A Prospective Randomized Controlled Clinical Trial of Standard versus Goal-Directed Perioperative Fluid Management (GDT) for Patients Undergoing Liver Resection

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title: A Prospective Randomized Controlled Clinical Trial of Standard versus Goal-Directed Perioperative Fluid Management (GDT) for Patients Undergoing Liver Resection.

Null Hypothesis: Goal-directed fluid management does not impact the incidence of postoperative complications in patients undergoing liver resection.

Objectives: Determine the impact of goal-directed fluid therapy on the incidence of 30-day overall postoperative morbidity.

Patient Population: 270 Patients undergoing elective liver resection. 135 patients on each arm.

Design: Single-blinded, prospective randomized trial.

Agents: Standard volume replacement solutions (crystalloid and colloid) and vasoactive agents will be administered to reach the goals of resuscitation according to pre-established protocols.

Time to completion: 2 years

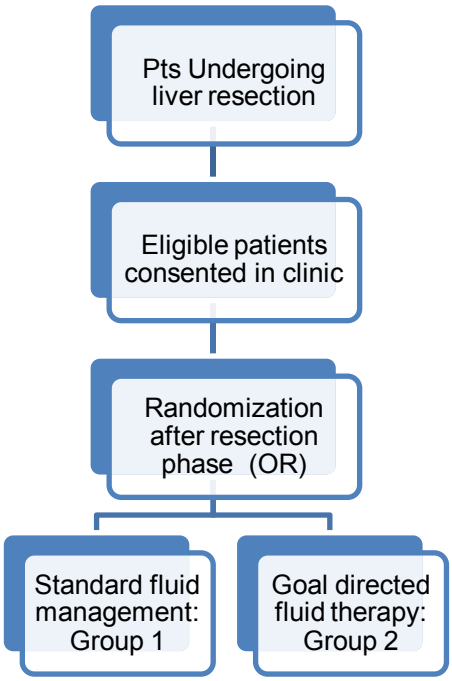
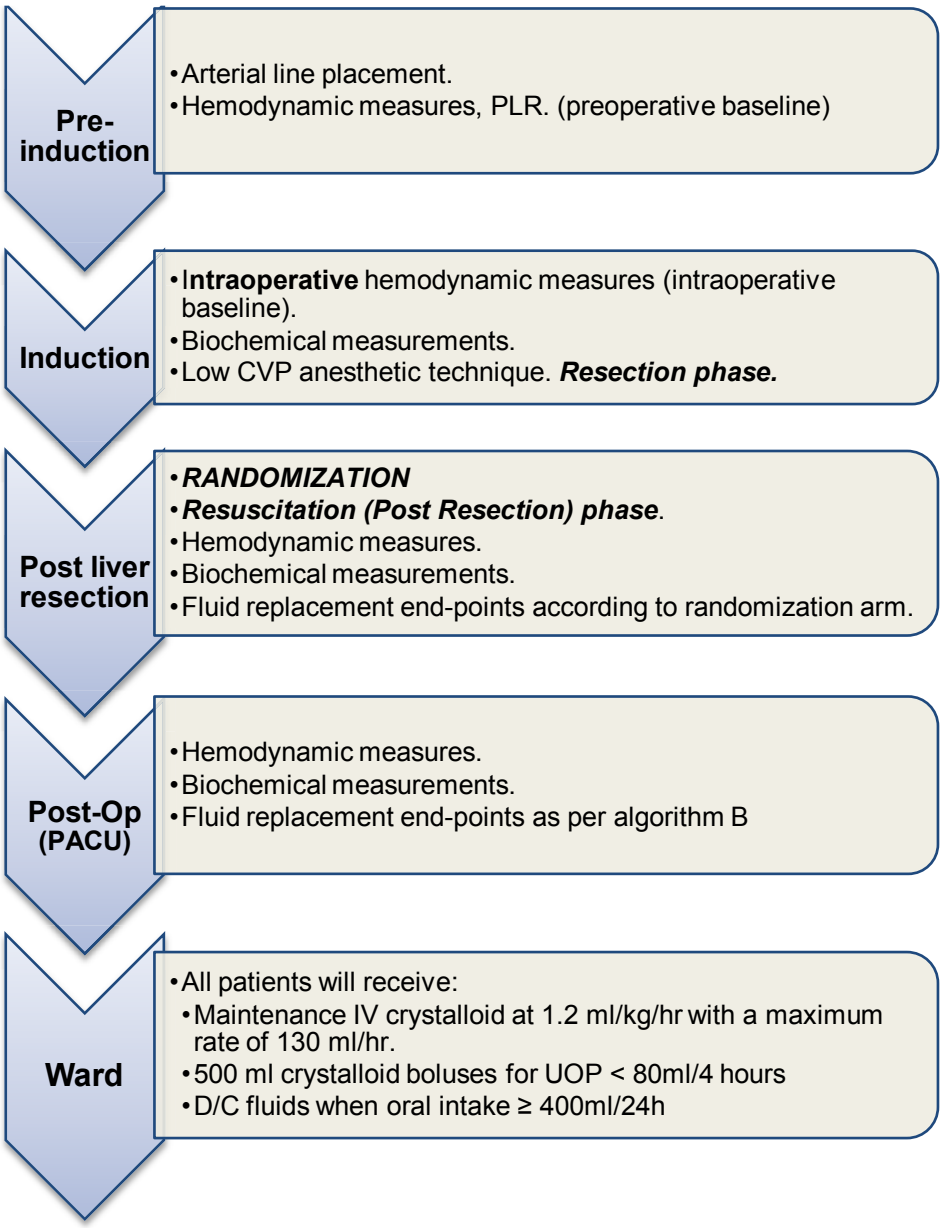


