Clinical Trial Protocol

"The PRICE Trial: Phlebotomy resulting in controlled hypovolemia to prevent blood loss in major hepatic resections"

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Funding: Ottawa Hospital Research Institute
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Principal investigator: Guillaume MARTEL, MD, MSc, FRCSC, FACS
Clinical Epidemiology Program, Ottawa Hospital Research Institute
Department of Surgery, University of Ottawa
501 Smyth Rd, CCW 1667
Ottawa, ON, K1H 8L6
Tel: +1-613-737-8899 ext. 71053
Fax: +1-613-739-6854
Email: gumartel@toh.on.ca

Co-investigators: Dean A. FERGUSSON, PhD, MHA (Clinical Epidemiology)

Elianna SAIDENBERG, MD, FRCPC (Hematology and Transfusion Medicine)

Christopher WHERRETT, MD, FRCPC (Anesthesiology)

Study coordinator: Aklile WORKNEH, MSc (Interdisciplinary Health Sciences)
Tel: +1-613-737-8899 ext. 71484
Email: aworkneh@ohri.ca

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Synopsis

Study Title	The PRICE Trial: Phlebotomy resulting in controlled hypovolemia to prevent blood loss in major hepatic resections	
Short title	The PRICE trial	
Study Design	Double-blind randomized control trial	
Study Participants	Any patient being considered for a major elective liver resection will be considered for trial enrollment. Patients undergoing a posterior right lobe or a central resection will also be considered.	
Planned Sample Size	62	
Planned Study Period	2 years	
	Objectives	**Outcome Measures**
Primary 1	To determine whether the use of phlebotomy compared to standard of care prior to liver resection leads decreased operative blood loss	Intraoperative blood loss
Primary 2	To determine trial feasibility	Trial accrual
Secondary 1	To determine whether phlebotomy leads to decreased blood product transfusion	Blood product transfusion rate
Secondary 2	To determine whether phlebotomy leads to decreased perioperative morbidity	30-day perioperative morbidity rate
Secondary 3	To determine the safety of phlebotomy compared to standard of care	7-day morbidity and mortality
Secondary 4	To determine whether phlebotomy leads to easier liver parenchymal transection.	Surgeon perception scale

Abbreviations

ALT	Alanine aminotransferase
ANH	Acute normovolemic hemodilution
CI	Confidence Intervals
cm	Centimeter
CPDA	Anticoagulant citrate phosphate dextrose adenine solution
CRF	Case report form
CVC	Central venous catheter
CVP	Central venous pressure
DSMB	Data safety monitoring board
g	Gram
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GP	General Practitioner
H_2O	Water
HF	Heart failure
HPB	Hepato-pancreato-biliary
ICMJE	International Committee of Medical Journal Editors
ID	Identification
INR	International normalized ratio
IV	Intravenous
kg	Kilogram
mL	Milliliter
MRN	Medical record number
NYHA	New York Heart Association
OHRI	Ottawa Hospital Research Institute
OHSN-REB	Ottawa Health Science Network Research Ethics Board
OR	Odds ratio
PHI	Personal health information
PI	Principal Investigator
PII	Personal identifying information
REB	Research Ethics Board
RR	Risk ratio

1 Introduction

1.1 Background and Rationale

Major liver resections are now commonly performed in specialized hepatobiliary surgical units. The indications for liver surgery include primary and metastatic liver cancers, as well as numerous benign conditions such as liver cysts, major bile duct injuries, liver adenomas or living-donor transplantation. The need for major liver surgery is growing exponentially in our society, as a result of the known increase in the incidence of liver cancer in North America, the evolving obesity epidemic leading to non-alcoholic steatohepatitis and cirrhosis, improved chemotherapeutic drugs leading to more patients being candidate for liver surgery, as well as the dramatic rise in the utilization of modern imaging techniques leading to the incidental diagnosis of numerous benign and malignant liver conditions. Importantly, the growing need for liver surgery affects all age, gender and ethnic groups, as certain conditions such as adenomas predominantly affect young healthy women, while liver cancer tends to affect middle-age and older patients. Finally, the advent of living-donor liver transplantation and the known shortage of deceased-donor organs lead many young and middle-aged adults to undergo major liver resections.

Liver surgery is highly complex and associated with significant healthcare costs, owing to its technical nature and significant perioperative complication rates. As recently as 1970, the reported operative mortality rate associated with liver surgery was as high as 17-24% [1], owing in large part to major hemorrhage [2]. Today, the average mortality rate following liver resection is 3.6% in a recent systematic review of the literature [3]. In the Province of Ontario, mortality rates of less than 3% are now routinely expected in liver surgery [4]. Despite improvements in perioperative mortality rates, perioperative morbidity rates remain as high as 50% in major series. Although patients undergoing liver surgery have benefited over the years from tremendous improvements in resection techniques, anesthesia and critical care, these operations remain fraught with complications owing in part to the risk of major intraoperative blood loss and hemorrhage.

Blood loss and blood transfusion are common complications in liver surgery: Despite major improvements in perioperative morbidity and mortality following liver surgery, major blood loss and blood transfusion remains a significant concern for surgeons, anesthesiologists and patients [5, 6]. Among high-volume institutions, median intraoperative blood loss during liver resection is between 300-800 mL [7-11]. The associated risk of blood transfusion is 17-41% [7-12]. Population-based analysis from the American College of Surgeons National Surgical Quality Improvement Program dataset reveals a transfusion rate of 22% among 2,448 hepatectomies performed in the United States in 2013 at 85 centers [12]. At our own center, review of data for a one-year period (2011-2012) of an electronic registry reveals median blood loss of 475 mL for all liver resections, 775 mL in major liver resections, and a 22% transfusion rate during hospitalization. A median of 2 units of packed red blood cells were given to transfused patients. Between 1995 and 2004, well over 10,000 liver resections were performed in Canada [13], and this figure has undoubtedly increased since then. Based on the above figures, one can estimate that liver resection is associated with the transfusion of approximately 440 units of blood per year in this country.

Risk and cost associated with blood loss and blood transfusion: Blood loss in liver resection is strongly associated with worse perioperative morbidity and mortality, independently from blood transfusion [8, 10, 14]. Jarnagin et al. have demonstrated in a large dataset comprising 1,803 patients that operative blood loss was independently associated with both, perioperative morbidity (OR 1.35, 95% CI 1.18, 1.55) and mortality (OR 1.69, 95% CI 1.44, 1.99) [8]. Excessive blood loss also renders liver surgery much more technically challenging, particularly when it originates from deep hepatic vein branches during transection of the liver parenchyma [15]. This type of brisk venous bleeding can rapidly obscure the surgical field and jeopardize the safety of resection.

Transfusion of blood products is associated with the rare risk of transmission of infectious diseases, transfusion reaction and clerical errors, and creates pressures for the national blood supply [16]. Moreover, blood transfusion is thought to have immunomodulatory effects, which may be associated with increased infectious complications, delayed postoperative recovery, as well as worsen long-term cancer-specific survival [17-19]. In a recent manuscript by Hallet et al, blood transfusion was independently associated with worsened 5-year overall survival and recurrence-free survival following liver resection for metastatic colorectal cancer [18]. Finally, blood transfusion is associated with a significant societal cost. A 2002 publication estimates the cost of one unit of allogeneic packed red blood cell to be US$ 264.81 [20]. Given the increasing incidence of liver resection and the need for transfusion in about one quarter of patients for a median of 2 units, it becomes clear that blood loss and blood transfusion are both important independent contributing factors to poor outcome and high societal cost following liver surgery.

Methods used to prevent blood loss during liver surgery: In order to minimize blood loss and blood transfusion in liver surgery, numerous cardiovascular, pharmacologic and surgical interventions have been devised (table 1). The evidence base supporting each intervention is highly variable. In clinical practice, surgeons and anesthesiologists utilize a widely variable combination of these techniques, based on personal experience and interpretation of the literature.

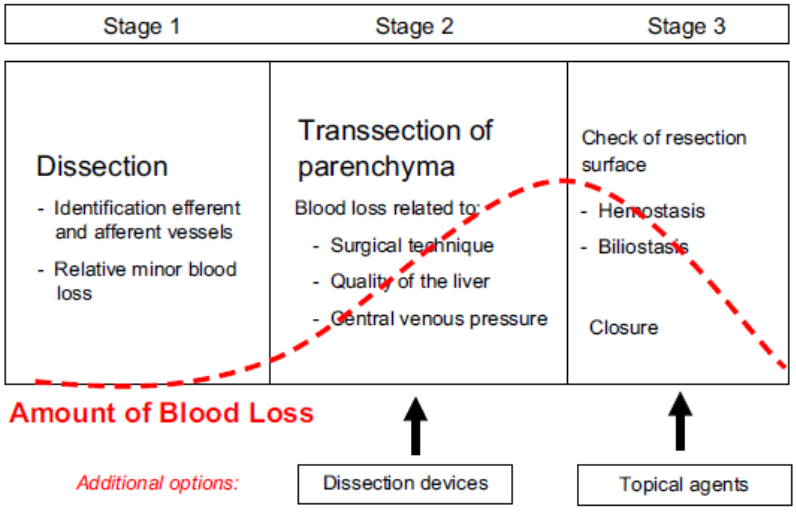
Table 1. Interventions to decrease blood loss and blood transfusion in liver surgery

Pharmacologic	Cardiovascular	Surgical
Antithrombin III	ANH	Hepatic inflow occlusion
Aprotinin	Autologous blood donation	Topical agents
Desmopressin	Hypoventilation	Energy transection devices
Recombinant factor VIIa	Low CVP	Transection methods
Tranexamic acid	Phlebotomy	

Abbreviations – ANH: acute normovolemic hemodilution; CVP: central venous pressure

Liver resection performed under conditions of low central venous pressure (CVP) (<5 cm H_2O) is widely regarded as the standard of care. Numerous studies have demonstrated that intraoperative blood loss during liver resection is almost linearly associated with CVP [21-24]. For instance, Jones et al. demonstrated that with a CVP of 5 cm H_2O or less median blood loss was 200 cc compared with 1000 mL over 5 cm H_2O (p=0.0001) [21]. In a recent meta-analysis of randomized trials, patients undergoing liver resection under low CVP conditions lost significantly less blood (-419 mL [95% CI -575, -264], p<0.00001) and demonstrated a trend towards fewer transfusions (RR 0.66 [95% CI 0.42, 1.03], p=0.067) [25]. Low-CVP liver surgery is widely adopted, both based on the available data and its physiologic soundness. In a recent survey of liver surgery centers in North America, Europe and Asia, Mise and colleagues reported that 85% of centers routinely restrict intraoperative fluid administration in an effort to lower the CVP [26]. Similarly, all recently surveyed Canadian liver surgeons report targeting a low CVP frequently or always during liver resection [27]. A low CVP is thought to reflect a lower pressure within the right atrium and inferior vena cava. As a consequence, the proximal pressure within the hepatic veins is also likely lower, which leads to less pronounced blood loss from hepatic vein branches during the liver parenchyma transection. As Alkozai and colleagues have argued (figure 1), the largest proportion of blood loss in liver surgery occurs during the parenchymal transection and is most likely to be influenced by the filling status of the patient and the associated CVP [5].

