RESEARCH PROTOCOL

Translated from the original version in French by Dr. Alison FOOTE (Grenoble-Alpes University Hospital) - November 22, 2018

Title: Benefit of prophylactic embolization on splenic rescue in trauma patients at high risk of splenectomy.
Title in French: Bénéfice de l'embolisation prophylactique sur le sauvetage splénique chez les patients traumatisés à haut risque de splénectomie.

Short title : **SPLASH**

Study design : Essai thérapeutique en groupes parallèles, multicentrique, contrôlé, randomisé
Multicenter, parallel, controlled, randomized therapeutic trial

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PROTOCOL –SUMMARY

Coordinating investigator: **Pr Catherine Arvieux**

Sponsor: **CHU de Grenoble (Grenoble Alpes University Hospital)**

Study Title: **Benefit of prophylactic embolization on splenic rescue in trauma patients at high risk of splenectomy.**

Main Objective:

To evaluate the benefit-risk of preventive splenic embolization versus surveillance among hemodynamically stable adult patients with severe closed spleen trauma at high risk of splenectomy. The goal is to show that embolization improves **the rate of spleen rescue at 1 month**, by evaluating its side effects compared to simple monitoring.

Primary endpoint: The spleen must be immunocompetent, ie, intact, or treated by surgical procedures that allow at least 50% preservation of the vascularized splenic tissue in the event of secondary laparotomy, or with necrosis of less than 50% by volume. This criterion is validated by the masked reading of the initial scan by a panel of two senior radiologists.

Secondary Objectives:

Secondary objectives are the evaluation of:

- spleen rescue rate at 6 months
- death or vascular or hemorrhagic complications
- hospitalizations and re-hospitalizations
- impact on professional activity
- impact on physical activity
- vascular reconstruction and immunosuppression

Secondary Endpoints :

These correspond to the risks incurred in both the embolization and surveillance groups during the period of inclusion (6 months):

- spleen rescue rate at 6 months
- death
- number of red blood cell packs transfused
- pleural effusion
- use of thoracic drainage
- venous thrombosis of the splenomesenteric-portal axis
- occurrence of : arterio-venous fistula, false aneurysm, pseudoaneurysm of a splenic pseudo-cyst
- Total hospital stay in a short stay bed
- Length of hospitalization in intensive care unit
- Need for re-hospitalization
- Total duration of time off work
- Evaluation of physical activity (WOMAC)
- Immunological assays for vascular reconstruction (kininoformation) and immunosuppression markers (D5, M1, M6)
- Kininoformation activity
- phenotypes of B lymphocytes (B naive, B memory)

The events specific to each group will also be recorded:

- need for splenic embolization (control group
- specific complications of embolization
- events linked to vascular access for embolization (hematoma, thrombosis, arteriovenous fistula, false aneurysm, pseudoaneurysm
- events linked to the contrast product (kidney failure, allergy)
- events linked to technique (inadvertent embolization of non-targeted territories)

Study design: Multicenter, parallel group, controlled, randomized therapeutic trial

Study Treatment: Proximal Prophylactic Embolization
Control group: Clinical surveillance

Total number of subjects:**140**

Investigators: surgeons, resuscitators or interventional radiologists from university hospitals or general hospitals

Number of investigative centers: 16

Study population

Inclusion criteria:

- Patients over 18 and under 75 years
- Hemodynamically stable patients (systolic BP ≥90mmHg and absence of hemorrhagic shock
- Closed splenic trauma within less than 48 hours
- High risk of splenectomy:
  - Moore grade 4 or 5 spleen damage on injected abdominal computed tomography or
  - Moore grade 3 spleen damage and at least one of the following characteristics:
    - large hemoperitoneum (when visible at the pelvic level)
    - associated serious damage NISS - New Injury Severity Score greater than or equal to 15
- Patient volunteering to participate in the study, having signed the consent form or with the agreement of the family if the patient is not able to give consent, after adequate information and delivery of the patient information document.
- Person affiliated with a social security scheme and/or beneficiary of such a scheme

Non-inclusion criteria**:**

- Patients whose usual residence is outside the EEC
- Patient with hemodynamic instability (systolic blood pressure <9 despite resuscitation)
- Patient with open splenic trauma
- Patient with an indication for surgery excluding the possibility of monitoring the splenic trauma
- Patient with an indication for embolization of an organ other than the spleen at the time of inclusion
- Patient with indication for splenic embolization due to a post-traumatic vascular abnormality (active contrast agent leakage, pseudo-aneurysm or early splenic arteriovenous fistula).
- Patients under 18 and ≥ 75 years of age
- Patient with a previously pathological spleen (tumor, infection, intrasplenic vascular abnormality)
- Patient with Moore grade I, or II trauma
- Patient with Moore grade V trauma with total ischemia of the spleen
- Patient having had partial or complete splenectomy before inclusion
- Patient with acquired or innate immune deficiency
- Any contraindications to the realization of embolization
- Pregnant woman
- Person deprived of liberty by judicial or administrative decision, person subject to a legal protection measure
- Patient currently in a clinical study or who participated in a clinical study in the month prior to inclusion
- Patient with, or a history of, mental or psychiatric disorder or any other factor limiting their ability to participate in an informed manner and to adhere to the protocol
- Patient with acquired hemostasis (anticoagulant therapy) or an innate abnormality

Total length of study: 66 (48months of recruitment)

Total length of study for the participant: 6 months for both groups

Primary endpoint: splenic rescue rate at 1 month after trauma

SUMMARY

The spleen, a secondary lymphoid organ, is the organ most frequently affected in the event of closed abdominal trauma[1].

In 10-20% of cases[2 3], the trauma patient is admitted in a state of hemorrhagic shock and requires immediate surgical management with, in most cases, hemostatic splenectomy. Complications of splenectomy are either postoperative (pancreatitis, hemorrhage, infections)[4] or occur later on. Fulminant infection, whose immunological mechanisms are still poorly understood, is particularly feared in children. In adult trauma patients the risk is lower (1.5 / 1000)[5], but nevertheless 100 times higher than that of the non-splenectomized subject [6]. In those undergoing splenectomy, this syndrome justifies the prescription of an anti-pneumococcal vaccine and oral penicillin as a prophylactic antibiotic for two years following splenectomy, as well as preventive antibiotic therapy for any infectious syndrome and preventative measures (malaria, pets) for life; but adherence is low, less than 20%[7].

