Embolization in Splenic Trauma (ELSA)

Study Protocol & Statistical Analysis Plan

NCT03613454

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Embo**l**ization in **S**plenic **T**rauma (ELSA)

Trial Protocol

FUNDER

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TRIAL REGISTRATION

Clinicaltrials.gov: NCT03613454

ABBREVIATIONS

AAST	American Association for the Surgery of Trauma
AE	Adverse Event
ARC	Alabama Resuscitation Center
CRF	Case Report Form
dSAE	Distal Splenic Artery Embolization
DSMB	Data Safety and Monitoring Board
eCRF	Electronic Case Report Form
ED	Emergency Department
EFIC	Exception From Informed Consent
ELSA	Embolization in Splenic Trauma
EMS	Emergency Medical Services
FDA	Food and Drug Administration
GA	General Anesthesia
GCP	Good Clinical Practice
GCS	Glascow Coma Score
IRB	Institutional Review Board
ISS	Injury Severity Score
NOM	Non-operative Management
OR	Operating Room
pSAE	Proximal Splenic Artery Embolization
REDCap	Research Electronic Data Capture
SIR	Society of Interventional Radiology
UAB	University of Alabama at Birmingham
VP	Vascular Plug

1. PROTOCOL SUMMARY

Questions addressed

Our aim is to perform a randomized, prospective, pilot study comparing the use of coils versus vascular plugs for proximal splenic artery embolization in the setting of high-grade splenic trauma.

The questions addressed in this trial include:

1. Is it feasible to perform this type of study in this patient population by meeting patient accrual goals and obtaining adequate patient follow-up?
2. What are the clinical, technical, and economic outcomes associated with proximal splenic artery embolization using coils or vascular plugs?

Study population

Inclusion criteria: ≥18 years of age; trauma resulting in grade III or higher splenic injury on contrast-enhanced CT as defined by the AAST guidelines; splenic injury to be treated by non-operative management as decided by attending trauma surgeon and interventional radiologist; patient will undergo proximal splenic artery embolization as decided by the attending interventional radiologist

Exclusion criteria: inability to obtain informed consent; uncorrectable coagulopathy; patient is immunocompromised; pregnant; breast-feeding; non-English speakers; prisoners

Interventions

Patients will be screened for eligibility. Eligible patients will be referred for proximal splenic artery embolization and randomized to coils versus vascular plugs. Proximal splenic artery embolization will be performed. Relevant data from patient arrival and hospitalization will be collected. CT scan over-read will be performed by an attending abdominal radiologist. Follow-up data at approximately 30 days will be obtained (see

sections 6 "Patients, Recruitment, and Randomization", 7 "Interventions", and 9 "Data Collection").

Outcome assessment

We plan to demonstrate the feasibility of performing this type of study in this patient population by meeting patient accrual goals and obtaining adequate patient follow-up. Secondarily, we will assess outcomes of both groups using technical success (ability to embolize the mid-splenic artery with the prescribed device), device failures, intra-procedural complications, procedural time, equipment costs, radiation exposure, need for secondary embolic agents, length of stay, post-embolization transfusion requirements, delayed complications, and splenic salvage rates as secondary endpoints.

Trial coordination

Dr. Gunn and Dr. Jansen will be principle investigators. Rebecca Lee will be program manager.

2. TRIAL PERSONNEL

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3. INTRODUCTION/ BACKGROUND

Trauma is the leading cause of death and disability in the United States for all age groups and the single most important cause for years of life lost for persons under the age of 65 [1]. As a major, urban, academic medical center, UAB Hospital is one the busiest trauma centers in the country treating approximately 4,500 major trauma patients annually. Many of these patients present with significant abdominal injuries. Major abdominal trauma, whether by blunt forces or penetrating injuries, carries a significant risk for patient mortality. The spleen is one of the most commonly injured organs in abdominal trauma [1]. Hemodynamically unstable patients whose primary site of injury is the spleen require splenectomy. However, the management of hemodynamically stable patients with traumatic injuries to the spleen is less well-defined. The recognition of the key role of the spleen in producing antibodies, monocytes, and activated lymphocytes has led to a paradigm shift in the management of splenic injuries towards preservation when possible. Currently, the majority of patients with splenic injury are managed without surgery [8].

Splenic preservation rates are improved for patients with high-grade splenic injuries when NOM is supplemented by image-guided, trans-catheter splenic artery embolization (SAE) [3-6]. SAE is currently the standard of care for hemodynamically stable patients with high-grade splenic injuries. SAE is primarily performed using proximal splenic artery embolization (pSAE). pSAE is most often accomplished using either coils or vascular plugs as the embolic agent, both of which are FDA-approved.