Figure 1. The mechanisms of bleeding and the relative amount of blood loss (dotted line) during the three surgical stages of partial liver resections. From Alkozai et al. [5], with permission



Intraoperative CVP can be controlled by the anesthesiologist using a variety of techniques. Most commonly, the patient is kept relatively intravascularly volume depleted by minimizing intravenous fluid administration. Other techniques can be used to supplement the use of intravenous fluid management, such as hypoventilation, as well as the use of diuretics or venous vasodilating agents.

Phlebotomy and controlled hypovolemia to prevent blood loss in liver surgery: Intraoperative phlebotomy and controlled hypovolemia is a novel intervention that can be used to decrease blood loss and blood transfusion in elective liver surgery. This simple intervention consists of the removal of whole blood from the patient prior to the initiation of parenchymal liver transection. Following removal of the portion of liver, the phlebotomized blood is given back to the patient.

Whole blood phlebotomy leads to a decrease in the net circulating volume and results in a mild to moderate decrease in CVP. Acute phlebotomy of 8 mL/kg is thought to decrease the circulating blood volume by 10-12% [28], a state that is comparable to class 1 early hemorrhage. Class 1 hemorrhage is considered a non-shock state that is comparable to the donation of one unit of whole blood [29]. Acute blood loss of less than 15% of the total blood volume leads to arterial baroreceptor response, which in turn leads to increased sympathetic tone and decreased vagal tone [30]. This leads to compensation, primarily in the form of increased peripheral vascular resistance, leading to maintained arterial blood pressure and critical tissue perfusion [30]. At 10-15% of blood volume loss, cardiac output decreases minimally, as do right arterial pressure and CVP.

Whole blood phlebotomy has not been used widely in elective liver resection. Hashimoto and colleagues have reported the results of a small trial comparing phlebotomy (0.7% of body weight or 7 g of blood/kg) versus control in 79 patients undergoing living donor liver resection [15]. This study yielded a difference in parenchymal transection blood loss (140 mL vs. 230 mL, 2.15 mL/cm^2 vs. 3.75 mL/cm^2) favoring the phlebotomy group. Given that blood loss in living donor liver resection is typically extremely low these results were considered clinically significant. That said, this trial also utilized autologous blood donation, which may have confounded the results. One other small trial of 30 patients published only in Chinese would also suggest that phlebotomy with controlled hypovolemia resulted in decreased blood loss and blood transfusion [31].

In the context of liver transplantation, Massicotte and colleagues have carried out a before-and-after study, where intraoperative phlebotomy was utilized as part of a novel management protocol, which also included the use of cell saver, the avoidance of blood product transfusion, and the minimization of intravenous crystalloid administration [31]. In this work, where 0% vs. 44.5% of patients underwent phlebotomy, both blood loss (1,479 vs. 903 mL) and red cell transfusion (2.8 vs. 0.4 units/patient) were significantly decreased, together with lower CVP prior to caval clamping (9.2 vs 6.4 cm H_2O). Another study has further examined the effect of phlebotomy followed by phenylephrine infusion in patients undergoing pre-transplantation perihepatic dissection [28]. They reported that phlebotomy decreased CVP and portal venous pressure (PVP). Following phenylephrine infusion to restore arterial pressure, PVP was unaffected, while CVP increased without accurately reflecting changes in cardiac filling.

In addition to the above work, our group has acquired experience with 23 patients who underwent phlebotomy prior to elective major liver resection [32]. In this cohort, phlebotomy of 5.3-10.1 mL/kg was successfully carried out with a median total intraoperative blood loss of 375 mL or 4.7 mL/kg and 8.7% transfusion rate, which compares favorably with our 2011-2012 cohort of major resections that had a median blood loss of 775 mL. Massicotte et al. also reported using phlebotomy for elective liver resections, although they did not specifically provide data on these patients [33]. Finally, in a survey of worldwide liver surgery centers, a small number of centers reported using phlebotomy in the event that hepatic vein bleeding was excessive during liver transection [26].

***Difference with acute normovolemic hemodilution*:** The reader could confuse phlebotomy in liver surgery with acute normovolemic hemodilution (ANH). ANH, in contrast to simple phlebotomy, is a technique that has been used in a number of operative disciplines such as thoracic surgery, urology, and liver surgery. ANH consists of withdrawal of large volume of whole blood to achieve target hemoglobin of 80 g/L, followed by the purposeful replacement of the lost blood with intravenous crystalloid and/or colloid to maintain euvolemia rather than hypovolemia. During the procedure any lost blood is thought to be more diluted. The whole blood that is removed before the procedure is given back to the patient at the end of the surgery.

ANH has not gained wide acceptance in elective liver surgery. Reasons for this include that ANH may in fact render the liver operation technically more challenging based on the high volume of administered fluid to maintain euvolemia, the lack of objective decrease in intraoperative bleeding, as well as the cumbersome nature of the procedure. In contrast, phlebotomy involves the withdrawal of a much

smaller blood volume (7-10 mL/kg), without subsequent replacement with intravenous fluids [15, 28, 33]. A typical patient undergoing phlebotomy would have approximately 500-700 mL removed, whereas the average volume removed with ANH by Jarnagin et al. was 2,250 mL [34]. This is a critical distinction, which leads to a different mechanism of action. Phlebotomy leads to controlled hypovolemia, rather than euvolemia, as in the case of ANH. This is postulated to lead to decreased blood loss and decreased requirement for blood transfusion.

Safety considerations with phlebotomy in liver surgery: Intraoperative phlebotomy for elective liver surgery should be considered a simple and safe intervention. The following lines of argument support this position: 1) phlebotomy is already being performed in clinical practice; 2) other interventions are similar to phlebotomy with satisfactory safety profiles; and 3) the risks associated with phlebotomy are known and can thus be anticipated and prevented.

Phlebotomy in clinical practice: Phlebotomy has been utilized in clinical practice for several hundreds of patients. Two small trials have included a total of 49 patients undergoing phlebotomy for liver resection, with excellent safety profiles [15, 31]. As well, phlebotomy has been routinely used in some centers for liver transplantation, which typically applies to much sicker patients with highly disturbed physiology [28, 33]. None of these patients required dialysis. Massicotte et al. have also reported employing this technique in elective liver resections [28]. Finally, our own group has acquired experience with 26 such patients and have observed no major (Clavien-Dindo grade 3a or greater) complications [35].

Other similar interventions: Phlebotomy, by virtue of the blood drawing, can be compared to ANH. The use of ANH is a well-known technique in anesthesia. It has been described extensively and tested in over 40 randomized controlled trials in various fields of surgery [36]. In this current trial, we have incorporated exclusion criteria that are conservative and were modeled after the ANH experience in liver surgery [34]. In that trial, there was no difference in perioperative morbidity between ANH and control.

Expected risks associated with phlebotomy: There are few risks directly attributable to phlebotomy. However, a small volume of phlebotomy could potentially lead to any physiologic effect associated with blood loss. These effects could have implications for any major organ system, due to decreased perfusion (eg. myocardial ischemia, cerebrovascular accident, acute renal failure, coagulopathy, hepatic insufficiency, etc.). That being said, these risks exist with liver surgery, whether or not a phlebotomy is performed, simply on the basis of potential significant blood loss. In order to be considered fit enough for liver surgery; patients cannot have excessive comorbid illnesses that could be grossly exacerbated by the operation. The patient population that is thus considered for surgery is a relatively fit one that can tolerate phlebotomy. Furthermore, the inclusion and exclusion criteria that have been built in the protocol exclude those at a greater risk of adverse event associated with decrease organ perfusion.

Other potential risks associated with phlebotomy pertain to the collection of whole blood and its auto-transfusion at the end of surgery. There is a potential risk for clerical error with the blood. Similarly, there is a theoretical risk of bacterial contamination of the collection bag, tubing, and as a consequence, whole blood. To minimize these risks, all study procedures have been developed conjointly between surgery, anesthesia, and the Transfusion Medicine department at our center. The collection bags will be provided by Transfusion Medicine, labeled with the patient identifier, handled and processed in the same manner as any other blood product in the operating room. This procedure will allow for the safe handling of all blood specimens, in accordance with all protocols already in place at our center.

Why study phlebotomy and controlled hypovolemia? Whole blood phlebotomy is a relatively novel intervention in elective liver resection. Although it has now been utilized successfully in numerous patients, its efficacy and effectiveness have not been rigorously tested against the existing standard of care. The current state represents a rare opportunity to evaluate a new intervention in surgery before it is widely disseminated and adopted. Moreover, it is particularly important to test this intervention using a randomized controlled trial, as numerous other co-interventions exist to decrease blood loss and blood transfusion, thus potentially confounding any non-randomized study that seeks to examine this topic.

What are the principal research questions to be addressed? The primary research objective is to determine whether the use of phlebotomy compared with standard of care prior to liver resection leads to decreased operative blood loss. Secondary objectives are to determine whether phlebotomy leads to 1) decreased blood product transfusion, 2) decreased perioperative morbidity, and 3) easier liver parenchymal

transection. The safety of phlebotomy (adverse events) will also be studied, as will be the feasibility of the current trial in terms of enrolment, protocol administration and study coordination.

1.2 Objectives and Outcome Measures

Primary Objective: To determine whether the use of phlebotomy compared with standard of care prior to liver resection leads to decreased intraoperative blood loss, and to determine trial feasibility

Secondary Objectives: (1) To determine whether phlebotomy leads to decreased blood product transfusion, (2) To determine whether phlebotomy leads to decreased perioperative morbidity, (3) To determine the safety of phlebotomy compared to standard of care, (4) To determine whether phlebotomy leads to easier liver parenchymal transection.

1.3 Trial Design

This work proposes a proof of principle randomized controlled trial, using a conventional two-armed parallel design. One half of participants will be randomly allocated to the intervention (phlebotomy + standard practice), while the other half will be allocated to the control (standard practice). Consecutive patients will be randomized (1:1 allocation ratio) to the two study arms, with stratification by surgeon and indication.

Intraoperative phlebotomy is a short-term intervention. All relevant data to be collected after surgery will be available within 30 days of the operation. As such, all data will be collected while the patient remains admitted in hospital, as well as at the postoperative clinic visits. For patients who return to the clinic before 30 days from the surgery and for whom no further follow-up is required, the study coordinator will carry out one follow-up phone call to the patient at the 30-day point. No further follow-up will be required after 30 days.

2 Methods: Participants, Intervention, and Outcomes

2.1 Study Setting

The study will take place at the Ottawa Hospital, an academic hospital in Canada.

2.2 Eligibility Criteria

Any patient being considered for a major elective liver resection will be considered for trial enrollment. Patients considered for a posterior right lobe or central resection will also be considered. Patients who are undergoing a concurrent additional abdominal or thoracic procedure (e.g. colonic resection) will also be included.

