DAMAGE CONTROL LAPAROTOMY: A RANDOMIZED CONTROLLED TRIAL

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Protocol Title:	DAMAGE CONTROL LAPAROTOMY: A RANDOMIZED CONTROLLED TRIAL
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Population:	Adult trauma patients undergoing emergent laparotomy at Memorial Hermann Hospital-Texas Medical Center(MHH-TMC)
Number of Sites:	Singe center, MHH-TMC
Study Duration:	Two years
Subject Duration:	Time while hospitalized plus 6 months

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General Information

This protocol describes a clinical trial comparing damage control laparotomy (DCL) to definitive laparotomy (DEF) in trauma patients undergoing emergent laparotomy. DCL was described in the 1980s and rapidly gained traction over the following decades with increasing rates of utilization and a liberalization in the indications for use. In a DCL, the life-threatening injuries are addressed – bleeding is stopped, enteric spillage is controlled – and the abdomen is left open with a temporary dressing. The patient is then transported to the intensive care unit (ICU) for resuscitation (with the abdomen still open). Once adequately resuscitated, the patient returns to the operating room (OR) for re-exploration of the abdomen, definitive repairs of injuries, and closure of the abdomen. A major hurdle to performing a clinical trial of DCL is surgeon equipoise. There are indications for DCL for which surgeons would not have the clinical equipoise to randomize a patient. Significant preliminary data has identified a group of patients for which there is equipoise to randomize. This proposed trial aims to compare outcomes of patients undergoing DCL versus DEF for which there is surgeon equipoise to randomize.

Background Information

Injury is the leading cause of death in Americans aged 1-45 years and 20-40% of all trauma related deaths are due to truncal hemorrhage.[1,2] Emergent laparotomy is the most common treatment for patients with life-threatening truncal hemorrhage and intra-abdominal injury, yet very little high-quality data exists to guide clinical decision-making during the procedure. In particular, there is controversy regarding the indications for DCL.

A DCL is an abbreviated laparotomy in which hemorrhage is stopped, ongoing gastrointestinal contamination is controlled, the abdomen is left open, and the patient is taken to the ICU for resuscitation. Once the patient's body temperature has been normalized, hemodynamic status improved, and any coagulopathy corrected, the patient returns to the OR for definitive repair of injured structures and closure of the abdomen. This is in contrast to a definitive laparotomy (DEF), in which all portions of the operation are completed and the abdomen is closed at the initial surgery.

DCL was developed and rapidly adopted in the 1990s due to the high rate of mortality in massively transfused patients undergoing laparotomy for hemorrhage. The initial studies comparing DCL to DEF were retrospective, small in number, and suffered significant selection bias.[3,4] The seminal paper by Rotondo et al, in which the term 'damage control laparotomy' was coined, focused on a cohort of patients with penetrating trauma who received a massive transfusion (>10 units red blood cells prior to end of primary laparotomy). When including all patients, no mortality difference was seen between DEF (n=22, mortality 45%) and DCL (n=24, mortality 42%). It was only in a subgroup analysis of the "maximum injury subset" (arbitrarily defined as one or more major vascular injuries and two or more visceral injuries), that a significant mortality benefit between DEF (n=9, mortality 89%) and DCL (n=13, mortality 23%) was seen.

Despite the fact that the Rotondo study was small, retrospective, and with very narrow inclusion criteria, it provided actionable evidence that in select, severely injured patients, DCL improved outcomes. Because of this improvement in outcomes, the utilization of DCL rapidly increased for a wide variety of operative trauma settings, with rates approaching 36% in

experienced, Level 1 trauma centers.[5,6,7] With more patients undergoing DCL, the associated risks and benefits became better understood.[8] Potential benefits include decreased mortality and avoidance of hypothermia, acidosis, and coagulopathy (the "lethal triad" in trauma surgery). Risks include high rates of incisional hernia, all forms of surgical site infections (SSI), enterocutaneous fistulas, pneumonia, sepsis, and organ failure.[9,10,11,12] The use of DCL has significant implications not just on mortality, but also on morbidity, patient-centered long-term outcomes, and healthcare resource utilization.