Coils have a long history of efficacy and safety for embolization and are thus familiar embolic agents to most endovascular specialists. Further, coils large enough to embolize the mid-splenic artery can be deployed through a standard micro-catheter, which means they can be used in even the most tortuous splenic arteries. However, multiple coils may be needed in the same patient to achieve hemostasis in the mid-splenic artery. This attribute may increase overall cost, iodinated contrast use, procedural time, and the radiation exposure to the patient and medical staff. Additionally, given the high-flow nature of the splenic artery, even an appropriately sized coil may migrate distally. Some of these limitations are overcome through the introduction of coils that are both longer

and larger than traditional coils, namely POD® coils (Penumbra, Alameda, CA, USA). Using these larger coils can decrease the number needed to obtain hemostasis. These coils come in two varieties: 1) a helical coil sized to the vessel diameter that anchors the coil pack in the high-flow vessel thereby reducing the risk of distal migration and 2) a packing coil that is used to fill in the spaces within the helical coil. A typical pSAE using coils will involve the deployment of one helical coil followed by multiple packing coils until hemostasis is achieved.

Vascular plugs attempt to overcome the limitations of coils. For example, the deployment of a single vascular plug can typically provide hemostasis in the mid-splenic artery, theoretically reducing procedural time, contrast load, and radiation exposure. Despite this, vascular plugs are usually less familiar devices to endovascular specialists. Another drawback of vascular plugs is that they cannot be deployed through a standard micro-catheter but rather require the advancement of a larger, stiffer 0.035 inch system into the mid-splenic artery. This may limit their use in very tortuous splenic arteries. Vascular plugs reaching up to 8mm in size (Amplatzer™ IV, Abbott Medical, Abbott Park, IL, USA) can be deployed through a standard 5F diagnostic catheter. Larger vascular plugs (Amplatzer™ II) require at least a larger 6F guiding catheter.

Currently, the selection of embolic agent for pSAE is primarily based on operator experience and preference. The efficacy, technical success, and cost of using coils compared to vascular plugs has been evaluated in such conditions as pelvic congestion syndrome [10], yet, to the best of our knowledge, these embolic agents have never been compared for their use in pSAE, much less in a randomized, prospective fashion. We anticipate this pilot trial to demonstrate the feasibility of a larger study and provide sufficient information to identify appropriate primary endpoints. The innovation of this proposal is strengthened by the inclusion of over-reads of pre-procedural CT scans, which will allow accurate grading of splenic injury and information regarding associated vascular injury to the spleen. If found, significant differences between our study groups in either clinical outcomes, technical parameters, or cost would have an immediate impact on how we care for trauma patients both locally and nationally.

4. AIMS AND OBJECTIVES

Aim 1: To demonstrate the feasibility of performing a trial of pSAE in trauma patients with splenic injuries (see section 8 "Outcomes").

Objective 1a: To demonstrate that at least 50% of eligible patients can be enrolled into a randomized clinical trial.

Objective 1b: To demonstrate that successful follow-up at 30 days will be obtained in at least 80% of enrolled patients.

Aim 2: To evaluate clinical outcomes in order to identify endpoints for a larger trial (see section 8 "Outcomes").