Inclusion criteria:

- Participant is willing and able to give informed consent for participation in the study.
- Male or female, aged 18 years or above.
- Any patient being considered for a major elective liver resection (3 or more liver segments being operated upon)
- Any patient being considered for central resection of the liver (segments 4b and 5)
- Any patient being considered for posterior right lobe resection of the liver (segments 6 and 7)

Exclusion criteria: The participant may not enter the study if any of the following apply:

- Age <18 years
- Pregnancy
- Refusal of blood products
- Active cardiac conditions
    - Unstable coronary syndromes
    - Decompensated HF (NYHA functional class IV; worsening or new-onset HF)
    - Significant arrhythmias
    - Severe valvular disease
- History of significant cerebrovascular disease
- Renal dysfunction (patients with an estimated GFR <60 mL/min)
- Abnormal coagulation parameters (INR >1.5 not on warfarin and/or platelets count <100 $X10^9$/L)
- Evidence of hepatic metabolic disorder (bilirubin >35 μmol/L)
- Presence of active infection
- Preoperative autologous blood donation
- Hemoglobin <100g/L

2.3 Interventions

Procedures for all patients: One to two days prior to surgery, Transfusion Medicine will be notified of the upcoming procedure. The patient's name and medical record number (MRN) will be provided, together with a request for the number of collection bags based on the patient's weight. Patients enrolled in the trial will be brought to the operating room where the surgical, nursing, and anesthesiology team will prepare the patient for surgery in the usual fashion. An arterial line, as well as a central venous catheter, will be inserted, in accordance with the standard of care in liver surgery. A non-invasive cardiac index monitor may be utilized, at the anesthesiologist's discretion. Anesthesiologists involved in the trial will be assigned to patients included in the study by the anesthesia office. The anesthesiologist will prepare the patient for phlebotomy, irrespective of trial allocation – which will only be revealed to the anesthesiologist once the surgery is under way.

Control arm: Patients randomized to standard practice will receive the intervention deemed to be consistent with the standard of care in the field.

An epidural catheter will be inserted unless thought to be contraindicated by the anesthesiologist or refused by the patient. The epidural catheter will be used as part of the anesthesia management throughout the case, as is standard. Drugs infused in the epidural catheter will include both a narcotic agent, and a local anesthetic. A central venous catheter will be inserted.

The mainstay of management in standard practice should be to achieve a low CVP ($\leq$5 cm H_20) throughout the liver parenchymal transection portion of the procedure. The methods used to achieve a low CVP (minimization of intravenous fluids, hypoventilation, diuretics, vasodilators, etc.) will be at the anesthesiologist's discretion. Following the completion of the parenchymal transection, the surgeon will indicate this to the anesthesiologist, who will then have the opportunity to administer additional intravenous fluids if judged necessary. If at any point during the procedure, the anesthesiologist judges that the maintenance of a low CVP becomes unsafe for the patient, he/she will take steps in accordance with standard practice to rectify the situation.

Intervention arm: For patients randomized to phlebotomy, the intervention will consist of the standard of care, plus whole blood phlebotomy.

The attending anesthesiologist will carry out the intervention. Phlebotomy will consist of the withdrawal of 7-10 mL/kg of whole blood from the patient, as tolerated, (e.g. for a patient weighing 70kg, 490 to 700 mL of whole blood). A range of volumes is provided, so as to allow the anesthesiologist some leeway in managing the hemodynamic effects of the intervention.

Phlebotomy will be carried out using one of several vascular access options. Strict aseptic technique will be maintained, including proper swabbing of all ports, closing and sealing the system to prevent backflow of air or other potential contaminants into the line, and ensuring that the collection tubing is clamped twice before disconnecting it from the vascular access.

A scale will be used to collect up to the desired weight. Assuming a desired phlebotomy of 450 mL (ie. one collection bag of whole blood), then 450 g of blood will be measured on the scale. Given that the specific gravity of whole blood at 37 °C is known to be 1.0506 [37], the anesthesiologist will record the weight of blood withdrawn and will then back-calculate the true volume for patient care purposes.

The phlebotomy should be interrupted if the patient experiences a drop in arterial blood pressure of more than 20%, despite the administration of vasopressors. Similarly, the phlebotomy should be interrupted if the anesthesiologist judges that it is best for the patient to do so.

Following phlebotomy, the volume of removed blood should <u>not</u> be replaced by the administration of intravenous fluids; however, the volume of IV fluid administered during surgery be measured. In addition, the anesthesiologist should aim to keep the CVP low ($\leq$5 cm H_20) for the duration of the hepatic resection procedure, as is standard practice in liver surgery.

In the case of patients requiring combined resections (eg. liver and colon), the liver resection portion of the procedure will always be conducted first so as to avoid any potential hemodynamics or regional blood flow issues for the colonic resection. Once the surgeon indicates that the parenchymal transection portion of the liver resection is completed, the anesthesiologist should transfuse the phlebotomized whole blood back into the patient, using standard transfusion precautions.

In the event that the patient should require an unplanned transfusion of packed red blood cells or fresh frozen plasma during the parenchymal transection portion of the operation, the anesthesiologist should first administer the phlebotomized whole blood and then carry on with allogeneic blood products, at his/her discretion.

Normally the collected blood is transfused back regardless of blood loss. Collected blood should be transfused in the operating room and not transported elsewhere. Collected blood must be transfused within

eight hours if kept in a cooler, or four hours if kept at room temperature. Any unused collected blood will be returned to Transfusion Medicine, where it will be discarded. All supplies must be returned to Transfusion Medicine at the end of surgery.

The following technical steps will take place for patients randomized to phlebotomy:

Supplies:
- Transfusion Medicine will send the requested number of whole blood collection bags labeller with the patient's name and MRN and several plastic clamps in a Styrofoam cooler.
- The label must be checked using the standard protocol for checking all blood products.
- Plastic blue tubing clamps and a digital scale are available from the operating room.

Selection of vascular access:
- Vascular access options, in suggested order of preference:
  - A 14-gauge antecubital IV (or other large proximal vein/IV caliber). Collection time for a unit is 5-10 minutes by this route
  - The 16-gauge port of a triple lumen central venous catheter (CVC). The CVC must have been inserted on the day of collection. Collection time is 20-30 minutes.

Collection of blood:
- Attempts should be made to time the start of collection such that phlebotomy is complete shortly before start of the hepatic resection stage.
- Strict aseptic technique with proper swabbing of all ports is required.
- The system must remain closed/sealed to prevent backflow of air or other potential contaminants into the line. Ensure the collection tubing is clamped twice before disconnecting from the vascular access.
- Place a green towel on the floor and a weigh scale on the towel. Place the bag on the scale and weigh it and record the empty weight (usually about 75-85g).
- Determine a target or maximum including the empty bag weight. The volume of whole blood to be removed is 7-10 mL per kg of body weight, as tolerated.
- With all options it is important to maintain flow in order to prevent clotting in the catheter or tubing.

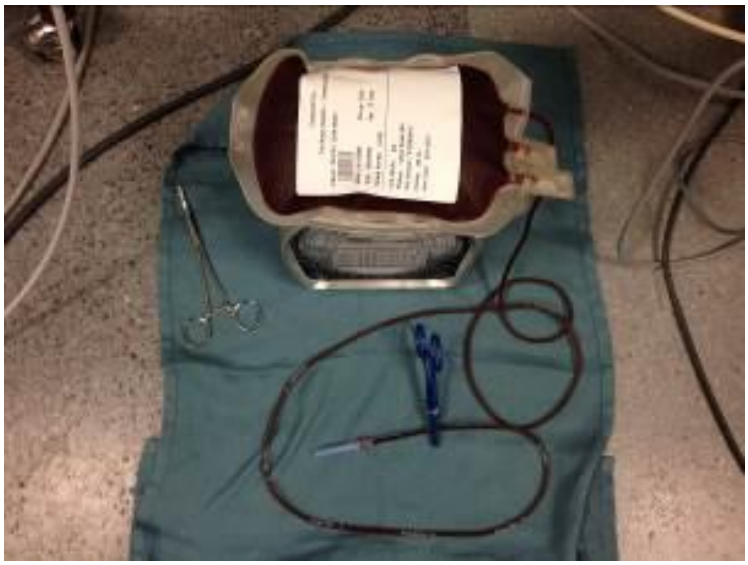
Using an antecubital IV:
- Place a blue clamp on the collection tubing close to the needle.
- Remove the cap from the needle and place needle into saline locked IV.
- Unclamp to start the collection.
- Monitor the weight of the collected blood and collect up to 400 additional grams of blood in a bag.
- If necessary, raise the operating table and place the patient in Trendelenburg position as tolerated to increase venous pressure and the siphon effect.
- Frequently and gently agitate the bag to facilitate mixture of the blood with the CPDA anticoagulant.

***Additional steps if using a triple lumen CVC*:**
- Attach a stopcock to the brown hub of the CVC.
- Attach an Interlink Injection Site ("saline lock") to the stopcock.
- Place a green towel on the pillow next to the CVC.
- Insert the venipuncture needle of the collection tubing directly into the saline lock.
- Carefully tape the CVC tubing and the collection tubing to the green towel, so that the needle does not disconnect.
- Using a stopcock and sideport syringe can traumatize red blood cells and should only be used to restart flow if other techniques to maintain flow do not work.
- It is frequently necessary to increase flow and prevent clotting by using a clamp to gently "strip" or milk the tubing and push the blood along.

***Completion of collection*:** (figure 2)
- Clamp the collection line near the needle and disconnect it from the vascular access.
- Place the bag on a Mayo stand.
- Cut the venipuncture needle off and dispose it in the sharps container.
- Tie two knots in the tubing, one next to the clamp and one near the bag.

- You can also cut the line near the bag as long as there is at least one knot and one clamp between the cut and the bag.
- Decontaminate the scissors and the Mayo stand using a peroxide-based product (eg. Virox).
- Place the bag in the cooler.
- Collected blood must be transfused within eight hours if kept in a cooler, or four hours if kept at room temperature.

Figure 2. Filled collection bag on scale, needle capped and clamped



Fluid management:

- For phlebotomy without hemodilution, the collected blood is not replaced with crystalloid or colloid (this is different from acute normovolemic hemodilution).
- Normally the collected blood is autotransfused back regardless of the blood loss. Collected blood should be transfused in the OR and not transported elsewhere.
- Otherwise it must be returned to Transfusion Medicine and discarded. All supplies must be returned to Transfusion Medicine.

