Title:
Intelligent Clinical Decision Support for Preoperative Blood Management

Short Title:
SPATH-trial

Registration: NCT07223853

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Funding:
K23HL166880 (National Heart Lung and Blood Institute)

Revision	Version Date	Summary of Changes	Consent Change?
1	2025.06.14	Initial Draft	
2	2025.09.16	Updates to statistical analysis plan and clarifications re outcome definitions	N
3	2025.10.15	Clarifications on study design and audio recordings for participants who agree to exit interviews	Y
4	2025.10.30	Add ClinicalTrials.gov registration	N

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Non-Technical Summary

20 million patients have surgery in the United States every year, with approximately 1 million of those patients requiring blood transfusion. Safe and timely transfusion during surgery can be life-saving. However, the process of preparing blood for surgical transfusion requires a laboratory test known as a “type and screen”, a blood test that measures the patient’s blood type and whether they have any red blood cell antibodies, and “crossmatching”, a process where blood is screened to ensure its compatibility with the patient. These laboratory tests take at least an hour to complete. Therefore, for patients with at least moderate risk of needing blood during surgery, we typically run some or all of these tests in the preoperative period so blood is readily available when needed during surgery.

We are currently too cautious in how often we are completing these tests for surgical patients, largely because we only use information about the planned surgery, and not any information about the patient, when we decide which patients need these blood tests. At Barnes Jewish Hospital, over 60% of surgical patients have preoperative blood testing done, even though less than 7% actually need blood during surgery. To some degree, this is appropriate, because we want to be safe. But excessive preparation does come with a cost for the US healthcare system, estimated to be on the order of $1 billion dollars a year, and also contributes to blood waste, which is a big problem given ongoing blood shortages.

The goal of this study is to evaluate an artificial intelligence system that provides customized information on a patient’s risk of needing blood during surgery – using information about both the patient and the surgery they are having – to help doctors better prepare blood for patients who are likely to need it, while avoiding too much preparation for patients who don’t. This artificial intelligence system, called S-PATH, was developed using a large database of over 3 million surgical patients at over 700 hospitals around the US. It has now been built into the electronic health record so that doctors and nurses can see these personalized risk estimates as part of their normal workflow. We think that having access to S-PATH’s personalized estimates of surgical transfusion risk will help doctors make better decisions about which patients need preoperative blood testing before surgery, and we hope that use of this tool will improve patient safety and help save money.

This study is a cluster-randomized controlled trial comparing having access to the S-PATH tool versus usual care processes. Currently, patients come to our preoperative assessment clinic before surgery, and the nurse practitioners who work there decide whether the patient needs preoperative blood testing using a chart, called an MSBOS, that lists recommended orders for different surgeries. We plan to enroll these nurse practitioners into the study and randomize them to either have access to the S-PATH tool in addition to the MSBOS chart versus continuing to only use the MSBOS chart. Patients will also be randomized based on the nurse practitioner they are assigned to when they come to clinic.

The primary outcome will be the number of type and screen blood testing orders placed before surgery. The safety outcome will be use of emergency release blood, which might otherwise be given when blood is needed but blood testing is not yet complete. A data safety monitoring board will also monitor adverse outcomes related to transfusion such as hemolytic transfusion reactions. Secondary outcomes will include the frequency of transfusion during surgery, and measures of how frequently the nurse practitioners viewed the S-PATH tool and followed its recommendations.

We plan to consent and train individual nurse practitioners in the appropriate use of the S-PATH tool. We are requesting a waiver of informed patient consent because the S-PATH tool is minimal risk. Specifically, it provides information on transfusion risk and suggestions on orders but the nurse practitioners will be free to decide what they think is most appropriate. In addition, the decision for whether the place blood orders will be reviewed again by the surgery and anesthesiology teams on the day of surgery. For both control and intervention arms, there is the possibility that patients who do not have presurgical blood orders will require transfusion during surgery. Emergency release blood is safe and readily available to be used in this situation. For both control and intervention arms, there is also the possibility of harm from receiving blood transfusion.

1 Background and Rationale

Preoperative preparation for blood transfusion can be life-saving during surgery.

Surgery is an indispensable part of health care; it provides treatment across a diverse spectrum of diseases, including cardiovascular disease, trauma, cancer, and maternal and child health, and helps to save lives, reduce disability, and improve quality of life[1]. However, surgery also entails risk, including the life-threatening risk for major bleeding.[2] Timely red blood cell administration during surgery can be critical to maintain oxygen delivery to vital organs, thus preventing bleeding-associated morbidity and mortality. It is estimated that 20% of the red cells transfused in the United States are administered in the surgical setting.[3]

Safe red blood cell administration requires several steps in order to ensure appropriate matching of the red cell unit to the patient, each of which requires time and labor.[4] First, the patient's blood must be drawn to determine their blood type, and to screen for the presence of alloantibodies; this is a laboratory test typically referred to as a "type and screen" (T/S), and it takes approximately one hour. Next, a donor red cell unit that is compatible with the patient's plasma is identified, tagged as such, and set aside; this step is referred to as a "crossmatch". This step can take minutes to days if the patient has red cell alloantibodies.[5] Failure to ensure donor unit compatibility with the recipient's antibodies results in a hemolytic transfusion reaction, which can be life-threatening.

Given the time required to prepare a compatible red cell unit for transfusion, guidelines recommend that patients at risk for intraoperative transfusion undergo some portion of the pretransfusion testing process in the preoperative period,[6,7] so that blood can be available in a timely manner when it is needed during surgery.[8] With adequate preparation, intraoperative transfusion can be safe and effective in reducing complications associated with surgical bleeding.

Excessive preoperative blood preparation can be harmful.

At the same time, excessive preoperative testing and blood preparation can have substantial public health consequences. As advocated by the Choosing Wisely campaign,[9] presurgical blood orders for patients who do not ultimately require transfusion is wasteful and places an unnecessary cost and labor burden on the healthcare system. It is estimated that over 20 million surgical procedures are performed in the United States every year.[10] Over 50% of these patients have presurgical blood orders,[8,11] despite intraoperative transfusion occurring in less than 10% of surgeries.[11,12] Given an estimated cost of $20-100 per patient[11,13–15] for presurgical blood orders, the US healthcare system likely spends on the order of $1 billion dollars a year on blood preparation associated with surgery. Even a 10% reduction in the number of patients with presurgical blood orders would achieve meaningful savings.

Excessive orders can also have negative consequences for red cell waste. When crossmatch orders are placed, red cell units are set aside where they are unavailable to other patients. This forces the blood bank to carry more inventory, which has been associated with an increased rate of red cell waste due to expiration.[5] Responsible conservation of blood products is critical to maintaining the adequacy of the nation's blood supply, especially given the trend in declining blood donations,[16] which has only accelerated during the COVID-19 pandemic.[17] Concerns about the sustainability of the US blood system have been highlighted by two recent reports commissioned by the Department of Health and Human Services.[18,19] Therefore, avoiding presurgical blood orders for patients at low risk of transfusion has significant public health implications.

Preoperative blood orders are currently determined by the surgical procedure alone, despite patient factors playing a substantial role in transfusion risk.

Given the considerations presented above, it is important to accurately estimate a patient's risk of transfusion so that presurgical blood preparation can be performed for patients who need it, while avoiding wasteful preparation for patients who do not. The current standard of care is to estimate transfusion risk and determine preoperative blood orders based on the planned procedure alone, via the creation of a maximum surgical blood ordering schedule (MSBOS).[20–23] For example, guidelines recommend omitting a T/S from patients undergoing procedures with a historical procedure-specific transfusion rate less than 5%.[21,22] Determination of crossmatch orders is less standardized; information on the procedure-specific transfusion rate, mean units transfused (transfusion index), and 90th percentile utilization have all been used.[20,22,24] A typical MSBOS is a table containing a list of procedures with their associated blood order recommendations (Table 1).

Regardless of approach, all prior methods for creating an MSBOS have exclusively used procedure characteristics alone to determine presurgical blood orders. However, patient characteristics also impact transfusion risk considerably. For example, preoperative anemia, renal dysfunction, patient age, gender, and weight have all been associated with an increased risk for surgical transfusion.[25–29] The central hypothesis motivating this study is that implementation of a personalized machine learning (ML) model – incorporating both patient- and procedure-specific characteristics – as a clinical decision support (CDS) system to guide presurgical blood orders would result in increased ordering precision, i.e., fewer excess orders (decreased costs, less waste) and fewer missed orders, i.e., patients requiring transfusion during surgery without adequate preparation (increased patient safety).

Procedure	Routine presurgical blood order
Open heart surgery	T/S, crossmatch 4 units
Hysterectomy	T/S only
Appendectomy	None

Table 1 – Example MSBOS showing typical pre-surgical blood order recommendations.

Preliminary Data

Model development. We developed and validated several ML classifiers to predict the probability of intraoperative red cell transfusion using procedure- and patient-specific variables commonly available in the preoperative setting. Models were trained using the American College of Surgeons (ACS) National Quality Improvement Program (NSQIP) database[30] of 3 million surgical cases across 722 hospitals from the years 2016-2018, and tuned for the specific task of guiding presurgical blood orders. Input variables included the procedure, its associated procedure-specific transfusion rate, and patient-specific variables including patient demographics, comorbidities, and preoperative laboratory values (Figure 2). A complete model

pipeline was created to enable reproducible model implementation and prediction for new patients, including missing value imputation and data normalization.

