Improving the Efficiency and Effectiveness of Chronic Blood Transfusions in the Hematology Clinic Using an Adaptive Algorithm Designed to Optimize Red Cell Use in Patients with Different Specific Transfusion Needs.

By

Joshua Medow, MD, MSc, FAANS, FACS, FNCS, FAHA, FCCM

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This dissertation is approved by the following members of the Final Oral Committee
Eneida Mendonca MD, PhD Associate Professor Department of Biostatistics and Medical Informatics
David DeMets PhD Professor Emeritus Department of Biostatistics and Medical Informatics
Robert Dempsey MD Professor and Chairman Department of Neurosurgery
David Page PhD Professor Department of Biostatistics and Medical Informatics
Christine Sorkness PharmD Professor of Pharmacy and Senior Associate Executive Director ICTR
Umberto Tachincardi MD Associate Dean and Professor of Biomedical Informatics
Elliot Williams MD, PhD Professor of Medicine, Hematology Section

Abstract

Background: Patients with myelodysplastic disorders who require chronic transfusions are often given packed red blood cells (PRBCs) based on a care plan that is copied over from previous visits. This has resulted in transfusions when the patient likely did not require one. A better approach would be to set a target hemoglobin level upon return to clinic. However, there is significant variability in response to PRBC transfusions due to disease progression and marrow suppressive chemotherapy. This can make both the dosing and the timing of transfusion difficult to predict, underscoring the need for an individualized model to guide PRBC transfusions. Based on this a computer algorithm for decision support that individualizes transfusion recommendations for myelodysplastic patients.

Methods: The Digital Intern (iVMD) algorithm for transfusion prediction was implemented to predict the response to the transfusion being ordered. The calculator pulls information from the electronic medical record (EMR) (Epic Systems) to calculate transfusion half-lives for up to 6 prior transfusions. These half-lives are used predict the response to transfusion given the patients current hemoglobin and weight. These options are then presented to the ordering provider for the transfusion dose, in PRBC units, and the follow-up time over which the patient is expected to stay at or above the selected target Hgb. We performed a prospective trial over a 12-month period evaluating the proximity of the model to the return hemoglobin level and return date with the primary outcome being the percentage of patients that return with a hemoglobin at or above the selected target (within 0.5g/dL) in an intent to treat fashion. We also compared the number

of 1 vs multi-unit PRBC transfusions and total number of PRBC units transfused using the predictive algorithm vs those not using the predictive algorithm during the same time period.

Results: Over 12 months, PRBC transfusions were ordered using the predictive algorithm of which 117 had complete data for analysis. A target hemoglobin of 8 was selected in 80% of cases. PRBC transfusions were 45% for single unit and 55% were two units which represents a significant increase in single unit transfusions from non-algorithm patients treated at the same time meaning that multi-unit PRBC transfusions were significantly reduced for the short-term follow-up that these patients often receive. The total number of units transfused also was reduced compared to historical and simultaneous controls. The mean predicted time to return after transfusion was 10.5 days and 75% of patients had follow-up within 3 days of the predictive algorithm selected return time. Overall 90.6% of patients returned with a hemoglobin at or above target.

Conclusion: The predictive algorithm reduces the number of PRBC transfusions and the number of multi-unit transfusions prospectively. Simultaneously, over 90% of patients remained at or above the target hemoglobin selected by the ordering provider. Further studies to expand the role of this and other adaptive algorithm technologies should be done because they have the potential to reduce costs and improve outcomes. If applied correctly, artificial intelligence may significantly impact the future of quality medical care provided worldwide.

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Committee Chair:
Eneida Mendonca MD, PhD Associate Professor Department of Biostatistics and Medical Informatics

Committee Members:
David DeMets PhD Professor Emeritus Department of Biostatistics and Medical Informatics
Robert Dempsey MD Professor and Manucher Javid Chairman Department of Neurosurgery
David Page PhD Professor Department of Biostatistics and Medical Informatics
Christine Sorkness PharmD Professor of Pharmacy, Senior Associate Executive Director ICTR
Umberto Tachincardi MD Associate Dean and Professor of Biomedical Informatics
Elliot Williams MD, PhD Professor of Medicine, Hematology Section

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Dedication

To my wife, who may not have thought that this endeavor was such a great idea and yet bit her lip and let me be me…thank you today and always.

To my children, thank you for trying to understand why daddy isn't home as much as he should be. I'll try harder to be a better father as you always have been and always will be my top priority.

To my parents, when a child is asked who his heroes are, few would answer "My parents." The world should only know that *my parents* are legends.

To my sister Lana whose dedication to the human psyche is both noble and astonishing.

To the many who couldn't be here today in a way we can understand but yet are always with me… Bubbie and Papa, Grandma and Grandpa, Sara and Irving, Selma and Harry, Lil and Sammy, Macy, Jack Lloyd, and Gino: You'll forever be in my heart, on my mind, in my dreams, and I'm sure…perched on my shoulders reminding me to do the right thing.

My love for you all is eternal.

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Chapter 1: Statement of Purpose and Introduction

1.1 Statement of Purpose

Packed Red Blood Cells (PRBCs) are a living tissue that are fractionated out of whole blood donated from living humans. There are no synthesized red cells for transfusion and transfusion recipients are at risk of developing reactions from blood products and from diseases that are not tested for because they are yet unknown. Since PRBCs are a finite resource, managing them appropriately helps ensure that there will be blood available for patients when they need it and that the cost of the product does not become prohibitively expensive because of high demand. Removing the inefficiency from the blood ordering process can help reduce the number of needless transfusions saving patients from complications and the health system from exorbitant costs.

1.2 Introduction

Patients with anemia may display similar clinical findings regardless of cause when it comes to fatigue and other indicators of quality of life. Albeit true that the primary disease process responsible for the anemia will have different presenting symptomatology and life expectancy, the pathophysiology and need for transfusions presents itself as an engineering problem that may be best served by an approach that involves adaptive computer algorithms that are tailored to the individual patient's needs. For example, the type and degree of anemia will determine the need for transfusions at all. The need for a particular hemoglobin level will likely be determined by the patient's other comorbid conditions and their quality of life as a function of their hemoglobin content. This introduction will attempt to identify the physiology and

management issues in patients with anemia and then will specifically address a subset of chronically anemic patients requiring frequent transfusions.

Chapter 2: Background

An understanding of red cell development, the function of hemoglobin, and the physiology of gas exchange is important in defining the need for PRBC transfusions. The literature supporting PRBC transfusions including outcomes and costs to the system can help better define goals and targets for transfusion. This chapter will focus extensively on the many facets of the literature regarding hemoglobin and PRBC transfusions and their particular impact on patients with myelodysplastic disorder.

2.1 Anemia Physiology and Management

2.1.1 Red Blood Cell Physiology and Oxygen Transport

Red Blood Cell (RBCs) constitute the principal means by which oxygen transport occurs. Under normal circumstances, oxygen is carried through circulating blood primarily bound to hemoglobin, with a negligible amount, approximately 2%, dissolved in plasma; in the severely anemic patient breathing supplemental O_2; however, physically dissolved O_2 comprises as much as 20% of blood oxygen content. Yet decreases in hemoglobin do not always result in changes in oxygen delivery (DO_2) and oxygen consumption (VO_2); physiological compensatory mechanisms exist to counter mild to moderate changes in hemoglobin. Under normal conditions with adequate coronary artery reserve, cardiac output increases as arterial oxygen content (CaO_2) decreases such that DO_2 is maintained; this mechanism is dependent on coronary vascular dilation allowing for increased coronary blood flow. Oxygen consumption (VO_2) is, in turn, further buffered by the ability of peripheral tissues to alter oxygen extraction (EO_2) in hypoxemic states by altering microvascular blood flow, resulting in lower venous oxygen content (CvO_2) and stable tissue PaO_2.[1]

As tissues vary in their percentage of oxygen extracted from circulating blood at baseline, the extent of their ability to increase EO_2 under anemic conditions is mirrored. The heart, with the largest baseline EO_2 of 60%, is least able to compensate for hypoxemia, in comparison to tissues with lower baseline extraction rates such as the brain (30%), kidney (< 10%) and skin (< 10%). In addition to the greater workload of providing increased cardiac output to peripheral tissues under anemic conditions, increased coronary blood flow is necessary to maintain stable cardiac tissue PaO_2. Accordingly, cardiac function dictates the limit of anemia clinically tolerated in any given patient.

In the search for clinically relevant thresholds for RBC transfusion, the term "critical DO_2" has been defined as the level of DO_2 below which VO_2 cannot be maintained and begins to decrease. At the DO_2 critical level, signs of oxygen impairment become apparent, both globally, as indicated by increased lactic acid production, as well as regionally, by tissue-specific markers of hypoxia such as ST-segment changes on electrocardiogram and P300 latency on electroencephalogram. As DO_2 approaches critical, so also does the compensatory increase in O_2 extraction approach its maximum limit critical EO_2. Critical EO_2, which varies between tissues, influences critical DO_2; tissues with a lower critical EO_2 have a higher critical DO_2. In addition, critical DO_2 is also influenced by VO_2, with critical DO_2 needing to be higher to support metabolism when VO_2 increases.[1]

2.1.2 Experimental Studies – Finding the Limits of Compensation with Anemia

Data from studies in experimental animal models and in humans have shed light on the limits of physiological compensation in anemia. In the 1970s, experimental models of anemic hemodilution found a critical DO_2 of 10ml O_2/kg/min in anaesthetized dogs, corresponding to a

critical hematocrit of 10%.[2, 3] Subsequent canine studies under similar conditions placed the critical DO_2 lower,[4] and even lower in anaesthetized pigs.[5] Critical hemoglobin in anaesthetized pigs subject to acute isovolemic hemodilution demonstrated that VO_2 became delivery-dependent.[6, 7] Although the absolute values obtained from these experimental studies cannot be extrapolated to humans, critical hemoglobin across species appears to be remarkably constant, at approximately 20–25% of normal resting hemoglobin.[1]

In humans, the first report of such measures was documented in an 84-year-old Jehovah's Witness who refused transfusion and died postoperatively at a hemoglobin concentration of 1.6 g/dl. The oxyhemoglobin dissociation curve, after correction for changes in pH and PCO_2, shifted rightward at a hematocrit of 8%, indicating compensatory decrease in hemoglobin oxygen affinity as a mechanism of facilitating oxygen offloading to peripheral tissues during extreme anemia.[8] Given that the critical DO_2 level varies with different baseline metabolic requirements, subsequent studies undertook measurements during conscious states in which VO_2 is higher. Weiskopf et al.[9] demonstrated that healthy resting humans are able to tolerate acute isovolemic hemodilution down to a hemoglobin level of 5 g/dl, although mild reversible reduction in mental acuity is seen at this level.[10-12] In 32 conscious individuals at rest, no significant change in VO_2 or plasma lactate concentration were found despite decreases in oxygen transport (DO_2) during progressive isovolemic hemodilution with 5% albumin and/or autologous plasma down to a hemoglobin level of 5 g/dl. Two subjects developed significant electrocardiographic ST changes, although these were noted in younger volunteers and were attributed to body position or activity and increased heart rate, respectively, and both resolved without sequelae.[9] In the presence of coronary artery disease, however, the hemoglobin threshold increases. Evidence of cardiac dysfunction in animal models has been reported at a

level of 7 g/dl in the presence of 75% coronary artery stenosis.[13] Other studies in dogs with critical stenosis of the left anterior descending artery show the lowest median hemoglobin tolerated without myocardial contractile dysfunction was 7.5 g/dl. This effect was reversible and corrected by PRBC transfusion which increased arterial hemoglobin by 1.9 g/dl and was able to restore regional oxygen consumption, oxygen extraction, as well as myocardial contractile function.[14]

2.1.3 Anemia and Quality of Life

Anemia is a common occurrence in patients with cancer.[15] Anemia can have a considerable impact on quality of life (QOL), particularly with respect to fatigue;[16] however, fatigue is often under-recognized and under-treated.[17] Patients that require chronic transfusions often have problems with synthesis. The diseases most effecting synthesis are acute leukemias and myelodysplastic disorders. In principle, red cell transfusions for patients with chronic anemia should be given at intervals to maintain the hemoglobin just above the lowest concentration that is not associated with symptoms of anemia, but it may be difficult to determine what this concentration is for individual patients. Many patients with chronic anemia are apparently asymptomatic with a hemoglobin concentration > 8 g/dl but, when patients' symptoms have been formally evaluated using functional assessment scales, those with hemoglobin concentrations > 12 g/dl reported less fatigue and better quality of life.[16] This hemoglobin concentration however may not be safely or economically attainable by PRBC transfusion. The use of PRBC transfusion as a treatment for anemia declined dramatically after the approval of the first erythropoiesis-stimulating agent (ESA) in 1989.[18, 19] However, the use of ESAs is predicated on the ability of the bone marrow to successfully

produce reticulocytes.

2.1.4 Transfusion Independence in Patients with Myelodysplastic Syndromes

The myelodysplastic syndromes (MDS) are a group of clonal hematopoietic disorders characterized by dysplastic cellular elements and chronic peripheral cytopenias.[20, 21] Anemia is the most common type of cytopenia; however, neutropenia and/or thrombocytopenia also may be present. Approximately 39% of patients with MDS have anemia alone, 27% have a decrease in erythrocytes and in 1 other cell type, and 15% have pancytopenia.[22, 23] The MDS are clinically heterogeneous and may be mild and stable for many years or may progress rapidly to acute myeloid leukemia (AML).[20] Therefore, the median survival of patients with MDS ranges widely, from 6 years in lower risk patients to only 4 months in higher risk patients.[24]

The outcomes of patients with MDS typically correspond to disease characteristics, such as the percentage of bone marrow myeloblasts at diagnosis, the number and severity of hematopoietic lineages affected by cytopenia, and the presence of chromosomal abnormalities.[22] However, the chronicity of cytopenias associated with MDS causes morbidity and mortality even in the absence of disease progression to AML.[25] Greater than 80% of patients with MDS have anemia at the beginning or during the course of their disease and often require PRBC transfusion support.[26] Because of the chronicity of MDS-associated anemia, these patients may develop long-term dependence on PRBC transfusions and require transfusion management measures, such as iron-chelation therapy.[27] Furthermore, transfusion dependence in patients with MDS significantly affects their survival and health-related quality of life (HRQOL).[28-30]

Supportive care, especially RBC transfusion for the management of anemia, is considered the standard of care for patients with low-risk MDS according to the International Prognostic

Scoring System (IPSS).[24, 31] However, most patients with MDS, regardless of their IPSS risk category, will rely on RBC transfusions at some point during the course of their disease.[20, 23] With disease progression, some patients require more frequent transfusions.[29, 32] Frequent PRBC transfusions may cause significant clinical complications, such as transfusion reactions, infection, and iron overload.[29, 30, 33-35] In a study of 50 patients with MDS, approximately 80% of transfusions had associated complications.[29] Greater than 50% of patients developed transfusion reactions or required the use of pre-medications, and approximately 33% of patients developed antibodies to RBCs, platelets, or granulocytes.[29] A substantial number of patients either required specially selected antigen-negative PRBCs (27%) because of the presence of antibodies to blood cells or required leukocyte reduction of PRBCs and platelets by filtration (40%).

Iron accumulation is an inevitable and serious complication of long-term RBC transfusion therapy for anemia that results in progressive dysfunction of several organ systems, in particular, the heart, liver, and endocrine system.[30, 33] Iron-chelation therapy using deferoxamine is indicated for most patients who have received 20 to 30 transfusions, for patients who have reached a ferritin level of approximately 1500g/L, or for patients with transfusion-dependent, low-risk MDS who have a survival prognosis of 1 year.[30, 36] However, difficulties in the administration of deferoxamine (subcutaneous infusion) result in compliance issues. Oral iron-chelating therapies are in development that may improve iron-overload management in PRBC transfusion-dependent patients.[37]

In the general population, the degree of dependence on PRBC transfusions may have a negative impact on patient outcomes. An analysis of survival rates of patients who received RBC transfusions was assessed in a cohort of 6779 patients in the U.S.[38] The overall annual mortality rate in that analysis was 31% in the first year after transfusion, 14% in the second year, and 10%

in each subsequent year through the fifth year after transfusion. Furthermore, the results indicated that the mortality rate increased with age. Compared with patients younger than age 41 years, 1-year mortality rate after transfusion was more than double for patients ages 41 years to 65 years and more than triple for patients age >65 years (10.5%, 27.1%, and 38.2%, respectively).[38] Similarly, results from a recent analysis of transfusion needs in the U.K. indicated that the median age at transfusion was 67 years, and shorter patient survival was associated with increased patient age, increased number of PRBC units transfused, transfusion of plasma or platelets, and nonsurgical indications for transfusions.[39] These data may indicate that transfusion dependence poses a significant age-related risk to patients with MDS, who are often age >65 years of age. Alternatively, the findings may indicate that patients who require more blood transfusions have more serious disease.

PRBC transfusion dependence associated with MDS represents an economic burden to health care resources. However, dependence on PRBC transfusions is considered inconvenient by most patients because of time required for travel, waiting, and transfusion, and it also has economic consequences for patients.[34] The rising cost of blood collection, testing, and blood product transfusion is a result primarily of added safety measures, increased use of fractionated products, donor deferral, increased donor screening, and the use of leukoreduction.[40, 41] In the U.S., the median unit cost of a blood transfusion per patient has been estimated to be between $500 and $550.[29, 40] In a French study that evaluated the health, economic, and quality-of-life effects of recombinant human erythropoietin and recombinant human granulocyte-colony stimulating factor (G-CSF) for the treatment of MDS, 60 patients were randomized to receive either cytokine treatment or supportive care only.[42] The mean costs per subject were €26,723 (€13,109) in the treatment arm and €8746 in the supportive care arm (€1 1 U.S. = $1.20). This

difference was attributed mainly to the cost of drugs. However, the mean transfusion costs were much lower for responders who completed the study than for those who received supportive care only (€2085 vs. €7579, respectively).[42]

The cost of PRBC transfusions has continued to increase significantly over time. For example, in a systematic review of studies evaluating the cost of PRBC transfusion, the cost of a transfusion increased 61% between 2000 and 2001 in the U.S.22 In a 2004 survey of 4 centers, 38 patients with MDS received a median of 42 RBC transfusions over 24 months.[32] The average cost per RRBC transfusion was €436 ($526), and the median 24-month cost per patient was €11,118 ($13,395). These costs included 2 filtered PRBC units, blood collection, administrative costs, and staff time but did not include the cost of iron-chelation therapy or indirect costs (e.g., time spent at the transfusion facility, travel time, and waiting time for the patient and a caregiver/family member). Patients with MDS exhibit decrements in their HRQOL.[30, 43] In a study of 53 patients with MDS, HRQOL scores were significantly lower compared with age-matched and gender-matched, healthy individuals when HRQOL was measured with the European Organization for Research and Treatment of Cancer Assessment tool. In that study, patients with MDS had significant impairment of physical, social, and emotional functioning as well as clinically significant increases in fatigue and dyspnea compared with healthy individuals. The quality-of-life measures fatigue and dyspnea were improved with treatment of anemia. Increasing hemoglobin has resulted in an improved, HRQOL for patients with MDS or those with anemia secondary to other cancers.[43, 44]

2.1.5 Transfusion Safety

To combat the complications of anemia, PRBC transfusions are given particularly when other means to drive red cell production would not be effective. Blood transfusions however are not without risk. Immediate risks can be divided into infectious and immunologic categories. The most common infectious agent transmitted is cytomegalovirus,[45] which does not pose a significant problem for immunocompetent patients but many chronically transfused patients are immunocompromised are consequently at risk unless CMV free blood is used. Post-transfusion hepatitis remains the most frequent clinically significant infection. The recently developed ability to screen donors for antibody to hepatitis C, [46] however, can reduce the estimated risk from 1:100 to the range of 1:300 to 1:900. Despite screening for blood contaminated with hepatitis B and HIV, the risk for these infections remains small but present.[47] The immunologic risks associated with blood transfusions range from mild, febrile, nonhemolytic reactions to fatal hemolytic reactions often related to human error.[48] In immunocompromised patients transfusion-associated graft-versus-host disease can present itself, and can even be seen, albeit rarely, in immunocompetent patients who have received blood from related donors.[49] Other PRBC transfusion related complications that could be reasonably attributed to a transfusion episode (based on medical literature and expert clinical opinion) included febrile non-hemolytic transfusion reaction, air embolism, or phlebitis, acute hemolytic transfusion reaction, allergic reaction, Transfusion Related Acute Lung Injury (TRALI), Transfusion Associated Circulatory Overload (TACO), delayed hemolytic transfusion reaction, congestive heart failure (CHF), hyperkalemia, and iron overload.

2.1.6 PRBC Use and Practice (Current State of the Art)

Blood safety is not the only problem with transfusions. Concerns about blood inventory also support the case for the judicious use of red blood cell transfusions. Although blood transfusions in humans were first reported early in the nineteenth century, the procedure became routine after blood banks were established a century later.[50] Between 11 - 15 million units of PRBCs are transfused in this country annually[51] and 85,000,000 are transfused annually worldwide.[52] The growth of red blood cell use, however, has been variable. Although use doubled during the decade of 1970 to 1980, it leveled off in the mid-1980s because of the fear of HIV transmission.[53] A serious shortage of PRBCs that might have resulted from declining collection rates has been countered by declining transfusion rates.[51] The dual concerns about blood safety and inventory necessitate cautious transfusion practice. The national efforts toward improving physician transfusion practice by the National Heart, Lung, and Blood Institute,[54] the National Institutes of Health,[55-57] and the Joint Commission on Accreditation of Health Care Organizations[58] make it timely to develop automated strategies for PRBC transfusion.

Recent guidelines for PRBC transfusion practice have incorporated transfusion thresholds into appropriateness criteria. A threshold of 80 g/L (8 g/dL) was suggested by the Transfusion Practices Committee of the American Association of Blood Banks[59] and a threshold of 70 g/L (7 g/dL) was suggested by the NIH Consensus Conference on Perioperative Blood Transfusion[55] and the AABB[52]. The 5% decline in red blood cell transfusions observed from 1986 to 1988 points to the growing acceptance of these lower transfusion thresholds; however, results would likely be better if there existed better data to help drive practice.

A more recent trend has been to limit blood transfusions to one unit at a time with a follow-up hemoglobin or hematocrit after each transfusion. This change in practice has likely

resulted in an additional reduction in red cell transfusions; however, the accuracy of this relatively new transfusion practice doesn't individualize transfusions to the patient's needs, is inefficient because needed blood may be delayed, and wasteful because more labs are drawn when not always necessary which costs money and wastes a small portion of the patient's blood volume with each draw. While this attempts to reduce variability in the transfusion of PRBCs, current practices continue to vary considerably between providers, suggesting that unnecessary transfusions remain a problem.

2.1.7 AABB Guideline for PRBC Transfusions (not Leukemia / Myelodysplastic Specific)

Physicians most commonly use hemoglobin or hematocrit levels to decide when to transfuse PRBCs.[60] However, more recent guidelines[61, 62] emphasize that transfusion should be given for symptoms of anemia and should not be based on hemoglobin concentration alone. Optimal use should involve administering enough PRBCs to maximize clinical outcomes while avoiding unnecessary transfusions that increase costs and expose patients to potential infectious or noninfectious risks. Large observational studies have shown important differences in management of critical care,[63-65] orthopedic surgery,[64, 66] and cardiovascular surgery[64, 67] patients. On the basis of data from all of the available randomized trials, the AABB panel found little evidence to support a liberal transfusion strategy.[52] The restrictive transfusion thresholds used in the 3 largest randomized, controlled trials were 7 g/dL[68, 69] and 8 g/dL.[59] Given these data, the AABB panel recommended (strong recommendation) a restrictive transfusion strategy that uses these thresholds in most patient populations (hemodynamically stable critical care, surgical, and medical). For patients with cardiovascular disease, the panel also suggested (weak recommendation) a restrictive transfusion strategy because a large clinical trial (FOCUS) showed

a statistically nonsignificant increase in myocardial infarction in the restrictive transfusion group but not an increase in mortality. If a restrictive transfusion strategy were widely implemented and replaced a liberal strategy, PRBC transfusions would decrease by approximately 40% (RR, 0.61 [CI, 0.52 to 0.72]) on average. This would reduce blood use and the risks for infectious and noninfectious complications of transfusion.

The AABB goes a step further to recommended avoiding transfusion based only on a hemoglobin trigger. Instead, the decision should be guided by such individual factors as bleeding, cardiopulmonary status, and intravascular volume.[52] However, they fail to identify those metrics which should be used to drive appropriate transfusion practice. In contrast, the European Society of Cardiology has recommended withholding transfusion in patients with acute coronary syndrome unless the hemoglobin concentration decreases to below 8 g/dL.[70] Despite the recommendation to avoid transfusion based on a trigger hemoglobin level, it should be noted that the choice of hemoglobin level for a particular individual based on symptomatology and comorbid conditions may be useful. In other words, a trigger hemoglobin for all patients regardless of disease related physiology is likely ill-conceived (except for certain disease processes particularly related to a heart condition). The identification of a specific target hemoglobin that is customized for the individual anemic patient however, may in fact be a good idea. That target hemoglobin level might be automatically devised on patient symptom history or chosen by provider experience with the patient. With a target chosen, the next step would be to identify how to best achieve the desired target upon return to clinic.

2.1.8 Guidelines for the Management of MDS related Transfusions

The myelodysplastic syndromes (MDS) represent a heterogeneous group of hematopoietic disorders affecting predominantly older individuals (median age 69 years). The overall disease incidence is about 4 per 100,000 population but this rises to >30 per 100,000 in the over 70-year age group. At presentation, up to 80% of cases of MDS will have a hemoglobin that is <10 g/dl.[71] Anemia in MDS is usually due to ineffective erythropoiesis but other factors that may accentuate anemia, e.g. nutritional deficiencies, hemorrhage, hemolysis and infection, should be considered and treated appropriately. Chronic anemia is seldom life threatening but can lead to significant morbidity and reduction in quality of life (QOLY). Supportive care with blood product transfusions is the primary management strategy for the majority of patients with MDS. Approximately 80% of MDS patients are anemic at the time of presentation and more than 40% require regular RBC transfusions at some stage of disease, while platelet transfusions are less often required. Studies in cancer patients have demonstrated a positive correlation between increases in the hemoglobin level (with recombinant Erythropoietin therapy) and improvements in QOLY.[72, 73] Recommendations for iron chelation treatment in myelodysplasia are based on limited data (evidence grade B, level III). Iron chelation should be considered once a patient has received 5 g iron (approximately 25 units of red cells) but only in patients for whom long-term transfusion therapy is likely, such as those with pure sideroblastic anemia. The transfusion burden to MDS patients and to society, in terms of quality of life and cost, is much greater than generally appreciated. The cause of anemia should be established, and treatment with red cell transfusions should not be given where effective alternatives exist, e.g. treatment of iron deficiency, megaloblastic anemia and autoimmune hemolytic anemia, unless the anemia is life threatening.

2.1.9 Strategies for Reducing Transfusion Dependence in MDS

Treatment with recombinant human erythropoietin decreases transfusion requirements in some patients with MDS.[42, 74, 75] Significant factors that were predictive of a response were baseline endogenous s-Epo levels <100 U/L, absent or no transfusion needs, no excess blasts, and hypoplastic bone marrow. Immunosuppressive agents have been used previously for treating aplastic anemia and subsequently were investigated for efficacy in MDS. In a study of 61 transfusion-dependent patients who received with antithymocyte globulin (ATG), 34% of patients became transfusion-independent.[76] Transfusion dependence was defined as receiving >3 separate transfusions of >=2 units of RBCs at intervals of 2 to 4 weeks to maintain hemoglobin levels.

