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Cost-Benefit Analysis of a Pediatric Patient Blood Management Program

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COST-BENEFIT ANALYSIS OF A PEDIATRIC PATIENT BLOOD MANAGEMENT PROGRAM

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF DOCTOR OF PHILOSPHY IN NURSING

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON

CIZIK SCHOOL OF NURSING

BY

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The University of Texas Health Science Center at Houston
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October 20, 2022
Date

To the Dean for the School of Nursing:

I am submitting a dissertation written by Karen DiValerio Gibbs and entitled "Cost-Benefit Analysis of a Pediatric Patient Blood Management Program." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Nursing.

Cathy L. Rozmus, Committee Chair

We have read this dissertation and recommend its acceptance:

Accepted:
Dean for the School of Nursing

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Cost-Benefit Analysis of a Pediatric Patient Blood Management Program

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Abstract

Introduction

Red blood cell (RBC) transfusions can be a life-saving and important intervention used to replace blood loss or manage anemia, but they also come with risks from transfusion-associated adverse events (TAAEs). Patient blood management (PBM) involves a multidisciplinary approach to optimize care of patients who may need a transfusion, including blood conservation modalities, patient-centered decision making, among others. The impact of PBM in the pediatric setting is not well understood, particularly the impact on TAAEs and the economic impact of these programs.

The following specific aims were pursued: (1) To investigate the effect of a PBM program on transfusion utilization and the incidence of TAAEs, and (2) to compare the costs related to supporting a health-system level PBM program to the costs of transfusion utilization.

Methods

This study used a retrospective cohort design to evaluate the impact of a PBM program on patient outcomes in a pediatric hospital system. Clinical and demographic information from pediatric patients between the ages of four months and eighteen years who had an inpatient hospitalization were compared for the year prior to the program (2015) and the year post-implementation (2019). Transfusion utilization was compared

before and after the program using generalized estimating equation. A cost-benefit analysis examined program costs and compared them to program outputs.

Results

This study examined a total of 35,245 hospitalizations and over 3,800 transfusions in the pre- and post-intervention years. The post-intervention year had lower pre-transfusion hemoglobin values and smaller volumes of RBC transfusions ordered, and this was statistically significant ($p<0.01$). While this study did not see a statistically significant difference in the incidence of TAAEs, fewer hospitalizations had RBC transfusions ordered in 2019 when compared to 2015. When examining transfusion utilization while adjusting for potential confounders, group year was not statistically significant ($p = 0.11$). Overall, activity-based transfusion costs based on projections were higher in the post-intervention year.

Conclusion

This study explored the impact of a PBM program on pediatric hospitalized patients at a large tertiary academic medical center. The results suggest that this work was effective in reducing the mean hemoglobin pre-transfusion for RBC transfusion and reduced the mean volume of transfusion when adjusted for severity of illness and length of stay. The results of the cost-benefit analysis suggest that this investment in safety did not correspond with decreased utilization costs, but there were limitations in the analysis. More research is needed to understand the impact of reductions in transfusion-associated adverse events and their true cost.

Keywords: patient blood management, transfusion safety, cost-benefit analysis

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Summary of Study

Patient blood management is a strategy for optimizing transfusion, but there have been limited studies evaluating a larger patient blood management program in pediatrics.

The research protocol for this study was approved on April 12, 2021, by Baylor College of Medicine Institutional Review Board and December 7, 2021, by the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects with Baylor College of Medicine serving as the IRB of record. An appropriate data use agreement was obtained between both institutions. This study sought to investigate the effect of a patient blood management program on transfusion utilization and the incidence of transfusion-associated adverse events, and to compare the costs related to supporting a health-system level patient blood management program to the costs of transfusion utilization.

There were no changes to the proposal, but internal salary data related to the personnel costs of the program was not available, and therefore external estimates were used.

Cost-Benefit Analysis of a Pediatric Patient Blood Management Program

Research Proposal

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Cost-Benefit Analysis of a Pediatric Patient Blood Management Program

Blood transfusions are used to quickly restore oxygen carrying capacity due to acute blood loss from injury or trauma-induced coagulopathy. Though transfusions are a crucial intervention in the context of trauma and treatment of hematologic and oncologic diseases, the balance of risk to benefit must be carefully considered. Transfusion-associated adverse events can cause clinically significant complications, including fatal reactions and the Joint Commission identified blood transfusion as one of the top overused interventions or treatments (Joint Commission, 2012). Transfusion-related adverse events can be the result of physiologic response to the blood components being transfused but also a result of system-level aspects of transfusion management (Delaney et al., 2016). Pediatric patients have twice the incidence of transfusion-related adverse events compared to adults, at a rate of 6.2 reactions per 1,000 transfusions (Oakley, Woods, Arnold, & Young, 2015).

Unfortunately, some of the physiologic mechanisms of transfusion reactions are not entirely understood. Certain patients may have a higher risk for transfusion reactions, notably patients who have received transfusions before who may have developed antibodies that elicit allergic responses, or as a result of immunosuppression with donor cells attacking the host (Delaney et al., 2016). More commonly, transfusion reactions are a result of errors in the collection, storage, or administration process (Bolton-Maggs, 2017). The Serious Hazards of Transfusion (SHOT) hemovigilance program in the United Kingdom found that “error-related reports account for 87% of all notifications” (Bolton-Maggs, 2017, p. 395) to the data collection program. Some examples of system-

level reported causes of transfusion reaction include transfusing an incompatible blood component to a patient or transfusing too much volume to induce circulatory overload.

In response to these potentially preventable transfusion-related adverse events, hemovigilance programs began in France in the 1990s to improve the quality and safety of the blood product supply chain from the donor to recipient in response to the HIV crisis (Jain & Kaur, 2012). Initially, the focus centered on surveillance to quantify transfusion-related adverse events and soon broader patient blood management interventions arose from that initial effort to focus on transfusion in the context of clinical care of patients (Jain & Kaur, 2012). Patient blood management (PBM) is defined as an "evidence-based, multidisciplinary approach to optimizing the care of patients who might need transfusion" (Joint Commission, 2019). PBM includes a variety of interventions surrounding the decision to transfuse, including "patient evaluation and clinical management…application of appropriate indications, as well as minimization of blood loss and optimization of patient red cell mass" (Joint Commission, 2019, p. 5). The Society for the Advancement of Blood Management demonstrates in their organizational chart that the combination of interdisciplinary blood conservation modalities, patient-centered decision making, optimization of coagulation, and management of anemia can lead to improved patient outcomes (Goobie et al., 2019, p. 223). These interventions can include restrictive hemoglobin thresholds for transfusion of red blood cell products, transfusion guidelines, massive transfusion protocols, among others (Goobie et al., 2019).

From the beginning of 2016 through the end of 2018, several interventions were undertaken as a part of a larger patient blood management program. In November 2015, a Transfusion Safety Officer (TSO) was hired to focus on transfusion safety throughout the

system. The orientation process for that role meant that the TSO did not begin implementing interventions until 2016. Clinical decision support interventions began with weight-based dosing for red blood cell transfusions in June 2016. Shortly after, development on an evidence-based guideline with a multidisciplinary team began in October 2016. This process included a forty-member multidisciplinary team with a thorough literature review, recommendations using the GRADE methodology (Schünemann et al., 2013), and was finalized with system-wide communication and provider education that began in January 2018 and was completed in March 2018. Positive patient identification through a blood product administration module in the health record allowed for additional safety checks and data collection. The objective is to investigate the effect of this patient blood management program on transfusion utilization and the incidence of transfusion-related adverse events and to compare costs to benefits of the program. During this four-year time period, several service line specific initiatives took place that would shift the location of care from the inpatient setting to the outpatient setting in an infusion center and a critical care tower opened.

The hypothesis of this study is that these interventions will cause reduced utilization of pediatric red blood cell transfusion and an increased incidence of transfusion reaction from increased awareness and improved recognition. This is anticipated to lead to reduced costs throughout the system.

Specific Aims

To test the central hypothesis, the following specific aims will be pursued:

1. To investigate the effect of a patient blood management program on transfusion utilization and the incidence of transfusion-related adverse events.

2. To compare the costs related to supporting a health-system level patient blood management program to the costs of transfusion utilization.

Significance and Innovation

Significance

Effectiveness of patient blood management has been investigated in both adult and pediatric patients. A systematic review of patient blood management interventions in adult patients undergoing surgery found that "comprehensive anemia management, minimizing iatrogenic blood loss," along with the optimization of the "patient-specific physiological balance of trauma" (Althoff et al., 2019, p. 794) did reduce the number of patients exposed to allogenic red blood cell transfusion, number of units per allogenic red blood cell transfusions per patient, length of hospital stay, total number of complications, and mortality. The finding in this meta-analysis was consistent through several categories of surgery and incorporated seventeen studies of over 235,000 patients. National level programs, such as the SHOT hemovigilance program, have improved reporting of transfusion reactions and improved overall safety (Bolton-Maggs, 2017).

When looking more closely at specific interventions that fall under the larger umbrella of patient blood management, several interventions have been shown to maintain or improve patient outcomes while minimizing risk from or exposure to transfusion in pediatrics. One of these interventions includes standardizing the hemoglobin level at which a transfusion is indicated. Lacroix et al. (2007) conducted the first randomized controlled trial to evaluate transfusion thresholds in critically ill pediatric patients and demonstrated non-inferiority of lower hemoglobin thresholds to higher thresholds with respect to mortality. Red blood cell transfusion threshold studies

have been repeated in pediatric patients with sepsis (Karam et al., 2011), pediatric patients with burns (Voigt et al., 2018), and most recently pediatric cardiac surgery patients (Deng et al., 2019). Given the overall infrequent incidence of transfusion-associated adverse events, these studies had sample sizes too small to identify the impact of hemoglobin thresholds on transfusion reactions and primarily focused on other patient outcomes such as mortality, transfusion utilization, and other related clinical outcomes.

In looking at the role of laboratory monitoring, a Cochrane systematic review and meta-analysis also found few studies evaluating viscoelastic monitoring, namely thromboelastography (TEG) and rotational thromboelastometry (ROTEM), for trauma induced coagulopathy in adult trauma patients (Hunt et al., 2015). After analyzing the findings of the three studies found in the review, Hunt et al. (2015) failed to demonstrate the utility of ROTEM or TEG when evaluating diagnostic accuracy, but they noted the need for research to evaluate the utility of these tests further.

Other promising patient blood management interventions include the use of antifibrinolytic medications or factor prothrombin complex concentrates to reduce blood loss or minimize transfusion requirements. The CRASH-2 Trial was a randomized controlled trial comparing tranexamic acid to placebo in adult trauma patients and found that early treatment reduced both the risk of death and demonstrated cost effectiveness but did not have an impact on blood products transfused (Roberts et al., 2013). In pediatrics, tranexamic acid has been associated with decreased mortality in trauma (Eckert et al., 2014), but transfusion utilization or adverse events have not been studied well in trauma. Tranexamic acid has been shown to reduce transfusion requirements in other pediatric surgical procedures associated with significant blood loss, namely

scoliosis surgery (Johnson et al., 2017) and craniofacial surgery (Basta, Stricker, & Taylor, 2012). In adult studies, four factor prothrombin complex concentrate has been demonstrated to improve survival (Zeeshan et al., 2019) and has shown reduction of bleeding and lower red blood cells transfused in both pediatric and adult surgical patients (Fominskiy et al., 2016). Although these adult studies have demonstrated the utility of antifibrinolytic drugs such as tranexamic acid or human factor concentrate replacements, the impact on pediatric trauma patients is still unknown.

Clinical decision support systems in the electronic health record are another way of encouraging prudent transfusion ordering as well as checking for safety. A study evaluating the impact of clinical decision support at the point of ordering on transfusion utilization in a large hospital system targeted to adult patients, suggested that clinical decision support was able to save approximately $1.6 million in red blood cell purchase costs (Goodnough et al., 2014). Clinical decision support demonstrates the opportunity to not only reduce unnecessary exposure to transfusion, but to also potentially save the healthcare system operational costs as well.

Interventions in pediatric patients are generally less studied compared to most interventions in the adult population. As children have different mechanisms of injury and physiologic responses to trauma than adults, in addition to the general aspects of child growth and development, adult studies are insufficient to guide care decisions. Although some evidence exists in related pediatric populations, one should not assume that the effect is similar in the context of pediatric care. Economic analyses of transfusion-related events have been performed on the population level in Spain (Ribed-Sánchez et al., 2018), Australia (Trentino et al., 2015), and the Netherlands (Janssen et

al., 2018) for adults. De-Gast Bakker et al. (2013) looked at cost of transfusion in a randomized, controlled trial on restrictive compared to liberal transfusion strategies in pediatric patients undergoing surgery for congenital cardiac defects. Although the authors investigated the impact of cost, they only incorporated the cost of transfusions and was not powered to investigate transfusion-related adverse events. Randomized controlled trials are not the ideal design to evaluate the impact of an infrequent clinical scenario, even one associated with high morbidity, mortality, and cost. To date, an economic evaluation of a patient blood management program in pediatric patients has not yet been published.

Innovation

A large cohort study with patients of varying clinical conditions will help strengthen our understanding of the impact of patient blood management in pediatric patients. Due to the infrequent incidence of transfusion reactions, smaller studies were not powered to investigate differences between groups. This proposal is innovative because this approach evaluates the effects of patient blood management on an entire health system from a population level rather than the impact of a single test or intervention. In healthcare, many approaches to problems include complex interventions. By using large data sets from a large pediatric health system, the research would be able to reach statistical power to be able to detect changes in the incidence of transfusion-related adverse events and evaluate the impact on charges related to transfusion administration and transfusion-related adverse events that the earlier studies were not able to evaluate. Currently, most studies in the context of transfusion only evaluate a single intervention or in a very specific patient population, and this study is one of the