All of the studies comparing injured patients undergoing DEF and DCL are retrospective, subject to survival and collider bias, and have a wide variation in injury severity, transfusion requirements, surgeon rationale, and patient selection. A recent consensus statement in 2015 evaluating the appropriateness of various indications for DCL entirely lacked high-quality evidence. No RCTs assessing DCL exist for trauma.[13]

One difficulty in performing a RCT of DCL is there are a multitude of indications for which a majority of surgeons do not have the clinical equipoise to randomize patients. That is, no surgeon would randomize a patient with a severe liver injury in which the only method of hemorrhage control was gauze packing of the liver – an act which necessitates leaving the abdomen open as the gauze must be removed once bleeding has stopped. If a patient develops such significant bowel edema from resuscitation, the surgeon may not be able to physically close the incision or may do so with such tension that abdominal compartment syndrome (ACS) results.

Given this common operation (at our institution 1 trauma laparotomy is performed every 36 hours), high rate of mortality (26% in all DCLs), high rate of morbidity, and a lack of quality evidence, RCTs to compare DEF and DCL among patients undergoing emergent laparotomy for trauma are needed.

Preliminary Studies

Retrospective cohort study evaluating morbidity following DCL[5]

In 2015, I presented a retrospective cohort study at the Southwestern Surgical Congress (currently in production by the American Journal of Surgery) which quantified the average treatment effect of DCL compared to DEF. In this study of bleeding patients undergoing emergent laparotomy, DCL was associated with an 11% increase in enteric suture line failure, an 11% increase in fascial dehiscence, and a 19% increase in surgical site infection compared to DEF. While the statistical model used in this project was unique and the results interesting, the project was retrospective and suffered the same biases as the initial trials promoting the use of DCL.

Prospective Quality Improvement (QI) Project

In November 2013, I began a single-center QI project in which all emergent laparotomies were prospectively followed and outcomes recorded. Surgeons performing a DCL filled out a notecard in which they wrote the indication for DCL and perioperative data. After one year of following emergent laparotomies, we began discussing the appropriateness of all laparotomies at faculty meetings. The aims of the QI project were: 1) to safely decrease the rate of DCL, 2) to

identify indications for DCL in which there was surgeon equipoise, and 3) to examine surgeon variability in the performance of DCL.

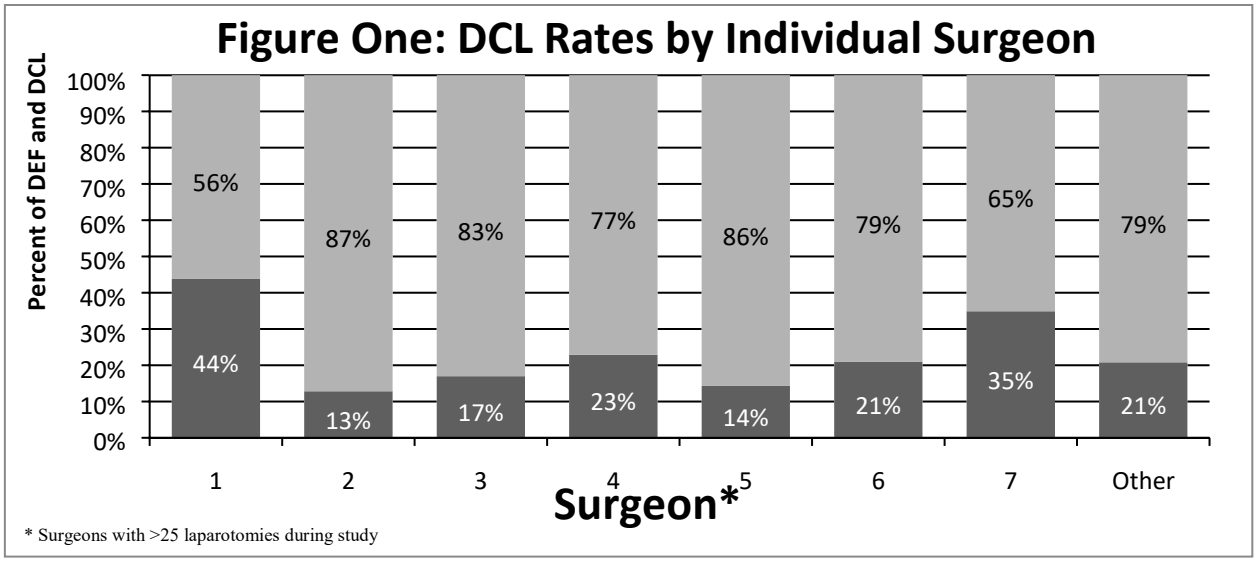
In Table 1, the list of indications for all DCLs during the time period is detailed. The list and percentage of all DCLs deemed potentially unnecessary is also listed. During the QI project, the necessary indications for DCL in which there was widespread agreement and no equipoise to potentially randomized patients include the following: non-absorbable gauze packing for hemorrhage control (only 7% potentially unnecessary DCLs), hemodynamic instability defined as continuous vasopressor use or ongoing transfusions (0% potentially unnecessary DCLs), to expedite time to IR for hemorrhage control (0% potentially unnecessary DCLs), and ACS prophylaxis (0% potentially unnecessary DCLs).