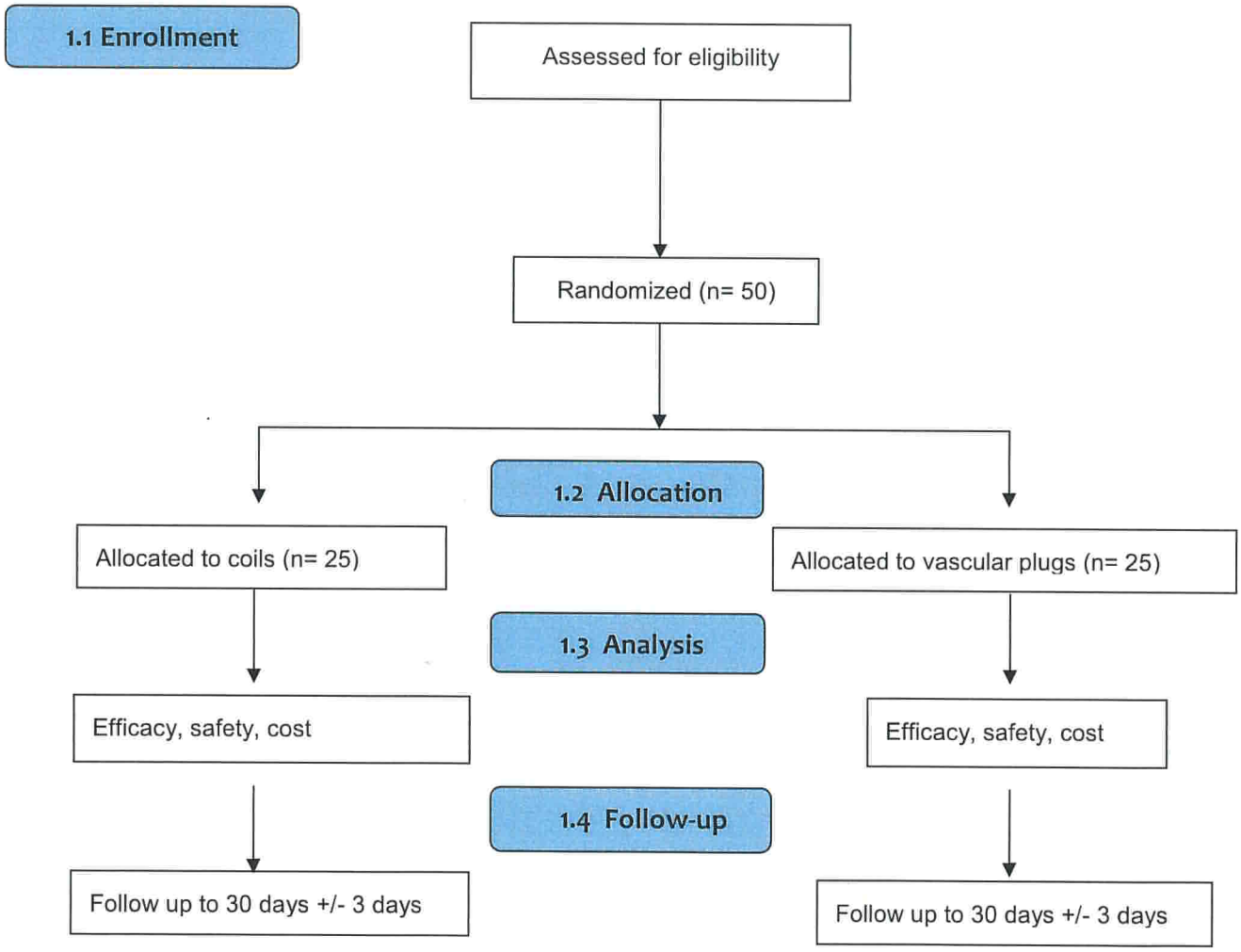
Objective 2a: To compare clinical outcomes of pSAE using coils versus vascular plugs.

Objective 2b: To compare technical outcomes of pSAE using coils versus vascular plugs.

Objective 2c: To conduct a cost analysis of using coils versus vascular plugs.

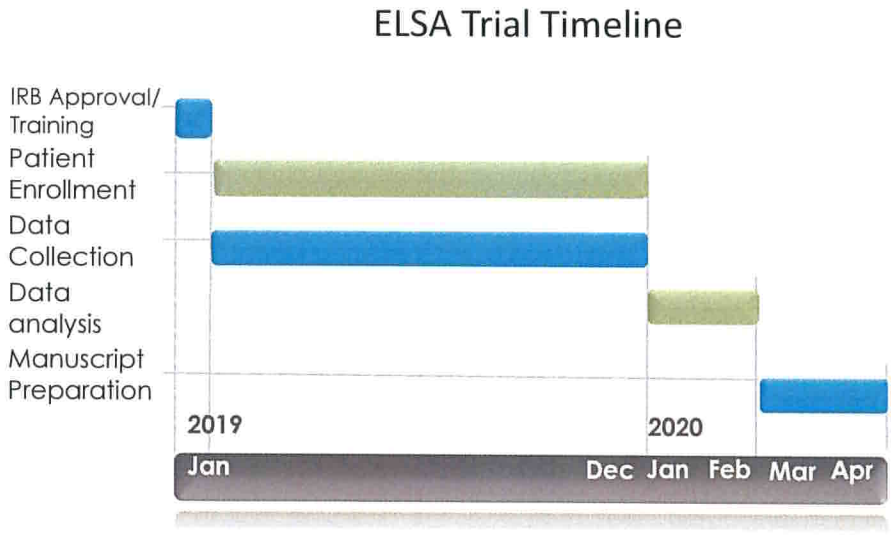
5. DESIGN AND INTERVENTION

Randomized clinical trial. Patient flow is summarized in the CONSORT diagram below.