Chart 1. Flow of management through different phases of the protocol


Pre-induction
•Arterial line placement.
•Hemodynamic measures, PLR. (preoperative baseline)
Induction
•Intraoperative hemodynamic measures (intraoperative baseline).
•Biochemical measurements.
•Low CVP anesthetic technique. Resection phase.
Post liver resection
•RANDOMIZATION
•Resuscitation (Post Resection) phase.
•Hemodynamic measures.
•Biochemical measurements.
•Fluid replacement end-points according to randomization arm.
Post-Op (PACU)
•Hemodynamic measures.
•Biochemical measurements.
•Fluid replacement end-points as per algorithm B
Ward
•All patients will receive:
•Maintenance IV crystalloid at 1.2 ml/kg/hr with a maximum rate of 130 ml/hr.
•500 ml crystalloid boluses for UOP < 80ml/4 hours
•D/C fluids when oral intake ≥ 400ml/24h

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective:

- Evaluate the impact of goal-directed fluid management on the incidence of overall postoperative morbidity in patients undergoing liver resection.

Secondary Objective:

- Assess the impact of GDT compared to standard fluid therapy on the total time patients experience low cardiac output perioperatively (i.e. intraoperative and in the first 24 postoperative hours).
- Assess the impact of GDT compared to standard fluid therapy on the total volume of fluid given intraoperatively and during the first 72 hrs postoperatively.
- Assess the impact of GDT compared to standard fluid therapy on the requirement for blood transfusion.
- Compare the total dose (mcg/kg) of vasoactive agents used in the first 24 hrs between the standard management and GDT groups.
- Measure the difference in end-organ perfusion markers between GDT and standard therapy for fluid management.
- Assess the impact of GDT compared to standard fluid therapy on net fluid balance for the total admission time.
- Assess the impact of GDT compared to standard fluid therapy on the systemic inflammatory response.

3.0 BACKGROUND AND RATIONALE

An association between early postoperative complications (particularly infectious) and decreased long-term survival after liver resection for malignant disease has been previously documented.[1-6] In the last two decades, improved surgical technique and management of complications have been responsible for a significant reduction in perioperative mortality rates, which now range between 0.1%-3%. However, grade 3 and 4 complications (most clinically relevant – see appendix 2) have been reported to range between 28 – 30%;[7-9] moreover, overall postoperative morbidity reaches 45% in single-institution reports.[10-12] Furthermore, in a recent paper derived from the Patient Safety in Surgery (PSS) Study, Virani et. al presented 30-day morbidity and mortality rates after liver resections in 14 private-institutions in the US. They found morbidity and mortality rates of 22.6% and 2.6%, respectively; this large population-based study, however, did not capture bile collections

(bilomas) among their complications, thus underestimating the morbidity rate. Somewhat intuitively, this retrospective analysis also showed that patients who developed complications had an increased 30-day mortality rate when compared to patients that had an uneventful recovery (0.7% compared to 9%; p <0.0001)[13]. These findings underscore the significant impact of postoperative morbidity and justify further attempts at reducing it.

The optimal peri-operative fluid management strategy is yet to be determined. For years, the debate has centered (perhaps erroneously) around the comparison of colloid *vs* crystalloid solutions, each of which have their own advantages and shortcomings in specific clinical scenarios. In the past, trials have failed to recognize the fact that different resuscitation fluids belong to different drug classes and have individual pharmacologic profiles and indications.[14] In a large multicenter randomized trial, published in New England Journal of Medicine, Finfer et al. found no significant outcome differences in patients admitted to general intensive care units and randomized to receive normal saline compared to 4% albumin; this large trial however was underpowered for subgroup analyses and estimation of differential mortality among different patient populations.[15] A meta-analysis recently published by Delaney[16] suggested that the use of albumin for resuscitation in patients with sepsis was associated with a marginal, yet signicant reduction in mortality (pooled OR: 0.82 [95% CI 0.67-1.0]; p = .047). Conversely, The Cochrane collaboration has reported three reviews analyzing available data on the debate of colloid compared to crystalloids for critically ill patients,[17-19] these reviews have failed to find a survival benefit for any of the two and recommends that the use of colloids be abandoned outside of randomized studies given their higher cost.[18]

Results from these studies have prompted a shift away from the use of colloids as resuscitation fluids (particularly in the critical care community). Perhaps more concerning, some reports have pointed out significant risks associated with the use of colloids (specifically increased incidence of renal dysfunction and need for renal replacement therapies).[20] These studies however, still fail to address the individual patient's homeostasis in the selection of a resuscitation solution, failing to recognize both colloids and crystalloids as very different drugs with specific therapeutic indications.

In the last several years, there has been increasing evidence demonstrating the existence of two different types of fluid shifts that likely occur simultaneously in the perioperative period; these are physiologically distinct and their management should be appropriately tailored to meet the requirements of the specific patient. The existence of the commonly regarded "third

space" has been questioned[14, 21] and the classical Starling principle that gave physiologic support to the use of colloids for maintenance of intravascular volume has been complemented to account for the volume status of each individual and the role of the glycocalix.[21, 22] The concept of a fluid-consuming third space often results in a very liberal resuscitation approach after intraabdominal surgery, according to which *more is better*, frequently leading to significant fluid overload and its ensuing consequences. In a well conducted prospective study Lowell et al. evaluated the outcomes of 48 consecutive patients admitted to a surgical ICU.[23] They found a striking increase in mortality associated with weight gain as a surrogate marker of fluid overload (figure 1).