Beyond these four indications, significant surgeon variation in decision-making exists, indicating equipoise amongst the group. Surgeon equipoise exists for the following indications for DCL: second look (73% potentially unnecessary DCLs), hemodynamic instability with a definition other than continuous vasopressor use or ongoing transfusion (33% potentially unnecessary DCLs), to expedite transfer to CT or the ICU (100% potentially unnecessary DCLs), and to plan an additional wash out of the abdomen due to contamination (100% potentially unnecessary DCLs).

Table 1. QI Project – Nov 2013 – Sept 2015		
Definitive laparotomies	318 (78%)	
Damage control laparotomies	92 (22%)	DCLs deemed unnecessary
Indications for DCL:		
Packing	55 (58%)	4 (7%)
Second look	15 (16%)	11 (73%)
Hemodynamic instability	15 (16%)	5 (33%)
Continuous vasopressors	8	0 (0%)
Ongoing transfusions	6	0 (0%)
Other definition	6	5 (83%)
Expedite CT/ICU	2 (2%)	2 (100%)
Expedite IR	1 (1%)	0 (0%)
ACS prophylaxis	5 (5%)	0 (0%)
Contamination	1 (1%)	1 (100%)

**preliminary data*

This variation in the utilization of DCL for specific indications was accompanied by a significant variation in surgeon-specific rates of DCL (Figure 1), which varied from 14-44% and could not be accounted for by the severity of patient injury.



We hypothesize that, among randomized patients, DCL results in increased mortality or major abdominal complications (MAC), defined as an organ/space SSI, enteric suture line failure, fascial dehiscence, or unplanned return to OR after fascial closure for an abdominal complication, within 30 days.

Objectives

To prove or disprove the hypothesis, the specific aims of the proposed project are:

Aim 1: To perform a single-center, randomized, controlled trial to compare the effect of DCL to DEF on death or MACs within 30 days, additional clinical outcomes, including morbidity, mortality, and lengths of stay.

Aim 2: To compare resource utilization of DEF and DCL, comparing the direct costs of DCL and the direct costs of the complications associated with DCL and DEF.

Aim 3: To measure long-term, patient-centered outcomes of the study patients, including health status data, incidence of post-traumatic stress disorder, and return to work.

Aim 4: To assess feasibility and provide estimates of effect size of individual outcomes for the planning and execute a multicenter, RCT of DCL compared to DEF.

Primary outcome: death or MAC – a binary, composite variable defined as the development of an organ/space SSI, enteric suture line failure (aka anastomotic leak), fascial dehiscence, or an unplanned return to the OR for an abdominal complication – within 30 days.

Secondary outcomes:

- Non abdominal morbidities – acute kidney failure, adult respiratory distress syndrome, deep vein thrombosis (DVT), pulmonary embolism, pneumonia, and

urinary tract infection, all identified based on standardized definitions used in the National Trauma Databank, to which MHH-TMC already provides patient data.

- Hospital-, ICU-, ventilator-free days – defined as: 30 – total hospital days/ICU days/ventilator days alive = hospital-, ICU-, and ventilator-free days.
- Hospital costs – to be obtained from MHH-TMC
- Patient-centered outcomes – Standard Gamble, EuroQOL-5D(5L), and the Post-Traumatic Stress Disorder Check List-Civilian (PCL-C) to be administered at discharge and 6 months after discharge.

Study Design

This is a single center, RCT involving patients requiring an emergent trauma laparotomy within the first 90 minutes following ED admission due to a severe abdominal injury.