Differentiation agents.

Valproic acid is a short-chain fatty acid that affects differentiation and inhibits histone deacetylase to facilitate the re-expression of suppressed genes. In a study that evaluated valproic acid in patients with MDS or AML secondary to MDS, it was observed that 8 of 18 patients (44%) achieved hematologic improvement according to IWG response criteria.[77]

Immunomodulatory drugs.

Thalidomide. The use of thalidomide for the treatment of patients with MDS has resulted in transfusion independence, even in patients who had long-term, transfusion-dependent anemia.[78]

Lenalidomide.

Lenalidomide treatment has significantly reduced dependence on PRBC transfusions and restored normal cytogenetics in patients with MDS, particularly those with a chromosome 5q.[79-83]

2.1.10 Blood Transfusion Economics

Most of the available information related to transfusion economics is based on either patient charges or blood center costs for the units procured. Neither approach addresses the hospital's total transfusion costs which include supplies, nursing time, post transfusion labs, complications etc. As the hospital transfusion service becomes increasingly visible to hospital administrators who are seeking cost containment, the completeness of a fully allocated hospital transfusion program become increasingly important.

Screening and monitoring costs vary minimally between patients with cancer or blood disease; however, there is significant variation in blood acquisition and administration payments. Patients with cancer or blood disease had the highest mean payment (mean, $737; SD, $1,502), Blood acquisition costs in the other study were only 21% to 32% ($154 to $248 in 2008 dollars) of the total PRBC transfusion-related costs. Acquisition and administration payments accounted for 50% to70% of total payments, but could not be differentiated by acquisition and administration payments with certainty in the claims data. Patient testing and administration and monitoring of RBC transfusions and pre-transfusion processes were 24% to 36% of total costs. Managing acute transfusion reactions and vigilance using labs etc. contributed to 0% to 2% of costs.[84] Long-term management of acute complications such as medication costs and additional

outpatient management were not included in the analysis, all of which may result in underestimation of the overall economic burden of PRBC transfusions.

2.2 Clinical Informatics and Intelligent Systems

It's commonplace for computers to do the "grunt work" that we all used to have to do by hand. The tabulations and concatenations that were always considered mundane are now making life easier for workers and simultaneously helping to reduce the number of errors introduced into data sets making analysis more accurate and trustworthy. As computer systems have evolved, they have been able to do things that are far more advanced including advising users about decisions that can improve outcomes. This field of computerized decision support is gaining significant traction in recent years, particularly in medicine, and is founded on the basis of artificial intelligence.

2.2.1 Basic Definitions of Intelligent Systems

Artificial Intelligence is defined as "the theory and development of computer systems able to perform tasks that normally require human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages." The concept was developed by Alan Turing in 1950. Further work came out of a 1956 workshop at Dartmouth sponsored by John McCarthy. In the proposal for that workshop, he coined the phrase a "Study of Artificial Intelligence." There are many other definitions for AI however as the field of study is ever changing and expanding.

Machine Learning is a subset of artificial intelligence and is defined as "the study of algorithms and mathematical models that computer systems use to progressively improve their

performance on a specific task." With that definition however, a computer algorithm with predetermined weights, set by a priori knowledge, could be considered to have learned. Thus, a more recent definition has specifically addressed machine learning as a field of artificial intelligence that uses statistical techniques to give computer systems the ability to "learn" from data, without being explicitly programmed on how to interpret that data.

2.2.2 The Infancy of Artificial Intelligence

In 1950 English mathematician Alan Turing wrote a landmark paper titled "Computing Machinery and Intelligence" that asked the question: "Can machines think?" The **Turing test** is a test of a machine's ability to exhibit behavior indistinguishable from that of a human. Turing proposed that a human evaluator would judge between a human and a machine designed to generate human-like responses. The evaluator would be aware that one of the two participants is a machine will all three participants separated from each another. The questions and answers would be limited to text entered via a keyboard. The test results do not depend on the machine's ability to give correct answers to questions, only how closely the computer's answers resemble those of a human. The machine has passed the test if the evaluator cannot reliably tell the machine from the human. Passing the Turing Test does not truly show that the machine was thinking. It only shows the similarity in the responses. The responses can be further subcategorized into 2 groups. Weak equivalence shows the same result but with a different method at arriving at the result of a question. Strong equivalence, however, not only shares the same result but also the same process to achieve that result.

2.2.3 Adaptive Algorithms and Artificial Intelligence

Often times adaptive algorithms are synonymous with machine learning. However, not all adaptive algorithms need to have be learned by a machine analyzing data. If an algorithm takes into consideration specific parameters and one or more responses to at least one of those parameters is used to vary the output of the algorithm, the algorithm can be considered adaptive. As an example, if an algorithm considers prior responses to blood transfusions of multiple patients and predicts a transfusion amount will last for a presumed period of time for an individual patient, its adaptability may very limited. However, if the algorithm uses patient specific prior responses and only those patient's responses are used to predict a response to a transfusion, the algorithm becomes more adaptive. In this manner the algorithm does not give an overall result for all patients, it gives a result that is tailored for the individual patient. This has considerably more power to deliver on the idea of precision medicine.

If an algorithm is designed by a human rather than a machine, it is not truly considered machine learning. It is still artificial intelligence because there is intelligence built in to the system that can be communicated out of the system. Had the mathematical approach with its weights and general shape been chosen and optimized by a machine, then machine learning can be said to have been employed in the process.

For this dissertation, the PRBC transfusion algorithm is adaptive and yields patient specific results but it does not truly involve machine learning. The specific lessons learned from clinical application of this algorithm were that a non-linear formula with weights that are optimized towards more recent PRBC transfusion epochs can be highly accurate. It would have been reasonable to use a machine learning technique such as a support vector machine to build an optimized algorithm to do the same job with the knowledge that the data to support the decisions would need to be patient specific.

Chapter 3: Innovation

A predictive algorithm was designed for the purpose of individualizing PRBC transfusions for patients with chronic transfusion needs. It is predicated on algorithms developed for different transfusion situations and their application to all blood product components. iVMD owns much of the intellectual property in this realm with some of the intellectual property under patent review and assigned to Wisconsin Alumni Research Foundation (WARF).

3.1 Overview

The adaptive algorithm was designed using a process of first order kinetics whereby a decrease in the amount of product is described in a non-linear fashion. In this instance we calculate out a half-life in days from each prior transfusion response where both a pre-transfusion and post-transfusion hemoglobin or hematocrit are obtained. The drift in hemoglobin (hematocrit) is then accounted for by changes in vascular volume as calculated by change in weight and also for any bleeding that can be accounted for. The resultant half-life for each event is then calculated with the most recent half-life accounting for a greater portion of the average and the others accounting for the other 50%. The final average half-life is clipped at 120 days which is the duration of a normal circulating red cell in a normal human. If the half-life is longer than that, the patient is likely able to synthesize what they need unless there is a hemorrhage, blast crisis, or other marked and otherwise unpredictable event. In circumstances where the patient is on marrow suppressive chemotherapy, the assumption that is made is that they do not synthesize red cells at all. The other assumption is that the patient does not destroy red cells at a more accelerated rate than the average human. This separate calculator does not utilize prior transfusion information in completing the calculation but instead uses only the patient's weight

to calculate out a basic volume of distribution and then figures the dose of PRBCs needed to achieve the target hemoglobin at a particular point in time. A variation on the approach mentioned is to calculate the patient's personal red cell half-life and the standardized red cell half-life and choose the shorter of the two is in process but not studied for the purposes of this project.

3.2 Implementation and Derivation

To operationalize this patient specific, target driven, automated approach to transfusion, a weight in Kg is identified at the time of a transfusion and again upon follow-up hemoglobin check. If only a hematocrit is available as either a lab check or as a target it is divided by 3 to yield an approximated hemoglobin to calculate from. If the history for this information is not available, a current weight is used alone and the blood volume correction sub-algorithm is not executed. If no weight is entered, obtaining a weight is suggested otherwise a standardized weight of 80Kg is inserted at the discretion of the ordering provider and is used instead of the 70Kg standard to keep in line with the blood bank approach to an average human weighing 80Kg in their records.

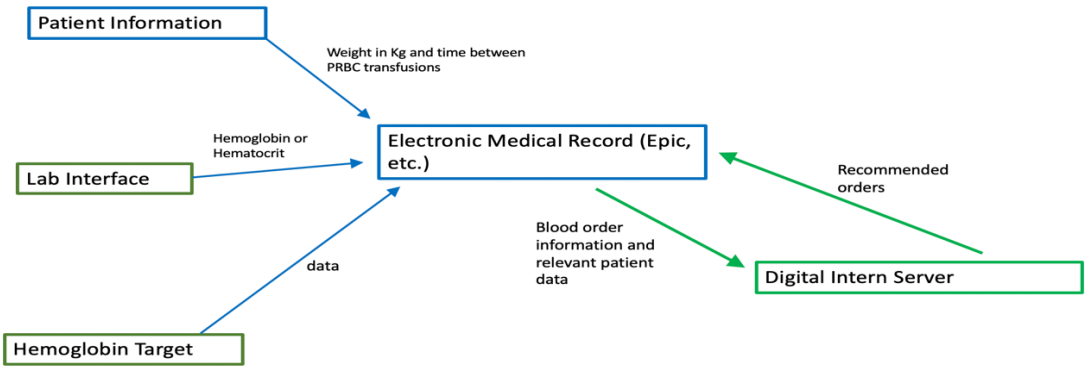


Figure 1. EMR data porting and workflow.

Using data from the EMR as depicted in figure 1, the volume of distribution is calculated with a sub-algorithm using the formula:

*Standard Predicted Hemoglobin Increase = # of units of PRBCs *((80/ Patient Weight))*

The change in patient weight from pre to post transfusion (if available) is accounted for using the following formula:

*Blood Volume Correction Hemoglobin Correction = ((((Post Transfusion Weight – Pre Transfusion Weight)*0.08)/3))*(Post Transfusion Weight/80)*

Any data on hemorrhage volume prior to the most recent hemoglobin is accounted for in a sub-algorithm as well using the formula:

*Extravasation Hemoglobin Correction = (Extravasation Amount in mL/100)*0.15*

Each of these corrections is then applied to the pre-transfusion hemoglobin as documented by the formula:

Corrected Pre-transfusion Hemoglobin = Measured Pre-transfusion Hemoglobin + Standard Predicted Hemoglobin Increase + Blood Volume Correction Hemoglobin Correction + Extravasation Hemoglobin Correction

This corrected hemoglobin is then compared to the post-transfusion hemoglobin and a half-life calculation for the encounter is calculated according to the formula:

*Half Life = -(Time Between Hemoglobin Labs*Log(2))/Log(Post-transfusion Hemoglobin/Corrected Pre-transfusion Hemoglobin)*

Finally, a weighted average of the half-lives is calculated with the most recent half-life counting for 50% of the final half-life average. This is accomplished by averaging all previous half-life calculations for the past year except the most recent calculation. That average is then added to the most recent half-life calculation and that value is averaged and used to calculate the weighted half-life value. This weighted half-life along with a target hemoglobin is then used to calculate the return in days for a given target and a given number of units to transfuse using the formula:

*Return Days = (Weighted Half-Life*Log(Target Hemoglobin/(Current Hemoglobin+(Number of Units to Transfuse* Standard Predicted Hemoglobin Increase))))/-Log(2).*

If no history exists, a default half-life of a transfusion of PRBCs of 18 days replaces the missing value. This value is based on the clearance of red cells if none were produced with native red cells existing for 100 – 120 days[85] and is the same value used as if the patient were on marrow suppressive chemotherapy. The number of days to return for a transfusion is a function then of the patient's target hemoglobin upon return and the patient's particular red cell half-life unless no data or marrow suppressive chemotherapy is used. Using a calendar, the date of return for the patient for a 0-unit, 1-unit, 2-unit, or 3-unit PRBC transfusion is calculated and is adjusted for

weekends and holidays such that the patient would return sooner if the target hemoglobin is unlikely to be met after the advised date. If a patient is already below target, the result is a negative number and the only available options are those values where the number of days is positive.

A 0.5 gm hemoglobin deficit from the target is considered acceptable per our hematologists given the variations in hemoglobin concentration in a unit of PRBCs, the variation in age of the PRBC unit which affects the viability of the red cells, the volume differences in a unit of PRBCs, and the differences in same study measurements of the hemoglobin lab result itself.

Although the patients often return to clinic in other practices on a distant date, this patient population generally has to return for other laboratory testing sooner. It is not uncommon for them to have repeat hemoglobin levels earlier. For this reason, a formula was developed to predict the expected the return hemoglobin on the date that the patient has a repeat hemoglobin and is described as:

Predicted Return Hemoglobin = (10^((Days Since Transfusion-Log(2))/Weighted Half Life)) * (Pre Transfusion Hemoglobin+(Units Transfused*(80/Patient Weight in Kg)))*

These calculations were then programmed into the EMR and were placed into the workflow of the staff ordering blood and labs for patients.

Chapter 4: Specific Aims

Given that there is considerable variability in most physician practices both in patient pathophysiology and goals of treatment for anemia it would be difficult to find a single method that is identified as the "correct" approach to PRBC transfusion. Most often, it is thought that a reduction in variability is most necessary to help control costs and improve outcomes. But what reduction in variability doesn't account for is the individual needs of the patient. For example, if a group of chronically transfused patients is always given the same 2 unit PRBC transfusion regardless of symptoms or hemoglobin level, the variability is nil but the risk of over or under transfusion is a very real problem. The proposition of reducing variability in approach rather than in the number of units transfused is overarching specific aim.

4.1 Significance

On the basis of data from all of the available randomized trials, the AABB panel found little evidence to support a liberal transfusion strategy.[52] The restrictive transfusion thresholds used in the 3 largest randomized, controlled trials were 7 g/dL[68, 69] and 8 g/dL.[59] Given these data, the AABB panel recommended (strong recommendation) a restrictive transfusion strategy that uses these thresholds in most patient populations. Between 11 - 15 million units of PRBCs are transfused in this country annually.[51] If a restrictive transfusion strategy were widely implemented and replaced a liberal strategy, PRBC transfusions would decrease by approximately 40% (RR, 0.61 [CI, 0.52 to 0.72]) on average. This would reduce blood use and the risks for infectious and noninfectious complications of transfusion, and overall costs to the medical system in the United States as a whole.

4.2: General Hypothesis

PRBCs are used inefficiently in the hematology clinic resulting in unnecessary transfusions that increase medical costs and the potential for adverse effects from blood transfusions that could have been avoided.

4.2.1 Study 1 Specific Aim

The current standard of care for ordering PRBCs does not involve any calculation about the patient's needs. It is often guessed upon at best and at worst is simply copied from the patient's care plan from the previous visit which means that a patient with an adequate hemoglobin level may get a transfusion that is completely unwarranted. A computer driven, adaptive algorithm predicts the correct PRBC dose to achieve a target hemoglobin set by the physician and have the patient return to clinic with a hemoglobin value that is greater than or equal to the target hemoglobin level-0.5gm. So, a set target hemoglobin by the provider of 7gm would be acceptable if the measured hemoglobin upon return was 6.5gm.

Hypothesis: An algorithm that is used to calculated the PRBC needs of the patient should achieve the set goal target minus 0.5gm at least 80% of the time upon return-to-clinic.

Derivation for Data Collection: Not all patients will return to clinic for PRBCs as their disease process may warrant an early return to clinic for other causes. A mathematical permutation to the adaptive algorithm has been designed to account for the declining hemoglobin curve over time thus an early or late return to clinic lab result can be

accounted for rather than having to exclude the many patients that don't return to the clinic on their predicted date of return.

Explanation of Approach: The algorithm uses weight and distance from the target hemoglobin level and planned return date to determine the correct PRBC dose. The aim is to determine the percentage of the time that the algorithm accurately predicts the hemoglobin level upon return to clinic understanding that there is considerable variability in the amount of hemoglobin in a unit of PRBCs, that there is variability in the measurement of the hemoglobin level by the lab, and understanding that there are occurrences of bleeding, blast crisis or marrow failure, red cell destruction, etc. that will cause patients to have a significantly lower hemoglobin than predicted upon return.

4.2.2 Study 2 Specific Aim

A current metric in transfusion medicine is the ratio of 1 unit: multi-unit transfusions ordered. With the understanding that there could be many reasons to transfuse more than 1 unit including hemorrhage, longer duration desired to be away from the clinic etc., this metric is a key metric for all blood banks in the US.

Hypothesis: The number of 1 unit to multi-unit transfusions using the adaptive algorithm design tool will be statistically significantly higher than in the control group.

Explanation of Approach: Most patients with these disorders are seen and labs are obtained very frequently due to other abnormal labs such as platelet count etc. In those

patients where the automated system was not implemented, patients often received 2 units of PRBCs based on a care plan that was simply cut and pasted without attention to their transfusion needs. This could happen even if the patient had an acceptable hemoglobin with no need for PRBC transfusion. Because of this we believe that, in general, the number of one-unit PRBC transfusions to multi-unit PRBC transfusions is a quality metric for most patients in this population and can be used to show the effectiveness of the system to controlling unnecessary transfusions. Furthermore, larger transfusions generally are less efficient when it comes to duration until the next transfusion. For example, 1 PRBC unit may get the patient 7 days until the next predicted PRBC transfusion whereas the 2 PRBC units may only get the patient to 12 days until the next predicted transfusion.

4.2.3 Study 3 Specific Aim

The evaluation of the number of PRBCs transfused collectively and per patient will be mined and compared back to previous case controls to evaluate if the decision support tool reduces PRBC transfusion.

Hypothesis: The adaptive algorithm will suggest a lower pre-transfusion hemoglobin level and a lower average number of units per transfusion per patient as compared to the control group.

Explanation of Approach: Since most patients were getting transfused without a target hemoglobin, often based on cutting and pasting the care plan from previous visits, we feel

that the automated approach will decrease the pre-transfusion hemoglobin levels such that patients that do not need transfusion will not be getting them.

Chapter 5: Study Design and Methodology

The study design is a prospective trial evaluating the PRBC transfusion practices of hematology physicians at the UW Health Clinical Sciences Center in the outpatient clinic setting. Two faculty members agreed to follow the transfusion recommendations of the innovation unless clinical judgement demonstrated a clear failure of the algorithms to provide clinically reasonable suggestions. To this date, there were no clinically unreasonable recommendations thus far. The population of hematology patients evaluated was limited to adults with acute leukemias and myelodysplastic disorders.

5.1 Design and Mining Methods

An electronic report was written by UW Health systems analysts using relational databases under the Epic EMR umbrella. The fields of interest consisted of the names, ages, case mix index (CMI), diagnosis, service providers, hemoglobin and hematocrit labs with corresponding dates obtained, date of PRBC transfusions, location of transfusion, number of PRBC units recommended by the algorithms, and number of PRBC units transfused. The resulting data set is enormous and thus the QlikView software package is used to narrow the searched results. In the case of this study, all PRBC transfusions are within the desired date range. Then the data is focused so that only PRBC transfusions ordered by hematologists is selected. Data is then assembled into a report and exported into a Microsoft Excel spreadsheet. In Excel, the data is ordered so that only the outpatient setting lines are evaluated. Then the data is concatenated so that multi-unit transfusion are combined into a single line provided that they happened during the same outpatient encounter. The data is then sorted based on diagnosis and only the diagnoses that meet the inclusion criteria are selected. 24 months of data were acquired

in total. The first 12 months are based on results before the PRBC transfusion algorithms were implemented. A count of the number of PRBC transfusions is obtained by MRN. 2 of 12 faculty used the transfusion algorithms and their study data was compared to control data obtained from before the transfusion algorithms went live. The collective data of the entire 12 faculty practice was also compared during the same time frames as were the results between the faculty who used the transfusion algorithms and those who did not. The final sorted data in the spreadsheet had statistical formulae applied.

5.2 Clinical Setting

UW Health is the academic health system for the University of Wisconsin-Madison. The population is 85% urban and 15% rural. The demographics are 82% white, 5% African descent, 6% Hispanic/Latino, 5% Asian, and 2% other. The ambulatory practices include small community-based practices and a series of larger central practices in the greater Madison area. There are also multiple specialty clinics which are generally housed at the main UW Health campus. Dane County represents the largest population base for UW Health making up two-thirds of UW Health's patient base. The affiliated physician group includes ~1,300 physicians (including ~275 primary care physicians) that are responsible for 2.3 million ambulatory patient visits and more than 41,000 inpatient admissions per year. UW Health adopted the Epic Systems electronic health record in 2004 (2008 for in patient use) and has now created a Health Information Management Center, which is devoted to the integrity of system-wide electronic health record data. QlikView is a software package by Qlik Software Systems that has been implemented as a means of mining data from the Epic EMR in real-time. Support has been provided by UW Health systems analysts to generate the fields needed for the

QlikView tool to operate and then physicians involved with the project are able to pull data from the application in to Microsoft Excel and use the statistical equations in it for data analysis.

5.3 Population Sample

Patients from the adult hematology clinic that have been seen during the past 24 months who have received at least one PRBC transfusion as an outpatient with at least 2 hemoglobin or hematocrit laboratory values. The same population sample was used to obtain data that was applied to each of the 3 specific aims listed above.

5.4 Inclusion Criteria

Patients that were cared for by providers in the UW Health hematology clinic requiring PRBC transfusion(s) because of an acute leukemia or myelodysplastic disorder because these disorders are most likely to need recurrent PRBC transfusions.

- Age greater than or equal to 18 years.
- Chronic PRBC transfusion needs with acute leukemia or myelodysplastic disorder.
- Outpatient management of PRBC transfusion needs (inpatient episodes excluded but not the patients themselves).

5.5 Exclusion Criteria

Sudden low hemoglobin or hematocrit values requiring inpatient hospitalization for massive transfusion where the low lab values cannot otherwise be accounted for or predicted by the data obtained from the EMR.

- Massive, unexplained drop in hemoglobin because of catastrophic marrow failure, blast crisis, etc.
- Inpatient PRBC transfusions.
- Hematologic disease processes that are unlikely to require frequent PRBC transfusions.
- Age under 18 years.

5.6 Data Sources and Transfusion Series Description

112 patients and 337 transfusions met criteria over a 24-month period. The clinical data were mined from the EMR and initially analyzed with QlikView into a manageable data table prior to being exported into an Excel spreadsheet for final analysis. 68 patients with 160 PRBC transfusions met criteria for the desired population prior to the transfusion algorithms going live while 44 patients with 177 PRBC transfusions occurred after the algorithms were implemented met criteria for evaluation of the 12 hematology faculty in the clinic. A total of 287 units of PRBCs were transfused pre and 293 PRBCs were transfused post algorithm deployment. Of these totals 26 patients with 94 transfusions pre and 29 patients post transfusion algorithm implementation were treated by the two hematology faculty involved with the study. For those two faculty, a total of 160 units of PRBCs were transfused pre and 158 PRBC units were transfused post algorithm deployment. 117 transfusions had complete data for analysis. A target hemoglobin of 8gm was selected in 80% of cases overall regardless if the faculty was a part of the greater 12-person group or only of the 2-person study group. Forty-five percent of PRBC transfusions were single unit and 55% were two-unit PRBC transfusions.

5.7 Statistical Analysis Methodology

In order to address *specific aim 1*, the number of times that a patient returned to clinic with a hemoglobin that was at or above the 0.5 gm below the target hemoglobin was evaluated. There was no comparison group. This specific aim was descriptive and performed to help ensure that the algorithm was able to meet the desired goal of being correct 80% of the time. The non-algorithm group never truly had a target hemoglobin documented and thus could not be used as a comparison group. It was known that the patient would often return earlier than expected because of other medical needs. To better assess our model, the prediction mathematics were reversed. In this manner the model used the actual return days as the independent variable. This was applied for each patient and the model was used to predict a hemoglobin upon that return date. From this data, correlations of measured return hemoglobin and return days as compared to that predicted by the algorithm were graphed.

For *specific aim 2*, statistical analysis was performed using a Student's t-test. This t-test was utilized to determine if the two populations studied were different in a statistically significant manner in the number of single to multi-unit transfusions. p-Values were obtained accordingly.

For *specific aim 3*, statistical analysis was again performed using a Student's t-test. For the same reasons in *specific aim 2*, this t-test was utilized to determine if the two populations studied were statistically different in the number of units per transfusion and in the pretransfusion hemoglobin level. p-Values were obtained accordingly.

Chapter 6: Results

For *specific aim 1*, the mean predicted time to return after transfusion was 10.5 days and 75% of patients had follow-up within 3 days of the selected algorithm described return time. Overall 90.6% of patients returned with a hemoglobin at or above target. A target hemoglobin of 8gm was selected in 80% of cases overall while 20% of cases had a target hemoglobin of 7gm. Given that patients often returned early or later for other medical needs the independent and dependent variables were reversed allowing for comparisons between return days and measured hemoglobin as compared to that predicted by the algorithm's mathematical model. This data is plotted in figures 2 and 3.

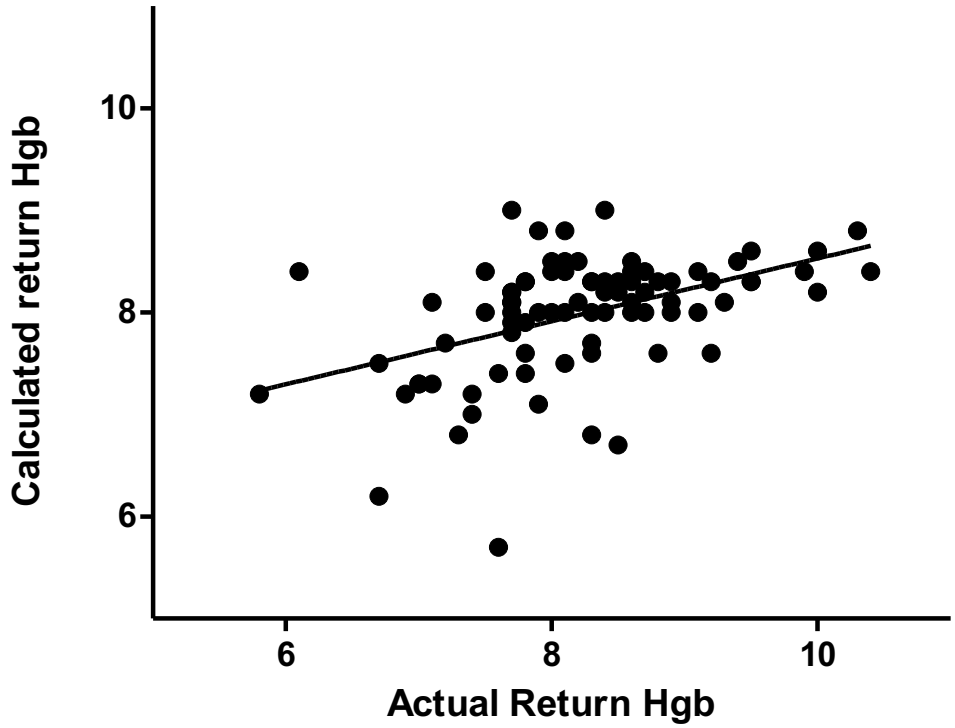


Figure 2. XY Plot of calculated return hemoglobin vs. measured hemoglobin upon return.