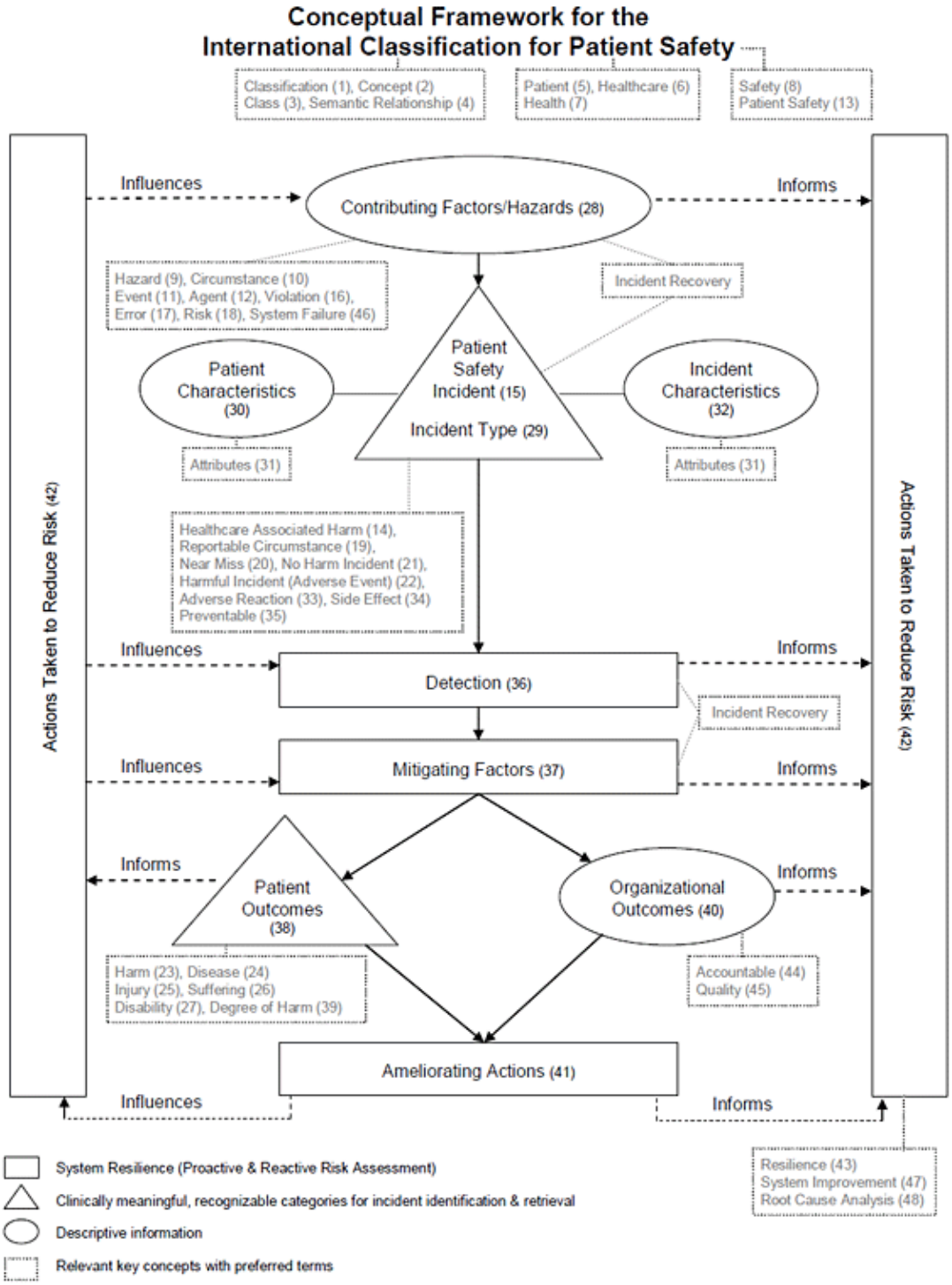
first studies to assess patient blood management program in a large pediatric population. In addition, this research will add to the growing body of literature on optimization of RBC transfusion in pediatric patients, potentially leading to de-implementation, or "the process of identifying and removing harmful

Conceptual Framework

The World Health Organization Conceptual Framework for the International Classification for Patient Safety (2009) serves as the foundation for this study (see Figure 1), with a focus on quantifying the harms related to the transfusion. Given limitations in measuring other aspects of the framework, this proposal centers around patient-centered outcomes. Within this framework, transfusion-related adverse events are identified as a healthcare-associated harm that have further downstream effects not only on patient outcomes, but also on organizational outcomes and quality. From a system-level, early detection, and mitigating factors will subsequently impact true harm to the patient. The goal for quality and safety work is to achieve the triple aim: improving the quality of care delivered, improving population health, and reducing health care costs (Berwick et al., 2008). As the cost implications for a larger program of patient blood management has not been performed in a pediatric population, the objective is to evaluate the impact of these programs in this setting.

Figure 1

The World Health Organization Conceptual Framework for the International Classification for Patient Safety (WHO, 2009).



Approach

Study Design, Sample, and Setting.

This investigation will utilize a retrospective cohort design to analyze clinical and demographic data from the electronic health record (EPIC, Verona, WI) and from Blood Bank records. Pediatric patients from the age of four months to the age of eighteen years at the time of the encounter will be included if they were hospitalized in a large pediatric health system with hospital encounter discharge dates between January 1, 2015 to December 31, 2019.

Measurements for Aim #1: To investigate the effect of a patient blood management program on transfusion utilization and the incidence of transfusion-related adverse events.

To establish the impact of the program, the transfusion utilization and incidence of transfusion-related adverse events from 2015 (the pre-intervention year) will be compared to those in 2019 (the maintenance phase). The following patient-specific data elements will be extracted from the electronic data warehouse within the electronic health record (Epic; Verona, WI) for patients whose encounter discharge dates were between January 1, 2015 and December 31, 2015 for the pre-intervention group and January 1, 2019 to December 31, 2019 for the post-intervention group. Clinical and demographic information will be collected to compare the baseline characteristics between the two groups. The patient data that will be collected includes the patient's medical record number, encounter number, date of birth, sex, race/ethnicity, payor status, date of hospital encounter, date of hospital discharge, weight in kilograms, ICU length of stay, hospital length of stay, severity of illness (3M™ APR DRG Classification System), transfusion

administration during the hospitalization, and presence of trauma team activation (CPT code G0390). The patient's medical record number will be used to identify multiple hospitalizations during the time period. If the patient received a transfusion, additional data elements will include date of transfusion(s), previous hemoglobin level prior to each administration of the transfusion, volume of red blood cell unit(s) or milliliters (mL), total volume and numbers of red blood cell units transfused during the admission, location of administration of transfusion(s) (i.e. emergency room, inpatient units, or critical care units), and incidence of transfusion-related adverse events. To investigate transfusion-associated adverse events, the following transfusion-associated adverse events will be included: transfusion-related acute lung injury, transfusion-associated circulatory overload, acute or delayed hemolytic transfusion reactions, anaphylactic transfusion reactions, transfusion-transmitted bacterial infection, immunologic transfusion reactions (urticaria) and febrile non-hemolytic transfusion reaction. Presence of adverse events will be identified through the diagnosis code for transfusion reactions of any kind, specifically ICD-9 and ICD-10 codes since the transition of coding systems spanned the duration of the study. All cases will be cross-referenced with Transfusion Safety records through the Blood Bank. All the different types of adverse events will be analyzed under the broad characterization of adverse events. If sufficient power is achieved, specific adverse events will be analyzed individually by the respective ICD-9 and ICD-10 codes.

Measurements for Aim #2: To compare the costs related to supporting a health-system level patient blood management program to costs of transfusion utilization.

For the purposes of the economic evaluation of the program, this analysis will assume the perspective of the hospital system. The program inputs that will be measured will include personnel costs, equipment and materials, and training time specifically related to the patient blood management work. For personnel estimations, the salary for transfusion safety officer for the duration of the intervention (November 2015 to December 2019) will be included. To preserve privacy, the median salary for an advanced practice provider will be included for the analysis of salary costs. For those with only intermittent participation in these events, the salaries with estimated hours of effort for the guideline and clinical decision support development, including the guideline methodologist, Epic analyst, and salary of those physicians and nurses involved in the development and review for the duration of meetings and document review. No additional facility indirect costs were considered as significant growth occurred during this time period with the opening one community hospital and a critical care tower as it could not be specifically attributed to the patient blood management program alone. The increase in transfusion medicine physician staff and infrastructure was primarily to support the coagulation program. The training time for the staff based off hourly wage for nurses from human resources and the overall number of nurses who completed the online training and time to complete that module. Physician training did not occur outside of regular academic meetings and will not be included in this estimate. Salary data will be obtained from human resources and generalized to the role of the specific team members.

To evaluate the program outputs, the costs of acquisition of a red blood cell transfusion will be estimated along with estimates of the direct and indirect costs. For the cost of a single transfusion, the acquisition price for one unit of packed red blood cells

that covered the donation center's cost for collecting, processing, and testing for each unit will be calculated and multiplied by the number of transfusions for 2015 and 2019, including partial units for infants and smaller children. The average cost of one unit of red cells for the years 2015 and 2019 will be acquired from the institution's blood bank records, along with number of units dispensed in those years. Estimates for direct and indirect costs will be calculated from previous research and adjusted for inflation the respective years. Shander et al. (2010) found activity-based costs for a blood transfusion from four US hospitals to average between $760 per unit transfused (2010, p. 759). The range of values will be used for sensitivity analyses, using the range of $522 and $1183, adjusted for inflation each calendar year to quantify the uncertainty around the estimates of the effect (Shander et al., 2010, p. 759).

Procedure for Data Collection.

The protocol will be submitted to IRB for review at both the University of Texas Health Science Center and Baylor College of Medicine prior to initiation with a request for a waiver of consent. The electronic health record will be queried for the data elements. To ensure that the elements of the data request are correct, a random selection of charts will be used to validate the data extracted by manual chart review. All data will be stored in a password protected folder on a protected server with the University of Texas Health Science Center at Houston.

Risk & Benefit to the Subjects.

The level of risk that this proposal subjects the participants to is minimal. As this study is a query of previously collected data, patients will not require any additional encounters for data collection. After the data are extracted from the electronic health

record and data validation is complete, the data will be de-identified using an assignment by another code and assigning age at admission rather than using birth date. Data will be stored on a password protected drive to ensure no loss of patient privacy where only the principal investigator and the dissertation committee will have access to the data. Staff information such as salary costs will be hosted on the same secure servers to maintain participant privacy. For staff salary information, privacy will be maintained by using the median salary for that job classification rather than direct figures.

Patients have the potential to benefit from the results of this study as the findings of the study could help healthcare professionals better understand the effect of safety programs implemented in a hospital system.

Data Analysis Plan for Aim 1.

Aim 1: To investigate the effect of a patient blood management program on transfusion utilization and the incidence of transfusion-related adverse events.

Data analysis will be done using IBM SPSS Statistics v. 24.0 (Armonk, NY). Significance will be set to $p<.05$ using two-sided tests. Baseline clinical and demographic information will be presented as summary statistics and reported for the pre-intervention year of the program (2015) and the sustainability phase of the program (2019). Generalized estimating equation will be used to evaluate the proportion of hospital encounters where the patient received red blood cell transfusions in 2015 compared to 2019. Poisson regression will be used to evaluate the differences in incidence of transfusion-related adverse events in patients with transfusions. Linear regression will be used to evaluate the hemoglobin level prior to transfusion. Covariates for those analyses will include patients with multiple admissions during the specified time period, age,

severity of illness, massive transfusion protocol activations, ICU length of stay, and overall length of stay.

Data Analysis Plan for Aim 2.

Aim 2: To compare the costs related to supporting a health-system level patient blood management program to the costs of transfusion utilization.

Regarding the cost evaluation, direct and estimated indirect costs of the programs will be compared and historical data from 2015 will be used to project utilization and will assume that without focused interventions, red blood cell transfusion utilization will continue at that rate. Total direct and estimated indirect program costs and outputs will be calculated for the pre-intervention phase and the maintenance phase. Utilization projections of rate ratios of transfusion from the first year of measurement (prior to the program kickoff) will be compared to the final year of the program to evaluate for differences in transfusion administration charges and charges for treatment related to transfusion reaction using χ^2 tests. Variance adjustment will be applied for correlation between multiple admissions for the same patient, age, overall length of stay, ICU length of stay, and overall length of stay.

Potential Pitfalls and Limitations

As this proposal describes a retrospective data collection, there is potential for error by not prospectively collecting data which may mean that some patient events or costs may be missed. To ensure data validity, findings from the electronic health record query will be verified with other reporting systems used for regulatory requirements. A selection of charts will be reviewed manually to safeguard from potential data errors in the code written for the query from the patient level data. Although the proposal may

miss some unidentified potential confounding factors, the design includes relevant factors identified from previous studies in this area as baseline demographic and clinical data.

For the economic evaluation, as the cost data was not collected prospectively, the estimated values may not reflect the actual costs incurred by the program nor the outputs, but the estimation of uncertainty will provide a range of values that would be expected.

Another potential pitfall includes that during the intervention, a large critical care tower opened in May of 2018, increasing the number of critically ill children that were admitted to the hospital. By using ICU admission as a potential covariate, this potential confounder can be controlled for in the analysis. Since this analysis excludes outpatient transfusions, this approach will exclude the transition of care from the inpatient to outpatient settings that has occurred between 2015 and 2019. As transfusion reactions are estimated to be under-identified, there is a potential limitation in identifying all cases, but the cases identified by diagnosis codes will be cross referenced with the actively collected data collected by the Blood Bank on transfusion reactions.

References

Berwick, D. M., Nolan, T. W., & Whittington, J. (2008). The triple aim: Care, health, and cost. Health Affairs, 27(3), 759–769. https://doi.org/10.1377/hlthaff.27.3.759

Commission, T. J. (2019). Patient Blood Management Certification Review Process Guide. https://www.jointcommission.org/assets/1/6/2019_Patient_Blood_Mgmt_Organization_RPG_(1).pdf

De Gast-Bakker, D. H., De Wilde, R. B. P., Hazekamp, M. G., Sojak, V., Zwaginga, J. J., Wolterbeek, R., De Jonge, E., & Gesink-Van Der Veer, B. J. (2013). Safety and effects of two red blood cell transfusion strategies in pediatric cardiac surgery patients: A randomized controlled trial. Intensive Care Medicine, 39(11), 2011–2019. https://doi.org/10.1007/s00134-013-3085-7

Goobie, S. M., Gallagher, T., Gross, I., & Shander, A. (2019). Society for the advancement of blood management administrative and clinical standards for patient blood management programs. 4th edition (pediatric version). Pediatric Anesthesia, 29(3), 231–236. https://doi.org/10.1111/pan.13574

Janssen, M. P., van Tilborgh, A. J. W., de Vooght, K. M. K., Bokhorst, A. G., & Wiersum-Osselton, J. C. (2018). Direct costs of transfusion reactions - an expert judgement approach. Vox Sanguinis, 113(2), 143–151. https://doi.org/10.1111/vox.12614

Organization, T. W. H. (2009). Conceptual Framework for the International Classification for Patient Safety. http://www.who.int/patientsafety/taxonomy/ICPS_Statement_of_Purpose.pdf

Ribed-Sánchez, B., González-Gaya, C., Varea-Díaz, S., Corbacho-Fabregat, C., Bule-Farto, I., & Pérez de-Oteyza, J. (2018). Analysis of economic and social costs of adverse events associated with blood transfusions in Spain. Gaceta Sanitaria, 32(3), 269–274. https://doi.org/10.1016/j.gaceta.2017.10.021

Schünemann, H., Brożek, J., Guyatt, G., & Oxman, A. (2013). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. https://gdt.gradepro.org/app/handbook/handbook.html

Shander, A., Hofmann, A., Ozawa, S., Theusinger, O. M., Gombotz, H., & Spahn, D. R. (2010). Activity-based costs of blood transfusions in surgical patients at four hospitals. Transfusion, 50(4), 753–765. https://doi.org/10.1111/j.1537-2995.2009.02518.x

Trentino, K. M., Farmer, S. L., Swain, S. G., Burrows, S. A., Hofmann, A., Ienco, R., Pavey, W., Daly, F. F. S., Van Niekerk, A., Webb, S. A. R., Towler, S., & Leahy, M. F. (2015). Increased hospital costs associated with red blood cell transfusion. Transfusion, 55(5), 1082–1089. https://doi.org/10.1111/trf.12958

Upvall, M. J., & Bourgault, A. M. (2018). De-implementation: A concept analysis. Nursing Forum, 53(3), 376–382. https://doi.org/10.1111/nuf.12256

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Introduction

Red blood cell (RBC) transfusions are used to replace blood loss from traumatic injury and otherwise improve the oxygen carrying capacity from anemia that results from iatrogenic or other identified causes. RBC transfusions are commonly used in the management of trauma, hematologic and oncologic diseases, and in the context of surgery and were identified as one of the top overused interventions or treatments (Joint Commission, 2012). As with most medical interventions, potential lifesaving benefits are mitigated by the potential risks. RBC transfusion-associated adverse events, ranging from mild reactions to death, can be the result of physiologic response to the blood components being transfused or result of system-level aspects of transfusion management (Delaney et al., 2016). Pediatric patients have twice the rate of transfusion-associated adverse events (TAAEs) when compared to adult patients, with a rate of 6.2 per 1,000 transfusions (Oakley, Woods, Arnold, & Young, 2015).