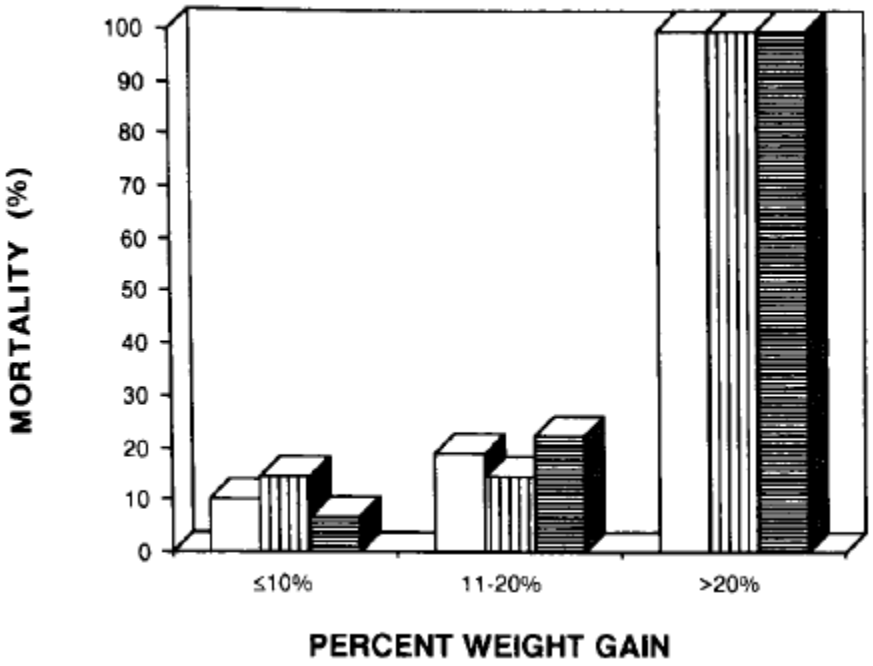


Fig. 1. Perioperative weight gain and mortality of patients. No patient survived if perioperative weight gain was more than 20%. * *P* < 0.008 *compared to* weight gain less than 10%.[23]

A rational approach to perioperative fluid management should be patient and procedure specific and driven by objective data that could, at least theoretically, decrease the deleterious effects of perioperative hyper or hypovolemia.[24, 25] We seek to evaluate this hypothesis in patients undergoing liver resection guiding fluid therapy with the use of continuous minimally-invasive hemodynamic monitoring.

Respiratory arterial pulse pressure variations (PPV) are the best predictors of fluid responsiveness in mechanically ventilated patients during general anesthesia and pulse wave contour analysis has been previously validated as a reliable dynamic method to assess the fluid status and predict fluid responsiveness.[26-29] Other devices used clinically to guide fluid optimization such as the pulmonary artery catheter or central venous lines, are more invasive and associated with potential complications. Trans-esophageal Doppler which has been shown to have adequate correlation with PPV as a predictor of fluid responsiveness, has multiple shortcomings including the practical impossibility to use this technique in the awake patient, thus curtailing the global hemodynamic information that we obtain from it and limiting it to the intraoperative period. In consequence, this technique doesn't provide baseline preoperative data or postoperative hemodynamic information to guide management.[14] Noblett et al. reported on their trial in patients undergoing colorectal surgery who were randomized to liberal management vs Doppler-directed fluid resuscitation.[30] They found a shortened hospital stay, fewer complications and earlier return of intestinal fuction in the intervention group. However, they found no difference in the total amount of fluids administered between the groups. The conclusion from their paper insinuates that it is likely that the timing of fluid administration and the prevention of early gut ischemia are the drivers of the improved outcomes in patients receiving goal-directed therapy.

This report by Noblett, as well as others, has also shown differential alterations in intra and post-operative levels of various acute phase reactants (IL-6, IL-10, TNF-α, C-reactive protein, procalcitonin, among others) in response to surgical stress during elective procedures.[30-33] Furthermore, higher levels of some of these cytokines have been associated with the degree of tissue injury, hypoperfusion states[34, 35] and increased postoperative complications.[36]

These data indicate a possible link between the adequacy of intraoperative fluid management and intensity of the inflammatory response to surgical trauma. There is however no data to our notice evaluating this relationship in patients undergoing liver resection in the context of tightly measured fluid management. The present study proposal provides an excellent opportunity to gain insight both into the potential impact of different fluid strategies on the inflammatory response as well as the relation between the later and the development of postoperative complications.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Prospective single-blinded randomized trial. Eligible patients will be consented for the trial prior to surgery. However randomization will not occur until the operating room. After the liver has been resected, intraoperative randomization will be done by envelopes. Preoperative preparation and induction will be standard for all patients. In the OR all patients will have an arterial line placed preinduction and baseline hemodynamic data recorded from the Edwards EV1000 system. In the study, all intraoperative fluid therapy will be managed with the standard LCVP anesthetic technique for hepatic resection, and then at the completion of the resection all fluid therapy will be managed according to randomization arm (Goal-directed fluid therapy-**appendix 1** compared to standard fluid management- see detail below) for reconstruction and closure. In the postoperative phase, management will be standardized for both arms as outlines below.