Study Calendar:

We anticipate this pilot project to take 16 months to complete. December 2018: IRB approval, training and education of study staff, training and education of trauma and interventional radiology physicians; January 2019 – December 2019: patient enrollment; data collection and monitoring; January 2020 – February 2020: Data analysis and data monitoring; March - April 2020: Final data analysis; manuscript preparation and submission.



6. PATIENTS, RECRUITMENT, AND RANDOMIZATION

6.1 Setting

This study will be performed at the University of Alabama Hospital.

6.2 Study population

6.2.1 Inclusion criteria

a) ≥18 years of age
b) Trauma resulting in grade III or higher splenic injury on contrast-enhanced CT as defined by the AAST guidelines
c) Splenic injury to be treated by non-operative management as decided by attending trauma surgeon and interventional radiologist
d) Patient will undergo proximal splenic artery embolization as decided by the attending interventional radiologist

6.2.2 Exclusion criteria

a) Inability to obtain informed consent
b) Uncorrectable coagulopathy
c) Patient is immunocompromised
d) Pregnant
e) Breast-feeding
f) Non-English speakers
g) Prisoners

6.3 Recruitment

An attending trauma surgeon will evaluate all trauma patients. Patients with a confirmed grade III or higher splenic injury on contrast-enhanced CT will be considered for entry into the study. Typically, hemodynamically unstable patients or stable patients with additional injuries that would require abdominal surgery are managed operatively while all others are candidates for non-operative management. The decision to proceed with

splenic artery embolization will be made by an attending interventional radiologist in conjunction with the attending trauma surgeon.

Clinicians will be assisted by research associates (RAs) from the Alabama Resuscitation Center (ARC), who are available 24 hours per day, and will screen all patients with grade III (and higher) splenic injuries for entry into the study. The RAs will discuss the protocol with the patient and/or their representative, and notify the trauma team if they are prepared to participate. The RA will notify both the attending trauma surgeon, and the interventional radiologist, that the patient is potentially eligible for the study. Once the attending interventional radiologist deems the patient an appropriate candidate for SAE, the interventional radiology team will screen the patient for eligibility. Once deemed eligible, informed consent for the procedure *and* the study will be obtained by the interventional radiology service from either the patient or their legally-authorized representative. If the patient is unable to consent for themselves *and* the legally-authorized is not physically present, the patient will be considered excluded from the study. All study and consent discussions will take place in a private room, away from other patients, so that conversations cannot be overheard and potential subjects cannot be publicly identified.

6.4 Randomization

After meeting the above criteria and obtaining informed consent, the patient will be randomized to either the coil arm or arm. Randomization will occur by sealed numbered envelopes. The sealed envelopes will be located in the Interventional Radiology Reading Room in the Heart and Vascular Center (6th floor, North Pavilion). This is a secure area requiring badge access at all times.

7. INTERVENTIONS

The trial will compare two different devices: Coils (POD®, Penumbra, Alameda, CA, USA), and vascular plugs (Amplatzer™, Abbott Medical, Abbott Park, IL, USA).

7.1 POD® coils

Coils are FDA-approved endovascular occlusion devices that are longer than traditional coils and are deployed through a high-flow mirco-catheter (Figure 1). Each type of coil comes in two varieties: 1) a helical coil sized to the vessel diameter that anchors the coil pack in the high-flow vessel and 2) a packing coil that is used to fill in the spaces within the helical coil. A typical pSAE using coils will involve the deployment of one helical coil followed by multiple packing coils until hemostasis is achieved.

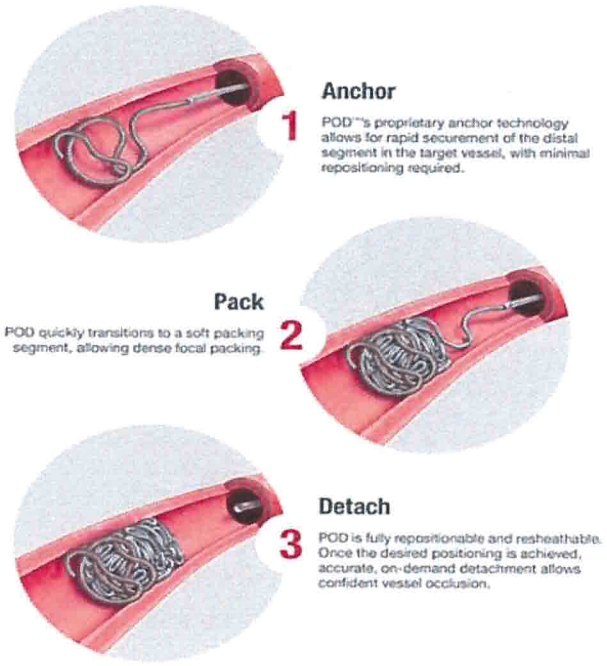


Figure 1. Graphical depiction of a typical embolization using helical and packing POD coils. (Image from Penumbra.com)