Physiologic mechanisms for transfusion reactions are not entirely understood, with some patients inherently having a higher risk for TAAEs. Some known risk factors include patients who have received transfusions before who may have developed antibodies that elicit allergic responses or immunosuppression with donor cells attacking the host (Delaney et al., 2016). While physiologic responses to transfusion account for a portion of TAAEs, an overwhelming majority of TAAEs are a result of system-level errors in the collection, storage, or administration process of transfusing blood products (Bolton-Maggs, 2017). Error-related reports account for 87% of all notifications (Bolton-Maggs, 2017, p. 395) to the Serious Hazards of Transfusion (SHOT) hemovigilance program in the United Kingdom. Transfusing incompatible blood components, excessive

transfusion volumes that result in fluid overload, and transfusion-associated infections from donor blood components are examples of system-level reported causes of TAAEs.

In the 1990s, France began hemovigilance programs that were intended to ensure the safety of the blood product supply chain from the donor to recipient in response to the HIV crisis (Jain & Kaur, 2012). Surveillance to quantify TAAEs were the initial focus of these efforts, and eventually broadened to include not only activities within the blood bank, but also in the context of clinical care of patients (Jain & Kaur, 2012). From these efforts, patient blood management (PBM) emerged as an "evidence-based, multidisciplinary approach to optimizing the care of patients who might need transfusion" (Joint Commission, 2019). PBM includes several interventions surrounding the decision to transfuse, including "patient evaluation and clinical management…application of appropriate indications, as well as minimization of blood loss and optimization of patient red cell mass" (Joint Commission, 2019, p. 5). The combination of interdisciplinary blood conservation modalities, patient-centered decision making, optimization of coagulation, and management of anemia can lead to improved patient outcomes (Goobie et al., 2019, p. 223). Some PBM interventions can include restrictive hemoglobin thresholds for transfusion of RBC products, transfusion guidelines, massive transfusion protocols, among others (Goobie et al., 2019).

This study sought to investigate the effect of a PBM program on transfusion utilization and the incidence of TAAEs in a pediatric population and to compare the costs related to supporting a health-system level PBM program to the costs of transfusion utilization. The hypothesis of this study is that these PBM interventions will cause reduced utilization of pediatric RBC transfusion, an increased incidence of TAAEs from

increased situational awareness, and that the benefits of this program will outweigh the costs. The following specific aims were pursued:

1. To investigate the effect of a patient blood management program on transfusion utilization and the incidence of transfusion-associated adverse events.
2. To compare the costs related to supporting a health-system level patient blood management program to the costs of transfusion utilization.

Background

Currently health services research in the realm of patient blood management and hemovigilance has identified strategies to reduce exposure to unnecessary transfusions and has shown some success in adult hospital settings (Leahy, Hofmann, Towler, et al., 2017; Warner, Schaefer, Madde, et al., 2019). In adult patients undergoing surgery, Althoff and colleagues found that "comprehensive anemia management, minimizing iatrogenic blood loss," along with the optimization of the "patient-specific physiological balance of trauma" (Althoff et al., 2019, p. 794) reduced the number of patients exposed to allogenic red blood cell transfusion, number of units of red blood cell transfusions per patient, length of hospital stays, total number of complications, and mortality. These findings were consistent through several categories of surgery and incorporated seventeen studies of over 235,000 patients. The SHOT hemovigilance program and other national level hemovigilance programs have improved both reporting of transfusion reactions and overall transfusion safety (Bolton-Maggs, 2017).

Several interventions under the larger concept of PBM have been shown to maintain or improve pediatric patient outcomes while minimizing risk from or exposure to transfusion, including reducing the hemoglobin threshold that triggers transfusion,

viscoelastic monitoring, antifibrinolytic administration, and using clinical decision support to support clinical decision-making.

With respect to standardizing the hemoglobin level at which a transfusion is indicated, a systematic review and meta-analysis indicated that reduced transfusion thresholds can reduce exposure to RBC transfusion without changes in mortality or morbidity in adults (Carson et al., 2021). Lacroix et al. (2007) conducted the first randomized controlled trial to evaluate transfusion thresholds in critically ill pediatric patients. Lacroix and colleagues (2007) demonstrated non-inferiority of lower hemoglobin thresholds to higher thresholds with respect to mortality. RBC transfusion thresholds have been studied in many other pediatric populations, including pediatric patients with sepsis (Karam et al., 2011), pediatric patients with burns (Voigt et al., 2018), and pediatric patients undergoing cardiovascular surgeries (Cholette, et al. 2011, Deng et al., 2019). Unfortunately, pediatric studies to date have been underpowered to determine the impact of transfusion thresholds on TAEEs.

Several laboratory assays have been evaluated for their applicability to PBM. Viscoelastic monitoring is a point of care whole blood test that provides insight into the kinetics of an individual's clotting process, from formation through breakdown (Sayce, Neal, & Leeper, 2020). A systematic review and meta-analysis also found few studies evaluating thromboelastography (TEG) and rotational thromboelastometry (ROTEM), two types of viscoelastic monitoring, for trauma-induced coagulopathy in adult trauma patients (Hunt et al., 2015). Hunt and colleagues (2015) failed to demonstrate the utility of ROTEM or TEG when evaluating diagnostic accuracy but called for further research due to limitations in numbers of studies and concerns regarding risk of bias.

Other promising PBM interventions include using antifibrinolytic medications or factor prothrombin complex concentrates to reduce blood loss or minimize transfusion requirements. The CRASH-2 Trial was a randomized controlled trial comparing tranexamic acid (TXA) to placebo in adult trauma patients and found that early treatment reduced both the risk of all-cause mortality and death related to bleeding (CRASH-2 Trial Collaborators, 2013). The CRASH-2 Trial also demonstrated the cost effectiveness of TXA but did not demonstrate a reduction on blood products transfused (Roberts et al., 2013). In pediatrics, TXA has shown a similar effect with decreased mortality in trauma patients (Eckert et al., 2014). Unfortunately, transfusion utilization and TAAEs have not been studied well in trauma, likely due to small sample sizes. TXA has been evaluated in other pediatric surgical procedures associated with significant blood loss, namely scoliosis surgery (Johnson et al., 2017) and craniofacial surgery (Basta, Stricker, & Taylor, 2012) and was found to reduce transfusion requirements in both populations. In adult studies, four factor prothrombin complex concentrate (PCC) has been demonstrated to improve survival (Zeeshan et al., 2019) and has shown a reduction of bleeding and reduced transfusions in both pediatric and adult surgical patients (Fominskiy et al., 2016). While adult studies have demonstrated the utility of antifibrinolytic drugs such as TXA or PCCs, the impact on pediatric trauma patients has not been established in the research.

PBM has both patient-level interventions, as described earlier, and systems-level interventions, such as clinical decision support (CDS) systems in the electronic health record (EHR). CDS can be used to encourage prudent transfusion ordering through information displayed at the point of care or linking to relevant references for the clinician. Many EHRs also have alert functionality that can be used to support safety

systems for potential errors in dosing and administration. For example, alerts may notify a clinician when a transfusion was ordered if the patient's hemoglobin is higher than the threshold or provide brief education at the point of order entry. A large-scale study that sought to evaluate the impact of an alert at the point of ordering on transfusion utilization in a large hospital system targeted to adult patients found that CDS was able to save approximately $1.6 million in red blood cell purchase costs (Goodnough et al., 2014). CDS may be an effective tool to reduce unnecessary exposure to transfusion, but to also save the healthcare system operational costs as well.

Unfortunately, interventions in pediatric patients are generally less studied compared to most interventions in the adult population. With respect to trauma, children have different mechanisms of injury and physiologic responses to trauma than adults along with variations due to growth and development. Often, adult studies are insufficient to guide care decisions for pediatric patients. Economic analyses of TAAEs have been performed on the population level for adults in a variety of countries, including Spain (Ribed-Sánchez, et al., 2018), Australia (Trentino et al., 2015), and the Netherlands (Janssen et al., 2018). In one of the randomized, controlled trials that looked at restrictive transfusion strategies in pediatric patients undergoing surgery for congenital cardiac defects, De-Gast Bakker et al. (2013) looked at cost of transfusion, but they only incorporated the cost of transfusions and was not powered to investigate TAAEs. Randomized controlled trials are not the ideal design to evaluate the impact of infrequent harms, and many studies evaluating the efficacy of PBM interventions are underpowered to detect differences in risk of harms. To date, a system-wide economic evaluation of a patient blood management program in pediatric patients has not yet been published.

Conceptual Framework

This study design was influenced by the World Health Organization Conceptual Framework for the International Classification for Patient Safety (2009) (Figure 1). In this framework, system level concepts are integrated to describe the complexity of patient safety. This framework incorporates contributing factors such as the incident type, patient and incident characteristics, mitigating factors, detection, and how actions can be taken by individuals and health systems to reduce risk.

Methods

Design

A retrospective cohort design was used to evaluate the impact of the patient blood management program. Clinical and demographic data were extracted from the electronic health record (Epic®, Verona, WI) for pediatric patients between the ages of four months to eighteen years at the time of the hospital encounter.

To complete the economic analysis, a cost-benefit analysis approach was used from the perspective of the hospital system. Program inputs evaluated included personnel costs, equipment and materials, and training time related to the PBM work for the period of the PBM intervention period of 2015 to 2019.

Human Subjects Protections

This study was approved by the Baylor College of Medicine Institutional Review Board and the University of Texas Health Science Center Committee for the Protection of Human Subjects. A Data Use Agreement between Baylor College of Medicine and the University of Texas Health Science Center at Houston was obtained to utilize data collected from the electronic health record at Texas Children's Hospital, which has an

academic affiliation with Baylor College of Medicine. Reciprocity between academic organizations was obtained with Baylor College of Medicine Institutional Review Board being the IRB of record for this study.

Sample and Setting

This study was conducted at a large quaternary pediatric hospital health system in the greater Houston metropolitan area. The health system serves a large southeast Texas region and has a total of three hospitals that care for pediatric patients and pregnant people in both the inpatient, outpatient, and community settings. A pediatric patient blood management program that consisted of a transfusion safety officer role, an evidence-based multi-disciplinary guideline with electronic health record clinical decision support, and a structured education program for physicians and nurses was implemented beginning in 2016. A number of PBM interventions along with EHR blood product administration and additional clinician education took place between 2016 and 2018. For the purposes of this analysis, the patients who were discharged in the calendar year of 2015 were used as the pre-intervention year, and the patients discharged in 2019 were analyzed as the post-intervention year. While PBM refers to all aspects of blood transfusion, including all fractionated blood components and whole blood administration, this analysis will focus only on RBC transfusions given that was the primary focus of the interventions in this time period.

To evaluate the impact of the patient blood management program, pediatric patients who were between the ages of four months to eighteen years at the date of admission to the hospital were included. Infants under four months were excluded from this analysis due to physiologic differences in vitamin K-dependent clotting factors and

maternal antibodies being present making the approach to transfusion different than with older children (Lau, 2017). Patients who were admitted for short-term stays under observation status, patients who only presented to the emergency center and were discharged home without admission, and those who only were in the hospital for surgical procedures without admission were excluded. Patients were included in the analysis if they were discharged from their hospital admission between January 1, 2015, and December 31, 2015, for the pre-intervention group and discharged between January 1, 2019, and December 31, 2019, for the post-intervention group.

For the purposes of this analysis, this cost benefit analysis adopted the perspective of the direct and indirect costs related to the PBM program were compared to the costs of transfusion utilization. Program inputs in the form of personnel costs and training time related to the PBM work were compared with program outputs of costs of transfusion.

Procedure for Data Collection

After receiving approval, data were extracted through the electronic health record electronic data warehouse. Subjects were identified through a query from the electronic data warehouse for all patients admitted to Texas Children's Hospital and divided into two groups: those who were discharged between January 1, 2015, to December 31, 2015, and those who were discharged between the dates of January 1, 2019, and December 31, 2019. Clinical and demographic were obtained for those patients, and if the patients had a transfusion ordered during the admission, additional information about the transfusion volume, hemoglobin prior to the RBC administration, and others was collected.

For the economic analysis, median and salary range data were collected from the occupational employment and wage statistics from the United States Bureau of Labor

Statistics Occupational Employment and Wage Statistics May 2021 Metropolitan and Nonmetropolitan Area Occupational Employment and Wage Estimates: Houston-The Woodlands-Sugar Land, TX (2022). Each of the roles that participated in the guideline development process and transfusion safety work were queried from the reports for the Houston-The Woodlands-Sugar Land region as defined by the OEWS survey, which includes Austin, Brazoria, Chambers, Fort Bend, Galveston, Harris, Liberty, Montgomery, and Waller counties. Reported 10^{th} percentile, median, and 90^{th} percentile salaries were obtained for the roles involved in this geographic area.

Measurements

Transfusion Utilization

For each hospitalization of patients who were discharged in the 2015 and 2019 groups, the following information was collected: medical record number, hospital encounter number, date of birth, sex, race/ethnicity, payor status, date of hospital encounter, date of hospital discharge, weight in kilograms, intensive care unit (ICU) length of stay, hospital length of stay, severity of illness, (3M™ APR DRG Classification System), and if the patient had a charge for a transfusion administration during the hospitalization.

For the patients who received a transfusion during those time frames, additional information was collected from the EHR. For each transfusion, the date of the transfusion was collected, volume of red blood cell unit(s) or milliliters (mL), total volume and numbers of red blood cell units transfused during the admission, hemoglobin level within twenty-four hours prior to the transfusion order, volume of the transfusion, patient weight, and if the patient had a diagnosis code that indicated they experienced a TAEE.

The following TAEEs were evaluated using International Classification of Diseases (ICD) codes: transfusion-related acute lung injury, transfusion-associated circulatory overload, acute or delayed hemolytic transfusion reactions, anaphylactic transfusion reactions, transfusion-transmitted bacterial infection, immunologic transfusion reactions (urticaria) and febrile non-hemolytic transfusion reaction. Presence of trauma team activation from the CPT code was not consistently identified in key cases and therefore was not used in this analysis.

Economic Analysis of Hospital-Based PBM Interventions

To estimate the inputs of the program, salaries and estimated hours of efforts for those involved in the PBM work were calculated. This calculation includes the salaries of the following roles and their time estimated that was dedicated to PBM interventions: transfusion safety officer, guideline methodologist, EHR analyst, and multidisciplinary team used to develop the guideline and implement the associated CDS. No additional indirect costs were considered as significant growth occurred during this period in which another community hospital and critical care tower opened in this hospital system. The indirect costs related to increasing capacity of transfusion medicine service line could not be directly attributed to the PBM program and therefore were excluded from this analysis. Capital costs of the EHR blood product administration module were not available and were not included in this analysis. Additional costs included the training time for staff. These costs were estimated off nursing hourly wage and the overall number of nurses who completed the online training and time to complete that module. Since physician training did not occur outside of regular academic meetings, it was not included in this estimate.