Intervention

Control – DCL
Intervention – DEF

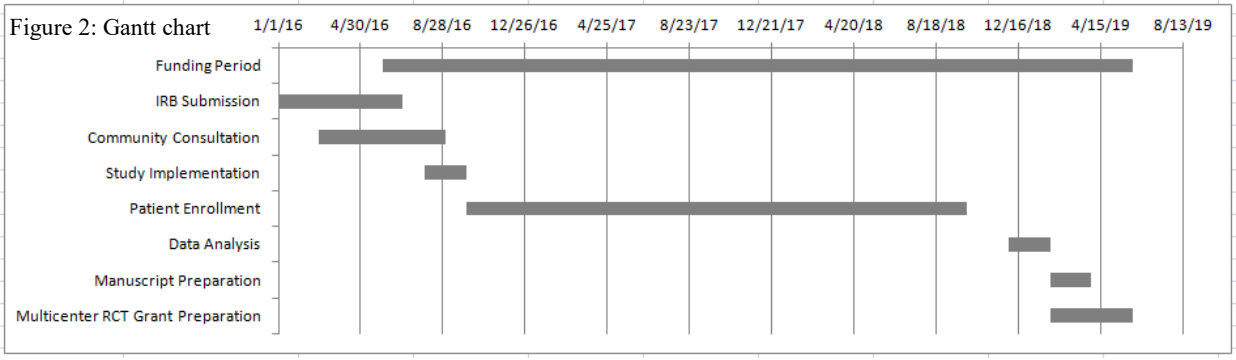
Setting

This study will be conducted at the Texas Trauma Institute at Memorial Hermann Hospital-Texas Medical Center (MHH-TMC). It is one of two Level 1 trauma centers in the Houston metropolitan area, an area in which over 6 million people reside, and is the busiest trauma center in the country, with over 6,000 trauma admissions per year. Approximately 220 emergent trauma laparotomies are performed each year, of which 25-35% are DCLs.

Time Period

IRB submission will occur in January 2016, with community consultation beginning shortly thereafter. Eligible patients will be enrolled starting on July 7, 2016. Enrolled subjects will be followed during their post-laparotomy hospitalization and for 6 months following their hospital discharge to assess patient-centered outcomes.

Figure 2: Gantt chart



Outcomes

The primary outcome for this study will be a composite variable composed of the following death or major abdominal complications (MAC) within 30 days:

- Deep or organ/space SSI, as defined by the Centers for Disease Control and Prevention[14]

- Enteric suture line failure (enteric anastomotic leak) – leakage of enteric contents from gastrointestinal anastomosis
- Fascial dehiscence or evisceration – separation of closed fascia with or without protrusion of intestines (to be determined by independent, blinded surgeon)
- Unplanned return to OR after fascial closure for intra-abdominal complication

We hypothesize that patients randomized to DCL will have a higher rate of the primary outcome than those randomized to DEF.

Secondary outcomes will include non-abdominal morbidities, in-hospital mortality or discharge to hospice (as patient is being discharged in order to die with comfort, this will be considered the same as an in-hospital mortality), hospital-/ICU-/ventilator-free days, total hospital stay costs as provided by Memorial Hermann, and patient-centered outcomes.

Non-abdominal complications will be identified based on standardized definitions used in the National Trauma Databank and include: acute kidney failure, adult respiratory distress syndrome (ARDS), deep venous thrombosis (DVT), pulmonary embolism, pneumonia, and urinary tract infection.

Per-patient cost information will be obtained from the hospital and used to study the healthcare resource utilization of DCL.

For patient-centered outcomes, the patients' health state will be queried at discharge and 6 months after discharge using the Standard Gamble and EuroQol-5D(5L).[15,16] The Posttraumatic Stress Disorder Check List-Civilian [PCL-C] will also be administered 6 months after discharge. Additionally, time to return to work will also be obtained at the 6 month interview.

Overall safety data (compared to historical controls) will be assessed every 6 months throughout the study period by a data safety and management board (DSMB), which will be organized by CeTIR and headed by Dr. Curtis Wray. The DSMB will also include an anesthesiologist, another independent surgeon, a former trauma patient without a medical background who underwent emergent laparotomy, and an independent statistician.