In the 85% of patients who are hemodynamically stable on arrival, non-operative treatment is recommended because it allows a better splenic rescue rate than conservative surgical treatment[1 8], but because of the need for secondary splenectomy for hemorrhage the final rate of spleen rescue was only 60% in a major retrospective reviewing the trauma experience of East coast US centers prior to the era of embolization[9].

In recent years, the development of splenic embolization in expert trauma centers has increased the rate of spleen rescue to more than 80%[10-13]. However, these results come from retrospective series for the most part and the question has never been rigorously evaluated in a randomized trial. This technique is not free of complications whose specificity has not always been well established (30%)[14 15] and it also has a failure rate of 10-15%[2]. The indication currently accepted in France is the presence of an active leak of contrast medium on the CT scan, which is treated by "curative" embolization. In view of the ability of embolization to maintain immunological functions[16], certain expert centers[13] have extended the embolization indications to patients who have predisposing factors for secondary splenic hemorrhage that have been well identified in retrospective series: (a) pseudoaneurysms and arteriovenous fistulas (AVF); (b) severe damage (Moore grade 3) associated with a large hemoperitoneum (ie visible at the pelvic level) and/or the presence of associated extradigestive lesions; (c)) very severe splenic involvement (Moore grades 4 and 5). In these situations, the failure rate of non-operative treatment is greater than 75%[2 13]. Because of the high risk of secondary rupture[17], preventive embolization of pseudo-aneurysms and post-traumatic splenic AVF is currently performed in routine practice in French and foreign expert centers, but for the other risk situations described above, practices are still very heterogeneous depending on the center.

Thus, as highlighted in the conclusion of a recent American Association for the Surgery of Trauma (AAST) report[3] on North American trauma team practices, the benefit / risk ratio of prophylactic splenic embolization in high-risk splenectomy situations must be proven by a prospective study before more widespread practice makes assessment difficult[3].

The aim of this work is to evaluate the benefit/risk ratio of the practice of preventive splenic embolization versus surveillance among hemodynamically stable adult patients with severe spleen trauma at high risk of splenectomy. The goal is to show that embolization improves the rate of spleen rescue at 1 month, and evaluating its side effects at 6 months and its medico-economic implications compared to simple monitoring.

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I- Study Rationale

I-1 Epidmiological data

The spleen is a secondary lymphoid organ[18] involved in organizing the adaptive immune response. It is the organ most frequently affected by a closed abdominal trauma [19]. In France between 3000 and 4000 splenectomies are performed per year (ATIH-PMSI data, 3414 splenectomies were performed in France in 2006, with about half being indications for trauma).

From 10 to 20% of patients with spleen trauma are polytraumatized [20]. The New Injury Severity Score (NISS) is a widely used anatomical score[21] giving an overall score for the anatomic lesions of a polytraumatized person. Each organ involved is scored according to the Abbreviated Injury Scale (AIS) from 1 (mild) to 5 (total destruction or devascularization of the organ) according to the criteria of the American Association for the Surgery of Trauma (AAST). The NISS score is calculated from the AIS of the 3 most serious lesions as follows: NISS= $a^2 + b^2 + c^2$ (for example, a patient with a cerebral contusion rated AIS=3, a spleen fracture rated AIS=4 and minor hepatic injury rated AIS=2 will have an NISS of 9 + 16 + 4 = 29). A trauma is considered severe when NISS ≥15[21].

For splenic involvement, the AIS classification of 1989 was modified in 1994[1,22]. It takes into account the type of damage (hematoma, tearing), the localization in the splenic gland (intra-parenchymal or subcapsular) and the percentage of devascularized tissue (Table 1).

Table 1. AIS classification of splenic lesions according to Moore et al[1,23]

Grade	Subcapsular hematoma	Intra-parenchymal hematoma	Capsular tear	Devascularization
1	<10% spleen surface, not extensive	no	Depth < 1cm Not hemorrhagic	0
2	10-50% spleen surface, not extensive	Diameter < 5 cm Not evolutive	Depth 1-3 cm Bleeding does not involve trabecular vessels	0
3	> 50% % spleen surface, or rupture or spreading or bleeding	Evolutive or diameter > 5cm	Depth > 3cm O r involves trabecular vessels	<25%
4		Ruptured	Lesion reaching segmental or hilar vessels	>25%
5		Complete splenic fragmentation	Hilar lesion(s) causing complete devascularization (100%) of the spleen	

A study of the distribution of trauma according to the severity of the anatomical injury shows that half of the patients present severe splenic damage, Moore 3-5 (Table 2). In stage 5, Moore's classification encompasses both the total devascularization of the spleen and its fragmentation. In the first case splenectomy is crucial in a patient still in haemorrhagic shock, but in the second case embolization can be effective [13].

Table 2. Patient Distribution by Moore's Grade – EAST Multicenter Study[24] and Montpellier Study (G Brault-Noble, Submitted to *J Trauma*)

GRADE	EAST[24] **1094 patients**	Montpellier **208 patients**
Grade 1	25%	16%
Grade 2	27%	33%
Grade 3	23%	24%
Grade 4	**18%**	**11%**
Grade 5	**07%**	**13%**
Total Grades 3-4-5	*48%*	*48%*

I-2 Treatment of splenic trauma

I-2-1 Hemorrhage and/or hemodynamic instability

Total splenectomy is imperative when there is a state of hemorrhagic shock [6] and / or hypothermia with a risk of coagulopathy[25]. The excision of the spleen is then part of a surgical strategy of shortened laparotomy, which corresponds to 10-15% of patients with splenic trauma[26-28]. In unstable patients, the decision for total splenectomy is therefore based on patient-related criteria (severity of hemodynamic instability, age, terrain, polytrauma) and on the operative findings (level of involvement) for the spleen and associated intra-abdominal and/or retroperitoneal lesions[29].

I-2-2 Hemodynamically stable

In a stable patient, non-operative treatment both avoids the postoperative complications of splenectomy and the best splenic rescue rate. It is initially feasible in approximately 80% of patients[6 8 30 31 32-34]. The intervention remains permissible in the polytraumatized patient presenting a splenic lesion who must undergo urgent prolonged surgery (for example for a fracture of the spine) with, moreover, positioning in the prone position making emergency laparotomy impossible in case of decompensation.