7.2 Vascular plugs

Vascular plugs are FDA-approved endovascular occlusion devices that require an 0.035 inch system within the splenic artery for deployment (Figures 2 and 3). The Amplatzer™

IV vascular plug can be deployed through a traditional 5F diagnostic catheter. However, the largest Amplatzer™ IV vascular plug is only 8 mm in size, which may be too small for some splenic arteries. In these cases, a larger Amplatzer™ II vascular plug is needed although these vascular plugs require a larger system for deployment.

Figure 2. Picture of an Amplatzer™ IV VP (from St. Jude Medical)

Figure 3. Picture of an Amplatzer™ II VP (from St. Jude Medical)

7.3 Proximal Splenic Artery Embolization Procedure

An attending interventional radiologist will perform all SAE procedures using either moderate conscious sedation or general anesthesia depending on the patient's condition. The vascular access site is prepared and draped in standard sterile fashion.

Local anesthesia will be achieved with lidocaine. The right common femoral artery is the most commonly used vascular access for splenic artery embolization but the left common femoral artery may be used for certain patients. No radial artery access will be used. Regardless, the artery is accessed under direct sonographic guidance with a micro-puncture set. The micro-puncture set is then exchanged for a vascular sheath over a wire and attached to a heparinized saline flush. A celiac axis angiogram is then performed. The attending interventional radiologist will choose the diagnostic catheter based on his/her preference. The attending interventional radiologist will review the celiac angiogram to identify an appropriate landing zone in the mid-splenic artery distal to the origin of the dorsal pancreatic artery but proximal to the origin of the pancreaticomagna artery in order to preserve collateral flow to the spleen via the transverse pancreatic artery. The vessel's diameter at this location will be measured and recorded. For patients randomized to coil embolization, a high-flow micro-catheter is navigated to the location of embolization with the assistance of a micro-wire. The micro-wire-micro-catheter combination will be left to the discretion of the attending interventional radiologist. Once the micro-catheter is in place, a splenic angiogram will be performed. Coil embolization will then proceed per the manufacturer's instructions for use until satisfactory hemostasis is achieved. For patients randomized to vascular plug embolization, the appropriately-sized catheter or sheath is advanced to the location of embolization. The tools used to access the mid-splenic artery will vary depending on the operator's experience and patient anatomy. Once the catheter is in place, a splenic angiogram will be performed. Vascular plug embolization will then proceed per the manufacturer's instructions for use until satisfactory hemostasis is achieved. For both coil and vascular plug embolization, absence of flow at the level of the embolic agent in the mid-splenic artery will serve as the endpoint for satisfactory hemostasis. Regardless of the embolic used the interventional radiologist will perform intermittent angiograms (one per minute) to determine if stasis has been achieved. The time to hemostasis will be recorded. If hemostasis is not achieved after 15 minutes, then a secondary embolic can be employed. If a secondary embolic agent such as particles or gelfoam is needed for patients in either group, this will be recorded. All potential secondary embolic agents are FDA-approved devices and commercially available. Additionally, if the operator is unable to navigate into the mid-splenic artery with the necessary tools to perform the

required embolization, this will also be recorded. In this circumstance, the procedure will be recorded as a technical failure and the operator will then proceed to treat the patient as he/she deems appropriate. Catheters and wires will be removed after hemostasis is obtained in the mid-splenic artery. As is standard at our institution, the arteriotomy will be closed with a FDA-approved, commercially available vascular closure device, if possible. If the patient isn't a candidate for a vascular closure device, then hemostasis at the arteriotomy will be obtained with manual pressure, as is standard at our institution.

7.4 CT Over-read

The initial CT images and read will be over-read by an attending abdominal radiologist for these reasons:

1) Ensure consistency of reports.
2) Assess for other vascular injuries that may have been overlooked initially (arterial pseudoaneurysms, arteriovenous fistulas, etc).

The over-read will not replace the initial diagnostic read and will not delay patient care in any way (see section 9 for "Data Collection").