Study Population

Screening

Clinical research staff will be available on a 24/7 basis to conduct screening and collect data on those patients meeting inclusion criteria. Direct patient observation and data collection will begin immediately upon the patient's arrival to the ED and will continue until 1) it is determined that patient does not meet all inclusion criteria, 2) the surgical procedure has been completed, or 3) the patient dies.

Inclusion/Exclusion Criteria

All patients presenting with trauma requiring emergent laparotomy will be screened for eligibility for the study. Emergent laparotomy is defined as: (1) time in ED ≤90 minutes and (2) admission to the OR directly from the ED or IR or prehospital transport (bypass ED and straight to OR from LifeFlight or EMS). Patients meeting all inclusion criteria will be enrolled in the study.

Inclusion criteria

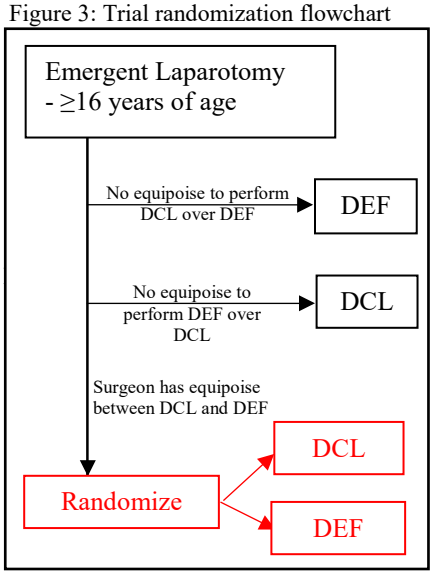
- Emergent laparotomy

- Patient has injuries for which surgeon has equipoise to perform a DEF or DCL
- Age ≥16 years (age cut-off for admission to adult trauma service at MHH-TMC)

Exclusion criteria:

- Indication for DCL for which there is no surgeon equipoise:
  - Need for gauze packing of liver or retroperitoneum for hemorrhage control
  - Immediate need to go to IR for hemorrhage control
  - Concern for ACS – defined as physically unable to re-approximate fascia or >10mmHg change in peak airway pressure during fascial closure
  - Hemodynamic instability – defined as persistent hypotension, ongoing transfusion requirement, or continuous vasopressor use
- Indication for DEF for which there is no surgeon equipoise:
  - Negative and non-therapeutic laparotomies
  - Isolated cystorrhaphy
- Prisoners; known pregnancy; patients with burns > 20% of total body surface area (resuscitation and treatment differs significantly from trauma patients without burns); patient/legally authorized representative opted out of exception from informed consent (opt out bracelet)
- Currently enrolled in another interventional study

Figure 3: Trial randomization flowchart



Subjects sixteen years of age and older are considered as adult trauma subjects in a large percent of the trauma centers. Sixteen and seventeen year olds are able to drive in most states and are at high risk for motor vehicle accidents resulting in blunt or penetrating injuries. Excluding this age group would significantly decrease the external validity of the proposed project.

Additionally, it is difficult to differentiate a 16 or 17 year old from one who is 21 or older at the time care is initiated in the ED until positive identification can be obtained. Children below the age of 15 or 50 kg body weight will be excluded from this trial. Children‘s intravascular volume is different than the adult‘s, requiring adjustments to the standard adult treatment protocols.

Study Procedures

Randomization

Allocation will occur through sequentially numbered, opaque envelopes kept in the research assistants’ office and opened in the operating room. An independent statistician will determine the randomization sequence and oversee the labeling of cards and envelopes. A 1:1 allocation ratio using a permuted block design of 4 or 6 will be used to ensure equal number of patients in each group.

Randomization will occur during the emergent trauma laparotomy. The research assistant will query the attending trauma surgeon periodically throughout the procedure to determine their

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equipoise between DCL and DEF. If the patient meets all eligibility criteria, that patient will be randomized to DCL (control) or DEF (intervention). The research staff will open the opaque envelope to notify the attending surgeon which group to which the subject has been randomized.

Data Collection

All data will be collected by research assistants utilizing a standardized case report form and entered into a RedCap™ database. Each subject will be assigned a study-specific number. Data will be collected from the clinical pre-hospital emergency medical services run sheets, in hospital records, and the trauma registry. Data will be collected until hospital discharge and questionnaires at discharge and 6 months later.