Non-operative treatment requires vigilant monitoring because of the potential development of a complication [35 36]. Non-operative treatment was initially developed for less severe lesions according to Moore's classification and then was progressively adopted for more serious lesions. In the extensive retrospective study of Peitzman[24] of 1488 adults with spleen trauma, prior to the splenic embolization era, the final splenic rescue rate was 55%. Non-operative treatment was implemented for only 62%, 26% and 5% of the Moore grade 3, 4 and 5 spleen injuries, respectively, with a failure rate increasing with anatomic severity of 19%, 33% and 75%. In this study, the presence of a large hemoperitoneum was also an independent prognostic factor for failure of nonoperative treatment with an overall rate of 73% splenectomy in this subgroup.

Alternatively, conservative surgical treatments of the spleen are multiple: hemostatic agents (effective only on the less severe spleen lesions, Moore 1-3), partial splenectomy (sometimes simple to perform if the anatomy is favorable and when the trauma concerns only one of the two poles of the spleen), a perisplenic mesh (a resorbable prosthesis that contains a system of concentric bursae), allowing, once the spleen has been mobilized and the clots evacuated, to perform a hemostatic compression respecting the pedicle. According to the authors the spleen is considered to be immunologically functional provided that vascularization of at least 25-50% of the organ remains[37]. In practice, with the development of splenic embolization, repair techniques are less often realized because they had limited effectiveness, many complications and were most often in performed in patients with active bleeding, which are currently the best candidates for a radiological intervention.

I-2-3 Splenic Artery Embolization (SAE)

I-2-3-1 SAE Technique[38]

When a diagnosis of traumatic parenchymal and / or vascular hemorrhagic injury has been made, hemostasis is achieved by percutaneous embolization via an angiography catheter. The technique is significantly different from tumor embolization techniques, functional organ reduction or arteriovenous malformation techniques in three important ways: temporary embolization using resorbable material is usually sufficient to generate the local formation of a thrombus; secondary recanalization of the occluded vessel is not a problem, vascular occlusion should be performed exclusively at the bleeding site, and embolization should not cause any tissue damage, or at least as little as possible. When there is a parietal traumatic lesion of a large permeable (and therefore catheterizable) vessel that it is unconceivable to occlude (iliac, femoral or subclavian artery), hemostasis can be obtained by the placement of a covered stent.

Percutaneous access is most often right or left femoral. The use of fluoroscopic bone markers or ultrasound guidance can be quickly implemented in case of difficulty in puncture so as not to waste time on vascular access. If the patient is already equipped with an arterial access, we can "borrow" it as the first pathway. The use of a vascular introducer (5-French) is very useful to allow rapid exchange of catheters. In major trauma of the pelvis or major cutaneo-muscular dilapidation, a brachial or axillary approach should not be neglected

If the patient has already received a CT scan with iodinated contrast agent, the catheterization will be carried out immediately on the recognized or suspected hemorrhagic sites. In the absence of CT, frontal aortography should be systematic to guide selective catheterization. The negativity of the aortography does not however eliminate the presence of hemorrhagic lesions that only selective or even supra-selective series can invalidate. The angiographic signs of lesion with hemorrhagic potential are multiple (Table 1) and must all lead to embolization, even if an active contrast leak is not visualized. The most commonly used catheters are pre-shaped ones, such as the Cobra and Simmons. Of caliber French 4 or 5, they often allow one to realize the diagnosis and the treatment. In case of difficult catheterization or to embolize very selectively, the recent advances in materials have made very efficient French 3 (even 2) micro-catheters available for delivering micro-emboli.

Curaspon®, a temporary embolus of the animal gelatin type is resorbed in three weeks, and is the embolus of preference. Fragments of variable size and shape are used according to the habits of the interventionalist; only the use of the powdered product is clearly discouraged. Indeed, similarly to PVA (polyvinyl alcohol) type particles, which also have the disadvantage of forming definitive emboli, the powder provides only very distal embolization that is not relevant in the present context, and can generate extensive visceral infarction and abscesses. Coils, definitive emboli constituted of metallic helixes sometimes covered with thrombogenic fibers, are widely used in certain sites, or in case of failure of Curaspon® that can occur in the event of major disturbances of hemostasis

I-2-3-2 Complications of SAE

The complications of this technique[39] occur in about 15% of cases[14 40]. These are mainly, the persistence of the hemorrhage, post embolization syndrome (fever and major pain), the migration of the coils, thrombosis of the splenic and/or portal vein, septicemia, pancreatitis, bronchopneumopathies ; affect the access route41 (thrombosis, wounds, hematoma, arteriovenous fistula, false aneurysm, and pseudoaneurysm); complications related to the contrast medium (renal failure, allergy); pleural effusions, or the occurrence of a splenic pseudo-cyst. In the multicenter study of de Haan[10] that included 140 traumatized spleens, the specific complications of embolization were 6 splenic abscesses (4%), persistent bleeding in 11% of cases, and one case of femoral artery injury, with an overall complication rate of 20%. We have published a series of 20 patients who had splenic embolization with similar results, an overall complication rate of 23%, a specific complication rate of 6% and a 90% spleen rescue rate. In this work, the occurrence of a large pleural effusion seemed particularly frequent in embolized patients (32% thoracic drainage).

I-2-3-3 Indications for SAE

The use of arterial angiography has increased significantly in recent years and all retrospective studies show a marked improvement in the splenic rescue rate when splenic embolization is performed[40 10 12 13 33 42]. In the

multicentric study by Haan[10] the overall rate of spleen rescue was 93% for Moore grade II-III patients and 83% for those with Moore grade IV-V.

The monocentric study of Sabe[13] is a retrospective evaluation of a trauma-based SAE protocol at the Cleveland Center (USA) for the following high splenectomy risk situations: contrast material extravasation or pseudoaneurysm on abdominal CT; Moore grade 3 lesion and significant hemoperitoneum; Moore grade 4 lesion. In the group followed from 2002 to 2007, there was 30% of SAE and the spleen rescue rate was 351/398 (88%) significantly better than that of patients in the two historical series from the same center (1991-1998): 3% SAE, spleen rescue 125/222 (56%) and 1998-2001: 17% SAE, 166/195 spleen rescue (85.1%) Overall mortality was significantly decreased in the most recent series (5% versus 6% and 12%) The author notes that out of the 20 patients with Moore splenic trauma grade 5, three stable patients who should have had a splenectomy according to the protocol, finally benefited from effective embolization for 2/3 The interest of extending SAE indications to patients with severe head trauma or multiple trauma to reduce the deleterious consequences of anemia is also highlighted in this work.

