

**Embolization of the Splenic Artery after Trauma (ELSA-2)**

Protocol

**FUNDER**

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**TRIAL REGISTRATION**

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# Abbreviations

AAST American Association for the Surgery of Trauma

AE Adverse Event

CRF Case Report Form

eCRF Electronic Case Report Form

ED Emergency Department

ELSA Embolization in Splenic Trauma

FDA Food and Drug Administration

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

# Protocol Summary

## Question addressed

Our aim is to conduct a multi-center, Bayesian, randomized clinical trial to evaluate the primary technical success of coils and vascular plugs for proximal splenic artery embolization in the setting of high-grade splenic trauma. We have previously demonstrated the feasibility of such a study in a single center pilot trial [1].

## Study population

*Inclusion criteria: ≥*15 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

Eligible patients will be referred for proximal splenic artery embolization and randomized to coils or vascular plugs.

## Outcome assessment

The primary outcome is primary technical success, defined as the ability to deploy the assigned embolic device in the mid-splenic artery with resultant occlusion of the artery within 15 minutes of deployment. Secondary clinical outcomes include splenic preservation, complications, device failures, procedural complications, time to stasis, radiation exposure, need for secondary embolic agents, length of stay, and transfusion requirements.

## Trial coordination

The trial is coordinated by the Center for Injury Science (CIS) at the University of Alabama at Birmingham. Dr. Gunn and Dr. Jansen are the study principal investigators. Shannon Stephens is the trial manager.

# Trial personnel

## Principal investigators

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# Introduction/ Background

Splenic injuries are common [2].

Hemodynamically unstable patients with splenic injuries usually require immediate splenectomy. The management of hemodynamically stable patients with injuries to the spleen is less well-defined, and recognition of the key role of the organ in producing antibodies, monocytes, and activated lymphocytes has led to a shift in the management of splenic injuries towards preservation when possible.

Splenic preservation rates for patients with high-grade splenic injuries are improved when non-operative management (NOM) is supplemented by image-guided, trans-catheter splenic artery embolization (SAE) [3-16]. 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), and pSAE is most often accomplished using either coils or vascular plugs as the embolic agent. Both devices are FDA-approved for this indication.

The selection of embolic agents for pSAE is mostly based on operator experience and preference; although, patient-specific factors such as vessel diameter and tortuosity play a role. The only study to compare the efficacy of these two devices for pSAE is our single-center pilot/feasibility trial, “Embolization of the Splenic Artery after Trauma” (ELSA) [1].

ELSA attempted to randomize 50 patients with splenic injuries to embolization with either coils or plugs. We demonstrated the feasibility of conducting such a study, in terms of enrolment (46/50, or 92%, of eligible patients were enrolled), adherence to treatment allocation, and collection of outcome data (complete data were obtained on all enrolled patients). We demonstrated that coils were associated with a higher posterior probability of primary technical success, but as the posterior probability was <95%, we did not regard the finding as convincing. As a pilot study with feasibility as a primary outcome, ELSA was not powered to detect a difference.

We will therefore now conduct a multi-center follow up clinical trial, with the aim of evaluating the effectiveness of the two treatments.

# Aim

The aim of ELSA-2 is to compare the effectiveness (in terms of primary technical success) of coils and plugs, for proximal splenic artery embolization in trauma patients with high-grade splenic injuries.

# Design

Multi-center randomized clinical trial. Please see CONSORT diagram below.



# PATIENTS, RECRUITMENT, AND RANDOMIZATION

## Setting

This study will be performed in five level I trauma centers:

1. University of Alabama at Birmingham (lead site)
2. University of Texas Health Sciences Center at Houston
3. Wake Forest Baptist Medical Center
4. Ohio State University Wexner Medical Center
5. Prisma Health Greenville Memorial Hospital

## Study population

The inclusion and exclusion criteria are:

### Inclusion criteria

1. *≥*15 years of age
2. Trauma resulting in grade III or higher splenic injury on contrast-enhanced CT
3. Splenic injury to be treated by non-operative management as decided by attending trauma surgeon and interventional radiologist
4. The attending interventional radiologist determines that the patient will undergo proximal splenic artery embolization with the specific method to be decided by randomization.

### Exclusion criteria

1. Inability to obtain informed consent
2. ≤ 50kg
3. Uncorrectable coagulopathy
4. Patient is immunocompromised
5. Pregnant
6. Breast-feeding
7. Non-English speakers
8. Prisoners

## 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 SAE will be made by an attending interventional radiologist in conjunction with the attending trauma surgeon.