Data collected will include: demographics, prehospital and injury information, hospital information including ED, OR and post-operative care, discharge information, follow up clinic visits, healthcare cost assessments, and the health status questionnaires completed at discharge and 6 months following injury.

Only laboratory values ordered for and used in standard clinical practice will be collected. No study-specific laboratory tests will be ordered. No biologic specimens will be kept or used.

Follow up

No study-specific follow-up will be required. Six-month questionnaires will be performed by phone call. $5 Starbucks gift cards will be provided to patients who complete the 6 month follow up questionnaires.

Data and Safety Monitoring

For DCL patients, adverse events are the primary outcome. Both patients in the DEF and DCL groups are at risk for the same adverse events and the event rate in the proposed groups is unknown. To assess for harm, blinded, univariate outcomes between the two groups will be assessed every 6 months throughout the study period by a data safety and management board (DSMB), which will be organized by CeTIR and headed by Dr. Curtis Wray. The DSMB will also include an anesthesiologist, a former trauma patient without a medical background who underwent emergent laparotomy, and an independent statistician. At the first meeting following 50% recruitment, a formal Bayesian analysis will be presented to the DSMB to assess the probability of benefit or harm of DCL.

One potential problem area is surgeon adherence to randomization. While the Division of Acute Care Surgery has an excellent record of trauma surgeon buy in for randomized, controlled trials (Early Whole Blood trial, PROPPR, Irricept®), it remains a concern that surgeons will choose not to enroll potentially eligible patients or fail to implement the randomized treatment. To help mitigate surgeon deviation, preliminary work showing indications for which there is equipoise among practicing surgeons has been performed. Additionally, all emergent laparotomies will be evaluated the following day to assess eligibility. If not randomized, the PI will provide real-time surgeon feedback to improve future compliance. Protocol deviations of randomized patients will be documented and reported in publications. Patients will be analyzed on an intent-to-treat basis, so randomized patients will be statistically analyzed in the group to which they were randomized.

Statistics

Sample Size

Over a 2 year period, we aim to enroll 56 patients, 28 in each arm based upon: 1) preliminary data with a MAC rate of 55% in DCL patients and 18% in the DEF patients, 2) alpha=0.05, 3) power=0.80, and 4) dropout rate=10%.

Table 2: Sample size calculations	
Enrolled Patients	Expected Difference in MAC (DCL – DEF)
36	47% (65% – 18%)
56	37% (55% – 18%)
108	27% (45% – 18%)

Approximately 55-66 DCLs are performed per year, therefore over 2 years of patient enrollment, enrolling 56 patients meeting eligibility is realistic.

Randomization

Allocation will occur through sequentially numbered, opaque envelopes kept in the research assistants' office and opened in the operating room. An independent statistician will determine the randomization sequence and oversee the labeling of cards and envelopes. A 1:1 allocation ratio using a permuted block design of 4 or 6 will be used to ensure equal number of patients in each group.

Randomization will occur during the emergent trauma laparotomy. The research assistant will query the attending trauma surgeon periodically throughout the procedure to determine their equipoise between DCL and DEF. If the patient meets all eligibility criteria, that patient will be randomized to DCL (control) or DEF (intervention). The research staff will open the opaque envelope to notify the attending surgeon which group to which the subject has been randomized.

Data Analysis Plan

The number of screened patients and reasons for exclusion will be reported. Protocol violations and reasons for those violations will be reported and detailed. Differences in primary and secondary outcomes across treatment groups will be compared on an intent-to-treat basis using the Wilcoxon rank-sum test, Pearson's Chi-squared, and Fisher's Exact test, for continuous, binary, and sparse binary outcomes, respectively. Exploratory analyses will model outcomes via linear or logistic regression with treatment as the predictor, controlling for any covariates found to be imbalanced across treatment assignment. An independent statistician will provide all data analyses and present them to the DSMB for review.