Splenic arterial embolization is therefore currently used routinely in the case of extravasation of CT contrast material in a relatively hemodynamically stable patient able to be transported to the angiography unit. It is also carried out as a preventive measure in the following situations:

1. *Post-traumatic splenic pseudoaneurysms*., have an estimated frequency of 5 to 13% in adult patients who have had non-surgical treatment, and they are a cause of secondary rupture occurring anytime between D1 and M4 [43]. Even if *spontaneous thrombosis* is possible[44], *the high risk of secondary rupture* [45] [46] *justifies the systematic performance of* a control CT with injection at discharge, and an embolization if detected. Although arterio-veinous fistulas are much rarer they require the same treatment[47].
2. *Need for another emergency operation (orthopedic, neurosurgery etc)* making a splenic approach impossible in case of decompensation.
3. *Need for embolization of another organ with active contrast agent leakage (most often kidney or liver).*
4. *Severe polytrauma* with significant risk of decompensation in the event of splenic hemorrhage
5. *Severe spleen involvement: Moore grade 3 accompanied by abundant haemoperitoneum (presence of Douglas effusion on CT) or Moore grade 4-5.*

In conclusion, in France, in the majority of expert centers, splenic artery embolization is performed systematically in the following cases: extravasion of contrast medium on CT scan in patients who are sufficiently hemodynamically stable to be transported to the angiography unit; when there are one or more post-traumatic splenic arterio-veineuse pseudo-aneurysms; in the case of need for another emergency operation (in particular orthopedic, or neurosurgical); or when an embolization is performed for an organ with active hemorrhage.

Apart from these indications, the attitudes are more diverse for other situations at high risk of splenectomy: Moore spleen grades 4 and 5, or Moore grade 3 =plus another risk factor: presence of a bulky hemoperitoneum, or associated severe trauma.

I-2-4 Summary of current treatments for closed splenic trauma

Retrospective studies have shown that 10-15% of patients with splenic trauma should benefit from emergency splenectomy. For the remaining 85% who initially have non-operative treatment, some situations are at high risk (between 40% and 80%) of splenectomy: severe Moore grade 4 and 5 involvement, Moore grade 3 involvement and severe hemoperitoneum, or Moore grade 3 involvement and severe damage to at least one other organ. The objective of this study is to assess the benefit of preventive embolization in these situations.

I-3 Immunological role of the spleen

I-3-1Physiopathology

The spleen is the largest secondary lymphoid organ in the human body and is actively involved in organizing the immune response. One of the most important immunological roles of the spleen is the maturation of B lymphocytes, which are a major constituent of the immune system because they are at the origin of the production of antibodies[18]. The functional immunological part of the spleen is structured in the same way as the ganglion. The germinal centers of the secondary follicles are very active in the process of developing the immune response following its activation by a danger signal, resulting in the acquisition of B memory cells. It is the site of development of the antibody response, particularly with respect to bacterial polysaccharide antigens. The follicular dendritic cells of the marginal zone play an important role; they fix the bacteria present in the circulation, and present the antigens to the B cells [6].

I-3-2 Immunological consequences of splenectomy

The deterioration in immune function after splenectomy[6] is all the more significant if the subject is young or suffers from other pathologies (cancer, immunosuppression, radio- or chemotherapy, diabetes, alcoholism, etc.)[48]. This deterioration is the cause of fulminant post-splenectomy infection or "Overwhelming Post Splenectomy Infection" (OPSI), with a mortality reaching 40% in adults[49]. In children the risk is pronounced (4%) until age 15 [5], the most common infection being meningitis. In most cases this sepsis is due to a pneumococcal, meningococcal or *Haemophilus influenzae* infection. It is manifested by a fulminant infection preceded by 24h to 48h a non-specific pro-drome and then by the sudden onset of septicemia leading to multi-organ failure and, in nearly half the cases, to death within 24-48 hours. The diagnosis is often made on finding a very high number of germs on examination of a blood smear. The bacterium most frequently involved is *Streptococcus pneumoniae* (80-90% of cases); other bacteria involved may be *Haemophilus influenzae B* (6%), *Escherichia coli* (4%), *Neisseria meningiditis* (4%, especially in patients under 25)[6 50]. Other, less common germs may be involved, in particular *Samonella spp., Pseudomonas aeruginosa, Capnocytophaga canimorsus* (a saprophyte of the oral cavities of dogs and cats), *Burkholderia pseudomallei*, and the parasites *Babesia bovis* and *Plasmodium*.
The time to onset of fulminant infections after splenectomy is variable, but according to an English study[51] 50% of deaths occur within three months after surgery and 28% in the first three years; nevertheless cases occurring 40 and 65 years after splenectomy have been described. In adults, an Australian study including more than 600 splenectomies for trauma evaluated the risk at 0.2 cases/100 person-years[48 52], with a risk of OPSI of 1.5/1000 in splenectomized patients without a co-pathology[52]. These observations, combined with the variable effectiveness of the anti-pneumococcal vaccine (because of the great diversity of the strains, which are not all included in the vaccine), is at the origin of the recommendations of the expert conference (Paris-2003) which advocated, in addition to pneumococcal vaccination, an oral penicillin antibioprophylaxis. After splenectomy for trauma, there is therefore a consensus on the need for education of the patient (IM injection of cephalosporin in case of a febrile syndrome, bites or licking of damaged skin by a dog or cat, or tick bites), Pneumococcal vaccination (and vaccination against meningococcal anti-Haemophilus B in subjects under 30 years: Prevenar® and ACT-HIB® respectively) and oral penicillin for two years (mandatory for life in immunocompromised or hepatopathic patients). However, several studies have shown that these measures, restrictive for a young adult, were incorrectly prescribed and followed on only 20% of patients at most[49 53].