2.4 Outcomes and Timeline

Outcome Measures	Time-points of evaluation
Three methods will be used independently. In the operating room, all blood and fluid aspirated from the abdomen will be measured accurately using graduated suction containers. The amount of irrigation fluid will be carefully monitored and recorded. The weight of all surgical sponges will be measured. This information will be used by 1) the surgeon and 2) anesthesiologist to independently visually estimate blood loss, as is commonly done in clinical practice. In parallel, intraoperative blood loss will also be 3) calculated based on the Flordal equation, using preoperative and day 2 hemoglobin levels.	Day 0 Day 2
Feasibility outcomes (compliance with the interventions, randomization procedures, time to achieve enrollment, blinding procedures, as well as the generation of data for a larger trial addressing blood transfusion)	Various time points
Outcome Measures	**Timepoints of evaluation**
Blood product transfusion rate (packed red blood cells, fresh frozen plasma, cryoprecipitate, albumin, others)	Day 7 Day 30
Overall morbidity rate and serious morbidity rate (Dindo-Clavien grade 3a or greater) (Appendix 1)	Day 30
Perioperative overall morbidity, mortality, and adverse events	Day 7
Surgeon perception scale (Appendix 2)	Day 0

2.5 Sample Size

Based on internal data obtained at the study center in 2011-2012, the mean intraoperative blood loss in major liver resections is 777 ± 547 mL (n=21). With phlebotomy, the median blood loss was 400 mL [39]. Assuming a reduction in mean blood loss with phlebotomy from 775 mL to 400 mL (standard deviation 500 mL), one requires 56 patients to achieve 80% power and 5% alpha error. Assuming that the surgical plan for liver resection would be abandoned in 10% of patients after randomization [40], one would require randomization of 62 patients.

2.6 Recruitment

Patients of the Liver and Pancreas Unit will be considered for enrollment. All patients being considered for elective liver resection will be seen by an attending surgeon in the outpatient clinic.

3 Methods: Assignment of Interventions

3.1 Allocation

Consecutive patients will be randomized in a 1:1 (phlebotomy + standard practice, or just standard practice) allocation ratio to the two arms of the study, with stratification by indication for resection and the use of permuted blocks of variable length (2, 4, and 6). The randomization scheme will be created using sealedenvelopes.com by the study coordinator; the PI will be blinded. Verification of eligibility will be done by the surgeons in clinic, and managed by the coordinator prior to randomization. The randomization sequence will then be placed in a sealed double-opaque envelope to be given to the anesthesiologist the morning of the participant's surgery. Enrolled patients will be randomized once surgery is underway and the surgeon confirms that a major liver resection will in fact take place. Randomization will thus be in effect and the allocation will be revealed to the anesthesiologist, who will carry out the intervention or control arm, as appropriate.

3.2 Blinding

The patient will be blinded to the intervention, as allocation will be revealed following induction of general anesthesia. The anesthesiologist, operating room nurses, and study coordinator will not be blinded to the intervention, as this is clearly impractical in this setting.

The surgeon will be blinded to the intervention. Blinding of the surgeon will be completed by carrying out all physical steps necessary for phlebotomy for both treatment arms, including placing patient in Trendelenburg position, lifting the bed up, preparing the necessary IV tubing, and connecting the IV tubing to the CVC or peripheral IV. Furthermore, all equipment necessary for phlebotomy will be set up before revealing the trial allocation and the actual blood collection will take place behind large sterile drapes in order to maintain blindness. Following completion of the phlebotomy, the collection bag will be placed within a Canadian Blood Services transfusion card box and kept in the operating room. At the time of auto-transfusion of the whole blood, the collection bag and tubing will be wrapped in opaque green towels, so as to prevent the surgeon from knowing what is being given. In the case of randomization to the standard of care, a plain saline bag will be hooked up and wrapped in green towels in a similar fashion.

All operating room personnel will be instructed prior to the onset of surgery to maintain blindness for the surgeon and to not openly discuss the intervention. Large signs will be posted on the operating room doors leading in and out of the operating room so as to avoid discussing openly the intervention at times of shift change or turnover in nursing personnel. Blinding of the surgeon will constitute an element of feasibility that is being tested in this trial.

The anesthesiologist time will not be blinded. In the event that the patient should require a blood transfusion during the liver resection, the anesthesiologist will proceed to transfuse the phlebotomized blood (phlebotomy arm) or allogeneic packed red blood cells (standard practice arm) at the time where he/she judges to be the most clinically appropriate and in accordance with the study transfusion protocol. For the first unit transfused, the whole blood collection bag or unit of allogeneic packed red blood cell would be concealed from the surgeon by wrapping it in a green towel. Any subsequently transfused units of allogeneic packed red blood cells would not be required to be wrapped in a green towel, as these units would be in addition to the autologous blood or the first allogeneic unit, thus maintaining blinding. At any time during the study, the attending anesthesiologist can choose to unblind the surgeon for patient safety reasons.

4 Data Collection, Management, and Analysis

4.1 Data Collection Methods

Case report forms (CRFs) were created in collaboration with the surgical and anesthesiology teams to ensure that all relevant data would be collected. These CRFs consist of 1) Demographics and medical history details, 2) Intraoperative details – Surgeon, 3) Intraoperative details – Anesthesiologist, and 4) Postoperative details. Moreover they contain some source data.

The following points are source documents in the Intraoperative details – Surgeon CRF:

7. Liver appearance

11. Who did the transection?
12. Transection time
13. EBL
14. IF surgeon thinks phlebotomy was implemented
15. Was blinding maintained?
16. Surgical perception scale of how the surgery went.

The following points are source documents in the Intraoperative details – Anesthesiologist CRF:

7. Blood loss prior to parenchymal transection
8. Hemoglobin levels
9. Systolic blood pressure at start of resection
10. Systolic blood pressure at end of resection
11. Urine output (intraoperative)
13. Start resection time
14. End resection time
15. Hemodynamics including: time, CVP and CI, SVV, U/O for different times in the surgery
17. Target total volume for collection bags
18. Target total blood weight
19. Target weight of bag 1
20. Target weight of bag 2
21. Start weight of each bag, and the different times and weight of bag as it was filling
23. Net weight of blood on sponges
24. Volume in suction containers (use graduated container)
25. Volume of irrigation fluid.
26. Estimate of body fluids such as bile, ascites.
27. Estimate of other blood loss (drapes, gowns, etc.)
28. Anesthesiologist's estimate for EBL
29. Was blinding maintained from surgeon?
30. Was blinding maintained from fellow, if present?

The following points are source documents in the Post-operative details CRF:

13. Adverse Events and their grades: Adverse Events will be found in the electronic patient charts and will be graded on the Dindo-Clavien scale by the PI.

The surgeon, anesthesiologist and study coordinator are responsible for completing different sections of the CRF. All parties will receive briefing on the content of the CRF to ensure that the forms are filled out in a consistent manner.

4.2 Data Management

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database. For each study patient, relevant preoperative, intraoperative, and postoperative data will be collected by the study coordinator using the CRF (Appendix 4), and then entered into a password-protected database. The hard copies of the CRFs will be kept in a locked and secure drawer in the Liver and Pancreas Unit of The Ottawa Hospital by the study coordinator.

4.3 Statistical Methods

Three different intraoperative blood loss measurements will be used for analysis. Measurements will be taken from: a) surgeon estimation, b) anesthesiologist estimation, and c) calculated measure of blood loss [38]. Each measure of blood loss will be reported separately, in addition to computing the mean of the three methods. The mean difference in blood loss between the two trial interventions will be compared using unpaired t tests with 95% confidence intervals.

Continuous secondary outcomes will be examined using unpaired t tests, while dichotomous secondary outcomes will be reported using chi-square or Fisher's tests, as appropriate.

Primary, secondary, and feasibility outcomes will be analyzed after the last trial patient has been followed for 30 days. Safety data will be compiled by the study statistician in accordance with the trial Monitoring Plan and reviewed by a Data Safety and Monitoring Board.

The primary outcome of intraoperatobe blood loss will be compared based on indication for liver surgery (hepatocellular carcinoma or cholangiocarcinoma vs other malignant/benign indications) and based on other methods for blood loss prevention (inflow occlusion, tranexamic acid, CVP <5 cm H_2O), while feasibility outcomes will be reported using descriptive statistics.

5 Methods: Monitoring

5.1 Data Monitoring

The PI, co-investigators, and the study coordinator will comprise the trial Executive Committee. The Executive Committee will meet at least twice per year to review the trial progress. The PI, study coordinator, and the group of trial anesthesiologist will comprise trial Steering Committee. This committee will implement the study and aid in the review of all study procedures. The Steering Committee will meet at least twice per year to ensure the correct implementation of the study protocol.

A trial Monitoring Plan will be created together with the OHRI Clinical Research Facilitator & Monitor. A Data Safety and Monitoring Board (DSMB) will also be appointed and will have full responsibility for one interim analysis for safety and monitoring of response variables for adverse events while the trial is ongoing. This committee will function independently from all other study committees and serve in an advisory role to the Executive and Steering committees. The DSMB will recommend termination or continuation of the trial based on interim analyses.

5.2 Harms

The PI or co-investigator will determine if any serious and unexpected adverse events occur from randomization to post-op day 30. The study coordinator and PI, or co-investigator will examine changes in laboratory values, vital signs and clinical data and will determine if the changes are clinically important and different from what is expected during treatment of participants having undergone hepatic surgery and general anesthesia.

5.2.1 Adverse Events

As perioperative morbidity/complications represent an important secondary outcome in this trial, adverse events (AEs) will be carefully monitored and recorded. AEs can generally be described as any unfavorable and unintended sign, symptom or disease temporarily associated with the treatment, whether or not related to the study treatment.

For the purpose of this trial, any surgical, medical, or anesthesia-related AE that deviates from the usual care of patients undergoing major liver resection will be considered. All such AEs will be collected and recorded in the study AE Source From by the PI and/or study coordinator. The PI will then assign a grading to this AE, based on the Dindo-Clavien classification of perioperative complications (Appendix 1).

The following will thus not be considered AEs:

a. Intraoperative: bleeding (unless deemed unusually severe by the PI), hypotension (unless deemed unresponsive to usual mitigation strategies), oliguria
b. Postoperative: pain, hypotension (unless deemed unresponsive to usual mitigation strategies), oliguria, nausea, vomiting, sore throat, confusion (unless deemed related to medication), muscle aches, pruritus, chills, chest pain (unless deemed to be related to a defined AE such as acute coronary syndrome, etc.), anemia not requiring a transfusion, electrolyte disturbances (unless they do not respond to usual replacement therapy)

Any AE that is graded as Dindo-Clavien grade 3a or greater will be considered a severe adverse event (SAE). SAEs will be recorded on the study SAE Case Report Form (Appendix 5). All SAEs will be further assessed by the PI for expectedness and relatedness to the study procedures. On that basis, unexpected SAEs will be reported to the REB.

5.3 Auditing

The study may be monitored or audited in accordance with the current approved protocol, GCP, and relevant regulations and standard operating procedures.

6 Ethics and Dissemination

6.1 Research Ethics Approval

The protocol, informed consent forms, and any other study material will be submitted to the OHSN-REB for written approval. The Investigator will submit and, where necessary, obtain approval from the OHSN-REB for all substantial amendments to the original approved documents.
The principal investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

6.2 Protocol Amendments

If any protocol amendment or modification takes place, approval from the REB will be obtained before implementing any change. Once REB approval is obtained, the PI will brief all relevant parties (i.e. surgeons, anesthesiologists).