Given the small sample size of the trial, we will augment the frequentist model described above with a Bayesian analysis to estimate the probability of treatment effects of DCL and DEF.[17]

Ethics

This study qualifies for the "Exception from informed consent required for emergency research" (EFIC) as outlined in the FDA regulation 21CFR50.24.[18]

1. Subjects are in a life-threatening situation and collection of valid scientific evidence is necessary to determine the safety and effectiveness of the particular interventions
2. Obtaining informed consent is not feasible because the subject cannot give reasonable consent due to medical condition, intervention must be given before consent can be obtained from a LAR, and cannot prospectively select subject

3. There is prospect of direct benefit to subject because they are in a life-threatening situation requiring intervention, risks associated with this study are reasonable compared to standard of care therapy
4. The research could not practically be carried out without a waiver
5. Diligent attempts will be made to contact the LAR or family member for them to object to subject's continued study participation within the protocol-defined therapeutic window
6. IRB has reviewed and approved the informed consent procedures and documents to be used with the subjects or LAR for this study.
7. Additional protection of rights will be provided which will include: community consultation and public notification, an established executive committee, and efforts will be made to obtain informed consent from family members if the LAR is not available.

Our center has a long history of successfully conducting EFIC studies and will be performing the process in close conjunction with the UTH Committee for the Protection of Human Subjects (CPHS). After randomization, efforts to obtain individual or legally authorize representative consent will be sought.

Data Handling and Record Keeping

All data will be collected utilizing a standardized case report form and entered into a RedCap™ database. Each subject will be assigned a study-specific number. Data will be collected from the clinical pre-hospital emergency medical services run sheets, in hospital records, and the trauma registry. Data will be collected until hospital discharge and questionnaires at discharge and 6 months later.

All hard copy source documentation will be kept in a secured, locked cabinet in the research coordinator's office. All study documents will be maintained in a secure location for two years following study completion.

Quality Control and Assurance

Each item on the web forms will have validity checks performed to ensure that the data entered are accurate and that items are not skipped during entry by mistake. Checks will be developed by both clinical investigators and research assistants. Depending on the question, any item found that does not meet the respective edit criteria will have an appropriate error message displayed when the user tries to save the data. Errors will be classified as either "hard" errors meaning that a valid response is required before the data can be saved or as "soft" errors in which the entry operator can either correct the errors or override them to indicate that the data are correct although it does not meet the edit criteria. Examples of hard errors would be items such as identifiers and event dates. An example of a soft error would be values that are outside a pre-defined range. When the data record is saved, a form status field will be updated to indicate the current status of the form. There are currently four status states that the form can have. These statuses are: the form is incomplete, the form is complete, the form was saved with errors, and the form is complete with errors. For the first status, the entry user will have the option to save a record as ―incomplete‖ for situations where they have partially entered a form and must stop because of an interruption. This

will allow the user or the study coordinator to pull up the form at a later time and finish completing it. If the form was entered without any errors, then the record will be saved as complete. If the user overrides any soft errors found, the record will be saved as ―saved with errors‖.

Publication Plan

Planned publications include the following:

(1) Methodology paper detailing the steps to implement the proposed project;
(2) Clinical results paper of randomized controlled trial of DEF versus DCL;
(3) Patient-centered outcomes of randomized controlled trial of DEF versus DCL;
(4) Healthcare resource utilization study of DCL;
(5) Feasibility of multicenter RCT of DCL

References

[1] Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Injury Prevention and Control [online]. Accessed September 20, 2015.

[2] Tisherman SA, Schmicker RH, Brasel KJ, Bulger EM, Kerby JD, Minei JP, Powell JL, Reiff DA, Rizoli SB, Schreiber MA. Detailed Description of All Deaths in Both the Shock and Traumatic Brain Injury Hypertonic Saline Trials of the Resuscitation Outcomes Consortium. Ann Surg. Mar 2015;261(3):586-90.

[3] Stone HH, Strom PR, Mullins RJ. Management of the Major Coagulopathy with Onset during Laparotomy. Ann Surg. May 1983;197(5):532-35

[4] Rotondo MF, Schwab CW, McGonigal MD, Phillips GR, Fruchterman TM, Kauder DR, Latenser BA, Angood PA. 'Damage Control': an Approach for Improved Survival in Exsanguinating Penetrating Abdominal Trauma. J Trauma. Dep 1993;35(3):375-82

[5] Hatch QM, Osterhout LM, Ashraf A, Podbielski J, Kozar RA, Wade CE, Holcomb JB, Cotton BA. Current Use of Damage-Control Laparotomy, Closure Rates, and Predictors of Early Fascial Closure at the First Take-Back. J Trauma. June 2011(70):1429-36

