/Troponin	4 (11.4%)	1 (12.5%)	5 (11.6%)
• Hemolytic Workup	3 (8.6%)	1 (12.5%)	4 (9.3%)
• Creatinine	3 (8.6%)	0	3 (7.0%)
• Bleeding Workup	2 (5.7%)	1 (12.5%)	3 (7.0%)
• Group and Screen	1 (2.9%)	0	1 (2.3%)
• Direct Antiglobulin Test	1 (2.9%)	0	1 (2.3%)
• Chest X-Ray	1 (2.9%)	0	1 (2.3%)
• Blood Gas	1 (2.9%)	0	1 (2.3%)
• Brain Natriuretic Peptide	1 (2.9%)	0	1 (2.3%)

The responses suggested for time to reassessment before transfusion in this scenario should be short, with 17/43 (39.5%) suggesting reassessment 1-2 hours after transfusion and 7/43 (16.3%) suggesting 3-4 hours after transfusion (Figure 3-1). Seven respondents (16.3%) answered that the time to reassessment could occur >18 hours later or the next day. Respondents were asked for their rationale for the time to

reassessment in an open-ended question. Most respondents who chose a shorter time to reassessment stated it would be to assess for complications of transfusion, volume status, and to see if symptoms acutely improve after transfusion. Those who chose a longer time to reassessment (>12 hours) stated it would be to assess for changes in hemoglobin and because of the patient's relative stability in this scenario.

Figure 3-1: Time To Reassessment Suggested By Transfusion Experts in Case 1 (Asymptomatic Post-Operative Patient)



3.4.4 Scenario 2: Stable Anemic Inpatient to Be Discharged

> Presume this patient in the original stem was treated for pneumonia, became asymptomatic (no longer being dyspneic or feeling fatigued), and did not have surgery. His hemoglobin is 65 g/L (normal range: 135-175 g/L in men). The next family doctor's appointment can be made in approximately one week. The patient lives within a thirty-minute drive to a tertiary care hospital and has a family caregiver who could provide transportation during the day. Would you transfuse red cells to this patient before discharge?

In this scenario, 42 complete responses were recorded. Of those respondents, 16/42 elected to transfuse this patient before discharge (4 clinicians, 12 laboratory practitioners; 38.1% of total). Of those who elected to transfuse, all but one respondent elected to transfuse one unit (two respondents added the caveat that it would depend on the etiology of anemia). Those who elected not to transfuse the patient suggested informing the family doctor/hematologist to monitor and assess for the underlying cause.

The time to reassessment suggested in this case followed a normal distribution centering around 4-7 days (Figure 3-2), providing access to medical assessment was not a limiting factor. Respondents were asked to provide the physical assessments and laboratory tests in this outpatient scenario they would suggest in an open ended question. The responses given for the physical assessment in this outpatient scenario were similar to the inpatient scenario, with a focus on functional status, changes in vital signs, auscultation (mostly in laboratory practitioners), and volume status (mostly in laboratory practitioners) (Table 3-2). Additional responses included a cardiac exam (14 responses), auscultation (13 responses), bleeding/hemolysis assessment (7 responses), and an abdominal exam (1 response). Responses given for laboratory tests suggested were also similar to the inpatient scenario, with an emphasis on repeating the CBC/hemoglobin. However, there was further emphasis on finding the underlying cause (18 responses in the outpatient scenario compared to 9 in the inpatient scenario) and a reticulocyte count (7 responses in the outpatient scenario, none in the inpatient scenario).

Figure 3-2: Time To Reassessment Suggested By Transfusion Experts in Case 2 (Stable Anemic Patient To Be Discharged)

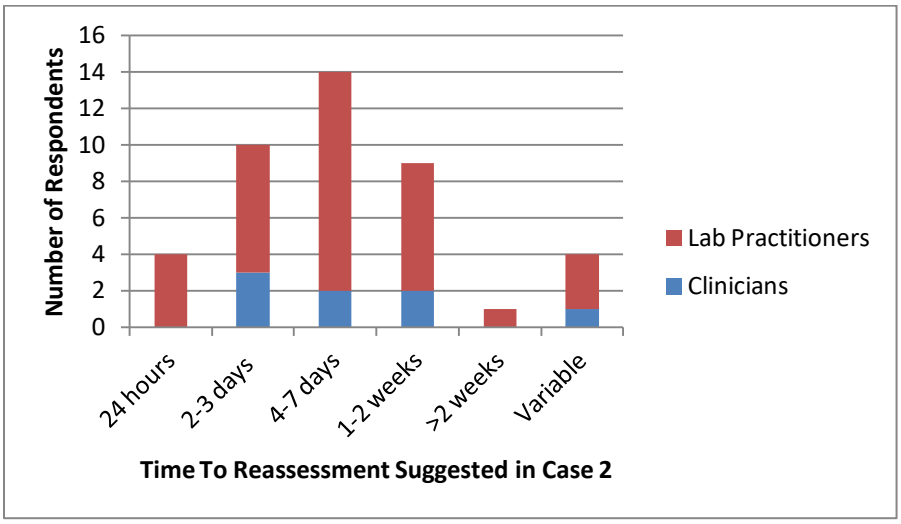


Table 3-2. Summary of Responses to Scenario 2 For Physical Assessments and Laboratory Tests Used In Reassessment

	Lab Practitioners	Clinicians (n=8)	Total (n=42)

	(n=34)		
Physical Assessments	Responses (%)		
• Changes in Vital Signs	25 (73.5%)	7 (87.5%)	32 (76.2%)
• Functional Status/Symptoms	20 (58.8%)	4 (50%)	24 (57.1%)
• Volume Status	14 (41.2%)	1 (12.5%)	15 (35.7%)
• Cardiac Exam	12 (35.3%)	2 (25%)	14 (33.3%)
• Auscultation	12 (35.3%)	1 (12.5%)	13 (31.0%)
• Bleeding/Hemolysis Assessment	6 (17.6%)	1 (12.5%)	7 (16.7%)
• Rectal/Abdominal Exam	1 (2.9%)	0	1 (2.3%)
Laboratory Testing	Responses		
• CBC	31 (91.2%)	6 (75%)	37 (88/1%)
• Determining Underlying Cause For Anemia	14 (41.2%)	4 (50%)	18 (42.9%)
• Reticulocyte Count	7 (20.6%)	0	7 (16.7%)
• Hemolytic Workup	2 (5.9%)	2 (25%)	4 (9.5%)
• Creatinine	3 (8.8%)	1 (12.5%)	4 (9.5%)
• Cardiac Workup/Troponin	2 (5.9%)	1 (12.5%)	3 (7.1%)
• Bleeding Workup	2 (5.9%)	1 (12.5%)	3 (7.1%)
• Chest X-Ray	2 (5.9%)	0	2 (4.8%)

3.4.5 Scenario 3: Asymptomatic Post-Operative Inpatient

> Presume this patient was readmitted for an abdominal perineal resection for rectal carcinoma. You see the patient on post-operative day 2 and his hemoglobin this morning is 75 g/L. The remainder of the CBC, electrolytes, creatinine, and coagulation screen are within normal limits. Physical examination shows no bleeding at the surgical site. There is some serosanguinous discharge on the wound dressing. The patient's blood pressure is 136/72 mmHg, heart rate is 88 beats per minute, respiratory rate is 18 breaths per minute (normal: 12-20 breaths per minute), and temperature is 37.1°C.

In this scenario, 42 gave a complete response to this question, where all respondents chose not to transfuse this patient. The majority of respondents stated that changes in patient vitals, a subjective change in the patient's status, and frank bleeding at the surgical site would prompt transfusion in this case. In regards to hemoglobin cutoffs, 29 (69.0%), 5 (11.9%), and 7 (16.7%) respondents would transfuse at a cutoffs of less than 70 g/L, 65 g/L, and 60 g/L respectively (Table 3-3); where laboratory practitioners had a

trend of allowing lower hemoglobins before transfusion. The majority of clinicians (5/8; 62.5% of clinicians) would transfuse if the patient needed to be brought back to the operating room compared to laboratory practitioners (9/34; 26.5% of laboratory practitioners).

Table 3-3: Comparison Between Clinicians and Lab Practitioners

	Clinicians (n=8)	Lab Practitioners (n=34)
Change in patient vitals	8	32
Subjective change in patient's status	8	24
Hemoglobin decreasing to <60 g/L	2	5
Hemoglobin decreasing to <65 g/L	0	5
Hemoglobin decreasing to <70 g/L	8	21
Further drop in hemoglobin (cutoff not defined	0	2
Frank bleeding at the surgical site	8	28
The patient will be need to be brought back to the operating room	5	9

The time to reassessment in this case was more variable, however, the majority of respondents suggested a reassessment time over >18 hours (usually the next day) (Figure 3-3). Respondents were asked whether or not their physical assessment and laboratory workup with reassessment would change in this post-operative scenario in an open-ended question. The majority of respondents stated that they would pay particular attention to ongoing visible blood loss (27/42; 64.3%) and changes in hemoglobin (18/42; 42.9%) (Table 3-4). Other responses included no change (11/42; 26.2%), more attention to changes in vital signs (10/42, 23.8%), cardiac signs/status (6/42; 14.3%), dependent on the clinical scenario (3/42; 7.1%), other post-operative complications (2/42; 4.8%), and volume status (1/42; 2.4%).

Figure 3-3: Time To Reassessment Suggested By Transfusion Experts in Case 3 (Stable Anemic Inpatient)

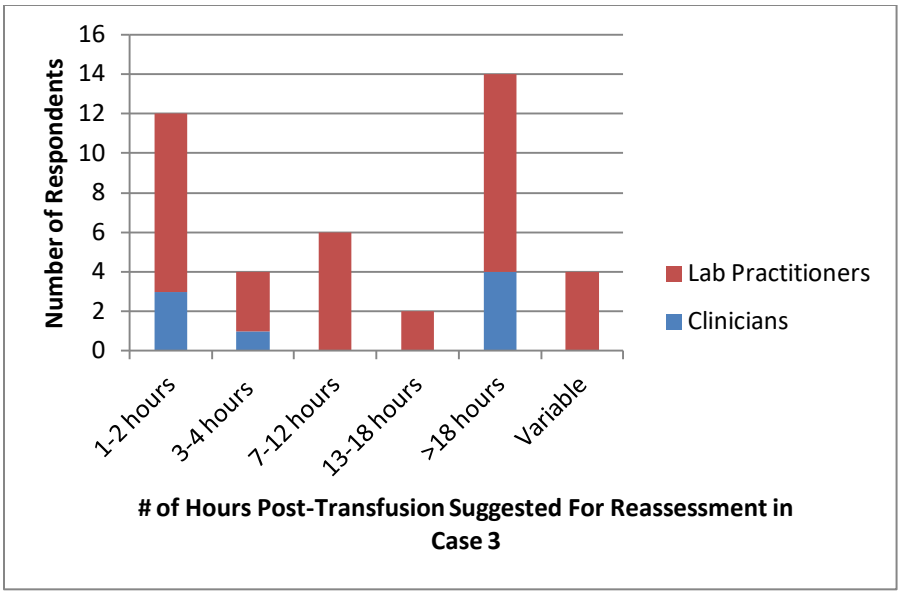


Table 3-4. Summary of Responses to Scenario 3 For Differences in Assessment

	Lab Practitioners (n=34)	Clinicians (n=8)	Total (n=42)
Changes in Assessment	Responses (%)		
• Ongoing Visible Blood Loss	21 (61.8%)	6 (75%)	27 (64.3%)
• Changes in Vital Signs	10 (29.4%)	0	24 (23.8%)
• Changes in Hemoglobin	13 (38.2%)	5 (62.5%)	18 (42.9%)
• No Change	8 (23.5%)	3 (37.5%)	11 (26.2%)
• Cardiac Signs/Status	6 (17.6%)	0	6 (14.3%)
• Depends on Clinical Scenario	2 (5.9%)	1 (12.5%)	3 (7.1%)
• Other Post-operative Complications	2 (5.9%)	0	2 (4.8%)
• Volume Status	1 (2.9%)	0	1 (2.4%)

3.5 Discussion

Given the lack of evidence in the literature directly supporting single unit transfusion strategies, we undertook a survey of transfusion medicine experts in Canada to determine what practice patterns are recommended. In general, transfusion medicine experts recommended a single unit transfusion strategy and this recommendation is extrapolated from other evidence supporting restrictive transfusion strategies;

surprisingly only one third of respondents noted that there was no evidence base to support this practice. The Canadian Society of Transfusion Medicine's list of Choosing Wisely recommendations and local guidelines were also cited, although these recommendations are also extrapolated from evidence supporting restrictive transfusion strategies. Given the lack of evidence in outpatient settings and the decreased opportunity for monitoring, there was much more variability in recommendations. Further research in this area on the effect of transfusions on quality of life is required in this area.

Recommendations for reassessment to determine if RBCs should be transfused mostly centered on repeat hemoglobin levels and patient functional status/symptoms. Specific physical examination should include a volume status assessment, auscultation, and cardiac exam. The time to reassessment to determine if a RBC unit should be transfused recommended by transfusion experts either tended to be short (1-2 hours) or a day later (>18 hours), although this appeared to pertain more to a shorter time to reassessment for physical exam and a longer time to reassessment for repeating laboratory tests such as a CBC. If the patient is an outpatient or a discharged inpatient, generally transfusing one unit is recommended by transfusion medicine experts with a family physician reassessing within one week. In the outpatient setting, there was more of an emphasis by transfusion medicine experts on performing assessments to determine the underlying cause. Given more transfusion experts suggested transfusion in an anemic patients with symptoms that could be potentially attributable to anemia compared to an asymptomatic patient due to be discharged, this highlights the importance of focusing on the patient rather than the hemoglobin level alone. In future guidelines, these recommendations could be suggested to give transfusing clinicians further guidance on transfusions.

A reassuring finding of our survey is that in the post-operative scenario, transfusion experts would choose to monitor a patient who has a hemoglobin level trending down but is asymptomatic. Transfusion experts focused on patients' symptoms and functional status the most, offering transfusions at lower hemoglobin levels than 60 g/L as long as the patient was asymptomatic or did not have evidence of overt bleeding. Therefore,

transfusion medicine experts who were both primarily laboratory practitioners and clinicians did not recommend "topping up" the hemoglobin in the setting of a slowly dropping hemoglobin alone.

Our survey respondents were mostly laboratory practitioners, consistent that the demographics of transfusion medicine experts in Canada. Responses from lab practitioners tended to emphasize consideration of the underlying diagnosis, volume status, and auscultation in the physical examination for reassessment. In the post-operative scenario, choosing to transfuse at lower hemoglobin cutoffs was also more common in laboratory practitioners. In this scenario, the majority of clinicians also would choose to transfuse if the patient had to be brought back to the operating room. Differences in practical experience may experience why there was a difference in regards to lab practitioners and clinicians, but further probing into the rationale between these groups may allow further insight to behaviour of clinicians who are not transfusion medicine experts. A future goal would be to repeat this survey to clinicians who are not transfusion medicine experts.

Our survey may not be representative of transfusion medicine experts worldwide, whose practice and background varies greatly. In choosing not to survey transfusing clinicians who are not transfusion medicine experts, one cannot contrast expert opinion with general practice. However, surveying such a broad group of practitioners would require careful methodological considerations to minimize selection bias and non-response bias. In addition, expert practice and recommendations are lower quality evidence that needs to be confirmed with further prospective studies.

By choosing a survey format rather than performing interviews or allowing only open-ended responses, respondents may have been biased to choose responses in the survey. An answer to a multiple choice question also does not allow for rich content that could be further explored. However, we had to balance this with the feasibility of surveying a larger group of respondents, the time demands for most physicians, and the potential bias that could be introduced by either the interviewer or in not having their responses confidential. We also tried to allow for richer content by allowing semi-open ended questions (allow an "other" response) and open-ended questions. Open-ended

responses were coded into themes by a single investigator, which could be a source of bias, but most responses were unambiguous and straightforward to code into themes.