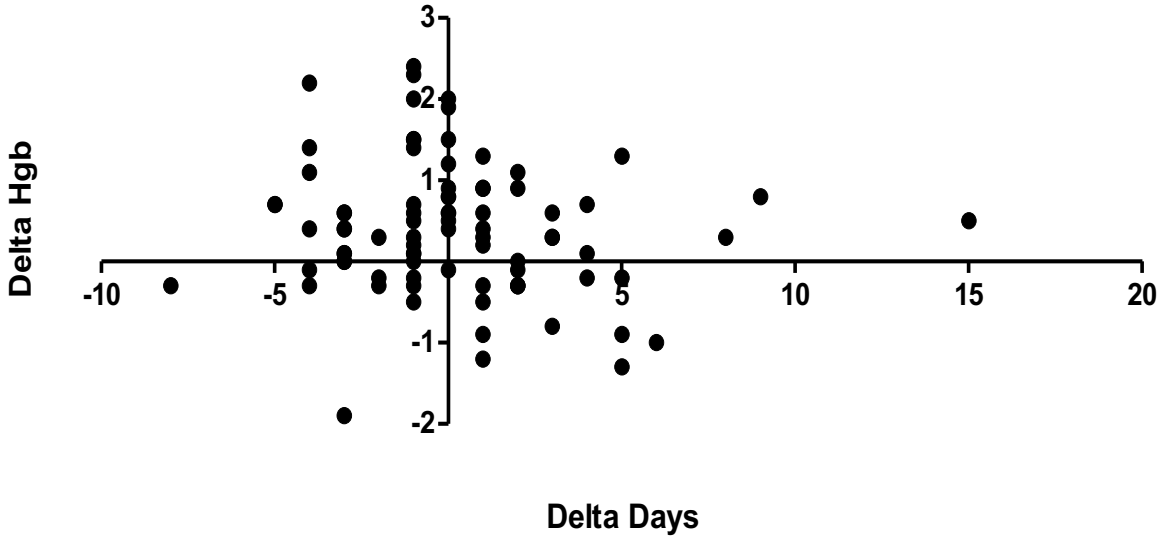


Figure 3. Plot of measured hemoglobin over predicted return date.

Number of XY Pairs	83
Pearson r	0.4566
95% confidence interval	0.2671 to 0.6120
P value (two-tailed)	< 0.0001
P value summary	***
Is the correlation significant?	
(alpha=0.05)	Yes
R squared	0.2085

For specific aim 2, the data collected is demonstrated in figure 4 which shows the number of 1 to multi-unit transfusions between the control and the algorithm group.

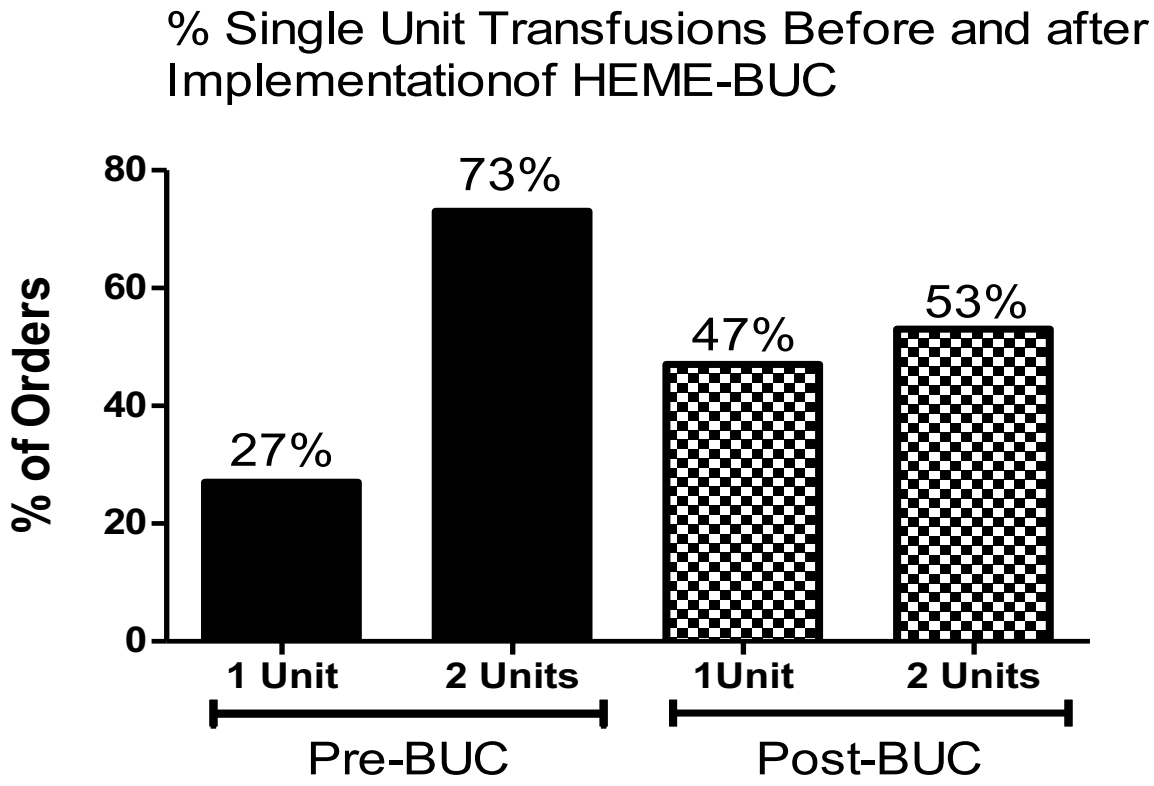


Figure 4. Percentage of 1 unit to 2-unit transfusions in the historical control and treatment years.

As used to describe results for *specific aim 3,* tables 1 – 3 demonstrate the transfusion data for the control (non-algorithm) and algorithm groups combined, the algorithm group only, and the control (non-algorithm) group. The significance and lack of significance is identified in each table.

All Providers	Pre Algorithm	Post Algorithm	P value (if done)
Number of Patients	68	44	
Total Transfusion	160	177	
Average # Transfusion / Patient	Mean 2.35 Median 2 Range 1-10	Mean 4.09 Median 3 Range 1-16	P=0.002 t-test for Mean
Total Units for time period	287 units	293 units	
Average Pre-Transfusion Hemoglobin	7.8 (52% had values)	7.6 (49% had values)	P=0.074 t-test for Mean
Average PRBC Units Transfused per Epoch	Mean 1.79	Mean 1.66	P=0.005 t-test for Mean
Average Units / Transfusion	Median 2	Median	

Table 1. Overall view of transfusion pre and post implementation of PRBC transfusion algorithms including faculty/patients not using the transfusion algorithms.

Algorithm Providers	Pre Algorithm	Post Algorithm	P value (if done)
Number of Patients	26	29	
Total Transfusion	94	103	
Average # Transfusion / Patient	Mean 3.54 Median 2 Range 1-10	Mean 3.55 Median 2 Range 1-13	P=0.99 t-test for Mean
Total Units for time period	160 units	158 units	
Average Pre-Transfusion hemoglobin	7.90 (48% had values)	7.49 (53% had values)	P=0.0009 t-test for Mean
Average PRBC Units Transfused per Epoch	Mean 1.70	Mean 1.53	P=0.015 t-test for Mean
Average Units / Transfusion	Median 2	Median 2	

Table 2. View of transfusion pre and post implementation of PRBC transfusion algorithms including faculty/patients ONLY using the transfusion algorithms.

Non Algorithm Providers	Pre Algorithm	Post Algorithm	P value (if done)
Number of Patients	42	16	
Total Transfusion	66	74	
Average # Transfusion / Patient	Mean 1.65 Median 1 Range 1-8	Mean 4.6 Median 2.5 Range 1-16	P=0.0006 t-test for Mean
Total Units for time period	Units 127	Units 135	
Average Pre-Tx hemoglobin	7.71	7.89	P=0.18 t-test for Mean
Average PRBC Units Transfused per Epoch	Mean 1.92	Mean 1.82	P=0.08 t-test for Mean
Average Units / Transfusion	Median 2	Median 2	

Table 3. View of transfusion pre and post implementation of PRBC transfusion algorithms including faculty/patients that were NOT using the transfusion algorithms.

Chapter 7: Discussion

It is called the "art of medicine" but what makes it an art? The anatomy and physiology of the human body are engineering marvels, something that we can appreciate as created with great beauty but so is a sports car. Albeit a smaller feat of engineering, it is still appealing to the senses. Clearly, in the case of the automobile, there is a near complete understanding of the machinery that makes it work optimally. When something on the automobile fails, quality diagnostic systems and an experienced mechanic should be able to fix the problem. No art of automobile repair is quoted. So, what makes the care of a human an art? Examining the definition of art, it is the "expression or application of human creative skill and imagination, typically in a visual form such as painting or sculpture, producing works to be appreciated primarily for their beauty or emotional power."[86] The key in that definition is the expression or application of human creative skill and imagination. As clinicians we approach medical problems differently. Some of us memorize lists and act on them, some just remember an instance similar to the one in the clinic that we'd seen before, others approach the diagnosis and problem more scientifically. Often times the result is more or less the same but we may perceive one approach as better than another. In the car, the machinery is far less complex and there are far fewer things to go wrong. If something does go wrong, it's possible to get a replacement part or make one. Not so for the human….at least for now. Perhaps if the machinery were better understood in the human our medical careers would be modeled after the auto mechanic. In the interim, our lack of understanding of the actual mechanics of the vast human functions means that by probabilities alone there will be things that we will treat and that the treatment will be met with some variable level of success. This hardly artistic but the euphemism of the art of

medicine sure sounds better. As the science improves so does our ability to diagnose and treat those things that ail us.

Since so much of life is based on probabilities it would seem reasonable that statistics would be predictive of the likelihood of a disease state and the likelihood of success treat that disease via a certain approach. Statistics alone however will not work optimally in the treatment of human disease, even if the sample size is large, because of the incredible variability of the patients. The fact that we might match many criteria together and study the outcome, doesn't purport that the treatment will be the optimal for that individual patient. In fact, an exact treatment, if available, would often need to be run many times over and the resultant assessed for which therapy would be best for that individual patient sitting in the office in front of us. As clinicians we go to our books, the latest research, our training and try to optimize the care for the patient in the most individualistic manner. With our patient loads being so substantial and requiring so much input it is however almost an impossibility to optimize every aspect of patient care and still see all the patients that we see. Therefore, it would be beneficial to consider having some of this work offloaded to other clinical providers. Logical as it seems, the problem here is that those providers are also inundated with work caring for patients. The next best thing is to develop protocols to help guide treatment. The problem with many of these protocols is that they are far too simplified to work effectively. Developing a machine that can adapt a resultant from historical data presented to it may prove to be effective in 2 ways. First, while not perfect, it could approximate an acceptable result closer than an oversimplified protocol. Second, because the machine approaches the problem the same way for each patient, and since the inner workings are known and it adapts in a predictable manner, the output is reproducible. This can help when other aspects of the patient are evaluated over a population that uses that same

machine. In this vein it is reasonable to look towards artificial intelligence to help with clinical decision support where the probabilities of success are high and the risks of failure is unlikely to produce a cataclysmic result.

Artificial Intelligence applications have existed in many industries for over 50 years. The ability to have a machine take over simple tasks has allowed more complex tasks to be performed by humans. This is not only efficient and cost effective, but it lends itself to improved job satisfaction and is best described in the literature about job scheduling.[87-89] The capability of computer processors has advanced significantly and because of these advancements, larger tasks and more complex tasks can be performed in a timely manner which makes the use of AI in medicine physically realizable.

7.1 Adaptive Algorithm Design

An adaptive algorithm is one that has an output that varies by one or more inputs. For example, two patients that require insulin for blood sugar control may require very different doses to attain the same blood sugar level. The algorithm might start off with the same insulin dose but would adjust according to the response of subsequent doses. In the end, the same blood sugar in two different patients would yield a different dose of insulin.

The origin of the mechanism by which the algorithm adapts however, can be quite different. The approach used in this dissertation incorporates a knowledge base that forms the foundation of calculations that are pre-programmed. There is no decision tree algorithm for this patient population only a weighted average that relies on the most recent performance of a transfusion in the specific patient being treated. This is done because the myelodysplastic patient population has a progressive disease progression that mirrors the patient's increasing transfusion

needs. Those patients who have a normal bone marrow would not benefit from this formula but instead might benefit from a formula that considers the distance that they are from the target hemoglobin at the time of a potential transfusion need. The data output from the weighted average, predictive, formula described in this dissertation is compared to a gold standard which included previous algorithms that I have published on this topic[90-92] and clinician reviews of matched input and output data. For the purposes of this dissertation, test cases were presented in advance of the clinic "go live" date and the predicted results were reviewed by hematology experts. When they agreed that the results appeared reasonable and that the concept behind the programming was sound, the software was deployed to the hematology clinic and studied.

Machine learning approaches typically rely on large datasets so that the results aren't skewed rendering them inaccurate. The approaches vary in many ways with the type of machine learning that is employed. The biggest obstacle from a clinical standpoint is that the inner workings of the learned algorithm and the derivation of any calculations are obscured. This is because the analysis of the data that formed the algorithm does not derive from physiological concepts but rather from clinical correlates of unknown meaning backed only by statistical values that were used to identify the relationships.

Only recently have machine learning algorithms found their way in to medical practice and few of them have had a significant impact in clinical treatment. Instead many algorithms in clinical use today are not adaptive and do not adjust in any manner and the resultant decision is not individualized for the patient being treated. Subsequently, in complex situations such as with sepsis management, they often fail to function in a manner that improves outcomes.[93-96]

7.2 Application of AI to the Medical Care of Patients

The primary aim of health-related AI applications is to analyze relationships between prevention or treatment techniques and patient outcomes.[97] The 1980s and 1990s brought the proliferation of the microcomputer and new levels of network connectivity. During this time, there was a recognition by researchers and developers that AI systems in healthcare must be designed to accommodate the absence of perfect data and build on the expertise of physicians.[98] Approaches involving fuzzy logic theory,[99] Bayesian Networks,[100] and neural networks[101, 102] have been applied to computer systems in healthcare. The two greatest applications of AI in medicine in recent years have been in radiology[103-106] and in cancer treatment.[107] However telehealth and virtual visits have been recently focused upon to help improve the timeliness of care delivered and as a means of reducing costs associated with decreased practitioner hours. The use of AI is predicted to decrease medical costs as there will be more accuracy in diagnosis and better predictions in the treatment plan as well as more prevention of disease.[108] The approach to which these various machine learning techniques are applied includes neural networks, support vector machines, and decision trees and forests. The latter potentially lends itself to a better understanding of the process by which a decision is made.

7.3 Application and Embedding of the Algorithm into the EMR for Patients with Chronic Transfusion Requirements

Chronic transfusion patients have many issues affecting their wellbeing. They have to return to clinic frequently for blood checks and often need transfusions to get them to a target cell count. Myelodysplasia patients are a specific patient population that require multiple red cell transfusions on a chronic basis. They have a care plan created for them to organize labs,

medications, and blood products. Unless something drastically changes, the care plan is likely to be copied over from clinic visit to clinic visit. When the care plan is copied, orders in that care plan are copied as well. If the patient had a blood transfusion with the previous care plan, the same order for blood is copied and the patient receives a blood transfusion. The consequence is that blood is transfused regardless of the patient's current hemoglobin and regardless of the planned target hemoglobin upon return. That might not seem like that big of deal but when considering the risks of transfusion reactions, heart failure, and infection, the discomfort of the needle stick, a return to clinic that might have been avoidable and is often beyond inconvenient, and the financial implications, the cost becomes very significant to the patient and the medical system.

Evaluating myelodysplasia patient population is easier than an entire population of cancer patients that need chronic transfusions because the population is more homogenous, they have transfusion requirements that generally increase with time, they have a longevity that is greater than most transfusion requiring cancers, and in general have a more predictive course. For these reasons, we chose to evaluate these patients.

In order to optimize the workflow for nursing staff in the clinic, it was important to implement the calculator into the care plan of the EMR and to have the output reflect something meaningful for the patient and the team. For this reason, the return to clinic date reflects only those dates where a clinic is open, such that the time of return is at or before the target hemoglobin is reached. The procedure for ordering blood within the care plan is as follows: When the patient returns to clinic, blood is drawn for a hemoglobin check. When the result posts, a BPA triggers for the nurse. This BPA relies on a specific Beacon Supportive Care

Treatment Plan being applied to the patient. The nurse selects the appropriate order set for the patient.

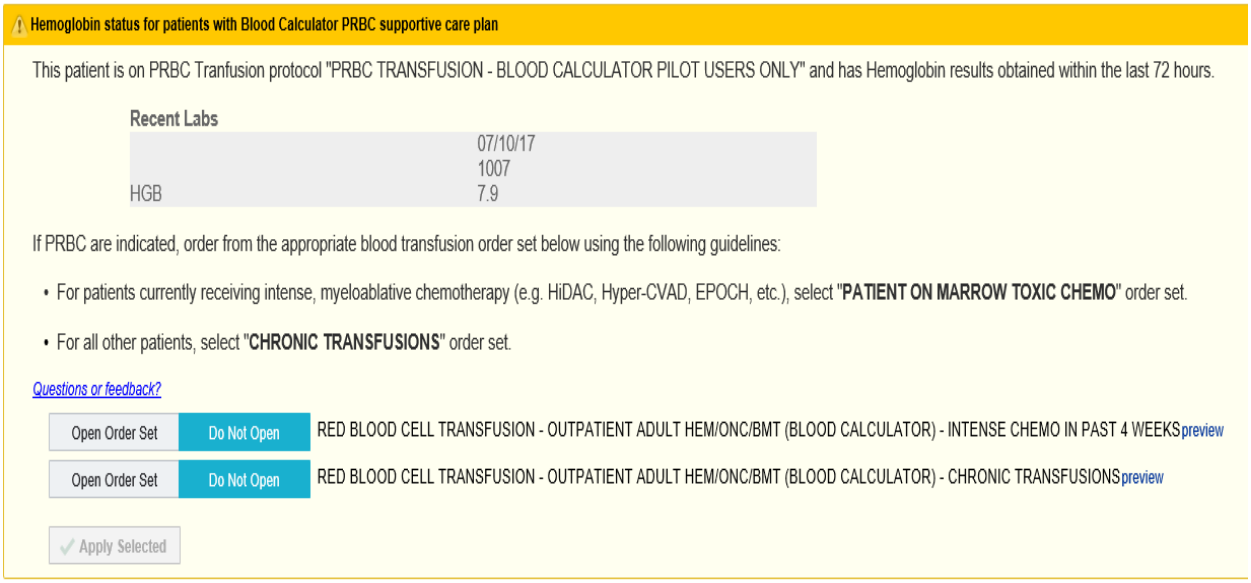


Figure 5. Screenshot of selection between intense chemotherapy and routine patient past performance with PRBC transfusions.

Upon selection, the order set opens with predicted return dates based on a target hemoglobin. The predicted return date equates with a number of units of PRBCs to be transfused:

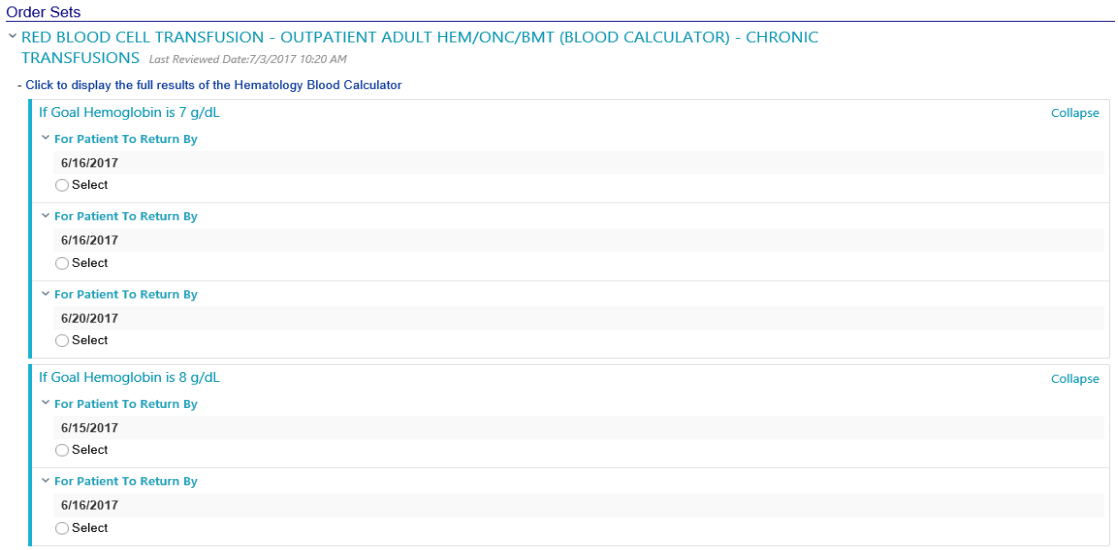
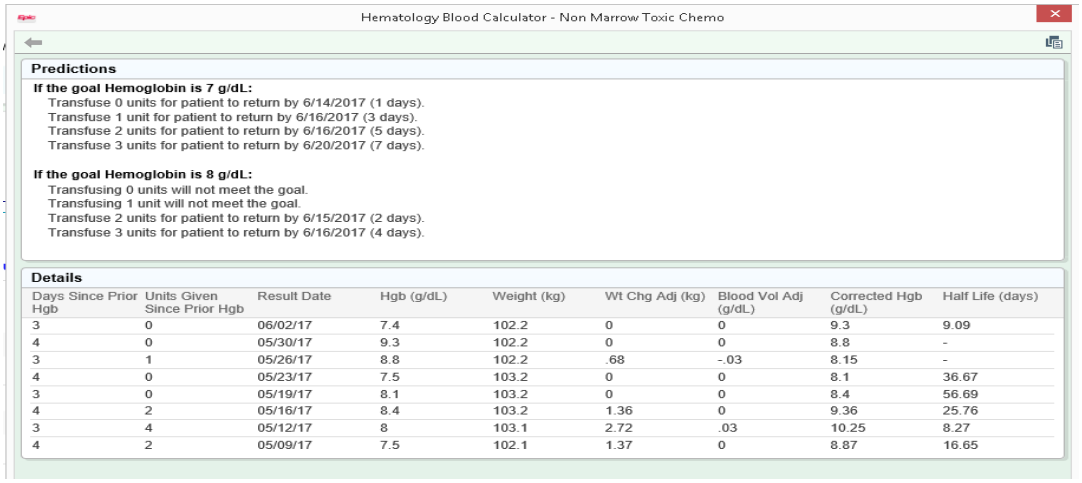


Figure 6. Selection of predicted patient return date for a given target hemoglobin.

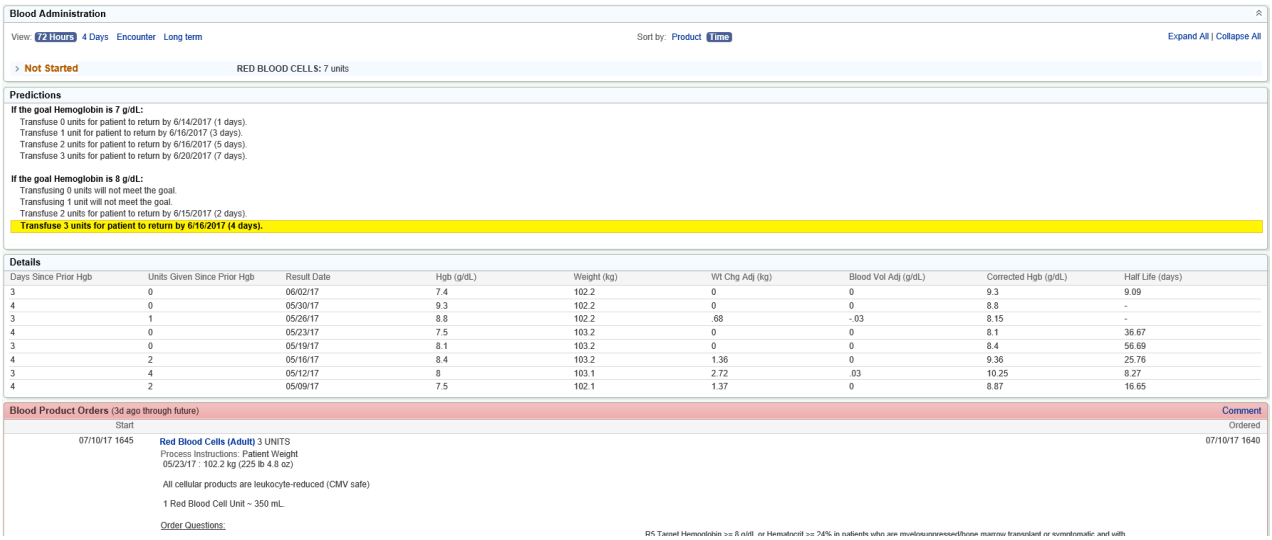
The details of the calculator can be pulled up by the ordering provider if desired:



Days Since Prior Hgb	Units Given Since Prior Hgb	Result Date	Hgb (g/dL)	Weight (kg)	Wt Chg Adj (kg)	Blood Vol Adj (g/dL)	Corrected Hgb (g/dL)	Half Life (days)
3	0	06/02/17	7.4	102.2	0	0	9.3	9.09
4	0	05/30/17	9.3	102.2	0	0	8.8	-
3	1	05/26/17	8.8	102.2	.68	-.03	8.15	-
4	0	05/23/17	7.5	103.2	0	0	8.1	36.67
3	0	05/19/17	8.1	103.2	0	0	8.4	56.69
4	2	05/16/17	8.4	103.2	1.36	0	9.36	25.76
3	4	05/12/17	8	103.1	2.72	.03	10.25	8.27
4	2	05/09/17	7.5	102.1	1.37	0	8.87	16.65

Figure 7. Screenshot of choice of hemoglobin, return date, and patient history that was used to develop the return date.

Since the nurse is making the selection, the provider has a need to see the prediction and ultimately see the target choice selected by the nurse. The provider screen is shown below.



Days Since Prior Hgb	Units Given Since Prior Hgb	Result Date	Hgb (g/dL)	Weight (kg)	Wt Chg Adj (kg)	Blood Vol Adj (g/dL)	Corrected Hgb (g/dL)	Half Life (days)
3	0	06/02/17	7.4	102.2	0	0	9.3	9.09
4	0	05/30/17	9.3	102.2	0	0	8.8	-
3	1	05/26/17	8.8	102.2	.68	-.03	8.15	-
4	0	05/23/17	7.5	103.2	0	0	8.1	36.67
3	0	05/19/17	8.1	103.2	0	0	8.4	56.69
4	2	05/16/17	8.4	103.2	1.36	0	9.36	25.76
3	4	05/12/17	8	103.1	2.72	.03	10.25	8.27
4	2	05/09/17	7.5	102.1	1.37	0	8.87	16.65

Figure 8. Selected choice with blood product order for transfusions pending/completed.

The above workflow is what is expected when the orders for transfusion are completed in the clinic. However, many times, patients are transfused in the infusion center which requires the orders to signed and held in that location as the patient will not be receiving the PRBC transfusion where the order is being placed. This workflow is confusing and not predictable by clinic overrun alone. Since these patients may receive PRBCs in either of these locations, the safer and most efficient approach is to have the orders signed and held until the transfusion location is determined. At that point the patient and the PRBC unit(s) are routed to the correct location for the transfusion to occur. In this case, the calculator BPA presents as it has above.