I-3-3 Immunological consequences of embolization

Even if deterioration on monocyte function appears after embolization[54], the majority of studies do not show any clinical deterioration of immunological function after embolization[16 55], and, above all, the increase in embolizations has not been accompanied by an increase in the OPSI rate in embolized patients. However, to our knowledge, very little work has been done on functional immunological analysis that allows one to obtain an objective answer to the question. We have carried out preliminary work comparing the immunological function of B cells in splenectomized and embolized patients (the IMMUNORATEEMBOL study, sponsored in 2009 by the Clinical Research and Innovation Department of Grenoble University Hospital). This work showed a recovery of the mature B cell populations in the spleen only in embolized patients, from the 18th month, without such recovery in the splenectomized patients. Kininoformation activity that reflects vascular stress status was significantly increased in both groups on D0 ($p < 0.01$) and normalized on D2 suggesting it to be linked to

trauma. The reserve of kininoformation proenzymes remained normal in embolized patients whereas it was significantly decreased in splenectomized patients ($p < 0.01$).

By analogy with splenectomy, the secondary occurrence of extensive splenic necrosis (> 50% of spleen volume) is probably accompanied by a deficit in its immune function, but this has not been proven.

I-4 Context of this study

A prospective randomized trial to judge the benefit-risk ratio of prophylactic splenic embolization in situations at high risk of splenectomy is a necessity because this practice is becoming frequent in many expert traumatology centers without, to our knowledge, a rigorous evaluation having been carried out.

The consequences of this project are potentially important because:
- Splenic trauma is the most frequent digestive trauma (more than 1500 splenectomies are performed following trauma in France, which corresponds to a rate of splenic trauma of nearly 4000 / year)
- Splenectomy has irreversible immunological consequences requiring life-long constraining measures that are currently not well followed by most splenectomized patients.
- The immunological consequences of splenic embolization are still poorly understood.
- Embolization presents certain complications.
- Since embolization is not performed in all centers that receive traumatized patients, this leads to secondary transfer of patients, for which the necessity must be totally justified because of the cost and the risk involved (risk of decompensation during transfer).

I-5 Feasibility of the study

I-5-1-Participating sites

In view of the epidemiological studies that have shown the very high cost in terms of mortality, morbidity and loss of autonomy related to trauma in predominantly young subjects[56], recognition of the importance of visceral traumatology as a discipline has emerged over the last dozen years with an awareness of the crucial importance of a multidisciplinary approach to the care of severely traumatized patients[27]. This necessary and fruitful multidisciplinarity is illustrated in this project by the choice, for each center having agreed to participate in the study, of appointing 3 specialists: a physician anesthetist,/resuscitator/intensivist, a radiologist, and a surgeon.

The numerous collaborative projects, cross-disciplinary between the disciplines and the centers, that have already been carried out by the participants in this study, as well as the existence of multidisciplinary care networks, attest to the long-standing ties between the various participants.

The North Alpine Emergency Network has set up a traumatology care network according to international Trauma System standards, at a regional scale (North-Alpine valleys) to allow an initial rapid orientation of the seriously injured, as well as the pooling of skills and technical platforms. Based on the expertise of the SAMU (French emergency medical service), the North Alpine Emergency Trauma System Network (TRENAU) includes a triage based on physiological and anamnestic aspects, and by associating the diagnosis of anatomical lesions by the presence of emergency doctors on the spot. Two RENAU centers classed Trauma Center Level 1 GRENOBLE and ANNECY University Hospitals (CHU)) participating in this study, are referent centers for the other RENAU centers, have a regular and experienced practice in arterial embolization for trauma. The ongoing register includes more than 1220 patients annually for a population of more than two million inhabitants, an incidence of serious injury of about 60/100000hab/year. The mortality observed in TRENAU is 7% for all patients and 13% for the most severe patients (Injury Severity Score: ISS > 15). This mortality seems lower than the different cohorts of the severely traumatized published for France, with a mortality of between 16 and 18%. Concerning splenic injuries, managed by the network in 2009 and 2010, 147 patients presented splenic lesions. The median age was 29 years [20 - 45] with a sex ratio M/F of 3. The average ISS patient was 27 (± 15) with an observed mortality of 6%; 22% (n = 32) underwent emergency surgery, and 6% (n = 7) of the remaining patients underwent secondary splenectomy. Fifteeen patients underwent embolization.

The SOP flow chart for the treatment of splenic trauma was developed from the work of several team members with different specialties: Pr Arvieux (Surgeon, CHU Grenoble), Dr Dubuisson (Surgeon, CHU Bordeaux), Dr

Lemoine (Surgeon, CHU Nîmes), Dr. G Brault-Noble (Surgeon, CHU Montpellier); Dr. Thony (Radiologist, CHU Grenoble), Dr. Bouzat (Anesthetist-Resuscitator, CHU Grenoble).

Collaboration in teaching the following Inter-University Degrees also illustrate the links between the participants in this work:

- Inter-University Diploma (IUD) in Visceral Traumatology, which was created 12 years ago, brings together hospital and university teaching surgeons from numerous university teaching hospitals and general hospitals: Bordeaux, Clermont-Ferrand, Dijon, Grenoble, Lyon, Marseille, Montpellier, and Nîmes, and allows fruitful exchanges and a constant collaboration with the surgeons trained during the IUD and with the specialist resuscitators and radiologists participating in teaching and practical work
- The Inter-University Diploma in Severe Traumatologie organized by the Universities of Grenoble and Lyon for doctors taking care of emergencies allows multidisciplinary collaborations.
- The organization, since 8 years, of a continuing education (FMC) session dedicated to visceral trauma by C Arvieux (CHU Grenoble) and F Pons (HIA Percy) during the French Congress of Surgery.

I-5-2 Recruitment capacity of the centers

The recruitment capacity of the centers can be evaluated thanks to 3 recent studies on the management of spleen trauma performed at the following hospitals: Grenoble, Montpellier, Nîmes.

- In the University Clinic of Digestive Surgery of Grenoble University Hospital, 250 patients with splenic trauma were treated between January 2004 and March 2011. The study focused on trauma related to skiing and snowboarding: it included 61 patients, with the obligation to perform an immediate splenectomy for 8 patients (13% of the trauma patients).
- Montpellier University Hospital admitted 220 cases of serious spleen trauma between 2004 and 2009 (208 exploitable cases), with immediate splenectomy performed for 35 patients (17%).
- At Nîmes University Hospital a prospective study on spleen trauma in the Languedoc-Roussillon region showed that on average 185 patients per year were admitted to the 10 hospitals of the county (Table 3).