Transfusion cost estimates were estimated using the number of transfusions administered during the pre- and post-intervention years with activity-based costing. Shander et al. (2010) found activity-based costs for a blood transfusion from four US hospitals to average $760 per unit transfused (2010, p. 759). The range of values will be used for sensitivity analyses, using the range of $522 and $1183, adjusted for inflation to quantify the uncertainty around the estimates of the effect (Shander et al., 2010, p. 759). All costs were adjusted to 2021 using the US Consumer Price Index (U. S. Bureau of Labor Statistics, n.d.) so that direct comparisons of transfusion costs could be compared with salary estimates. Because Shander et al. (2010) adjusted their activity-based cost analysis for 2008, for this study, an inflation rate of 32.5% was used according to the U.S. Consumer Price Index when comparing costs between December 2008 and December 2021 (Bureau of Labor Statistics, n.d). This resulted in using the following estimates for the activity-based costs: $1007.90 as an average cost per unit transfused with a range of $692.27 to $1568.88 per unit transfused.

Statistical Analysis

SPSS® (version 27, SPSS Inc., Chicago, IL) software was used for data analysis. Significance was set to $p<0.05$ using two-sided tests. Clinical and demographic data were analyzed using summary statistics for the pre-intervention year of the program (patients who were discharged in 2015) and the sustainability phase of the program (including patients who were discharged in 2019) using chi-squared tests and independent samples t-tests. Generalized estimating equation was used to evaluate the relationship between transfusion utilization using covariates of illness severity, ICU length of stay, and overall length of stay.

For the cost evaluation, direct and estimated indirect costs of the programs were compared and historical data from 2015 were used to project utilization and will assume that without focused interventions, red blood cell transfusion utilization will continue at that rate. Utilization projections of rates of transfusion per 10,000 hospitalizations and rates of transfusions per 10,000 hospital days from the first year of measurement (prior to the program kickoff) was compared to the final year of the program to evaluate for differences in transfusion administration costs.

Results

Patient Blood Management Intervention

Study Population Characteristics

A total of 35,245 hospital admissions were analyzed in this study. Of those admissions, 16,519 hospitalizations were characterized as the pre-PBM intervention group (discharged in 2015) and 18,726 in the post-PBM intervention group (discharged in 2019). Within each of these groups, there were 11,970 unique patients in the 2015 year and 13,459 unique patients in 2019. Demographic information of each group is presented in Table 1 and baseline clinical characteristics are listed in Table 2.

When comparing the characteristics of the admissions, the mean age at admission for both groups was seven years of age and slightly less than half of admissions were of female patients. A total of 41.6% of admissions identified as Hispanic or Latino (with 41.1% in 2015 and 42.1% in 2019).

Transfusion Administration

Of the 16,519 hospitalizations in 2015, 1,854 of those hospitalizations had RBC transfusions administered during the stay (11.22%). The post-intervention year saw

roughly the same number of transfusions, with transfusions administered during 1,960 hospitalizations of the 18,726 total (10.47%). As a surrogate measure to estimate RBC transfusion guideline recommendation adherence, volume of RBC transfusion administration and pre-transfusion hemoglobin level were analyzed (see Table 3).

A total of 11,423 transfusions were analyzed further, specifically to compare the mean volume of transfusion volume administered and the pre-transfusion hemoglobin level between the pre- and post-intervention years. In 2015, the mean volume ordered for an RBC transfusion was 10.81 ± 6.19 mg/kg (n=4,877 transfusion). In 2019, this value was reduced to a mean of 9.09 ± 4.41 mg/kg (n = 6,527 transfusions) and this difference was statistically significant using an independent samples t-test (t_{8372} = 16.537; $p < 0.05$).

When looking at the mean hemoglobin in the 24 hours prior to transfusion, the mean hemoglobin levels in 2015 group were 7.77 ± 1.57 g/dL compared to 7.34 ± 1.48 g/dL in the 2019 group. This difference was statistically significant using an independent samples t-test with equal variances assumed (t_{9043}= 13.436, $p < 0.05$).

Transfusion Reaction

A total of 25 transfusion reactions were identified in this sample, with 10 occurring in 2015 and 15 in 2019. This difference of incidence of transfusion reactions was not statistically significant ($\chi^2 = 0.47$, $df = 1$, p=0.49). See Table 4 for details of the transfusion reactions on both the pre- and post-intervention years.

Transfusion Utilization

To explore the relationship between transfusion utilization between the pre- and post-intervention groups, generalized estimating equation was used with the severity level as a categorical factor and covariates of total days in ICU and overall length of stay.

In this model, overall length of stay and severity level were significant predictors of transfusion utilization (see Table 5). In the model, increasing level of severity (categorized by the 3M^{TM} APR DRG Severity of Illness Level) led to increasing likelihood of having a transfusion during that administration ($p < 0.05$). The year and whether or not the hospitalization included ICU care were not statistically significant in the model ($p = 0.105$ and $p= 0.08$, respectively).

Economic evaluation

Program inputs

Salaries costs were the primary program input evaluated in this study and included staff salaries and estimated hours to the project. Detailed information regarding salary cost calculations per individual role is presented in Table 6. Percentiles of the pediatrician salaries were not available from the United States Bureau of Labor Statistics Occupational Employment and Wage Statistics May 2021, but minimum and maximums are presented in Table 6 using the 10th and 90th percentiles of other staff and median estimates for pediatricians. Median estimates for pediatricians were used for overall salary inputs costs given that ranges were unavailable. Including all the different participants for the guideline development and transfusion safety work, program inputs totaled to $355,863. Using a range of 10th and 90th percentiles for salary to provide a sensitivity analysis, these estimated costs ranged from $318,361 and $464,866.

Outputs transfusion

Activity-based cost estimates for transfusion were taken from Shander et al. (2010) and were adjusted for inflation to be comparable with salary estimates to 2021. Since Shander and colleagues' (2010) analysis was reported in 2009 dollars, these were

adjusted to be comparable with 2021 wage data with an 32.5% inflation rate between December 2008 and December 2021 according to the U.S. Consumer Price Index (U.S. Bureau of Labor Statistics, n.d.). As such, the activity-based costs were as follows for an RBC transfusion: minimum $692.27; mean $1007.90; maximum: $1568.88. See Table 7 for detailed information regarding activity-based cost estimates for the pre- and post-intervention groups. Using these estimates, transfusion activity-based costs averaged $4,917,544 in 2015 (range $3,377,585 to $7,654,566) and $6,595,698 in 2019 (range $4,530,215 to $10,266,751).

Transfusions per hospitalization were calculated by the total number of transfusions ordered divided by the number of hospitalizations for the pre- and post-intervention groups. To create a comparable measure, these estimates were multiplied by 10,000 admissions and activity-based costs were calculated using previously described estimates that were adjusted for inflation (Shander et al, 2010). Details about the estimates for the rates can be seen in Table 8 for calculations based on hospital admissions. To account for the differences in length of stay between the years, transfusions per 10,000 patient days were calculated and details can be found in Table 9.

Activity-based costs based on number of transfusions per 10,000 hospital admissions were higher in the 2019 cohort than in the 2015 cohort. This resulted in an overall increase of $245,273 (with a range of $374,518 to $848,764). When looking at transfusions per 10,000 patient days, this persisted with 44 more transfusions per 10,000 patient days and an increased cost as well. This difference was estimated to be an increase of $44,544 (range $30,595 to $69,337) per 10,000 patient days. These

Discussion

This study described transfusion practices during hospital admissions for pediatric patients and evaluated the impact of PBM interventions on RBC transfusion utilization, transfusion-associated adverse events, and the overall economic impact. Overall, hospital admissions increased notably between the pre- and post-intervention years with more hospitalizations that included ICU care . While this study found increased costs related to transfusion administration when looking at the number of transfusions ordered, fewer overall hospitalizations had RBC transfusions administered during their stay, lower volumes of RBCs were ordered per transfusion, and there was a lower hemoglobin value prior to the RBC transfusion being ordered.

As pediatric patients use weight-based dosing for medications and transfusion volumes, the volume of transfusion ordered and pre-transfusion hemoglobin are surrogates for understanding guideline adherence since the guideline and CDS explicitly made recommendations in this area. This study found statistically significant reductions in both the volume of transfusion and the pre-transfusion hemoglobin. While the mean difference is fairly small, this large sample size indicates that it is likely that the PBM work reduced exposure to transfusion through reducing the volume ordered at a time with CDS. Unfortunately, it was not possible to identify those who had decided against ordering a transfusion after reading the CDS at the time of order entry. Despite those limitations, the data show a reduction which suggests overall guideline adherence.

An increase in absolute numbers of transfusion associated circulatory overload were identified in the post-intervention group. As the overall mean volume of transfusion per kilogram of body weight decreased in the post-intervention group, this increase may

be attributable to the increase in situational awareness, recognition, and reporting rather than an increase in incidence.

This study failed to demonstrate that a PBM program was effective in reducing transfusion utilization at the hospitalization level when controlling for potentially confounding factors such as severity of illness, overall length of stay, and ICU admission. While this study identified increased costs of the program and increased absolute number of transfusions, the economic impact of potentially avoidable TAAEs was not able to be established. It is also possible that PBM program costs can not be recovered in the time frame used in this study.

In looking to the economic literature, the estimates using adjusted rates for activity-based costing were not too different from those included in Burns and colleagues (2019) for outpatient transfusion-related costs in Australia. While Burns and colleagues (2019) noted a lower total per unit costs of $659.59, this finding occurred in a public health service country, which theoretically could reduce costs through a public health system when compared with the United States. Other areas with public health systems such as the United Kingdom have identified lower transfusion costs (Stokes et al., 2018).

When looking at the cost-effectiveness program, the findings of this study differ when comparing to other programs. While Indelen and colleagues (2021) included different costs in their estimation compared with this study, they found an overall cost-effectiveness of a transfusion improvement program in Turkey in adult patients and noted a decrease in the number of transfusions as a result of this work. Consistent with the findings of Leahy et al. (2017), this PBM program also resulted in a reduced mean pre-transfusion hemoglobin level and decreased volume of transfusion. This study did not

find an overall cost-effectiveness when compared to Leahy and colleagues (2017), but it is notable that their analysis compared the number of red cell units issued with the denominator of total population regionally that the hospitals served in a public healthcare system.

Strengths and Limitations

This study's strengths include the volume of hospitalizations evaluated across a health system, where prior research was limited in the pediatric population and relied on large health system data that included adult patients or in smaller, more focused pediatric studies.

There are several potential limitations to the study. First, with any retrospective data, there were challenges in characterizing sub-populations that may require more transfusions or that may be at higher risk for transfusion reactions given the nature of the data collected in the EHR. For example, while many patients who are being treated for a hematologic or oncologic disorder and are more likely to need a transfusion are often admitted on the hematology/oncology floor or have their transfusion ordered by a hematologist or oncologist, this practice is not universally true. Billing data, while more easily available, often lacks the nuance that would give us a richer picture. We also know that transfusion reactions are under-identified with passive reporting systems (Sahu & Bajpai, 2020, Hendrickson, et al.2016; Raval, et al., 2015), and this limitation is possible in this sample as well.

Given those limitations, the use of additional variables such as the 3M^{TM} APR DRG Severity of Illness score, ICU length of stay, and overall length of stay were used as proxy variables. This study also excluded transfusions that were given in outpatient

settings such as the emergency center, infusion center, or clinic, as many of the PBM interventions were primarily targeting the inpatient settings.

Changes in the process as a result of the PBM efforts also added challenges to the data analysis. As a result of the PBM initiatives, several improvements were made to the EHR during the intervention period between 2016 and 2018 to improve provider transfusion ordering and nursing documentation. Given these differences, the ordering volume was used for the analysis, and although not all transfusions are given in their entirety, an overwhelming majority of them are.

For the economic analysis, there were several limitations. The costs were estimated retrospectively and not collected in real time, and therefore some of the hourly contributions may have been under- or over-estimated. Also, the capital costs of the software to implement the blood transfusion administration module within the EHR were not available, and therefore were not included in this analysis. Another limitation is that a major component of PBM is avoidance of TAAEs, which were not incorporated in this analysis because no activity-based costing estimates exist for pediatric TAAEs. Future research is needed in this area to better understand the economic impact of TAAEs in pediatrics.

Implications for Research and Practice

With the increasing focus on preventing patient harm, clinicians and researchers need to better understand the impact of PBM on pediatric patient outcomes. This research adds to the growing body of literature on optimization of RBC transfusion in pediatric patients. Further research could help us better identify how to support de-implementation of over-used interventions, or “the process of identifying and removing harmful and low-

value practices based on tradition and without scientific support" (Upvall & Bourgault, 2018, p. 379). Excess transfusion either through administering RBC transfusions when other methods to address anemia could be used, administering higher RBC transfusion volumes when not indicated, or other transfusion practices may be inadvertently causing harm to patients.

To better understand the economic impact of these interventions, pediatric researchers can further explore the activity-based costs for pediatric transfusions. Currently, there are no recent estimates for pediatric red blood cell transfusion activity costs which can take a significant amount of time for both nursing and the blood bank to prepare and administer the transfusion, observe responses, and intervene for any reactions. While this study estimated costs retrospectively, future research could gather these costs prospectively to better estimate the cost of these programs and compare them to patient outcomes. Another area of economic research includes the impact of pediatric transfusion reactions. This study quantified the overall incidence in hospitalized pediatric patients in a large system, but the economic impact is not well understood. While current estimates in the United States are not available, Ribed-Sanchez and colleagues (2018) have estimated the economic and social costs of adverse events associated with blood transfusions in Spain and Janssen and colleagues (2018) estimated these costs based off expert opinion in the Netherlands. Future research could quantify these for pediatric patients in the United States health context.

Conclusion

Patient blood management programs use interdisciplinary interventions to optimize transfusion with the intent to reduce unnecessary exposure to blood products

and promote patient safety (Goobie et al., 2019). This study explored the impact of a PBM program on pediatric hospitalized patients at a large tertiary academic medical center. The results suggest that this work was effective in reducing the mean hemoglobin pre-transfusion for RBC transfusion and reduced the mean volume of transfusion when adjusted for severity of illness and length of stay. The results of the cost-benefit analysis suggest that this investment in safety did not correspond with decreased utilization costs. More research is needed to understand the impact of reductions in transfusion-associated adverse events and their true cost.