Clinicians will be assisted by study staff at each site, who will identify all patients with grade III (and higher) splenic injuries, and then flag the patient to the trauma and interventional radiology teams. If the attending interventional radiologist and attending trauma surgeon deem the patient an appropriate candidate for pSAE, the study team will screen the patient for eligibility.

## Consent

### In person

If deemed eligible, informed consent for participation in the trial will be obtained, from the patient or their legally-authorized representative.

## Randomization

After meeting the above criteria and obtaining informed consent, the patient will be randomized to either the coil arm or plug arm, using permuted block randomization stratified by center. Randomization will take place electronically, using the trial’s REDCap eCRF. Following confirmation of eligibility, the operator will be notified whether the patient has been allocated to the coil or plug arm of the study.

# Interventions

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

## POD® coils

Coils are FDA-approved endovascular occlusion devices that are deployed through a high-flow micro-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 an adequate coil pack is achieved radiographically. All materials used to deploy the coils are FDA-approved, commercially available, and routinely used in practice at all participating centers.

Fig. 1: Embolization using helical and packing POD coils (images from Penumbra.com).



## Vascular plugs

Vascular plugs are FDA-approved endovascular occlusion devices that require an 0.035 inch system within the splenic artery for deployment (Figure 2). 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 (e.g., guiding catheters or vascular sheaths). All materials needed to deploy both the Amplatzer™ II and IV plugs are FDA-approved, commercially available, and routinely used in practice at all participating centers.

Fig. 2: Amplatzer IV VP (from St. Jude Medical).

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## Proximal Splenic Artery Embolization Procedure

### Operator

An attending interventional radiologist or surgeon will perform all pSAE procedures.

### Anesthesia

Operators can decide whether to use moderate conscious sedation or general anesthesia depending on the patient’s condition. Local anesthesia will be achieved with lidocaine or a similar drug.

### Vascular access

The vascular access site is prepared and draped in standard sterile fashion. The right common femoral artery is the most commonly used vascular access for splenic artery embolization but other arteries may be used for certain patients, as is common in standard clinical practice.

### Celiac axis angiogram

A celiac axis angiogram is then performed through a standard diagnostic catheter. The attending interventional radiologist or surgeon will choose the diagnostic catheter based on his/her preference. The attending interventional radiologist or surgeon 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, preserving collateral flow to the spleen via the transverse pancreatic artery, which is standard practice for a pSAE. The vessel’s diameter at the location of embolization will be measured and recorded.

### Coil embolization

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 and micro-catheter combination will be left to the discretion of the attending interventional radiologist or surgeon. 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. In short, the first coil used is a sized anchoring coil to stabilize the coil pack in the mid-splenic artery. Subsequently, the anchoring coil is filled with packing coils. The operator places any number of coils required to achieve an adequate radiographic coil pack, as is standard practice.

### Plug embolization

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 or sheath is in place, a splenic angiogram will be performed. Vascular plug embolization will then proceed per the manufacturer’s instructions for use. As is standard practice, only a single vascular plug is deployed.

### Time to hemostasis

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 or surgeon will perform intermittent non-subtracted angiograms (one per minute) to determine if stasis has been achieved. Non-subtracted angiograms are used initially to limit radiation exposure to the patient and staff. If hemostasis is suspected on the non-subtracted angiogram, a digital subtraction angiogram is then immediately performed for confirmation. If stasis is not confirmed, operators will continue to check for stasis with non-subtracted angiograms every minute. If hemostasis is confirmed, the time to hemostasis will be recorded. The time to hemostasis will be calculated from the time of vascular plug deployment or time of last coil deployment until hemostasis was achieved in the mid-splenic artery. For patients randomized to coils, operators will not be allowed to check for stasis with non-subtracted angiograms until they have determined to have achieved a radiographically-adequate coil pack.

### Use of secondary hemostatic agents

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. The time to stasis will be recorded as outlined in Section 7.3.7. All potential secondary embolic agents are FDA-approved devices, commercially available, and routinely used in practice at all participating centers.

### Technical failure

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. ***As such, all patients will receive standard of care therapy in this trial.***

### Arteriotomy closure

Catheters and wires will be removed after hemostasis is obtained in the mid-splenic artery. The arteriotomy will be closed with a FDA-approved, commercially available vascular closure device, if possible. Alternatively, hemostasis at the arteriotomy will be obtained with manual pressure.

## Patient Follow-up

Patients will be followed for 30 days (+/- 7) days after pSAE. For patients who are still inpatients, data will be collected from the medical record. For discharged patients, the local research assistant will contact the patient via telephone to collect relevant data in addition to reviewing the medical record.