In conclusion, the majority of transfusion medicine experts suggest to transfuse one unit at a time. Patient functional status, symptoms, and pertinent physical examination should be performed within a few hours whether a patient is transfused RBCs or is being observed in lieu of transfusion. Repeat hemoglobin levels can be performed usually the next day and the underlying cause should be investigated especially in the outpatient setting. In a post-operative setting, in the absence of overt bleeding or symptoms, "top-up" transfusions are not required and only continued monitoring of the patient is necessary.

However, despite this, our systematic reviews have not demonstrated concordance in published reviews or guidelines. There is also a paucity of specific evidence to support single unit transfusion strategies. In the next chapter, we will discuss a conceptual flow diagram developed from the information contained in this thesis thus far to design a retrospective database study to assess transfusing clinicians' practices and to generate hypotheses about the benefits and disadvantages of single unit transfusion strategies.

Chapter 4: Development of a Conceptual Flow Diagram

Retrospectively assessing transfusions at our local tertiary care centres would assess the practice gap between these centres and current expert opinion. Inclusion of primary care facilities such as outpatient general practitioner clinics provides less useful information as they are often not responsible for transfusion given the monitoring requirements, equipment needed, the expertise required, and proximity to a blood banking service. This will help assess practices to determine what factors are associated with transfusing a single unit at a time and then reassessing or transfusing multiple units at a time; and what outcomes would be studied to determine the effect of these strategies.

Before performing a retrospective study, we constructed a conceptual flow diagram using information gathered from our literature review and survey to help guide the concepts, variables, and relationships involved in our study. Developing this flow diagram helped to refine the study question and identify variable that should be collected to determine factors leading to the single unit transfusion strategy compared to a multiple unit transfusion strategy.

4.1 Key Concepts

4.1.1 Benefits of Multiple Unit Transfusion Strategies

One of the key concepts to explore is the potential benefit of adopting either strategy. Historically, the transfusion of multiple units was adopted as part of the 10/30 rule. As oxygen is required for vital organ function, transfusing to higher hemoglobin levels could improve patient symptoms, decrease adverse clinical events associated with anemia, and reduce mortality.

A multiple unit transfusion strategy could also reduce the number of transfusion episodes which would likely be associated with reduce workload in terms of time spent by laboratory technologists preparing each transfusion and the cost associated with each transfusion in terms of supplies, administration and hospital-based activity costs.

4.1.2 Benefits of Single Unit Transfusion Strategies

A restrictive transfusion strategy emerged from the randomized controlled trials that showed certain transfused patient groups had less morbidity and mortality when a lower hemoglobin threshold was used as a trigger for red blood cell transfusion. This in turn led to the suggestion that a single unit transfusion strategy with reassessment to determine if additional units were required was indeed optimal practice for the non-hemorrhaging patient. It was assumed that a single unit transfusion strategy would decreased RBC utilization and which in turn would lower the frequency of acute transfusion reactions such as transfusion-associated circulatory overload as well as costs associated with red blood cell production and adverse event investigations.

Although our literature review identified a few published studies suggesting decreased red blood cell utilization with a single unit strategy which appears to be the major outcome advantage of the single unit transfusion strategy. Unfortunately, patient centered outcomes such as adverse events, length of stay, and patient reported outcomes have not been assessed.

4.1.3 Disadvantages of Single Unit Transfusion Strategies

One study found promotion of a single unit transfusion strategy led to a shorter time to next transfusion; hence, total number of transfusion episodes during a patient's course of therapy would be increased. This could lead to additional processes such as repeating group and screens, cross-matches, and clerical requiring increased resources from the laboratory and nursing personnel. Also, transfusion requirements are variable in certain populations. A single unit transfusion strategy in patient population that has a higher transfusion burden may lead to symptoms and adverse clinical events from under-transfusion. In addition, a single unit transfusion strategy could have a great negative impact for patients receiving out-patient transfusions resulting in increased travel time and a negative impact on quality of life. These outcomes have not been studied.

4.1.4 Ordering Units and Transfusing Units

It is also important to assess differences in the intention of the physician and the events that occur. Even when multiple units are ordered, transfusion of units may not occur,

due to caregivers stopping transfusions due to transfusion reactions, cancelling or cutback in orders due to unavailability of blood or intervention by a transfusion medicine director performing prospective ordering review. In these situations, analyzing by red cell transfusion data rather than actual order date may bias the multiple unit strategy to have a shorter time to next transfusion, lower red cell utilization, and a higher proportion of instances where one unit is transfused at a time.

4.2 Key Variables

4.2.1 Independent and Dependent Variables

Independent variables are exposures and interventions that lead to changes in the dependent variables in the study, which are the outcomes of the study. The dependent variables or outcomes important to study would include the different advantages and disadvantages suggested by each strategy including: 1) red blood cell utilization, 2) clinical outcomes, 3) time to next transfusion, and 4) cost.

Independent variables must be considered in the design of any study. Confounders, which are third variables that correlate both with the independent/exposure variables and the outcome variable but are not part of the causal pathway, must be adjusted for (or balanced in the context of a randomized controlled trials) to ensure they are not incorrectly characterized as part of the causal pathway.[81] Mediators are third variables that are part of the causal pathway and effect modifiers which have statistical interactions where various levels have different effects on the relationship between the independent and dependent variables given that they can be confounders, mediators, or effect modifiers of the outcomes selected.[82,83] Without an understanding of the underlying biological mechanisms, it is impossible statistically to differentiate whether a variable is a confounder, a mediator, or effect modifier (Table 4-1).[83] Therefore, when designing a study it is most important to identify these potential variables and consider their place in causal pathways.

Table 4-1. Definitions and Examples of Confounders, Mediators, and Effect Modifiers

Example: Exposure: Number of RBC Transfusions → Outcome: Mortality			
Variable Type	Confounder	Mediator	Effect Modifier
Description	A variable that correlates with the exposure and outcome that does not lie in the causal pathway of the relationship between exposure and outcome	A variable that correlates with the exposure and outcome that does lie in the causal pathway of the relationship between exposure and outcome	A variable where the relationship between the exposure and outcome depends its various quantitative or qualitative levels
Example	Hospital location could dictate the lack of blood supply, which would have a negative effect on RBC transfusions but a positive effect on mortality, therefore if this is not accounted for there will be an underestimation of the true effect size	Presence of transfusion reactions is a variable that has positive correlates with transfusions and mortality, as well as being part of the causal pathway	Transfusion reaction severity affects mortality and more specifically mortality that could be attributed to transfusions (exposure)

4.2.2 Key Relationships between Variables – Construction of the Conceptual Flow Diagram

Independent variables can be loosely categorized into three separate categories in this flow diagram: 1) Patient-Related Variables, 2) Disease-Related Variables, and 3) Institutional Variables. The three categories overlap in many respects, but provide a framework to capture different independent variables that may affect our outcome.

4.2.3 Patient-Related Variables

Variables related to the patient are most significant in determining whether or not a patient gets transfused and whether a single unit or multiple unit transfusion strategy is used. These include patient age, gender, diagnosis, comorbidities, and medications. Specific variables and their rationale for inclusion are listed in Table 4-2.

Table 4-2. Patient-Related Variables Considered in our Conceptual Flow Diagram

Variable	**Rationale For Inclusion**	**Expected Effect on Red Cell Utilization**	**Expected Effect on Mortality**	**Expected Effect on Utilization of Single or Multiple Unit Transfusion Strategies**
Age	Anemia has higher incidence in older patients	Increased	Increased	Indeterminate
Sex	Incidence of anemia is higher in women	Increased	Indeterminate	Indeterminate
Comorbidities characterized by anemia (malignancy, chronic renal failure, surgery)	Anemia will lead to increased transfusion	Increased	Increased	Multiple
Cardiac Disease	Restrictive transfusion strategies have not been shown to apply	Increased	Increased	Multiple
Recent Surgery	Surgery increases the chances of bleeding	Increased	Increased	Multiple
Other comorbidities	Increased illness may lead to increased anemia	Increased	Increased	Indeterminate
Medications leading to anemia or	Anemia will lead to increased	Increased	Increased	Multiple

bleeding	transfusion			

4.2.4 Disease-Related Variables

Disease-related variables that are associated with the admission to hospital or health care service are closely related to our outcomes. These are separate from the comorbidities of the patient which are not necessarily related to the admission. They are listed in Table 4-3.

Table 4-3. Disease-Related Variables Considered in our Conceptual Flow Diagram

Variable	**Rationale For Inclusion**	**Expected Effect on Red Cell Utilization**	**Expected Effect on Mortality**	**Expected Effect on Utilization of Single or Multiple Unit Transfusion Strategies**
Hemoglobin Level	Most transfusions are triggered by hemoglobin levels	Increased (if lower)	Increased (if lower)	Multiple (if lower)
Hemoglobin on admission	Most transfusions are triggered by hemoglobin levels	Increased (if lower)	Increased (if lower)	Multiple (if lower)
Change of hemoglobin on admission	Anemia will lead to increased transfusion	Increased (if lower)	Increased (if higher)	Multiple (if lower)
Platelet count	Decreased platelet count increases the risk of bleeding	Increased (if lower)	Increased (if lower)	Multiple (if lower)

4.2.5 Institutional Variables

Institutional variables capture the fact that transfusion practice depends on the hospital and its policies regarding transfusion, where different interventions have been used to reduce inappropriate blood product usage. Certain specialities are higher users of transfusion, although this is potentially balanced by restrictive transfusion strategies being well studied in certain patient populations such as orthopedic patients. Transfusion practices have also changed over time with the emergence of restrictive transfusion strategies for many patients so the year the patient is admitted will need to be taken into account as another factor for transfusion. They are listed in Table 4-4.

Table 4-4. Institutional-Related Variables Considered in our Conceptual Flow Diagram

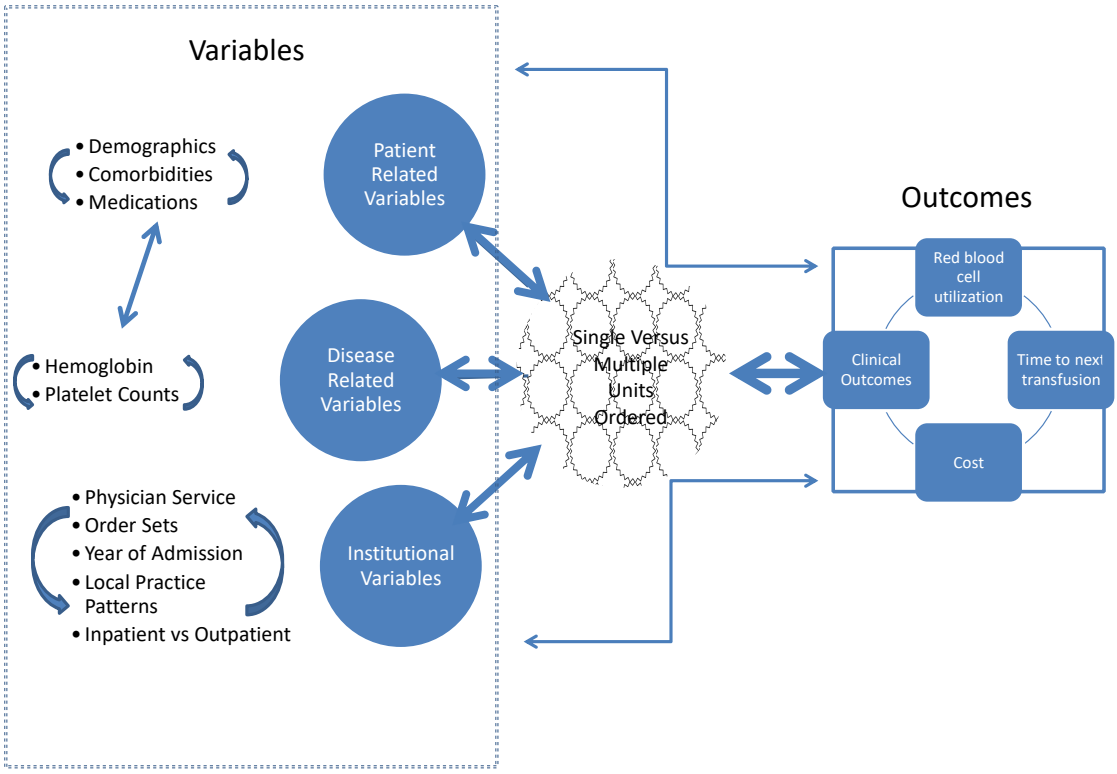
Variable	**Rationale For Inclusion**	**Expected Effect on Red Cell Utilization**	**Expected Effect on Mortality**	**Expected Effect on Utilization of Single or Multiple Unit Transfusion Strategies**
Location of hospital	Different institutions have different policies	Indeterminate	Indeterminate	Indeterminate
Inpatient versus Outpatient services	Outpatients are followed less frequently	Indeterminate	Increased (if inpatient)	Multiple (if outpatient)
Physician Service	Patients admitted to more acute care services and surgical services will likely have more transfusions	Increased (in acute and surgical settings)	Indeterminate	Indeterminate
Use of Order Sets	Order sets will skew towards one strategy	Indeterminate	Indeterminate	Indeterminate
Year of admission	Transfusion	Decreased (if	Decreased (if	Single (if later)

	practices have decreased over time	later)	later)	

4.3 Proposed Conceptual Flow Diagram

A tentative conceptual flow diagram from the variables and outcomes discussed above is displayed in Figure 4-1. Utilizing this conceptual flow diagram will help us select variables for the retrospective study. Performing the study may help us further refine this model in terms of determining the level of effect of different independent variables on outcomes and adding more variables. The use of these variables will be addressed in the next chapter discussing the study design.

Figure 4-1. Proposed Conceptual Flow Diagram



Chapter 5: Methodological Issues of Designing a Retrospective Study in the context of the Proposed Conceptual Flow Diagram

5.1 Introduction and Rationale for Exploratory Analysis Plan

We plan to do a six-year retrospective study (2010 to 2016) using data from transfused patients at Hamilton Health Sciences (HHS) and St. Joseph's Healthcare Hamilton (SJHH) to understand current practice and to inform the design of future prospective/experimental studies. Information from a retrospective study would also help to inform and develop further the conceptual flow diagram which was described in the previous chapter. However, before analysing all the data in the chosen time period, an exploratory analysis using one year of data (2014 - as exploratory analyses started in 2015) was performed to identify data availability and interpretation issues that would have to be resolved (exception – objective 1 for identifying exclusion criteria explained below).

5.2 Data Sources for the Exploratory Analysis Plan

We extracted 2014 data from the Transfusion Registry for Utilization Statistics and Tracking (TRUST) database developed by the McMaster Centre for Transfusion Research (MCTR). TRUST is a comprehensive database containing blood product, demographic, and clinical information on all hospitalized patients at three Hamilton Health Sciences (HHS) hospitals from April 2002 to present. A comprehensive list of TRUST data variables is provided in Appendix 5-1. Data are updated monthly from two sources: the Hospitals' Laboratory Information System (LIS) and the Hospitals' Discharge Abstract Database (DAD). Validation studies have been performed on the data to ensure concordance of the information between sources, the data encryption and the merging process. TRUST does not contain information regarding cause-specific mortality, costing information, or information regarding laboratory technologist time spent. Outpatient data are limited to outpatient clinics held at our centre and does not include information from outside laboratories. Relevant pharmacy data available starting 2010, a more extensive list of laboratory test results, and physician roster data were extracted from a second linked database called MASCOT.