Figure 2 – Model specification

Data sources:
- **Training:** NSQIP, 2016-2018 (n=3,049,617)
- **Internal validation:** NSQIP 2019 (n=1,076,441)
- **External validation:** BJH 2020 (n=16,053); 47 MPOG medical centers, 2020-2021 (n=3,455,295)

Input Variables
- **Patient demographics** age, weight, height, sex
- **Patient comorbidities** hypertension, heart failure, COPD, diabetes, dialysis, smoking
- **Preoperative laboratory values** hematocrit, platelet count, INR, PTT, creatinine, sodium, albumin, bilirubin
- **Procedure-specific transfusion rate**

Model outputs
- Predicted risk of red cell transfusion
- Recommendation for presurgical blood orders

Model performance was measured in comparison to a baseline model with only the procedure-specific transfusion rate, as is commonly used to create a conventional MSBOS[22], the current standard of care. The best-performing personalized ML model was the gradient boosting machine, referred to as the S-PATH model.

Retrospective and multi-center validation. S-PATH was then internally validated across 1,076,441 surgical cases captured by NSQIP in 2019. S-PATH generalizability was demonstrated by external validation across a cohort of 16,053 surgical cases at the host institution (BJH), in 2020, and across a cohort of 3,455,295 surgical cases performed at 47 medical centers participating in the Multi-center Perioperative Outcomes Group (MPOG) consortium[31] from 2020-2021[32]); these medical centers represent diverse academic and community practice settings in 27 US states.

Using a novel transfer learning technique based on the procedure-specific transfusion rate,[33] S-PATH demonstrated improved discrimination (i.e., ability to rank-order patients in transfusion risk) compared to the baseline MSBOS approach, a finding which generalized across internal and external validation. For example, area under the receiver operating characteristic (AUROC) curve was 0.924 for S-PATH versus 0.888 for the baseline MSBOS model in internal validation, and 0.939 for S-PATH versus 0.908 for the baseline MSBOS model in external validation at Washington University; median S-PATH AUROC was 0.926 (IQR 0.908-0.955) compared with a median MSBOS AUROC of 0.854 (IQR 0.816-0.881) in 47 MPOG hospitals.

To determine when to place presurgical T/S orders, guidelines recommend a 5% transfusion risk threshold.[21,22] Such a threshold would only achieve 83.7% sensitivity for detecting transfusion for the baseline MSBOS approach in internal validation, and 91.1% sensitivity in external validation at the host institution; in other words, 9-16% of patients requiring transfusion would not have had a presurgical T/S (i.e., missed orders) under current MSBOS guidelines, which would negatively impact patient safety. The S-PATH model was tuned to achieve 96% sensitivity, and consistently required approximately one-third fewer T/S orders to achieve 96% sensitivity compared to the baseline MSBOS approach for most hospitals, highlighting the generalizability of S-PATH performance and its potential to improve resource utilization while improving patient safety. Based on these results, S-PATH is one of the most broadly validated machine learning models in healthcare.

Prospective Validation. S-PATH has been integrated within the electronic health record (EHR) at Washington University and has been silently generating predictions since November 2024 for patients presenting to our preoperative assessment clinic, which is the intended patient population for the proposed cluster-randomized clinical trial. We have found that our current care processes for placing preoperative type and screen orders for surgical patients is imperfect, as 18% of patients who required transfusion during surgery did not have an active type and screen by the start of the procedure; all of these patients were correctly identified as in

need of a type and screen by S-PATH. In 4 months of prospective validation, S-PATH demonstrated 95% sensitivity for identifying patients at risk for surgical transfusion, consistent with our original design intention. These results demonstrate the continuing safety and consistency of S-PATH predictions when integrated within the EHR in the same manner as it would be used in the proposed trial.

Human-centered CDS design. We designed and refined the user interface of the S-PATH CDS tool through an iterative human-centered design process.[34–36] Specifically, we recruited 29 stakeholders (i.e., anesthesiologists, nurse anesthetists, preoperative clinic nurse practitioners, surgeons, and blood bank physicians) to participate in semi-structured interviews discussing design requirements for a CDS tool for presurgical blood ordering and scenario-based walkthroughs with a prototype S-PATH CDS design. Usability and workflow issues were identified and addressed with revisions to the prototype design.[37]

After 3 rounds of iterative refinement, we created an S-PATH CDS interface that is easy to use and aligned with clinician workflow at the point-of-care within the Epic EHR (Figure 3). Model predicted risk is presented along with a recommendation for presurgical blood orders and an explanation for the model's reasoning.[38] Resources are provided to facilitate appropriate interpretation of the tool's results. This design is compliant with the US Food and Drug Administration (FDA) draft guidance for machine learning tools in healthcare.[39]

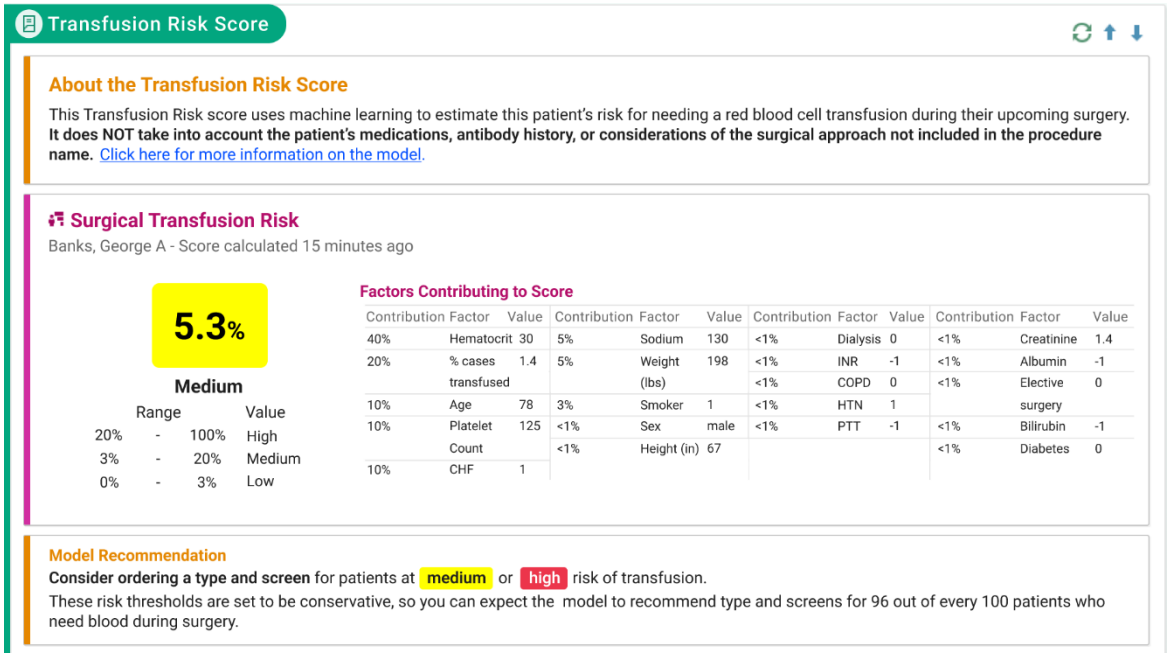


Figure 3 – S-PATH CDS interface. Model predictions are generated from live patient data within the EHR without requiring clinicians to manually input data. A human-centered design process was used to refine this design with input from stakeholders.

Summary. A personalized ML model (S-PATH) to predict risk for intraoperative transfusion was developed, validated across local and national settings,[12,32,33] and shown to have better performance for recommending presurgical blood orders (fewer missed orders, fewer excess orders) than the standard of care MSBOS approach. S-PATH was then incorporated within the EHR as a CDS tool and made available at the point-of-care with a user interface that is aligned with clinician needs and current workflow. The purpose of this study is to evaluate the real-world feasibility, acceptability, and preliminary effect of the S-PATH CDS tool in a cluster-randomized clinical trial.

2 Objectives

The objective of S-PATH cluster-randomized clinical trial are to evaluate the effect of having access to ML-based surgical transfusion risk predictions for clinicians working in our preoperative assessment clinic.

2.1 Primary Objective

The primary objective will be to measure the effect of having access to S-PATH predictions on the frequency of preoperative type and screens ordered by clinicians working in the preoperative assessment clinic.

2.2 Secondary Objectives

2.2.1 Key Secondary Objectives

Secondary outcomes will include (1) the frequency of patients having an active type and screen at the start of surgery (within the first hour), (2) the frequency of red cell transfusion during surgery, (3) the frequency of emergency release blood use, (4) the frequency of transfusion reaction

2.2.2 Other Secondary Objectives

Implementation outcomes will be measured to assess uptake and use of the S-PATH tool by participating clinicians. These outcomes will be measured at the clinician level and will include (1) frequency of viewing S-PATH predictions, (2) frequency of the clinician's preoperative type and screen order matching S-PATH's recommendation. These will be assessed monthly throughout the study.

Participants will also be asked to complete a survey regarding their perception on the usability of the S-PATH tool, understanding of tool predictions, and trust in the tool prior to the start of the study, and again at the end of the study.