Table 3: Number of Splenic Contusions in Languedoc Roussillon

Data provided by MC LEMOINE, Prospective evaluation of the treatment of splenic contusions in Languedoc-Roussillon. AOI 2009 CHU of Nîmes

	2006	**2007**	**2008**	**Moyenne**
Montpellier	59	76	74	70
Nîmes	30	23	14	22
Perpignan	12	10	8	10
Carcassonne	36	41	47	41

For Languedoc Roussillon, the four largest centers admitted an average of 35 patients with splenic trauma per year and per center. These figures are quite comparable to those of Grenoble (35.7 patients admitted per year).

In the two studies at Montpellier and Grenoble, total splenectomy at the initiation of management was performed in 13% and 17% cases respectively, which corresponds to initial non-operative treatment for 85%, corresponding to the literature data (in average 15% have initial splenectomy, see chapter 1-2-1). Thirty patients/year/center benefit from non-operative treatment, which corresponds to an average of 15 patients/year/center with Moore grade 3-5 trauma.

I-5-3 Inclusion of patients in the study

This study, which will include Moore 3-5 patients who receive initial non-operative management, is therefore aimed at 25 to 50% of splenic trauma patients admitted to a hospital.

It is usual to describe the difficulties in the inclusion of patients admitted in an emergency context, but in practice, when care is provided by centers specialized in Traumatology the necessary information for patients (and their families when the injured person is unable to receive this information) about the expected benefits and risks of surgical procedures and techniques such as arterial embolization, is routinely given by the physicians taking care of the patient. The proposal for inclusion in a study and information on the benefits and risks of a technique is then included naturally in the treatment. Thus, when at Grenoble University Hospital a prospective study (STIC 2008) was conducted on the immunological consequences of splenectomy and splenic embolization, all patients were included within the deadlines that had been set.

II- Study Objectives

II-1 Primary Objective

To evaluate the benefit-risk of the practice of preventive splenic embolization versus surveillance in hemodynamically stable adult patients with severe closed splenic trauma at high risk of splenectomy. The aim is to show that embolization **improves the rate of spleen rescue at 1 month**, while evaluating its side effects compared to simple monitoring.

Primary endpoint: splenic rescue rate at one month. The spleen must be immunocompetent, i.e., intact, or treated by surgical procedures allowing preservation of at least 50% of the vascularized splenic tissue in cases of secondary laparotomy, or with necrosis of less than 50% of the volume. This criterion is validated by the reading of the masked initial scan by two radiologists from the expert committee on imaging.

II-2 Secondary objectives:

Secondary objectives focus on the evaluation of:

- The splenic rescue rate at 6 months
- Vascular or hemorrhagic complications, and death
- Hospitalisations and re-hospitalisations
- Impact on ability to resume work
- Impact on physical activity
- Vascular reconstruction and immunosuppression

The secondary endpoints correspond to the risks incurred in both the embolization and the surveillance groups for the duration of inclusion (6 months).

- Rate of splenic rescue at 6 months
- Death
- Number of red blood cell packs transfused
- Pleural effusion
- Need for thoracic drainage
- Venous thrombosis of the spleno-mesenteric portal axis
- Arteriovenous fistula, false aneurysm, pseudo-aneurysm of a splenic pseudo-cyst
- Total hospital stay in a short stay unit
- Length of hospitalisation in an intensive care unit
- Need for re-hospitalisation
- Total time off work
- Evaluation of physical activity (WOMAC)
- Immunological assays for vascular reconstruction markers (kininoformation) and immunosuppression (D0, D5, M1, M6)
    - Kininoformatric activity
    - Lymphocyte B phenotypes (B naïve, B memory)

Events specific to each group will also be recorded:

- Need for splenic embolization (control group)
- Complications associated with embolization:
    - Related to vascular access to embolization (hematoma, thrombosis, arteriovenous fistula, pseudo-aneurysm)

- Related to the contrast agent (kidney failure, allergy)
- Related to the technique (inadvertent embolization of non-targeted territories)

II- 3 Definitions of criteria

Spleen rescue: The spleen must be immunocompetent, i.e., intact, or treated by surgical procedures allowing preservation of at least 50% of the vascularized splenic tissue in cases of secondary laparotomy, or with necrosis of less than 50% of the volume. This criterion is validated by the reading of the masked initial scan by two radiologists from the expert committee on imaging.

Splenic abscess diagnosed by the presence of an intra-splenic fluid collection on abdominal CT scan and hyperthermia > 38.5° OR hyperthermia > 38° associated with a biological inflammatory syndrome (Hyperleukocytosis > 12000, CRP > 20) AND absence of other diagnosed infection.

Abscess on wall of abdominal scar or femoral puncture point with discharge of pus or redness associated with a hyperthermia > 38°.

Deep abscess diagnosed by the presence of an intra-peritoneal fluid collection on the abdominal CT scan and hyperthermia > 38.5° OR hyperthermia > 38° associated with a biological inflammatory syndrome (Hyperleukocytosis > 12000, CRP > 20) AND absence of other diagnosed infection.

Allergy: reaction during or just after injection of iodinated contrast agent: occurrence of redness, rash, nausea, pruritus, facial edema, bronchospasm, low arterial blood pressure, pulmonary edema, neurological disorders, cardiac arrest or cardiorespiratory disorders.

Pulmonary Complication
Pneumopathy or pleural effusion, diagnosed by a clinical manifestation (dyspnea, fever or chest pain) that led to the request for a chest x-ray.

Thrombo-embolic complication
• Lower limb phlebitis diagnosed by lower extremity ultrasound scan performed due to clinical signs (pain, redness, unilateral edema, unexplained hyperthermia > 38°).
• Pulmonary embolism diagnosed by thoracic angioscan performed due to clinical signs (Dyspnea, tachycardia > 100).
• Splenic vein, superior or portal mesenteric vein thrombosis diagnosed on the routine abdominal CT scan before discharge.

External pancreatic fistula: with a level of amylase in the drainage fluid 5 times greater than blood level at D5 with flow > 50ml/day OR level of amylase 3 times greater than blood level from D3 for 3 days.

Hemorrhage defined by the need for the transfusion of at least 2 packs of packed red blood cells during hospitalization OR a fall in hemoglobin > 3g/dl with an identified bleeding site OR a fall in hemoglobin > 4g/dl without an identified bleeding site.

Splenic infarction diagnosed by the abdominal CT scan (% devascularization of splenic parenchyma)

Renal insufficiency: creatinine clearance calculated according to the Cockroft & Gault formula < 80ml/min

Peritonitis diagnosed on intraoperative bacteriological specimens

Acute pancreatitis diagnosed by abdominal CT scan OR hyperlipasemia > 3 times normal requested on clinical signs (epigastric pain)

Septicemia: hyperthermia > 38.5° and positive blood cultures.