During low central venous pressure (LCVP) anesthetic technique for partial hepatectomy, intraoperative fluid balance is divided in to two phases (as previously published)[8]:

- Prehepatic resection (the first phase), starts at anesthesia induction and ends at the completion of parenchymal transection and hemostasis. This phase takes advantage of fluid restriction and the vasodilatory effects of anesthetic drugs to provide LCVP anesthetic management. Fluid boluses and/or vasoactive drugs are administered at the discretion of the anesthesia provider to maintain systolic blood pressure > 90 mm Hg and urine output > 25 ml/hr while keeping the cvp <5 mmHg (currently, the vast majority of our patients do not require central line placement for the performance of liver resections. Low central venous pressure is assessed by the surgeon's direct assessment of the distention of the vena cava at the time of surgery). Maintenance fluid is 1cc/kg/hr.

  Prior to proceeding to the second phase the intraoperative fluid management after the hepatic resection, patients will be randomized to either

  Goal-directed fluid therapy (**see appendix 1**)

  Standard fluid management (**see appendix 1**).

- Posthepatic resection (the second phase), begins once the specimen has been delivered and hemostasis secured. During this phase, an attempt is made to return the patient to normovolemia. For our standard fluid management, blood loss is replaced volume to volume with albumin and crystalloid (6 cc/kg/hr x total operative time) will be infused to achieve the assumed fluid requirement (third space). After this fluid therapy, if BP<90mmHg or urine output< 25ml/hr, additional fluid boluses either colloid or crystalloid are given. Packed red-blood cells (PRBC) are included in resuscitation if the hemoglobin <7 g/dL. Fresh-frozen plasma (FFP) or platelets may be given at the request of the surgeon if surgical hemostasis is inadequate, international normalized ration (INR) >1.8 or platelets < 80,000 mcL.

The GDT arm will have fluid therapy guided by the Edwards EV1000 system. First, blood loss will be replaced 1:1 volume with albumin. After this infusion, additional fluid will be given based on the patient's SVV. If this value is greater than 2 standard deviations of the baseline value more albumin will be given until SVV is less than or equal to no greater than 2 standard deviations above the baseline SVV. If the SVV is at baseline or not greater than 2 standard deviations from the baseline value, no additional bolus fluid will be given (Appendix 1). The maintenance crystalloid fluid will continue at 1cc/kg/hr that was begun in the LCVP phase. Group and protocol assignment will be maintained from the beginning of the reconstruction phase during the index operation, until after the patients are transferred to the PACU and receive standardized postoperative management at the discretion of the treating physicians.

During the intervention period, continuous non-invasive pulse wave analysis will be performed (Edwards EV1000) and the information stored in the monitor. Download is enabled to a USB port and memory stick. In the group assigned to standard management the monitor will be covered and the data derived from it will not be available to the anesthesia care team; this blinding will only be removed for the involved researchers at the completion of the study for retrospective analysis and comparison. At this time only research staff and anesthesia staff will have knowledge of patients randomization assignment.

Adequacy of postoperative resuscitation will be determined by comparing end-tissue perfusion variables as well as inflammatory markers (a multiplex cytokine panel that includes IL-2, IL-4, IL-6, IL-10, IL-17, TNFα, and INFγ) before skin incision (as baseline), at the beginning of resuscitation phase, at time of completion of the case and the morning of the 2

first postoperative days. **See Table 2 – section 10.0 Evaluation during treatment/Intervention.** After evaluation of inflammatory response in the initial set of 20 randomized patients, it was determined that no statistically significant difference was likely to be found between the 2 randomization arms and the protocol was amended to discontinue the blood collections and cytokine analysis.

Continuous assessment of cardiac output as determined by the arterial waveform analysis, total fluid therapy, (crystalloid and colloid), units of pRBCs, total dose (mcg/kg) of each vasoactive agent, cumulative fluid balance and the incidence of overall 30-day postoperative complications will be recorded. These are defined in the MSKCC Adverse Events Program and organized by categories reflecting organ systems (listed below) and further subdivided into specific complications within those and graded as reflected in appendix 2. A detailed listing of complications and grading can be found at: http://vssurpweb1/AdverseEvents.

Categories
*None at 30 days post-op

Cardiovascular System

Endocrine System

Gastrointestinal System

General

Genitourinary System

Head and Neck

Hematologic or Vascular System

Infection

Metabolic

Musculoskeletal System

Nervous System

Pain

Pulmonary System

Wound or Skin

4.2 Intervention

Goal-directed fluid therapy (GDT): See details in section 9.0 Treatment/Intervention plan and Appendix 1.

Preresection Phase:

Standard low CVP anesthetic technique is initiated. Hemodynamic monitoring is performed as usual. Fluid boluses and/or vasoactive drugs are administered at the discretion of the anesthesia provider to maintan SBP ≥ 90mmHg and urine output ≥ 25ml/hr while maintaining the cvp <5mmHg, as determined by the surgeon's intraoperative assessment of the vena cava. Maintenance crystalloid fluid is kept at a minimal rate (1cc/kg/hr) during this phase.