7.5 Patient Follow-up

Patients will be followed for 30 days +/- 3 days after pSAE. For patients still admitted to the hospital, data will be collected from the medical record. For discharged patients with follow-up at UAB, data will be collected from the medical record. For discharges patients without follow-up, the program manager/research coordinator will contact the patient via telephone to collect relevant data (see section 9 "Data Collection").

8. OUTCOMES

Aim 1: Demonstrate feasibility by meeting enrollment and follow-up goals.

Objective 1a: Enroll at least 50% of eligible patients (50 patients total; 25 patients per arm)

Objective 1b: Obtain follow-up in at least 80% of enrolled patients

Aim 2: Assess for similarities and differences between the groups regarding clinical outcomes.

Objective 2a: Compare clinical outcomes of pSAE using coils versus vascular plugs (splenic salvage, immediate/delayed complications, patient length of stay, and post-embolization transfusion requirements)

Objective 2b: Compare technical outcomes of pSAE using coils versus vascular plugs (technical success (defined as the ability to access and embolize the mid-splenic artery), intra-procedural complications, necessity of a secondary embolic to obtain satisfactory hemostasis, and intra-procedural radiation doses)

Objective 2c: Conduct cost analysis of using coils versus vascular plugs (room time, equipment such as catheters, wires, and sheaths, and the cost of the embolic agent itself)

9. DATA COLLECTION

Data is abstracted into an electronic case report form (eCRF) by study staff. The eCRF uses the Research Electronic Data Capture (REDCap) system, a secure research database developed by the NIH. A full list of variables to be collected is shown below. Data logic checks are used to minimize data entry errors.

The following admission parameters will be collected:

a) Source of patient (transferred from another facility or from the scene of injury?)
b) Mechanism of injury
c) Date and time of arrival
d) Vital signs (temperature, heart rate, blood pressure, respiratory rate)
e) Use of vasopressors at time of arrival
f) Intubated at time of arrival
g) Glascow Coma Scale (GCS)
h) Injury Severity Scale (ISS)
i) Undergoing massive transfusion protocol?

The following blood tests, which are all measured routinely as part of the clinical assessment of trauma patients, are collected, as soon as possible upon arrival:

a) Arterial blood gas
b) Hemoglobin and hematocrit
c) Platelet count
d) Coagulation parameters including prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), and Anti-Xa
e) Thromboelastograph (TEG) or thromboelastogram (ROTEM)

The following data points will be extracted from the initial CT report (emergent):

a) Phase of enhancement
b) Splenic injury grade according to AAST guidelines

c) Signs of accompanying vascular injury such as pseudoaneurysm, extravasation, arterio-venous fistula, or hemoperitoneum
d) Presence or absence of other intra-abdominal or extra-abdominal trauma

The following data points will be collected from the embolization procedure:

a) Duration
b) Radiation dose
c) Contrast type and volume
d) Splenic artery diameter
e) Presence of pseudoaneurysm, arterio-venous fistula, or contrast extravasation on angiography
f) Embolization material
    a. Primary (coils vs. vascular plugs)
    b. Secondary (beads, coils, vascular plugs, foam, other)
g) Technical success
h) Intra-procedural complications (non-target embolization, migration of the coil or vascular plug, ineffective treatment requiring splenectomy, vessel rupture, injury at the access site, and splenic infarction/abscess)

The following data points will be collected from the over-read of the CT (non-emergent):

a) Phase of enhancement
b) Splenic injury grade according to AAST guidelines
c) Signs of accompanying vascular injury such as pseudoaneurysm, extravasation, arterio-venous fistula, or hemoperitoneum
d) Presence or absence of other intra-abdominal or extra-abdominal trauma

The following data points will be collected while the patient is admitted after the embolization procedure:

a) Amount of blood products required

b) Length of stay (ICU, floor, and total)
c) Delayed complications (Abscess, bleeding, infarction, acute kidney injury)
d) Secondary splenectomy (i.e. splenectomy needed after embolization)

The following data points will be collected at the 30 day follow up:

a) Delayed complications (Abscess, bleeding, infarction, acute kidney injury)
b) Secondary splenectomy

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10. RECRUITMENT TARGETS

Our group performs approximately 100 SAEs in a 12 month period. Thus, we will consider having enrolled at least 50% of the SAE patients (50 patients total; 25 patients/arm) as success.

11. STATISTICAL ANALYSIS

As stated, the primary outcome of this study is to demonstrate the feasibility of performing this type of trial in this patient population.

As a secondary aim, we anticipate being able to identify potential variables as primary endpoints for a larger study.