3 Trial Design

This study will be a prospective open-label cluster-randomized clinical trial, with clusters at the level of the clinician working in the preoperative assessment clinic. The study will be conducted in three phases resembling a stepped-wedge trial design with two steps (Figure 4).

In Phase I, all participants will not have access to the tool and will continue routine clinical care using the Maximum Surgical Blood Ordering Schedule (MSBOS) to guide type and screen ordering decisions.

In Phase II, half of the nurse practitioner participants will be randomly selected (stratified by clinical experience, full-time equivalent work level, and work location) to start having access to the S-PATH tool. There will be a wash-in period where participants in the intervention arm will view the tool predictions without using them for clinical decision-making. This period is designed as a pilot period to allow clinicians to become accustomed to the tool, to allow for the resolution of any usability or workflow concerns, and to provide further targeted training in tool use as necessary. During Phase II, recruitment for intern physicians will begin, and they will be randomized 1:1 to either intervention or control for the duration of their 1-month rotation.

In Phase III, all nurse practitioner participants will have access to the S-PATH tool, including those that were randomized to the control arm in Phase II. Just as in Phase II, there will be a wash-in period to allow participants who did not previously have access to the tool to become accustomed to the tool prior to using it for clinical care. Intern physicians will continue to be randomized 1:1 to intervention and control during Phase III each 1 month rotation.

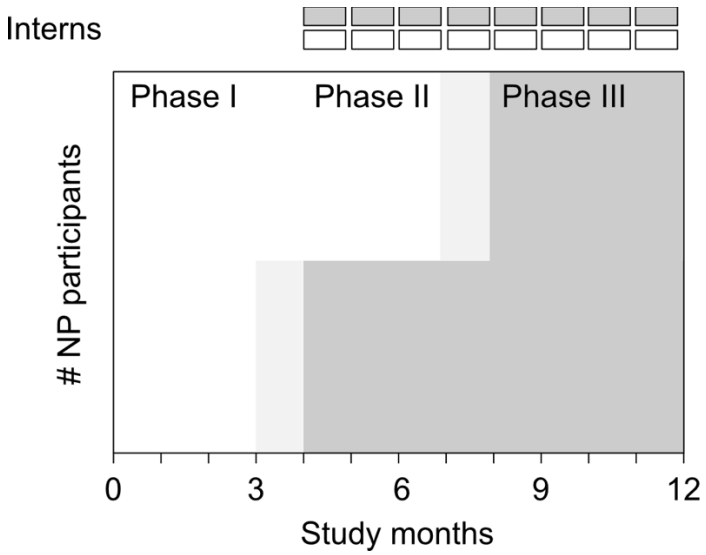


Figure 4 – S-PATH trial design. In Phase I, all participants will use the MSBOS per usual care (control). In Phase II, half of the nurse practitioner (NP) participants will be randomized to have access to the S-PATH tool (intervention). In addition, half of the intern physicians each month will be randomized to the intervention group. In Phase III, all NP participants will have access to the tool, and intern physicians will continue to be randomized 1:1. Between each phase, there will be a wash-in period to allow participants who will use the tool in the next phase to become accustomed to how the tool works.

4 Participants, Interventions, Outcomes

4.1 Study Setting

This will be an open-label, single center, cluster-randomized controlled trial at Barnes Jewish Hospital in St. Louis, MO, a large tertiary care academic medical center affiliated with Washington University School of Medicine (WashU) in St Louis. This study will be conducted within the Center for Preoperative Assessment and Planning (CPAP), an outpatient clinical service that evaluates approximately 90% of all elective surgical patients having surgery at Barnes Jewish Hospital. This clinic is staffed primarily by nurse practitioners (NP), who practice independently with oversight by an attending anesthesiologist. There are also two intern physicians who rotate in the clinic each month. The majority of preoperative blood orders at BJH are placed during the CPAP clinic visit. Each NP typically evaluates 30 patients per month in-person. Each intern physician typically evaluates 120 patients in person during their month-long rotation. Current clinic workflow is to assign patients to CPAP clinicians based on availability; clinicians do not specialize in specific surgical areas.

4.2 Participants and Eligibility

4.2.1 Clinician participants. Clinician participants for this study will be recruited from clinicians working in the preoperative assessment clinic, including nurse practitioners and intern physicians. Clinician subjects will provide informed consent for their participation in this study. We estimate there will be 46 NPs and 16 intern physicians eligible for recruitment throughout the duration of this study. NP participants will be randomized to either have early (i.e, Phase II) or late (i.e., Phase III) access to the S-PATH tool as shown in Figure 4. Intern participants will be randomized to either have access to the S-PATH tool or to control, i.e., with use of the existing Maximum Blood Ordering Schedule; early and late availability of the tool is not feasible for this population as they only spend 1 month on the CPAP clinical rotation.

4.2.2. Patient participants. Patients who are evaluated by enrolled clinicians in-person at the preoperative assessment clinic will also be included in the study, with their randomization group determined by the clinician assigned to evaluate them.

We are requesting a waiver of informed patient consent as the S-PATH clinical decision support tool is minimal risk as described in 7.3 Consent below. Based on our preliminary data, we estimate that approximately 1,100 patients per month meeting the below inclusion and exclusion

criteria will be evaluated in person at CPAP clinic, for an estimated total of 13,200 patients throughout the duration of this 12 month study.

4.2.3. Patient inclusion criteria. Patients will be included in the study if they are evaluated in-person at CPAP clinic and have an S-PATH model prediction. We expect approximately 70% of patients being seen in-person at CPAP clinic to have model predictions. Reasons for not having a prediction include unscheduled walk-in appointments and patients having rare procedures for which no reliable historical transfusion information is available to make a prediction.

4.2.4. Patient exclusion criteria. Patients will be excluded if they have a history of red cell alloantibodies or if they are not scheduled to have their surgery in one of the main operating rooms at Barnes Jewish Hospital (e.g., scheduled for surgery at one of the other BJC hospitals or in a remote procedural area like gastroenterology or interventional radiology).

4.3 Interventions

4.3.1 Usual care. In the control periods, participants will make usual care decisions on whether patients should have preoperative type and screen orders, guided by the existing Maximum Surgical Blood Ordering Schedule (MSBOS), which is currently in common use in CPAP clinic.

4.3.2 S-PATH intervention. In the intervention periods, participants will have access to the S-PATH clinical decision support tool in addition to the MSBOS. The S-PATH tool will be integrated within the electronic health record (EHR), such that it will show the patient's predicted transfusion risk, an explanation for how it arrived at that risk estimate, and a suggestion for whether to order a preoperative type and screen (Figure 5). Patients with >3% risk of surgical transfusion are recommended to have a preoperative type and screen. The interface also links out to a quick-start guide, which provides additional information on how the model was trained, how to appropriately interpret its predictions and explanations, important limitations in its use, and measures of model performance (Figure 6, also available at https://sites.wustl.edu/spath-tool/).

The S-PATH interface was designed following a human-centered design process, with input from 29 stakeholders representing surgery, anesthesiology, preoperative assessment clinic, and transfusion medicine (see Preliminary Studies for more information). This design is compliant with the US Food and Drug Administration draft guidance for machine learning tools in healthcare.[39]

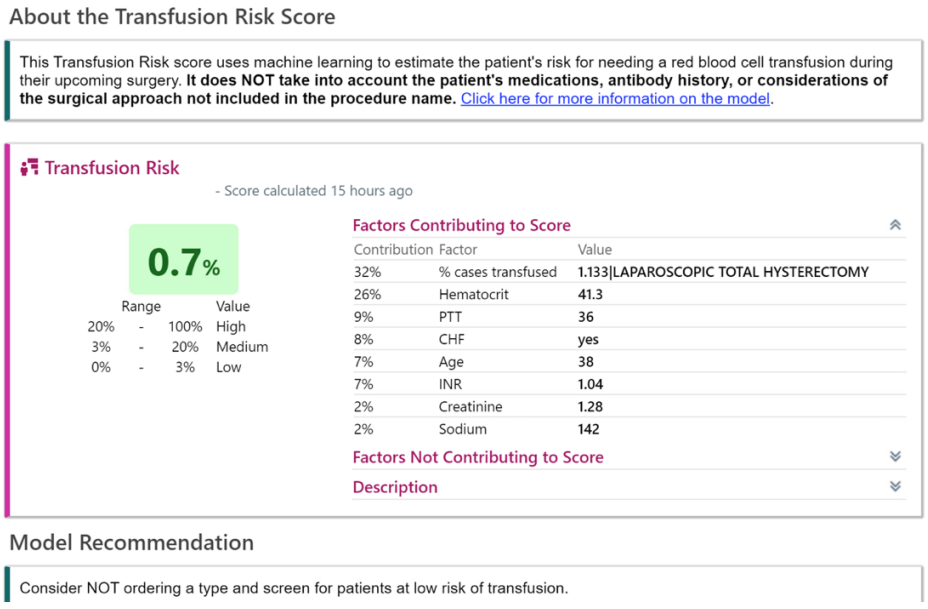
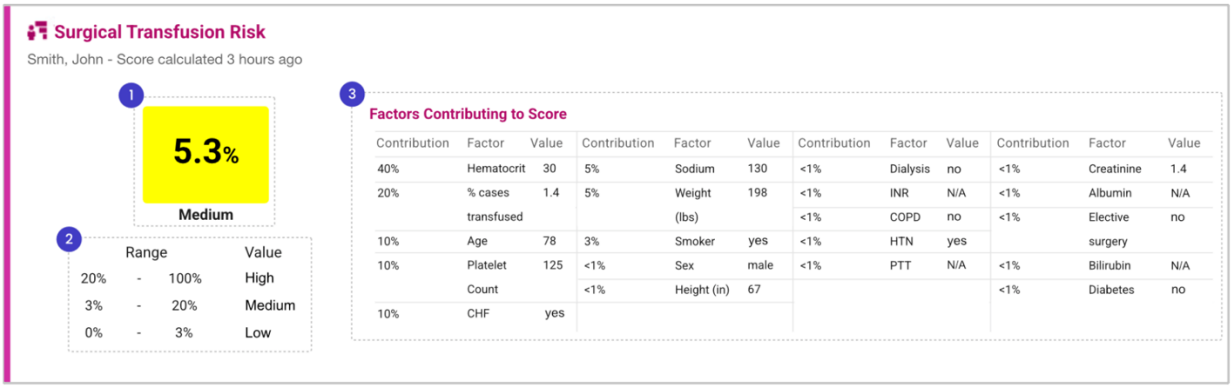


Figure 5 – Example S-PATH interface integrated within existing EHR navigator pages that clinicians working in the preoperative assessment clinic routinely visit.