References

Althoff, F. C., Neb, H., Herrmann, E., Trentino, K. M., Vernich, L., Füllenbach, C., Freedman, J., Waters, J. H., Farmer, S., Leahy, M. F., Zacharowski, K., Meybohm, P., & Choorapoikayil, S. (2019). Multimodal Patient Blood Management Program Based on a Three-pillar Strategy: A Systematic Review and Meta-analysis. *Annals of surgery*, *269*(5), 794–804. https://doi.org/10.1097/SLA.0000000000003095

Basta, M. N., Stricker, P. A., & Taylor, J. A. (2012). A systematic review of the use of antifibrinolytic agents in pediatric surgery and implications for craniofacial use. *Pediatric surgery international*, *28*(11), 1059–1069. https://doi.org/10.1007/s00383-012-3167-6

Bolton-Maggs P. (2017). Serious hazards of transfusion - conference report: celebration of 20 years of UK haemovigilance. *Transfusion medicine (Oxford, England)*, *27*(6), 393–400. https://doi.org/10.1111/tme.12502

Burns, K. E., Haysom, H. E., Higgins, A. M., Waters, N., Tahiri, R., Rushford, K., Dunstan, T., Saxby, K., Kaplan, Z., Chunilal, S., McQuilten, Z. K., & Wood, E. M. (2019). A time-driven, activity-based costing methodology for determining the costs of red blood cell transfusion in patients with beta thalassaemia major. *Transfusion medicine (Oxford, England)*, *29*(1), 33–40. https://doi.org/10.1111/tme.12523

Carson, J. L., Stanworth, S. J., Dennis, J. A., Trivella, M., Roubinian, N., Fergusson, D. A., Triulzi, D., Dorée, C., & Hébert, P. C. (2021). Transfusion thresholds for

guiding red blood cell transfusion. *The Cochrane database of systematic reviews*, *12*(12), CD002042. https://doi.org/10.1002/14651858.CD002042.pub5

Cholette, J. M., Rubenstein, J. S., Alfieris, G. M., Powers, K. S., Eaton, M., & Lerner, N. B. (2011). Children with single-ventricle physiology do not benefit from higher hemoglobin levels post cavopulmonary connection: results of a prospective, randomized, controlled trial of a restrictive versus liberal red-cell transfusion strategy. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*, *12*(1), 39–45. https://doi.org/10.1097/PCC.0b013e3181e329db

CRASH-2 trial collaborators, Shakur, H., Roberts, I., Bautista, R., Caballero, J., Coats, T., Dewan, Y., El-Sayed, H., Gogichaishvili, T., Gupta, S., Herrera, J., Hunt, B., Iribhogbe, P., Izurieta, M., Khamis, H., Komolafe, E., Marrero, M. A., Mejía-Mantilla, J., Miranda, J., Morales, C., … Yutthakasemsunt, S. (2010). Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet (London, England)*, *376*(9734), 23–32. https://doi.org/10.1016/S0140-6736(10)60835-5

de Gast-Bakker, D. H., de Wilde, R. B., Hazekamp, M. G., Sojak, V., Zwaginga, J. J., Wolterbeek, R., . . . Gesink-van der Veer, B. J. (2013). Safety and effects of two red blood cell transfusion strategies in pediatric cardiac surgery patients: a randomized controlled trial. *Intensive Care Medicine*, *39*(11), 2011-2019.

Delaney, M., Wendel, S., Bercovitz, R. S., Cid, J., Cohn, C., Dunbar, N. M., Apelseth, T. O., Popovsky, M., Stanworth, S. J., Tinmouth, A., Van De Watering, L., Waters,

J. H., Yazer, M., Ziman, A., & Biomedical Excellence for Safer Transfusion (BEST) Collaborative (2016). Transfusion reactions: prevention, diagnosis, and treatment. *Lancet (London, England)*, *388*(10061), 2825–2836. https://doi.org/10.1016/S0140-6736(15)01313-6

Deng, X., Wang, Y., Huang, P., Luo, J., Xiao, Y., Qiu, J., & Yang, G. (2019). Red blood cell transfusion threshold after pediatric cardiac surgery: A systematic review and meta-analysis. *Medicine*, *98*(11), e14884. https://doi.org/10.1097/MD.0000000000014884

Estcourt, L. J., Malouf, R., Trivella, M., Fergusson, D. A., Hopewell, S., & Murphy, M. F. (2017). Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support. *Cochrane Database Syst Rev*, *1*, CD011305.

Eckert, M. J., Wertin, T. M., Tyner, S. D., Nelson, D. W., Izenberg, S., & Martin, M. J. (2014). Tranexamic acid administration to pediatric trauma patients in a combat setting: the pediatric trauma and tranexamic acid study (PED-TRAX). *The journal of trauma and acute care surgery*, *77*(6), 852–858. https://doi.org/10.1097/TA.0000000000000443

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*, 175-191.

Fominskiy, E., Nepomniashchikh, V. A., Lomivorotov, V. V., Monaco, F., Vitiello, C., Zangrillo, A., & Landoni, G. (2016). Efficacy and Safety of Fibrinogen

Concentrate in Surgical Patients: A Meta-Analysis of Randomized Controlled Trials. *Journal of cardiothoracic and vascular anesthesia*, *30*(5), 1196–1204. https://doi.org/10.1053/j.jvca.2016.04.015

Goobie, S. M., Gallagher, T., Gross, I., & Shander, A. (2019). Society for the advancement of blood management administrative and clinical standards for patient blood management programs. 4th edition (pediatric version). *Paediatric anaesthesia*, *29*(3), 231–236. https://doi.org/10.1111/pan.13574

Goodnough, L. T., Maggio, P., Hadhazy, E., Shieh, L., Hernandez-Boussard, T., Khari, P., & Shah, N. (2014). Restrictive blood transfusion practices are associated with improved patient outcomes. *Transfusion*, *54*(10 Pt 2), 2753–2759. https://doi.org/10.1111/trf.12723

Hunt, H., Stanworth, S., Curry, N., Woolley, T., Cooper, C., Ukoumunne, O., Zhelev, Z., & Hyde, C. (2015). Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding. *The Cochrane database of systematic reviews*, *2015*(2), CD010438. https://doi.org/10.1002/14651858.CD010438.pub2

İndelen, C., Uygun Kızmaz, Y., Kar, A., Shander, A., & Kırali, K. (2021). The cost of one unit blood transfusion components and cost-effectiveness analysis results of transfusion improvement program. *Turk gogus kalp damar cerrahisi dergisi*, *29*(2), 150–157. https://doi.org/10.5606/tgkdc.dergisi.2021.20886

Jain, A., & Kaur, R. (2012). Hemovigilance and blood safety. *Asian journal of transfusion science*, *6*(2), 137–138. https://doi.org/10.4103/0973-6247.98911

Janssen, M. P., van Tilborgh, A. J. W., de Vooght, K. M. K., Bokhorst, A. G., Wiersum-Osselton, J. C. (2018). Direct cost of transfusion reactions—an expert judgement approach. *Vox Sang, 113*(2), 143-151. doi: 10.1111/vox.12614

Johnson, D. J., Johnson, C. C., Goobie, S. M., Nami, N., Wetzler, J. A., Sponseller, P. D., & Frank, S. M. (2017). High-dose Versus Low-dose Tranexamic Acid to Reduce Transfusion Requirements in Pediatric Scoliosis Surgery. *Journal of pediatric orthopedics*, *37*(8), e552–e557. https://doi.org/10.1097/BPO.0000000000000820

Joint Commission. (2012). Proceedings from the National Summit on Overuse. Retrieved from: https://www.jointcommission.org/overuse_summit/

Karam, O., Tucci, M., Ducruet, T., Hume, H. A., Lacroix, J., Gauvin, F., Canadian Critical Care Trials Group, & PALISI Network (2011). Red blood cell transfusion thresholds in pediatric patients with sepsis. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*, *12*(5), 512–518. https://doi.org/10.1097/PCC.0b013e3181fe344b

Lacroix, J., Hebert, P. C., Hutchison, J. S., Hume, H. A., Tucci, M., Ducruet, T., . . . Peters, M. J. (2007). Transfusion strategies for patients in pediatric intensive care units. *New England Journal of Medicine, 356*(16), 1609-1619.

Lau. W. (2017). Neonatal and pediatric transfusion. In G. Clark & T. Abe (Eds.), *Clinical guide to transfusion.* *https://professionaleducation.blood.ca/en/transfusion/clinical-guide/neonatal-and-pediatric-transfusion*

Leahy, M. F., Hofmann, A., Towler, S., Trentino, K. M., Burrows, S. A., Swain, S. G., Hamdorf, J., Gallagher, T., Koay, A., Geelhoed, G. C., & Farmer, S. L. (2017). Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. *Transfusion*, *57*(6), 1347–1358. https://doi.org/10.1111/trf.14006

Lightdale, J. R., Randolph, A. G., Tran, C. M., Jiang, H., Colon, A., Houlahan, K., et.al. (2012). Impact of a conservative red blood cell transfusion strategy in children undergoing hematopoietic stem cell transplantation. *Biological Blood Marrow Transplant*, *18*(5), 813-817.

Oakley, F. D., Woods, M., Arnold, S., & Young, P. P. (2015). Transfusion reactions in pediatric compared with adult patients: a look at rate, reaction type, and associated products. *Transfusion*, *55*(3), 563–570. https://doi.org/10.1111/trf.12827

Raval, J. S., Mazepa, M. A., Russell, S. L., Immel, C. C., Whinna, H. C., & Park, Y. A. (2015). Passive reporting greatly underestimates the rate of transfusion-associated circulatory overload after platelet transfusion. *Vox sanguinis*, *108*(4), 387–392. https://doi.org/10.1111/vox.12234

Ribed-Sánchez, B., González-Gaya, C., Varea-Díaz, S., Corbacho-Fabregat, C., Bule-Farto, I., & Pérez de-Oteyza, J. (2018). Analysis of economic and social costs of adverse events associated with blood transfusions in Spain. *Gaceta sanitaria*, *32*(3), 269–274. https://doi.org/10.1016/j.gaceta.2017.10.021

Roberts, I., Shakur, H., Coats, T., Hunt, B., Balogun, E., Barnetson, L., Cook, L., Kawahara, T., Perel, P., Prieto-Merino, D., Ramos, M., Cairns, J., & Guerriero, C. (2013). The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health technology assessment (Winchester, England)*, *17*(10), 1–79. https://doi.org/10.3310/hta17100

Sahu, A., & Bajpai, M. (2020). Determining the true incidence of acute transfusion reactions: Active surveillance at a specialized liver center. *Hematology, transfusion and cell therapy*, *42*(4), 326–332. https://doi.org/10.1016/j.htct.2019.09.006

Sahu, A., & Bajpai, M. (2020). Determining the true incidence of acute transfusion reactions: Active surveillance at a specialized liver center. *Hematology, transfusion and cell therapy*, *42*(4), 326–332. https://doi.org/10.1016/j.htct.2019.09.006

Sayce, A. C., Neal, M. D., & Leeper, C. M. (2020). Viscoelastic monitoring in trauma resuscitation. *Transfusion*, *60 Suppl 6*, S33–S51. https://doi.org/10.1111/trf.16074

Shander, A., Hofmann, A., Ozawa, S., Theusinger, O. M., Gombotz, H., & Spahn, D. R. (2010). Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion*, *50*(4), 753–765. https://doi.org/10.1111/j.1537-2995.2009.02518.x

Stokes, E. A., Wordsworth, S., Staves, J., Mundy, N., Skelly, J., Radford, K., & Stanworth, S. J. (2018). Accurate costs of blood transfusion: a microcosting of

administering blood products in the United Kingdom National Health Service. *Transfusion*, *58*(4), 846–853. https://doi.org/10.1111/trf.14493

Trentino, K. M., Farmer, S. L., Swain, S. G., Burrows, S. A., Hofmann, A., Ienco, R., Pavey, W., Daly, F. F., Van Niekerk, A., Webb, S. A., Towler, S., & Leahy, M. F. (2015). Increased hospital costs associated with red blood cell transfusion. *Transfusion*, *55*(5), 1082–1089. https://doi.org/10.1111/trf.12958

U. S. Bureau of Labor Statistics. (2022). *May 2021 Metropolitan and Nonmetropolitan Area Occupational Employment and Wage Estimates: Houston-The Woodlands-Sugar Land, TX*. https://www.bls.gov/oes/current/oes_26420.htm

U. S. Bureau of Labor Statistics. (n. d.). *CPI Inflation Calculator.* https://www.bls.gov/data/inflation_calculator.htm

Valentine, S. L., Lightdale, J. R., Tran, C. M., Jiang, H., Sloan, S. R., Kleinman, M. E., & Randolph, A. G. (2014). Assessment of hemoglobin threshold for packed RBC transfusion in a medical-surgical PICU. *Pediatric Critical Care Medicine, 15*(2), e89-94.

Voigt, C. D., Hundeshagen, G., Malagaris, I., Watson, K., Obiarinze, R. N., Hasanpor, H.,…Herndon, D. N. (2018). Effects of a restrictive blood transfusion protocol on acute pediatric burn care: Transfusion threshold in pediatric burns. *Journal of Trauma and Acute Care Surgery*, *85*(6), 1048-1054. doi: 10.1097/TA.0000000000002068.

Upvall, M. J., Bourgault, A. M. (2018) De-implementation: A concept analysis. *Nursing Forum*, *53*, 376-382.

Vossoughi, S., Perez, G., Whitaker, B. I., Fung, M. K., Stotler, B. (2018). Analysis of pediatric adverse reactions to transfusions. *Transfusion*, *58*(1):60-69.

Warner, M. A., Schaefer, K. K., Madde, N., Burt, J. M., Higgins, A. A., & Kor, D. J. (2019). Improvements in red blood cell transfusion utilization following implementation of a single-unit default for electronic ordering. *Transfusion*, *59*(7), 2218–2222. https://doi.org/10.1111/trf.15316

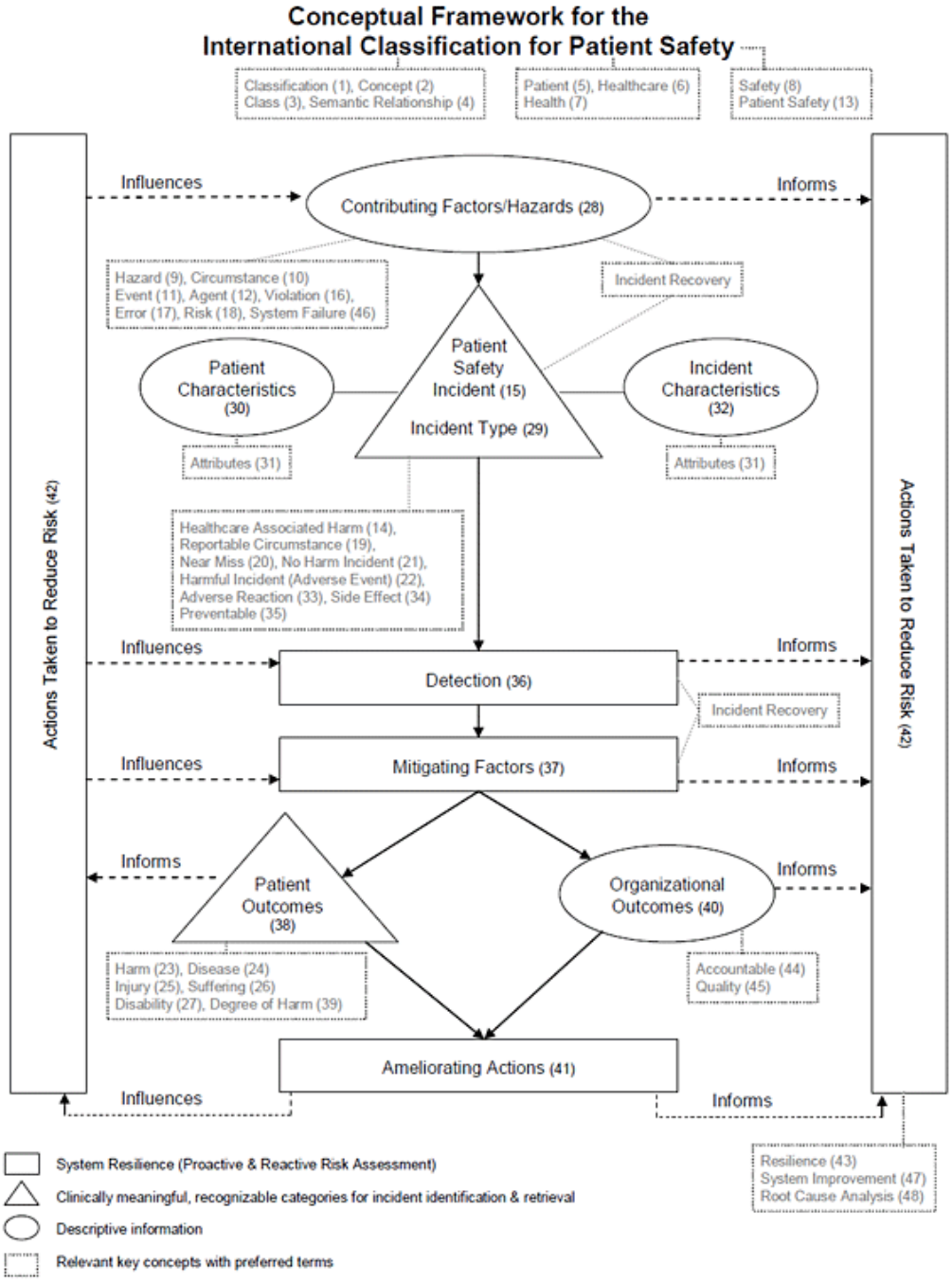
Willems, A., Harrington, K., Lacroix, J., Biarent, D., Joffe, A. R., Wensley, D., . . . Tucci, M. (2010). Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: a subgroup analysis. *Critical Care Medicine*, *38*(2), 649-656.