The principle investigators, project manager, and research coordinator will have access to data. Statistical analysis will be performed by Russell Griffin.

Continuous variables will be compared using the Student's t-test. Categorical statistics will be compared using Chi-squared probability testing with Fischer exact modification when warranted by frequency observed. Both univariate and multivariate Cox models will be examined to determine the ability of clinical variables to predict the likelihood of clinical success or failure (i.e splenic salvage). A pre-determined p value of 0.05 was considered the threshold for statistical significance.

12. TRIAL MANAGEMENT AND GOVERNANCE

The ELSA Trial Office is in the General Services Building at University of Alabama at Birmingham, and provides day to day support for the trial.

The primary investigators take responsibility for the design, execution, data collection, and data analysis for the study. The primary investigators also take responsibility for monitoring the study for safety and unanticipated adverse events/effects. The study team will meet at least once monthly during the study period.

The principal investigators will ensure that adequate systems are in place for monitoring the quality of the trial and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the trial.

The manufacturers of the coils and vascular plugs have no role in the design, conduct, analysis, or reporting of the trial.

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Participant's details are stored on a secure database and regular checks and monitoring are in place to ensure compliance. The data manager (in collaboration with the Principal Investigators) manages access rights to the data set. Participants are allocated an individual specific trial number and their details are anonymized on the secure database.

13. HUMAN SUBJECTS RESEARCH

13.1 FDA Requirements

This study will enroll 50 patients with splenic injuries. The study interventions are approved by the Food and Drug Administration (FDA) as a Class 2 under 21 CFR 892.1600. Because it is a nonsignificant risk device being used in accordance with its defined indications, an FDA Investigational Device Exemption (IDE) is not required.

13.2 Potential risks

The potential risks of splenic artery embolization include unintentional blockage of other arteries, unintended movement of the coils or plugs, vascular injury, ineffective treatment/continued bleeding in the spleen, injury at the vascular access site, infection, kidney injury from the x-ray dye, and infection.

Study participants experience the risk of randomization such that the procedure group to which they are allotted may or may not be as effective and/or safe as the other arm.

14. ADVERSE EVENT/EFFECT REPORTING

14.1 Definitions and classification

All untoward medical occurrences will be classified by:

a) Whether they involved a trial participant
b) Were related to the use of the devices
c) Seriousness
d) Whether anticipated/unanticipated.

Note that adverse *events* are non-device-related medical occurrences, whereas adverse *effects* are caused by the investigational device or procedure.

14.1.1 Untoward medical occurrence

An untoward medical occurrence is an unintended disease or injury or untoward clinical sign in a trial participant caused by or related to the investigational device, device-related procedure, or comparator. Not all complaints about investigational devices have to do with untoward medical occurrences. If a complaint does not involve a trial participant or other person, it is not medical and is called a "non-medical complaint." Non-medical complaints do not need to be logged.

14.1.2 Adverse events

If the untoward medical occurrence did involve a trial participant, but was not related to the device, it is an adverse event. These events are further classified as serious adverse events or non-serious adverse events (AE).

14.1.3 Serious adverse events

Serious adverse events are untoward medical occurrences in a subject that are not related to the investigational device, comparator, or trial procedures, but that meet the criteria of "serious." A serious adverse event is one that:

a) Led to a death
b) Led to a serious deterioration in the health of the subject that:
    i. Resulted in a life-threatening illness or injury, or
    ii. Resulted in a permanent impairment of a body structure or a body function, or
    iii. Required in-patient hospitalization or prolongation of existing hospitalization, or
    iv. Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
    v. Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

A planned hospitalization for a pre-existing condition or a condition required by the protocol, without serious deterioration in health, is not considered serious.

14.1.4 Adverse device effects

An untoward medical occurrence that happened in a subject and is related to the device or device procedure is an adverse device effect. If the occurrence does not meet the definition of serious, it is classified as an adverse device effect (ADE). Adverse device effects are a subset of adverse events.

14.1.5 Serious adverse device effects

An untoward medical occurrence that happens in a subject, is related to the investigational device, or procedure, and is serious, but is not unanticipated is a serious adverse device effect (SADE). Untoward medical occurrences that are not unanticipated, i.e. are unsurprising, are identified in the investigator's brochure or protocol and informed consent form.

As with serious adverse events, a serious adverse device effect is one which

a) Led to a death
b) Led to a serious deterioration in the health of the subject that:
    i. Resulted in a life-threatening illness or injury, or
    ii. Resulted in a permanent impairment of a body structure or a body function, or
    iii. Required in-patient hospitalization or prolongation of existing hospitalization, or
    iv. Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
    v. Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

A planned hospitalization for a pre-existing condition or a condition required by the protocol, without serious deterioration in health, is not considered serious.