Figure 6 – Snippet of model information website, available at https://sites.wustl.edu/spath-tool/ . This website also provides information on the demographics of the cohort the model was trained on, and model performance.

Guide to Interpreting the S-PATH Tool



1

Risk Score

Predicted probability that this patient will need a red cell transfusion during surgery

2

Risk Range

To be conservative (i.e., sensitivity 96%), the model recommends type and screens for patients with >3% risk. This is why the risk ranges are labelled with the medium risk band starting at 3%.

RISK RANGE LEGEND

LOW MEDIUM HIGH

3

Factors Contributing to Score

This box shows what the model knows about this patient and explains how it arrived at its risk score prediction for this patient. A value of N/A means it's missing (the model assumes it is normal).

- **Factor** : variable the model considered
- **Contribution** : the extent to which the variable contributed to the score
- **Value** : the value of the variable used in the model's calculation

Contribution	Factor	Value
40%	Hematocrit	30
20%	% cases transfused	1.4

EXAMPLE 1: This patient has a hematocrit of 30%, and that value is 40% of the reason why the model predicted a 5.3% risk. 1.4% of patients having the same procedure have historically needed blood, and that is 20% of the reason why the model predicted 5.3% risk.

Contribution	Factor	Value
<1%	Dialysis	no
<1%	INR	N/A

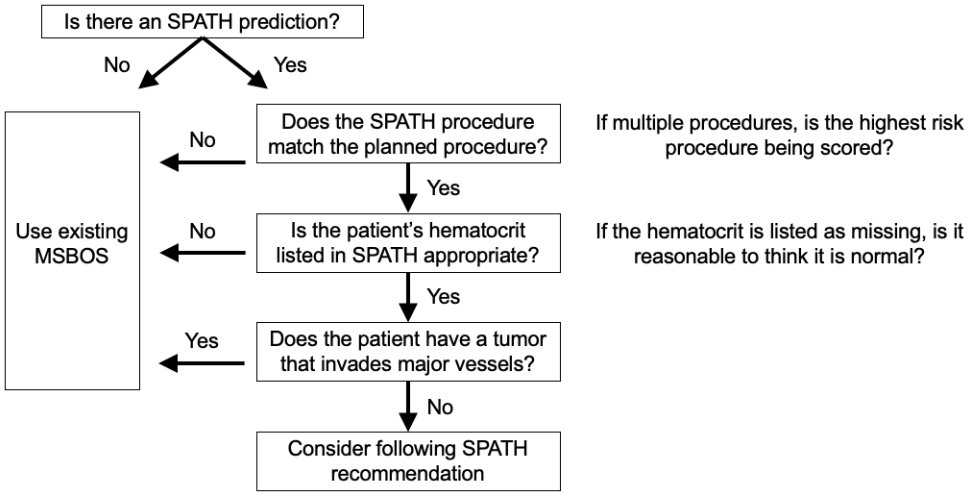
EXAMPLE 2: This patient is not on dialysis, and the INR value is missing, assumed normal. These two variables contribute minimally to the prediction.

Known Limitations

- The model does not take into account the patient's preoperative medications, red cell alloantibody history, or considerations of the surgical approach not included in the procedure name (for example, anatomic proximity to major blood vessels).
- Due to EHR limitations, the model may be misinformed about certain risk factors. For example, patient hematocrit values in CareEverywhere are not taken into account. If the primary procedure name is not an accurate representation of the planned surgery, the tool's risk estimate may be inaccurate as well.
- The model only makes predictions on the potential need for red blood cell transfusion. It does not advise on the potential need for platelets or other clotting factors.
- If the patient is undergoing a rare procedure, the model may not know the historical procedure-specific transfusion rate, and therefore the model will not attempt to make a risk prediction.
- The model does not update based on intraoperative information. It is intended to be used only in the preoperative period.

Prior to use of the tool in clinical care, participants will be trained in appropriate tool use, including discussion of the method by which it was trained, expected performance and ways in which it was validated, and key limitations to its use. The training will also emphasize that clinicians are to continue to use their clinical judgement when deciding whether to place a preoperative type and screen order, and that they are free to disregard the model prediction and recommendation for any reason. A sample reference card to help clinicians appropriately interpret S-PATH results is shown in Figure 7. This reference card and the quick start guide website shown in Figure 6 may be modified based on participant feedback. A link to a feedback form will be available within the S-PATH interface to allow clinicians to report problems, concerns, or near-miss events concerning the S-PATH tool to the study team.

Figure 7 – Decision guide to help clinicians appropriately interpret S-PATH predictions.



4.3.1. Case screening. Patients will be excluded from the study if they have a history of red cell alloantibodies, or if their surgery is not scheduled in one of the main operating rooms at Barnes Jewish Hospital (e.g., scheduled for surgery at one of the other BJC hospitals or in a remote procedural area like gastroenterology or interventional radiology). These exclusion criteria will be electronically applied. The location of the surgery and the patient's potential history of red cell alloantibodies will be automatically retrieved from the EHR the first time that patient's chart is opened using the preoperative assessment clinic context. If the patient meets any of the exclusion criteria, model predictions will not be shown; instead, a message will print explaining the reason for the patient's exclusion from the study.

4.3.2. Follow up for patients with new results from laboratory tests drawn during their CPAP visit. Patients frequently have laboratory tests drawn at their preoperative assessment clinic visit. The results of some of these tests may result in the model recommendation changing from "Consider NOT ordering a preoperative type and screen for patients at low risk of transfusion" to "Consider ordering a preoperative type and screen for patients at medium to high risk of transfusion". To detect these patients, model predictions will be generated the day after the CPAP visit for patients in the intervention arm, and a report will identify patients with predictions greater than the 3% risk threshold the day after their CPAP visit and who did not receive a type and screen test during their CPAP visit. CPAP currently dedicates one NP to following up on the previous day's laboratory results. This NP will be assigned to review this report and order a type and screen as necessary to be drawn on the day of surgery.

4.3.3. Modifications to the S-PATH model. We do not plan to modify the S-PATH model after the study starts. However, we may modify the model pipeline and display code if there changes

in the EHR that prevent the model from displaying correctly, retrieving appropriate data, or producing appropriate predictions.

4.3.4. Adherence. Clinicians will not be required to adhere to model recommendations. Rather, in both control and intervention groups, they will be encouraged to use their clinical judgement to determine appropriate preoperative blood orders, with the MSBOS (control) or MSBOS and S-PATH (intervention) for reference.

Because access to the S-PATH tool is controlled electronically, crossover between control and intervention groups will be minimized.

4.3.5. Concomitant Care. Clinicians involved in the patient's surgical care downstream of the preoperative assessment clinic visit will continue to provide care without any restrictions from the trial. These clinicians include the day-of-surgery anesthesia, surgical, and nursing teams, who will review the patient's case and are free to order additional type and screen tests based on their clinical judgement. These clinicians will not have access to S-PATH predictions. They will not be blinded to treatment allocation, as enrolled clinicians may write into their preoperative assessment notes that their decision was guided either by the MSBOS or the S-PATH tool.

4.4 Outcomes

All outcomes will be binary, assessed at the patient / surgical case level, and aggregated to provide overall frequencies.

4.4.1 Primary Outcome Measure

The primary outcome will be placement of a type and screen order during the preoperative clinic assessment visit, evaluated at the patient / surgical case level. This includes orders placed and collected during the preoperative clinic assessment visit, as well as orders signed during the preoperative clinic assessment visit or subsequent follow up care and held to be drawn on the day of surgery.