World Health Organization. (2009). Conceptual Framework for the International Classification for Patient Safety (Version 1.1) Retrieved from https://www.who.int/patientsafety/implementation/taxonomy/conceptual_framework/en/

Zeeshan, M., Hamidi, M., Feinstein, A. J., Gries, L., Jehan, F., Sakran, J., Northcutt, A., O'Keeffe, T., Kulvatunyou, N., & Joseph, B. (2019). Four-factor prothrombin complex concentrate is associated with improved survival in trauma-related hemorrhage: A nationwide propensity-matched analysis. *The journal of trauma and acute care surgery*, *87*(2), 274–281. https://doi.org/10.1097/TA.0000000000002262

Figure 1

World Health Organization Conceptual Framework for the International Classification for Patient Safety



Note. This figure is from the World Health Organization. (2009).

https://www.who.int/patientsafety/implementation/taxonomy/conceptual_framework/en/

Table 1

Sociodemographic Characteristics of Hospitalizations

Sociodemographic Characteristics	Pre-PBM Intervention Group (2015)	Post-PBM Intervention Group (2019)	Total	p value
Number of Hospital Admission	16519	18726	35245	
Unique Patients	11970	13459		
Mean age at admission (years)	7.14 (SD 5.65)	7.2 (SD 5.67)		p = 0.33
Gender				p = 0.05
Female	7864 (47.6%)	8877 (47.4%)	16741	
Male	8652 (52.4%)	9833 (52.5%	18485	
Ethnicity				p =0.126
Hispanic or Latino	6784 (41.1%)	7880 (42.1%)	14664	
Not Hispanic or Latino	9380 (56.8%)	10469 (55.9%)	19849	
Race				p <0.01
American Indian and Alaska Native	54 (0.3%)	78 (0.4%)	132	
Asian	811 (4.9%)	918 (4.9%)	1729	
Black of African American	3212 (19.4%)	3938 (21%)	7150	
Hispanic or Latino	1 (<0.1%)	2 (<0.1%)	3	
Native Hawaiian and other Pacific Islander	22 (0.1%)	37 (0.2%)	59	
White	12066 (73%)	13244 (70.7%)	25310	
Payor				p <0.01
Commercial	6956 (42.1%)	8030 (42.9%)	14986	
In-State Medicaid	5786 (35.5%)	4050 (21.6%)	9836	
Medicare	59 (0.4%)	55 (0.3%)	114	
Other Government	2978 (18%)	5484 (29.3%)	8426	
Other Payor	133 (0.8%)	208 (1.1%)	321	
Self-pay	444 (2.6%)	665 (3.6%)	1109	
Tricare	163 (1%)	234 (1.2%)	397	

Note. Gender, ethnicity, and race are self-reported upon admission. SD = standard deviation.

Table 2

Clinical Characteristics of Hospitalizations

Clinical Characteristics	Pre-PBM Intervention Group (2015) *n = 16519*	Post-PBM Intervention Group (2019) *n = 18726*	p value
Length of Stay in days[+] (mean)	6.75 (SD 20.79)	7.1 (SD 20.05)	p = 0.1
Length of Stay in days (median)	3	3	p = 0.8
Admission included ICU Stay^ *n (%)*	3056 (18.50%)	4513 (24.10%)	p < 0.01
Total Days in ICU across groups (mean)	0.91 (SD 5.55)	1.46 (SD 8.56)	p < 0.01
Total Days in ICU for only with ICU flag (mean)	4.9 (12.11)	6.02 (16.62)	p = 0.01
Total Days in ICU (median)	2	3	p = 0.2

3M APR DRG Severity of Illness Level			p < 0.01
Extreme	2344 (14.12%)	2485 (13.28%)	
Major	4698 (28.46%)	5119 (27.35%)	
Moderate	5654 (34.25%)	6969 (37.25%)	
Minor	3812 (23.09%)	4138 (22.12%)	
Transfusion ordered during hospitalization^	1854 (11.22%)	1960 (10.47%)	p = 0.02
Experienced Transfusion Reaction?	10 (0.54%)	15 (0.77%)	p = 0.49

Note. SD, Standard deviation

[+] Statistically significantly different using 2-sided independent samples t-test with $p < 0.05$.

^ Statistically significantly different using 2-sided χ^2 with $p < 0.05$.

Table 3

Clinical characteristics of transfusion

Clinical Characteristics	Pre-PBM Intervention Group (2015)		Post-PBM Intervention Group (2019)		p value
	mean	*SD*	*mean*	*SD*	
Pre-transfusion hemoglobin (mg/dL)*	7.78	1.57	7.34	1.48	$p < 0.01$
Volume of transfusion (mL/kg)*	10.81	6.19	9.09	4.41	$p < 0.01$

Note. SD, Standard deviation

* $p<0.05$ for independent samples *t*-test.

Table 4

Frequency of transfusion reactions

Transfusion Reaction	Pre-PBM Intervention Group (2015)	Post-PBM Intervention Group (2019)
ABO incompatibility	1	0
Anaphylactic reaction due to administration of blood and blood products	1	0
Febrile non-hemolytic transfusion reaction	2	5
Transfusion-associated circulatory overload	2	7
Transfusion-related acute lung injury	0	1
Vascular complications following transfusion	1	1
Unspecified transfusion reaction	3	3

Note. Some patients had multiple transfusion reactions in 2019.

Table 5

Generalized Estimating Equation of the Likelihood of Transfusion Utilization

			95% Wald Confidence Interval		Hypothesis Test			95% Wald Confidence Interval for Exp(B)		
Variable	B	SE	Lower	Upper	Wald χ^2	df	Sig	Exp (B)	Lower	Upper
(Intercept)	-1.238	0.0560	-1.348	-1.129	489.947	1	0.000	0.290	0.260	0.323
[ICUYN=No]	-0.077	0.0452	-0.166	0.011	2.909	1	0.088	0.926	0.847	1.012
[ICUYN=Yes]	0[a]							1		
[Severity=1.00]	-1.985	0.0812	-2.144	-1.826	597.416	1	0.000	0.137	0.117	0.161
[Severity=2.00]	-1.368	0.0602	-1.486	-1.250	516.567	1	0.000	0.255	0.226	0.286
[Severity=3.00]	-0.693	0.0520	-0.795	-0.591	177.807	1	0.000	0.500	0.452	0.554
[Severity=4.00]	0[a]							1		
[GroupYr=2015]	0.082	0.0509	-0.017	0.182	2.622	1	0.105	1.086	0.983	1.200
[GroupYr=2019]	0[a]							1		
Length Of Stay	0.010	0.0013	0.008	0.013	60.079	1	0.000	1.010	1.008	1.013
(Scale)	1									

Note. Dependent Variable: Received transfusion

Model: (Intercept), ICUYN, Severity, GroupYr, Length of Stay

a. Set to zero because this parameter is redundant.

Severity level is the 3M APR DRG Severity of Illness Level, categorized with minor as 1, moderate as level 2, major as 3, and extreme as 4.

Table 6

Economic Inputs for Patient Blood Management Program

Role Title	Salary 10th Percentile	Salary Median	Salary 90th Percentile	Hours	Activity Detail	Total Minimum	Total Median	Total Maximum
	Hourly, USD	*Hourly, USD*	*Hourly, USD*	*Estimated (hrs)*		*$USD*	*$USD*	*$USD*
Transfusion Safety Officer[a]	$47.45	$59.39	$62.02	4680	75% full time position x 3 years	$222,066	$277,945	$290,253
Guideline methodologist[b]	$25.80	$47.07	$79.53	936	30% FTE x 1.5 years	$24,149	$44,058	$74,440
Health Information Technician	$21.28	$35.96	$48.90	520	25% FTE x 1 year	$11,066	$18,699	$25,428
Physician (n=20)[c]	Not available	$140.35[c]	Not available	1	Meeting time for 17 meetings	Not available	$47,719[c]	Not available

Nursing (n=935)	$28.58	$37.31	$57.81	0.5	Training for 935 RNs	$13,361	$17,442	$27,026
Total Cost[d]						$318,361	$355, 863	$464,866

Note. Salary information sourced from Occupational Employment and Wages, May 2021. FTE=Full time equivalent. $USD=US Dollars.

[a]*Transfusion safety officer was a nurse practitioner and therefore the salary information was used.*

[b]*Project Management Specialist role was used to identify salary information*

[C]*Only mean hourly wage was offered for General Pediatrician salary.*

[d]*Mean hourly wage for pediatricians were used for calculating that portion of the minimum and maximum total costs.*

Table 7

Activity-Based Transfusion Actual Cost Estimates

	Transfusions	*Hospitalizations*	*Cost Min ($USD)*	*Cost Mean ($USD)*	*Cost Max ($USD)*
Pre-PBM Intervention Group (2015)	4879	16519	3,377,585	4,917,544	7,654,566
Post-PBM Intervention Group (2019)	6544	18726	4,530,215	6,595,698	10,266,751

Note. Activity-based cost estimates for transfusion were taken from Shander et al. (2010) and were adjusted for inflation to be comparable with salary estimates to 2021 (costs were reported in 2008 $USD). With an assumed 32.5% inflation rate between 2008 and 2021, the activity-based costs were as follows: (minimum $692.27; mean $1007.90; maximum: $1568.88).

Reference: Shander, A., Hofmann, A., Ozawa, S., Theusinger, O. M., Gombotz, H., & Spahn, D. R. (2010). Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion, 50*(4), 753–765. https://doi.org/10.1111/j.1537-2995.2009.02518.x

Table 8

Projected Activity-Based Cost Estimates per Admissions

	Transfusions per 10,000 admissions	*Estimated Minimum Cost ($USD)*	*Estimated Mean Cost ($USD)*	*Estimated Maximum Cost ($USD)*
Pre-PBM Intervention Group (2015)	2,953	2,044,273	2,976,329	4,632,903
Post-PBM Intervention Group (2019)	3,494	2,418,791	3,521,603	5,481,667
Calculated difference between 2015 and 2019	+541	374,518	545,273	848,764

Note: Activity-based cost estimates for transfusion were taken from Shander et al. (2010) and were adjusted for inflation to be comparable with salary estimates to 2021 (costs were reported in 2008 $USD). With an assumed 26.3% inflation rate between 2008 and 2021, the activity-based costs were as follows: (minimum $692.27; mean $1007.90; maximum: $1568.88).

Table 9

Projected Activity-Based Cost Estimates per 10,000 Inpatient Days

	Transfusions	*Total Inpatient Days*	*Transfusions per 10,000 Inpatient Days*	*Estimated Minimum Cost ($USD)*	*Estimated Mean Cost ($USD)*	*Estimated Maximum Cost ($USD)*
Pre-PBM Intervention Group (2015)	2,953	111,442	265	265	183,438	267,074
Post-PBM Intervention Group (2019)	3,494	113010	309	309	214,033	311,619
Calculated difference between 2015 and 2019	541	1,568	44	30,595	44,544	69,337

Note. Activity-based cost estimates for transfusion were taken from Shander et al. (2010) and were adjusted for inflation to be comparable with salary estimates to 2021 (costs were reported in 2008 $USD). With an assumed 26.3% inflation rate between 2008 and 2021, the activity-based costs were as follows: (minimum $692.27; mean $1007.90; maximum: $1568.88).

Appendix A

BCM IRB Approval Letter

December 22, 2021

Baylor College of Medicine
Office of Research
One Baylor Plaza, 600D
Houston, Texas 77030
Phone: (713) 798-6970
Fax: (713) 798-6990
Email: irb@bcm.edu

ADAM VOGEL
BAYLOR COLLEGE OF MEDICINE
TCH PEDI SURGERY

H-49187 - COST BENEFIT ANALYSIS OF A PEDIATRIC PATIENT BLOOD MANAGEMENT PROGRAM

APPROVAL VALID FROM 4/12/2021 TO 12/22/2025

Dear Dr. VOGEL

The Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals (BCM IRB) is pleased to inform you that the research protocol named above was reviewed and approved by Expedited procedures on 4/12/2021 by Board 6.

The study **does not require continuing review** but will require a 5 year renewal check in with the IRB Office. You will receive an email renewal reminder notice prior to study expiration; however, it is your responsibility to assure that this study is not conducted beyond the expiration date.

Please be aware that only IRB-approved informed consent forms may be used when written informed consent is required.

Any changes in study or informed consent procedure must be submitted to the IRB as an amendment for review and approval prior to implementation unless the change is necessary for the safety of subjects. In addition, you must inform the IRB of adverse events encountered during the study or of any new and significant information that may impact a research participants' safety or willingness to continue in your study.

Research that has been approved by the BCM IRB may be subject to further appropriate review and approval or disapproval by officials of the institution(s) where the research will be conducted. However, those institutional officials may not approve the research if it has not yet been approved by the IRB.

The BCM IRB is organized, operates, and is registered with the United States Office for Human Research Protections according to the regulations codified in the United States Code of Federal Regulations at 45 CFR 46 and 21 CFR 56. The BCM IRB operates under the BCM Federal Wide Assurance No. 00000286, as well as those of hospitals and institutions affiliated with the College.

Sincerely yours,

FLOR MUNOZ-RIVAS, M.D., M.S.
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Appendix B

Permission to Utilize Smart IRB Agreement

UTHealth
The University of Texas
Health Science Center at Houston

Committee for the Protection of Human Subjects
6410 Fannin Street, Suite 1100
Houston, Texas 77030

NOTICE OF PERMISSION TO UTILIZE SMART IRB RELIANCE AGREEMENT I

RB of Record: Baylor College of Medicine IRB

September 30, 2021

PI: Karen Gibbs,

HSC-SN-21-0310 -Cost Benefit Analysis of a Pediatric Patient Blood Management Program

L. Maximilian Buja ,

PROVISIONS: This permission relates to the research to be conducted under the above referenced title. Consent must comply with the UT required In Case of Injury section and HIPAA Authorization language.

Please contact the lead study team to determine what is required by the IRB of record.

The research should not be initiated until all necessary institutional approvals and signatures have been obtained including but not limited to a fully executed clinical trial agreement and Memorial Hermann Hospital approval (if the research is being conducted at a MHH facility).