Postresection Phase:

During this phase, which starts after the specimen is delivered, the goal is to restore normovolemia. Fluid replacement will occur in two stages: first, blood loss is replaced with a 1:1 albumin volume. Next, albumin will be infused to restore SVV to a value that is less than or equal to two standard deviations over the intraoperative baseline (immediately after induction). Crystalloid infusion is continued at 1cc/kg/hr. **(algorithm A)**

PACU:

Standardized management (algorithm B):

- Patients requiring continued mechanical ventilation will receive a tidal volume of 8 ml/kg body weight at a frequency of 6 to 12 breaths per minute to keep the end-tidal carbon dioxide between 35 to 40 mm Hg. Most patients will be extubated in the operating room and not require mechanical ventilation.
- Maintenance IV crystalloid at 1.2 ml/kg/hr with a maximum rate of 130 ml/hr.
- Strict Inputs and Outputs measured hourly in PACU.
- Boluses of 250 ml of albumin solution (given over 20 minutes) will be administered for SBP < 90mmHg and/or urine output < 40ml/2hr.
- Medications mixed as per pharmacy protocol, to be included in daily input.
- The use of vasoactive agents will be left to the discretion of the treating practitioner.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Device description:

The EV1000 monitor continuously measures key parameters of arterial pressure, cardiac output (CO), cardiac index (CI), stroke volume (SV), stroke volume variation (SVV), stroke volume index (SVI), systemic vascular resistance (SVR) and systemic vascular resistance index (SVRI).
This device has been used previously in the surgical and intensive care unit settings elsewhere and at MSKCC. Results from their use vary in terms of the outcomes reported, however its use provides significant hemodynamic information with minimal invasion.[27, 37-39]

This monitor has successfully undergone functional and performance testing, including software verification and validation, mechanical and electrical testing, bench studies, pre-clinical animal studies, comparison testing of clinical cases, and clinical usability. It has been shown to be safe and effective and substantially equivalent to the cited predicate devices for their intended use in the OR and ICU environments and has obtained FDA approval for these uses.[40]
The FloTrac sensor is a 501k device. An IDE is not required for this device which is already in use at Memorial Sloan-Kettering Cancer Center with appropriate SOPs in place.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the patient/subject population.

6.1 Subject Inclusion Criteria

- Adults (18 years old or greater) who are able to provide informed consent.
- Patients who undergo an open, elective liver resection. Including those initially approached laparoscopically but converted to an open resection and those undergoing additional procedures.

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6.2 Subject Exclusion Criteria

- Active coronary disease.
    - Patients with active coronary disease will be eligible if they have had a cardiac stress study showing no reversible ischemia and normal LV function within 3 months of operation.
- Active symptomatic cerebrovascular disease.
- Active congestive heart failure and ejection fraction <35%.
- Active severe restrictive or obstructive pulmonary disease and resting SpO2 <90%.

- Active renal dysfunction (Cr >1.8)
- Abnormal coagulation parameters (INR > 1.8 not on Coumadin, or platelet count < 100,000 per mcL)
- Presence of active infection including HIV
- Patients with active atrial fibrillation or flutter.
- Preoperative hypoalbuminemia (Albumin < 2g/dl).
- Female patients who are pregnant (female patients of child-bearing potential must have a negative serum pregnancy test ≤ 14 days prior to surgery or 15 to 30 days prior to surgery with a negative urine pregnancy test the morning of surgery).
- Presence of ascites.
- BMI > 45 or <17

7.0 RECRUITMENT PLAN

7.1 Number:

Based on sample size calculations estimating an 80% power for detecting a 15% decrease in the proportion of postoperative complications, assuming the standard arm will have a 30% overall complication rate (Type I error of 5%), 270 patients will be randomized 1:1 to the two arms.

7.2. Recruitment:

All patients scheduled to undergo liver resection who meet the established criteria will be approached for participation in this study during their preoperative visit. The trial itself, the expected outcomes as well as the risks and potential complications associated with it will be thoroughly discussed before enrollment. Informed consent will be obtained and documented in the patient's chart at this point. Study subjects will not receive any compensation for participation in the study. There will not be any additional costs for the patients derived from participation. In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. Patients will be recruited into the study during their preoperative clinic visit to the Hepatopancreaticobiliary Service and consent will be obtained by the attending surgeon.

The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

7.3 Women and minorities:

All patients regardless of gender, race or ethnicity will be recruited to this study.

8.0 PRETREATMENT EVALUATION

Once the patient has been evaluated by an attending surgeon in the Department of Surgery and considered a candidate for a liver resection, eligibility will be assessed. All patients will undergo the following preoperative work-up for liver resection:

- Complete history including demographics and physical exam.
- Preoperative testing will include electrocardiogram, chest imaging, comprehensive metabolic panel (including liver function tests), complete blood count and coagulation parameters.
- Negative serum pregnancy test within 14 days prior to surgery or 15 to 30 days prior to surgery with a negative urine test the morning of surgery. Medical clearance will be considered for every patient and obtained selectively on those patients who require it based on symptoms or past medical history.

9.0 TREATMENT/INTERVENTION PLAN

- In the operating room patients will receive intravenous sedation and infiltration of local anesthetic prior to placement of an arterial line. The arterial line will be connected to the Flo-Trac System and a Square Wave Test will be performed to assess for dynamic performance. The Square Wave Test is a pull and release snap-tab of the arterial flush to observe the the number of oscillations before returning to baseline. Optimally damped would be 1.5-2 oscillations before returning to baseline.