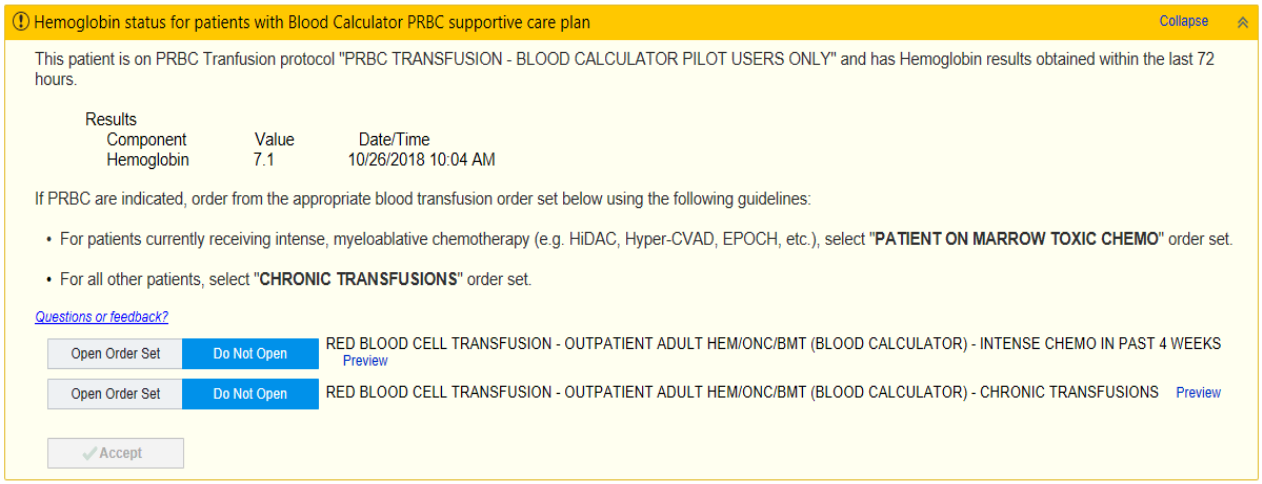


Figure 9. Screenshot of selection between intense chemotherapy and routine patient past performance with PRBC transfusions with possible re-route to different location.

Upon opening the order set, the nurse is presented with information as before with some new additions as well. The comment section from the nursing communication order that has the target hemoglobin will only show if it has been released it from the treatment plan. It will provide a guide for the section to select orders from.

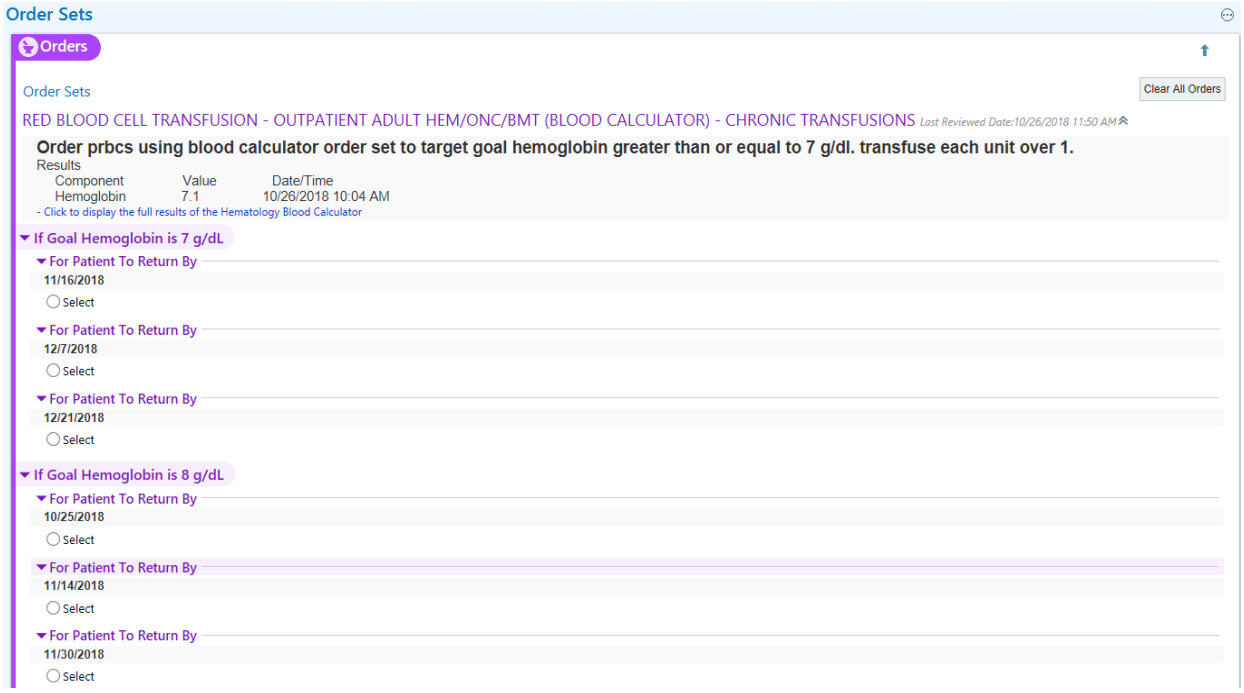


Figure 10. Selection of predicted patient return date for a given target hemoglobin with possible re-routing of blood product to different location.

There is no change to the way the nurse completes the orders.

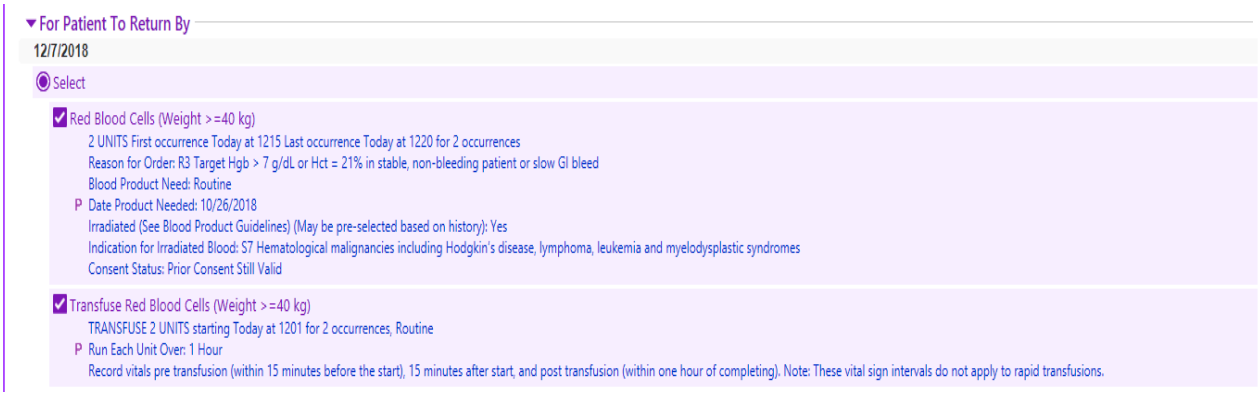


Figure 11. Return date for transfusion with possible re-routing of blood product to different location.

Similarly, there is no difference in how the orders will look in the sidebar prior to signing:

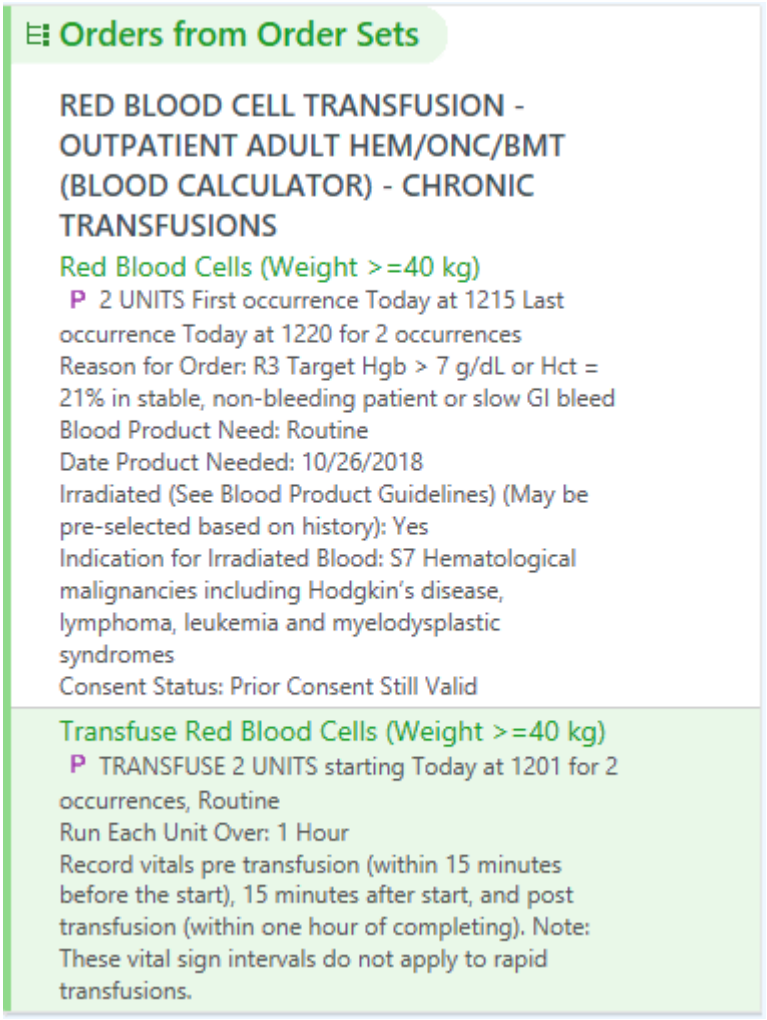


Figure 12. Order and transfusion instructions for PRBC units.

Once signed (which actually performed a sign and hold in the background), the navigator for the nurse highlights a new section called “Release PRBC.”

Figure 13. Side bar of navigator where PRBC orders are released prior to routing of the units for transfusion.

If doing the transfusion in clinic, clicking on that section reveals the screen below.

Figure 14. Select the time and location for the transfusion to occur.

After clicking "Click To Release Orders," the following screen pops up.

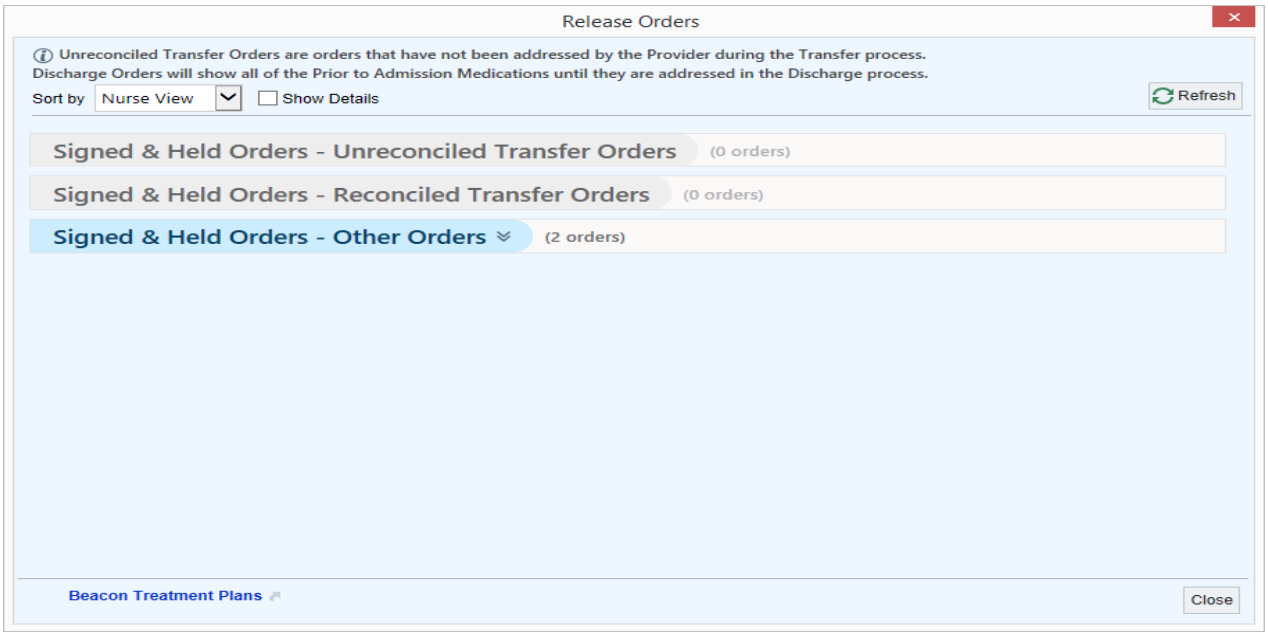


Figure 15. Location where transfusion is to occur with orders that are to be signed and held.

Orders to release are revealed by expanding the section titled "Signed & Held Orders."

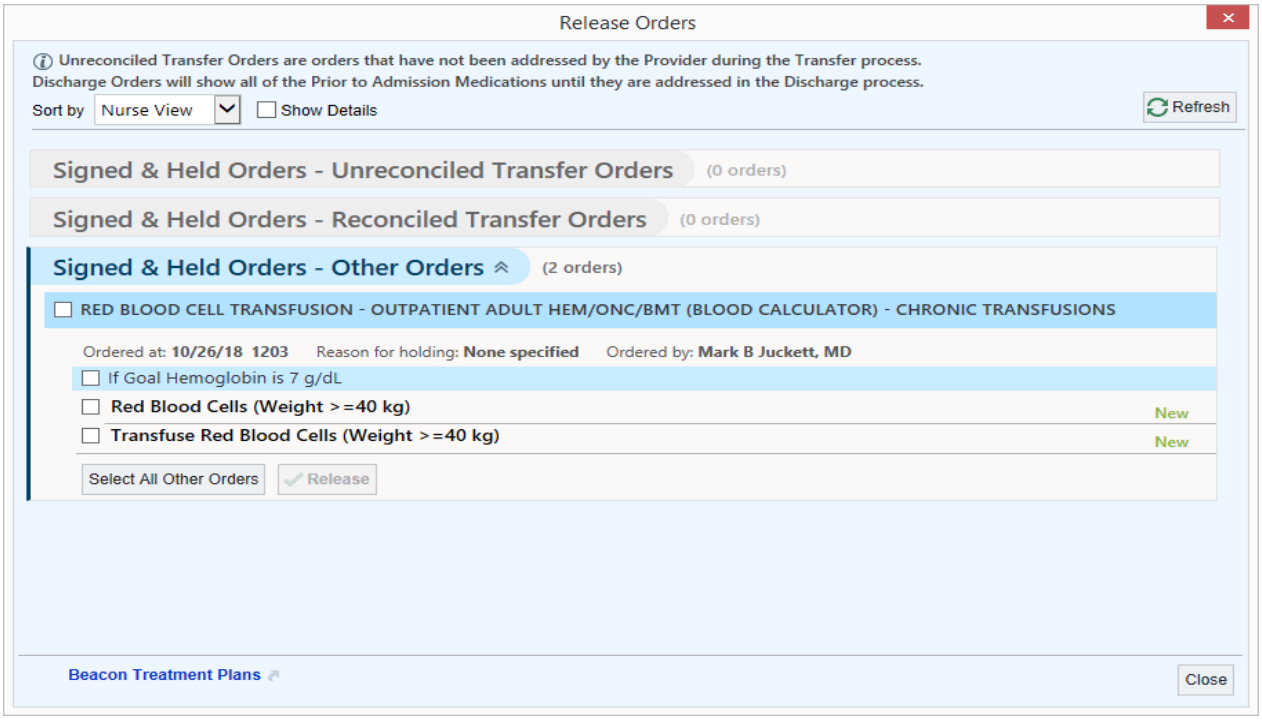


Figure 16. Revealed sign and held orders.

Upon clicking “Select All Other Orders,” the pop-up screen appears.

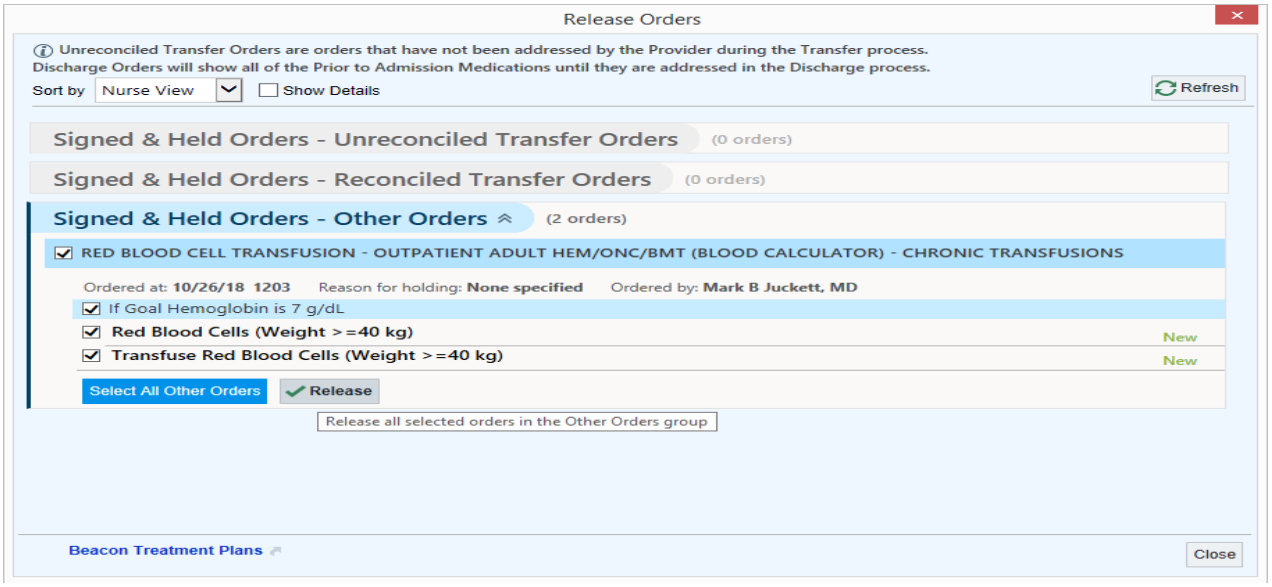


Figure 17. Transfusion related orders are selected.

After clicking “Release,” the pop-up screen empties.

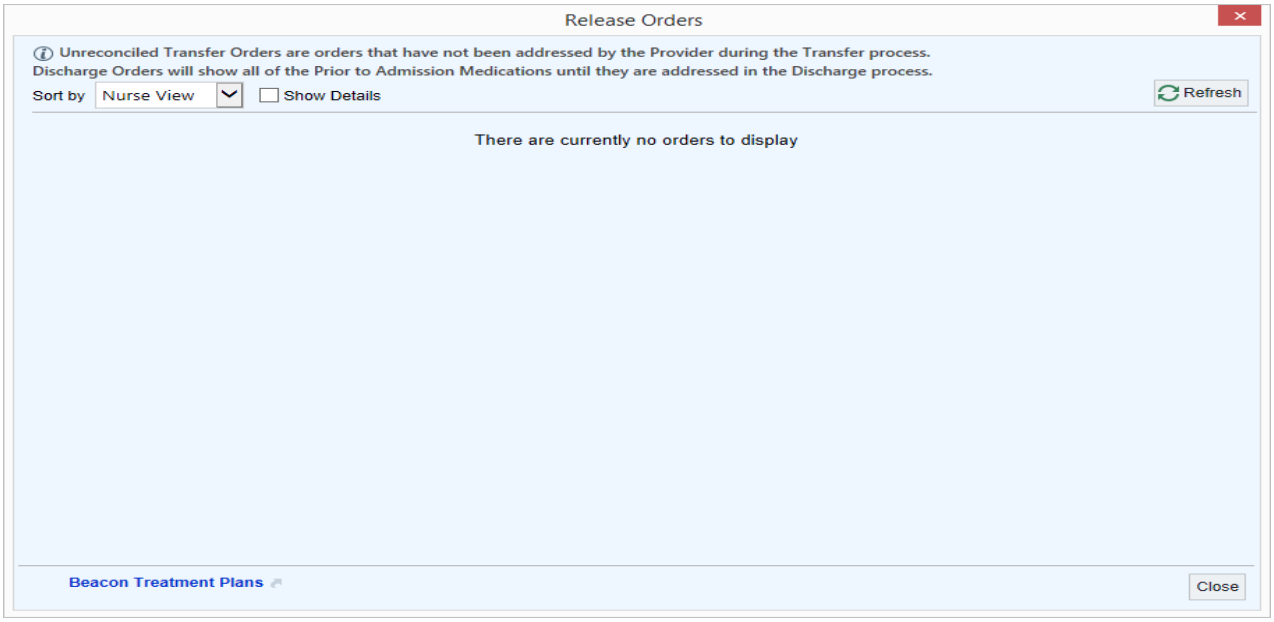


Figure 18. Orders are excepted and sign and hold screen clears.

After closing the pop-up, the “Release PRBC” section is now longer highlighted.

Figure 19. Navigator sidebar showing release of PRBCs to location where transfusion is to occur.

The “Release PRBC” section will not show at all if there are no signed and held blood orders in existence when the navigator is first opened. So, given the scenario above, the next time the patient is opened, that section will not show at all. If the patient is instead sent to the Infusion Center, the Infusion Center RN will also see a highlighted section in his/her navigator signifying the presence of signed and held blood orders.

Figure 20. PRBCs now released as normally.

And then the release process mirrors the release process for immediate release orders in the clinic.

Given that there is a workflow change for nurses and a new hemoglobin and date targeted approach for providers we thought it better to study how our algorithm would impact the patients of only two of the hematology clinic faculty. We then evaluated the data before and after the algorithm went live with this select group, with the patients that were not involved with the algorithm at all over the same time frame, and then with the conglomerate data of all of the patients together. All of this was performed over the same time period of 1 year pre algorithm and 1 year with the algorithm live within the EMR. As would be expected by attrition from death etc., the overall pre calculator group had more patients than the post calculator group (68 vs 44) for all total myelodysplasia patients regardless if the algorithm had been used in their care. The total number of transfusions was higher in the post calculator group as would be expected

given the general increased transfusion needs of myelodysplasia patients as their condition worsens (166 vs 177). With that information there were statistically significant more transfusion episodes per patient but a statistically significantly lower number of PRBCs transfused per transfusion (1.66 vs 1.79 p=0.005) and with a nearly equal number of total units transfused in each group (287 vs. 293). We would have expected significantly more PRBCs to have been transfused given the expected transfusion needs of the myelodysplastic disorder patient population. This proved true as the overall population received more PRBCs (4.22 vs 6.66 units/patient in pre vs post calculator group). The pre-transfusion hemoglobin was slightly lower in the post calculator group (7.6 vs 7.8) and that was nearly significant.

The data becomes more interesting when looking at the pre algorithm and live algorithm treatment group. This group had roughly the same number of patients (26 pre vs 29 treatment). The number of transfusions per patient was NOT statistically different (94 vs 103 total, 3.54 vs 3.55 per patient) and with 160 units transfused in aggregate vs 158 units with the algorithm running. When evaluated by units per transfusion, the number of units transfused was 1.7 on average for the pre algorithm group and 1.53 in the treatment group. This was statistically significant with p=0.015. One might have expected that as the disease progresses the number of PRBCs transfused would have increased but this did not happen. Had all of the patients remained stable, the transfusion rates would have been even better. As for the level of hemoglobin that patients were transfused at, the pre algorithm group was transfused at nearly an average hemoglobin of 8g (7.9g) while the target in the treatment group was 7.49g, nearly a half of a gram of hemoglobin less. To help clarify the meaning of these findings, the target hemoglobin, is the hemoglobin level selected by the provider that s/he feels best suits the patients' needs as a function of quality of life and overall optimization of care. This value is not

a value that we set as a part of the algorithm. The algorithm is affected by the target hemoglobin set by the provider and the value at which the patient is transfused. If the target hemoglobin upon return is 7 and the pre transfusion hemoglobin now is 7.2, how much blood should be transfused to attain a hemoglobin of 7 upon return? This is what the algorithm calculates based on the individual patient's past performance. Provided that the target hemoglobin hasn't changed (and it often does not change beyond the first few visits), a lower pre transfusion hemoglobin value is in large part related to a more accurate dose of PRBCs given to the patient at the previous clinic visit. Given that the standard of care was a care plan that was copied from EMR encounter to EMR encounter, it shouldn't come as a surprise that a larger than necessary transfusion would result in a higher return-to-clinic hemoglobin. This should prompt either no transfusion or a lower transfusion upon return to clinic, but instead using the current standard of care, more blood is ordered and the patient receives an un-necessary transfusion. Since the response to PRBCs is not curvilinear, a new equilibrium is reached such that the patient's return hemoglobin only climbs to an asymptotic level.

Along these lines, a standard unit of inpatient measurement of transfusion over utilization is the 1:2 unit transfusion ratio. Most inpatient transfusions do not require 2 units of PRBCs to attain the goal which is an artifact of the dogma of "if you're going to give 1 unit of PRBCs give 2." Ultimately this approach is wasteful and the literature on this approach has used the 1:2 unit transfusion ratio as a metric.[109] Of course, if the patient needs 2 or more units of blood it should be given. In a chronic transfusion patient population such as those with myelodysplasia, that multiunit transfusion may be indicated as it could potentially keep the patient out of the clinic for longer periods of time. Sadly however, many of these patients require platelet transfusions and monitoring of other issues regarding their health that necessitate a sooner return to clinic. In this

circumstance the 1:2 unit ratio can prove useful as a metric of wastefulness and the success controlling excess PRBC transfusions. When looking at the data we found that for the year prior to the algorithm going live, the number of 1 unit PRBC transfusions was approximately 27% of transfusions but 2 unit PRBC transfusions made up 73% of transfusions. When the algorithm went live, the ratio was 47% single PRBC unit transfusions to 53% 2 unit transfusions, a statistically significant finding.

Evaluating this algorithm on its ability to reduce PRBC units transfused however isn't enough if there is no evaluation of the patient's return-to-clinic hemoglobin level and that proximity to target. To calculate the accuracy of the algorithm, we reversed the mathematical process such that the predicted hemoglobin on the date of return was presented as a function of the hemoglobin level measured. As a step backward, the algorithm predicts how much blood a patient needs to attain a target hemoglobin upon return to clinic. As an example, a single unit may provide the patient a return date of 1 week, 2 units may yield a return date of 12 days, 3 units may predict a return date of 15 days. But patients do not always return on their scheduled return date because they may have medical needs that require them to return sooner. What if the hemoglobin was measured early, significantly earlier than scheduled? Under those circumstances the predicted hemoglobin needed to be matched to the hemoglobin measured on their date of return. To do this requires the model to predict a hemoglobin for any given date of return. This was done and the results plotted as XY pairs with a Pearson r of 0.4566 with a 95% confidence of 0.2671 to 0.6120 and a two tailed $p < 0.0001$ thus indicating a very strong correlation of the predicted hemoglobin using the algorithm model as compared to the actual measured hemoglobin.

When evaluating the non-treatment group pre algorithm data as compared to data acquired during the time the algorithm was live but not live with these patients the data is as expected. There is an attrition rate from 42 patients to 16 patients with an increase in total number of transfusions that increased significantly 1.65 vs 4.6 on average with a $p = 0.0006$. This is expected with myelodysplastic disorder patients since transfusion needs increase with time as the disease worsens. However, average pre transfusion hemoglobin increased from 7.71 to 7.89. This was not statistically significant and likely represents a higher return-to-clinic target hemoglobin in some of sicker patients. An interesting finding that was not statistically significant but mirrored the treatment group was that the average number of PRBCs transfused per transfusion declined. This appears to be a spillover effect because the patients in the non-algorithm group were treated by the same nurses as those in the algorithm group. From questioning the provider team and reviewing the data, it appears the providers and nurses caring for these patients did change their ordering of PRBCs by making an assessment of their own in some circumstances and ordering according to their clinical judgement (as opposed to copying the care plan verbatim).