Appendix C

Data Use Agreement

DATA USE AGREEMENT

This Data Use Agreement ("Agreement") is made and entered into as of this 24 day of May, 2021 by and between **BAYLOR COLLEGE OF MEDICINE** ("BAYLOR") with principal offices located at One Baylor Plaza, Houston, Texas 77030, and, The University of Texas Health Science Center at Houston "RECIPIENT") with principal offices located at 7000 Fannin Street, Houston, TX 77030, individually, a "Party," and collectively, the "Parties." The effective date of this Agreement is the date of the last signature.

WHEREAS, Dr. Cathy Rozmus will service as Principal Investigator, on the behalf of Karen Gibbs on this project.

WHEREAS, BAYLOR may Disclose or make available to RECIPIENT certain Protected Health Information ("PHI") in the form of a Limited Data Set, as defined below, and RECIPIENT may receive, Use, Disclose, transmit, maintain or create from the Limited Data Set certain information for purposes of research, public health, or health care operations as provided below; and

WHEREAS, BAYLOR, a Covered Entity as defined by the HIPAA Rules, and RECIPIENT are committed to comply with the Privacy, Security, Breach Notification, and Enforcement Rules at 45 C.F.R. Parts 160 and 164 of the Health Insurance Portability and Accountability Act of 1996, known collectively as the HIPAA Rules, and the Health Information Technology for Economic and Clinical Health Act (HITECH) amendments to the HIPAA Rules; and

WHEREAS, BAYLOR is required to obtain assurances from RECIPIENT that RECIPIENT will only Use or Disclose PHI as permitted by this Agreement, and;

WHEREAS, the Parties enter into this Agreement as a condition to BAYLOR furnishing the Limited Data Set to RECIPIENT once RECIPIENT has provided assurances about its Use and Disclosure of the Limited Data Set.

NOW, THEREFORE, in consideration of the mutual covenants and representations contained herein, the Parties agree as follows:

A. DEFINITIONS

Capitalized terns used but not otherwise defined in this Agreement shall have the same meaning as those terms in the HIPAA Rules.

1. **Limited Data Set** . Unless otherwise required by the HIPAA Rules, the term "Limited Data Set" shall include only the following Direct Identifiers of the Individual or of relatives, employers or household members of the Individual:

   a) Dates of treatment, admission, discharge
   b) Birth date, date of death
   c) Age (including age 90 or over)
   d) Geographic subdivisions such as state, country, town, city, precinct, and zip code
   e) Unique codes or identifiers that are not direct identifiers or replicates of a part of direct identifiers.

2. **Direct Identifiers**. Direct Identifiers of the Individual or of relatives, employers, or household members of the Individual are not allowed:
   a) Names
   b) All geographic subdivisions smaller than a State, including street address, city, county, precinct,

zip code, and their equivalent geographic codes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census: (1)The geographic

unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

c) All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
d) Telephone numbers, fax numbers
e) Electronic mail addresses
f) Social Security numbers, medical record numbers, health plan beneficiary numbers
g) Account numbers, Certificate/license numbers
h) Vehicle identifiers and serial numbers, including license plate numbers
i) Device identifiers and serial numbers
j) Web Universal Resource Locators (URLs)
k) Internet Protocol (IP) address numbers
l) Biometric identifiers, including finger and voice prints
m) Full face photographic images and any comparable image
n) Any other unique identifying number, characteristic, or code, except as permitted as a means of record identification to allow information de-identified to be re-identified.

3. **Commercial purposes**: The sale, lease, license, or other transfer of the Limited Data Set to a for-profit organization (other than RECIPIENT) and shall also include uses of the Limited Data Set by any organization, including RECIPIENT, to perform contract research, to produce or manufacture products for general sale, or to conduct research activities that result in any sale, lease, license, or transfer of the Limited Data Set to a for-profit organization.

B. SCOPE AND PURPOSE

1. This Agreement sets forth the terms and conditions pursuant to which BAYLOR will Disclose certain PHI in the form of a Limited Data Set to RECIPIENT.

2. Except as otherwise specified by this Agreement, RECIPIENT may make all Uses and Disclosures of the Limited Data Set necessary for the designated research, public health, or health care operations as described herein: research (Permitted Data Use"). If the Permitted Data Use is for research it will be used in accordance with the IRB approved protocol and provide the IRB protocol number: Baylor IRB protocol number H-49187.

3. Any and all other studies or uses of the Limited Data Set are expressly prohibited and may not be pursued by the RECIPIENT, any member of the RECIPIENT'S staff or any agent or subcontractor of the RECIPIENT without written approval of BAYLOR.

4. The Limited Data Set shall not be used for any commercial purposes.

5. In addition to the RECIPIENT, there are no other individuals, or classes of individuals, who are permitted to use or receive the PHI contained within the Limited Data Set for the Permitted Data Use.

6. The Limited Data Set to be provided by BAYLOR to the RECIPIENT per the Data Use Agreement for the Permitted Data Use consists of the following Direct Identifiers (see definition of Limited Data Set for allowed Direct Identifiers): dates of admission and discharge, birth date, age will be de-identified into categorical variables prior to transmission.

Additional data to be provided with the Limited Data Set that are not Direct Identifiers are as follows:

- sex
- race/ethnicity
- payor status
- date of hospital encounter
- date of hospital discharge
- weight in kilograms
- ICU length of stay
- hospital length of stay
- severity of illness (3M APR DRG Classification System)
- transfusion administration during the hospitalization
- presence of trauma team activation (CPT code G0390).

If the patient received a transfusion, additional data elements will include:

- date of transfusion(s)
- previous hemoglobin level prior to each administration of the transfusion
- volume of red blood cell unit(s) or milliliters (mL)
- total volume and numbers of red blood cell units transfused during the admission
- location of administration of transfusion(s) (i.e. emergency room, inpatient units, or critical care units)
- incidence of transfusion-related adverse events (transfusion-related acute lung injury, transfusion-associated circulatory overload, acute or delayed hemolytic transfusion reactions, anaphylactic transfusion reactions, transfusion-transmitted bacterial infection, immunologic transfusion reactions (urticaria) and febrile non-hemolytic transfusion reaction) using the diagnosis codes: 999.60 to 999.99 and ICD-10 codes including T80.22, T80.29, T80.3, T80.4, T80.4, T80.51, T80.91, T80.92 since the transition of coding systems spanned the duration of the study.

7. Describe in detail how RECIPIENT will secure and protect the Limited Data Set including but not limited to a description of the security of any databases to be used and how the Limited Data Set will be transmitted, if applicable, and stored : the data will be stored in a password-protected network drive at UTH with only access to people who on the approved research protocol.

C. OBLIGATIONS AND ACTIVITIES OF RECIPIENT

1. RECIPIENT agrees to the following:

   a) To not Use or further Disclose the Limited Data Set for any purpose other than as permitted by this Data Use Agreement or as Required by Law;

   b) To use appropriate data security measures and other safeguards to prevent inappropriate Use or Disclosure of the Limited Data Set other than as provided by this Agreement;

   c) To notify BAYLOR, in writing, of any Use or Disclosure of the Limited Data Set not provided for by this Agreement of which RECIPIENT becomes aware, including without limitation, any Disclosure of PHI to an unauthorized employee, agent or subcontractor of the RECIPIENT, within ten (10) days of its discovery;

d) To ensure that any agent and/or subcontractor of RECIPIENT to whom it provides the Limited Data Set agrees, in writing, to the same standards, restrictions and conditions that apply through this Agreement to the RECIPIENT.

e) To not identify the information contained in the Limited Data Set or contact the Individual/s.

f) To not create, receive, maintain, transmit, Use or Disclose the Limited Data Set outside of the United States.

2. This Data Use Agreement does not authorize the RECIPIENT to Use or Disclose the Limited Data Set for the Permitted Data Use in a manner that would violate the requirements of the HIPAA Rules if done by BAYLOR.

3. RECIPIENT will indemnify, defend and hold harmless BAYLOR and any of BAYLOR'S affiliates, and their respective trustees, officers, directors, employees and agents ("Indemnitees") from and against any claim, cause of action, liability, damage, cost or expense (including, without limitation, reasonable attorney's fees and court costs) arising out of or in connection with any unauthorized or prohibited Use or Disclosure of the Limited Data Set or any other breach of this Agreement by RECIPIENT or any subcontractor, agent or person under RECIPIENT'S control.

4. RECIPIENT understands that violations of the terms of this Agreement by RECIPIENT may be considered violations of the federal HIPAA Rules.

D. TRANSFER OF DATA

After execution of this Agreement, BAYLOR shall deliver the Limited Data Set and any additional data that are not direct identifiers as provided in Section B.7. to the RECIPIENT in the following secure manner: by secure email.

RECIPIENT: Name: Karen Gibbs
Title: Doctoral Student
Address: 6901 Bertner Ave, Houston, TX 77030
E-mail address: karen.d.gibbs@uth.tmc.edu
Phone: 832-728-0067
Other: kadivale@texaschildrens.org

E. TERM AND TERMINATION

1. This Agreement shall terminate when all of the Limited Data Set, including copies or replicas, provided by BAYLOR to RECIPIENT for the Permitted Data Use is destroyed, as evidenced by a Certificate of Destruction, or securely returned to BAYLOR. If it is not feasible to return or destroy the Limited Data Set, appropriate data protection and safeguards are extended to the Limited Data Set in accordance with the requirements of the HIPAA Rules and this Agreement for as long as the Limited Data Set remains in possession by the RECIPIENT.

2. Destruction of the Limited Data Set must be in accordance with industry standards and processes for ensuring that reconstruction, re-use, and/or re-disclosure of the Limited Data Set is prevented after destruction using a method effective for the media in which the Limited Data Set is contained.

3. Either Party may terminate this Agreement for a material breach by the other Party, if such breach is not cured to the satisfaction of the non-breaching Party within thirty (30) days after the non-breaching Party gives written notice of the breach to the breaching Party

F. MISCELLANEOUS

1. A reference in this Agreement to a section in the HIPAA Rules means the section as amended or as renumbered.

2. The parties agree to take such action as is necessary to amend this Agreement from time to time as is necessary for Covered Entity to comply with the requirements of the HIPAA Rules.

3. The respective obligations of RECIPIENT under Section C of this Agreement shall survive termination of this Agreement.

4. Any ambiguity in this Agreement shall be resolved to permit BAYLOR to comply with the HIPAA Rules.

5. There are no intended third party beneficiaries to this Agreement. Without in any way limiting the foregoing, it is the Parties' specific intent that nothing contained in this Agreement gives rise to any right or cause of action, contractual or otherwise, in or on behalf of the individuals whose PHI is Used or Disclosed pursuant to this Agreement.

6. Nothing in this Agreement shall be construed to create: (i) a partnership, joint venture, or other joint business relationship between the Parties or any of their affiliates; (ii) any fiduciary duty owed by one Party to another Party or any of its affiliates; or (iii) an agency or employment relationship between the Parties or any of their affiliates.

7. Failure or delay on the part of either Party to exercise any right, power, privilege or remedy hereunder shall not constitute a waiver thereof. No provision of this Agreement may be waived except by an agreement in writing signed by the waiving party. A waiver of any term or provision shall not be construed as a waiver of any other term or provision.

8. The persons signing below have the right and authority to execute this Agreement and no further approvals are necessary to create a binding agreement.

9. The provisions of this Agreement shall be severable and, if any provision of this Agreement shall be held or declared to be illegal, invalid or unenforceable, the remainder of this Agreement shall continue in full force and effect as though such illegal, invalid or unenforceable provision had not been contained herein.

10. The descriptive headings of the articles, sections, subsections, exhibits and schedules of this Agreement are inserted for convenience only, do not constitute a part of this Agreement, and shall not affect in any way the meaning or interpretation of this Agreement.

11. In the event of any conflict between the terms and conditions stated within this Agreement and those contained within any other agreement or understanding between the parties, written, oral or implied, the terms of this Agreement shall govern. Without limiting the foregoing, no provision of any other agreement or understanding between the parties limiting the liability of RECIPIENT to BAYLOR shall apply to the breach of any covenant in this Agreement by RECIPIENT.

12. This Agreement shall be construed in accordance with and governed by the laws of the State of Texas or jurisdiction of BAYLOR without regard to applicable conflict of laws principles. Any suit, action or proceeding against either Party with respect to this Agreement shall be brought in the state or federal courts located in Harris County, Texas, and the other Party hereby submits to the non-exclusive jurisdiction of such courts for the purpose of any such suit, action or proceeding.

13. Any notices pertaining to this Agreement shall be given in writing and shall be deemed duly given when personally delivered to a Party or a Party's authorized representative as listed below or sent by means of a reputable overnight carrier, or sent by means of certified mail, return receipt requested, postage prepaid. A notice sent by certified mail shall be deemed given on the date of receipt or refusal of receipt. All notices shall be addressed to the appropriate Party as follows:

If to BAYLOR
Baylor College of Medicine
Chief Compliance Officer
One Baylor Plaza
MS BCM265
Houston, Texas 77030

If to RECIPIENT
Karen Gibbs
Doctoral Candidate
6901 Bertner Ave
Houston, TX 77030

14. This Agreement is binding upon and inures to the benefit of the Parties hereto and their respective successors and permitted assigns. However, neither Party may assign any of its rights or delegate any of its obligations under this Agreement without the prior written consent of the other Party, which consent shall not be unreasonably withheld or delayed. Notwithstanding any provisions to the contrary, however, BAYLOR retains the right to assign or delegate any of its rights or obligations hereunder to any of its wholly owned subsidiaries, affiliates or successor companies. Assignments made in violation of this provision are null and void.

15. This Agreement, together with all exhibits, schedules, riders, and amendments, if applicable, which are fully completed and signed by authorized persons on behalf of both Parties from time to time while this Agreement is in effect, constitutes the entire Agreement between the Parties hereto with respect to the subject matter hereof and supersedes all previous written or oral understandings, agreements, negotiations, commitments, and any other writing and communication by or between the Parties with respect to the subject matter hereof. In the event of any inconsistencies between any provisions of this Agreement in any provisions of the exhibits, schedules, riders, and Amendment, the provisions of this Agreement shall control.'

16. An electronic copy or facsimile of a signature hereto will be binding upon the signatory as if it were an original signature.

IN WITNESS WHEREOF, the parties have executed this Agreement effective upon the Effective Date set forth above.

BAYLOR COLLEGE OF MEDICINE

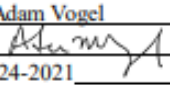
By: Leanne B. Scott, PhD (Authorized Signature)
Print name: Leanne Scott
Title: Executive Director, Sponsored Programs

Date: 09/21/2021

The University of Texas Health Science Center at Houston

By: Digitally signed by Kristin Parks Date: 2021.09.07 12:48:09 -05'00' (Authorized Signature)
Print name: Kristin Parks
Title: Director, CRFA SPA

Date: 09/07/21

Read and Understood: Principle Investigator signature
Name: Dr. Adam Vogel
Signature: 
Date: 5-24-2021

Stamped Approval Space

Appendix D

Reliance Agreement

Baylor College of Medicine
GIVING LIFE TO POSSIBLE

OFFICE OF RESEARCH

One Baylor Plaza, BCM310
Houston, Texas 77030-3411

(713) 798 – 6995
(713) 798 – 2721 FAX
azobu@bcm.edu

CONFIDENTIAL

December 7, 2021

Cynthia Edmonds, MLA
IRB Director
University of Texas Health Sciences Center Houston
Committee For the Protection of Human Subjects
Cynthia.L.Edmonds@uth.tmc.edu

Dear Ms. Edmonds,

Baylor College of Medicine is serving as the IRB of record for the following study:

Protocols:

- **Title**: Cost Benefit Analysis Of A Pediatric Patient Blood Management Program
- **Baylor Protocol#**: H-49187
- **Baylor Proposal#**: N/A
- **Funding Source**: N/A

The reliance of University of Texas Health Sciences Center Houston on Baylor College of Medicine for the review and approval of this protocol was determined and conducted according to the reciprocal agreement described in the UT System Reliance Agreement.