Before induction, baseline preoperative hemodynamic measures will be obtained (SV, CO). As baseline stroke volume (SV), we will use the mean ± 2 x SD of the measures obtained for 6 minutes while the patient is at rest, see table 1 below.

- Passive leg-raising (PLR) test.

The standard definition of volume responsiveness is a >15% increase in stroke volume in response to volume expansion. PLR consists of passive elevation of the lower extremities with the patient in the semirecumbent (30-45%) position. This maneuver rapidly mobilizes 300-500 ml of blood from the lower extremites to the intrathoracic compartment and reproduces the effects of similar volume fluid bolus. The increase in the preload will give an indication of the patient's preoperative fluid responsiveness and baseline location on the Starling curve. While measuring stroke volume (SV) and cardiac output (CO) before and immediately after PLR (1-3 minutes), an increase of 12.5 % or more in PLR – induced increase of stroke volume will predict an increase of stroke volume of 15% or more after volume expansion and the patient is considered volume responsive. Importantly this fluid challenge is reversible and therefore compatible with our low central venous anesthetic technique for liver resection.[41, 42] Figure 2.

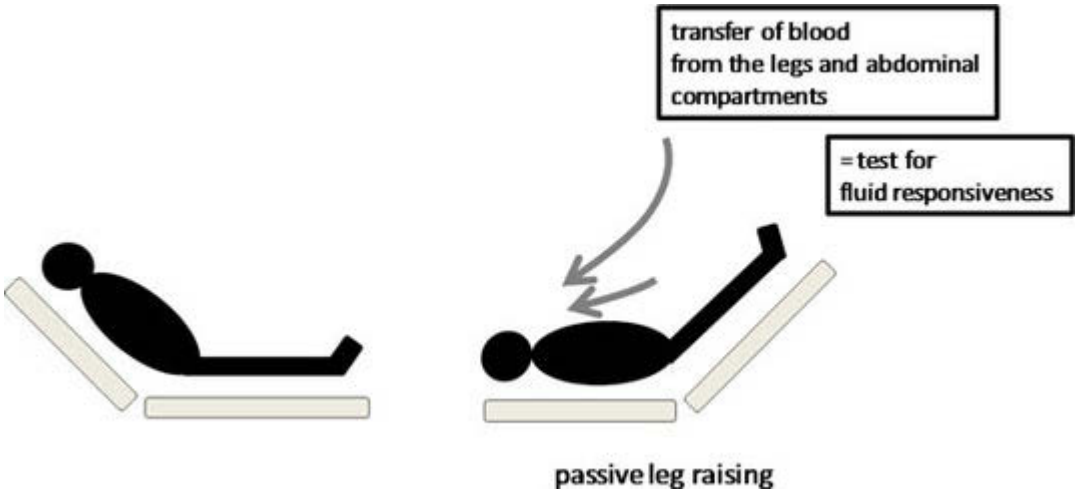

Figure 2. The best way to perform a PLR maneuver to predict volume responsiveness is to elevate the lower limbs to 45° (automatic bed elevation or wedge pillow) while at the same time placing the patient in the supine from a 45° semirecumbent position.[42]

- Induction and intubation will be carried out routinely and the patient will be placed on positive pressure ventilation. Baseline intraoperative hemodynamic parameters and biochemical markers will be obtained. For the patients in the standard management group, the EV1000 monitor will be covered and the surgeons and anesthesiologists will be blinded to the measured parameters.

Baseline hemodynamic data:

To obtain baseline hemodynamic measures, we will obtain six successive measures 60 seconds apart and calculate the mean and standard deviation:

Time	CO L/min	SV mL/b	SVI mL/b/m²	SVV %	
9:00 am	6.1	82	45	5	
9 01 am	5.9	81	45	6	
9:02 am	6.1	82	46	8	
9:03 am	6.1	84	47	7	
9:04 am	6.2	85	47	5	
9:05 am	6	82	46	7	
	6	83	46	6	Mean
	0.1	1.5	0.9	1.2	Std Dev.

Table 1.

Actual values from a sample patient to illustrate measured baseline ± standard deviation hemodynamic parameters. CO: Cardiac output; SV: stroke volume; SVI: stroke volume index; SVV: stroke volume variation (stroke volume variation will only be interpretable in the intubated patient).

These measurements will be obtained preoperatively at rest, after a passive leg raise maneuver to evaluate fluid responsiveness and after intubation to obtain baseline SVV.

The mean value ± two-times the standard deviation will be considered the baseline and will be the hemodynamic goal during the resuscitation and PACU phases. These numbers will be used for algorithm A. (**appendix 1).**

- Central venous lines will only be placed when clinically indicated by the anesthesia or

surgery practitioner. Central venous access is NOT required for participation in this protocol.

- All patients will undergo mechanical ventilation with a tidal volume of 8 ml/kg body weight at a frequency of 6 to 12 breaths per minute to keep the end-tidal carbon dioxide between 35 to 40 mm Hg. Patients will have continuous measurement of heart rate, blood pressure, ECG tracing, end-tidal CO2, oxygen saturation, temperature, urine output and BIS monitoring.

- Standard low central venous anesthetic technique will be applied to all patients.

- During the pre-resection phase, all patients will undergo LCVP anesthesia as we have previously reported.[8] This management strategy is detailed in section 4.1.

- During the resuscitation (post-resection) phase, patients in the standard fluid management group will receive replacement fluids as detailed in section 4.1.