6.3 Consent

Once a decision is made to offer surgery to the patient, the attending surgeon will obtain written consent for the surgery. At this time, the patient will also be screened for eligibility based on the type of proposed resection, as well as any exclusion criteria. The Trial Eligibility Form will be filled and signed by the surgeon, whether or not a patient is enrolled (Appendix 3). The surgeon will introduce the study and will obtain verbal permission from the patient that the study coordinator can approach them to go over the consent form with them. Once the clinical encounter is completed, the study coordinator will meet or call the patient to explain the consent form and present the study in detail: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. In addition, sometimes it is possible that the study coordinator cannot meet with the potential trial participant at the time of their clinical assessment. If the study coordinator is unavailable but the patient meets the criteria for the trial, the surgeon will introduce the study and give a copy of the consent form for review to the patient. Once the clinical encounter is completed, the study coordinator will call the patient to review the consent form with them and present the study in detail, risks and benefits will be provided, and a verbal consent will be obtained. On the day of the patient's preadmission appointment, the coordinator will meet with the patient and get written signed consent,

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their family physician or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. A French version of the Consent Form will also be available at all times.

6.4 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database. PHI and PII recorded for this study will include name, medical record number, medical history, test results, gender, and month/year of birth. PHI and PII will be maintained in a secure, password-protected, master study list accessible only to the investigators and the study coordinator. This file will be linked to other study documents, forms and databases by way of a unique study ID. The master study list will be maintained exclusively on Ottawa Hospital secure servers. All other study materials will be accessible only by study investigators and will be maintained on the Ottawa Hospital server. Computer access to these documents will be made from the HPB surgery office, a secure office environment within the Ottawa Hospital. Any data derived from the study and released to the DSMB or to the study statistician will be completely de-identified.

6.5 Declaration of Interests

There are no conflicts of interest to declare.

6.6 Access to Data

All collected forms will be computerized into a single dataset and delivered to the trial statistician at the Ottawa Hospital Research Institute Methods Centre. An interim analysis for safety will be carried out and presented to the DSBM. The data will be presented to the DSMB by the study coordinator. The primary investigator will not have access to these data until completion of the study.

6.7 Ancillary and Post-trial Care

There is no ancillary and post-trial care to report.

6.8 Dissemination Policy

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by a Canadian Surgical Research Fund grant. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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8 Appendices

8.1 Appendix 1: Dindo-Clavien Classification of Surgical Complications [from 35]

Grades	Definition
Grade 1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade 3	Requiring surgical, endoscopic or radiological intervention
3a	Intervention not under general anesthesia
3b	Intervention under general anesthesia
Grade 4	Life-threatening complication (including CNS complications*), requiring IC/ICU-management
4a	Single organ dysfunction (including dialysis)
4b	Multi organ dysfunction
Grade 5	Death of a patient

*Brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit.

8.2 Appendix 2: PRICE trial surgeon perception scale

PRICE TRIAL SURGEON PERCEPTION SCALE

To be filled by the surgeon immediately following liver parenchymal transection

Please rate the overall ease/difficulty with which this liver resection was completed:									
1	2	3	4	5	6	7	8	9	10
Easiest				Average					Hardest

Please rate the ease/difficulty with which the liver parenchymal transection was completed:									
1	2	3	4	5	6	7	8	9	10
Easiest				Average					Hardest

Please rate your impression of blood loss during the parenchymal transection:									
1	2	3	4	5	6	7	8	9	10
None/minimal				Average					Most/excessive

Please rate your impression of the filling status of the hepatic veins during the parenchymal transection:									
1	2	3	4	5	6	7	8	9	10
Empty/flat				Average					Full/excessive

Surgeon signature: _____

Date: _____

8.3 Appendix 3: PRICE trial eligibility form

PRICE TRIAL ELIGIBILITY FORM

To be filled by the surgeon who consents the patient for <u>any</u> liver surgery

<u>Each of criteria must be fulfilled</u>:

☐ The patient is able to give informed consent for participation in the study.

☐ The patient is aged 18 years or above.

☐ The patient has been consented for an elective **major** liver resection (3 or more liver segments being operated upon).

<u>None of the following exclusion criteria can be present</u>:

Exclusion Criteria	Circle Y/N, add values and date where needed	Sign off (initials)
The patient has been consented for an elective **minor** liver resection (less than 3 liver segments being operated upon).	Y / N	---
Age <18 years	Y / N	---
Pregnancy	Y / N	---
Refusal of blood products	Y / N	---
Active cardiac conditions ➢ Unstable coronary syndromes ➢ Decompensated HF (NYHA functional class IV; worsening or new-onset HF) ➢ Significant arrhythmias ➢ Severe valvular disease	Y / N	---
History of significant cerebrovascular disease	Y / N	---
Presence of active infection	Y / N	---
Preoperative autologous blood donation	Y / N	---
Renal dysfunction (patients with an estimated GFR <60	GFR: _____	

mL/min)	Date of blood collection: _____	
Abnormal coagulation parameters (INR >1.5 not on warfarin and/or platelets count <100 $X10^9$/L)	INR: _____ Date of blood collection: _____ Platelet count: _____ Date of blood collection: _____	
Evidence of hepatic metabolic disorder (bilirubin >35 μmol/L)	Bilirubin: _____ Date of blood collection: _____	
Hemoglobin <100 g/L	Hemoglobin: _____ Date of blood collection: _____	

Surgeon signature: _____

Date: _____

8.4 Appendix 4: PRICE trial Case Report Forms (CRFs) and source documentation

Demographics and medical history details

1. Date of birth (month/year):

   _____

2. Gender m / f

3. Comorbidities (please check all that apply)

   ☐ Current smoker
   - Number of pack years _____

   ☐ Former smoker
   - Number of pack years _____
   - Years since quitting _____

   ☐ Never smoked

☐ Myocardial infarction (history, not ECG changes only)

☐ Congestive heart failure

☐ Peripheral vascular disease (incl. AAA ≥6 cm)

☐ Cerebrovascular accident (CVA with mild or no residua or TIA)

☐ Hemiplegia

☐ Dementia

☐ COPD

☐ Rheumatologic disease

☐ Peptic ulcer disease

☐ Mild liver disease (no portal hypertension, incl. chronic hepatitis)

☐ Moderate/severe liver disease

☐ Other underlying liver disease

_____

☐ Diabetes mellitus without complication (excludes diet controlled alone)

☐ Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, brittle diabetes)

☐ Moderate/severe renal disease

☐ Malignant neoplasm without metastasis (exclude if >5 years from diagnosis)

☐ Metastatic solid tumor

☐ Leukemia (acute or chronic)

☐ Lymphoma

☐ AIDS (exclude if only HIV positive)

☐ Hepatitis B

☐ Hepatitis C

☐ Cirrhosis

☐ Other

_____

4. Previous abdominal surgeries (please list):_____

_____

5. Previous liver surgeries: _____

_____

6. Weight: _____kg and height: _____cm
7. Pre-operative weight loss (please provide numerical value and indicate units):

_____

8. History of jaundice ☐ Yes ☐ No
9. History of cholangitis ☐ Yes ☐ No
10. Biliary drainage: ☐ Yes ☐ No

    ☐ Stent ☐ PTC

    Date of first drainage: _____
11. Preoperative chemotherapy (within 6 months of surgery): y / n

    If yes, which type (and number of cycles): _____

    _____
12. Preoperative PV embolization: y / n
13. Intrabiliary stent placement: y / n

    Date of intrabiliary stent placement: _____

    Method of intrabiliary stent placement:

    ☐ ERCP ☐ PTC
14. Preoperative laboratory studies (within 90 days of surgery)

Blood work	Blood work results	Date of blood work
Hemoglobin (g/L)		
INR		
Platelet ($x10^9$/L)		
Total bilirubin (umol/L)		
Neutrophils ($x10^9$/L)		
Lymphocytes ($x10^9$/L)		
Albumin (g/L)		
AST (U/L)		
ALT (U/L)		
GGT (U/L)		
ALP (U/L)		
Creatinine (umol/L)		
CA19-9 (U/L)		
CEA (ug/L)		
AFP (ug/L)		

Intraoperative details – Surgeon

1. Surgeon: _____
2. Hepatobiliary fellow present: y / n
3. Resident present: y / n
4. Main liver procedure

    ☐ Right hepatectomy

    ☐ Right extended hepatectomy

    ☐ Left hepatectomy

    ☐ Left extended hepatectomy

    ☐ En bloc caudate resections

☐ Segmental resection

Description: _____

5. Extrahepatic procedures: _____

6. Number of segments resected: ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

7. Liver appearance
   - ☐ Normal
   - ☐ Blue
   - ☐ Fatty
   - ☐ Cirrhosis
   - ☐ Other: _____

8. Transection technique(s):
   - ☐ Crush-clamp
   - ☐ Water jet
   - ☐ Thunder beat
   - ☐ Ligature
   - ☐ harmonic
   - ☐ Staple
   - ☐ Hemopatch
   - ☐ Surgicel
   - ☐ Floseal
   - ☐ Argon
   - ☐ Tachosil
   - ☐ Cautery

9. In flow control:
   - ☐ Intrahepatic transection

☐ Extrahepatic transection

10. Pringle: y / n

☐ IF yes:

☐ Intermittent

☐ Continuous

☐ Total time (min): _____

11. Who did the transection:

☐ Surgeon

☐ 2 surgeons

☐ Surgeon + fellow

☐ Surgeon + resident

12. Transection time (min) _____

13. EBL (ml): _____

14. Do you think phlebotomy was implemented? y / n

15. Was blinding maintained? y / n

16. SURGEON PERCEPTION SCALE:

(To be filled by the surgeon immediately following liver parenchymal transection)

Please rate the overall ease/difficulty with which this liver resection was completed:
1 2 3 4 5 6 7 8 9 10
Easiest Average Hardest

Please rate the ease/difficulty with which the liver parenchymal transection was completed:
1 2 3 4 5 6 7 8 9 10
Easiest Average Hardest

Please rate your impression of blood loss during the parenchymal transection:
1 2 3 4 5 6 7 8 9 10
None/minimal Average Most/excessive

Please rate your impression of the filling status of the hepatic veins during the parenchymal transection: 1 2 3 4 5 6 7 8 9 10 Empty/flat Average Full/excessive

Surgeon Signature: _____

Intraoperative details – Anesthesiologist

1. Anesthesiologist: _____
2. Blood volume removed (ml) _____
3. ASA classification
   - ☐ I – Healthy patient
   - ☐ II – Mild systemic disease, no functional limitation
   - ☐ III – Severe systemic disease, definite functional limitation
   - ☐ IV – Severe systemic disease, constant threat to life
   - ☐ V – Moribund patient, not expected to survive
   - ☐ E – Emergency situation
4. Intraoperative fluid given

   Crytalloid (ml) _____

   Colloid (ml) _____
5. Pressors given: y / n

   a) If yes, type and total dose: _____
6. Epidural: y / n

   a) If yes, list drugs: _____
7. Blood loss prior to parenchymal transection: _____
8. Hemoglobin level _____
9. Systolic blood pressure at start of resection _____
10. Systolic blood pressure at the end of resection _____

11. Urine output (intraoperative, ml) _____

12. Transfusion of blood products (circle one) y / n

If yes, please specify product and number of units:

- ☐ Packed RBC: _____
- ☐ FFP: _____
- ☐ Platelets: _____
- ☐ Albumin: _____

13. Start resection: _____

14. End resection: _____

15. HEMODYNAMICS:

	Time	CVP	CI	SVV	U/O (Cumul.)
Pre-Incision:					
30-60 min post incision:					
Pre Phlebotomy:					
Post Phlebotomy/Pre-Resection:					
Post resection:					
Post transfusion/Fluid bolus					
Start Wound Closure:					

16. Patient weight: _____

17. Target total volume (7-10 mL/kg)		
18. Target total blood weight		Weight = Vol. x Spec. Gravity (1.0506)
19. Target weight Bag #1 (Max 473g)		Note 450 mL = 473g
20. Target blood weight Bag #2		

21.