7.4 Confirming Optimization of the Weights in the Transfusion Formula

The derivation of the algorithm is described in chapter 3.2 where the innovation and concepts are expressed in stepwise fashion. The weighting of the algorithm however was not clearly defined. This is because it was determined by expert opinion, unlike the use of half-lives which was based on data in the literature. A more scientific approach is necessary to evaluate a data set and confirm the weights of the algorithm are optimized. For this reason, a small program was written as a MATLAB script (The Mathworks, Inc) to cycle through integer

percentages from 0 to 100% each for the most recent half-life and the cumulative half-life prior to the current epoch so that the sum total of each percentage ratio was 100%. The same data set used from the results section (chapter 6) was analyzed. Accuracy was defined as a return hemoglobin that was greater than the predicted hemoglobin upon return minus 0.5g as was the methodology used in the results section. Interestingly, but not unexpectedly, minimum accuracy of the half-life approach to PRBC transfusion was 88.03% and was noted when the historical (cumulative) weighted average was approaching 100%, with minimal input from the most recent half-life calculation. Similar results were noted on the opposite spectrum but with an accuracy of 89.74%. 91.45% accuracy was noted to be the highest value and occurred when the weighted half-life accounted for between 30-35% of the historical (cumulative) half-life calculation. No single value in that range was best. The 50/50 weight proved to be 90.6% accurate as noted in the results chapter. While the values seem very similar, the standard deviation for percent accuracy was 0.0082. The improvement would be 103.66 standard deviations increased compared to the original algorithm weights. This improvement, however, doesn't make a practical difference in the planned return date or number of units of PRBCs to be transfused. It is likely that a much larger data set would yield a greater spread of values and a better Q for the signal that was obtained. Nevertheless, in adults where a whole unit of blood is transfused rather than a specific volume of blood, such as in children, there is likely too much slack in the transfusion size alone to have much of an effect with this change in accuracy. Had the accuracy been > 15% different, we might expect a potential change in the units transfused and the date of return.

The standard deviations in the return hemoglobin level was at a minimum of 0.8335gm when the historical half-life calculation was from 59 to 61% of the weight. At the 50% weight

the standard deviation was 0.8376gm. From the 30-35% historical half-life, where the best accuracy was found, the hemoglobin standard deviation ranged from 0.8715gm to 0.8594gm in decreasing, stepwise values. The overall trend demonstrated worse standard deviations at the extremes with the greatest standard deviation noted to be 1.0381gm when the historical half-life was 100% of the weight. When the weight was 100% in favor of the recent half-life, the standard deviation was 0.9288gm. There are two points to be made here. The first is that the difference in the standard deviations from the extremes is only 0.1093gm of hemoglobin and from the greatest standard deviation to the smallest standard deviation is 0.2046gm indicating that regardless of weighting the formula results are very similar. Second, the most precise ratio is only 0.335gm greater than the expected variability due to PRBC unit size and lab inconsistency. These results indicate that despite the expected variability innate to PRBC transfusions that the model is able to approximate the individual patient's PRBC needs with reasonable precision. When factoring optimized accuracy and precision, the clustering seems to favor the 50:50 ratio that was originally studied.

Ultimately, this exercise was quintessential in verifying the optimal weights between recent and historical performance of the algorithm. Understanding that the limited sample size impacts the optimization process is important and that a larger sample would provide more exacting results is what should help drive further large scale trials. Nevertheless, by reworking the weights it was able to be determined that the non-linear, half-life approach yielded a model that generally approximated the actual return hemoglobin levels of patients with various states of disease with the understanding that no single approach can account for large spontaneous hemorrhages, RBC destruction, or sudden marrow failure.

7.5 Technology Application in Clinical Situations and the Medical Device Designation

In May of 2018, the IOM Committee on the Public Health Effectiveness of the FDA 510(k) Clearance process issued its 245-page report titled "Medical Devices and the Public's Health. The FDA 510(k) Clearance Process at 35 years."[110] The committee illustrated the pathway forward for the three different classes of devices that have a predicate device that modeled the way for the new device to enter the market. The purpose of the report was to better understand and make recommendations about the scientific evidence used to support the regulatory decision to allow a device to come to market. Originally thought to represent a level of safety and effectiveness of a new device that is considered substantially equivalent to existing (predicated) devices, the reviewers concluded that the FDA cannot consider this to be true. The report stated "The 510(k) clearance process is not intended to evaluate the safety and effectiveness of medical devices with some exceptions." This was stated because without scientific data on the new device, the case cannot be made that in fact the device is truly safe. Instead the authors suggested developing a new framework that would incorporate premarket clearance with post-market surveillance of the device in question in order to provide "reasonable assurance" of the safety and effectiveness of class II devices.[111]

The concerns about the process are not entirely surrounded by safety and effectiveness but also have roots in the politics with companies concerned that a new approach at the FDA would delay products coming to market, reduce competition for already existing devices, and ultimately cause a reduction in potential jobs created here in the United States. The fact that the IOM report was ultimately drafted based on the failure of some 510(k) devices to prove safe and efficacious seems the more prudent concern but it must be balanced with the relative inefficiency and bias that has marred the FDA's reputation in the medical world as well as with public

opinion. The inefficiency issue that has plagued the FDA was highlighted by the Centers for Devices and Radiological Health. Ultimately this prompted the FDA to ask the IOM to evaluate the 510k process. The FDA did not ask about efficiency but rather if the 510k process promoted safety and innovation in the support of public health and if not, to comment on what could be done to achieve both.

In December of 2016 the 21st Century Cures Act was signed into law. It was designed to accelerate medical product development and bring new advances to patients more efficiently, providing new authority for the FDA to recruit and retain technical experts. It also provided for 2 programs, The Regenerative Medicine Advanced Therapy program and the Breakthrough Devices program. Additionally, the Cures Act also directs the FDA to create institutes to coordinate activities that cross various centers for major disease areas. This push towards improving throughput at the FDA doesn't necessarily suggest less scientific rigor but the extra $500 million over 9 years that is subject to appropriations still falls short of delivering upon the FDA's needs. Ultimately, in certain circumstances the FDA can choose to exercise its regulatory discretion and not regulate devices that fall within the realm of software that is open loop, meaning that the decision support provided by the device must be enacted upon by a provider since it does not directly interface with the patient. Effectively this approach is where our algorithm resides and the company that has ownership of this algorithm, iVMD, has been issued a letter from the FDA, after a final Q Sub round, that they will not plan to regulate the algorithm unless there is a danger that is reported about its use. The FDA's approach to medical software is confusing to developers who thought of their device as either a class I or possibly class II device who may have started the 510(k) process only to find out that they were no longer going to be regulated but at some time in the future could be regulated. For some, the 510(k) provides

a presumed stamp of approval that can help health care providers feel more secure about using the software and the lack of approval could make it harder for the developer to market the new software product.

Per the IOM report, the question is whether or not the stamp of approval is valid. In their review, the 510(k) falls short of protecting American's from devices the either do not work or, in the worst case scenario, are outright dangerous. Congress had substantially changed the 1976 Medical Device Amendments in the 1990's which did not require the FDA to request scientific proof of efficacy for moderate-risk devices determined to be substantially equivalent to a predicate device already approved. Interestingly, when filing a patent on such a device the inventor needs to show why it is different than devices already patented but then an "about face" is done through the FDA to show how the new device is substantially equivalent. In the end, legislative interference allows device manufactures to potentially manipulate the system to their advantage. Furthermore, the predicate device itself may not have even been appropriately evaluated if it was introduced prior to 1976. For this reason, the IOM committee concluded that the 510(k) process lacks the legal basis to be a reliable premarket screen of the safety and effectiveness of moderate risk devices and that a complete overhaul of the process is necessary. The funds allocated to the FDA however, are not enough to build a robust system to evaluate all of the devices within their intended scope.

Ultimately for this algorithm to be vetted, preliminary data at a single site to prove that the output is not dangerous or otherwise dysfunctional. If the study confirms that the desired metrics are met, the device should be released for general use within its intended scope to other institutions to prove that it can be used in other places outside of the originating institution. After that a post-market evaluation process should be in place to evaluate if the device produces

the desired results and is truly efficacious. Any concerns that would affect public health should also be reported. The open loop design of the algorithm provides at least one barrier for any decision that is deemed to be incorrect to be intercepted by a provider of patient care, preventing it from causing an adverse event. Currently, the FDA plans to evaluate the post market entrance of our device algorithm and others both from iVMD and other companies using open loop systems if clinically warranted. In the meantime, this dissertation provides pilot data on the effectiveness of our algorithm and with that data there were no known adverse events attributable to the algorithm's functionality.

7.6 Using a Targeted Approach to PRBC Transfusion – Initial Evaluation in Organ Donors

Current trends in patient blood management favor the use of more standardized transfusion practices. Studies to determine and implement optimal transfusion thresholds have led to more conservative use of blood products in a variety of clinical settings, and a large body of literature now supports these standardized, more restrictive strategies. The implementation of such standardized transfusion practices has resulted in a more cost effective use of PRBC transfusions and more importantly has resulted in improved patient outcomes in a variety of clinical scenarios.[112-114] The overarching technology for patient management embedded into the EMR known as the Digital Intern incorporated a method to predict transfusion needs for PRBCs in various patient populations that did not require chronic transfusions.[90-92] As with the current algorithm, this more generalizable algorithm uses patient weight as a means to predict an effective volume of distribution and subsequent number of PRBC units to transfuse to attain a set hemoglobin / hematocrit target. In the organ donation patient population, the ordering provider

can delegate authority for ordering the transfusion of PRBCs to the Digital Intern which quietly monitors the organ donor's labs and vital signs. While the provider will eventually need to sign the orders, the transfusions can occur without direct provider intervention. The transfusions are then carried out by nursing staff. Historically, evaluation of laboratory and clinical parameters by the managing physician would have empirically determined when and how much blood to transfuse prior to organ procurement. The data on 100 consecutive donors was compared to 91 historic controls. The overall mean time as a donor before procurement was 25.9 $\pm$ 15.2 hours and was no different between the groups (24.7 hr. control and 27.1 hr. Digital Intern p=0.2). The mean hematocrit during the donor time period was 32 $\pm$ 7% for the historic control group and 31 $\pm$ 6% for the Digital Intern group (p=0.8). Similarly the mean number of hematocrit values checked during the donor period was not different between the groups at 4.2 $\pm$ 2 and 4.5 $\pm$ 3 hematocrit values for the control and Digital Intern group respectively (p=0.5).[90]

Nineteen of the 100 donors (19%) in the Digital Intern group were transfused during the donor period compared to 26% (23 of 90) in the control group. Although the rate of transfusion was 7% lower in the Digital Intern group this difference in transfusion rate did not reach statistical significance (p=0.30). In the Digital Intern group, 5 donors were transfused at two separate times during the donor period and in the control group four donors were transfused twice and one donor was transfused three separate times.

In the Digital Intern group 19 donors received a total of 24 transfusions with a mean of 1.4 units/transfusion (median 1 unit, range 1-2 units) which was significantly less than in the control group where 23 donors had 29 transfusions with a mean of 2.0 units of RBCs/transfusion (median 2 units, range 1-4 units). The variability in the number of units transfused (dose), as defined by the coefficient of variation (CV) shows 15% less variability in transfusion dose for

the Digital Intern groups (36% (Digital Intern) vs 50 % (control), p=0.001). This reduced variability reflected the use of a standard algorithm to calculate dose in the Digital Intern managed donors.

	CONTROL	Digital Intern	P value
Age	38.8 years	39.8 years	NS
Gender	Male 59% Female 41%	Male 64% Female 36%	NS
Mean HCT as donor	32 ± 7%	31 ± 6%	NS
Number of HCT values	4.2 ± 2	4.5 ± 3	NS
Time as Donor	24.7 + 14.8 hours	27.1 ± 16.4 hours	NS
Transfused Pre-Donor	48%	36%	NS
Transfused as Donor	26%	19%	NS
Transfused Both	19%	12%	NS

Table 4. Donor patient characteristics and transfusion history.

Among those transfused as donors the mean hematocrit was 24.8 + 3% in the Digital Intern group which was significantly lower than in the historical control group at 27.8 + 4% (p=0.02). The variability of the physician managed historical control group also had a significantly wider range of pre-transfusion hematocrit is seen in the control group (p=0.003) and that the number of subjects transfused beyond the Digital Interns threshold of 24 in the control group approaches 50% (p=0.0002). The number of units transfused for any given pre-transfusion hematocrit was seen to vary more in the control group, (CV 28-65%), than in the Digital Intern group, (CV 28-35%) over the same hematocrit range. Concomitantly, the number of organs

procured per donor was significantly increased in the Digital Intern group (4.07 vs 3.54 organs/ donor p=0.019) which demonstrated that the use of the Digital Intern improved organ donation. The fact that a standardized approach that used a computerized algorithm, with a lower transfusion hematocrit target was able to improve organ function not only affirms the research on restricting PRBC transfusions but also proves that a computerized approach to transfusion medicine, in this patient populations, could reduce PRBC use.[90]

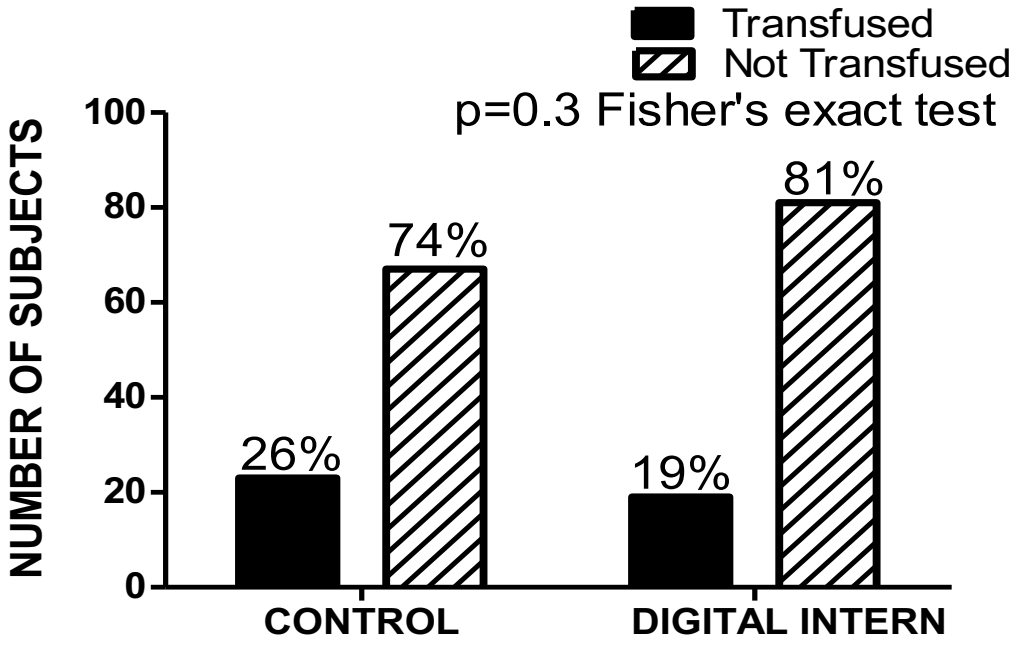


Figure 21. Number of donor patients transfused in the control and treatment groups.

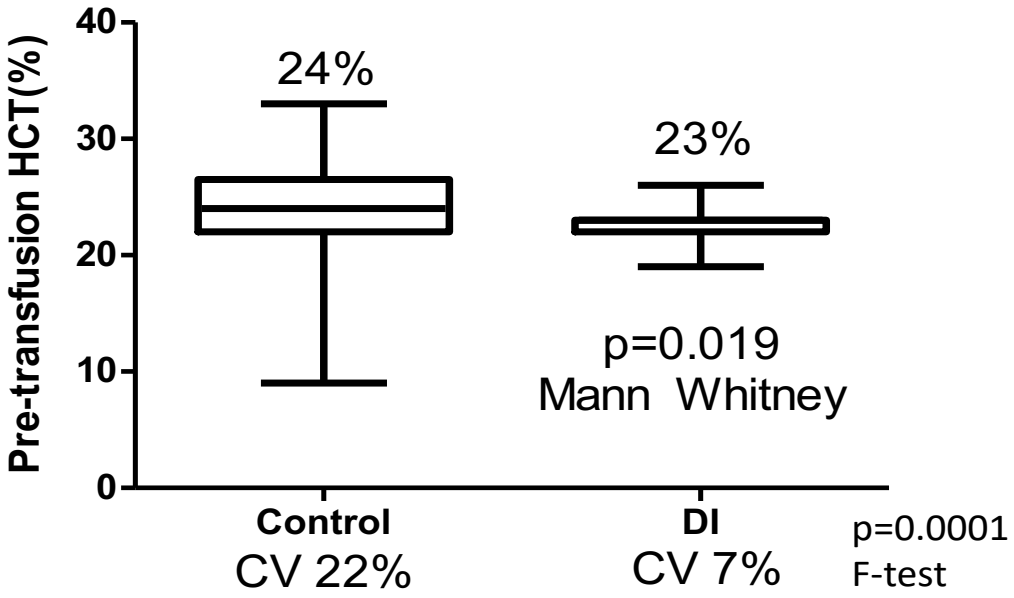


Figure 22. Pre transfusion organ donor hematocrit with median reported.

Transfusion medicine has placed an emphasis on defining more standardized practices for the use of blood products, a process termed patient blood management. These efforts have successfully shown that institution wide, standardized transfusion policies can reduce morbidity associated with transfusion without compromising excellent clinical outcomes for patients.[112-114] Many of these protocols have adopted more restrictive use of RBC transfusion with lower transfusion thresholds than have been historically considered necessary. In many studies' morbidity, defined by the incidence of end organ dysfunction, has been shown to be more prevalent in patients who were liberally transfused compared to those managed with more restrictive protocols. The one exception to this appears to be in the care of patients with ischemic cardiac disease where more liberal use of PRBC transfusion has a more positive impact.[115]

Beating heart organ donors include patients who meet the criteria for brain death as well as patients on life support where continued intensive and supportive care is considered to be

futile in terms of recovery. This group of donors is the major source of organs for transplantation. Clinical care of the beating heart donor is complex due to the multiple physiologic changes seen in critically ill patients and after cerebral death. These include dysfunctional temperature regulation, altered vascular tone with its associated hemodynamic instability (usually episodes of hypotension), endocrine dysfunction, and at times coagulopathy. Care of these donors prior to organ procurement often includes the transfusion of blood products to maintain tissue oxygen delivery and support hemostasis. Similar to general clinical practice the optimal use of transfusion in organ donors is poorly understood and transfusion practices are not standardized. Historically, these donors have been managed by physicians in the ICU setting with mechanical ventilation and extensive invasive monitoring. Similar to living, critically ill patients, the continuously changing physiology of the beating heart donor requires constant interpretation of both clinical parameters and laboratory data to provide optimal care. In this group of organ donors, the goal of optimal care is to preserve functioning organs for transplant. Guidelines/opinions on the medical management of this group of organ donors have been published; however, practice is quite variable from institution to institution as well as from physician to physician.

The use of blood products in beating heart donors is no exception to this variability in practice, and published guidelines can be found to support any of the different opinions/approaches to care. Only a single institution retrospective review from the University of Missouri detailing the transfusion practices in organ donors has been published. They report a PRBC transfusion rate of 69% in a presumed physician managed setting with no clearly defined transfusion threshold in place.[116] Some sources recommend transfusion to maintain hemoglobin over 10g/dL until the time of organ procurement for all donors,[117] while others have set the

threshold at 9 g/dL for all donors.[118] Some guidelines recommend different transfusion thresholds based on the clinical stability of the donor. For example, the Brazilian Associations of Intensive Medicine and Organs Transplantation recommend to transfuse all donors with hemoglobin < 7g/dL, not to transfuse any donor with hemoglobin >10g/dL, and to only transfuse donors that are between 7 and 10g/dL if they are not hemodynamically stable.[119]

The Digital Intern's proprietary computer-based algorithm is designed to provide standardized care to beating heart organ donors and to minimize physician time required to care for this group of patients. The program interfaces directly with the EMR and, based on set parameters, provides patient care orders to guide the care provided by ICU nursing and other ancillary staff.

The program uses a hematocrit threshold of <24% to determine the need for PRBC transfusion then uses mathematical algorithms including the hematocrit and the donor's weight to calculate the number of units (or volume) of PRBCs to transfuse. The Digital Intern then directly enters into the EMR an order for PRBC units, an order to transfuse those units, and orders for follow-up lab testing. One could argue that the hematocrit target of 24% could have been reduced to 21% because the data supports non-cardiac ischemia patients having a hematocrit of that value. Perhaps adjusting the threshold could be addressed in this patient population in a future study.

As shown here, delegating to the Digital Intern removed direct physician input and led to a non-significant reduction in the transfusion rate from 26 to 19%. Although the transfusion rate only decreased modestly the number of units per transfusion was significantly reduced from a median of 2 units in the control group to 1 in the Digital Intern patients. An equal number of donors were transfused more than once in each group and although not statistically significant

there is a trend toward fewer total units transfused per donor in the Digital Intern group from 2.5 units/donor (58 units) in the control group to 1.8 units/donor (34 units) in the Digital Intern managed group. Taken as a whole this data indicates that the use of the Digital Intern reduces the use of PRBC transfusion in the beating heart donor population.

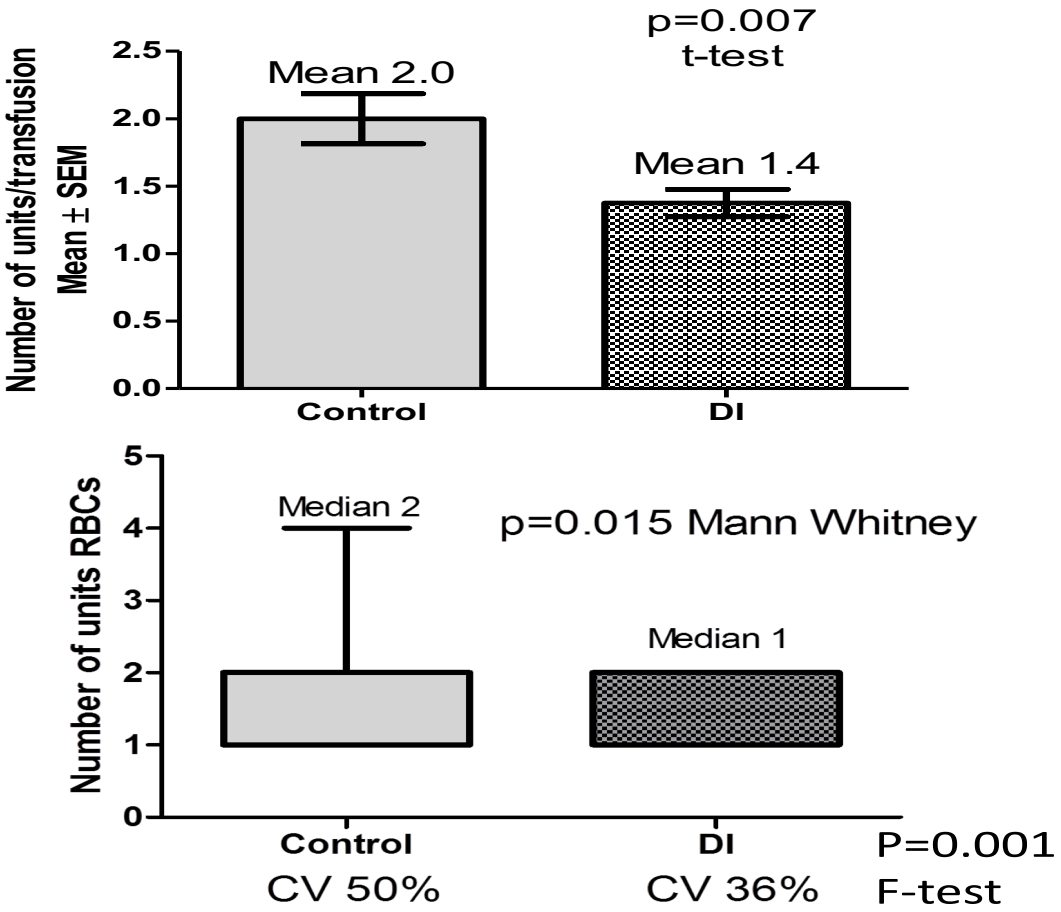


Figure 23. Number of PRBC units transfused in the control and treatment groups.

The data presented here clearly shows improved standardization of transfusion practice with implementation of the Digital Intern. There is significantly less variability in the number of units transfused and in the indication for the transfusion based on the pre-transfusion hematocrit.

CV for the pre-transfusion hematocrit was three times more (22 vs 7%) in the physician managed group compared to the Digital Intern. Similarly, the number of units transfused was much more consistent in the Digital Intern group. This reduced variability in practice is the result of the use of a standard algorithm to determine which donors to transfuse and how much blood should be given for a particular pre-transfusion HCT. In this study population, if the Digital Intern algorithm were to be applied to the control group 48% of the transfusions would not have been prescribed.

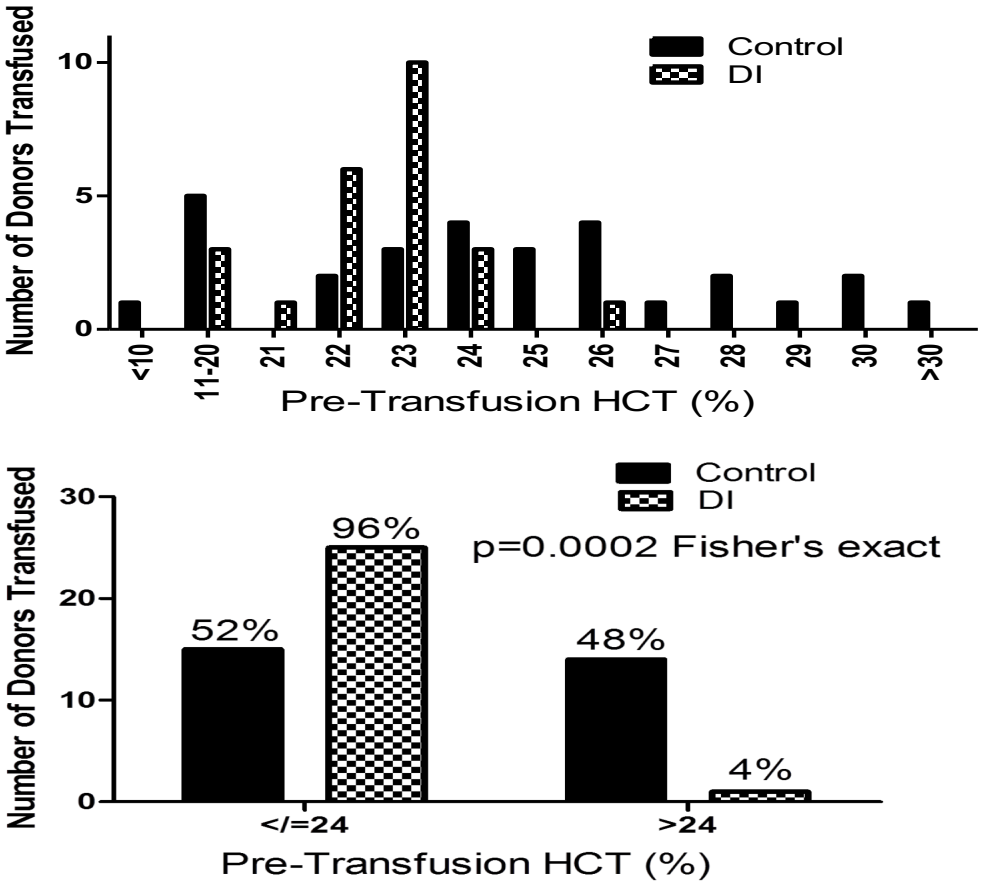


Figure 24. Number of donor transfusions as a function of pre-transfusion hematocrit.