- Replacement fluid for the patients in the GDT group will follow **algorithm A. (appendix 1)**

- Postoperatively, all patients will be kept in the PACU until the following morning. Management at this stage will be standardized and equal for both arms:

    - PACU standardized management (algorithm B):
        - Patients requiring continued mechanical ventilation will will receive a tidal volume of 8 ml/kg body weight at a frequency of 6 to 12 breaths per minute to keep the end-tidal carbon dioxide between 35 to 40 mm Hg. Most patients will be extubated in the operating room and not require mechanical ventilation.
        - Maintenance IV crystalloid at 1.2 ml/kg/hr with a maximum rate of 130 ml/hr.
        - Strict Inputs and Outputs measured hourly in PACU.
        - Boluses of 250 ml of albumin solution (given over 20 minutes) will be administered for SBP < 90mmHg and/or urine output < 40ml/2hr.

- Medications mixed as per pharmacy protocol, to be included in daily input.
- The use of vasoactive agents will be left to the discretion of the treating practitioner.

- When patients leave PACU, the arterial line will be removed upon transfer to the floor and fluid management will be as follows:
  - Maintenance IV crystalloid at 1.2 ml/kg/hr (maximum rate of 130 ml/hr) until taking > 400ml/24 hrs po, then d/c.
  - Urine output (UOP) to be maintained at 80ml/4 hours (20ml/hr averaged over 4 hour periods) with boluses of 500 ml crystalloid solution.
  - Lasix 10mg IV starting POD 2 for weight gain greater than 2kg pre operative weight if approved by treating practitioner.
  - If UOP is greater than 60ml/hr over 8 hours, IV rate may be decreased at the discretion of the treating practitioner.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

- Preoperative data will be collected and recorded: date of birth, weight, height, complete metabolic panel, complete blood count, coagulation profile.
- Standard intraoperative monitoring will be carried out for all patients.
- GDT patients will also be monitored by CO, SV and SVV. These data will similarly be obtained and recorded for the patients in the standard management group but it will not be available for the treating practitioners.
- Further measures of end-tissue perfusion will be assessed with arterial lactate levels and DO_2 (oxygen delivery) at baseline (before incision), at completion of the resection phase (intraoperatively), upon arrival to PACU (0 hours postoperatively), and on the morning of POD #1.
- Assessment and recording of all intraoperative and postoperative complications; the latter being considered as those occurring on or after postoperative day 1 until postoperative day 30. Complications occurring intraoperatively and after surgery on

the same day, are most likely technical in nature and will be considered perioperative complications in the analysis.

- Estimated operative blood loss.
- Cumulative volume used for resuscitation will be recorded (stratified by colloids and crystalloids)
- Total dose (mcg/kg) of pressors, inotropes or vasodilators used will be recorded and stratified by specific drugs.
- Volume and type of blood products transfused.
- Daily comprehensive metabolic panel, complete blood count (these will be recorded for seven days or until discharged if discharged earlier).
- Daily coagulation panel, discontinued by POD 3 if normal.
- Volume and type of fluid intake and output until POD 7 or patient tolerates oral intake of fluids > 400 ml/24 hrs
- Daily nasogastric tube drainage volume (if used) and length of NG drainage
- Daily weight until POD 7 or until patient tolerates oral intake of fluids > 400 ml/24 hrs.
- Day of tolerating oral intake of fluids > 400ml/24hrs
- Day of IV ≤ KVO
- Day of tolerating oral intake of solids
- Day of passage of flatus
- Day of foley removal.
- Day of passage of feces
- Day of discharge

Table 2. Details hemodynamic and laboratory values obtained at different stages. For laboratory values a 30 minute variation will be allowed to account for early or delayed sample collection in the PACU and/or surgical ward.

	Baseline Preop (pre intubation)	Baseline intraop (after intubation)	Resuscitation Phase	PACU (0 hrs postOp)	4 hrs postOp	8 hrs postOp	12 hrs postOp	Morning of POD 1	Morning of POD 2
Stroke Volume (μ ± SD)	x			x	x	x		x	
*Stroke Volume (μ ± SD)	x								
% change in SV	x								
Stroke Volume Variation- SVV (μ ± SD)		x	x						

Stroke Volume - SV (μ ± SD)			x	x	x	x	x		
Stroke volume index (μ ± SD)			x	x	x	x	x		
LABS									
Na				x					
K				x					
Cl				x					
Arterial Lactate	X		x	x				x	
HCO3	X		x	x				X	
Creatinine				x					
BUN				x					
Glucose				x					
Glomerular filtration rate-GFR (calculated)				x					
WBC				x					
Hemoglobin	X		X	x				X	
Hematocrit				x					

*Post passive leg raising test values.

11.0 TOXICITIES/SIDE EFFECTS

Goal-directed fluid therapy in major abdominal surgery has been reported before with no significant adverse events reported.[14, 24] The FloTrac system for minimally-invasive hemodynamic monitoring has also been tested in clinical trials with no adverse events reported.[37] An Adverse Event (AE) is defined as any new, untoward or unexpected medical occurrence or worsening of a pre-existing

medical condition in a research participant, that does not necessarily have a causal relationship with protocol treatment. All adverse events for this protocol will be defined as those listed in the MSKCC Surgical Secondary Event Program. Any grade 3 or higher as determined by this database will be reported to the IRB.