4.4.2 Secondary Outcome Measures

The following secondary outcomes will be measured at the patient / surgical case level:

- **Valid type and screen order at the start of surgery** (defined as resulted prior to 1h after anesthesia start). The 1 hour buffer is used to account for orders that were drawn prior to surgery but may not have resulted by the time the patient enters the operating room. This will include orders placed by the clinicians working in preoperative assessment clinic and any orders that may be placed by the day of surgery anesthesia or surgical teams. This will not include type and screen orders that have expired by the start of surgery. This is a *secondary efficacy outcome* that reflects type and screen ordering decisions by all members of the patient's care team.
- **Need for red cell transfusion during surgery**. Administration of allogeneic packed red blood cells during surgery will be retrieved from the electronic health record. Documentation of transfusion is mandatory and the electronic health record scan is used to confirm the correct patient. This is a *secondary efficacy outcome*, as lack of a type and screen may prevent discretionary intraoperative transfusion.
- **Emergency release blood use during surgery**. Administration of emergency release allogeneic packed red blood cells will be retrieved from the electronic health record. These are either documented as volumes under the MTP tab or individually scanned as uncrossmatched red cells. This is the *primary safety outcome* of the study as emergency release blood may be administered if red cell transfusion is urgently indicated but a type and screen is not available. The frequency of this outcome will be reported overall

across both groups, and stratified by whether the patient had an active type and screen at the start of surgery.

- **Red cell transfusion during surgery without an active type and screen at the start of surgery**. This is the *secondary safety outcome* intended to capture false negative results, i.e., patients who required transfusion during surgery but did not have a preoperative type and screen. This outcome will be collected electronically from the EHR and will capture patients for whom the type and screen was collected after the start of surgery so that crossmatched red cells could be issued.
- **Transfusion reaction**. Transfusion reactions are reported by clinical teams to the blood bank, and the transfusion medicine service investigates and classifies each transfusion reaction. These investigation reports will be transmitted to the study team for adverse event reporting and outcome collection. This is also a *secondary safety outcome* for the study. Transfusion reactions will be reported stratified by category, as hemolytic transfusion reactions are the most relevant to the trial.

Implementation outcomes will be measured at the clinician / participant-level monthly to assess uptake and use of the S-PATH tool.

- Frequency of viewing S-PATH predictions – retrieved from EHR audit log data, which shows the types of patient data that the clinician accesses.
- Frequency of the clinician accepting S-PATH's type and screen recommendation, i.e., frequency of the clinician's decision on whether to order a type and screen matching the order recommended by the model.

Clinician participants will also be asked to complete a survey regarding their perception on the usability of the S-PATH tool, understanding of tool predictions, and trust in the tool prior to the start of the study, and again at the end of the study.

4.5 Participant Timeline

Clinician participants will be recruited to participate. Following recruitment, nurse practitioner participants will be randomized to either early (i.e., month 4 of the study) or late (i.e., month 8 of the study) access to the S-PATH tool. Intern physician participants will be randomized to either have access to the S-PATH tool or to usual care; it is not practical to randomize intern physicians to early or late access to S-PATH as they will only work in the preoperative assessment clinic for 1 month.

Following randomization, clinicians in the intervention arm will receive 1:1 training on appropriate interpretation and use of the S-PATH tool, and questions will be addressed. Clinicians will be asked to complete a survey on S-PATH usability and trust in S-PATH predictions at the beginning and end of their time in the intervention group. Clinician participants will also be debriefed at the end of the study to collect their feedback and impressions on use of the S-PATH tool.

All scheduled patient encounters at the preoperative assessment clinic will be scored daily from the day prior to the encounter to four days following the encounter. Scores will only be shown to clinicians in the intervention arm. Scoring on the days following the encounter is intended to identify patients in the intervention arm whose predictions may have changed as the result of laboratory tests performed during the preoperative assessment clinic visit; this report will be reviewed daily and a type and screen will be ordered to be collected on the day of surgery as deemed appropriate.

4.6 Sample Size

We powered this study to ensure adequate sample size to evaluate whether the primary outcome (frequency of type and screen orders) differs between the control and intervention arms. Using preliminary data based on silent collection of S-PATH predictions from November 12, 2024 through March 31, 2025, we anticipate that each clinician will evaluate approximately 20 patients per month, and approximately 70% of patients will have S-PATH predictions; thus we estimate 14 patients per month per clinician will be eligible for inclusion in the study. Our preliminary data indicates that S-PATH may recommend type and screen orders for 46% of patients, while usual care may order type and screens for 71% of patients, an absolute difference of 25 percentage points.

There are 42 nurse practitioners (NPs) and 16 intern physicians eligible to be recruited for this study. For power analysis purposes, we make the conservative assumption that we will be able to recruit and retain 75% of eligible NPs (N = 32), who will each evaluate 14 patients eligible for S-PATH predictions per month over the course of the study. Using a stepped wedge cluster-randomized design with 2 steps (16 clusters switching at each step) and assuming an intra-class correlation coefficient of 0.1,[40–42] a two-sided α of 0.05, and 4032 patient encounters over the 32 NPs, we anticipate that we will have >99% power to detect a difference of 25% between arms for the primary outcome (46% in the intervention arm and 71% in the control arm). Even under more conservative assumptions (62% in intervention, 71% in control; ICC of 0.50) we anticipate > 84% power. Therefore, we anticipate that we will have ample power to detect the effect of interest in this study over a wide range of realistic scenarios.

4.7 Recruitment

Individual clinicians will be approached in-person to solicit consent for participation in this study. Informed consent will be solicited, including discussion of risks and benefits of participation in this study. Clinicians will be shown the consent document and key information form, either as a paper document or as a RedCap electronic version; either way, a member of the study team will be present in person to address any questions that arise. Clinicians will have as much time as they need to consider participating in the study. The study team member that performs these recruitment tasks will not be in the supervision hierarchy for any of the clinicians eligible for recruitment to minimize the possibility of coercion or undue influence in the consent process.

We are requesting a waiver of informed patient consent because the intervention is minimal risk as described in 7.3 Consent. Patient accrual will occur electronically based on the randomization group of the clinician to which they are assigned when they arrive at their preoperative assessment clinic visit.

4.8 Allocation

Nurse practitioner participants will be randomized 1:1 to either early (Phase II) access to S-PATH or late (Phase III) access to S-PATH. A computerized minimization method with random component will be used to provide randomized treatment assignments balanced by years of preoperative clinic experience and expected number of inpatient preoperative clinic encounters during the study.[43,44]

Intern physician participants will be randomized 1:1 to either access to S-PATH or to usual care at the beginning of their 1-month preoperative assessment clinic rotation.

4.9 Blinding

This is an open-label study. Clinician participants will be aware of their randomization group as clinicians in the intervention arm need to be trained in S-PATH use. Similarly, the study team will be aware of the clinician's randomization group to provide training and technical support.

Patients and other downstream clinicians (day of surgery anesthesia and surgical teams) will not be directly aware of the patient's randomization group. However, the preoperative assessment clinic note may disclose whether S-PATH was used in clinical decision-making, and both patients and other clinicians are able to read these notes.

5 Data Collection, Management, Analysis

All outcomes of the study will be electronically collected from the electronic health record (EHR) data warehouse, with the exception of suspected transfusion reactions, which will be transmitted by the Blood Bank to the study team as they occur. Data collected for this study will include patient demographic information and comorbidities as documented in the preoperative assessment clinic visit, preoperative laboratory test results, information on the date and time of the preoperative assessment clinic visit, the planned surgery, the surgery location, the clinician evaluating the patient in preoperative assessment clinic visits and their demographic characteristics, history of red cell alloantibodies, any type and screen orders placed prior to surgery and subsequent results, and transfusion of any blood products during surgery. To measure use of the S-PATH tool, electronic health record access logs for participating clinicians will also be retrieved.

Only the minimum necessary private patient information will be collected for the purposes of the study. Any protected health data will be kept in a secure digital environment that is digitally encrypted, password protected and limited to research team only. De-identified data may be kept and used in future studies not pre-specified in the above protocol. The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data collected. All data will be managed by Washington University IT Department and housed on secure password protected, encrypted servers.

In compliance with NIH guidelines, following completion of the study, all data will be deidentified prior to depositing the study data in the WashU Libraries Open Scholarship Digital Research Materials Repository. For deidentification purposes, clinician participants will be given a anonymized participant ID key and patient participants will be given an anonymized patient ID key distinct from their medical record number. Curation will be guided by the Data Curation Network (DCN) CURATED model, from which the dissemination information package (DIP) is created, given a registered DOI, retained in the repository and archived for a minimum of 10 years. The archival information package (AIP) will contain the original submission information package (SIP), the DIP, PREMIS compliant metadata, the readme file, and documentation of curation processes. Data may be used for future studies not mentioned in the protocol.

5.1 Statistical Methods

The primary statistical analysis will include both NPs and intern physicians in the same model, with the primary unit of analysis being the patient / surgical case level. Each patient / surgical case will have their randomization status determined by the randomization status of the clinician who evaluated the patient in the preoperative assessment clinic. NP participants will have been randomized either to the early (Phase II) or late (Phase III) access to S-PATH group, meaning that each NP will spend time in both the control and intervention groups depending on time point. Intern physicians will have been randomized 1:1 to either control or intervention for the duration of their 1-month rotation. A sensitivity analysis will be performed to analyze patients evaluated by NPs and intern physicians separately to ensure that biases were not introduced by including both groups in the same analysis, as they had different exposures to the intervention.

An intention-to-treat approach will be used; all patients and clinicians will be analyzed with the intervention group to which they were randomly assigned regardless of whether the clinician used the S-PATH tool or placed an order consistent with S-PATH's recommendation.