5.3 Proposed Objectives

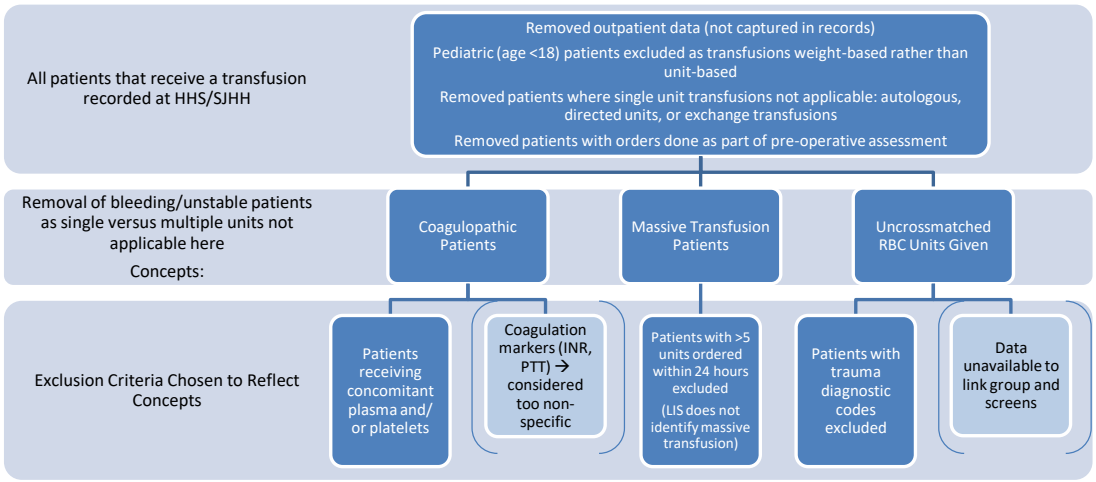
We attempted exploratory analyses to assess the objectives stated below. The analysis of objective 1 was performed on the data set from 2010 – 2014 (available data when this project was started in 2015): all other objectives were explored using just 2014 data.

1. Identification of patients who should be excluded from the analysis because of clinical indications that would make the choice of a single unit versus a multiple unit transfusion strategy not applicable.
2. Feasibility of using data from TRUST to identify comorbidities, and medications most relevant to transfusion.
3. Accuracy of using the physician code to assess the speciality of the most responsible physician (MRP).
4. Whether patients receiving single unit or multiple unit transfusions could be identified using ordering data and/or transfusion issue data.
5. Outcomes on patients in the single unit and multiple unit cohorts:
    a. Total RBC utilization
    b. Time between first and second RBC transfusions
    c. Pre-transfusion hemoglobins and cancelled units in transfusion orders

5.4 Objective 1: Identifying Patients with Exclusion Criteria

By including all patients who received a transfusion, we may include patients where a single RBC unit transfusion may not be clinically appropriate such as unstable patients, bleeding patients, or other emergent clinical situations requiring uncrossmatched transfusions. We sought to exclude these patients using characteristics that acted as surrogates for these situations such as receiving >5 units ordered within 24 hours, trauma diagnostic codes, and patients receiving concomitant plasma/platelets. This process is outlined in Figure 5-1.

Figure 5-1. Approach to Identify Patients to be Excluded From the Analysis



We were able to successfully apply this algorithm to the full 2010-2014 cohort and identified that 13,388/23,486 patients were excluded (Table 5-1). Inclusion and exclusion criteria were performed on the full cohort rather than patients in 2014 to avoid duplication of analyses.

Table 5-1. Inclusion and Exclusion Criteria Applied to the 2010-2014 Cohort

	Patients Remaining In Cohort	**Patients Excluded From Cohort**
Inclusion Criteria		
• Inpatients admitted to hospital receiving a red cell transfusion **from 2010-2014**	N = 23,486	N/A
• Inpatients admitted to hospital receiving a red cell transfusion during admission from 2010-2014	N = 23,472	N = 14

○ Transfusions occurred between admission and discharge dates (The inpatients entered through ER, whose transfusions occurred one day before admission date, were also included).		
Exclusion Criteria		
• Patients admitted with a trauma code	N = 19,981	N = 3,491
• Patients receiving plasma and cryoprecipitate during the transfusion episode	N = 16,801	N = 3,180
• Patients receiving more than 5 units within a 24 hour period	N = 16,634	N = 167
• Patients receiving autologous or directed units	N = 16,549	N = 85
• Patients whose orders were placed more than 24 hours before their transfusions	N = 10,776	N = 5728
• Pediatric patients	N = 10,098	N = 678
Total Cohort For Inclusion	**N = 10,098**	N/A

5.5 Objective 2: Feasibility of using TRUST/MASCOT data for Comorbidities and Medications

ICD-10 codes were used to characterize comorbidities that the patient had at the time of admission (pre-admission comorbidities) giving a general assessment of the burden of comorbidities for each patient (Appendix 5-2). We opted not to use most responsible diagnoses for ICD-10 codes as we wished to capture all relevant comorbidities, not particularly if the admission occurred due to these comorbidities (for example, wanting to capture cancer as a comorbidity rather than admissions occurring due to cancer). The Charleston Comorbidity Index was applied to patients whenever pre-admission comorbidities existed (~80% of patients).

Medications given before transfusion that could affect the need for transfusion and/or outcomes in our conceptual flow diagram such as anticoagulants, antiplatelet agents,

and erythropoietin stimulating agents were successfully extracted from MASCOT's pharmacy data. Medications given during hospitalization could also be extracted, but was felt not to be as relevant for decision making regarding transfusion strategies.

While data can be extracted from the databases, ensuring accuracy of this data will require validation with manual chart review. The results of these analyses are summarized in Table 5-2.

Table 5-2: Demographics, Comorbidities, and Medications of the Exploratory 2014 Analysis (Utilizing Ordering Data)

	Single Red Cell Group (First order of RBCs was one unit) (N=622)	**Multiple Red Cell Group** (First order of RBCs was multiple units) (N=1335)
Demographics		
Age (mean, SD)	69.8, 15.9	66.6, 16.6
Sex (% male)	324 (52.1)	653 (48.9)
Comorbidities --- Preadmission (N, %)	518 (83.3)	1072 (80.3)
Chronic Renal Failure	17 (2.7)	33 (2.5)
Cardiac Disease	184 (29.6)	378 (28.3)
Hematological Malignancy	8 (1.3)	23 (1.7)
Cancer	65 (10.5)	112 (8.4)
Charleston Comorbidity Index Mean, SD	5.62, 2.0	5.26, 1.87
Median (IQR)	5 (5, 6)	5 (4, 6)
Patients with non-zero Charleston Comorbidity Index [not including age in score] (N, %)	208 (33.4)	391 (28.5)
Medications (start) before the 1st RBC transfusion (N, %)		
EPO	2 (0.3)	9 (0.7)
Anticoagulants	178 (28.6)	292 (21.9)
Prophylaxis dose anticoagulants	181 (29.1)	289 (21.7)
Antiplatelets	44 (7.1)	61 (4.6)
Aspirin	145 (23.3)	241 (18.1)

5.6 Objective 3: Accuracy of the Physician Code to Identify Speciality of the Most Responsible Physician

Each patient admission has a physician code that represents the most responsible physician (each physician linked to their relevant admitting service): this is termed the admission physician code. Each RBC transfusion order/issue has a code for the physician who ordered the RBC for transfusion: termed ordering physician code. The admission physician code was used to identify the service to which the patient was admitted (such as cardiology, general surgery, hematology-oncology, etc), as using the ordering physician code would capture residents from other specialities not reflective of the admitting specialty service. The admission physician code obtained from TRUST was cross-referenced with physician codes from MASCOT which were both extracted from the DAD. We found that the physician services identified from both TRUST and MASCOT were concordant ~80% of the time.

The alternative to using admission physician codes was to use the physician name associated with each admission and manually categorize the physician service. While this approach may be more accurate, it is impracticable for the number of patients in our study.

5.7 Objective 4: Identifying the Single Unit versus Multiple Unit Cohorts

The exploratory analysis of the 2014 data identified a number of challenges and issues in defining patients receiving single unit or multiple RBC unit transfusions. Two strategies for identify patients in the single and multiple unit cohorts were explored:

1. Using ordering data to define the single and multiple unit cohorts;
2. Using transfusion data to define the single and multiple unit cohorts.

Transfusion ***ordering data*** in the LIS contains the date and time the order was entered into the system by a ward clerk/nurse after the physician order, how many units the physician ordered, and how many of those units were issued.

Transfusion ***issuing data*** contains the date and time that each RBC unit was issued for transfusion.

Once a RBC unit is issued, the LIS designates the units as “presumed transfused” unless the RBC is returned to the Blood Bank within 24 hours or the Blood Bank is notified that the unit was wasted.

5.7.1 Methodological Considerations - Using Ordering Data

Using ordering data would be ideal to not only assess what transfusion practices occur, but physician intention in regard to what they wanted to transfuse. However, following discussions with blood bank staff it was found all units ordered within the time frame of a valid group and screen (within 72 hours of the initial order) are categorized in the hospital LIS as a single order. Hence, a physician could order one unit today, one tomorrow, and one the next day and the system would recognize this as a 3 unit order. An attempt was made to create an algorithm to differentiate true multiple unit orders and multiple unit orders that were made up of single unit orders (Appendix 5-3). However, in the exploratory analysis of 2014 data, such an algorithm was not feasible given the number of assumptions that had to be made. The limitation of using ordering data is that multiple unit orders may be several single unit orders occurring within 72 hours, which would significantly underestimate the number of single unit orders and over estimate the multiple unit orders. Therefore, we opted not to use ordering data to define exposure cohorts.

5.7.2 Methodological Considerations - Crossover of Transfusion Strategies During Admission

We also found that ordering practices were not consistent throughout a patient’s hospital admission in our exploratory analysis of 2014 data (Table 5-3). Many patients had both single and multiple unit orders during their hospitalization which did not allow for some patients to be categorized into the two exclusive groups.

Table 5-3. Exploratory Analysis of 2014 RBC Transfusion Orders Demonstrating Transfusion Strategies Are Not Static

		Number of RBC units ordered: The 2nd order				
Number of RBCs ordered:		0	1	2	3	Total Categorization for Single/Multiple Unit Cohorts
	1	584	75	67	11	737
	2	1964	104	223	27	2871
	3	436	53	53	11	

On the rows, the number of units ordered for the first order for RBC transfusions per hospitalized patient is compared to the number of units ordered for the second order for RBC transfusion (up to three units) on the columns. For example, for patients where the first order was a single unit, 75 patients had a single unit ordered for the second order and 67 patients had two units ordered for the second order.

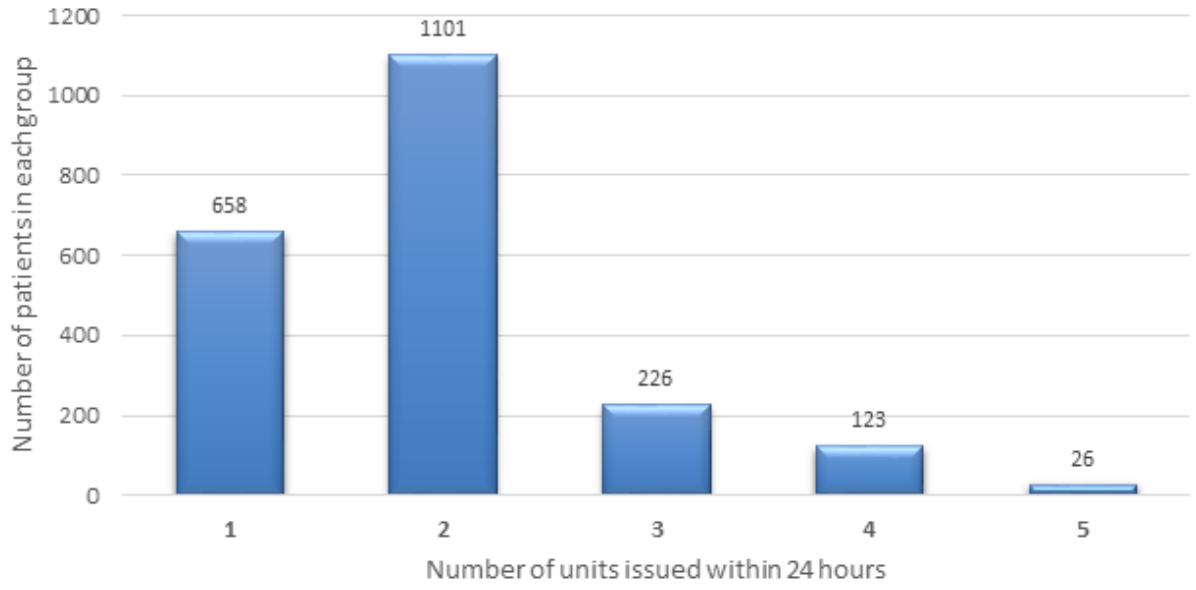
Although ordering data was felt to be flawed in determining exposure cohorts, this finding suggested that transfusion strategies used for each "transfusion episode" during a hospitalization were variable at the patient level. The definition of transfusion episode will be discussed later in this chapter. Options for categorization of exposure cohorts to account for inconsistency in strategies used include: assigning patients to the single or multiple unit cohort based on their first transfusion episode and disregarding categorization of subsequent transfusion episodes as having single or multiple units; or assessing only patients who exclusively had one strategy in all transfusion episodes throughout their hospitalization. Analyzing by the first transfusion episode simplifies the analyses and reduces the number of assumptions that need to be made. However, categorizing patients by their first transfusion episode has limitations as it is not representative of subsequent transfusion strategies, but does provide an exploratory assessment. Assessing patients who exclusively have single or multiple units for transfusion episodes would lead to significant selection bias.

5.7.3 Methodological Considerations - Using Transfusion Issue Data

Only issuing time is recorded in TRUST, not the transfusion start and end time; hence, it is impossible to know when a transfusions started and ended without manual chart review. RBCs that are issued and not returned to inventory within 24 hours are "presumed transfused". While we can assess how many transfusions occurred within a period of time, we cannot assess if the physician intended for multiple units to be given successively or if a reassessment was intended between units to determine the need for a subsequent unit. To deal with this time issue, a transfusion episode was defined and used to differentiate a single unit versus a multiple unit transfusion strategy. One unit issued (and presumed transfused) in a transfusion episode (24 hour period) would be defined as a single unit strategy; whereas, more than one unit given within a transfusion episode would be categorized as a multiple unit transfusion strategy.