	Bag #1		**Bag #2**
Starting Wt.		**Starting Wt.**	
Target Wt.		**Target Wt.**	

Time	Weight

Time	Weight

22. Start Transection time: _____ CVP: _____ Cl: _____ SVV: _____ U/O: _____

Estimated Blood Loss at end of case:

23. Net weight of blood on sponges	
24. Volume in suction containers (use graduated container)	
25. Volume of irrigation fluid.	
26.Estimate of body fluids such as bile, ascites.	
27. Estimate of other blood loss (drapes, gowns etc.)	
28. Anesthesiologist's estimate:	

29. Was blinding maintained from surgeon? y / n

30. Was blinding maintained from Fellow? y / n

31. Net EBL: _____

Anesthesiologist Signature: _____

Postoperative details

1. Immediate postop (PACU) lab results:

    a. Hemoglobin (g/L): _____

    b. Platelet count (x10^9/L): _____

    c. INR: _____

    d. Creatinine (umol/L): _____

    e. Bilirubin (umol/L): _____

    f. AST (U/L): _____

    g. ALT (U/L): _____

    h. PO4 _____

2. POPD #: _____

    a. Hemoglobin (g/L): _____

    b. Platelet count (x10^9/L): _____

    c. INR: _____

    d. Creatinine (umol/L): _____

    e. Bilirubin (umol/L): _____

    f. AST (U/L): _____

    g. ALT (U/L): _____

    h. PO4 _____

3. POPD #: _____

    a. Hemoglobin (g/L): _____

    b. Platelet count (x10^9/L): _____

    c. INR: _____

    d. Creatinine (umol/L): _____

    e. Bilirubin (umol/L): _____

f. AST (U/L): _____

g. ALT (U/L): _____

h. PO4 _____

4. POPD #: _____

a. Hemoglobin (g/L): _____

b. Platelet count (x10^9/L): _____

c. INR: _____

d. Creatinine (umol/L): _____

e. Bilirubin (umol/L): _____

f. AST (U/L): _____

g. ALT (U/L): _____

h. PO4 _____

5. POPD #: _____

a. Hemoglobin (g/L): _____

b. Platelet count (x10^9/L): _____

c. INR: _____

d. Creatinine (umol/L): _____

e. Bilirubin (umol/L): _____

f. AST (U/L): _____

g. ALT (U/L): _____

h. PO4 _____

6. POPD #: _____

   a. Hemoglobin (g/L): _____

   b. Platelet count (x10^9/L): _____

   c. INR: _____

   d. Creatinine (umol/L): _____

   e. Bilirubin (umol/L): _____

   f. AST (U/L): _____

   g. ALT (U/L): _____

   h. PO4 _____

7. POPD #: _____

   a. Hemoglobin (g/L): _____

   b. Platelet count (x10^9/L): _____

   c. INR: _____

   d. Creatinine (umol/L): _____

   e. Bilirubin (umol/L): _____

   f. AST (U/L): _____

   g. ALT (U/L): _____

   h. PO4 _____

8. POPD #: _____

   a. Hemoglobin (g/L): _____

   b. Platelet count (x10^9/L): _____

   c. INR: _____

   d. Creatinine (umol/L): _____

   e. Bilirubin (umol/L): _____

f. AST (U/L): _____

g. ALT (U/L): _____

h. PO4 _____

9. Length of stay (d) _____

10. Post-operative transfusion of blood products (circle one) y / n

11. POD# _____

- If yes, please specify product and number of units:
  - ☐ Packed RBC: _____
  - ☐ FFP: _____
  - ☐ Platelets: _____
  - ☐ Albumin: _____

_____ _____

RC signature Date

****The rest of this form is to be completed by a surgeon**

12. Diagnosis

- ☐ Metastatic colorectal
- ☐ Metastatic other (specify)
- ☐ HCC
- ☐ Biliary cancer
- ☐ Other: _____

13. List all adverse events and their grade:

Adverse Event	Grade	MD initial

Full Scale	
Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention
Grade III-a:	intervention not under general anesthesia
Grade III-b:	intervention under general anesthesia
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management
Grade IV-a:	single organ dysfunction (including dialysis)
Grade IV-b:	multi organ dysfunction
Grade V:	Death of a patient

14. Liver pathology (nontumour)

- ☐ Normal
- ☐ Cirrhosis/fibrosis
- ☐ Steatosis/steatohepatitis
- ☐ Other (specify): _____

_____ _____

Surgeon signature Date (dd/mm/yyyy)

8.5 Appendix 5: Adverse Event/Serious Adverse Event Case Report Form

The Ottawa Hospital RESEARCH INSTITUTE | L'Hôpital d'Ottawa INSTITUT DE RECHERCHE

Participant ID # _____

Adverse Event/Serious Adverse Event Case Report Form

"The PRICE Trial: Phlebotomy resulting in controlled hypovolemia to prevent blood loss in major hepatic resections"

AE/SAE #	Description	Start Date	End Date/Ongoing	Date Site Became Aware	Grade	Serious (Y/N)	Expected (Y/N)	Attribution	Outcome	MD Initials & Date

Grade	Attribution	Outcome
1 – Mild	0 - Definite	0 - Fatal
2 – Moderate	1 - Probable	1 – Not recovered/not resolved
3 – Severe	2 - Possible	2 – Recovered w/sequelae
4 – Life Threatening	3 - Unlikely	3 – Recovered w/o sequelae
5 – Death (Fatal)	4 - Unrelated	4 – Recovering/Resolving

8.6 Appendix 6: Informed consent, English and French

PARTICIPANT INFORMED CONSENT FORM

Title of Study: The PRICE Trial: Phlebotomy resulting in controlled hypovolemia to prevent blood loss in major hepatic resections

Principal Investigator (PI): Dr. Guillaume Martel, (613) 737-8899 x76979

Sponsor: Ottawa Hospital Research Institute (OHRI)

Funding: Canadian Surgical Research Fund

Participation in this study is voluntary. Please read this Participant Informed Consent Form carefully before you decide if you would like to participate. Ask the study doctor and study team as many questions as you like. We encourage you to discuss your options with family, friends and/or your healthcare team.

Why am I being given this form?

You are being asked to participate in this research study because you are a patient who will be having a portion of the liver removed surgically (liver resection), here at The Ottawa Hospital. We want to help reduce bleeding during and after this operation. The information we learn from this study will also help us plan a bigger national study in the future.

Why is this study being done?

Major liver surgery, the procedure that you will be having, can sometimes lead to significant blood loss or hemorrhage. Blood loss in liver surgery is a key reason for worse outcomes and complications after surgery. Sometimes, blood loss may require you to have a blood transfusion. Research studies in North American hospitals suggest that up to one quarter of patients require a blood transfusion at the time of surgery or shortly after. Blood transfusions are usually very safe, but they can lead to allergic reactions or to the transmission of infectious diseases in extremely rare cases.

Surgeons and anesthesiologists utilize many techniques to decrease the risk of bleeding and hemorrhage during liver surgery. Many of these techniques will be used during your surgery, as they are part of the standard of care.

The goal of this research is to determine if whole blood phlebotomy will reduce bleeding and blood transfusion in patients having a liver operation.

Phlebotomy is a simple technique for which the anesthesiologist removes one or two pints of blood from you into a special collection bag. This is done in a similar fashion as if you were donating

blood at a blood donation clinic. The exact amount of blood is decided upon based on your body weight (7-10 mL/kg). This will be done while you are asleep and the surgery is underway. You will be carefully monitored by the anesthesiologist. Your blood will never leave the sterile collection bag, specifically designed for that purpose. Once the liver surgery is completed, but before you wake up, your blood will be given back to you.

This technique is thought to decrease the pressure within the large veins of the liver (known as the hepatic veins). As a result, we expect less bleeding while the liver is being cut. As mentioned, once the piece of liver is removed from you, your blood will be given back to you.

We estimate that 62 participants will be enrolled in the study from The Ottawa Hospital.

How is the study designed?

Whether you get the surgery by the usual method or the usual method plus phlebotomy will be decided randomly. Randomization means that you are put into a group by chance, similar to flipping a coin.

This study will be double-blinded, which means that you will not be told in advance if you will have the phlebotomy during surgery or not. Your surgeon will also not know what you are receiving; only the anesthesiologist will be aware of the intervention and only after surgery is underway. Blinding helps to remove any bias or pre-conceived notions from affecting the outcome of the study. You will be told 30 days after surgery.

What is expected of me?

If you decide to participate in this study, you will undergo a major liver resection, as explained by your surgeon. There is nothing required of you as part of this study.

Your stay in hospital and the care you receive will not be affected by this study. After you are discharged from hospital, you will have appointments scheduled to visit your surgeon on a regular basis. This will happen whether you participate in the study or not. If you choose to participate, all data will be collected while you remain admitted in hospital, as well as at the postoperative clinic visits. You will not have anything extra to do. You may be called once by the study coordinator one month after surgery.

How long will I be involved in the study?

Phlebotomy is a short-term intervention. It will only last for the duration of your liver surgery, while you are asleep under anesthesia. All relevant data to be collected after surgery will be available within 30 days of the operation. Your participation in the study will last during the time of surgery and the one telephone call one month after surgery.

Your participation in the study may be stopped for any of the following reasons:

- The study doctor feels it is in your best interest.
- You need treatment that would interfere with the study.
- You do not follow the study staff's instructions.

What are the potential risks I may experience?

It is unlikely that phlebotomy will result in more risk than the standard of care. Previous research using this technique has not shown any special additional risk associated with receiving a

phlebotomy. In fact, previous research suggests that patients receiving phlebotomy bleed less during surgery and have the same risk of complications as other liver surgery patients.

Phlebotomy could theoretically lead to any physiologic effect associated with blood loss. These effects could have implications for any major organ system, due to decreased blood flow. These could include but are not limited to myocardial ischemia (heart attack), cerebrovascular accident (stroke), acute renal failure (kidney failure) possibly requiring dialysis, coagulopathy (blood clotting abnormalities), or hepatic insufficiency (liver failure). That being said, these risks already exist with any liver surgery, simply on the basis of potentially significant blood loss. In order to be considered for liver surgery, you have already been seen by your surgeon and considered fit enough. Patients who are fit enough for liver surgery can also generally tolerate phlebotomy. You were asked to participate in the study because you met special study criteria based on your medical history, and this makes you eligible to participate in our study.