5.1.1. Descriptive statistics

Basic descriptive statistics will be computed overall and stratified by randomization group for all demographic characteristics of participating clinicians and patients. Imbalance between intervention groups will be assessed using univariable statistical tests, such as the Mann-Whitney U test for continuous variables and Chi-square test for categorical variables.

5.1.2 Analysis for the primary outcome

Placement of type and screen orders: The primary outcome for this cluster-randomized trial is the placement of type and screen orders by enrolled clinicians at the preoperative assessment clinic visit, assessed at the patient level as a binary outcome. The frequency with which these type and screen orders were placed will be calculated separately for patients / surgical cases in the intervention condition and control condition. To test the statistical null hypothesis that there is no difference in the proportion of patients with type and screen orders in the control vs the intervention arm, we will employ a generalized estimating equations (GEE) approach. The primary analysis will be a modified logistic regression[45] with robust standard errors clustered on provider to estimate relative risks and risk differences. We will model our data similarly to the Hussey and Hughes[46] approach for analyzing stepped wedge studies, which includes a fixed effect for the treatment group (SPATH vs MSBOS) to test for differences between groups, and a fixed temporal variable to adjust for variation over calendar time. We will also adjust for a set of baseline covariates at the patient-level (age, sex, weight, race, preoperative hematocrit, procedure-specific transfusion rate, preoperative INR, platelet count, and partial thromboplastin time) and clinician-level (experience) to enhance precision of the treatment-effect estimate and account for chance imbalances.[47] A significant difference between the treatment groups ($P < 0.05$), with higher proportions of type and screen orders in the control compared to the intervention group, will support the hypothesis that access to the S-PATH CDS system results in fewer type and screen orders.

5.1.3 Analyses for secondary outcomes

Emergency release blood utilization: The safety outcome is binary, assessed at the patient level, and will be analyzed using a noninferiority analysis. This noninferiority analysis will assess whether access to the S-PATH CDS system is noninferior to usual care with regard to the use of emergency release blood. Based on our preliminary data, emergency release blood use is rare, and currently occurs for 1 in 200 (0.5%) surgical cases at the host institution. In discussion with key stakeholders and by comparison with results from other institutions that revised their Maximum Surgical Blood Ordering Schedule (MSBOS), we determined that a 1.2-fold increase in emergency release blood use would be clinically meaningful. To test this hypothesis, we will estimate the relative risk for emergency release blood use using a GEE and a noninferiority limit of 1.2 for the relative risk. If the upper confidence limit for the relative risk estimate is below the noninferiority margin of 1.2, we will reject the null hypothesis that the intervention is worse than the control and conclude that the intervention is noninferior with regards to emergency release blood use.

Other secondary outcomes: The following secondary outcomes are all binary outcomes assessed at the patient level, and they will be analyzed using a GEE approach clustered by clinician as described for the primary outcome:

- Active type and screen orders at the start of surgery
- Red cell transfusion during surgery
- Red cell transfusion during surgery without an active type and screen at the start of surgery

- Transfusion reaction

5.1.4. Sensitivity and Subgroup Analyses

Sensitivity Analyses. As a sensitivity analysis, we plan to prospectively evaluate the S-PATH's predictions as if they had been followed, regardless of the observed type and screen ordering decision made by the enrolled clinician. Specifically, we will compare the frequency of the primary outcome between the intervention and control groups as if the S-PATH recommendation had been followed in the intervention group. We will also compare the frequency of red cell transfusion during surgery without a type and screen using this approach, as this will represent the false negative rate of S-PATH versus usual care.

As additional sensitivity analysis, we will analyze data collected during Phase II of the trial (when the early group of NPs had started using S-PATH but the late group of NPs were still performing usual care) as a parallel cluster-randomized trial using a generalized estimating equation approach assuming a binomial distribution and log link function. We anticipate that this approach may have lower power but will be less subject to temporal trends given the shorter duration of Phase II (3 months).

As mentioned in section 5.1, we also plan to analyze data from patients seen by NP participants separately from patients seen by intern physicians, using the same analytic techniques as described in the primary analysis. The study protocol for training and exposure to the S-PATH intervention did differ between these two groups, so this sensitivity analysis is designed to address the possibility that biases might have been introduced by aggregating data from both provider groups in the main analysis.

Subgroup Analyses. Subgroups will be examined to evaluate the effectiveness of the intervention across the following predefined subgroups for the primary and safety endpoints: patient gender, patient race, and surgical service.

5.1.5. Implementation outcomes

This study is designed as a hybrid Type I implementation-effectiveness trial.[48] Therefore, we plan to evaluate implementation outcomes to assess the implementation strategy for the S-PATH intervention and to identify barriers or facilitators S-PATH use.

Clinician-focused implementation outcomes: These outcomes will be assessed at the clinician level monthly and in aggregate and described with simple descriptive statistics. The frequency of viewing S-PATH predictions will be reported as the proportion of that clinicians' eligible patient encounters where they viewed the S-PATH tool. The frequency of the clinician accepting S-PATH's recommendation will be reported as the proportion of that clinician's eligible patient encounters where their type and screen decision matched S-PATH's recommendation. Associations between clinician characteristics (such as clinician type, experience, responses to pre- and post-study surveys) and clinician-focused implementation outcomes will be explored using simple descriptive statistics, the chi-square test statistic, or logistic regression models appropriate.

Patient- and procedure-level predictors of non-acceptance. Rationale: Non-acceptance of S-PATH recommendations may suggest misalignment of the model with clinician judgement; in other words, clinicians may disagree with S-PATH because they have safety concerns about the recommended order. The goal of this exploratory analysis is to identify patient subgroups for whom clinicians were more likely to not accept S-PATH recommendations; these represent opportunities for improving the model or the implementation strategy.

We will first compute simple descriptive statistics illustrating S-PATH non-acceptance rates stratified by procedure code, surgical service, procedure-specific transfusion rate, patient-level

demographic characteristics (age, sex, weight), and preoperative laboratory values. These variables are chosen as those that most influence the model's prediction or clinician behaviors based on preliminary work. Continuous variables will be categorized into quartiles for this univariable analysis. The Chi-square test with Bonferroni correction will be used to assess for statistically significant differences in non-acceptance between levels of each variable. Variables with significant univariable differences in non-acceptance by level will be included in a multivariable logistic regression model to identify independent predictors of S-PATH non-acceptance.

5.1.6. Exit interviews

At the end of their study participation, clinician participants will be sent a survey via email, which will solicit feedback on their impressions of the S-PATH tool. Clinicians will also have the option to opt into participating in an exit interview. Semistructured exit interviews will be conducted virtually with a member of the study team using the Zoom videoconferencing platform. A semistructured interview guide will be used to elicit feedback on barriers and facilitators to S-PATH use. Interviews will be recorded and transcribed using the Zoom platform, and analyzed using an inductive open coding approach.

6. Monitoring

6.1 Adverse event and safety monitoring

6.1.1 Data Safety Monitoring Board

A Data Safety Monitoring Board will be convened to monitor participant safety during the trial. Members will include: Michael Mathis (expertise in machine learning, electronic health record data), Jessica Spence (expertise in cluster-randomized clinical trials and statistics), Steven Frank (expertise in transfusion medicine), Justin Starren (expertise in medical ethics and informatics). The DSMB will meet prior to Phase II of the trial to review procedures for the protection of human subjects and baseline safety data. The DSMB will meet again prior to the initiation of Phase III of the trial to reviewing interim safety outcomes.

A DSMB in the context of this pragmatic clinical trial exists for the purpose of providing the investigators, the IRB, and the sponsor with objective, scientific monitoring of the conduct of the study from the standpoint of ensuring (1) the protection and safety of human subjects and (2) the validity and integrity of the trial. The DSMB serves as an independent group advisory to the funding agency. To fulfill its functions, the DSMB will review the original protocol and any subsequent amendments, perform expedited monitoring of all serious adverse events (SAEs), perform ongoing monitoring of non-SAEs and safety outcomes, determine whether study procedures should be changed or the study should be halted because of serious safety concerns and/or major problems with the study conduct, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also monitor implementation of procedures to ensure privacy and data confidentiality.

No formal stopping rules for safety, efficacy, or futility are planned. However, blinded interim analysis of the safety outcomes of the trial will be reviewed at the mid-trial DSMB meeting (see 6.2 Interim Analyses below)

If at any time during the course of the study, the DSMB judges that risk to subjects may significantly outweighs the potential benefit, the DSMB shall have the discretion and responsibility to request all necessary information for detailed analyses, and if warranted, recommend that the study be terminated. Factors that might lead to consideration of stopping would include a significant number of AEs that can reasonably be attributed to participation in the study, clearly more harm in one group than the other, inability to recruit and measure the

required number of participants to conduct the primary outcome analyses, poor intervention adoption, serious protocol violations, or other circumstances that would render the study unlikely to produce scientifically valid findings. The DSMB will carefully weigh the risk of completing the trial as planned against the risk of prematurely stopping the trial for safety or futility.