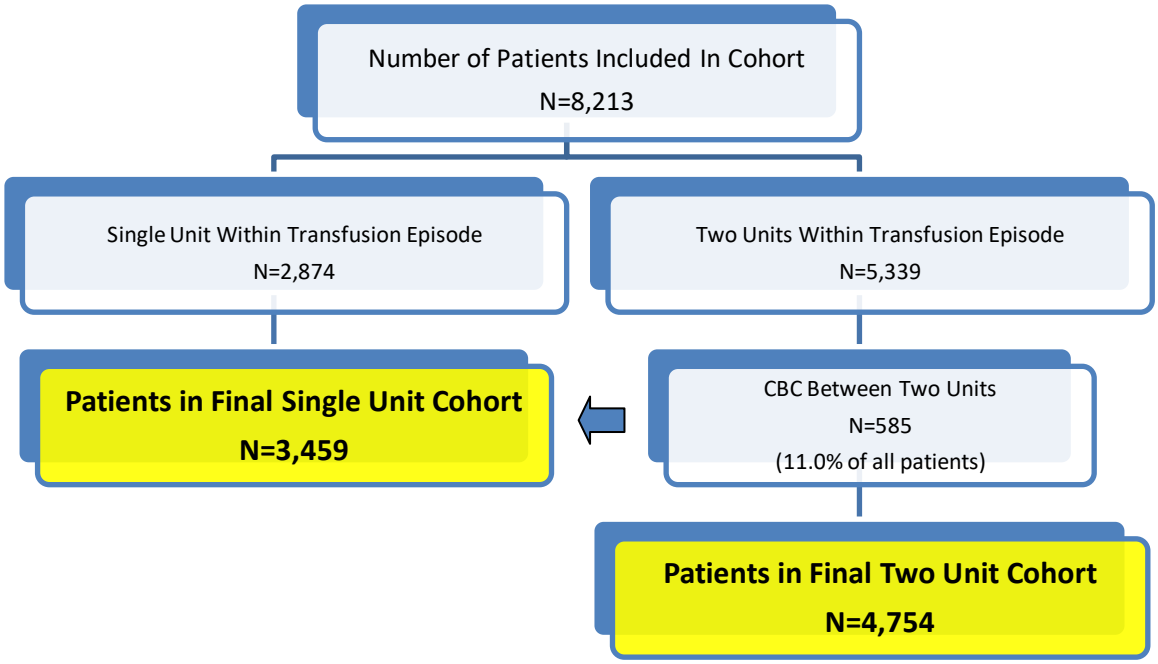
For issuing data, we only included patients receiving two units in a transfusion episode rather than those patients who were issued more than two units in a transfusion episode, as the latter is consistent with a less stable clinical scenario where the choice of a single unit transfusion strategy may not apply. This strategy excluded approximately 18% of our cohort (Figure 5-2). However, it is possible that some patients who received two RBCs within a transfusion episode could also represent a single unit order with a reassessment after the transfusion to see if the second unit was required. According to the survey presented in a previous chapter, most transfusion medicine experts either recommended repeating hemoglobin levels with the next morning bloodwork or sooner as part of the reassessment strategy; hence, we further assessed the 2014 data to see how many of the two-unit RBC orders could be reclassified as single unit orders based on a hemoglobin determination being done between transfusions. Hence, if two RBC units were given in a "transfusion episode" with repeat hemoglobin between units, even if the repeat hemoglobin was part of morning bloodwork, it would be consistent with single unit transfusion and reassessment. If multiple units were transfused within 24 hours without a complete blood count (CBC) between units, this would be consistent with a multiple unit transfusion.

Figure 5-2. Number of Units Transfused During First Transfusion Episode for Patients Using 2014 Exploratory Data



The analysis of the 2010-2014 data to classify the single and multiple unit cohorts using issuing data within a transfusion episode and hemoglobin determinations between RBCs transfused is summarized in Figure 5-3.

Figure 5-3. Proportion of Single and Two-Unit Transfusions Using Issuing Data with a Complete Blood Count and with a CBC Between Units



While single unit and multiple unit transfusions both had hemoglobin determinations done within a transfusion episode greater than 90% of the time (93.1% and 95.6% respectively), a hemoglobin was done between units only 11% of the time for transfusion episodes with two units. This suggests that the CBC between units may have been performed as a reassessment, which would make the two transfused units within the transfusion episode consistent with a single unit transfusion strategy with reassessment rather than a two unit transfusion strategy. This strategy to define cohorts has the limitation of the reassessment being based on hemoglobin determine alone and not an assessment of physical signs or symptoms.

5.8 Objective 5: Methodological Considerations for Outcomes

5.8.1 Total Red Blood Cell Utilization

If patients were grouped into single unit or multiple unit cohorts based on their first transfusion and if patients were consistently transfused with the categorized strategy

throughout their hospitalization, the total red blood cell utilization could be determined for each patient's hospitalization. However, because of the inconsistency between single versus multiple unit transfusions during a patient's hospitalization, conclusions based on grouping patients by their first transfusion would be difficult to interpret. Patients who were transfused exclusively based on the single unit transfusion strategy may have lower red blood cell utilization, but would putatively represent patients with less severe illness and bleeding. Because both of these options could provide misleading data, total red blood cell utilization would not be a reliable and meaningful outcome to use in our retrospective analysis.

5.8.2 Transfusion Gap Time

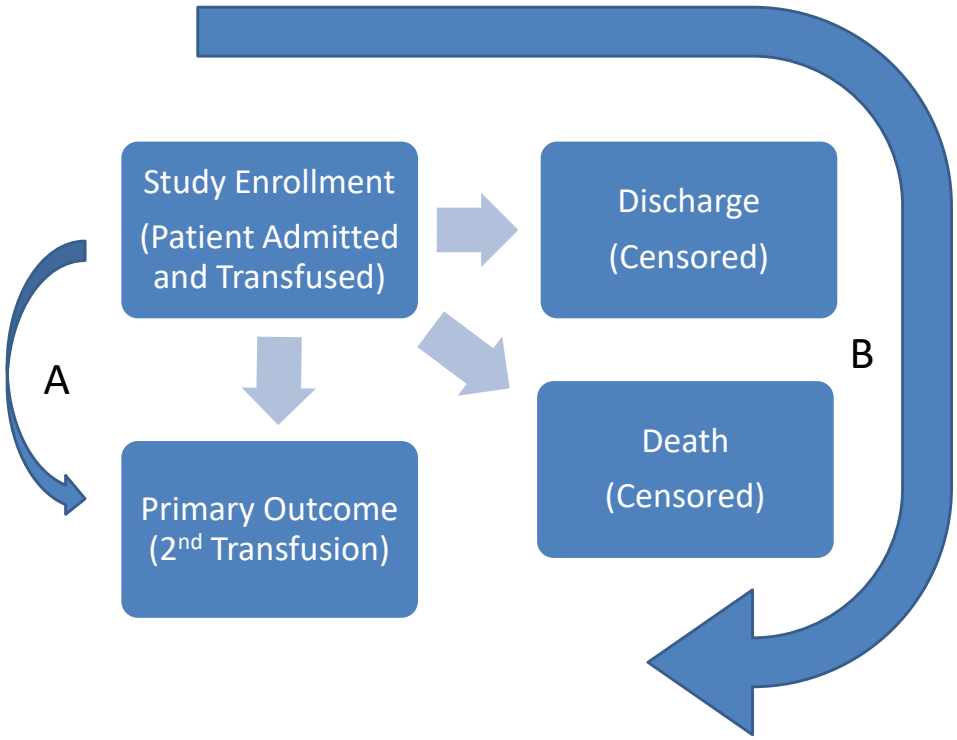
Time to next transfusion episode (transfusion gap time) is a useful outcome to measure as it is possible that the single unit transfusion strategy could result in more transfusion episodes potentially increasing the workload for hospital health care employees (laboratory technologists to front-line care providers). Determining the time to next transfusion alone in patients with rapidly given second and subsequent units may skew results and is more likely an indicator of severity of illness.

For transfusion gap time, we chose to perform survival analyses using stratified Cox regression. A typical Cox proportional hazard assumes a common baseline hazard function for all subjects (patients), where the proportional hazard assumption is that the hazard of any individual is a fixed proportion of the hazard for any other individual (or where the proportional hazard assumption states that prognostic or treatment factors under investigation have multiplicative effects on the hazard function of an underlying survival distribution).[84] A stratified Cox regression allows for variables that fail the proportional hazard assumption to be stratified, rather than making the assumption that all variables shift the baseline hazard rate up or down proportionally (ie as a ratio) as in a Cox proportional hazards model. Patients who belong to different stratum would have different baseline hazard functions. Therefore, a stratified Cox regression will "combine" different hazard rates in a non-proportional manner depending on the presence or absence of the stratified variables, and then all the other variables that are non-stratified will shift that hazard rate up or down proportionally. Gap time analysis to

assess all transfusions throughout the hospitalization was not reasonable because of the ordering inconsistency within an individual patient; however, assessing the transfusion gap time between the first and second transfusions would require fewer assumptions while providing useful preliminary information.

The different pathways patients can take in our study are shown in Figure 5-4. After study enrollment, patients either have a second transfusion which is our primary outcome (pathway A), or are censored when they do not have another transfusion before discharge or death (pathway B). Therefore, patients have competing risks of events that occur during their observation period. The cumulative intensity of patients going through pathway A, while taking into account the fact that patients may also go through pathway B, would be assessed in our competing risk model.

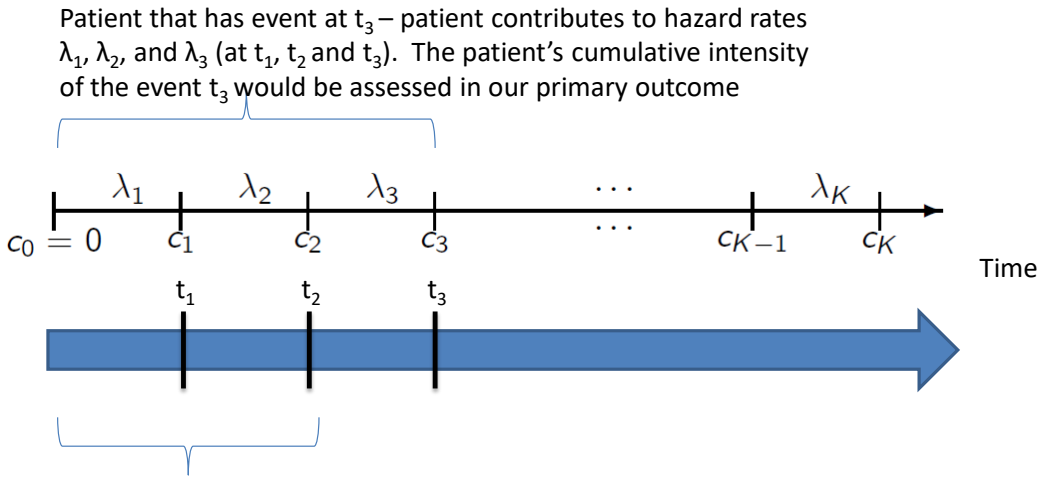
Figure 5-4. Diagram Demonstrating Different States Assessed in a Competing Risk Model



The cumulative intensity function that assumes the hazard changes over time periods of the study (where for example: patients with longer stays are more likely to be

transfused, patients with shorter stays may be discharged before a second transfusion). As time goes on in the study, all of the different hazard rates over time need to be assessed cumulatively to determine the rate (or cumulative intensity) of the second transfusion over time. A diagram demonstrating a constant that is changed by different hazard rates over time and how patient data contributes to it is in Figure 5-5. This approach is more clinically useful as it takes into account that not all hospitalized patients who receive a transfusion will receive a second transfusion. This method could also take into account that patients can receive more than two transfusions, as they are not censored after the event, though we are only considering the gap time between first and second transfusions due to inconsistent ordering patterns in our analyses. Absolute hazards of transfusion cannot be assessed over time with the cumulative intensity functions, but instead the relative hazards of transfusion in single and multiple unit cohorts (defined by the first transfusion episode) can be compared.

Figure 5-5. Diagram Demonstrating Changing Hazards in a Competing Risk Model



This diagram demonstrates that patients can have multiple outcomes other than the event (transfusion) during their hospitalization. Therefore, the competing risk of the event must be weighed against all other outcomes where censoring occurs. The cumulative intensity (c) is affected as hazard (λ) changes over time (t), capturing the fact that some patients will have the event at different time points and some will be censored. The time where a patient has an event is factored into the cumulative intensity of all the different changes in hazard over time.

In summary, gap time from the initial transfusion to the second transfusion can be assessed in two ways. In ordering data, it can be assessed as the gap time between one order to the second. Using issuing data, it can be assessed as the time between the last unit issued in a transfusion episode to the first unit issued in the second transfusion episode. While a time period is used to define groups which can confound an outcome that depends on time, we anticipate that the 24 hour period using issuing data will have less of an impact compared to the 72 hour period using ordering data. Hence, the primary outcome selected is the gap time between transfusion episodes using issuing data. We will analyze patients receiving 2 RBC units in a transfusion episode who are re-categorized as single unit patients based on a repeat hemoglobin between the two RBC units as a separate category in this analysis as they would skew the gap time to be shorter if grouped with patients issued one unit during a transfusion episode.

5.8.3 Pre-Transfusion Hemoglobin, Cancelled Units, and Other Outcomes

Pre-transfusion hemoglobins will be assessed using the hemoglobin level closest in time prior to the order and up to a maximum of 24 hours before the transfusion issue time. This information will give a broader assessment of appropriateness of transfusion. An exploratory analysis of 2014 data showed that approximately 90% of pre-transfusion hemoglobins are within 24 hours of the transfusion. The mean/median hemoglobin values for the single and two unit cohorts were 85.1 g/L (SD 13.6) and 83.0 (SD 15.6) respectively. The proportion of patient cohorts defined from issuing data from 2014 with different pre-transfusion hemoglobin thresholds are in Table 5-4.

Table 5-4. Exploratory Analysis of Pre-Transfusion Hemoglobin Thresholds Based on Cohorts Defined By Issuing Data from 2014

	Pre-Transfusion Hemoglobin Threshold (g/L)				Total
	≥90	80-89	70-79	<70	
Single Unit Cohort	252	228	243	60	783
Two Unit Cohort	286	162	308	167	923
Total	538	390	551	227	1759

The number of cancelled units in an order (defined as units ordered for a transfusion but not transfused, either because they are not issued or are returned to the blood bank after issue), can be assessed using ordering data. Exploratory data from 2014 for cancelled units in the first order during hospitalization is summarized in Table 5-5. The proportion of multiple unit orders that had units cancelled would require chart review to determine why units were cancelled as this may be due to reassessment, transfusion reactions, or even death.

Table 5-5. Exploratory Analysis of 2014 First RBC Transfusion Orders During Hospitalization Demonstrating the Proportion of Orders with Transfusions Completed or Not Completed

	The 1st order		
# units ordered	**Not Complete**	**Complete**	**Total**
1	38	719	757
	5.02%	94.98%	
2	951	1454	2405
	39.54%	60.46%	
3	297	281	578
	51.38%	48.62%	

Data from 2014 exploratory analyses looking at the first RBC order from a hospitalization demonstrates that not all units ordered are actually issued/transfused. For example, of 757 orders of a single unit, 5% did not have any units transfused. For 2,405 orders of two units, nearly 40% had one or both units not transfused.

The other main outcomes of interest that were specified in our conceptual flow diagram that were considered include clinical outcomes (morbidity from anemia or transfusion, mortality) and cost. Clinical outcomes such as mortality can be assessed, but LIS and DAD data do not contain any detailed information about cause of mortality, morbidities, or robust information regarding transfusion reactions. Because total red blood cell utilization cannot be calculated, cost would also not be feasible to assess in a retrospective design.

5.9 Conclusion

The 2014 data analysis was useful for identifying methodological issues related to classification of exposures and outcome events when using a retrospective analysis and inform the design and analysis plan for the four-year cohort. We concluded that:

- Data from TRUST could be utilized to develop inclusion and exclusion criteria for patients where studying single unit versus multiple unit transfusions would be applicable
- Data from TRUST/MASCOT could be used to identify comorbidities, medications, and the service of the most responsible physician ordering transfusions; however, validation studies are needed.
- Only data from the first transfusion episode in a hospitalization could be used for the retrospective analysis as transfusion therapy (single versus multiple order strategy) is not consistently applied during a patient hospitalization.
- The single and multiple unit cohorts are best defined by RBCs issued in a transfusion episode (24 hour period)
    - Patients with more than two units issued in a transfusion episode were not assessed as these patients were considered to be bleeding or unstable
    - A hemoglobin determination can be used to categorize two unit transfusions that are likely single unit transfusions with reassessment.
- The primary outcome should be the gap time between the first and second transfusion episode.

- Other outcomes that are obtainable using TRUST data, include pre-transfusion hemoglobins and cancelled units using ordering data

In the next chapter, the design of the retrospective study will be discussed.