# Outcomes

## Primary outcome

Primary technical success - the ability to deploy the assigned embolic device in the mid-splenic artery with resultant occlusion of the artery within 15 minutes of deployment.

## Secondary outcomes

Splenic preservation, complications, device failures, procedural complications, time to stasis, radiation exposure, need for secondary embolic agents, length of stay, and transfusion requirements.

#  Recruitment targets

Based on the results of our pilot/feasibility study, we anticipate that a trial with 250 patients will have 86% probability of success where success means a >90% posterior probability that coils are superior to plugs for primary technical success, assuming that the rate of primary technical success, as in the pilot was 88% for plugs vs. 96% for coils. If the true rates are 85% vs. 95% then we will have >90% chance of success. We aim to recruit 250 patients across five sites, over a period of 24 months. We anticipate that each site will enroll ~50 patients during the study period. Each site is a certified level I trauma center that performs a significant number of SAEs for trauma each year. Based on enrollment from our feasibility trial, this is a reasonable and achievable enrollment target.

# SITES

The following centers will participate in the trial:

## University of Alabama at Birmingham

Anticipated case volume: 60 patients

Site principal investigator: Dr. Theresa Caridi (Interventional Radiology)

## University of Texas Health Sciences Center at Houston

Anticipated case volume: 60 patients

Site principal investigator: Dr. Ahmed Kamel Abdel Aal (Interventional Radiology)

## Wake Forest Baptist Health

Anticipated case volume: 60 patients

Site principal investigators: Drs. Michael Miller (Interventional Radiology), Raisa Durrani (Interventional Radiology), and Preston Miller (Surgery)

## Ohio State University Wexner Medical Center

Anticipated case volume: 35 patients

Site principal investigators: Drs. Mina Makary (Interventional Radiology), Carrie Sims (Surgery), and Henry Wang (Emergency Medicine)

## Prisma Health Greenville Memorial Hospital

Anticipated case volume: 35 patients

Site principal investigator: Dr. Michael Devane (Interventional Radiology)

# DATA MANAGEMENT

## Source documentation

All hard copy source documentation will be kept in a secured, locked cabinet in the sites’ research coordinators’ offices. All study documents will be maintained in a secure location for the time frame designated by each participating site’s requirements.

## Electronic Case Report Form

Data is abstracted into an electronic case report form (eCRF) by local study staff. The eCRF uses the Research Electronic Data Capture (REDCap) system, a secure research database.

The data manager (in collaboration with the Principal Investigators) manages access rights to the data. Participants are allocated an individual specific trial number and their details are anonymized on the secure database.

The REDCap database is backed up on multiple servers.

## Data collection

A full list of variables to be collected is shown below.

The following admission parameters will be collected:

1. Source of patient (scene/transferred)
2. Mechanism of injury
3. Date and time of ED arrival
4. Vital signs (temperature, heart rate, blood pressure, respiratory rate)
5. Use of vasopressors at time of arrival
6. Intubated at time of arrival
7. Glasgow Coma Scale (GCS)
8. Injury Severity Scale (ISS)
9. 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:

1. If available, Arterial blood gas
2. Hemoglobin and hematocrit
3. Platelet count
4. If available: Coagulation parameters including prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), and Anti-Xa
5. If available: Thromboelastograph (TEG) or thromboelastogram (ROTEM)

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

1. Phase of enhancement
2. Splenic injury grade according to AAST guidelines
3. Signs of accompanying vascular injury such as pseudoaneurysm, extravasation, arterio-venous fistula, or hemoperitoneum
4. Presence or absence of other intra-abdominal or extra-abdominal trauma

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

1. Duration
2. Radiation dose
3. Contrast type and volume
4. Splenic artery diameter
5. Presence of pseudoaneurysm, arterio-venous fistula, or contrast extravasation on angiography
6. Embolization material
	1. Primary (coils vs. vascular plugs)
	2. Secondary (beads, coils, vascular plugs, foam, other)
7. Technical success
8. Time to stasis
9. 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 while the patient is admitted after the embolization procedure:

1. Amount of blood products required
2. Length of stay (ICU, floor, and total)
3. Delayed complications (Abscess, bleeding, infarction, acute kidney injury)
4. Secondary splenectomy (i.e. splenectomy needed after embolization)

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

1. Delayed complications (Abscess, bleeding, infarction, acute kidney injury)
2. Secondary splenectomy

## Error Checking

Each item on the web forms has validity checks performed to ensure that the data entered are accurate and that items are not skipped during entry by mistake. Depending on the question, any item found that does not meet the respective edit criteria will result in an error message when the user tries to save the data.