[6] Cotton BA, Reddy N, Hatch QM, LeFebvre E, Wade CE, Kozar RA, Gill BS, Albarado R, McNutt MK, Holcomb JB. Damage Control Resuscitation is Associated with a Reduction in Resuscitation Volumes and Improvement in Surivival in 390 Damage Control Laparotomy Patients. Ann Surg. Oct 2011;254(4):598-605

[7] Higa G, Friese R, O'Keefe T, Wynne J, Bowlby P, Ziemba M, Latifi R, Kulvatunyou N, Rhee P. Damage Control Laparotomy: a Vital Tool Once Overused. J Trauma. Jul 2010;69(1):53-9

[8] Harvin JA, Wray CJ, Steward J, Lawless RA, McNutt MK, Love JD, Moore LJ, Wade CE, Cotton BA, Holcomb JB. Control the Damage: Morbidity and Mortality after Emergent Trauma Laparotomy. Submitted to American Journal of Surgery. Presented at Southwestern Surgical Congress, 2015.

[9] DuBose, Scalea TM, Holcomb JB, Shrestha B, Okoye O, Inaba K, Bee TK, Fabian TC, Whelan J, Ivatury RR, AAST Open Abdomen Study Group. Open Abdomen Management after Damage Control Laparotomy for Trauma: a Prospective, Observational AAST Multicenter Study. J Trauma Acute Care Surg. Jan 2013;74(1):113-20

[10] Burlew CC, Moore EE, Cuschieri J, Jurkovich GJ, Codner P, Nirula R, Millar D, Cohen MJ, Kutcher ME, Haan J, MacNew HG, Ochsner G, Rowell SE, Truitt MS, Moore FO, Pieracci FM, Kaups KL, WTA Study Group. Who Should We Feed? A WTA Multi-Institutional Study of Enteral

Nutrition in the Open Abdomen after Injury. J Trauma Acute Care Surg. Dec 2012;73(6):1380-87
[11] Teixeira PG, Inaba K, Dubose J, Salim A, Brown C, Rhee P, Browder T, Demetriades D. Enterocutaneous Fistula Complicating Trauma Laparotomy: a Major Resource Burden. Am Surg. Jan 2009;75(1):30-2
[12] Hatch QM, Osterhout LM, Podbielski J, Kozar RA, Wade CE, Holcomb JB, Cotton BA. Impact of Closure at the First Take Back: Complication Burden and Potential Overutilization of Damage Control Laparotomy. J Trauma. Dec 2011;71(6):1503-11
[13] Roberts DJ, Bobrovitz N, Zygun DA, Ball CG, Kirkpatrick AW, Faris PD, Parry N, Nicol AJ, Navsaria PH, Moore EE, Leppaniemi AK, Inaba K, Fabian TC, D'Amours S, Brohi K, Stelfox HT. Indications for Use of Thoracic, Abdominal, Pelvic, and Vascular Damage Control Interventions in Trauma Patients: a Content Analysis and Expert Appropriateness Rating Study. J Trauma Acute Care Surg. Oct 2015;79(4):568-79.
[14] Centers for Disease Control and Prevention, Healthcare Infection Control Practices Advisory Committee (HICPAC). Guideline for Prevention of Surgical Site Infection [online]. Accessed November 29, 2015.
[15] Shaw JW, Johnson JA, Coons SJ. US Valuation of the EQ-5D Health States: Development and Testing of the D1 Valuation Model. Medical Care. March 2005;43(3):203-20.
[16] Alghnam S, Schneider EB, Castillo RC. Insurance Status and Health-Related Quality-of-Life Disparities after Trauma: Results from a Nationally Representative Survey in the US. Qual Life Res. Sep 2015. [Epub ahead of print]
[17] Wijeysundera DN, Austin PC, Hux JE, Beattie WS, Laupacis A. Bayesian Statistical Inference Enhances the Interpretation of Contemporary Randomized Controlled Trials. J Clin Epidemiol. Jan 2009;62(1):13-21.
[18] U.S. Food and Drug Administration, Code of Federal Regulations Title 21. Section 50.24, Exception from Informed Consent Requirements for Emergency Research [online]. Accessed November 29, 2015.