III- Subject characteristics

III-1 Patient recruitment

Patients will be included in the study upon admission to surgery or intensive care at one of the Traumatology Reference Centers participating in the trial. These centers are mainly university or general hospitals that receive the vast majority of splenic trauma cases in their region

All adult patients with splenic trauma admitted to the emergency departments of the university and general hospitals participating in the study will be recruited, subject to their informed consent. The latter will be obtained before surgery or embolization to the extent that the patient is able to provide consent. If the patient is not in a position to receive the information, the consent will be collected from his/her entourage.

III-2 Inclusion Criteria

- Patients aged over 18 and less than 75 years
- Hemodynamically stable patients (systolic BP ≥90mm Hg and absence of hemorrhagic shock)
- Having a blunt splenic trauma within the previous 48 hours
- At high risk of splenectomy :
    - Spleen damage Moore grade 4 or 5 on injected abdominal computed tomography
    - Spleen damage Moore grade 3 and at least one of the following:
      - Significant hemoperitoneum (visible at the pelvic level).
      - Associated serious damage (NISS -New Injury Severity Score greater than or equal to 15)
- Volunteers to participate in the study, having signed the consent form or with agreement of the family if the patient is not able to give consent after adequate information and delivery of the information document,
- Affiliated to a social security /health insurance scheme or beneficiary of such a scheme.

III-3 Non-inclusion criteria

- Patients who are resident outside of the EU
- Patient with hemodynamic instability (Systolic blood pressure <9 despite resuscitation)
- Patient with open splenic trauma
- Patient with an indication for surgery preventing the possibility of monitoring splenic trauma
- Patient with indication for embolization of another organ other than the spleen
- Patient with indication for splenic embolization due to post-traumatic vascular abnormality (active contrast agent leakage, pseudoaneurysm or early splenic arteriovenous fistula).
- Patients under 18 and ≥ 75 years of age
- Patient with a previously pathological spleen (tumor, infection, intrasplenic vascular abnormality)
- Patient with Grade 1-2 trauma
- Patient with grade 5 trauma with total ischemia of the spleen
- Patient who had partial or complete splenectomy before inclusion
- Patient with acquired or innate immune deficiency
- All contra-indications to the realization of an embolisation
- Pregnant woman
- Person deprived of liberty by judicial or administrative decision, person subject to a legal protection measure
- Patient currently in a clinical trial or who participated in a clinical trial in the month prior to inclusion
- Patient with a mental or psychiatric disorder, or a histoery of such, or any other factor limiting their ability to participate in an informed manner and to adhere to the protocol
- Patient with acquired or innate hemostasis abnormality (anticoagulant therapy

III-4 Allowed or prohibited associated treatments

No associated treatment is prohibited. All associated treatments or prescriptions of all kinds must be reported in the case report book

IV- Study design

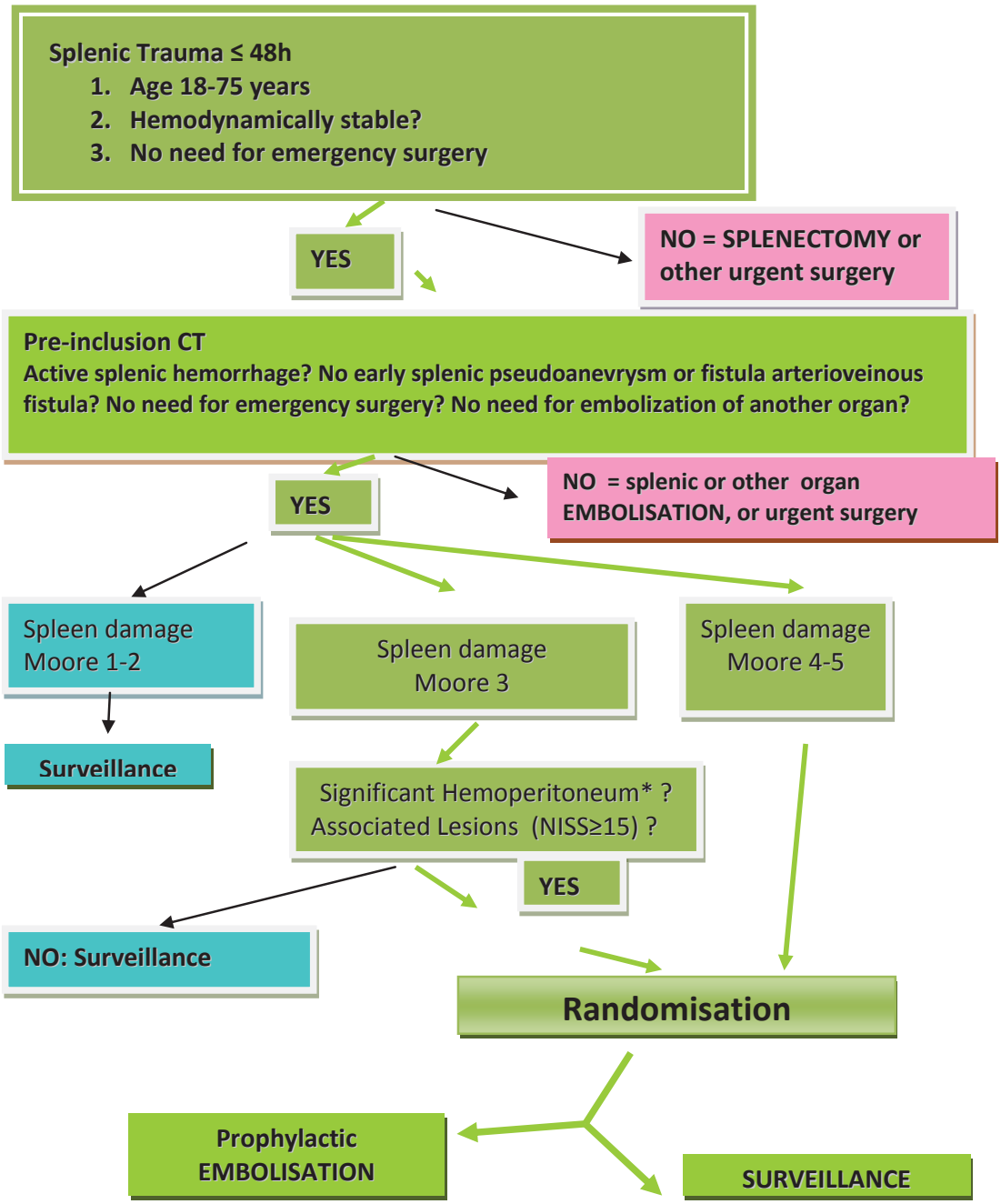
IV-1 Type of study

This is a multicenter parallel-group, randomized controlled clinical trial.