14.1.6 Unanticipated serious adverse device effect

An untoward medical occurrence that happens in a subject; is related to the investigational device, device procedure, or comparator; is serious; and was

unanticipated is classified as an unanticipated serious adverse device effect (USADE). Serious adverse device effect which are *anticipated* are listed below.

14.2 Reporting period

The reporting period includes any adverse events which occurred between randomization and discharge.

14.3 Reporting procedure

All members of the patient management teams will be instructed as to the possible adverse events prior to the start of the trial and will be given an emergency contact number to immediately report any suspected adverse event to the site investigators.

Any possible untoward medical occurrence is identified will be evaluated and classified by the site PI, as follows:

a) Relation to the devices: "Effect" (device-related) vs "event" (device-unrelated)
b) Seriousness: Serious (meeting the criteria listed above) or not
c) Anticipated: Anticipated (matching the conditions shown in the list below) or unanticipated

14.3.1 Adverse events (AE)/adverse device effects (ADE)

Adverse events and adverse device effects which are not deemed serious will be recorded using the "PHOXSTAT Adverse Event Recording Form".

14.3.2 Anticipated serious adverse events/serious adverse device effects (SADE)

Anticipated adverse device effects include:

a) non-target embolization (<1%)
b) migration of the coil or vascular plug (<1%)
c) ineffective treatment requiring splenectomy (~10%)
d) injury at the vascular access site (~1%)
e) splenic infarction/splenic abscess (~3%)
f) vessel rupture

Anticipated serious adverse events include:

a) Given that iodinated contrast is used during the procedure, there is a very low risk for nephrotoxicity or allergic reaction to contrast (~1%).

Anticipated serious adverse events and adverse device effects will also be recorded using the "ELSA Adverse Event Recording Form". In addition, a "ELSA Serious Adverse Event/Serious Adverse Device Effect" form must be completed, and emailed to the ELSA Trial Office within 48 hours. All reports of anticipated serious adverse events/SADE will be forwarded to the medical monitor.

14.3.3 Unanticipated serious adverse events/serious adverse device effects (USADE)

Unanticipated serious adverse events and adverse device effects will also be recorded using the "ELSA Adverse Event Recording Form". In addition, a "ELSA Unanticipated Serious Adverse Event/Serious Adverse Device Effect" form must be completed, and emailed to the ELSA Trial Office within 48 hours. In addition, the Study PI must be notified, by telephone within 48 hours.

On notification of a USAE/USADE report, the ELSA Trial Office will, within 3 business days:

a) Forward the report to the medical monitors
b) Notify the UAB IRB

In addition, the ELSA Trial Office will, within 7 days, notify the FDA, using the MedWatch form.

14.4 Role and responsibility of the Independent Medical Monitor

Independent medical monitors will review all adverse events/effects and provide an unbiased written report of the events. At a minimum, the medical monitors must comment on the outcomes of the event or problem and in case of an serious adverse event/serious adverse device effect, comment on the relationship to participation in the trial.

If the death is considered unexpected and is either suspected or probably due to treatment, this event will be promptly reported to the medical monitor, who must indicate

whether he/she concurs with the details of the report provided by the principal investigator.

Dr. Jeff Kirby (Division Chief, Acute Care Surgery) is the independent medical monitor for this study. He has committed to comply with the following statements:

The monitor:

a) Is independent of the research team.
b) Possesses sufficient educational and professional experience to serve as a subject advocate.
c) Will promptly report discrepancies or problems to the IRB.

All follow up data to be collected while the patient is at UAB Hospital would already be collected, regardless of study participation. Again, data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Participant's details are stored within REDCap, a secure database used throughout the institution. Regular checks and monitoring are in place to ensure compliance. The data manager (in collaboration with the principal investigators) manages access rights to the data set. Participants are allocated an individual specific trial number and their details are anonymized. Regarding patient follow-up, the study doesn't require that the patient participate in any additional follow up than they would otherwise do if not enrolled in the study. The research coordinator will supplement follow up by making inquiries into the patient's subsequent condition at 30 days through the patient's chart. If no follow up is documented in the chart, then the research coordinator will attempt to conduct a telephone interview with the patient. However, we recognize that patients may drop-out of the study due to lack of follow-up. We will plan to continue enrolling patients until we have at least three months of post-procedure follow-up on the requisite 25 patients in each arm.

15. REFERENCES

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