In addition, there is always a small chance of risks that we do not know about. The potential extremely rare additional risks we know about are listed below:

- Potential risk for clerical error with the blood (<1%)
- Theoretical risk of bacterial contamination of the collection bag, tubing, and as a consequence, whole blood (<1%)

Risks of Insurability:

We will take all reasonable steps to keep your research information confidential. Should someone not involved in the research find out that you took part in this research study, or if you choose to share your results (if they are provided to you), there is a possibility that this could affect your insurability under certain policies of insurance, depending on the exclusions in such policies.

Can I expect to benefit from participating in this research study?

You may not receive any direct benefit from your participation in this study. Your participation may allow the researchers to provide better treatments in the future for participants who need the same operation.

This study will select by chance which treatment you will receive. Participants in one arm of this study may do better or worse than participants in the other arm.

Do I have to participate? What alternatives do I have?

You can choose not to participate in this study. If you choose not to participate, you will still receive the usual operation that is done for your liver resection. Your study doctor will discuss this option with you.

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now, and then change your mind later without affecting the medical care, education, or other services to which you are entitled or are presently receiving at this institution.

If I agree now, can I change my mind and withdraw later?

You may withdraw from the study at any time without any impact on your current or future care at this institution.

- If you decide to stop your study participation, you need to tell your surgeon or your nurse before you have your operation.

- You may also choose to discontinue your participation in the study.
- If you withdraw your consent, the study team will no longer collect your personal health information for research purposes, unless it is needed for review of safety.

What compensation will I receive if I am injured or become ill in this study?

In the event of a study-related injury or illness, you will be provided with appropriate medical treatment and care. Financial compensation for lost wages, disability or discomfort due to an injury or illness is not generally available. You are not waiving any of your legal rights by agreeing to participate in this study. The study doctor and The Ottawa Hospital Research Institute still have their legal and professional responsibilities.

Will I be paid for my participation or will there be any additional costs to me?

The phlebotomy procedure will be provided to you free of charge as long as you are participating in the study. However, you will not receive any payment or have to pay for anything if you participate in this study.

How is my personal information being protected?

- If you decide to participate in this study, the investigator(s) and study staff will look at your personal health information and collect only the information they need for this study. "Personal health information" is health information about you that could identify you because it includes information such as your name, address, telephone number, date of birth, new and existing medical records, or the types, dates and results of various tests and procedures.
- Information that identifies you will be released only if it is required by law.
- All information collected during your participation in this study will be identified with a unique study number (for example participant # AB01), and will not contain information that identifies you.
- Documents or samples leaving the Ottawa Hospital will only contain the coded study number.
- A Master List provides the link between your identifying information and the coded study number. This list will only be available to Dr. G. Martel and his staff and will not leave this site.
- The Master List and coded study records will be stored securely.
- You will not be identified in any publications or presentations resulting from this study.
- For audit purposes only, your original study records may be reviewed under the supervision of Guillaume Martel's staff by representatives from:
    - the Ottawa Health Science Network Research Ethics Board (OHSN-REB),
    - The Ottawa Hospital Research Institute.
- Research records will be kept for 10 years, after this time they will be destroyed.
- Research records will be kept for 10 years, as required by the OHSN-REB.

A description of this clinical trial is available on http://www.ClinicalTrials.gov (NCT02548910). This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Do the investigators have any conflicts of interest?

There are no conflicts of interest to declare related to this study.

What are my responsibilities as a study participant?

It is important to remember the following things during this study:

- Ask your study doctor or the study coordinator if you have any questions or concerns.
- Call the study doctor if you experience any side effects, even if you are unsure whether it has anything to do with this study.

Will I be informed about any new information that might affect my decision to continue participating?

You will be told in a timely fashion of any new findings during the study that could affect your willingness to continue in the study. You may be asked to sign a new consent form.

Who do I contact if I have any further questions?

If you have any questions about this study, or if you feel that you have experienced a study-related injury or illness, please contact Dr. Guillaume Martel at 613-737-8899 x76979 or the study staff at 613-737-8899 x 71484.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has reviewed this protocol. The Board considers the ethical aspects of all research studies involving human participants at the Ottawa Hospital Research Institute. If you have any questions about your rights as a study participant, you may contact the Chairperson at 613-798-5555, extension 16719.

Consent to Participate in Research

- I understand that I am being asked to participate in a research study on reduction in blood loss during major liver resection via the phlebotomy procedure.
- This study was explained to me by _____.
- I have read, or have had it read to me, each page of this Participant Informed Consent Form.
- All of my questions have been answered to my satisfaction.
- If I decide later that I would like to withdraw my participation and/or consent from the study, I can do so at any time.
- I voluntarily agree to participate in this study.
- I will be given a copy of this signed Participant Informed Consent Form.

_____	_____	_____
Participant's Printed Name	Participant's Signature	Date

Investigator or Delegate Statement

I have carefully explained the study to the study participant. To the best of my knowledge, the participant understands the nature, demands, risks and benefits involved in taking part in this study.

_____	_____	_____
Investigator/Delegate's Printed	Investigator/Delegate's Signature	Date

Assistance Declaration

Was the participant assisted during the consent process? ❑ Yes ❑ No

❑ The consent form was read to the participant/substitute decision-maker, and the person signing below attests that the study was accurately explained to, and apparently understood by, and consent was freely given by the participant/substitute decision-maker.
❑ The person signing below acted as a translator for the participant/substitute decision-maker during the consent process. He/she attests that they have accurately translated the information for the participant/substitute decision-maker, and believe that the participant/substitute decision-maker has understood the information translated.

_____	_____	_____
Name of Person Assisting (Print)	Signature	Date

French

FORMULAIRE DE CONSENTEMENT ÉCLAIRÉ À L'INTENTION DU PARTICIPANT

Titre de l'étude : L'essai clinique PRICE : phlébotomie et hypovolémie contrôlée visant à prévenir les pertes sanguines lors de résections hépatiques majeures

Chercheur principal : Dr. Guillaume Martel, 613-737-8899 x71053

Sponsor: Institut de recherche de l'Hôpital d'Ottawa (IRHO)

Appui financier: Canadian Surgical Research Fund

Votre participation à cette étude s'effectue sur une base entièrement volontaire. Veuillez lire ce formulaire de consentement soigneusement avant de décider si vous souhaitez participer. Posez au médecin responsable de l'étude et à l'équipe responsable de l'étude autant de questions que vous le souhaitez. Nous vous encourageons à discuter de vos options avec votre famille, vos amis ou votre équipe soignante.

Pourquoi me remet-on ce formulaire ?

On vous invite à prendre part à cette étude de recherche parce que vous allez avoir une opération visant à réséquer une portion de votre foie (résection hépatique), afin de traiter une tumeur dans cette partie du corps et ce, à l'Hôpital d'Ottawa. Cette étude vise à réduire le saignement encouru pendant et après cette chirurgie. L'information acquise durant cette étude servira aussi à la planification d'une autre plus grande étude, à l'échelle nationale.

Pourquoi effectue-t-on cette étude ?

La chirurgie hépatique majeure, la procédure que vous allez avoir, peut parfois occasionner des pertes sanguines importantes ou une hémorragie. Le saignement durant la chirurgie du foie peut entraîner des résultats défavorables ou complications suite à la chirurgie. Les pertes sanguines peuvent aussi entraîner une transfusion sanguine. Plusieurs études nord-américaines ont démontré que jusqu'à un quart des patients requirent une transfusion sanguine pendant ou après la chirurgie. Malgré que les transfusions sanguines soient d'habitude très sécuritaires, elles peuvent très rarement amener des réactions allergiques ou la transmission de maladies infectieuses.

Les chirurgiens et anesthésistes se servent de techniques variées afin de minimiser le risque de saignement ou de transfusion durant toute chirurgie hépatique. Plusieurs de ces techniques seront utilisées durant votre opération, puisqu'elles font partie du standard de pratique.

Cette étude a pour but de déterminer si la phlébotomie de sang complet peut amener une réduction du saignement ou du taux de transfusion chez les patients subissant une chirurgie du foie.

La phlébotomie est une technique simple pour laquelle l'anesthésiste vous retirera un ou deux pintes de sang et ce dans un sac de collection spécialement conçu. La procédure est semblable à tout don de sang, qui pourrait avoir lieu dans une collecte de dons. La quantité exacte de sang à prélever est déterminée par votre poids (7-10 mL/kg). Le prélèvement aura lieu lorsque vous serez endormi sous anesthésie, durant la chirurgie. L'anesthésiste vous surveillera étroitement durant

toute la procédure. Votre sang ne quittera jamais le sac de collection stérile, conçu à cet effet. Suite à votre chirurgie du foie, votre propre sang vous sera redonné et ce avant que vous vous réveilliez.

Il est postulé que cette technique sert à diminuer la pression dans les grandes veines du foie (les veines sus-hépatiques). Par conséquent, nous nous attendons à encourir moins de saignement pendant la coupe du foie. Tel qu'indiqué, votre sang vous sera redonné une fois que nous avons terminé d'enlever le morceau de foie.

Nous anticipons la participation d'environ 62 patients à l'Hôpital d'Ottawa.

Quelle est la méthodologie de l'étude ?

L'affectation à la chirurgie avec phlébotomie plus méthode usuelle ou à la méthode usuelle s'effectuera aléatoirement. Cela signifie que vous serez affecté à un groupe au hasard, comme tirer à pile ou face.

Cette étude s'effectuera à double-insu, ce qui signifie que vous ne serez pas informé du groupe auquel vous aurez été affecté (phlébotomie ou méthode usuelle). Votre chirurgien ne saura pas à quel groupe vous aurez été affecté; seul votre anesthésiste sera au courant de l'intervention et ce uniquement lorsque votre chirurgie sera en cours. Les études à l'insu permettent d'éliminer tout biais ou toute notion préconçue qui pourraient influer sur les résultats de l'étude. Vous serez informé du groupe auquel vous avez été affecté 30 jours après la chirurgie.

Que serai-je appelé à faire ?

Si vous décidez de participer à cette étude, vous allez subir une résection hépatique majeure, telle qu'expliquée par votre chirurgien. Vous n'aurez rien à faire de spécial durant cette étude.

Votre séjour à l'hôpital et les soins que vous recevrez ne seront pas affectés par votre participation à cette étude. Suite à votre sortie de l'hôpital, vous aurez des rendez-vous de contrôle avec votre chirurgien, sur une base régulière. Ce sera le cas, que vous participez à l'étude ou non. Si vous choisissez de participer à l'étude, toutes les données nécessaires seront amassées à partir de votre dossier médical durant votre hospitalisation, ainsi que durant vos rendez-vous en clinique suite à votre congé. Vous n'aurez rien de spécial à faire. Il est possible que la coordinatrice de l'étude vous appelle une fois, un mois après la chirurgie.

Quelle sera la durée de ma participation à cette étude ?