6.1.2 Safety Monitoring

The primary patient-related risk relevant to presurgical blood orders is the possibility of patients requiring intraoperative transfusion in the absence of presurgical blood orders (i.e., false negative recommendations). This can occur with usual care and with use of the S-PATH tool. When this happens, transfusion can be delayed to allow for blood preparation orders to be placed and processed. Alternatively, if the need for transfusion is urgent, emergency release blood (universal donor, type O) can be administered. Although emergency release blood is very safe, in rare circumstances (0.01-0.1%),[49–52] a patient might have a hemolytic transfusion reaction (for example, if they have unanticipated red cell alloantibodies), which are usually mild and clinically insignificant. The other risks associated with transfusion (infection, volume overload, acute lung injury etc.) are otherwise identical between emergency release and cross-matched blood.

Therefore, adverse event and safety monitoring for this trial will focus on monitoring for the following: (1) patients receiving intraoperative transfusion without a type and screen prior to the start of surgery, (2) patients receiving emergency release blood, and (3) hemolytic transfusion reactions. All 3 of these occurrences will be considered adverse events (AE). Serious adverse events (SAE) will be defined as AE that result in death, organ failure, or results in persistent or significant disability. All suspected AEs and SAEs will be logged by the study coordinator in the study REDCap project and forwarded to the PI for review, adjudication, and investigation. AE summary reports can be generated at any time for the DSMB and the IRB, for both regularly scheduled reviews as well as in the event of any SAEs requiring expedited reporting.

Monitoring for intraoperative transfusion without a preoperative type and screen and for emergency release blood use will occur electronically by querying the EHR data warehouse as described in 4.4.2.

Monitoring for transfusion reaction will occur by leveraging the Blood Bank's existing monitoring framework for detecting transfusion-related adverse events. Specifically, the Blood Bank is an AABB-accredited and FDA-regulated facility that is mandated to track, investigate, and report on all transfusion service adverse events. The study coordinator will communicate with Blood Bank staff to retrieve the names of all surgical patients who were reported to have a transfusion-associated AE. Manual chart review will be performed to determine the clinical consequences of each suspected transfusion reaction and to screen for SAE. Patients will be followed by chart review for 30 days after the index transfusion event to ascertain whether a SAE occurred. Mortality resulting from transfusion will be reported to the Blood Bank and the FDA as required.

At each DSMB meeting, safety information for this study will be reported to the DSMB by group but with the true identity of the study groups masked. This will maintain proper blinding of the DSMB and study personnel responsible for the scientific oversight and direction (PI and statistical advisors) and outcome data acquisition and analysis (coordinator and analysts). However, if there are extraordinary concerns regarding participant safety, the DSMB may request unblinded data, e.g., on unexpected SAEs, in order to determine the nature and extent of harm of the interventions under study. When this occurs, a protocol to be established with input from the DSMB during the trial initiation phase will be followed to ensure continued masking of the study personnel as noted.

6.2 Interim Analyses

Blinded interim reporting on safety outcomes will be presented at the mid-trial DSMB meeting for review. These safety outcomes include, in decreasing order of expected prevalence, (1) the frequency of transfusion without an active type and screen within the first hour of surgery, (2) the frequency of patients receiving emergency release blood, (3) the frequency of patients experiencing hemolytic and other types of transfusion reaction.

Statistical analyses of these outcomes will be presented with blinding of the intervention groups. Unadjusted binomial confidence intervals will be presented along with the prevalence of each safety outcome in each blinded study group. The DSMB will consider stopping the trial if there are non-overlapping confidence intervals for the prevalence of any safety outcome between the trial arms. Based on preliminary data on safety outcome 1 (the current frequency of patients receiving transfusion without a T&S prior to the start of surgery = 0.4%) and assuming recruitment targets described in 4.6 Sample Size, we anticipate being powered to detect a 3-fold difference in the prevalence of this outcome by the mid-trial DSMB meeting.

The DSMB will evaluate the data to determine whether the trial should continue as planned, be modified, or be stopped. The DSMB may also request additional statistical analyses, including full statistical adjustment for the safety outcomes, if needed to clarify emerging safety signals. If extraordinary concerns arise regarding patient safety, the DSMB may request unblinded data prior to making a recommendation.

6.3 Harms

Expedited reporting. All unexpected SAEs must be reported to the DSMB, IRB, and Blood Bank within 5 business days of discovery, regardless of any judgment of their relatedness to the study treatment. All SAEs that result in patient death must be reported to the IRB, DSMB, and Blood Bank within 1 business day. This reporting timeframe is consistent with the Washington University IRB's requirements as described below. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, dosing history of a suspect medication/treatment (if applicable), concomitant medications, the participant's medical history and current conditions, and all relevant laboratory data. An initial notification by email with all related study forms shall be made to the DSMB within 1 or 5 business days of the detection of an unexpected SAE depending on severity. Any additional information about the case that may be obtained after the initial notification shall be communicated to the DSMB in a timely manner. The DSMB may require a conference call to review all the relevant information and the site study physician's determination of whether there was any possible relevance to the study, and discuss and approve the investigators' Corrective and Preventive Action Plan, if warranted.

IRB requirements for AE reporting. The Washington University IRB requires that within 5 business days of the PI learning of an unanticipated problem (UP) or major protocol deviation, the PI informs the Director of IRB panel and all relevant oversight committees at the university, and that mortality be reported within 1 business day. Within 15 business days of the PI becoming aware of non-serious AE, changes in risk/benefit, or events requiring report to the sponsor, these will be reported. An annual report will be submitted to the IRB and consortium institutions and to the sponsor summarizing all AEs, serious or not.

7. Ethics and Dissemination

7.1 Protocol

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design,

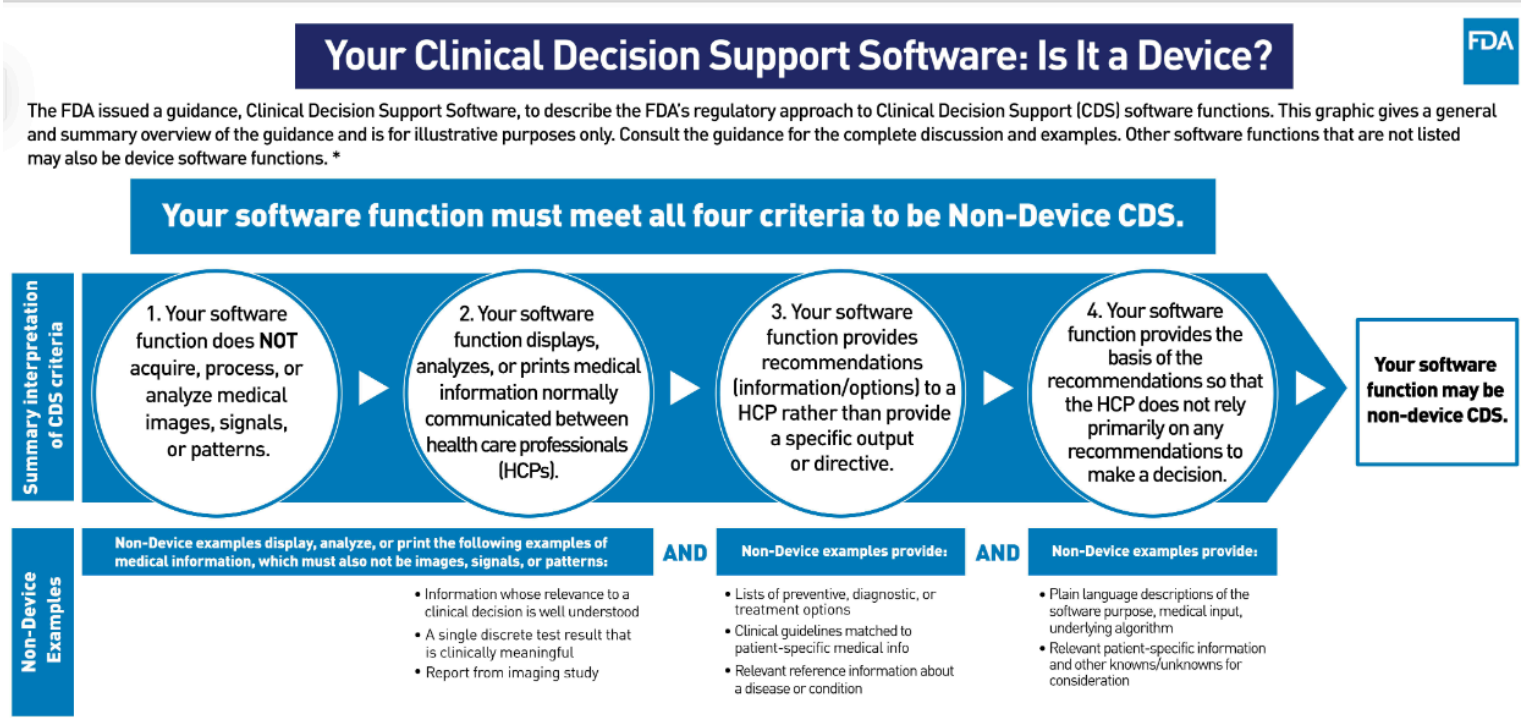
patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the WUSTL IRB. As discussed above, small changes to the S-PATH interface or reference materials are anticipated and will not be regarded as protocol modifications.

7.2 Consent

Clinician participants will provide written informed consent. This study is seeking approval for a waiver of informed patient consent.