Errors are 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 are items such as event dates. An example of a soft error are values that are outside a pre-defined range.

When the data record is saved, a form status field is 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 is 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”. CIS staff have web-access to listings of subject specific errors needing correction by site. These errors can be corrected at the site or in the CIS (given documentation of the change).

All site investigators will be trained to follow regulatory procedures when making any changes in the paper forms or source documentation (no erasures, cross through error, write in correction, date, and initial). Once a follow-up about any errors has been done by CIS and the error has been corrected or certified as accurate, the status will change to “complete with errors.”

Once a record has been saved by the site or CIS as complete, they will no longer be allowed to make changes to the records. Any changes that result from obtaining new information would be made by CIS staff. At the end of the trial after all possible corrections are made, the database will be locked and further changes will not be made.

## Error correction follow-up

Since there are times when data does not meet the required edit criteria such as out of range values, the sites still need to be able to save their data. However, such errors need to be followed up to ensure that the error was not by mistake. In this case, any soft error indicated will be logged to an error log data table which will later generate be used to generate a report that must be followed up on. This report will include the option for the user to enter the correct value(s) if the record was saved by mistake or to indicate that the value saved was correct in which case they must provide an explanation as to why the error was overridden. These reports must be transmitted back to CIS where staff will process the corrections. This process is particularly important for clarifying missing data. Once these reports are received back by the CIS staff and processed, the respective data record will be updated to the forth status of “complete with errors.” Since clinical staff must sign these reports, these reports will serve as audit records.

# QUALITY ASSURANCE

## Site initiation visits

The Principal Investigator (Dr. Gunn) will conduct site initiation visits prior to any of the sites being greenlighted for recruitment. Site visits may be conducted remotely. Additional monitoring visits may be conducted as necessary.

## Staff training

Training of research staff and study teams who will be responsible for recruitment and randomization of subjects will take the form of a “training the trainer” model. Each site will then become responsible for the education of their personnel in the conduct of the ELSA-2 trial, albeit with close support from the CIS team.

# Statistical Analysis

## Primary outcome

The primary analysis will be to estimate a posterior probability distribution for the difference in primary technical success rates between plugs and coils. This analysis will use a non-informative prior distribution. As a decision criterion, the trial will be considered a ‘success’ if there is ≥90% posterior probability that the success rate for coils is higher than from plugs. In keeping with the Bayesian design we will report the estimated difference along with 90%, 95%, and 99% posterior highest density credible intervals to provide greater information for clinical decision making. A secondary analysis will consider including the data from the pilot in the form of a prior distribution, recalculating the posterior credible intervals accordingly.

## Secondary outcomes

Analyses for secondary outcomes will follow a similar Bayesian structure with ‘success’ also defined as a >90% posterior probability that coils are superior to plugs. Posterior credible intervals will also be reported for secondary outcomes and further analyses will report results after including available pilot study data into a prior distribution.

## Interim analyses

Interim analyses will be done after 75 participants have been randomized to each study arm. We will consider stopping the study early if there is a >99% posterior probability that one arm is superior at the interim analysis for the primary outcome.

# Trial management

## Oversight

The ELSA Trial is run by the Center for Injury Science (CIS) at the University of Alabama at Birmingham. CIS will provide day to day support for the trial.

The principal investigators take responsibility for the design and execution of the study.

Data collected during the course of the research will be kept 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.

## Site management

Each site has a principal investigator, who is responsible about the conduct of the study in each location.

# Human Subjects Research

## Risks to Subjects

This trial will randomize 250 subjects who have sustained a high-grade, traumatic splenic injury. Based on past data, the majority of traumatic injuries occur in male subjects 45 years of age and younger. The majority of this population will have no significant pre-existing medical history. Children estimated to be less than 15 years of age, women who are known to be pregnant, and prisoners will be excluded from this trial. As all devices used in this trial are approved by the FDA, we anticipate no new risks to those seriously injured trauma patients.

## Potential Risks

Eligible subjects for this trial will have been identified as requiring splenic embolization due to their traumatic injury. There is a potential risk that treatment may be delayed due to the randomization process. To monitor the potential risk, the clinical research staff will document relevant times including: time of ED admission, time of referral to interventional radiology, time of randomization, time of commencement of procedure. If a delay or risk is identified, appropriate information/data will be sent to the medical monitor to decide if further action needs to be taken. Severely injured subjects who require splenic embolization will frequently incur complications such as death, multi-organ failure (MOF), respiratory complications, and infections. There is no expectation of increased harm in either groups. Subjects will have no additional costs for participating in the study.

## Protection Against Risks

Consent to participate will be obtained as described in section 6.4. Subjects will be given the opportunity to continue or withdraw from the study at any point.