Chapter 6: Retrospective Study Design of Single Versus Multiple Unit Transfusion Strategies

In this chapter, the design of a retrospective study to explore practice patterns of ordering single versus multiple RBCs for transfusion is presented. Our original objectives were identified in Chapter 5 and were based on the conceptual flow diagram (Chapter 4); however, the exploratory analysis of one year of data (Chapter 5) identified a number of issues that have been considered in the design of this retrospective four year study.

6.1 Research Question

In adult (age ≥18) inpatients at tertiary care hospitals in HHS and SJHH between January 1, 2010 to December 31, 2016 who were transfused RBCs during their first hospitalization, is there a difference in the gap time between the first and second transfusion episode depending on whether the patient was transfused using a single unit or multiple unit strategy during their first transfusion episode?

6.2 Study Design

A retrospective cohort study design was selected.

6.2.1 Rationale for Choosing a Retrospective Study Design

A prospective cohort study or a randomized controlled trial would be the strongest study designs to address the benefits and risks of a single versus multiple unit transfusion strategy; however, the paucity of evidence to predict the effect of single unit transfusion strategies in reducing red blood cell utilization and how transfusion strategies would affect patient outcomes or time to next transfusion makes it premature to justify at this time such expensive and resource intensive designs. Hence, a retrospective study design was selected as a reasonable and cost-effective approach to look at current practice and identify methodological issues with data collection and outcome selection for a future study regarding single versus multiple unit transfusion strategies. However, it is recognized that retrospective cohort studies are limited by their inability to control for all possible confounders which could lead to bias. A comparison between a

retrospective cohort study, a prospective cohort study, and a randomized control trial; as well as their advantages and disadvantages are outlined in Table 6-1.

Table 6-1. A Comparison Between Cohort Study Designs (Retrospective and Prospective) and Randomized Clinical Trials

	Retrospective Cohort Studies	Prospective Cohort Studies	Randomized Control Trials
Methodological Rigor	+	++	+++
Prospective Data Collection	No	Yes	Yes
Randomization	No	No	Yes
Cost/Time Requirement	+	++	+++
Common Biases (variable dependent on actual study methodology)	+++ Missing data/outcomes Selection Bias Information Bias Recall Bias Confounders	++ Selection Bias Loss to follow-up Information Bias Confounders	+ Selection Bias Loss to follow-up

6.3 Specific Study Objectives

a) To characterize the proportion of patients that have one unit of RBCs transfused in the first “transfusion episode” (defined as the 24 hour period from the time the first RBC was issued), compared to two RBCs transfused during their first hospitalization.

i. For those patients who had two RBC units transfused within their first transfusion episode, to determine how many had a CBC between units which could be consistent with a single unit transfusion strategy with clinical reassessment between units.

b) To determine the gap time between the first and second transfusion episodes for inpatients where the first transfusion was for one unit of RBCs or two units of RBCs.
    i. To assess the gap time between first and second transfusion episode in inpatients who had their first transfusion episode as a single unit strategy or a two-unit strategy, after adjusting for confounders using stratified Cox regression in a competing risk model.
c) To assess the mean/median pre-transfusion hemoglobin before single unit and two-unit RBC issues as well as the proportion of patients with different pre-transfusion hemoglobin levels (<70 g/L, 70-79 g/L, and >80 g/L).
d) To characterize the total number of single unit orders compared to multiple unit orders (using ordering data).
e) To determine which types of orders have units cancelled (defined as units ordered for a transfusion that are not transfused, either because they are not issued or returned to the blood bank after issue).
    i. To assess how many single or multiple unit orders have RBC units that are cancelled.
    ii. To assess how many patients have units cancelled.

6.4 Eligibility Criteria

6.4.1 Inclusion Criteria

All adult inpatients (age ≥18) at HHS and SJHH who received a RBC transfusion between January 1, 2010 and December 31, 2016 were eligible for the study. This time frame was selected as MASCOT data (containing pharmacy information) was available as of 2010. The rationale for including only inpatients was the lack of clinical and demographic data on outpatients being available in TRUST and because single unit

transfusion strategies may not apply to outpatients given they are extrapolated from studies supporting restrictive transfusion strategies in primarily hospitalized patients. Pediatric patients were not included as these patients are often transfused by weight rather than unit and in our exploratory analyses including pediatric patients greatly skewed our results.

6.4.2 Exclusion Criteria

Patients meeting the inclusion criteria will be excluded based on the following:

a) Patients admitted with an ICD10 trauma code
    i. Patients who need emergent transfusions or are deemed to require significant transfusion needs (more than one RBC unit) due to their clinical circumstance. These patients will always require more than one unit of RBCs and thus would skew our analyses.
b) Patients issued more than 2 RBC units within a 24 hour period
    i. This criterion identifies patients who are likely to have a massive hemorrhage protocol activated (since this cannot be captured from the electronic health records) or who are actively bleeding/unstable.
    ii. Patients receiving uncrossmatched RBCs could also not be captured from electronic health records.
c) Patients receiving plasma and cryoprecipitate during the transfusion episode
    i. These patients were excluded as transfusion of multiple types of blood products would likely indicate coagulopathy which could make transfusion with a single of multiple RBC unit strategy not applicable.
d) Patients receiving autologous or directed RBCs, or units as part of an exchange transfusion.
    i. Single or multiple unit strategies do not apply to these patients.
e) Patients identified as outpatients and those who are not admitted to hospital.
    i. The use of single unit transfusion strategies are extrapolated from studies demonstrating benefits of restrictive transfusion strategies in inpatients; hence, generalizability to outpatients is not known. As a result, we felt that

excluding outpatients would allow for a more focused cohort appropriate for study.

f) Patients whose RBC orders were placed more than 24 hours before their transfusions.
    i. In exploratory analyses, there were a large proportion of orders where transfusion would occur up to a week later. The majority of these orders were pre-operative and are not suitable for this analysis.
g) Patients where more than two RBC units were transfused in the first transfusion episode (defined as the 24 hour period from the first RBC unit issued).

6.5 Exposure Cohorts

Exposure groups will be defined by either one or two RBC units issued in the first transfusion episode. A transfusion episode is defined as a 24 hour period which starts at the time the first RBC unit is issued during the patient's first hospitalization in the study period. Therefore, we define our exposure groups by the following:

a) Single unit transfusion cohort
    i. In the first transfusion episode only one RBC unit was issued;
    OR
    ii. In the first transfusion episode, two units were issued, but a hemoglobin was resulted between the two units.
b) Two unit transfusion cohort
    i. In the first transfusion episode, two units were issued, but a hemoglobin was not resulted between the two units

6.6 Data Sources

Data for the study comes from TRUST and MASCOT databases (see Chapter 5, page 54 for details).

6.6.1 Baseline Data Collected and Data Management

The following baseline data will be collected on all eligible patients from the hospital LIS, TRUST, or MASCOT:

- Demographic Information: age, sex, year of cohort entry, hospital;
- Physician service (derived from TRUST physician codes): General Medicine, Cardiology, Intensive Care, Medical Oncology, Hematology Oncology, Obstetrics and Gynecology, General Surgery, Cardiovascular Surgery, Vascular Surgery, or other;
- ICU Admission;
- Comorbidities (pre-admission, see Appendix 5-2): chronic renal failure, cardiac disease, hematological malignancy, any malignancy, any procedure code before the transfusion, and Charleston Comorbidity Index (relevant codes to calculate this index are specified in Appendix 6-1);
- Laboratory findings: hemoglobin on hospital admission, platelet count on admission, hemoglobin before transfusion episode, platelet count before the transfusion episode, hemoglobin post-transfusion episode;
- Medication use (at time of transfusion): erythropoietin stimulating agents, anticoagulant use, antiplatelet use;
- Number of hospitalizations in the year after index hospitalization.

The data will be stored and encrypted on a secure server in the Computer Services Unit (CSU) at McMaster University. Only the study biostatistician and the study coordinator will have access to the data. Once data linkage occurs between data sources, subjects will be de-identified by giving them a study numbers and a chart completion code (CCC). The study code log will be saved to an encrypted file, printed, and stored in a locked location for confidentiality. All data on the MCTR server in Computer Services is backed up daily onto a password protected computer drive which is stored in an off-site location.

6.7 Outcomes

6.7.1 Primary Outcome

Our primary outcome will be the gap time defined as the period between the end of the first transfusion episode and the beginning of the second transfusion episode for a

patient's first hospitalization during the study period. For this study, only the first admission for each patient will be included as repeated analyses of the same patient over different admissions are difficult to account for data dependency. This methodology has been used successfully in other studies.[85]

For the single unit cohort only patients who are issued one RBC unit during the transfusion episode will be included in the analysis. Patients issued two units with repeat hemoglobin between will be analyzed as a separate cohort in this analysis as they could skew the primary outcome to a shorter gap time. The two unit cohort will consist of those issued two units during the transfusion episode without a hemoglobin between units for this analysis.

6.7.2 Secondary Outcomes

The following secondary outcomes will be assessed using two cohorts: the single unit cohort will include all patients using the two definition of the single unit cohort (6.5 a, i and ii - single unit given during a transfusion episode and two units transfused with a hemoglobin between RBCs), and the two unit cohort. These analyses will be based on the patient's first hospitalization.

a) Gap time using the combined definition of the single unit cohort and the two unit cohorts.
b) The number and proportion of orders with cancelled for single unit orders, two-unit orders, three unit orders, etc.
c) The proportion of patients with cancelled units during the index hospitalization.
d) Mean/median pre-transfusion hemoglobin for the single and two unit cohorts (pre-transfusion hemoglobin defined as the hemoglobin level closest in time prior to the order and up to a maximum of 24 hours before the transfusion issue).

6.7.3 Subgroup Analyses

Subgroup analyses will be performed on the primary outcome by the factors that we presume *a priori* would affect a clinician's decision to transfuse either a single unit or two RBC units:

- Year of cohort entry (2010, 2011, 2012, 2013, 2014, 2015, 2016)
    - Choosing Wisely recommendations from the Canadian Society of Transfusion Medicine were released in October 2014.
- Physician Service
    - Based on admission physician code
- Hematological Malignancy
    - Pre-admission ICD-10 Codes:

      Upon review of order sets at Hamilton Health Sciences (HHS), the hematology-oncology ward is the only order set that has a standing order for transfusing two units of packed RBCs when the hemoglobin drops below 80 g/L. If our analyses confirm that the majority of transfusions in this subgroup are multiple unit transfusions, we will perform a post-hoc secondary analysis of the entire cohort with the data from this subgroup removed.
- Cardiac Disease
    - Based on pre-admission ICD-10 Codes
- Patients admitted to the ICU during the hospitalization will also be analyzed as a high risk subset (as defining patients into subgroups based on events that occur after study enrollment is improper from a methodological perspective).
    - Patients in this subgroup analysis will have their first transfusion episode after ICU admission used for enrolment rather than the first transfusion episode after hospital admission

Patients will be followed until they are discharged from hospital or death occurs.

6.8 Analysis

Continuous outcome variables will be reported as means with standard deviations and skewed data will be reported as median, minimum, 5^{th}, 25^{th}, 50^{th}, 75^{th}, 95^{th}, and maximum percentiles. Dichotomous and categorical variables will be summarized as proportions.

For the primary outcome: the association between the RBC utilization cohorts (6.5 a), i and ii) and the time from the end of the first transfusion episode to the start of the second transfusion episode within the same index hospitalization will be analyzed using Cox proportional hazards regression with competing risk of the primary outcome, discharge or death (which specified in Chapter 5). The subset of variables from 6.6.1 will included in the model through backward elimination. Variables selected for inclusion into the model using backward elimination will also be compared to those included through two other common selection methods: adaptive lasso and model averaging; and stepwise regression.[86] Cox PH assumption will be tested for the selected variables.[87] The ones which fail the Cox PH assumption (with log transformation at 0.05 significant level) will be used as stratification variables. Hazard ratios with 95% confidence intervals will be reported, and the cumulative intensity plots for comparison of the different cohorts will be presented.

For secondary outcomes: patients issued a single unit transfusion for the first transfusion episode will be compared to those issued a two unit transfusion for: 1) baseline characteristics, 2) pre-transfusion hemoglobins, and 3) orders cancelled. Statistical testing will occur with the chi-squared/Fisher's Exact test for categorical data; and the t-test or the Mann Whitney U test for continuous data depending if data are in a normal distribution (t-test) or the distribution is skewed (Mann Whitney U test). A p value of less than 0.05 will be considered significant, after adjusting for multiple tests of significance using the Bonferroni method if applicable. The number of orders with cancelled units for different unit orders will also be reported descriptively as a matrix (where the columns will represent the different unit orders and the rows will represent the number of cancelled units).

6.9 Sample Size

The sample for this study will be chosen as a convenience sample as complete data including information on drug administration would not exist before 2010 in the TRUST/MASCOT databases. Selection bias and non-participation bias will be minimized as all transfused in-patients who met the eligibility criteria were enrolled and studied. A formal sample size calculation was not possible based on the available

literature from the systematic search (Chapters 2A and 2B), and the small number of studies limits generalizability to our population. The convenience sample chosen is larger than the majority of studies found in the literature to date.

6.10 Data Validation

While in the last chapter we have demonstrated feasibility of collecting data from TRUST and the LIS to perform the study, we will select 30 charts at random from each cohort to determine if the following characteristics are concordant between data extracted from TRUST and the patient chart:

- Appropriate categorization of the patient to either the single or the two unit cohort
    - This will compare data in TRUST to the number of transfusions given in a 24 hour period by manual chart review;
- Presence of the following comorbidities found during chart review as defined below compared to pre-admission ICD-10 comorbidity codes:
    - Chronic renal failure - defined by increased creatinine above the upper limit of the local laboratory reference range or physician documentation of chronic renal failure
    - Cardiac disease - defined by increased troponin above the local laboratory reference range, physician documentation of cardiac disease, or procedural evidence of cardiac dysfunction (abnormal echocardiogram, cardiac stress test, or cardiac catheterization)
    - Hematological malignancy - defined by physician (clinician or pathologist report) documentation of presence of hematological malignancy
    - Cancer - defined by physician (clinician or pathologist report) documentation of presence of cancer
- Medication use before the start of the first transfusion, specifically:
    - Erythropoeitin stimulating agents, anticoagulants, antiplatelet agents, aspirin

At least 70% agreement between the chart information and the data extracted from TRUST/MASCOT will be considered acceptable. For example, if TRUST identifies the

patient as being in the single unit cohort, having chronic renal failure, cancer, and was on low molecular weight heparin; chart review would have to confirm at least 3 out of 4 variables as correct to adjudicate that the data extracted by TRUST and chart review are concordant for that patient chart. If at least 48 charts (≥70%) are found to have concordant data, the data will be considered validated. If this is not the case, further validation studies will be done to determine the source of error in regards to the transfusion data, medication use, and/or to choose more accurate codes for comorbidities.

6.11 Ethical Considerations

This research design is a retrospective observational study; we will not seek individual informed consent. This is a non-interventional study and we will not be contacting patients, nor undertaking actions that will impact on their health care. Individual contact of each patient identified in the study would also make this study impracticable. The data are historical and merged into TRUST and MASCOT with the intention of research and quality assurance. As well TRUST and MASCOT have research ethics board approval to collect and store the data. Retrospective chart reviews often do not require individual consent as patients are not put at risk as long as their information is safeguarded. However, protecting patient health information is of the utmost importance. The research study utilizing TRUST and MASCOT will be reviewed by the research ethics board and all aspects of the study will operate under Good Clinical Practice (GCP) requirements to ensure that patients' interests are protected with this research study. We do require patient-level data to extract information, where the TRUST biostatistician will generate a study code log of all patients to include the medical record number (MRN), a coded study id, and a second identifier called a chart completion code (CCC). The study code log will be saved to an encrypted file, printed, and stored in a locked office for confidentiality. This personal identifying information will only be used for initial identification of the study cohort and for data collection, following which the data will be anonymized and replaced with a study identification number and reported in aggregate. The study data will be retained in a secure, password-protected file.