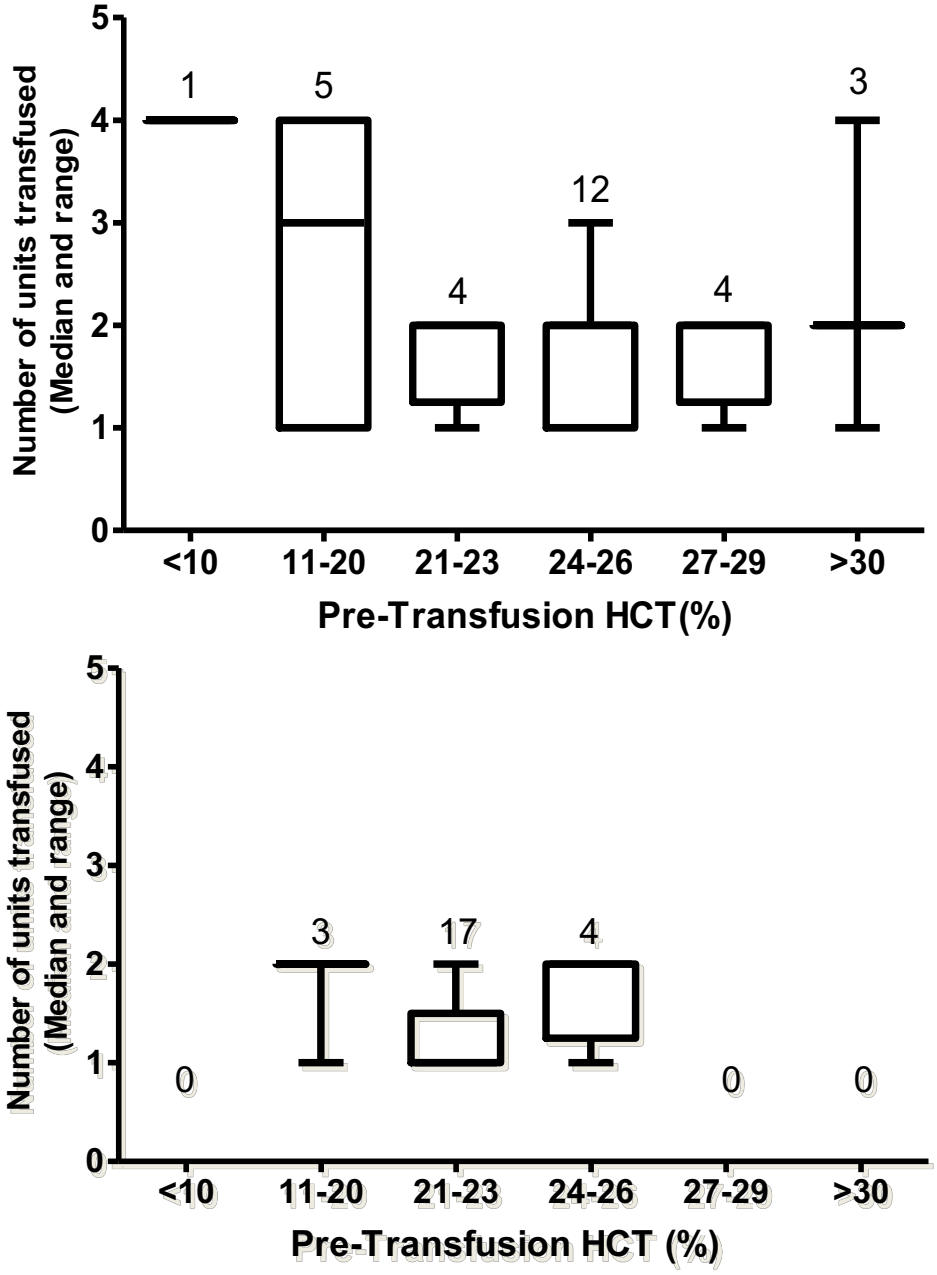


Figure 25. Number of units transfused for a given pre-transfusion hematocrit level.

Based on the transfusion practices seen in this study, the Digital Intern system has the potential to significantly reduce the use of PRBC transfusions in beating heart organ donors over time.

	Control	Digital Intern	p value
Organs/ Donor	3.54 organs	4.07 organs	0.019
Organs Used/Donor	3.30 organs	3.84 organs	0.019
Organs Discarded/Donor	0.24 organs	0.23 organs	NS

Table 5. Organs per donor procurement data.

The ultimate outcome in this population is the availability of optimally functioning organs for transplant. The long term function of transplanted organs is beyond the scope of this study however the number of transplantable organs procured per donor has been consistently higher since the implementation of the Digital Intern in these donors. This would suggest an improvement in transplant outcome yet it remains to be seen if donors managed via the Digital Intern system will result in an increase in long term organ function. Finally, preliminary data presented in abstract form alone suggests a significant savings of health care dollars in the form of reduced physician ICU billable hours of work to care for this group of donors.

In the previous report on the PRBC transfusion practice of the Digital Intern it was demonstrated that the computer support approach was more consistent in terms of its ability to limit transfusion to the defined, evidence based transfusion threshold when compared to physician managed transfusions; however, the effectiveness of the transfusion dose calculated by the Digital Intern in terms of achieving the set hematocrit target and the duration of the targeted dose was not known. We therefore set out to describe the outcomes of PRBC transfusions

prescribed by the Digital Intern in the organ donor population in order to provide further support for the use of this algorithm-based approach to PRBC transfusion.

Over a five-year period 120 organ donors were cared for with the assistance of the Digital Intern system. Of these 22 donors (18%) were transfused RBCs during the donor period. Six of the 22 were transfused twice during the donor period for a total of 28 transfusions. No donor was transfused more than twice.[90]

Thirteen (59%) donors were diagnosed with brain death and nine (41%) had medical/neurologic status where continued medical intervention was considered futile and were organ donors after cardiac death. Thirteen transfused donors were medical admissions of which eight (62%) had hypertensive/vascular anomaly associated intracranial hemorrhage resulting in anatomic cerebral injury. The other five medical admissions were the result of cardio-pulmonary disease (including unwitnessed cardiac arrest and pulmonary emboli) that resulted in diffuse anoxic brain injury. Nine transfused donors were admitted following trauma events (eight motor vehicle accidents and one gunshot wound to the head) all of whom suffered from traumatic brain injury as the cause of either brain death (6 cases) or as the determining factor in medical futility assessment (3 cases).

Donor Type	**Brain Dead Donor 13 (59%)** **Donation After Cardiac Death 9(41%)**
Mechanism of Death	Medical Admission 13(59%) Trauma Admission 9(41%)
HCT Pre-Tx (mean)	22.8 $\pm$ 1.7 %
HCT Post-Tx (mean)	27.1 $\pm$ 2.7 %
HCT change (Post-Pre, mean)	4.2 $\pm$ 2.6 %
Units per Tx	1.4 $\pm$ 0.5 units (range 1-2 units)
HCT change per Unit (mean)	3.2 $\pm$ 2.1 %/unit

Table 6. Organ donor transfusion data.

In twenty-six of the 28 transfusions there was at least one follow-up hematocrit to assess for response to the transfused dose prescribed by the Digital Intern. The post transfusion target hematocrit of 24% also used in the previous study was achieved in all but one PRBC transfusions (25/26 transfusions, 96%,).

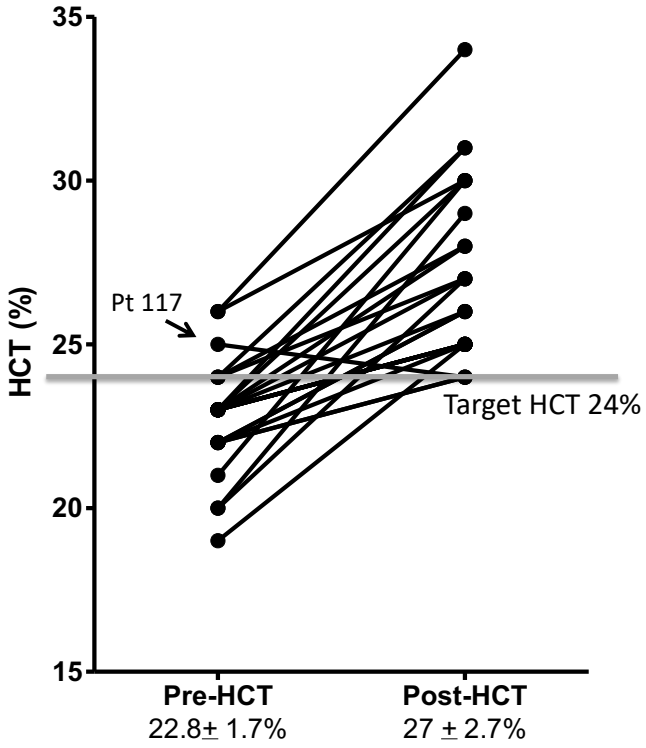


Figure 26. Change in hematocrit after transfusion prescribed by the Digital Intern.

The mean number of units transfused was 1.4 ± 0.5 units. The mean change in hematocrit after transfusion was 4.2 + 2.6% (range -1 to 9%), thus the mean change per unit of RBCs was 3.2 + 2.1% (range -1 to 8%). The mean time from the last transfusion until organ procurement was 19.8 ± 12.0 hrs. (range 7.2-55.2 hrs.) and an average of 2.9 ± 1.7 follow-up hematocrit values were done between last transfusion and procurement (range 1-8 hematocrit

values). Two transfusions were done just prior to procurement and no follow-up hematocrit was obtained. Three transfusions were ordered outside of the Digital Intern's threshold of 24% (one at 25% and two at 26%). These units were transfused in the first few hours of transition to donor status and may have been ordered in the window period after donor decision was made and before the Digital Intern system was initiated for these cases.

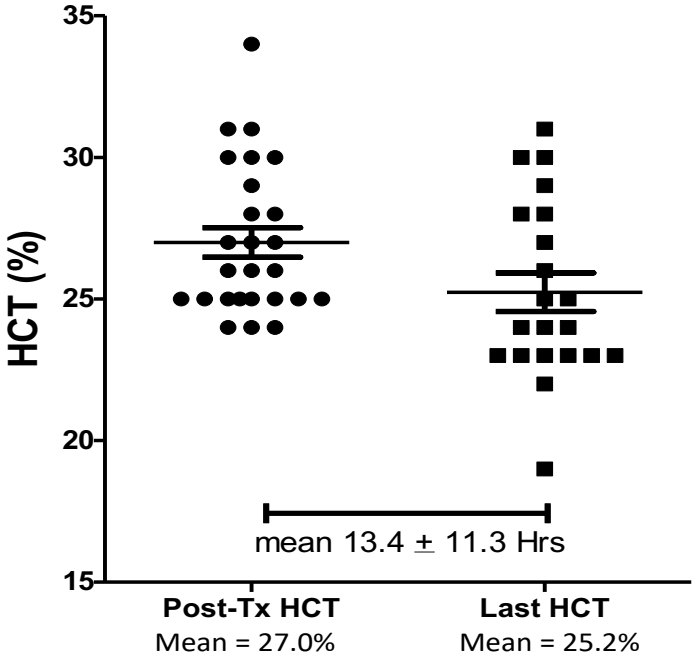


Figure 27. Post transfusion hematocrit drift prior to organ procurement.

After transfusion there was a gradual decline in hematocrit over time in all but one transfusion where the HCT remained stable within 1% over 11hours of follow-up. The mean decline in hematocrit (post-transfusion hematocrit - last hematocrit done) was 1.9% (median 2.0%, range -1 to 5%) over a mean of 13.4 + 11.3 hours between the values (median 10 hours, range 1.5 to 50 hours. This translated into a rate of hematocrit decline 0.24 $\pm$ 0.25% per hour after transfusion (median 0.15%/hour, range -0.1 to 0.8%/hour).

Six of the twenty-two transfused donors were transfused twice during the donor period. Three of these cases were trauma admissions (2 motor vehicle accidents and one gunshot wound) and three were medical cases (two cases with intracranial hemorrhage and one case of unwitnessed cardiac arrest). The mean time of the donor period for this group was 41.7 ± 15.3 hours which was longer than the mean donor time for the entire Digital Intern cohort of cases at 27.2 ± 16.6 hours (one tail t-test p=0.03). The mean time between transfusions was 16.7 ± 8.0 hours (range 5- 30 hours) and the mean time from the last transfusion until organ procurement was 18.1 ± 6.2 hours (range 10.4-28.6 hours) which is not different from the 19.8 hours seen in the single transfusion cases. There was a mean of 3 ± 1.4 hematocrit values checked between transfusions (range 1-5 hematocrit values). In one case two transfusions were given based on consecutive hematocrit values. This is also the only case where the post transfusion hematocrit did not achieve the target hematocrit after the first transfusion. This patient was admitted with multiple traumatic injuries after a motor vehicle accident and the transfusions were early on in the donor time period and were likely due to ongoing hemorrhage.

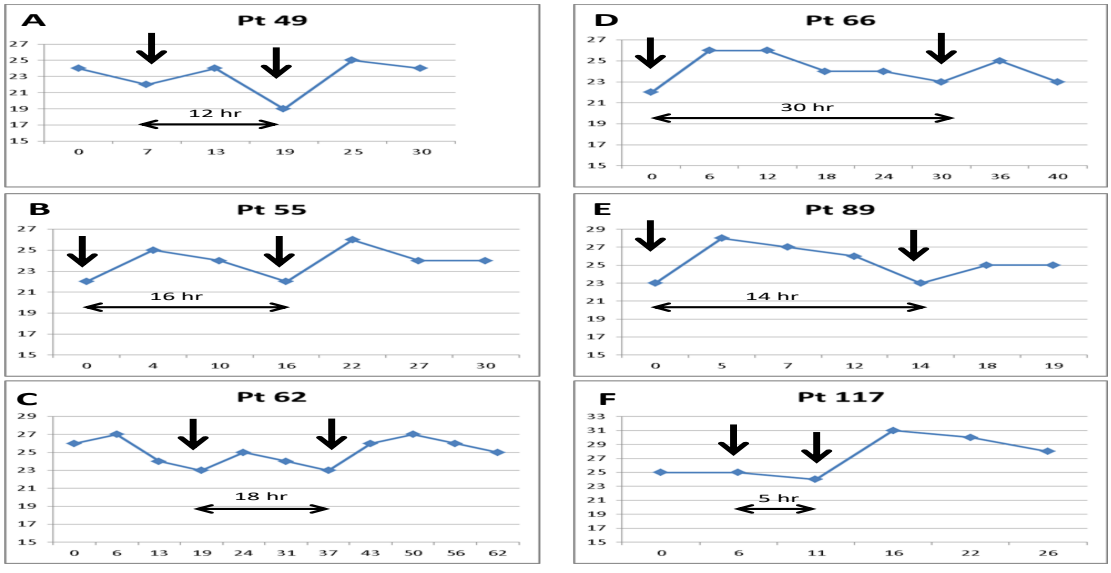


Figure 28. Hematocrit values for donors that required a second transfusion.

Minimizing inappropriate blood use through evidence-based guideline is one of the five main tenets of patient blood management. In terms of PRBC transfusion the goal is to achieve the optimal balance between transfusing enough blood to prevent end organ damage and over transfusing exposing the patient to unnecessary risks of transfusion including exposure to infectious agents, transfusion reactions, and the possibility of alloimmunization.[112, 120-123] The decision to transfuse is commonly initiated or triggered by hemoglobin or hematocrit thresholds that have been well defined over the past decade and are based on evidence in support of restrictive transfusion practices. These recommendations have been formalized in the American Association of Blood Bankers guidelines and guidelines from other groups.[124] The guidelines are straight forward and a threshold hematocrit of 21% is recommended for most patients.

The amount of blood be transfused is not addressed by the use of transfusion thresholds. The transfusion dose can be determined/calculated based on the use of a defined target hematocrit to be achieved with the transfusion. In other words, a transfusion threshold is used to indicate when to transfuse and a transfusion target is used to determine how much blood to transfuse. Ideally the prescribed transfusion will achieve the targeted hematocrit goal and, in the absence of ongoing blood loss or destruction, maintain that target hematocrit for as long as possible.

Despite being widely published and well accepted, clinical guidelines are not always well followed in day to day practice. The application of transfusion guidelines is no exception to this. In a study by Seitz, et al 42% of 59 intensive care units studied reported having restrictive transfusion policy in place that were in line with current AABB guidelines however transfusion

rates in patients with hemoglobin > 7 were as high as 20% indicating a substantial lack of compliance with the institutional guidelines.[125]

The Digital Intern provides patient specific, actionable recommendations, and management options that are presented at appropriate times to enhance care. When used in conjunction with an EMR system these programs can be constructed with defined patient specific data and should be crafted using evidence-based knowledge. One of the most commonly studied examples of this technology is the Best Practice Alert (BPA). A BPA can be triggered when pre-set variables are identified or when pre-defined actions such as patient orders are initiated. BPAs have been successfully used to remind ordering providers of the AABB guidelines for PRBC transfusions with reported reduction in the use of PRBCs by as much as 40%.[126-129] Most of the reduced PRBC use in these cases is seen when the BPA indicates to the ordering provider that the patient's most recent hematocrit does not meet thresholds for transfusion. However, this type of system still leaves the opportunity to over-transfuse when more units than needed are transfused, in other words when the dose of transfusion is in excess. This is where our current support algorithm, the Digital Intern goes a step beyond what electronic decision support has accomplished to date by using a target-based approach and calculates a blood transfusion dose to achieve that target. We demonstrated that this approach provides significant increased standardization of transfusion practice in the organ donor population at our institution. In the second study we demonstrated that the calculated dosing of PRBC transfusions by the Digital Intern system was able to achieve its targeted hematocrit in all but one (25 of 26 transfusions, 96%) of the evaluable transfusions indicating that the calculated dose rarely falls short of the target. In several cases the post transfusion increase in hematocrit was more than expected and is likely due to the variable physiology of the donor population

including fluids shifts etc. Equally, if not more importantly the post transfusion hematocrit levels were maintained for an average of approximately 20 hours prior to organ procurement. This demonstrates that the calculated transfusion dose did not require immediate re-transfusion due to under dosing. In all but one transfusion there was a slow decline in hematocrit over time (0.24%/hour). This was not sufficient to warrant a second transfusion in 16 of the 22 cases. There were other cases with ongoing blood loss, and longer donor time periods that were transfused more than once; however, as with the single transfusions the required target was achieved in all of the second transfusions. In these cases, the time between transfusions was more than 16 hours and the time from the second transfusion to procurement was 17 hours. This helps support the Digital Intern's prescribed transfusions were not under-dosed. The Digital Intern provided PRBC transfusion dosing that consistently and sustainably achieved the intended target hematocrit in the organ donor population studied. The published data on the use of the Digital Intern in the organ donor populations was subsequently used to drive the application of this system to all inpatient populations.

7.7 Using a Targeted Approach to PRBC Transfusion – General Inpatient Population

Patient blood management (PBM) is the process of implementing evidence-based guidelines and processes to assure the appropriate use of transfusion with the ultimate goal of optimizing patient outcomes. Minimizing the inappropriate use of blood products based on adherence to transfusion guidelines is one of the main tenets of PBM.[123, 126, 130] Historically single unit PRBC transfusions was thought to be inadequate to correct anemia and hence was not considered to be worth the risks associated with transfusion. This biased, none-evidence-based thinking made the 2-unit PRBC transfusion the norm for decades… "If you're going to give 1

unit give 2." The thinking about potentially frivolous transfusions in the 1980's became a hot topic with the HIV/AIDS epidemic. There were continued improvements in the safety of the blood supply but concerted efforts to reduce the use of blood products and change the standard two unit PRBC transfusions to single unit transfusions have pushed organizations to better control their blood product usage. Numerous reports in the literature have shown significant reductions in the unnecessary use of PRBCs as a result of PBM programs that encourage a single unit transfusion practice suggesting that increasing the rate of single unit transfusions (over multiple unit transfusions) is one of the most powerful means of reducing inappropriate PRBC use.[109, 131-133]

The use of electronic decision support in the form of standardized blood order sets and BPAs have been shown to improve compliance with the appropriate use of single unit RBC transfusions. Defaulting PRBC orders to single unit transfusions in electronic orders is a well-documented maneuver to encourage reduced blood use and in March of 2016 we modified our PRBC order set to default to one unit for all orders placed.

Two of our papers reported on the implementation of a group of computer algorithms (previous chapter) that together comprise the Digital Intern had demonstrated success in reducing variability and decreasing PRBC use. This was in-line with current transfusion guidelines for the general inpatient population. Given the promising performance of the Digital Intern PRBC algorithm in the organ donor population we expanded the use of the algorithm to the rest of the in-patients. The Digital Intern PRBC dose calculator was embedded into the PRBC order set of the EMR, Health Link (Epic, Verona WI, USA). This new version of the algorithm has been named the Blood Utilization Calculator or BUC. When a non-surgical indication for RBC transfusion is selected the BUC calculated a recommended transfusion dose, in number of units,

and the recommended dose is inserted automatically as the number of units ordered. The ordering provider can override the recommendation by manually changing the number of units in the order.

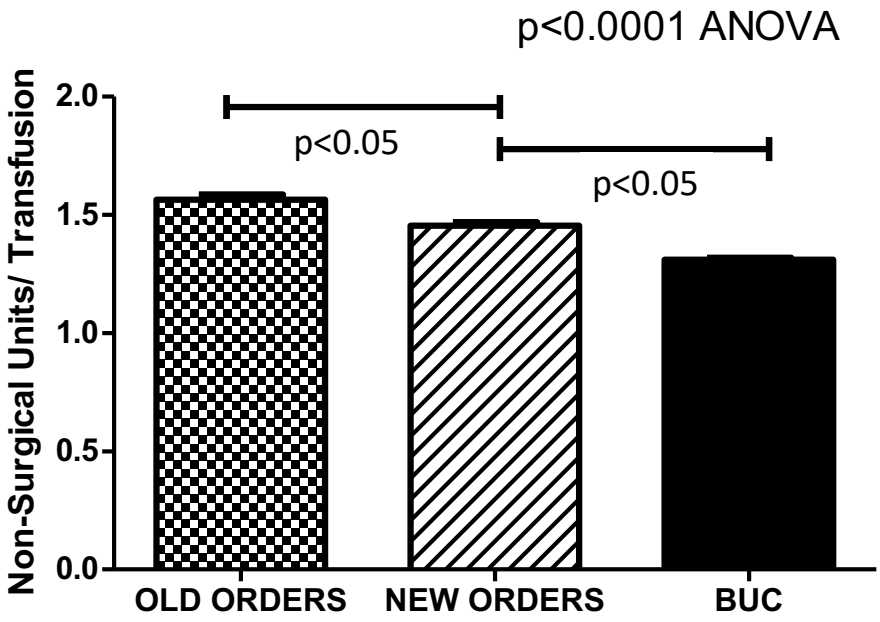


Figure 29. Original Orders, 1 Unit Orders, and BUC orders as sequentially rolled out.

The effects of electronic one-unit default orders followed by the implementation of the BUC, which might recommend up to 6 units of PRBCs, on the use of single unit transfusions at our institution were evaluated. In addition, we explored how the BUC calculated recommendations were accepted based on the clinical services that are ordering RBC transfusions in both medical and surgical (post-operative) settings. Finally, the financial impact of these interventions were reviewed in terms of cost reductions secondary to reduced PRBC use over time.

The BUC was activated within the adult red blood cell order set on July 30, 2016. Prior to its implementation a computer-based training/educational module was released to all medical

staff through organization wide newsletter. The module contained both a written description of the calculator as well as a slide set that included screen shots of examples of how the BUC recommendations would be presented to the ordering provider.

Code	Indication
R1	Life-threatening hemorrhage or anticipated/ongoing blood loss.
R2	Suspected bleeding, symptomatic or drop in Hemoglobin ≥ 3g/dL or Hematocrit drop ≥ 10%.
R3	Target Hgb > 7 g/dL or HCT > 21% in acute upper GI bleeding.
R4	Target Hgb > 7 g/dL or HCT > 21% in stable, non-bleeding patient.
R5	Target Hgb > 8 or HCT > 24% in patients who are myelosuppressed/ bone marrow transplant or symptomatic with disease significantly impaired O_2 delivery, acute coronary syndrome (e.g. MI, unstable angina).
R6	High risk patients (ECMO, TAAA, stroke/cerebral vasospasm, sickle cell disease).
R7	Massive Transfusion.
R8	Other

Table 7. PRBC Transfusion indications.

Figure 30 shows two of the example screen shots used in the example based training module. In panel A the BUC would recommend 1unit, for indications R3 or R4, and 2 units for indication R5. The recommendation in panel B would be for no transfusion (0 units) as the patient in the example is already at or above the selected target hemoglobin/hematocrit level. When no transfusion is recommended by the BUC an additional comment is presented stating

"Based on this indication the patient does not require blood at this time because they are already above the target hemoglobin/hematocrit level".

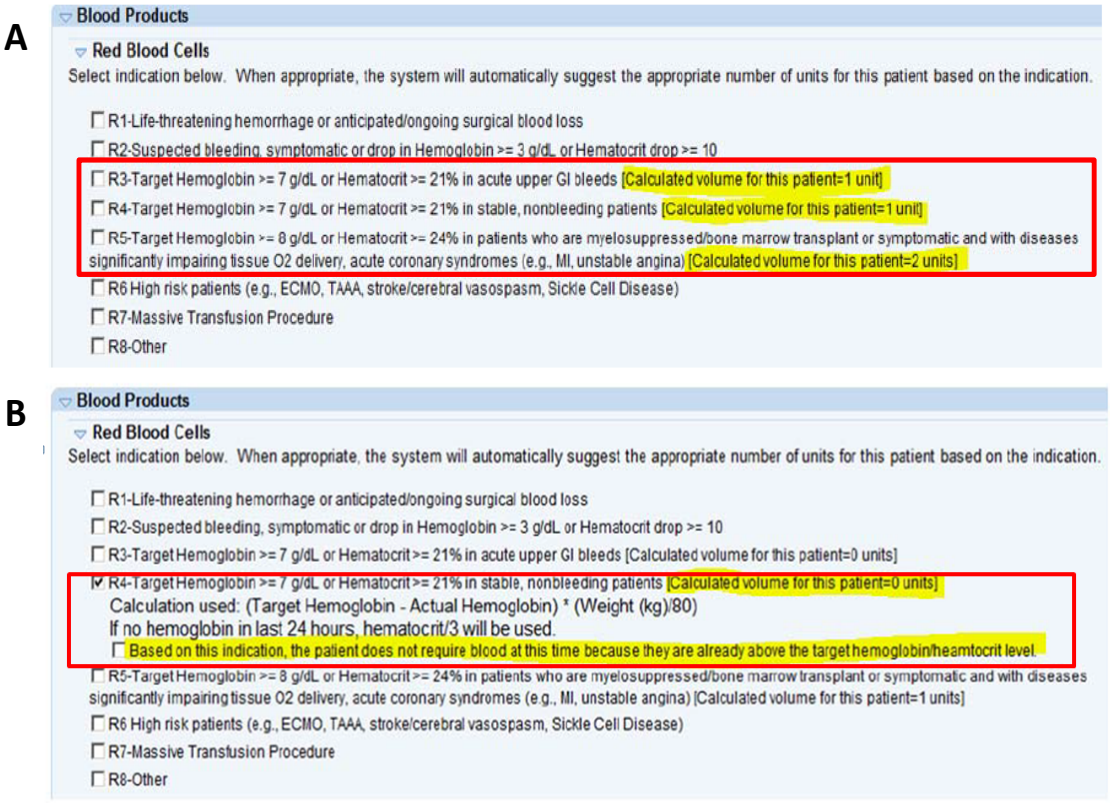


Figure 30. EMR order entry screen.