La phlébotomie est une technique utilisée à court terme. Cette dernière se limite au temps de votre chirurgie, pendant que vous êtes sous anesthésie. Toutes les données nécessaires à l'étude seront disponibles durant les premiers 30 jours suivant votre chirurgie. Pendant cette période, vous n'aurez rien à faire. Votre participation à l'étude durera le temps de votre chirurgie, ainsi que pour un appel téléphonique environ 30 jours après votre chirurgie.

On pourrait mettre fin à votre participation à cette étude, pour l'une ou l'autre des raisons suivantes :

- Le médecin de l'étude croit que cela est dans votre intérêt fondamental.
- Vous avez besoin de traitements additionnels qui pourraient interférer avec l'étude.
- Vous ne respectez pas les consignes du personnel de l'étude.

Quels sont les risques possibles associés à ma participation à cette étude ?

Il est peu probable que l'utilisation de la phlébotomie se traduise en une augmentation du taux de complications, par rapport à la technique usuelle. Les études de recherche antérieures portant sur la phlébotomie n'ont pas démontré de risques particuliers additionnels reliés à l'utilisation de cette technique. En fait, ces études semblent démontrer que les patients recevant une phlébotomie subissent moins de pertes sanguines et ce avec le même taux de complications que les autres patients ayant une chirurgie du foie.

La phlébotomie peut théoriquement occasionner toute réaction physiologique reliée à la perte de sang. Ces réactions pourraient avoir des effets pour tous les systèmes d'organes majeurs et ce suite à une réduction du flux sanguin régional. Ces effets pourraient inclure (mais ne sont pas limités à ces derniers) un infarctus du myocarde (crise cardiaque), un accident cérébrovasculaire (ACV), une défaillance rénale aiguë (défaillance des reins) qui pourrait nécessiter de la dialyse, une coagulopathie (anomalie reliée aux facteurs de coagulation), ou une insuffisance hépatique (défaillance du foie). Ceci étant dit, tous ces risques existent déjà avec toute chirurgie hépatique en vertu du potentiel de pertes sanguines importantes. De plus, tout patient étant considéré pour une chirurgie hépatique doit au préalable avoir été vu et déclaré assez en santé par le chirurgien. Les patients qui sont généralement assez en santé pour subir une chirurgie hépatique sont aussi généralement capables de tolérer une phlébotomie. On vous invite à participer à cette étude parce que vous remplissez certains critères de sélection basés sur votre historique médical; par conséquent on vous considère éligible à participer à cette étude.

De plus, il existe toujours une petite possibilité de risques qui nous sont inconnus. Les risques potentiels qui sont extrêmement rares sont les suivants :

- Risque potentiel d'erreur administrative avec le sang (<1 %)
- Risque théorique de contamination bactérienne du sac de collection, de la tubulure et, par conséquent, du sang (<1 %)

Risques relatifs à l'assurabilité :

Nous prendrons toutes les mesures nécessaires pour maintenir la confidentialité de vos renseignements. Si une personne n'intervenant pas dans cette étude de recherche devait apprendre que vous avez pris part à cette étude, ou si vous deviez choisir de partager vos résultats (advenant que ces derniers vous soient remis), il est possible que cette information puisse influer sur votre assurabilité, selon la police d'assurance, et en fonction des exclusions relatives à de telles polices.

Puis-je m'attendre à retirer des bienfaits en lien avec ma participation à cette étude?

Il est possible que vous ne retiriez aucun avantage direct en prenant part à cette étude. Votre participation à cette recherche pourrait aider les chercheurs à améliorer les soins de patients ayant besoin de la même opération à l'avenir.

L'affectation à la chirurgie avec phlébotomie s'effectuera aléatoirement. Les participants affectés à un groupe pourraient avoir de meilleurs ou pires résultats que ceux affectés à l'autre groupe

Suis-je tenu de participer ? Quelles sont mes autres options ?

Vous pouvez choisir de ne pas prendre part à cette étude. Si vous choisissez de ne pas y participer, vous serez opéré afin de réséquer votre tumeur, selon la technique usuelle en chirurgie hépatique. Votre médecin de l'étude discutera de ces options avec vous.

Votre participation à cette étude s'effectue sur une base entièrement volontaire. Vous pouvez choisir de ne pas prendre part à cette étude, ou d'y prendre part maintenant et changer d'idée plus tard, sans que votre décision n'influe sur vos soins médicaux, votre éducation ou tout service auquel vous avez droit ou dont vous bénéficiez actuellement dans cet établissement.

Puis-je changer d'idée plus tard et mettre fin à ma participation ?

Vous avez le droit de retirer votre consentement en tout temps, sans que votre décision n'influe sur la qualité de vos soins actuels ou éventuels dans cet établissement.

- Si vous décidez d'interrompre votre participation à l'étude, vous devez le communiquer à votre chirurgien ou infirmière avant votre opération.
- Vous pouvez également choisir de mettre fin à votre participation à l'étude.
- Si vous retirez votre consentement, l'équipe de l'étude cessera de recueillir vos renseignements personnels sur la santé aux fins de la recherche, à moins que ces derniers soient requis à des fins de révision de la sécurité.

À quel type d'indemnisation puis-je m'attendre si je devais subir un préjudice ou tomber malade en lien avec ma participation à cette étude ?

Dans le cas peu probable d'effets secondaires ou de blessures, nous vous fournirons les traitements ou les soins médicaux nécessaires. La compensation financière pour la perte de revenu, l'invalidité ou tout malaise associé à une blessure n'est normalement pas offerte. En participant à cette étude, vous ne renoncez à aucun de vos droits légaux. Le médecin de l'étude et l'Institut de recherche de l'Hôpital d'Ottawa seront toujours tenus de respecter leurs responsabilités professionnelles et légales.

Serai-je rémunéré pour ma participation à cette étude ou encourrai-je des frais additionnels en prenant part à cette étude ?

La phlébotomie sera effectuée gratuitement, tant que vous participez à cette étude. Vous ne recevrez aucun paiement et n'aurez rien à débourser pour participer à cette étude.

Comment assurera-t-on la protection de mes renseignements personnels ?

- Si vous décidez de prendre part à cette étude, on vous assignera un code numérique qui sera utilisé pour toute la durée de l'étude et servira à identifier votre dossier, vos documents et résultats.
- Une liste maîtresse servira de lien entre vos renseignements personnels et votre code numérique de l'étude. Seuls le docteur Martel ou son personnel pourront accéder à cette liste et cette dernière ne sera pas transmise à l'extérieur du site.
- La liste maîtresse et les dossiers codés de l'étude seront entreposés de manière sécuritaire.
- La divulgation de vos renseignements d'identification ne sera permise que si requise par la loi.
- Tout document ou échantillon transmis à l'extérieur de l'Hôpital d'Ottawa sera codé à l'aide d'un code numérique de l'étude. Aucune publication ou présentation résultant de cette étude ne pourra servir à vous identifier.
- Les représentants des établissements suivants pourront procéder à l'examen de vos dossiers médicaux originaux, sous la supervision du personnel du docteur Martel, uniquement à des fins de vérification :
    - Le Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa (CÉR-RSSO)
    - l'Institut de recherche de l'Hôpital d'Ottawa.

- Les dossiers de recherche seront conservés pour une période de 10 années, conformément aux exigences de CÉR-RSSO
- Une fois la période de rétention terminée, tous les dossiers papier seront déchiquetés ou jetés aux rebuts confidentiels, et les fichiers électroniques seront supprimés.

Une description de cet essai clinique est disponible à l'adresse http://www.ClinicalTrials.gov (NCT02548910). Ce site Web ne renfermera aucun renseignement permettant de vous identifier. Tout au plus, le site Web présentera un résumé des résultats. Vous pouvez effectuer des recherches dans ce site Web en tout temps.

Les chercheurs sont-ils aux prises avec des conflits d'intérêts ?

Il n'existe aucun conflit d'intérêts à déclarer en lien avec cette étude.

Quelles sont mes responsabilités à titre de participant à cette étude ?

Il est important de se rappeler les choses suivantes au cours de cette étude :
- Adressez-vous au chirurgien ou à la coordinatrice de l'étude si vous avez des questions ou des préoccupations.
- Informez votre chirurgien de tout changement relatif à votre état de santé

Serai-je informé de nouveaux renseignements qui seraient susceptibles d'influer sur ma décision de continuer à prendre part à cette étude ?

Nous vous informerons dès que possible de tout nouveau renseignement qui serait susceptible d'influer sur votre volonté de continuer à prendre part à l'étude. Il est possible que vous soyez alors appelé à signer un nouveau formulaire de consentement.

Avec qui communiquer si j'ai d'autres questions ?

Pour toute question au sujet de l'étude, ou si vous croyez avoir été victime d'une blessure découlant de cette étude, veuillez communiquer avec le docteur Martel au (613) 737-8899 71053 ou le personnel de l'étude au (613) 737-8899 x 71484.

Le Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa (CÉR-RSSO) a révisé ce protocole. Le CÉR-RSSO est chargé de l'ensemble des aspects éthiques de toutes les études de recherche menées auprès de sujets humains effectuées à l'Institut de recherche de l'Hôpital d'Ottawa. Pour toute question au sujet de vos droits à titre de sujet de recherche, veuillez communiquer avec le président du Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa, au 613-798-5555, poste 16719.

Consentement à la participation à la recherche

- Je reconnais que l'on sollicite ma participation à une étude de recherche sur l'utilisation de la phlébotomie visant à minimiser les pertes sanguines en chirurgie hépatique .
- _____ m'a fourni les explications nécessaires au sujet de cette étude.
- J'ai pris connaissance de chacune des pages de ce Formulaire de consentement éclairé à l'intention du participant.
- On a répondu à toutes mes questions de manière satisfaisante.
- Si je décide plus tard au cours de l'étude de retirer mon consentement, il me sera possible de le faire en tout temps.
- Je consens volontairement à prendre part à cette étude.
- On me remettra un exemplaire signé de ce Formulaire de consentement éclairé à l'intention du participant.

_____

Nom du participant (en caractères d'imprimerie) | Signature du participant | Date

Énoncé du chercheur ou du délégué

J'ai expliqué soigneusement au participant à la recherche la nature de l'étude susmentionnée. Pour autant que je sache, le participant apposant sa signature à ce consentement reconnaît la nature, les exigences, les risques et les avantages que comporte sa participation à l'étude.

_____

Nom du chercheur / délégué (en caractères d'imprimerie) | Signature | Date

Déclaration relative à l'assistance

Le participant a-t-il reçu de l'assistance au cours du processus de consentement ?
❑ Oui ❑ Non

❑ On a lu le formulaire de consentement au participant / au mandataire et la personne apposant sa signature ci-dessous atteste avoir fourni des explications précises au participant / décideur substitut, qui semble l'avoir comprise et ce dernier a donné librement son consentement.

❑ La personne apposant sa signature ci-dessous a fait fonction de traducteur pour le participant / le décideur substitut au cours du processus de consentement. Elle atteste avoir traduit fidèlement l'information pour le participant / le décideur substitut, et je crois que le participant / le décideur substitut a compris l'information traduite.

Nom de la personne ayant fourni l'assistance (en caractères d'imprimerie)	Signature	Date