An ethical concern with studies based on routinely collected data is that patients who are admitted to hospital do not give express consent for their information to be stored for research. However, patient charts are often studied in retrospective reviews without express consent. Research ethics exists to ensure that patient interests are protected when research is being completed. Therefore, the current standard of research ethics boards reviewing studies to determine potential patient harm is a reasonable approach. In the future, using this type of data for future research and quality assurance should require transparency and dialogue to determine if the purported benefits of allowing the use of personal data for improving clinical care and health care processes outweigh the potential harms to patient confidentiality.

6.12 Limitations

Limitations of this study pertain to its retrospective nature and include: 1) limitations of the cohort definitions, 2) bias and confounding, and 3) data validation. The limitations of both the cohort definitions have been discussed at length previously.

Multiple forms of bias occur in retrospective studies. Information bias exists as different patients will have transfusion depending on blood tests ordered by clinicians. Selection bias occurs as participants in the exposure groups (ie those who are issued two units may be less stable) are not similar and therefore the relationship between the exposure and the outcome may not have internal validity. Our decision to include only the first hospitalization where patients were transfused could exclude significant transfusions that occur in subsequent hospitalizations. Future analyses may assess and adjust for multiple hospitalizations with transfusion. Patients where a multiple unit transfusion strategy was used may have other factors not considered or where data could not be collected through TRUST in analyses that would have prompted choice of that strategy. For example, because chart review is not performed for all patients, we cannot capture if a patient would have been transfused multiple units due to the presence of bleeding. Major bleeding was considered by excluding patients with concomitant transfusions of plasma and cryoprecipitate and transfusion of more than five RBCs within 24 hours (to reflect patients with massive hemorrhage) for which single unit transfusion strategies may not apply. Other factors that clinicians use in their rationale to provide transfusion

may not be assessed as well. For example, accounting for hemoglobin levels and change of hemoglobin levels from baseline before admission is limited by data not being captured by outside laboratories. A physician may decide to treat anemia with transfusion if they perceive the onset to be acute, which is not captured with LIS data from inpatients. We attempted to adjust for confounders for our primary outcome and used both issuing and ordering data to confirm our findings. However, limitations of retrospective studies should be recognized in not being able to adjust for all confounders and being hypothesis generating.

Data validation is a prevalent issue in studies utilizing routinely collected data not intended for research purposes. While RBC units that are issued and not sent back to the blood bank are presumed to be transfused, we cannot determine this for certain unless a chart review of nursing notes was performed. We have already acknowledged that ordering data is inaccurate for units ordered within the same group and screen; and cannot rule out that error in communication between physicians, ward clerks, nurses, and blood bank technologists could have led to inaccurate transcription of issuing data without performing a thorough chart review.

ICD-10 codes and physician codes are entered into administrative databases used to identify the patient's diagnosis and comorbidities. Methods such as using a physician code to determine the specialty of the most responsible physician from the TRUST database can be inaccurate. Choosing specific diagnostic codes may improve the accuracy of the diagnoses they reflect and may require manual chart validation. Categories of diagnostic codes, such as trauma codes, may not be reflective of the population that we wish to study. For example, if all patients with a trauma code were excluded our study as they would lead to marked hemorrhage and not be applicable to a single unit transfusion strategy, we may exclude patients who have minor injuries for which a single unit transfusion strategy may apply. This may be mitigated by manually selecting ICD-10 codes for trauma. This may apply to surgeries as well, although surgeries that predispose to bleeding may be more difficult to accurately predict. Other studies have suggested that choosing a narrower set of ICD-10 codes for diagnoses and comorbidities may be more accurate when these codes are validated against actual diagnoses in a manual chart review.[88,89]

Cross-referencing data from multiple databases suggests that physician codes are accurate in determining the speciality of the most responsible physician, but we cannot guarantee complete accuracy without performing a manual chart review. While TRUST has had validation studies to demonstrate that data is concordant between different databases that were used to form TRUST, validation studies of transfusion outcome data (for example, TRUST contains data about units issued for transfusion but does not capture actual transfusion data, units that are issued are assumed to be transfused), diagnoses, and comorbidities needs to be done with manual chart review to ensure internal validity. Even if the validation studies planned for this study demonstrate the accuracy of data from TRUST/MASCOT, one cannot conclude that the data extracted for all the patients in the study are accurate. Standards are lacking regarding what constitutes data validation or what is acceptable for data validation.

Nevertheless, despite the many limitations that the study presented has, it should be emphasized that this is preliminary work to describe the practice of single versus multiple unit transfusions. As stated previously, this work is meant to inform the design of a prospective study. While the conclusions reached from this study are incomplete due to limitations of the data collection and confounders, the results are helpful in generating hypotheses.

6.13 Conclusion

This retrospective study will help to inform a future prospective study or a randomized control trial, and help to elucidate trends in practice and target more detailed studies to determine the benefit of single unit transfusion strategies. The results of our retrospective study may add supportive evidence to using a single unit transfusion strategy. Hypotheses generated with this study may guide further chart review for more accurate studies regarding cancelled units and red blood cell utilization. Assessment of issuing data with CBCs and pre-transfusion hemoglobins will inform if different physician specialties should be educated about performing reassessments with transfusion.

Chapter 7: Conclusion and Future Directions

To summarize the findings discussed in the thesis: 1) guidelines and studies are lacking in their recommendations to support single RBC unit transfusion strategies, 2) most transfusion medicine experts in Canada support the practice of single unit transfusion strategies and have consistent recommendations for reassessing to transfusion a(nother) unit, 3) retrospective analysis may be hypothesis generating to support single unit transfusion strategies in certain patient populations, and 4) a prospective RCT is required to assess the true benefit of single unit transfusion strategies.

Guideline and expert recommendations often provide the basis for which hospitals and clinicians form decisions and policy. Though we did not survey transfusing clinicians about their practice, our retrospective analysis suggests the majority of transfusion orders are for multiple units. A stronger evidence base is required to demonstrate benefits of single unit transfusion strategies that are not extrapolated from studies demonstrating the benefits of restrictive transfusion triggers. This is especially true in less clinically stable patients, where evidence in critically ill patients or patients with gastrointestinal bleeding supports restrictive transfusion strategies.

Because there is a paucity of guidance for how to reassess patients to provide further transfusion, recommendations provided by Canadian transfusion medicine experts may be published in a guideline or reflected in hospital policy to guide clinical practice. This would recognize the low methodological quality of the evidence and the fact that reassessment needs to be individualized to the patient. However, there are common aspects to reassessment that should serve as a starting point to guide clinicians.

Retrospective studies can be a starting point to understand current practices and provide hypotheses supporting single unit transfusion strategies, but are limited by bias and confounding. Different methods of defining single and multiple unit cohorts have different sets of limitations and retrospective studies need to be transparent about these limitations when reporting results. Where retrospective studies may be the most useful is to identify practice patterns which would be amenable to intervention by a policy supporting single unit transfusion strategies or a randomized controlled trial. For

example, if a high proportion of multiple unit transfusion strategies is observed in a specialty group (such as hematology) or in a particular centre, a policy or intervention there would presumably have the greatest effect if an efficacy study was done.

Information regarding factors that affect the choice of single or multiple unit transfusion also needs to be captured to ensure that confounders can be adjusted for. These factors need to be considered and assessed even in prospective studies if randomization does not occur. If a randomized controlled trial is done, balance of confounding features of both groups should occur if the sample size is large enough and the randomization process has been done correctly. However, assessing these factors will be of interest to physicians when interpreting the results of the study. We suggest the conceptual flow diagram outlined in this thesis as a starting point to consider these factors in both retrospective and prospective studies.

If higher quality evidence emerges that single unit transfusion strategies are beneficial, this needs to be explicitly stated in guidelines such as the AABB guidelines for red blood cell transfusion. Because modern guideline development methodology does not over-interpret or extrapolate from related studies, specific randomized control trial evidence needs to occur to support single unit transfusion strategies. If this evidence can be produced, I would propose that the proportion of single unit transfusion strategies and transfusions occurring at different pre-transfusion hemoglobin levels be used as quality indicators of clinical transfusion practice. Other quality indicators of transfusion such as number of RBC transfusions per capita may be reflective of varying demand due to demographics or clinical situations. However, proportion of single unit transfusions, allowing for exceptions in unstable, bleeding patients would provide a metric that is more reflective of physician intention.

If single unit transfusions as a quality indicator was universally adopted, tools such as more robust electronic data collection could be used to produce assessments of transfusion practice in the future. Improved data collection across multiple jurisdictions would also assist in allowing better studies using retrospective studies to inform other prospective studies. The biggest benefit is that transfusions would be used as therapy

only when required; limiting cost (including activity-based cost), improving supply of red blood cells, and protecting patients from the adverse effects of inappropriate therapy.

References

1. Hillis CM, Shih AW, Heddle NM. Best practices in the differential diagnosis and reporting of acute transfusion reactions. International Journal of Clinical Transfusion Medicine 2016;4:1-14.
2. Rock G. Changes in the Canadian blood system: the Krever Inquiry, Canadian Blood Services and Hema-Quebec. Krever Commission. Transfus Sci 2000;22:29-37.
3. Proposed Standard Definitions for Surveillance of Non-Infectious Transfusion Reactions. International Haemovigilance Network 2011. (Accessed March 12, 2015, at http://www.ihn-org.com/wp-content/uploads/2011/06/ISBT-definitions-for-non-infectious-transfusion-reactions.pdf.)
4. Goldman M, Webert KE, Arnold DM, et al. Proceedings of a consensus conference: towards an understanding of TRALI. Transfusion medicine reviews 2005;19:2-31.
5. Davenport RD. Pathophysiology of hemolytic transfusion reactions. Seminars in hematology 2005;42:165-8.
6. Cyr M, Eastlund T, Blais C, Jr., Rouleau JL, Adam A. Bradykinin metabolism and hypotensive transfusion reactions. Transfusion 2001;41:136-50.
7. Aubron C, Nichol A, Cooper DJ, Bellomo R. Age of red blood cells and transfusion in critically ill patients. Ann Intensive Care 2013;3:2.
8. Vamvakas EC, Blajchman MA. Transfusion-related immunomodulation (TRIM): an update. Blood Rev 2007;21:327-48.
9. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340:409-17.
10. Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. BMJ 2015;350:h1354.
11. Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA 2016;316:2025-35.
12. Tinmouth A, Chin-Yee I. The clinical consequences of the red cell storage lesion. Transfus Med Rev 2001;15:91-107.
13. Chasse M, Tinmouth A, English SW, et al. Association of Blood Donor Age and Sex With Recipient Survival After Red Blood Cell Transfusion. JAMA Intern Med 2016;176:1307-14.
14. Middelburg RA, Briet E, van der Bom JG. Mortality after transfusions, relation to donor sex. Vox Sang 2011;101:221-9.
15. Pai M, Cook R, Barty R, Eikelboom J, Lee KA, Heddle N. Exposure to ABO-nonidentical blood associated with increased in-hospital mortality in patients with group A blood. Transfusion 2016;56:550-7.
16. Norum J, Moen MA. Practice and costs of red blood cell (RBC) transfusion in an oncological unit. Anticancer Res 2008;28:459-64.
17. Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activity-based costs of blood transfusions in surgical patients at four hospitals. Transfusion 2010;50:753-65.
18. Trentino KM, Farmer SL, Swain SG, et al. Increased hospital costs associated with red blood cell transfusion. Transfusion 2015;55:1082-9.
19. Canel C, Mahar S, Rosen D, Taylor J. Quality control methods at a hospital. Int J Health Care Qual Assur 2010;23:59-71.
20. Bodenheimer T. The American health care system--the movement for improved quality in health care. N Engl J Med 1999;340:488-92.
21. Homer CJ, Forbes P, Horvitz L, Peterson LE, Wypij D, Heinrich P. Impact of a quality improvement program on care and outcomes for children with asthma. Arch Pediatr Adolesc Med 2005;159:464-9.

22. Brody H. Medicine's ethical responsibility for health care reform--the Top Five list. N Engl J Med 2010;362:283-5.
23. Wolfson D, Suchman A. Choosing Wisely(R): A case study of constructive engagement in health policy. Healthc (Amst) 2016;4:240-3.
24. Crosby J. Choosing Wisely Canada recommendations. Can Fam Physician 2016;62:568.
25. Allen JG. The case for the single transfusion. N Engl J Med 1972;287:984-5.
26. Choosing Wisely Canada: Why Give Two When One Will Do? 2016. (Accessed 2016-09-19, at http://www.choosingwiselycanada.org/in-action/toolkits/why-give-two-when-one-will-do/.)
27. Simon TL, Alverson DC, AuBuchon J, et al. Practice parameter for the use of red blood cell transfusions: developed by the Red Blood Cell Administration Practice Guideline Development Task Force of the College of American Pathologists. Arch Pathol Lab Med 1998;122:130-8.
28. Muller MM, Geisen C, Zacharowski K, Tonn T, Seifried E. Transfusion of Packed Red Cells: Indications, Triggers and Adverse Events. Dtsch Arztebl Int 2015;112:507-17; quiz 18.
29. Patient Blood Management Guidelines: Module 4 (Critical Care). Australian Government National Health and Medical Research Council, 2012. (Accessed 2016-09-14, 2016, at https://www.blood.gov.au/pbm-module-4.)
30. McEvoy MT, Shander A. Anemia, bleeding, and blood transfusion in the intensive care unit: causes, risks, costs, and new strategies. Am J Crit Care 2013;22:eS1-13; quiz eS4.
31. Collins TA. Packed red blood cell transfusions in critically ill patients. Crit Care Nurse 2011;31:25-33; quiz 4.
32. Corwin HL. Anemia and red blood cell transfusion in the critically ill. Semin Dial 2006;19:513-6.
33. Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. Crit Care Med 2009;37:3124-57.
34. Liu C, Grossman BJ. Red blood cell transfusion for hematologic disorders. Hematology Am Soc Hematol Educ Program 2015;2015:454-61.
35. American Society of Anesthesiologists Task Force on Perioperative Blood M. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management*. Anesthesiology 2015;122:241-75.
36. Patient Blood Management Guidelines: Module 2 (Perioperative). Australian Government National Health and Medical Research Council, 2012. (Accessed 2016-09-14, 2016, at https://www.blood.gov.au/pbm-module-2.)
37. Patel MS, Carson JL. Anemia in the preoperative patient. Anesthesiol Clin 2009;27:751-60.
38. Garcia-Erce JA, Gomollon F, Munoz M. Blood transfusion for the treatment of acute anaemia in inflammatory bowel disease and other digestive diseases. World J Gastroenterol 2009;15:4686-94.
39. Shah N, Andrews J, Goodnough LT. Transfusions for anemia in adult and pediatric patients with malignancies. Blood Rev 2015;29:291-9.
40. Bercovitz RS, Josephson CD. Transfusion Considerations in Pediatric Hematology and Oncology Patients. Hematol Oncol Clin North Am 2016;30:695-709.
41. Morley SL. Red blood cell transfusions in acute paediatrics. Arch Dis Child Educ Pract Ed 2009;94:65-73.
42. Practice strategies for elective red blood cell transfusion. American College of Physicians. Annals of internal medicine 1992;116:403-6.
43. Welch HG, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. Annals of internal medicine 1992;116:393-402.
44. Guidelines for red blood cell and plasma transfusion for adults and children. Int J Risk Saf Med 1997;10:255-71.
45. Shander A, Moskowitz DM, Javidroozi M. Blood conservation in practice: an overview. Br J Hosp Med (Lond) 2009;70:16-21.