In the 24 months researched orders for 35,503 PRBC units were placed under one of the eight selectable indications shown in table 1 for a mean of 1,479 units per month. Of these units 12,296 (mean 512 units per month) were ordered under the non-surgical indications of R3, R4, or R5 from which a BUC recommendation for transfusion dose would be presented to the ordering provider. This represented 35% of the total RBC units ordered organization wide (range 21-48% of total units per month).

Over the entire study time period a significant increase in the use of single unit transfusion was seen with incremental changes after each of the two interventions intended to drive this effect. The number of one-unit transfusion orders written for the three non-surgical indications increased from 247 ± 19 orders/month in the historical control time period to 358 ± 19 orders/month after the order set defaulted to one-unit transfusions (New Orders) and then again to 445 ± 14 orders/month after implementation of the BUC.

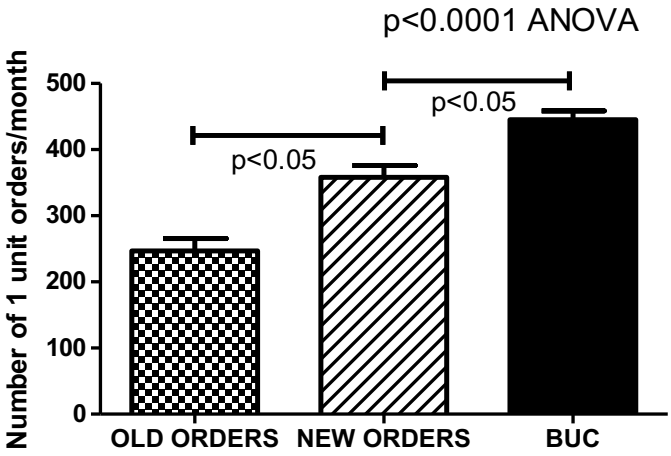


Figure 31. Progress of 1-unit orders per month as rolled out sequentially.

Similarly, single unit transfusions expressed as a percent of all transfusions increased from 38%, to 52% and then to 59%, again, all statistically significant increases. Finally, the ratio of one to two-unit transfusions demonstrated the same significant increase from 0.72 in the historical control orders to 1.20 in the New Orders and then up to 1.67 after the implementation of the BUC.

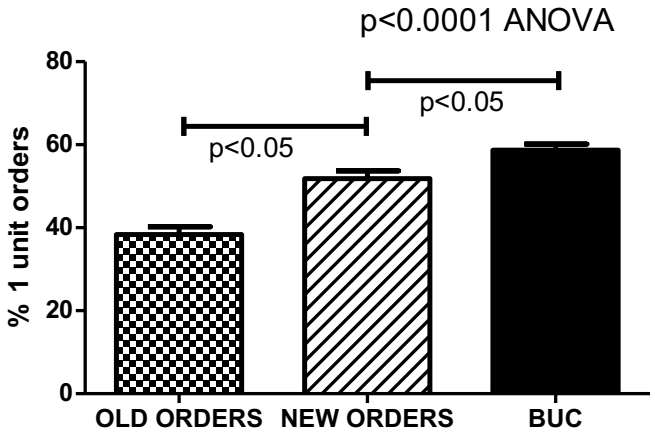


Figure 32. The percentage of 1-unit orders as rolled out sequentially.

There were 8,087 transfusions (317 transfusions per month on average) ordered under R3, R4, or R5 (the BUC indications) during the study; 1,069 in the historical orders time period, 1,942 during the New Orders time, and 5,075 after the BUC was in use. There was a 19% decrease in blood used per transfusion (0.3 units less per transfusion, p< 0.0001 by ANOVA) after the implementation of the BUC.

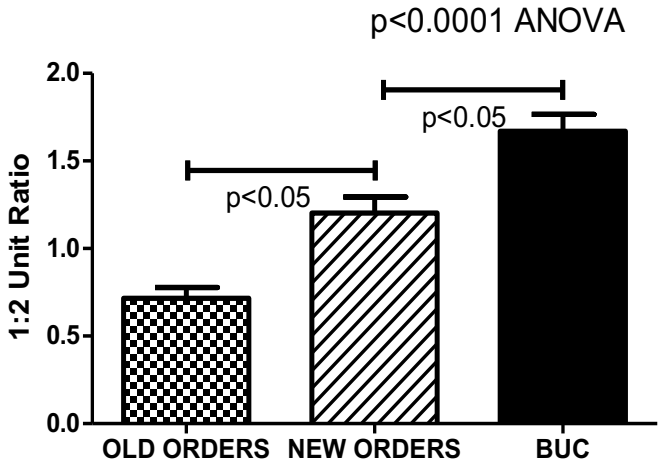


Figure 33. Ratio of 1 to 2 unit PRBC orders as rolled out sequentially.

Over the last 5-7 years the average acquisition cost for a unit of PRBCs in North America has been approximately $225 ($210-245/unit).[134] At this rate the savings in reduced PRBCs is approximately $257,000.00 per year. This represents approximately 4-5% of our laboratory's annual blood budget. Activity based cost analysis takes into account the multiple additional costs of transfusing a unit of blood and are estimated to be between $750-$1,000.00 per PRBC unit (mean $875.00/ unit transfused). The estimated cost savings in activity-based costs would be approximately $990,000.00 annually since the BUC started.

The hospital dashboard monitors the PRBC units ordered for all indications. For the three indications that trigger the BUC; R3, R4, and R5, the dashboard keeps track of both the number of units recommended by the BUC as well as the actual number of units ordered for those indications.

Since the BUC implementation, there has been a consistent discrepancy between the number of units recommended by the BUC and the actual number of PRBC units ordered in favor of the later. Over the 14 months of BUC recommendations there has been an average of 71 $\pm$ 19 units/month (range 36-110 units/month) more ordered (blue line) than recommended (green line). Figure 34 demonstrates what the BUC recommended and what was given prior to the go live date. It also demonstrates what the BUC would have recommended had the system been live prior to the go live date.

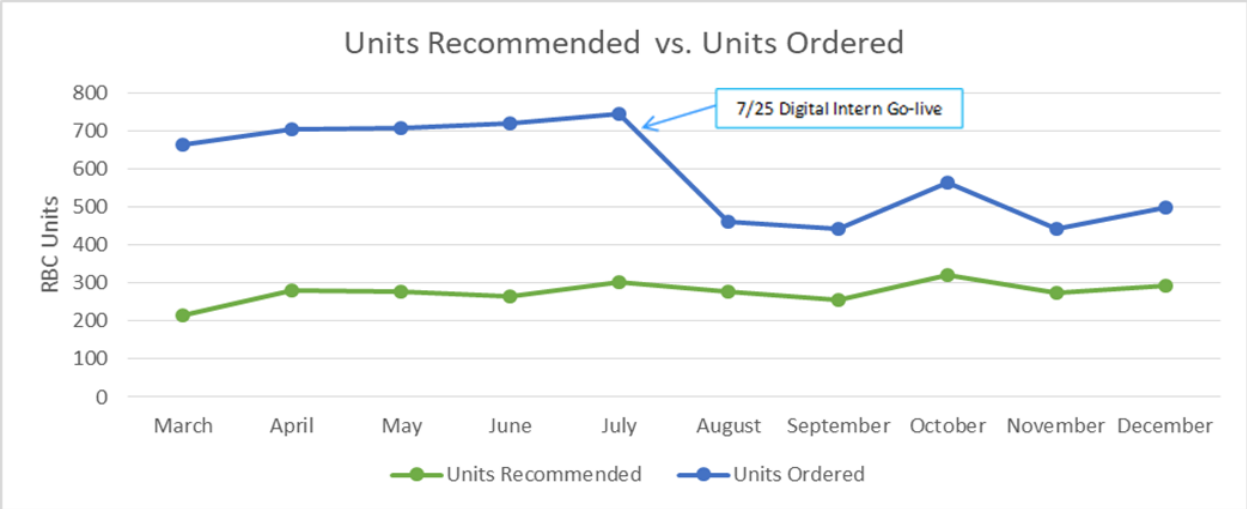


Figure 34. Units ordered and recommended over time.

The dashboard also monitors acceptance of the BUCs recommendation for PRBC units by clinical service for each order. Many services only transfuse PRBCs a few times per year so we limited this analysis to services that ordered non-surgical PRBC transfusions a minimum of 100 orders over the 14-month study (7-8 orders per month on average). In this group there were 16 medical and 12 surgical services represented. The medical services placed 73% of the orders and the surgical services placed the remaining 27% of orders under the BUC indications.

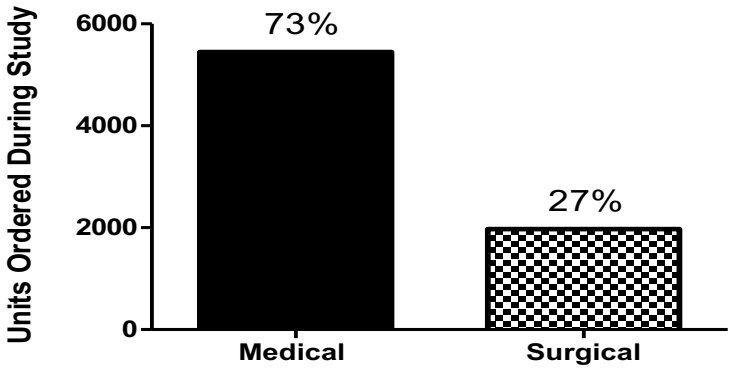


Figure 35. Percentage of units ordered by medical and surgical services.

The BUC recommended transfusion dose was accepted by the ordering provider in 49% of orders. The 16 medical services followed the BUC recommendation in 57 $\pm$ 3% of orders (range 35-71%) compared to 31 $\pm$ 3% of the orders from the 12 surgical based services studied (range 11-60%, $p < 0.0001$ by student-t test).

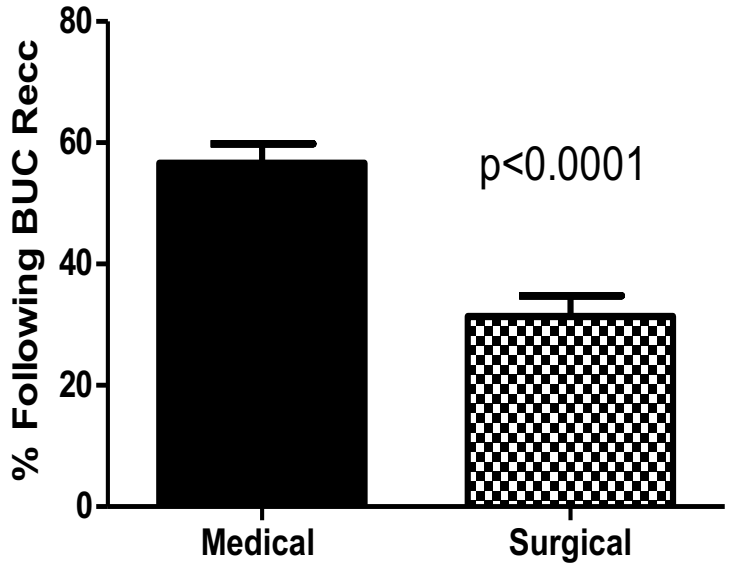


Figure 36. Percentage of providers following BUC recommendations by service type.

Although the medical services accepted the BUC recommendation at a higher rate than the surgical services, because the medical services accounted for over 70% of the orders placed the non-compliance with the BUC recommendations was actually more evenly distributed between the services (medical 58% and surgical 42% of the gap, based on the actual number of orders from each group).

	Count of Orders	% BUC Acceptance
GENERAL MEDICINE 3B	126	71
GENERAL MEDICINE 2B	109	71
FAMILY MEDICINE	182	70
HOSPITALIST MEDICINE 1	233	69
GENERAL MEDICINE 1A	124	69
HOSPITALIST MEDICINE 3	205	69
HOSPITALIST MEDICINE 2	192	68
HOSPITALIST MEDICINE 5	190	65
GENERAL MEDICINE 2A	127	65
GENERAL MEDICINE 3A	122	62
HOSPITALIST MEDICINE 4	174	62
EMERGENCY MEDICINE	157	60
BONE MARROW TRANSPLANT	700	58
MEDICAL CRITICAL CARE	582	56
HEMATOLOGY	1088	53
ORTHOPEDIC SURGERY	189	46
NEUROSURGERY	140	45
SURGICAL ONCOLOGY	209	40
EMERGENCY GENERAL SURGERY	113	40
VASCULAR SURGERY	193	37
SURGICAL CRITICAL CARE	309	37
TRANSPLANT	117	36
CARDIAC SURGERY	196	34
TRAUMA SURGERY-ADULT	115	32
LIVER TRANSPLANT	182	28
RENAL TRANSPLANT	147	24
GYNECOLOGY	118	24
UROLOGY	111	10

Table 8. Acceptance of BUC recommendations.

Of the 71 units/month gap between the recommended units and the actual units ordered, 82% of the recommendations that were not followed were PRBC orders in excess of the BUC suggestion. These were split between zero-unit recommendations that were transfused one unit (35%) and one-unit recommendations that were transfused 2 units (47%). Given this information, there is a significant opportunity for reduced PRBC use by focusing on closing the gap between the BUC recommended dose and the ordered dose. A complete closure of the gap could result in an additional savings of as much as $745,000 on an annual basis.

% reduction in gap	Number of units reduced/month	Reduced acquisition costs/month	Reduced Activity Based costs/month
25%	18	$4,050.00	$15,750.00
50%	36	$8,100.00	$31,500.00
75%	53	$11,925.00	$46,375.00
100%	71	$15,975.00	$62,125.00

Table 9. Potential cost reduction by closing the gap between BUC recommended units and actual ordered units of RBCs on an annual basis.

Reducing the number of unnecessary transfusion is one of the main tents of PBM and encouraging single unit transfusions, when one unit will achieve the clinical goals, has been shown to be one of the key strategies to curb over-transfusion. Key to this change in practice is the fact that single unit transfusions are no longer considered ineffective. A Canadian study lead by Ma, mathematically manipulated the hemoglobin response to all transfusions to mimic them all being single unit transfusions and found that the single unit transfusions would have met the target hemoglobin of 7 g/dL in 98% of the cases studied.[132] In a large study in the UK, Heyes et al showed an increase in the use of single unit transfusions from 30 to 53% of all transfusions with no adverse patient effects and significant reduced costs. The Choosing Wisely campaign has also embraced the concept of single unit transfusion and has spearheaded the "Why give 2 when 1will do" concept.[109, 131]

The use of single unit transfusion has also been supported in high risk groups including patients with hematologic cancers. Berger et al studied the effects of a single unit transfusion policy implemented by their institution on patients with hematologic malignancies undergoing intense chemotherapy and/or bone marrow transplant. The hospital policy limited blood availability to only one unit at a time. They found an increase in single unit transfusions from 25

to 84% as well as a 25% decrease in total units transfused in this patient population.[135, 136] No changes in adverse outcomes or survival were identified.

The use of electronic/computer decision support has been demonstrated to both encourage and or enforce adherence to well accepted transfusion guidelines (most of which follow restrictive transfusion practice) including the preferred use of single unit transfusions.[126, 127, 137] Modification of provider's orders to default to single unit transfusions has been used successfully used to reduce multiple unit transfusions in several published studies. Yerrabothala and colleagues demonstrated that the proportion of 2 unit transfusions decreased from 47 to 15% when a single unit policy was adapted with a total decrease in units transfused of 27%.[137] Similarly Yang et al initiated a "Why give 2 when 1 will do" computer based campaign at three community hospitals and showed an increase in single unit transfusions from 38-71%.[133]

Our group has focused our PBM electronic decision support on the development of target based, transfusion dose calculating, algorithms. These algorithms were originally evaluated in the transfusion of organ donors prior to procurement where we have demonstrated improved standardization of transfusion practice[112] and transfusion doses that met a selected target hematocrit in 96% of transfusions.[123, 124] This data prompted a larger exploration of how embedding the PRBC calculator from the Digital Intern program into the EMR PRBC order set has resulted in a significant increase in single unit transfusions. The increase in single unit transfusions we report here was initially the result of a simple default to one unit in all of the PRBC orders initiated. The subsequent implementation of the BUC resulted in a further increase in single unit orders while allowing for multiple unit orders when more than one unit is required to meet the selected indication target. The calculated dose recommended by the BUC was subsequently ordered in just less than one-half of the orders placed. Not surprisingly, in the

majority (82%) of the orders that did not follow the BUC recommendation, more units than the BUC calculated were ordered resulting in the gap in Figure 34. There are several possibilities that could account for this gap, one being that there is a mistrust of the BUC dosing, resulting in lack of buy-in from ordering providers for the BUC recommendation. Before the BUC was "live" in the medical record an educational description of the calculator including a slide set with examples of the BUCs functionality was distributed to the entire medical staff via a regularly circulated hospital newsletter. This educational effort was not a mandatory training so it is likely that many providers did not review the materials and thus were not aware of the BUC or its purpose and function and therefore may have been reluctant to follow the automated recommendations presented to them. For those clinical services that are most commonly failing to consider the BUC recommendations, clinical service-specific education about the BUC functionality has been planned in hopes of improving buy-in. This should help close the gap over time. When this re-education is complete we plan to re-assess the acceptance of the BUC recommendations and expect to see an increase in BUC acceptability. Another potential factor to account for the gap is the reluctance to follow the recommendation based on a concern that the calculator may not be applicable to certain patient populations. In discussion with clinicians in hematology, one such group are those patients with hematologic diseases that has render them transfusion dependent. This is what has prompted the development of the predictive calculator that is discussed in this dissertation.

Finally, the continued belief that single unit transfusions are of no clinical utility is still prevalent among ordering providers and overcoming this bias with targeted education will be key to continued improvement at our institution.

The financial benefits of reducing PRBC transfusions are clear and the flip in the 1:2 unit transfusion ratio we have seen has resulted in decreased blood costs. Increasing compliance with the BUC recommendations and continuing to expand the indications and approaches for special subpopulations should enhance the financial benefits of the BUC in terms of total blood use. We must also remain aware of the downstream cost reductions associated with reduced PRBC transfusion including the additional infusion supplies, nursing time, associated laboratory testing, prolonged hospitalizations, and the costs associated with the adverse effects of transfusion such as work up of transfusion reactions. These additional costs are captured by activity based cost analysis which has estimated to be between $750 and $1,000 for unit of RBCs transfused.[134, 138] Based on this the cost savings from the BUC (including closure of the 71 unit/month ordering gap) could be in the $1.4-1.9million per year.

The BUC has demonstrated promise in its ability to reduce PRBC transfusion by increasing the use of single unit transfusion when indicated. With refinement of the process and improved clinician, use of the tool will continue to have a positive impact on PRBC use across the entire organization and hopefully will be translated to other facilities as well.

7.8 Target Hemoglobin Levels of Patients with Chronic Transfusion Requirements

As noted in a previous chapter, chronic PRBC transfusions carry a host of adverse consequences and yet without them, patients may not be able to survive their disease or live a quality of life that isn't forced to yield to fatigue and general malaise. WHO considers anemia a hemoglobin < 13 g/dL. A prospective trial in elderly patients demonstrated that anemia with hemoglobin levels of between 10 and 12 g/dL had a higher risk of hospitalization and mortality.[139] This could be a consequence of disease presence rather than a cause but it does

illustrate the risks associated with anemia as symptom. Most causes of anemia can be treated with the need for transfusion provided that the level of anemia is not so low that a transfusion is immanently needed. In those patients where there is need the question becomes at what level is a transfusion necessary. For critically ill patients we consider a transfusion of PRBCs for hemoglobin < 7 g/dL.[68] However, the functional status of the patient may define the level of hemoglobin needed and patients with evidence of coronary ischemia a hemoglobin level of 8 g/dL may be indicated.

Chronically transfused patients are generally assigned a target hemoglobin by their provider, possibly based upon their prior performance at a particular hemoglobin level, possibly based upon the provider's experience with that patient population. However, the target hemoglobin may not be effectively chosen for that patient's chronic need. For example, if a patient experienced fatigue when their hemoglobin was 7g/dL but had another reason for that fatigue such as a low-grade infection or reaction to a new medication, the target may be chosen to be 8 g/dL. This new target may represent the needed level as the fatigue or other symptoms may have not been entirely related to the hemoglobin level at all. When analyzing our data, we noticed that only 23 out of 117 transfusions, or 19.7%, had a target level of 8 g/dL. When asking the providers about their choice of target it was impossible to get them to give specific reasons for a particular patient's target of 8 g/dL which then begs the question, could most patients with chronic transfusion needs have a 7 g/dL target? The answer is likely yes and a lower target for patients that can tolerate it will generate less transfusion related risks, less frequent needs for transfusions and associated clinic visits, and less cost to the system both directly and as a function of opportunity cost to the patient. We've covered eliminating the inadvertent electronic "copy and paste" of previous transfusion orders as a means of reducing unnecessary PRBC

transfusions and we've gone a step further by calculating a prediction of when patients should return for transfusions to help reduce clinic visits that are too soon for PRBC needs alone. And while this approach has proven particularly useful, adding on a reduced target hemoglobin level in appropriate patients can greatly amplify the results seen in this dissertation.

Chapter 8: Conclusion

The use of computerized algorithms for the treatment of patients can significantly help tailor care to their specific needs thereby improving outcomes and reducing costs. Refinement of design and implementation that integrates fully into the workflow of healthcare providers can improve acceptance of more algorithms into medical practice. Documented in this dissertation is the use of a computerized algorithm that improved many aspects of the PRBC transfusion process. This represents only a small area of computerized decision support in medicine. Further opportunities can be imagined to exist not just in formulae but also in decision trees and forests. Potential machine learning applications can further develop algorithms based on new data and new situations where that data can be applied. For more complex physiological problems, quality machine learning applications may devise de novo algorithms that solve problems that have yet to be solved and may help us "un-learn" things in medicine that are more dogma than science. In the end, it's how we apply what we learn and our tools learn that will drive the next revolution in healthcare.

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Appendix A: IRB Approval/Application

Minimal Risk IRB (Health Sciences)
5/30/2018

Submission ID number:	2018-0725
Title:	Evaluation of the clinical use of the Hematology Blood Utilization **Calculator (HEME BUC); An adaptive Electronic Decision Support Algorithm for transfusion dependent patients.**
Principal Investigator:	JOSHUA E MEDOW
Point-of-contact:	JOSEPH P CONNOR
IRB Staff Reviewer:	MONICA ESQUIBEL

The MR IRB conducted a review of the above referenced initial application. The study was determined to qualify for exemption under campus policy, because:

The research is not federally supported, does not fall under VA regulations, and is not FDA-regulated. In addition, the research falls within the following category(ies) of exempt research outlined under campus policy:

Category 4: Secondary research for which consent is not required.

This study involves the use and disclosure of protected health information (PHI) and is therefore subject to the HIPAA Privacy Rule. Please access the ARROW application to determine the mechanism through which the study team will be able to use and disclose PHI (i.e., through written authorization from subjects, oral authorization from subjects, a waiver of authorization, or use of a limited data set).

NOTE: If the research under this exemption application becomes federally supported or changes such that it becomes subject to VA or FDA regulations, the exemption status no longer applies.

To access the materials the IRB reviewed and accepted as part of the exemption determination, please log in to your ARROW account and view the documents tab in the submission's workspace.

Although the human subjects research described in the ARROW application referenced above was determined to meet the federal criteria for exemption and thus does not require continuing review, please be aware of your responsibilities related to the conduct of the research and when additional IRB review is required. Prior to starting research activities, please review the

Investigator Responsibilities for Exempt Human Subjects Research guidance (https://kb.wisc.edu/hsirbs/78821) which includes a description of the types of changes that must be submitted to ensure the research continues to comply with the conditions of the exemption and/or category(ies) of exemption.

If you have general questions, please contact the Health Sciences IRBs at 608-263-2362. For questions related to this submission, contact the assigned staff reviewer.

University of Wisconsin-Madison
MR IRB Application

Study#: 2018-0725

Principal Investigator:
JOSHUA MEDOW

BASIC STUDY INFORMATION

1.1 Indicate the appropriate IRB. NOTE:
- If you are unsure which IRB to select, please refer to the guidance or contact an IRB office for assistance.

*

☐ Education and Social/Behavioral Science IRB

☐ Health Sciences IRB

◆ **Minimal Risk IRB (Health Sciences)**

1.2 Provide a short, lay-terms study title.

* Evaluation of the clinical use of the Hematology Blood Utilization Calculator (HEME BUC)

1.3 Provide the full, formal study title. NOTE: This is the title that will appear in correspondence.

* Evaluation of the clinical use of the Hematology Blood Utilization Calculator (HEME BUC);
An adaptive Electronic Decision Support Algorithm for transfusion dependent patients.

1.4 Is this study being transferred from another institution?

Answer Yes to this question only if
a) the principal investigator (PI) for this application is coming to UW-Madison, UW Health, or the Madison VA from another institution and
b) they plan to open a study here that is already IRB-approved at their previous institution.

* ☐ Yes ☐ **No**

1.5 Identify the Principal Investigator. JOSHUA MEDOW

1.6 Identify the points of contact for this study (limit of four).

NOTE:

- Points of contact can edit the application and will receive email notifications about this submission. For the HS and MR IRBs only, points of contact can also submit materials on behalf of the PI.
- If the PI is serving as a study point of contact, indicate that here.

*

JOSEPH CONNOR

PI INFORMATION

Principal Investigator: JOSHUA MEDOW

* 2.1 Is the PI's primary appointment through the University of Wisconsin – Madison?

◆ **Yes** ☐ No

2.1.1. Confirm the PI's primary appointment.

	Title	Type	UDDS	Department Combined Name
◆	**ASSOCIATE PROFESSOR**	**FA**	**A535700**	**SMPH/NEURO SURG/NEURO**

The appointment under which the PI will conduct this research is not listed above.

☐

TYPE OF APPLICATION

1.1 Indicate the type of application:

* Initial review application: Health care records research only - help link

STUDY TEAM

NOTE: All members of the study team (key personnel) must be listed on this page. Study team members can be listed as having either edit/email access or read-only access, but all study team members (apart from the PI and POC) must be listed in one category or the other.

If the study team includes anyone (including students) who is not affiliated with (e.g., employed by, holds an appointment at) the UW-Madison, University Hospital (formerly UWHC), or Madison VA (Wm S. Middleton VA Hospital) AND for whom you are requesting that UW-Madison serve as IRB of record, these individuals must be listed in either 3.1 or 3.2. If the study team includes anyone who is not affiliated with the UW-Madison, University Hospital (formerly UWHC), or Madison VA (Wm. S. Middleton VA Hospital) for whom you are NOT requesting that UW-Madison serve as IRB of record, DO NOT list these individuals in either 3.1 or 3.2. The study protocol must include all external collaborators and their roles in this study.