This waiver is justified because:

1. *The intervention is not an FDA-regulated device.* Figure 8 shows the Food and Drug Administration's guidance on the criteria for clinical decision support software that are not considered medical devices.[53] The S-PATH tool meets all of the criteria:
    a. S-PATH does not acquire, process, or analyze medical images, signals, or patterns. It explicitly does not use any time-series features, and only considers the patient's most recent laboratory values and other demographic and surgical information.
    b. S-PATH displays surgical transfusion risk and the values for the patient's risk factors that contribute to its risk estimate, all of which are medical information that normally is communicated between healthcare professionals. The relevance of the surgical transfusion risk estimate to the clinical decision to order a type and screen is well understood. Existing guidelines for the creation of a Maximum Surgical Blood Ordering Schedule (MSBOS), the current standard of care approach, advocate for the use of the procedure-specific historical transfusion risk as the risk estimate and specifically describe use of a 5% risk threshold for ordering a type and screen. S-PATH displays the same procedure-specific historical transfusion used for MSBOS creation, and also provides a more personalized risk estimate based on the patient's characteristics.



c. S-PATH provides information and recommendations to a healthcare professional and does not substitute, replace, or direct judgement. S-PATH provides a recommendation for whether to consider ordering a type and screen, but clinician participants are free to make the clinical decision they feel is appropriate.
d. S-PATH provides the basis for its recommendations so that the clinician can independently review the basis for the recommendations and do not primarily rely on its recommendations to make a decision. As shown in Figure 5, S-PATH provides information on which of the patient's characteristics that most contributed to its risk prediction so the clinician can evaluate the accuracy of its recommendation. Training will be provided specifically to help clinicians identify situations where S-PATH might be misled. Clinicians will also have access to the existing MSBOS when making their decisions.

2. *The intervention is minimal risk* – The intervention does not expose clinician or patient participant to risks beyond what is routinely encountered in everyday life. The reasons for this are threefold: (1) The intervention (S-PATH tool) provides information and recommendations to the clinician in CPAP clinic, but it does not override their clinical judgement. In addition, there are many clinician stakeholders who review the type and screen status of the patient prior to surgery, including the surgeon and day of surgery anesthesia team. (2) For both the control (routine care) and intervention (S-PATH) arms, there is the possibility that patients who do not have a preoperative type and screen will require intraoperative transfusion. Our preliminary data indicates that this may occur less frequently with S-PATH compared to usual care (see Preliminary Data / Prospective Validation). Emergency release blood is readily available (within 5 minutes) and is routinely used in this situation. (3) For both control and intervention arms, there is the possibility that patients with unnecessary presurgical blood orders will receive unnecessary discretionary transfusions, resulting in increased exposure to all transfusion-associated risks. Therefore, there are risks to both inadequate and excessive presurgical blood orders for both intervention and control.
3. *The research could not be conducted without the waiver*. Given the sample size required to adequately power this study (3,780 patients, see 4.5 Sample Size), it is not feasible to consent individual patients.
4. *The rights and welfare of patients are not adversely affected.* The use of a waiver of consent in this situation would not violate any legal statutes given that the intervention is minimal risk.

Figure 8 – FDA guidance illustrating criteria for a clinical decision support tool to not be regulated as a medical device.

7.3 Protections Against Risks

IRB approval of the study protocols and procedures will be obtained prior to implementation, and the Data Safety Monitoring Board will review the procedures for the protection of human subjects at the outset of the project.

Use of the S-PATH system is a variation of routine clinical care; instead of using the conventional Maximum Surgical Blood Ordering Schedule (MSBOS) to determine presurgical blood orders based on the patient's planned procedure (routine care), the S-PATH system incorporates both patient- and procedure-specific information to produce its estimated surgical transfusion risk and recommendation for blood orders. For both routine care and the S-PATH intervention, the clinician remains the final arbiter of the blood ordering decision.

As part of the consent and training process, clinician participants will be informed that the recommendations of the S-PATH system in no way overrides their clinical judgement. In

addition, it will be emphasized that S-PATH use is optional, and that clinicians are free to use the conventional MSBOS alongside the S-PATH system. For clinicians in the intervention arm, training will be provided on the limitations of the S-PATH system, including clinical scenarios where S-PATH accuracy might be reduced. Limitations are also explicitly incorporated into the user interface in a way that is easily interpretable. Patients with a prior history of red cell alloantibodies, for whom type and screen and crossmatching blood would take longer time, are explicitly excluded from this study.

We will implement the following measures to minimize risks to clinician and patient participants:

- *Risk for patients requiring intraoperative transfusion in the absence of presurgical blood orders.* If the need for transfusion is urgent to protect patient safety, emergency release blood can be administered. Emergency release blood is currently available within all of the operating room areas at Barnes Jewish Hospital, and can be retrieved within 5 minutes. It is already routinely utilized for this purpose, i.e., for patients encountering unexpected surgical bleeding where the time to obtain crossmatched blood exceeds clinical need. Anesthesiology clinicians who provide intraoperative care will be notified of this study, and additional educational materials will be provided about the availability of emergency release blood prior to study initiation. The frequency of emergency release blood utilization and adverse events associated with transfusion will be monitored and reviewed by the Data Safety Monitoring Board (DSMB) as described in the Data Safety Monitoring Plan. An unblinded statistician will conduct statistical analyses on these safety outcomes for each meeting for DSMB members to review.
- *Risk of disruption to clinical workflow.* To minimize this risk, we conducted a human-centered design process in partnership with stakeholders and users to align the S-PATH system with clinician workflow and to ensure its ease of use. Training will be provided to clinicians in the intervention arm prior to trial initiation to reduce the burden of learning a new workflow. A wash-in period will be provided to allow clinicians to become accustomed to the S-PATH interface before potentially using it in clinical care. In addition, S-PATH use will be optional. Contact information for the study team will be provided to participants so that technical issues and concerns about workflow impact can be promptly addressed.
- *Risk for breach of confidentiality.* Clinician participants will be assigned an anonymous identifier. Identifying information will be kept separate from study data in a password-protected file. All study data, including log files, electronic health record data, and audio files, will be stored on a password-protected HIPAA-compliant server managed by Washington University Research Information Services (RIS). All paper study data will be stored in a locked filing cabinet in the PI's office.

7.3.1 Vulnerable Subjects

No protected patient classes are specifically involved in this study.

7.4 Potential Benefits of the Proposed Research to Participants and Others

There is a potential for participants to benefit from the S-PATH intervention; however, there is no guarantee. For clinician participants, S-PATH use for presurgical blood orders may simplify clinical workflow because S-PATH is integrated within the electronic health record, unlike the conventional MSBOS. Many of the clinically relevant variables are automatically transferred and displayed by the CDS system, which facilitates the ease of data review.

For patient participants, personalized identification of surgical transfusion risk as performed by the S-PATH system might improve patient safety by recommending blood orders for patients at

higher risk of transfusion due to patient-specific factors, who otherwise might have been missed by the conventional MSBOS. There may also be patients who are spared the cost and discomfort of unnecessary presurgical blood type testing because the S-PATH system identifies that their personalized transfusion risk is lower than otherwise might be assumed based on the conventional MSBOS. A reduced prevalence of type and screen orders among low risk patients may also decrease the risk of discretionary transfusion and its antecedent risks.

7.5 Importance of Knowledge to be Gained

Evaluation of the S-PATH system is important because of its potential to change presurgical blood ordering practice, with considerable public health impact for patient safety, blood conservation, and reduced healthcare costs. In addition, insights derived from this study will contribute to the advancement of the delivery science for artificial intelligence in healthcare.

7.6 Confidentiality

Identifying data will be protected as described in 5 Data Collection and Management.

7.7 Declaration of Interests

The investigators of no financial conflicts of interest. Computer code for the S-PATH model is available on a public repository[54] and there are no plans for commercialization.

7.8 Dissemination

This study will be registered on ClinicalTrials.gov and results information will be submitted to ClinicalTrials.gov as outlined in the policy and according to the specific timelines stated in NIH policy. Washington University has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements.

We will present the research findings for the trial at national scientific meetings and publish the results in peer reviewed journals. The trial protocol will be also be published in a peer reviewed journal.

7.9 Data Sharing Policy

Per NIH guidelines, all data are planned to be preserved and shared after anonymization. Recruitment progress and final results will be documented at clinicaltrials.gov. To anonymize the data, all clinicians and patients will be assigned random identifiers to replace clinician names and patient medical record numbers. No dates for surgical encounters will be retained. All other incidental identifiers (such as mentions of care team member names, encounter numbers, or hospital units) will be stripped.

Data will be deposited in the WashU Libraries Open Scholarship Digital Research Materials Repository. Curation is guided by the Data Curation Network (DCN) CURATED model, from which the dissemination information package (DIP) is created, given a registered DOI, retained in the repository and archived for a minimum of 10 years. The archival information package (AIP) will contain the original submission information package (SIP), the DIP, PREMIS compliant metadata, the readme file, and documentation of curation processes.

Data will be findable for the research community through the Becker Library commons. For all publications, a separate study ID will be created. Each study will be assigned a separate digital object identifier (DOI). This data DOI will be referenced in the publication to allow the research community easy access to the exact data used in the publication.

Data will be made available within 12 months of the grant period ending or on publication of a manuscript using the data, whichever comes first. Data will be retained in the WashU Libraries Open Scholarship Digital Research Materials Repository for at least 10 years.

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