46. Beyer I, Compte N, Busuioc A, Cappelle S, Lanoy C, Cytryn E. Anemia and transfusions in geriatric patients: a time for evaluation. Hematology 2010;15:116-21.
47. Australian and New Zealand Society of Blood Transfusion Ltd: Guidelines For The Administration Of Blood Products. 2016, 2011. 2016-09-14,
48. Patient Blood Management Guidelines: Module 3 (Medical). Australian Government National Health and Medical Research Council, 2012. (Accessed 2016-09-14, 2016, at https://www.blood.gov.au/pbm-module-3.)
49. Guideline on the Administration of Blood Components. British Committee for Standards in Haematology, 2012. (Accessed 2016-09-14, 2016, at http://www.b-s-h.org.uk/media/5152/admin_blood_components-bcsh-05012010.pdf.)
50. Patient Blood Management Guidelines: Module 5 (Obstetrics and Maternity). Australian Government National Health and Medical Research Council, 2015. (Accessed 2016-09-14, 2016, at https://www.blood.gov.au/pbm-module-5.)
51. National Institute for Health and Care Excellence Guidelines: Blood Transfusion. 2015. (Accessed 2016-09-14, 2016, at https://www.nice.org.uk/guidance/ng24.)
52. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014. (Accessed 2017-01-31, at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.)
53. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
54. Covello TPC, Quinn JG, Kumar-Misir A, et al. Assessing the efficacy of a single-unit red blood cell transfusion policy at a multisite transfusion service using a computerized retrospective audit. ISBT Science Series 2016;11:125-31.
55. Berger MD, Gerber B, Arn K, Senn O, Schanz U, Stussi G. Significant reduction of red blood cell transfusion requirements by changing from a double-unit to a single-unit transfusion policy in patients receiving intensive chemotherapy or stem cell transplantation. Haematologica 2012;97:116-22.
56. Ma M, Eckert K, Ralley F, Chin-Yee I. A retrospective study evaluating single-unit red blood cell transfusions in reducing allogeneic blood exposure. Transfus Med 2005;15:307-12.
57. Yerrabothala S, Desrosiers KP, Szczepiorkowski ZM, Dunbar NM. Significant reduction in red blood cell transfusions in a general hospital after successful implementation of a restrictive transfusion policy supported by prospective computerized order auditing. Transfusion 2014;54:2640-5.
58. Allameddine A, Heaton M, Jenkins H, Andrews S, Sedman B, Poarada C. The single-unit blood transfusion: Experience and impact in haematology patients [abstract]. Haematologica 2015;100:19.
59. Aronson CA, Halperin EA, Fantus RJ, Roy L, Barrionuevo M. First year for blood management in a midwest hospital system [abstract]. Transfusion 2013;53:233A-4A.
60. Evans R, Avdic A, Smith A, Tucker S. Comparing the safety and efficacy of red blood cell transfusion dose in hematopoietic stem cell transplant patients: Single versus double unit transfusions [abstract]. Biology of Blood and Marrow Transplantation 2014;1):S102-S3.
61. Olan I, Gunn K. Blood is a gift-why use two when one will do [abstract]. British Journal of Anaesthesia 2012;108:ii10-ii1.
62. Sutton BC, Roberts DR, Wright MJ, et al. Reducing platelet (PLT) and red blood cell (RBC) utilization in a 325-bed hospital [abstract]. Transfusion 2013;53:231A.
63. Tavares MF, DiQuattro P, Sweeney JD. Encouraging single unit red cell transfusion prescription for in-patients can be effective in reducing red cell usage [abstract]. Transfusion 2013;53:54A.
64. Whitten KL, Blann M, Rhyne C, Umezurike I. Reducing RBC usage by implementing a blood management/transfusion safety program [abstract]. Transfusion 2015;55:201A-2A.

65. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52:377-84.
66. Woodward CA, Chambers LW. Guide to Questionnaire Construction and Question Writing. Ottawa: Canadian Public Health Association; 1997.
67. Mack N, Woodsong C, MacQueen K, Guest G, Namey E. Qualitative Research Methods: A Data Collector's Field Guide. North Carolina: Family Health International; 2005.
68. Goering PN, Streiner DL. Reconcilable differences: the marriage of qualitative and quantitative methods. Can J Psychiatry 1996;41:491-7.
69. Richardson JT. Instruments for obtaining student feedback: a review of the literature. Assessment & Evaluation in Higher Education 2005;30:387-415.
70. Baruch Y. Response rates in academic studies: a comparative analysis. Human Relations 1999;52:421-34.
71. Nulty DD. The adequacy of response rates to online and paper surveys: what can be done? Assessment & Evaluation in Higher Education 2008;33:301-14.
72. Burns KE, Duffett M, Kho ME, et al. A guide for the design and conduct of self-administered surveys of clinicians. CMAJ 2008;179:245-52.
73. Asch DA, Jedrziewski MK, Christakis NA. Response rates to mail surveys published in medical journals. J Clin Epidemiol 1997;50:1129-36.
74. Cunningham CT, Quan H, Hemmelgarn B, et al. Exploring physician specialist response rates to web-based surveys. BMC Med Res Methodol 2015;15:32.
75. Dillman D, Smyth J, Christian L. Internet, Mail, and Mixed-Mode Surveys: The Tailored Design Method. New York: Wiley; 2009.
76. Choosing Wisely Canada. Transfusion Medicine: Ten Things Physicians and Patients Should Question. 2014. (Accessed 2016-10-09, at http://www.choosingwiselycanada.org/recommendations/transfusion-medicine/.)
77. Dillman D. Mail & Telephone Surveys: The Total Design Method. Toronto: Wiley; 1978.
78. Stenhammar C, Bokstrom P, Edlund B, Sarkadi A. Using different approaches to conducting postal questionnaires affected response rates and cost-efficiency. J Clin Epidemiol 2011;64:1137-43.
79. Todd AL, Porter M, Williamson JL, Patterson JA, Roberts CL. Pre-notification letter type and response rate to a postal survey among women who have recently given birth. BMC Med Res Methodol 2015;15:104.
80. Edwards PJ, Roberts I, Clarke MJ, et al. Methods to increase response to postal and electronic questionnaires. Cochrane Database Syst Rev 2009:MR000008.
81. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet 2002;359:248-52.
82. Babyak MA. Understanding confounding and mediation. Evid Based Ment Health 2009;12:68-71.
83. Rosner B. Fundamentals of Biostatistics. Pacific Grove, California: Duxbury; 2000.
84. Breslow NE. Analysis of Survival Data under the Proportional Hazards Model. International Statistical Review / Revue Internationale de Statistique 1975;43:45-57.
85. Heddle NM, Arnold DM, Acker JP, et al. Red blood cell processing methods and in-hospital mortality: a transfusion registry cohort study. Lancet Haematol 2016;3:e246-54.
86. Zou H. The Adaptive Lasso and Its Oracle Properties. Journal of the American Statistical Association 2006;101:1418-29.
87. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515-26.

88. Bezin J, Girodet PO, Rambelomanana S, et al. Choice of ICD-10 codes for the identification of acute coronary syndrome in the French hospitalization database. Fundam Clin Pharmacol 2015;29:586-91.
89. Molnar AO, van Walraven C, McArthur E, Fergusson D, Garg AX, Knoll G. Validation of administrative database codes for acute kidney injury in kidney transplant recipients. Can J Kidney Health Dis 2016;3:18.

Appendix 2A-1. Search Strategies Used in MEDLINE and EMBASE

Searches	
1	Red blood cell transfusion: a clinical practice guideline from the AABB.m_titl.
2	Prudent Strategies for Elective Red Blood Cell Transfusion.m_titl.
3	(Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care).m_titl.
4	"Practice Guidelines for Blood Component Therapy. A Report by the American Society of Anesthesiologists Task Force on Blood Component Therapy".m_titl.
5	(Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies).m_titl.
6	murphy mf.au.
7	wallington tb.au.
8	6 and 7
9	(Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients).m_titl.
10	"Practice parameter for the use of red blood cell transfusions: developed by the Red Blood Cell Administration Practice Guideline Development Task Force of the College of American Pathologists.".m_titl.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	guideline adherence.mp. or exp Guideline Adherence/
13	practice guidelines.mp. or exp Practice Guideline/
14	guideline*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
15	strateg*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique

	identifier]
16	recommendation*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
17	"clinical practice".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
18	12 or 13 or 14 or 15 or 16 or 17
19	erythrocyte.mp. or exp Erythrocytes/
20	RBC*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
21	"red blood cell*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22	"red cell*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
23	blood.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24	"packed red blood cell*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
25	PRBC*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

26	19 or 20 or 21 or 22 or 23 or 24 or 25
27	transfus*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
28	erythrocyte transfusion.mp. or exp Erythrocyte Transfusion/
29	blood transfusion.mp. or exp Blood Transfusion/
30	blood component transfusion.mp. or exp Blood Component Transfusion/
31	"restrictivetransfus*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
32	27 or 28 or 29 or 30 or 31
33	18 and 26 and 32
34	1 or 2 or 3 or 4 or 5 or 8 or 9 or 10
35	33 or 34
36	limit 35 to (guideline or meta analysis or practice guideline or systematic reviews)

Appendix 2A-2. Search Strategy Used for Web of Science

#15	#14 AND #13 AND #6 *DocType=All document types; Language=All languages;*
#14	TS=(blood and transfus*) *DocType=All document types; Language=All languages;*
#13	#12 OR #11 OR #10 OR #9 OR #8 OR #7 *DocType=All document types; Language=All languages;*
#12	TS=PRBC* *DocType=All document types; Language=All languages;*
#11	TS=(packed red blood cell*) *DocType=All document types; Language=All languages;*
#10	TS=(red and cell*) *DocType=All document types; Language=All languages;*
#9	TS=(red and blood and cell*) *DocType=All document types; Language=All languages;*
#8	TS=rbc* *DocType=All document types; Language=All languages;*
#7	TS=erythrocyte* *DocType=All document types; Language=All languages;*
#6	#5 OR #4 OR #3 OR #2 OR #1 *DocType=All document types; Language=All languages;*
#5	TS=(recommendation*) *DocType=All document types; Language=All languages;*
#4	TS=(strateg*) *DocType=All document types; Language=All languages;*
#3	TS=guideline* *DocType=All document types; Language=All languages;*
#2	TS=(practice guideline*) *DocType=All document types; Language=All languages;*
#1	TS=(guideline and adherence) *DocType=All document types; Language=All languages;*

Appendix 2A-3. Search Strategies Used for both Clearinghouse & Trip Database

Search Strategy used for both Clearinghouse & Trip Database

(guideline* OR recommendation*) AND (RBC* OR red blood cell* OR PRBC* OR Erythrocyte*) AND (transfus*)

Appendix 2B-1. Search Strategies used for MEDLINE and EMBASE for Studies

1	(cancer- and chemotherapy- induced anemia).m_titl.
2	from 1 keep 8
3	Appropriateness of allogeneic red blood cell transfusion: the international consensus conference on transfusion outcomes.m_titl.
4	(Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline).m_titl.
5	(2011 update to the society of thoracic surgeons and the society of cardiovascular anesthesiologists).m_titl.
6	significant reduction of red blood cell transfusion requirements by changing from a double-unit.m_titl.
7	"packed red blood cell*".mp.
8	PRBC*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9	"red blood cell*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
10	rbc*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11	"red cell*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12	exp Erythrocytes/
13	erythrocyte*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

14	7 or 8 or 9 or 10 or 11 or 12 or 13
15	transfus*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
16	"bloodtransfus*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
17	erythrocyte transfusion.mp. or Erythrocyte Transfusion/
18	Blood Transfusion/
19	15 or 16 or 17 or 18
20	"single-unit*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
21	"double-unit*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22	"one unit at a time".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
23	1-unit.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24	2-units.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
25	20 or 21 or 22 or 23 or 24
26	14 and 19 and 25

27	2 or 3 or 4 or 5 or 6
28	26 or 27
29	limit 28 to humans

Appendix 2B-2. Search Strategies used for Web of Science for Studies

#17	#16 AND #10 AND #7 *DocType=All document types; Language=All languages;*
#16	#15 OR #14 OR #13 OR #12 OR #11 *DocType=All document types; Language=All languages;*
#15	TS=2-units *DocType=All document types; Language=All languages;*
#14	TS=1-unit *DocType=All document types; Language=All languages;*
#13	TS=one unit at a time *DocType=All document types; Language=All languages;*
#12	TS=double-unit* *DocType=All document types; Language=All languages;*
#11	TS=single-unit* *DocType=All document types; Language=All languages;*
#10	#9 OR #8 *DocType=All document types; Language=All languages;*
#9	TS=erythrocyte transfus* *DocType=All document types; Language=All languages;*
#8	TS=blood transfus* *DocType=All document types; Language=All languages;*
#7	#6 OR #5 OR #4 OR #3 OR #2 OR #1 *DocType=All document types; Language=All languages;*
#6	TS=erythrocyte* *DocType=All document types; Language=All languages;*
#5	TS=rbc* *DocType=All document types; Language=All languages;*
#4	TS=red cell* *DocType=All document types; Language=All languages;*
#3	TS=red blood cell* *DocType=All document types; Language=All languages;*
#2	TS=PRBC* *DocType=All document types; Language=All languages;*
#1	TS=packed red blood cell* *DocType=All document types; Language=All languages;*

Appendix 3-1: Survey Administered to Respondents

Part 1: Demographic Information

1). Which province is your primary practice location? *

Please choose **only one** of the following:

- ○ Alberta
- ○ British Columbia
- ○ Manitoba
- ○ New Brunswick
- ○ Newfoundland/Labrador
- ○ North West Territories
- ○ Nova Scotia
- ○ Nunavut
- ○ Ontario
- ○ Prince Edward Island
- ○ Quebec
- ○ Saskatchewan
- ○ Yukon

2). You identify your gender as: *

Please choose **only one** of the following:

- ○ Female
- ○ Male
- ○ Other

3). How many years have you been in practice? *

Please choose **only one** of the following:

- ○ 1-3

- ○4-6
- ○7-10
- ○11-15
- ○16-20
- ○>20

4). Where is your primary place of practice? *

Please choose **only one** of the following:

- ○Tertiary Care Ward/OR
- ○Transfusion Medicine Laboratory
- ○Outpatient Clinic
- ○Research Department
- ○Other

5). Approximately how many units of red cell transfusions do you personally order for patients in an average month? (Please include units you authorize/gatekeep but not units ordered by delegates or residents independently) *

Please choose **only one** of the following:

- ○Less than one a month
- ○1-5 per month
- ○6-10 per month
- ○11-20 per month
- ○>21 per month

6). In general, what is your practice or recommendation for administering red blood cells for a stable, non-bleeding, anemic inpatient requiring transfusion? *

Please choose **only one** of the following:

- ○Transfuse one RBC unit, then reassess

- ○ Transfuse two RBC units, then reassess
- ○ Other

7). In general, what is your practice or recommendation for administering red blood cells for a stable, non-bleeding, anemic outpatient requiring transfusion? *

Please choose **only one** of the following:

- ○ Transfuse one RBC unit, then reassess
- ○ Transfuse two RBC units, then reassess
- ○ Other

After transfusion of red blood cells, what information do you use to reassess if a patient requires further transfusion? Are there specific criteria that you think about or look for when you reassess (such as a post Hb level, vitals, specific symptoms, volume status, etc)? Please list and describe in as much detail as possible.

Please write your answer here:

_____

8). Do any guidelines and/or evidence inform this practice? *

Please choose **only one** of the following:

- ○ Yes
- ○ No

Please indicate which one(s):

Please choose **all** that apply:

- ☐ "Choosing Wisely" recommendations
- ☐ Local guidelines
- ☐ Society Organizational Guidelines/Recommendations
- ☐ Studies demonstrating the benefit(s) of restrictive transfusion strategies
- ☐ Other:

Part 1 Complete!