3.1 Identify study team members with edit/email access. NOTE: Study team members listed here

will be able to edit the application and receive email notifications regarding this study. Only the PI and Point of Contact can formally submit materials to the IRB.

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3.2 Identify study team members with read-only access. NOTE: Study team members listed here will be able to read the application but will not be able to edit the application or receive email notifications.

STUDY TEAM: ROLES

NOTE: Depending on the nature of the study or project, it is possible that some or all study team members will not fit into the categories below. If this is the case, select Not Applicable.

4.1 Identify the study team members who will be involved in identification and recruitment of subjects for this study, if applicable.

Person
There are no items to display

☐ Not applicable

4.2 Identify the study team members who will be responsible for obtaining informed consent, if applicable.

Person
There are no items to display

☐ Not applicable

4.3 Identify the study team members who will be intervening or interacting with subjects (e.g., administering surveys, conducting physical interventions), if applicable.

Perso
There are no items to display

☐ Not applicable

4.4 Identify the primary point of contact for this study. NOTE: If the PI is serving as the primary point of contact, indicate that here.

* JOSEPH CONNOR

PROJECT SPONSORSHIP AND BILLING INFORMATION

6.1 Does this submission primarily represent a trainee project?

* ☐ Yes ☐ **No**

6.1.1 If yes, identify the student(s)/trainee(s).

Student/Traine	Categor	Cours
There are no items to display		

6.2 Is this an investigator-initiated project?

NOTE: The UW-Madison Health Sciences IRBs define investigator-initiated research as research that is originated and designed by individuals, independently of any sponsor or funding agency. Such research is not conducted under the auspices of a formal sponsor, such as a pharmaceutical company, and the protocol is not developed or generated by a funding agency (e.g., National Cancer Institute, Cystic Fibrosis Foundation).

To be considered investigator-initiated research, the following must apply:

- The project receives no or very limited industry funding or support (e.g., support is limited to the provision of the drug or device)
- If an IND or IDE exists, it is held by an individual investigator and not a study sponsor

* ☐ **Yes** ☐ No

FUNDING: GENERAL

7.1 Are you or do you plan on receiving funding to support this project (includes internal UW-Madison/University Hospital/UWMF funds)?

* ☐ Yes ☐ **No**

CONFLICT OF INTEREST (COI)

13.1 Please review the study team member Outside Activities Report (OAR) and managed entities data below:

All study team members have completed their Ouside Activities Report for the year.

NOTE: Per campus policy all study team members must submit an OAR every year and

keep it up to date.

These study team members have managed entities:

JOSHUAMEDOW

iVMD	Accepted

* 13.1.1 Do any of the managed entities sponsor the study?

☐ Yes ☐ **No**

* 13.1.2 Do any of the managed entities own or license a technology being used in the study (including any agent, device, or software)?

☐ Yes ☐ **No**

13.1.3 If any of the management plans identified in 13.1 are not relevant to the study please explain why. Dr. Medow is part owner of iVMD a company that is marketing a program (The Digital Intern) similar to the algorithm used in this study. The algorithms used in our blood product orders have no connections to iVMD.

* 13.2 Do any study team members involved in the design or conduct of the research (including their spouses and dependent children) own intellectual property that will be used in the study or project?

☐ Yes ☐ **No**

* 13.3 Besides the sponsor(s) of this project or entities listed above, do any study team members have a fiduciary or financial relationship with entities that will be involved in this study or that may be significantly affected by it?

☐ Yes ☐ **No**

* 13.4 Do any of the study team receive any incentives for recruiting human subjects or any other purpose directly related to the study or project?

☐ Yes ☐ **No**

DETERMINATION OF VA STATUS

NOTE: All studies that fall under Madison VA purview must be reviewed by the VA Research and Development (R&D) Committee in addition to being reviewed by the Health Sciences or Minimal Risk IRB. For information about the VA R&D Committee review process, please call 608-280-7007.

15.1 Indicate if any of the following apply to this study or project:

*

None of the above

NOTE: If the study or project rents or uses Madison VA (Wm. S. Middleton VA Hospital) facilities, contact the

Madison VA Research Office to ensure the appropriate permissions are in place.

15.2 If any of the selections in 15.1 above are chosen, please upload a copy of the completed VA Information Security Officer/Privacy Officer (ISO/PO) checklist.

File

There are no items to display

SCIENTIFIC REVIEW: UW CARBONE CANCER CENTER (UWCCC) PROTOCOL REVIEW MONITORING COMMITTEE (PRMC) AND CLINICAL RESEARCH UNIT (CRU)

* 17.1 Is the scientific question of the protocol cancer related?

☐ Yes

☐ **No**

* 17.2 Are you specifically targeting cancer patients for enrollment in this study?

☐ Yes

☐ **No**

* 17.3 Does this study involve the review and/or use of biological specimens/data/images/records from cancer patients?

☐ Yes ☐ **No**

17.4 Will this study use the Clinical Research Unit (CRU)?
NOTE: If the answer to this question is Yes, you must upload a copy of the CRU application to the Submit activity form. You will see the Submit activity form when you click on the Submit link to submit the completed IRB application.

* ☐ Yes ☐ **No**

SCIENTIFIC REVIEW: OTHER

18.1 Does this study require scientific review by ICTR Scientific Review Committees? NOTE: If none of the options in 18.1.1 apply, scientific review is required.

* ☐ Yes ☐ **No**

18.1.1 If no, select why scientific review is not required.

Retrospective medical records research study

CLINICALTRIALS.GOV REGISTRATION

Registration at Clinicaltrials.gov may be required for Federal Drug Administration (FDA), International Committee of Medical Journal Editors (ICMJE) publication purposes, or as a condition of receiving federal funding as described below. Click on the help link above for additional information on these requirements.

20.1 Does this study need to be registered at Clinicaltrials.gov to meet the FDA's registration requirements? Note: The FDA requires study registration along with results and adverse event reporting for:
a) all phase II - IV interventional drug or biologic trials, and
b) trials of devices that are either
i. controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, or
ii. pediatric postmarket surveillance required by FDA

* ☐ Yes ☐ **No**

* 20.1.1 Does this study need to be registered at Clinicaltrials.gov to meet the ICMJE or NIH requirements? Note: The ICMJE and NIH require the registration of all health-related interventional studies investigating relationships between the health-related intervention and any health outcomes (interventions include: drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, and process-of-care changes).

☐ Yes ☐ **No**

STUDY LOCATION: GENERAL

1.1 Is this a multi-site study? NOTE: A multi-site study involves at least one site or individual NOT affiliated with the UW-Madison/University Hospital (formerly UWHC)/Madison VA (Wm. S. Middleton VA Hospital). Select Yes if this study:

- Will be conducted at sites outside the UW
- Includes study team members NOT affliated with the UW
- Involves sending or receving samples/data/images to/from collaborators outside the UW

* ☐ Yes ☐ **No**

1.1.1 If yes, does the study have a coordinating center? NOTE: A lead site or coordinating center is typically responsible for coordinating activities at all other sites, receiving and analyzing data, and developing and updating the study protocol as needed.

☐ Yes ☐ No

1.1.1.1 If yes to question 1.1.1, is the UW-Madison/Madison VA (Wm. S. Middleton VA Hospital) serving as the coordinating center?

☐ Yes ☐ No

1.1.1.2 If no to question 1.1.1, how is it being ensured that all sites have IRB approval prior to initiating study activities?

1.2 Will UW-Madison, Madison VA (Wm. S. Middleton VA Hospital), or University Hospital (formerly

UWHC) personnel or personnel under UW-Madison IRB purview conduct research activities at sites outside of the US?

* ☐ Yes ☐ **No**

1.2.1 If yes, specify.

There are no items to display

STUDY LOCATION(S): UW-MADISON SITES

3.1 Select the UW-Madison/University Hospital (formerly UW Health)/Madison VA (Wm. S. Middleton VA Hospital) location(s) at which this study will occur. Check all that apply:

University Hospital (formerly UWHC)

3.1.1 If other, specify.

STUDY SUMMARY

1.1 Upload the stand-alone scientific protocol associated with this application. NOTE: A protocol is required for the types of studies listed below. This list is NOT exhaustive and the IRB may request a protocol in other cases as appropriate.

- All multi-site studies (regardless of risk level) All studies requiring scientific review
- All studies involving drugs or devices
- All studies posing more than minimal risk to subjects

Fil

There are no items to display

1.1.1 If no protocol was uploaded, select the reason(s) below.

Health care records research only

1.1.1.1 If other, provide a justification.

1.2 Will study activities involve interaction and/or communication with human subjects, even if only to obtain informed consent?

* ☐ Yes ☐ **No**

1.3 Provide the expected duration of the study (i.e., the time from IRB approval to completion of all study activities).

* 5 years

SPECIAL CONSIDERATIONS AND PROCEDURES

2.1 If your study involves any of the following special procedures or considerations, additional information may be needed. Select all that apply. If none apply, check Not Applicable.

*

Review or use of information from health care records, which includes information within:
*Medical records
*Billing records

RESEARCH DESIGN AND PROCEDURES

1.1 What is the overall purpose of this project or study?

* As part of a large project to provide decision support for the appropriate use of blood products the University Hospital has been implementing decision support algorithms by embedding them into the order sets for blood products. The unique need of the transfusion dependent patient led to the implementation of the Hematology Blood Utilization Calculator (HEME BUC) into HealthLink in June of 2017. The goal was to individualize transfusion of red blood cells in the patients. The current application is to allow data from the patients medical record to be abstracted to determine the impact the HEME BUC on transfusion practice in this patient population.

1.2 What are the specific aims of this project or study?

* 1. Are the transfusions provided with the HEME BUC assistance meeting target hemoglobin when the patient returns.
2. Has the HEME BUC changed the interval between transfusions in this type patients (do patients need to spend less time in clinic getting blood).
3. Has the HEME BUC resulted in a change in how much blood is being use for these patients overtime.

1.3 Background: What prior information or knowledge exists to support the conduct of this project or study?

* Historically blood transfusions have been ordered empirically in the transfusion dependent patient and here at UW most patients were being transfused 2 units of red blood cells every two weeks irrespective of their specific need. This was done as there was no better way to predict how to keep them at or above the desired target hemoglobin level. The HEME BUC is a mathematic algorithm that learns from data in the patients record and predicts the half life of transfusion in that particular patient. This gives the ordering provider options for how much blood to give coupled with the time interval between transfusions. A simplified version of the HEME BUC has been in the standard red blood cell transfusion orders for 2 years and has resulted in a significant reduction in blood used hospital wide.

1.4 Briefly describe the procedures and interventions that will be performed for this project or study and all study arms involved.

* When the HEME BUC is used in the clinic the information from that transfusion is collected by

HealthLink in a Synopsis Flowsheet overtime. The data from this synopsis will be used along with the patients primary hematologic diagnosis (ie the reason they are transfusion dependent) will be taken from the problem list in the patients chart. The data collected will be related to each transfusion ordered with the input of the HEME BUC algorithm and will include data about the patients disease, the parameters selected by the ordering provider for the transfusion (target Hgb level, and return days/number of units to transfuse selected by the provider) and then the follow up day and Hgb level to asses for response to the prescribed transfusion. The primary outcome of this study is to determine the percentage of transfusions prescribed with the HEME BUC that were successful in terms of whether or not the patient's Hgb level was at or above target when they came back for scheduled follow-up. Additional analysis will include; description of the diseases being managed with the HEME BUC, What the typical pre-transfusion hgb level were, how often each of the selectable target Hgb levels were selected by the ordering providers, and how often patients came back at the time prescribed by the HEME BUC (or how clode to the selected return each actual return was).

1.5 Will subjects be randomized?

* ☐ Yes ☐ **No**

RESEARCH DESIGN AND PROCEDURES: CONTINUED

NOTE: Depending on the nature of your study or project, these questions may not apply. If this is the case, select Not Applicable.

2.1 Describe the current alternatives to participation in this research study, including treatments subjects could undergo outside of the research study. If there is no accepted treatment or no effective treatment, state this.

☐ Not Applicable

2.2 Describe how this patient population is treated clinically.

☐ Not Applicable

2.3 List the procedures that will be performed solely for research purposes (i.e., those that are not performed as part of standard of care).

Review of medical records

☐ Not Applicable

RISKS AND BENEFITS: GENERAL

1.1 Describe any potential direct benefits to subjects. If there are no direct benefits, state this.

* There are no direct benefits to the patient from the data collection and publication of the performance/function of the calculator.

1.2 Describe the potential benefits of this research to society.

* The use of the calculator may have patient benefit. The calculator may show that the patient only needs blood every 3 or 4 weeks (or on the other hand that they might benefit from blood more frequently than the typical 2 week empiric schedule used in the past) thus reducing the time spent in clinic (or the time that they spend feeling poor secondary to anemia). These would be considered improvements in quality of life.

Any benefits to calculator guided transfusion identified could be expanded to patients at other institutions benefitting many transfusion dependent patients. The data could support alternative transfusion strategies and thus could reduce help reduce patients exposure to blood products in the future.

1.3 Does this study involve direct physical intervention with subjects? NOTE: A physical intervention refers to study procedures that may pose a risk (however minimal) to a subject's body (e.g., blood draws, MRI scans, drug or device trials, exercise, dietary restrictions/supplements). Examples of activities that are NOT physical intervention include obtaining informed consent and administering surveys.

* ☐ Yes ☐ **No**

1.4 Will subjects incur any costs as a result of study participation (e.g., pharmacy preparation fees, payment for a device, billing of study procedures to subject's insurance)?

* ☐ Yes ☐ **No**

1.4.1 If yes, describe any costs. NOTE: Costs to subjects must be included in the consent form.

RISK/BENEFIT ANALYSIS

4.1 Describe any potential psychosocial risks to subjects, such as psychological stress or confidentiality risks (including risk to reputation, economic risks, and legal risks).

* This is chart review and there is a small risk of breach of privacy.

4.2 Describe how ALL the risks of the study will be minimized.

* The data will be collected from secured hospital computers or secured CITRIIX connection to UWHC UCONNECT site. Abstracted data will be transferred into a secured Excel datasheet that will be stored on a restricted drive on a secured server in the department of Pathology. No paper records will be used.

4.3 Explain why the risks to the subjects are reasonable in relation to the anticipated benefits.

* The risk of privacy breach is small and diligently kept to minimal. The results could impact future patients in terms of reduced blood use or reduce time in clinic getting transfused. The results could benefit the entire health care system by reducing the costs of providing transfusions to this population of patients.

4.4 Describe the provisions in place to identify and address unanticipated problems or

complications.

* There are no patient interactions or procedures so no complications should occur. Any unanticipated problems will reported to the IRB according to posted guidance.

4.5 Does this study constitute minimal risk research? NOTE: Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

* ☐ **Yes** ☐ No

4.5.1 If no, describe the data and safety monitoring plan for this study. NOTE: If a formal Data Safety Monitoring Board or Data Monitoring Committee exists, provide a general description of the committee or board's membership (e.g., number of members, expertise, and whether members are independent of the sponsors/researchers) and the expected frequency of their meetings.

PRIVACY AND CONFIDENTIALITY

1.1 Describe the precautions that will be used to ensure subject *privacy* is protected (e.g., research intervention is conducted in a private room; collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research).

* The collection of information about subjects will be limited to the amount necessary to achieve the aims of the research.

1.2 Select how subjects are identified in the research records. Check all that apply:

*

Directly: Information identifying subjects is stored directly on data records

1.3 Describe the measures that will be implemented by your research team to safeguard the identifiable subject information from unauthorized use or disclosure for both paper and electronic forms of information. Include how and where data will be stored.

* The data will be collected from secured hospital computers or secured CITRIIX connection to UWHC UCONNECT site. Abstracted data will be transferred into a secured Excel datasheet that will be stored on a restricted drive on a secured server in the department of Pathology. The patient identifiers will be kept in the dataset until the study is published (in case more information were to be needed after requesting this from the IRB) after which each subject will be given a sequential subject number and identifiers destroyed. No paper records will be used.

1.4 Are you planning to retain data collected for this study for purposes not described in this application (e.g., future unrelated research project)?

* ☐ Yes ☐ **No**

1.4.1 If yes, do you confirm that any future uses not described in this application will be submitted separately for IRB review?

☐ Yes ☐ No

PRIVACY AND CONFIDENTIALITY: CONTINUED

2.1 Will data be stored on laptops or portable devices?

* ☐ Yes ☐ **No**

2.1.1 If yes, what additional safeguards have been put in place (e.g., link for coded data will be stored separately, data will be deidentified) to protect these data from risk of breach of confidentiality (e.g., theft of laptop, loss of portable device)? NOTE: Consult with your IT department about security of data storage on laptops or portable devices.

2.2 Will subject data, specimens, or images be shared outside the UW-Madison, the Madison VA (Wm. S. Middleton VA Hospital), or University Hospital (including UWMF clinics)? NOTE: This is not referring to industry- sponsored clinical trials or cooperative group studies. For such studies, select Not Applicable.

☐ Yes

☐ **No**

☐ Not Applicable

WAIVER OF INFORMED CONSENT

2.1 Are you requesting a waiver of informed consent for all components of the study?

* ☐ **Yes** ☐ No

2.1.1 If no, list the component(s) of the study for which the waiver is being requested (e.g., retrospective chart review).

2.2 If your study enrolls minors, are you requesting a waiver of assent and parental permission?

☐ Yes ☐ No

☐ Not Applicable

2.3 Provide a justification for how the following criteria for a waiver of informed consent will be met: 1) The study involves no more than minimal risk to the subjects; 2) The waiver will not adversely affect the rights and welfare of the subjects; 3) The study could not practicably be carried out without the waiver.

* 1. The study poses minimal risk to subjects because the activities are limited to the use of data from the medical record and there are sufficient measures in place to protect the data.
2. the research does not adversely affect the subjects rights and welfare because only those who have valid access to their medical records will collect study data and the use of the data is not expected to affect the patients from whom the data are the derived.
3. It is impractical to obtain informed consent from the subjects because the study team will not have any interactions with the patients. The small risk of privacy breach is the only potential risk to the patients.
4. Tracing patients to obtain consent would be impractical if not impossible in many cases. Due to the disease processes involved many of the subjects may have already passed away from that process before data collection.

HIPAA: GENERAL

NOTE: For guidance on the HIPAA privacy rule, including what constitutes individually identifiable information and Protected Health Information (PHI), refer to the HIPAA website. If the purpose of this study or project is to create a database or registry, contact the HIPAA Privacy Officer to determine whether it needs to be registered.

1.1 Will the research involve the access, collection, use, or disclosure of individually identifiable information?

* ☐ **Yes** ☐ No

1.1.1 If yes, are you or any member of the study team conducting the study under a Madison VA (Wm. S. Middleton VA Hospital), University Hospital (formerly UWHC), or UW Medical Foundation appointment or an appointment that is within the UW-Madison Health Care Component (HCC)? NOTE: The HCC of the UW-Madison currently includes SMPH clinical departments; School of Pharmacy (clinical units only); School of Nursing; University Health Services (non-student records only); State Laboratory of Hygiene; and Waisman Center (clinical units only).

◆ **Yes**
☐ No

HIPAA: CONTINUED

3.1 Select what you are requesting in order to fulfill HIPAA requirements:

*

Request for Waiver of Authorization

3.2 Select which of the following identifiers will be associated with the health information you propose to collect for study purposes. Check all that apply to your study. If none of these identifiers will be collected for your study, select None of the Above.

*

Names
All elements of dates (except year) related to an individual including: *Dates of admission, discharge, or service *Dates of birth or death
Age of individuals over 89 years old, including year of birth indicative of such age
Medical record numbers

REQUEST FOR WAIVER, ALTERED, OR PARTIAL WAIVER OF AUTHORIZATION

5.1 List the specific health information that you propose to use in this study.

* MRN
Name
Age
Hematologic Diagnosis and CMI score Date of Transfusion
pre-transfusion hemoglobin value target hemoglobin selected by provider
return to clinic interval selected by provider (in days) number of units of blood transfused
Actual return interval (in days) return hemoglobin value.

5.2 Will PHI be disclosed outside the HIPAA covered entity under which you are conducting the study (e.g., UW Health Care Component/Affiliated Covered Entity OR Madison VA (Wm. S. Middleton VA Hospital) Covered Entity)?

* ☐ Yes ☐ **No**

5.2.1 If yes, you must contact the UW-Madison HIPAA privacy officer or the Madison VA privacy officer.

5.3 Describe your plan to protect PHI from unauthorized use or disclosure.

* The data will be collected from secured hospital computers or secured CITRIIX connection to UWHC UCONNECT site. Abstracted data will be transferred into a secured Excel database that will be stored on a restricted drive on a secured server in the department of Pathology. No paper records will be used.

5.4 Describe your plan for destroying identifiers at the earliest possible opportunity.

* Patient identifiers will be maintained until the study is done and the data published.

5.5 Explain why the study cannot practicably be conducted without the waiver of authorization or altered authorization.

* The minimum necessary PHI needed will be collected. It will be difficult for the study team to obtain authorization given that there is no contact with the patients whose information will be used for the

research. The research will span many months and not all patients will remain in the UW system during this time. In addition others may not recall the event being studied. Finding all subject would be impractical to impossible and many of them will be deceased by the time the data is being collected.

5.6 Federal law prohibits the re-use or disclosure of PHI in connection with this research to any person or entity other than those authorized to receive it, except: (1) as required by law; (2) for authorized oversight of the research; or (3) in connection with other research for which the HIPAA Privacy Rule permits the PHI to be used or disclosed. Do you agree to abide by these limitations in order to obtain a waiver of authorization?

* ☐ **Yes** ☐ No

REVIEW OF INFORMATION FROM HEALTH CARE RECORDS (DATA AND/OR IMAGES)

1.1 Will the study involve contacting subjects to obtain additional information for this study?

* ☐ Yes ☐ **No**

1.2 Select all of the sources of the health care records and, if applicable, protected health information that will be used for this study:

*

HealthLink

1.2.1 Specify clinic, department, or other database or paper records system or sources.

1.3 Describe the means by which potentially eligible health care records will be identified (e.g., ICD9 codes). Please also specify who will identify eligible records.

* The patient list (those who had transfusions ordered via the HEME BUC) will be requested through the Clinical Research Data Service.

1.4 If health care records are being used to identify potential subjects, do you confirm that all key personnel accessing and reviewing medical records have valid clinical access? NOTE: Valid clinical access means that all key personnel reviewing records have a clinical role, independent of this research study, for which access to patient health care records is already present.

☐ Yes ☐ **No**

☐ Not Applicable

1.4.1 If 1.4 is answered no, do you confirm that all key personnel accessing health care records have authorized access to identify subjects via these records? NOTE: Authorized access to identify subjects means research personnel have obtained access to patient lists or other records for the purposes of subject identification through the formal authorization process of the record holder. If

access cannot be confirmed for UW Health health
care records, contact UW Health-UWHC Information Technology Services to obtain access. For other health systems, contact that organization's medical records department.

◆ **Yes** ☐ No

REVIEW OF RECORDS/DATA/IMAGES: CONTINUED

2.1 Identify any vulnerable groups whose health care records will be targeted for collection, if applicable.

*

None of the above

2.2 Describe the population whose health care records will be accessed for this study or project.

* Patients who are seen in the Hematology clinics with a variety of diagnosis that have left them dependent on red blood cell transfusions to maintain a clinically acceptable hemoglobin level and have had their transfusions ordered through the HEME BUC order set.

2.3 Provide the date range of the data to be collected from the health care records for the study or project (e.g., 1/1/1990 - 12/31/2000).

* 6/1/2017-5/22/18

2.4 Upload a data collection sheet or a list of all data elements that will be collected.

*

File

DATA ELEMENTS FOR COLLECTION FOR HEME BUC STUDY.docx

2.5 Provide the estimated number of records/data/images that will be accessed for this project.

* 60

2.6 Will the data collected as part of this study or project be used for purposes other than those that are described in this application?

* ☐ Yes ☐ **No**

2.6.1 If yes, do you confirm that all future uses will be submitted as separate applications to the IRB?

☐ Yes ☐ No

SUPPLEMENTAL INFORMATION

1.1 Does this submission represent a replacement of a protocol previously approved by a UW-Madison IRB (e.g., one closed under the campus Five Year Renewal Policy)?

* ☐ Yes ☐ **No**
☐ Not applicable

1.1.1 If yes, please provide the reason for the replacement (e.g., IRB required closure due to Five Year Renewal Policy):

1.1.2 If yes, provide the previous number assigned to this protocol by the UW-Madison IRB that approved the study:

2.1 Provide any additional relevant documents (e.g., supplemental statistical justification information), if applicable.

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2.2 Describe what additional documents were added in 2.1.

FINAL PAGE

1.1 Do you certify that (1) the information presented in this application is accurate; and (2) if the application is being submitted on behalf of the Principal Investigator (PI) rather than by the PI, the information presented was done so with the PI's agreement?

* ☐ **Yes** ☐ No

To complete and submit this application to the IRB office, please follow the steps below:

1. Select Ready to Submit or Exit on this page to be directed to the application workspace.
2. In the application workspace, click the Submit activity to send the application to the IRB office.

NOTE: The Submit activity is only available to certain study team members.

Tip: Select Hide/Show Errors at the top of this page to identify any omissions in the application before submitting it to the IRB office.

Appendix B: MATLAB Script

```
clear
xlsxt = readtable('//Users/medow/Desktop/PhD/Dissertation_Data_Set.xlsx');
%import data table from Excel
work_array = table2array(xlsxt);  %convert data table into an array
for y = 1:size(work_array,1)
    excluded_weighted_halflife(y) = 2*(work_array(y,3) -
(work_array(y,2)*.5));  %split out the previous weighted half life from
current half life
end
for y = 1:size(work_array,1)
    for x = 1:101
        rework_halflife = (((101-x)/100) * work_array(y,2)) + (((x-1)/100) *
excluded_weighted_halflife(y)); %adjust the weights from 0 to 100% between
current half life and previous weighted half life
        predicted_hgb_calc(y,x) = (10^((work_array(y,8) * -
log10(2))/rework_halflife)) * (work_array(y,4) + (work_array(y,9) * (70 /
work_array(y,10)))); %calculate the predicted return hgb
        %work_array(:,8) = Actual Return Days  work_array(:,4) =
        %Pretransfusion hemoglobin  work_array(:,9) = Units Transfused
        %work_array(:,10) = Weight Kg
    end
end
for x = 1:101
    predicted_hgb_greater_count = 0;
    for y = 1:size(work_array,1)
        hgb_diff(y,x) = work_array(y,5) + 0.5 - predicted_hgb_calc(y,x);
%Find where the return hgb + an offset is more than the predicted return hgb
        if hgb_diff(y,x) >= 0
            predicted_hgb_greater_count = predicted_hgb_greater_count + 1;
%Count the number of times the hgb is at or above goal
        end
    end
    percent_accuracy(x) = predicted_hgb_greater_count / y; %Calculate the
percentage at or above the goal hgb for a given half life/previous weighted
half life ratio
    temp_hgb_diff_array = hgb_diff(:,x);  %Get all values for a single half
life/previous weighted half life ratio into a single 1x101 array
    standard_deviation(x) = std(temp_hgb_diff_array);  %Calculate the
standard deviation for a given half life/previous weighted half life ratio
end
max_accuracy = max(percent_accuracy);
min_accuracy = min(percent_accuracy);
max_sdev = max(standard_deviation);
min_sdev = min(standard_deviation);
max_counter = 0;
for x = 1:101
    if percent_accuracy(x) == max_accuracy
        max_counter = max_counter + 1;
        max_location(max_counter) = x;
    end
end
sdev_accuracy = std(percent_accuracy);
```