A serious adverse event (SAE) is an undesirable sign, symptom or medical condition that is fatal or life-threatening

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires prolongation of existing hospitalization, unless hospitalization is for:
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
  - is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

NOTE:

The following hospitalizations are not considered to be SAEs:

- Admission for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state which was planned prior to entry into the study; appropriate documentation is required in such a case
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

All complications will be prospectively recorded.The hepatobiliary surgery service runs a biweekly meeting in which all complications are discussed and prospectively recorded into the Memorial Sloan-Kettering Surgical Secondary Events Program Database. At this meeting attendings discuss individual patients and assess the outcomes in order to record complications according to predefined criteria. **appendix 2 and 3.** Research personnel directly involved in the protocol will not influence this process.

A Hepatopancreaticobiliary research study assistant will query the Surgical Secondary Events Program Database at 30 days after each patient's operation and prospectively collect morbidity data for patients enrolled in the study.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The null hypothesis is that GDT in patients undergoing liver resection does not alter the incidence of postoperative complications. A 15% decrease (from 30% to 15%) in the

incidence of 30-day complications will be considered clinically significant and will represent the primary outcome measure. The incidence of these will be assessed after each patient's postoperative visits.

Secondary outcomes include the impact of GDT on low cardiac output time, total volume of fluid used perioperatively, the requirement for blood transfusion, the total dose of vasoactive drugs, end-organ perfusion markers and the net fluid balance 48 hrs postoperatively.

13.0 CRITERIA FOR REMOVAL FROM STUDY

At any point during the study, the attending surgeon or anesthesiologist may decide to go off protocol in their resuscitation strategy if they deem it necessary for patient safety. Randomized patients will not be replaced for any reason. If a patient is transferred to the Intensive Care Unit, they will have that recorded as a complication and will be removed from the study. Management will continue in the patient's best interests and according to ICU guidelines.

14.0 BIOSTATISTICS

This is a randomized comparison of goal-directed compared to standard fluid management in patients undergoing liver resection. Primary endpoint is overall postoperative morbidity.

270 patients will be randomized 1:1 to the two arms. This sample size provides 80% power for detecting a 15% decrease in the proportion of overall postoperative complications (i.e regardless of grade of severity), assuming the standard arm will have a 30% complication rate (two-sided Type I error of 5%). It also allows for an interim analysis halfway through enrollment, using O'Brien-Fleming boundaries both for efficacy and futility. If $p<=0.005$ at the interim analysis enrollment will stop with the conclusion that goal-directed fluid management significantly decreases postoperative morbidity. If $p>=0.468$ at the interim analysis enrollment will stop with the conclusion that goal-directed fluid management does not significantly decrease postoperative morbidity. If $0.005<p<0.468$ then the trial will continue to full enrollment. With an approximate enrollment of 11 patients per month, accrual should be complete in 2 years.

Secondary endpoints will be compared between the two arms using the Wilcoxon rank-sum test, except for the categorical endpoints of blood transfusion and systemic inflammatory response, which will be compared using Fisher's exact test.

Since one of our main goals for this study is to establish what the individual amount of resuscitation is for each patient, tailored to their hemodynamic status, we decided to use their baseline value ± 2 standard variations as their homestatic stroke volume variation. An elevation above 2 standard deviations would be statistically unlikely to represent a normal variation of the measurement and will thus be considered a hemodincamically significant deviation from baseline.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

This is a single-blinded randomized trial. After eligibility is established and consent is obtained, patients will be registered in the Protocol Participant Registration (PPR) system.

Eligible patients will be consented for the trial prior to surgery. However randomization will not occur until the operating room. After the liver has been resected, intraoperative randomization will be done by envelopes. Randomization will be stratified by diagnosis (metastatic liver disease compared to primary disease where primary disease will encompass liver cancer and extrahepatic biliary cancer).

16.0 DATA MANAGEMENT ISSUES

All collected data that will only be used for the purposes of the study. It will be maintained in a confidential clinical research database by research study personnel only and under direct

supervision of the principal investigator. The database will be kept in a password protected computer and will not be transferred outside of the hospital network. A minimum dataset will be kept in CRDB . The data will be linked to the patients by means of unique tracking subject numbers the key to which will be also password protected and only to be accessed by research personnel. Data will be reported to the IRB as required.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team at pre-established intervals.

The principal investigator will maintain final responsibility for data during the study and during the final analysis of data. Breaches of protocol, problems with informed consent, or discrepancies in data accuracy will be reported to the IRB as required.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb5.mskcc.org/intranet/_assets/_tables/content/359709/DSMPlans07.pdf*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol

monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board. During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

The responsible investigator will ensure that this study is conducted in agreement with the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments). The study will seek in every way to protect the rights of human subjects. The potential risks including adverse drug reactions and potential benefits in terms of reducing transfusion requirement and postoperative recovery will be discussed in detail with patients. Potential side effects as outlined above will be discussed with the patients. No patient will be required to participate in the study and participation or lack of participation will not affect the patient's subsequent care or treatment. The patient will not incur any financial cost as a result of participation in the study. Participation will be purely voluntary and subjects will not be reimbursed for participation in the study. Throughout the study, patient confidentiality will be maintained. No results of the study will be presented or discussed in a fashion that will allow identification of a particular patient in the study. All adverse events will be fully disclosed to the IRB in a timely fashion as required.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

17.2.1 NA

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)

4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

Appendix 1 - Algorithms for goal-directed fluid therapy (GDT).

Appendix 2 - Complication grade classification.

Appendix 3 - Incidence of complications after liver resection at MSKCC in 2010.