Part 2: Clinical Scenario

You are managing a 65-year old man who presented to the emergency room with shortness of breath on exertion and was admitted to the medicine ward for treatment of pneumonia. His admission hemoglobin is 65 g/L (normal range: 135-175 g/L in men) with a MCV of 82 fL (normal range: 80-100 fL). You call his family physician and she notes that the patient is a new patient in her practice and his baseline hemoglobin is in the low 80s. The cause of this chronic anemia is currently being investigated. The patient otherwise has no significant past medical history.

He is somewhat dyspneic with a respiratory rate of 26 breaths per minute (normal: 12-20 breaths per minute) on 2 litres nasal prong (oxygen saturation at 95%) and feels tired. The patient has no signs or symptoms of bleeding. Physical exam demonstrates crackles on the right side consistent with consolidation in the right lung in a chest x-ray and the patient appears euvolemic. Laboratory work shows that the remainder of the CBC, electrolytes, creatinine, and coagulation screen are within normal limits.

9). Based on the information given thus far, would you transfuse red cells to this patient? *

Please choose **only one** of the following:

- ○ Yes
- ○ No, I would observe this patient

9a). You elected to observe the patient, what would prompt you to transfuse? *

Please choose **all** that apply:

- ☐ A change in patient vitals (such as tachycardia or hypotension)
- ☐ Subjective change in patient's status (such as the patient feeling more short of breath, having symptoms of anemia like chest pain or lightheadedness)
- ☐ Hemoglobin decreasing to <60 g/L
- ☐ Other:

9b). You elected to transfuse the patient, how many units would you transfuse? *

Please choose **only one** of the following:

- ○ One red cell unit
- ○ Two red cell units
- ○ Other

10). Following observation or the transfusion of red cell unit(s), what physical assessments and laboratory tests would you suggest be performed to decide if a unit should be transfused (or another unit if transfusion occurs)?

Physical Assessments *

Please write your answer here:

_____

Laboratory Tests *

Please write your answer here:

_____

11). When should a reassessment occur to decide whether a red cell unit (or another red cell unit if you chose to transfuse) should be transfused? *

Please choose **only one** of the following:

- ○ 1-2 hours after transfusion
- ○ 3-4 hours after transfusion
- ○ 5-6 hours after transfusion
- ○ 7-12 hours after transfusion
- ○ 13-18 hours after transfusion
- ○ >18 hours after transfusion
- ○ Other

12). Please provide a rationale for your answer to question 11. *

Please write your answer here:

_____

13). Presume this patient in the original stem was treated for pneumonia, became asymptomatic (no longer being dyspneic or feeling fatigued), and did not have surgery. His hemoglobin is 65 g/L (normal range: 135-175 g/L in men). The next family doctor's appointment can be made in approximately one week. The patient lives within a thirty minute drive to a tertiary care hospital and has a family

caregiver who could provide transportation during the day. Would you transfuse red cells to this patient before discharge? *

Please choose **only one** of the following:

- ○Yes
- ○No

13a). Instead of transfusing red cells to this patient before discharge I would: *

Please choose **only one** of the following:

- ○Inform the family physician and/or another clinic to monitor
- ○Other

13b). You elected to transfuse this patient, how many units would you transfuse? *

Please choose **only one** of the following:

- ○One red cell unit
- ○Two red cell units
- ○Other

14). How soon after discharge should the patient be reassessed for transfusion (assuming that access to an MD is not a limiting factor)? *

Please choose **only one** of the following:

- ○24 hours
- ○2-3 days
- ○4-7 days
- ○1-2 weeks
- ○Other

15). What physical exam and laboratory tests should be considered when reassessment of this patient occurs in the outpatient setting to decide whether another until should be transfused?

Physical Assessments:

Please write your answer here:

_____

Laboratory Tests

Please write your answer here:

_____

Presume this patient was readmitted for an abdominal perineal resection for rectal carcinoma. You see the patient on post-operative day 2 and his hemoglobin this morning is 75 g/L. The remainder of the CBC, electrolytes, creatinine, and coagulation screen are within normal limits. Physical examination shows no bleeding at the surgical site. There is some serosanguinous discharge on the wound dressing. The patient's blood pressure is 136/72 mmHg, heart rate is 88 beats per minute, respiratory rate is 18 breaths per minute (normal: 12-20 breaths per minute), and temperature is 37.1°C.

Upon reviewing previous CBCs done pre-operatively and post-operatively, the baseline hemoglobin was 102 g/L pre-operatively. Post-operatively day 0 and 1 hemoglobin values were 87 g/L and 81 g/L respectively.

16). Based on the information given thus far, would you transfuse red cells to this patient and with how many units?

Please choose **only one** of the following:

- ○ Yes
- ○ No

16a). You have chosen to observe the patient and not transfuse red cells at this time. What would prompt you to order a red cell transfusion?

Please choose **all** that apply:

- ☐ Change in patient vitals
- ☐ Subjective change in patient's status
- ☐ Hemoglobin decreasing to < 60 g/L
- ☐ Hemoglobin decreasing to < 65 g/L
- ☐ Hemoglobin decreasing to < 70 g/L

- ☐ Frank bleeding at the surgical site
- ☐ The patient will need to be brought back to the operating room
- ☐ Other:

16b). You elected to transfuse the patient, how many units would you transfuse?

Please choose **only one** of the following:

- ○ One red cell unit
- ○ Two red cell units
- ○ Other:

17). When should a reassessment occur to decide whether a red cell unit (or another red cell unit if you chose to transfuse) should be transfused?

Please choose **only one** of the following:

- ○ 1-2 hours after transfusion
- ○ 3-4 hours after transfusion
- ○ 5-6 hours after transfusion
- ○ 7-12 hours after transfusion
- ○ 13-18 hours after transfusion
- ○ >18 hours after transfusion
- ○ Other

18). Is the physical assessment and laboratory workup with reassessment to decide if another unit should be transfused different in this post-operative scenario? Please describe:

Please write your answer here:

_____

Part 2 Complete!

Optional Survey Feedback

We thank you again for participating in this survey.

Is there anything else about this study / survey you would like to let us know about?

Please write your answer here:

_____

Submit your survey.
Thank you for completing this survey.

Appendix 5-1. Type of data extractable from data sources and data extracted (in bold)

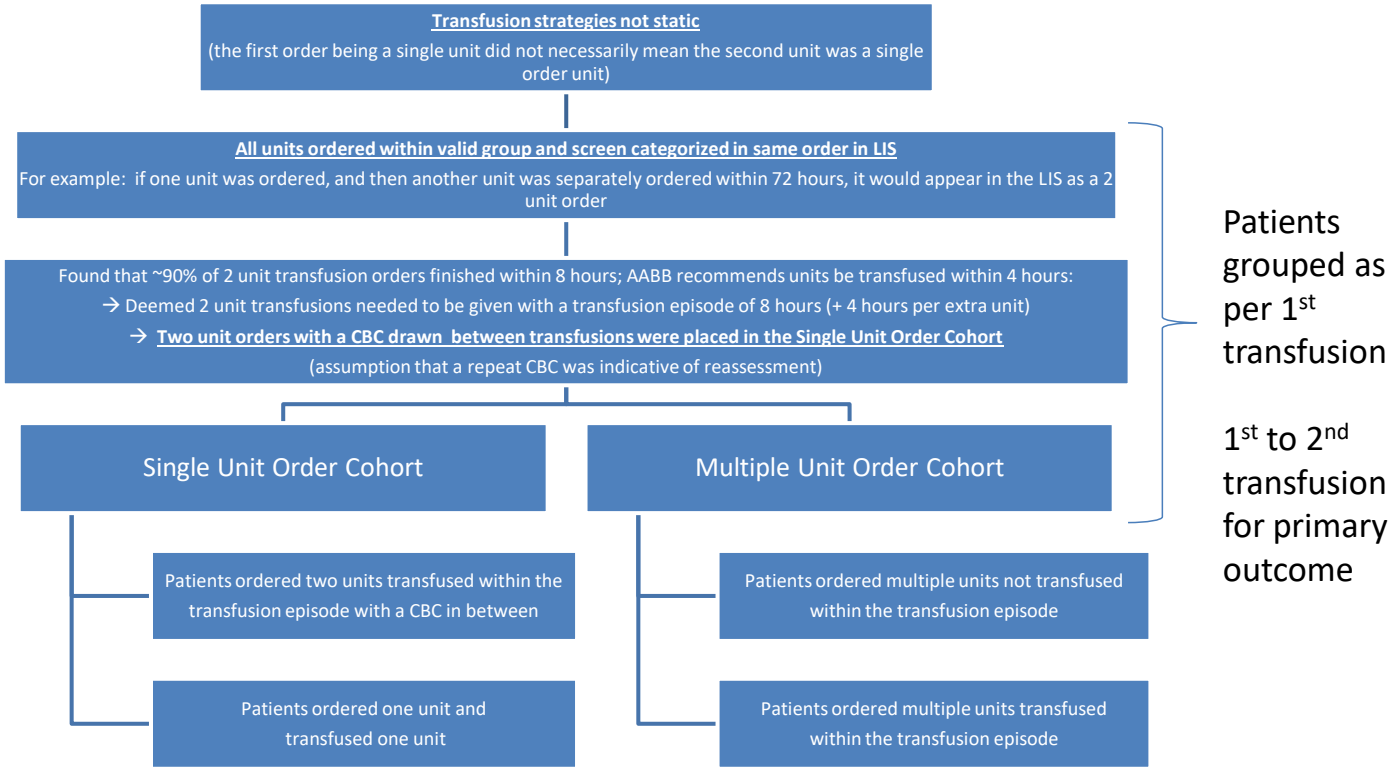
TRUST Database		**MASCOT Database**
Data Elements to be Extracted from the Laboratory Information System (LIS)	***Data Elements to be Extracted from the Medical Records Database***	
Inventory Site Location Product Name (received from CBS. Products to include: **Red cells, Plasma, Platelets, Cryoprecipitate,** Albumin, Factor Concentrates, IVIG, Synagis, and Immune serum globulins) Product Unit Number **Unique CBS identifier for product** Lot # Product CBS code **CBS ID (Codabar and ISBT)** ABO group of product Rh type of product (if applicable) Production collection date Product expiry date Receive Date and Time **Issue date/Time** Volume of Product issued **Transfusion date** **Product Status name (Transfused/Discarded/Expired etc.)** **Product dose transfused** **Location of transfusion** **Transfusion unit comments (transfusion reaction, unit returned etc.)** **Status change Date/ Time** Parent Pool Name Parent Pool code **Parent product Collection Date** **Product markers (i.e., irradiated; CMV neg., etc.)** **Ordering Physician** **Patient Facility** **Hospital ID Chart Number** **Account number** **Gender** **Age**	**Institution** **Hospital ID** **Chart Number** **Health Insurance Number (HIN) (encrypted)** **Postal code(first 3 digits)** **Gender** **Age** Newborn birth weight **Account number** **Date/Time of admission** **Admission Category** **Entry Code** **Discharge Date/Time** **Discharge disposition** **Length of hospital stay (total days)** **Acute LOS (total days)** **Trauma Score** **Complexity Level** **Complexity Age group** **Comorbidity** **Resource Intensive Weight (RIW)** **Diagnosis Code** **Diagnosis Type**	*Laboratory test information:* **Troponin Level (all dates associated with troponin level, value of troponin test, and whether the value is above the upper limit of normal** **Drug Administration Record including order start and stop date/time) for:** • **Anticoagulants** ○ **Warfarin/Coumadin** ○ **Dabigatran** ○ **Rivaraoxaban** ○ **Apixaban** ○ **Edoxaban** ○ **Unfractionated Heparin** ○ **Low Molecular Weight Heparins** ▪ **Dalteparin** ▪ **Enoxaparin** ▪ **Tinzaparin** ○ **Fondaparinux** • **EPO Agents** ○ **Aranesp/Darbepoetin alfa** ○ **Eprex/Epoetin alfa** • **Antiplatelet Agents** ○ **Clopidogrel/Plavix** ○ **Ticagrelor/Brilinta** ○ **Prasugrel/Effient**

Account number ABO group of patient Rh type of patient **Date of Admission and Time** **Date of discharge and Time** **Location identifier** **Patient Status** **Patient Special marker (i.e., irradiated; CMV neg., etc.)** **Patient's hemoglobin values, platelet counts,** **Coagulation results (PT, PTT, fibrinogen),** **Creatinine** **Test collection date/time** **Test receive date/time** **Test verification date/time** Presence of antibodies Date of antibody screened	**(Most responsible diagnosis and all the other diagnosis types)** **Doctor Code** **Doctor Type** **Doctor Service** **Procedure Date** **Procedure Code** **Procedure Doctor** **Procedure Doctor Service** Procedure OR Room Procedure Anaesthetist Anaesthetic Technique Unplanned return to OR **ICU unit number** **SCU admission date** **SCU discharge data** **Length of SCU stay (days and hours)** Blood Transfusion Data (Yes /No) **Red cells transfused** **Platelets transfused** **Plasma transfused** **Albumin transfused** **Other blood products transfused** Autologous Transfused	

Appendix 5-2. ICD-10 Codes Used to Define Comorbidites

Cancer:	All C codes; all codes starting with D0, D1, D2, D3, D4
Cardiac Disease:	All I codes
Hematological Malignancy:	D46 (myelodysplastic syndrome), D47.4 (MF), D47.7/D47.9 (other hematological neoplasms NOS), D76 (HLH), C81-C96 (excluding C77)
Chronic Renal Failure:	N18 and N19; N032, N033, N034, N035, N036, N037, N052, N053, N054, N055, N056, N057, N250, Z490, Z491, Z492, Z940, Z992

Appendix 5-3. Cohort Definitions Used In the Exploratory 2014 Analyses



Appendix 6-1. Charleston Comorbidity Index ICD-10 Codes (courtesy of collaborative work between ICES and the Kidney Clinical Research Unit in London, Ontario)

Label	Meaning	ICD-10 codes (starting with)	
AMI	Acute Myocardial Infarction	I21, I22, I252	1 point each
CHF	Congestive Heart Failure	I099, I255, I420, I425-I429, I43, I50, P290	
PVD	Peripheral Vascular Disease	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959	
CVD	Cerebrovascular Disease	G45, G46, H340, I60-I69	
Dementia	Dementia	F00-F03, F051, G30, G311	
COPD / Other Respiratory Disease	Chronic Obstructive Pulmonary Disease or other Respiratory diseases	I278, I279, J40-J47, J60-J67, J684, J701, J703	
Rheumatologic Disease	Rheumatic-like Diseases	M05, M06, M315, M32-M34, M351, M353, M360	
Digestive Ulcer	Ulcers of the Digestive System	K25-K28	
Mild Liver Disease	Liver Disease - Mild	B18, K700-K703, K709, K713-K715, K717, K73, K74, K760, K762-K764, K768, K769, Z944	
Diabetes	Diabetes - No Chronic Complications	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149	
Diabetes w/ Chronic Complications	Diabetes with Chronic Complications	E102-E105, E107, E112-E115, E117, E122-E125, E127, E132-E135, E137, E142-E145, E147	2 points each
Hemi or Paraplegia	Hemiplegia or Paraplegia	G041, G114, G801, G802, G81, G82, G830-G834, G839	
Renal Disease	Renal (Kidney) Disease	N032-N037, N052-N057, N18, N19, N250, Z490-Z492, Z940, Z992	
Primary Cancer	Cancer (No secondary found)	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97	

Moderate / Severe Liver Disease	Liver Disease - Moderate or Severe	I850, I859, I864, I982,K704, K711, K721, K729, K765, K766, K767	3 points
Metastatic Cancer	Cancer (Metastatic - secondary)	C77-C80	6 points each
HIV Infection	HIV / AIDS	B20-B22, B24	