Please do not hesitate to contact me if you have any questions.

Sincerely,

Amara Azobu

Digitally signed by Amara Azobu
DN: cn=Amara Azobu, o=Baylor College of Medicine, ou=IRB, email=azobu@bcm.edu, c=US
Date: 2021.12.07 16:28:03 -06'00'

Amara Azobu, MS, CIP
Director, Research Compliance
Institutional Review Board (IRB) Administrator
Baylor College of Medicine
Department of Sr. VP & Dean of Research
(713) 798-6995 Direct
(713) 798-2721 Fax
azobu@bcm.edu

CURRICULUM VITAE

Karen DiValerio Gibbs, MSN/MPH, RN, PHNA-BC, CPN
karendgibbs@gmail.com

EDUCATION

Degree	Institution	Date
PhD Candidate	University of Texas Health Science Center Cizik School of Nursing Houston, TX Dissertation title: Cost-Benefit Analysis of a Pediatric Patient Blood Management Program	Expected 2022
Post-Master's Certificate in Nursing Education	University of Texas Health Science Center Cizik School of Nursing Houston, TX	2019
Dual Master of Science in Nursing and Master of Public Health (MSN/MPH)	Johns Hopkins University Baltimore, MD	2010
Bachelor of Science in Nursing (BSN)	University of Texas at Austin Austin, TX	2007

LICENSURE & CERTIFICATIONS

License	State	Active
Registered Nurse (RN) License # 742190	Texas Board of Nursing	Expires 7/31/2024

Certification	Certifying Body	Inclusive Dates
Certified Pediatric Nurse (CPN) Certification #20123288	Pediatric Nursing Certification Board	Certified 12/11/2012, Expires 2/28/2023
Advanced Public Health Nurse, Board Certified (PHNA-BC)	American Nurses Credentialing Center	Certified 5/2/2013, Expires 5/1/2023

PROFESSIONAL EXPERIENCE

Institution	Position Title	Inclusive Dates
Texas Children's Hospital Houston, TX	Pediatric Emergency Room Nurse	2007-2009
Johns Hopkins Hospital Baltimore, MD	Vascular Access Team Registered Nurse	2010
Johns Hopkins University School of Nursing Baltimore, MD	Clinical instructor	2010
Pulse Staffing Houston, TX	Pediatric Neurology Clinic Nurse	2011
Memorial Hermann Hospital Houston, TX	Education/Resource Specialist II	2011-2013
Texas Children's Hospital Houston, TX	Research Specialist for the Evidence-Based Outcomes Center	2015-2019
Texas Children's Hospital Houston, TX	Clinical Specialist for Pediatric Acute Care Nursing	2019-2022
University of Texas Health Science Center at Houston Cizik School of Nursing Houston, TX	Graduate Research Assistant	2020-2022
Baylor College of Medicine Houston, TX	Clinical Instructor	2022-Present
University of Texas Health Science Center at Houston Cizik School of Nursing Houston, TX	Scientific Research Project Manager	2022-Present

PROFESSIONAL TRAINING

Advanced Quality Improvement and Patient Safety Program, Texas Children's Hospital, Houston, TX; March 30-September 16, 2016

PROFESSIONAL TRAINING CONTINUED

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Workshop: Systematic Review and Meta-Analysis and Methodologist Track; Seattle, WA, October 3-6; 2017

Simulation Instructor Course, Texas Children's Hospital, Houston, TX; April 28, 2021

Advanced Simulation Instructor Course: Scenario Design, Texas Children's Hospital, Houston, TX; May 18, 2021.

HONORS AND AWARDS

Outstanding Graduating Student, University of Texas at Austin School of Nursing, 2007.

Outstanding Nurses of 2022 Honoree, Texas Nurses Association District 9, 2022.

Nursing Excellence Award: Nurse with an Advanced Degree of the Year, Texas Children's Hospital, 2022.

PhD Student Award, Sigma Theta Tau Zeta Pi Chapter, 2022.

Excellence in Nursing Award Bronze Medalist, Good Samaritan Foundation, 2022.

FUNDED GRANTS

1. Pediatric Nurses' Experiences in Caring in the Time of COVID: A qualitative study. Sigma Theta Tau Zeta Pi Chapter Evidence Based Practice and Research Award, $1,000, Co-Principal Investigator.

2. Hospitalized and Hungry: A Qualitative Study Assessing the Efficacy of an Inpatient Food Insecurity Intervention Among Immigrant Families. Dr. Hema Desai Pediatric Hospital Medicine Research Pilot Funding Award, $5,000, Co-Investigator.

PUBLISHED MANUSCRIPTS

Tubbs-Cooley, H. L., Lavin, R., Lyndon, A., Anderson, J., Baernholdt, M., Berry, P., ...**Gibbs, K.D.** ... Friese, C. R. Stronger together: The case for multidisciplinary tenure track faculty in academic nursing. *Nursing Outlook.* https://doi:10.1016/j.outlook.2021.03.016.

Gibbs, K. D., Shi, Y., Sanders, N., Bodnar, A., Brown, T., Shah, M. D., & Hess, L. M. (2021). Evaluation of a Sepsis Alert in the Pediatric Acute Care Setting. *Applied Clinical Informatics*, *12*(3), 469–478. https://doi.org/10.1055/s-0041-1730027

PUBLISHED MANUSCRIPTS

Crane, S., **Gibbs, K. D.**, Nosich, R., Yang, Y., & Pawelek, E. (2021). Challenges in the implementation of electronic systems for patient report of symptoms in oncology: a scoping review. *Journal of Hospital Management and Health Policy*. https://doi.org/10.21037/jhmhp-20-108

Lea, N. C., **Gibbs, K**., Johnson, C., Lam, A., Wuestner, E., & Hui, S. R. (2022). Transfusion-Associated Adverse Events: A Case Report of Nurse Hemovigilance and Recognition of Respiratory Distress. *Journal of infusion nursing : the official publication of the Infusion Nurses Society*, *45*(5), 264–269. https://doi.org/10.1097/NAN.0000000000000483

Gibbs, K. D., Jones, J. T., LaMark, W., Abdulmooti, S., Bretz, L., Kearney, K. D., Narendorf, S. C., & Santa Maria, D. M. (2022). Coping during the COVID-19 pandemic among young adults experiencing homelessness and unstable housing: A qualitative study. *Public health nursing (Boston, Mass.)*, 10.1111/phn.13136. Advance online publication. https://doi.org/10.1111/phn.13136

Gibbs, K. D., Loveless, J., & Crane, S. (2022). A guide to using technological applications to facilitate systematic reviews. *Worldviews on evidence-based nursing*, 10.1111/wvn.12611. Advance online publication. https://doi.org/10.1111/wvn.12611

BOOKS AND CHAPTERS

Gibbs, K. D. & Jackson, A. (2022). Clinical Practice Guidelines. In S. Wallace & G. Golukakrishnan (Eds.) *Evidence-Based Medicine: From the Clinician and Educator Perspective*. Nova Science Publishers: Happuage, NY.

PRESENTATIONS

International

Gibbs, K. D. & Garey, A. (July 2020). Evolution of EBP Education in a Large Pediatric & Women's Academic Hospital System. Sigma Theta Tau International Conference, Virtual (due COVID-19, previously scheduled at Abu Dhabi, United Arab Emirates).

Gibbs, K. D., Whisenant, M., Maliackal, A., Pawelek, E., Crane, S. (12-28 October 2021). Electronic Visualizations of Patient-Reported Outcome Measure Data: A Systematic Review (virtual poster). International Society for Quality of Life Research (ISOQOL) 28th Annual Conference, Virtual (due to COVID-19).

Klinepeter, E. **Gibbs, K. D.**, Choate, J., Nelson Hall, T. (May 11-14, 2022). Family Perspectives on Behavioral Health Hospitalizations for Children with Autism Spectrum Disorder (poster). International Meeting for Autism Research; Austin, TX.

PRESENTATIONS CONTINUED

National

Gibbs, K. D. (June 9-11, 2011). The Creation of a Continuing Education Program for Nurses in Uganda (poster). Association of Community Health Nurse Educators, Chicago, IL.

Gibbs, K.D., Crews, N., Hensch, L. (October 19-22, 2019). Guiding Safe Blood Transfusion Practices with Evidence (poster). AABB Annual Meeting, San Antonio, TX.

Gibbs, K. D., Jones, J., LaMark, W., Abdul-Mooti, S., Bretz, L., Santa Maria, D. (February 2, 2021). The impact of COVID-19 on substance use and mental health among youth experiencing homelessness (poster). International AIDS Society COVID—19 Conference: Prevention.

Nguyen, L., Freeman, A., Kobina, A., Keough, C., Asaithambi, R., Hadvani, T., Parikh, V. **Gibbs, K.**, Wallace, S. A. (April 30-May 4, 2021) Needs Assessment of Evidence-Based Practice Skills for Pediatric Hospitalists and Nurses in Community Hospital Settings. Pediatric Academic Societies. Electronic poster presentation.

Gibbs, K. D., Wilson, D., Corso, N., McMonigle, S. (April 27-30, 2022). Stronger Belief in EBP is Associated with More Implementation and Higher Perceived Competencies among Pediatric and Obstetric Nurses. Society for Pediatric Nurses Conference; Anaheim, CA.

Masciale, M., Lopez, M., Carretero Murillo, M., Fredricks, K., **Gibbs, K. D**., Asaithambi, R. Haq, H., Bocchini, C. E. (April 21-25, 2022). Hospitalized and hungry: a mixed methods study describing inpatient food insecurity among immigrant caregivers of hospitalized children. Pediatric Academic Societies 2022; Denver, CO.

Masciale, M., Haq, H., Carretero Murillo, M., **Gibbs, K. D**., Asaithambi, R. Fredricks, K., Espinoza-Candelaria, G., Lopez, M., Dominguez, J., Jaramillo, M. A., Bocchini, C. E. (April 21-25, 2022). "Even Though the Cage is Made of Gold, It's Still a Prison": A Qualitative Study of Immigrant Caregiver Barriers in Access to Care and Public Benefit Support in the United States. Pediatric Academic Societies 2022; Denver, CO.

Crane, S., Pieper, S., **Gibbs, K. D.** (September 15-17, 2022). "Approaches to Facilitate Patient-Reported Outcome Symptom Assessments in Children and Adolescents with Cancer." Association of Pediatric Hematology/Oncology Nurses 46th Annual Convention; West Palm Beach, FL.

PRESENTATIONS CONTINUED

Local

Gibbs, K. D. (July 29, 2015). The Key to Unlocking the Evidence: How to Use Available Literature to Answer Clinical Questions. Texas Children's Hospital Nursing Professional Day; Houston, TX.

Gibbs, K. D., Loveless, J., Jackson, A., Gordon, M., Graves, K. (July 14, 2016). PICO: Asking the Well-Built Clinical Question. Texas Children's Hospital Nursing Professional Day, Houston, TX.

Gibbs, K. D., Porter, S., Loveless, J., Procido, C., Jackson, A. (September 13, 2016). Evidence-Based Nursing Practice at the Bedside. Texas Children's Hospital Nursing Professional Day, Houston, TX.

Abela, K., Acorda, D., Cain, C., **Gibbs, K.** (June 9, 2017) Relationship of Food Insecurity to Sociodemographic and Hospitalization Characteristics in Hospitalized Children in Texas. (poster) University of Texas Health Science Center at Houston School of Nursing Research Day, Houston, TX.

Gibbs, K. D., Hensch, L. (August 8, 2018). Pediatric Blood Transfusion Thresholds: Evidence for Lower Hemoglobin Triggers. Texas Children's Hospital Professional Day, Houston, TX.

Abela, K., Acorda, D., Cain, C., **Gibbs, K. D.** (August 8, 2018). Relationship of Food Insecurity to Sociodemographic and Hospitalization Characteristics in Hospitalized Children in Texas. Texas Children's Hospital Professional Day, Houston, TX.

Gibbs, K. D., Cain, C., Peters, L., Watson, E. (September 19, 2019). So You Want to Get Your Master's Degree, but You Don't Want to be a Nurse Practitioner – A Panel Discussion. Texas Children's Hospital Professional Day, Houston, TX.

Loveless, J., **Gibbs, K. D.** (September 19, 2019). Improving Care via Evidence-Based Clinical Standards. Texas Children's Hospital Professional Day, Houston, TX.

Gibbs, K. D. (January 28, 2021). A Practical Guide to Systematic Review. University of Texas Health Science Center at Houston Cizik School of Nursing Center for Nursing Research Seminar Series, Houston, TX (invited).

Murillo, M. C., Lopez, M., **Gibbs, K. D.**, Asaithambi, R., Fredricks, K., Haq, H., Espinoza-Candelaria, G., Dominguez, J., Jaramillo, M., Bocchini, C., Masciale, M. (May 20, 2021) "Even Though the Cage is Made of Gold, It's Still a Prison": A Qualitative Study of Immigrant Caregiver Barriers in Access to Care and Public Benefit Support in the United States. Center of Excellence in Health Equity, Training and Research Summer Research Summit; Houston, TX. *Award for Best Faculty/Staff-Led Project.*

PRESENTATIONS CONTINUED

Local

McMonigle, S., & **Gibbs, K. D.** (January 27, 2022). Stronger Belief in EBP is Associated with More Implementation and Higher Perceived Competencies among Pediatric and Obstetric Nurses. Texas Children's Hospital Inaugural Student Nurse Grand Rounds, Houston, TX (invited).

Acorda, D., **Gibbs, K. D.** (April 2, 2022). *The pediatric nurse practitioners guide to find evidence about clinical questions in an efficient way.* Houston Chapter for the NAPNAP Potpourri Conference; Houston, TX.

PROFESSIONAL MEMBERSHIPS

Organization	Role	Inclusive Dates
Sigma Theta Tau International	Member	2010-Present
Society for Pediatric Nurses	Member	2012-Present
American Nurses Association	Member	2015-2021, 2022-Present
Texas Nurses Association	Member	2015-2021, 2022-Present
GRADE Working Group	Member	2015-Present
Pediatric Trauma Society	Member	2017-Present
American Public Health Association	Member	2009-2012, 2016-2018

PROFESSIONAL SERVICE

Editorial positions, boards, and peer review services

Associate Editor, Wong's Nursing Care of Infants and Children, 12th edition (Planned Publication Date: 2023)

Committee, educational, and volunteer service.

Co-chair, Texas Children's Hospital Evidence-Based Practice and Research Nursing Shared Governance Council, October 2021-September 2022

TEACHING

Course	Institution	Role	Dates
Evidence-Based Practice Course	Texas Children's Hospital	Co-instructor	2016, 2017, 2018
Evidence-Based Nursing Practice Course	Texas Children's Hospital	Co-instructor	2016
Essentials of Evidence-Based Nursing Practice	Texas Children's Global HOPE Nursing Leadership Program	Co-instructor	2020-2021

VOLUNTEERING

Nurse Volunteer, International Medical Corps, Haiti, March 2010

Public Health Nursing Volunteer, USS Iwo Jima Continuing Promise, Guyana; October 2010

Nurse Volunteer, Samaritan's Purse; Titayen, Haiti; July 2011