## Vulnerable populations

This trial may include subjects aged 15 and older. Subjects aged 15 years and older are considered as adult trauma subjects in most trauma centers in the United States. Fifteen, sixteen and seventeen year olds are able to drive in most states and are at high risk for motor vehicle accidents resulting in splenic injuries. Excluding this age group would decrease our efforts to randomize 250 subjects in a two year period of time. Children below the age of 15 or 50kg body weight will be excluded from this trial. Pregnant women will also be excluded from the ELSA-2 trial, in whom the risks and benefits of embolization (with attendant ionizing radiation exposure) compared with splenectomy may differ. Prisoners admitted to the ED from a correctional facility will be excluded from enrollment. It is possible that subjects may be enrolled into the ELSA-2 trial who are under police observation as suspects. These subjects will remain in the study until discharge or incarcerated.

## Roles/Responsibilities of Medical Monitor

An independent medical monitor will review all adverse events/effects and provide an unbiased written report of the events. The medical monitor 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 an event/effect 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 Kerby (Director, Division of Acute Care Surgery) is the independent medical monitor for this study. He has committed to comply with the following statements:

The monitor:

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

The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for serious adverse events determined by either the investigator or medical monitor to be possibly or definitely related to participation must be promptly reported to the IRB.

# Adverse event/effect reporting

## Definitions and classification

### Adverse events

Adverse *events* are non-device-related medical occurrences, further classified as serious adverse events (SAE) or non-serious adverse events (AE).

### 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:

1. Led to a death
2. Led to a serious deterioration in the health of the subject that:
	1. Resulted in a life-threatening illness or injury, or
	2. Resulted in a permanent impairment of a body structure or a body function, or
	3. Required in-patient hospitalization or prolongation of existing hospitalization, or
	4. Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
	5. 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.

### Adverse device effects

An untoward medical occurrence that 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.

### 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

1. Led to a death
2. Led to a serious deterioration in the health of the subject that:
	1. Resulted in a life-threatening illness or injury, or
	2. Resulted in a permanent impairment of a body structure or a body function, or
	3. Required in-patient hospitalization or prolongation of existing hospitalization, or
	4. Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
	5. 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.

### Unanticipated serious adverse device effect

An unanticipated serious adverse device effect (USADE) is defined by the FDA as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.” Serious adverse device effect which are *anticipated* are listed below.

## Reporting period

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

## 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:

1. Relation to the devices: “Effect” (device-related) vs “event” (device-unrelated)
2. Seriousness: Serious (meeting the criteria listed above) or not
3. Anticipated: Anticipated (matching the conditions shown in the list below) or unanticipated

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

Adverse events and adverse device effects which are not deemed serious will be recorded using the “ELSA-2 Adverse Event Recording Form”.

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

Anticipated adverse device effects include:

1. non-target embolization (<1%)
2. migration of the coil or vascular plug (<1%)
3. ineffective treatment requiring splenectomy (~10%)
4. injury at the vascular access site (~1%)
5. splenic infarction/splenic abscess (~3%)
6. vessel rupture

Anticipated serious adverse events include:

1. 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-2 Adverse Event Recording Form”. In addition, a “ELSA-2 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.

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

Unanticipated serious adverse events and adverse device effects will also be recorded using the “ELSA-2 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-2 Trial Office within 10 days. In addition, the Study PI must be notified, by telephone within 48 hours.

On notification of a USAE/USADE report, the ELSA-2 Trial Office will, within 10 days:

1. Forward the report to the medical monitor
2. Notify the UAB IRB
3. Notify participating investigators

## Role and responsibility of the Independent Medical Monitor

An independent medical monitor will review all adverse events/effects and provide an unbiased written report of the events. The medical monitor 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 an event/effect 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 Kerby (Director, Division of Acute Care Surgery) is the independent medical monitor for this study. He has the required educational and professional experience to serve as a subject advocate, and will promptly report discrepancies or problems to the IRB.

# ROLE OF THE FUNDER

This study is funded by Penumbra, Inc., the manufacturer of the endovascular coils, who have no role in the design, conduct, analysis, or reporting of the trial.

# Publication policy

Publications related to this trial will be authored by A.J. Gunn (PI, first author), the site PIs, Shannon Stephens (trial manager), Joshua Richman (biostatistician), and Jan Jansen (PI, senior author). Additional authors may be added as required.

Proposals for ancillary publications will be reviewed by A.J. Gunn and J. Jansen and would normally be expected to include the PIs, Shannon Stephens (trial manager), and Joshua Richman (biostatistician).

# References

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