As the first arm of the study is interventional (embolization), unlike the second (surveillance), blinding cannot be considered at the time of inclusion in the study. Nevertheless, the allocation arm of CT images at inclusion (D0, needed to validate the inclusion criteria), at one month (D30, to validate the primary endpoint) and at 6 months (D180) will be masked before CT images are read by the two radiologists belonging to the Expert Imaging Panel.
As patient recruitment and center experience will vary from one institution to another, randomization will be stratified by center.

IV-2 Overall organization of the trial

IV-2-1 Experimental Flow chart



***Visible effusion at the pelvic level**

IV-2-2 Course of the study and experimental procedures

IV-2-2-1 Initial management of care

The immediate management of patients with splenic trauma will follow the usual practices of the different centers. Eligible patients are patients admitted to the emergency department, shock treatment or intensive care, or to surgery in the participating centers and presenting the inclusion and exclusion criteria defined in the previous paragraph. An exhaustive list of these patients will be made in each center in order to compare numbers and characteristics of eligible and included patients.
In routine practice, all hemodynamically stable patients with abdominal trauma have preoperative whole-body multi-barrel CT scans with contrast injection. Patients with a history of allergy or who have demonstrated intolerance to iodine will be treated using the antiallergic protocol in force in the hospitals. The initial CT scan should include abdominopelvic sections without injection, then, after opacification at arterial and parenchymal times (60-90 sec). The quantity of iodine injected will be at least 1 ml / kg at a concentration of 300 to 350 mg / ml. The imaging data collected during the study (CT examinations and embolization) should be archived on a centralized and secure archiving system or on CD or DVD. In the case of CT examinations performed outside the investigative center, the imaging data must be sent by CD or tele-transfer to the radiologist of the investigating center and stored by the latter.

In each center, information about the trial and the proposal to participate will be made by the resuscitator or the surgeon in charge of the patient, either directly to the patient or to his relatives, depending on the patient's condition.

The assessment of the severity of the splenic trauma, according to Moore's grade, will be made by the radiologist in charge of the embolization. The homogeneity in type and severity of splenic trauma lesions among the centers will be verified by the Expert Imaging Committee.

Centralized randomization with stratification by center using blocks of random size will be carried out by the investigator (resuscitator or surgeon in charge of the patient) according to the electronic observation site (e-CRF). After collection of the written consent and inclusion, the investigator will randomly assign the patient to a treatment arm directly using a randomization number automatically provided by the e-CRF site. Once the randomization number is attributed the patient is considered as included in the trial and in the intention to treat analysis, even if the patient is prematurely discharged from the trial (eg. due to withdrawal of consent).

Data are to be entered in the e-CRF. Nevertheless, any visit should be the subject of a patient file (source file) gathering all the data from the interview and the clinical examination. The inclusion visit and visits during the follow-up will be carried out by a doctor, hereinafter called "investigating doctor".

From the moment of inclusion, the data in the e-CRF will be filled-in by the investigator during the entire hospitalization.

IV-2-2-2 Splenic arterial embolization

The embolization should be performed by a interventional vascular radiologist working autonomously and as part of her/his professional practice being “on-call” for interventions. to the interventional guards / on-call, All the interventionists of each center should be registered at the beginning of the trial.

The intervention should be performed in an interventional radiology room with an angiography device with at least subtraction, serial images at 3 frames per second and fixed-arch with multiple angulation features.

All catheterization and embolization equipment should be readily available and permanently in stock, including plugs and coils of appropriate size, long-valve inserts, preferably hydrophilic and pre-curved, or catheter guides.

The arterial approach will preferably be performed via the femoral artery, or in case of a unfavorable anatomy of the celiac trunk by a humeral approach, with an introducer having a maximum diameter of French 6.

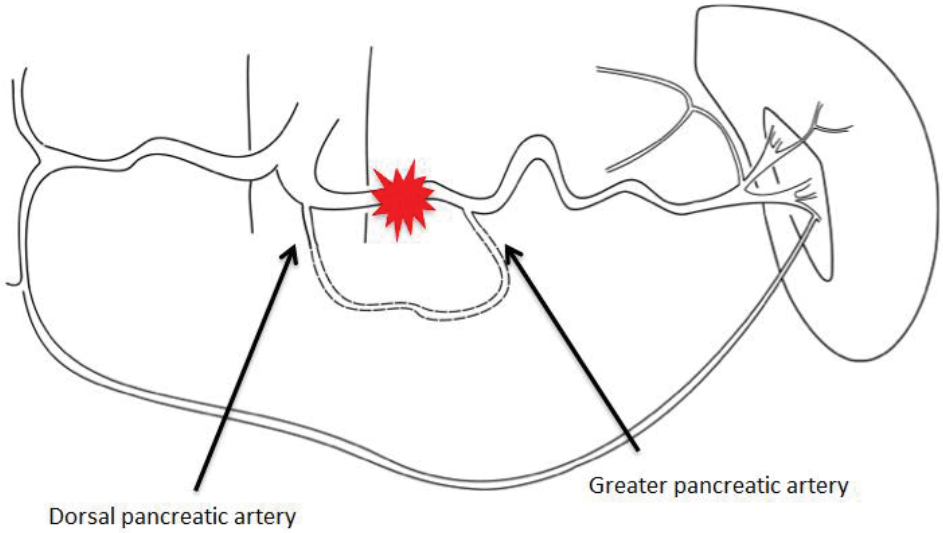
The choice of catheterization equipment is at the discretion of the operator.

Embolization procedures are described in the following paragraphs.

IV-2-2-2-1: Proximal Embolization

The embolization material is positioned in a compact bundle, at the level of the trunk of the splenic artery, upstream of its division into branches and if possible downstream of the dorsal pancreatic artery. If possible the embolization is done using a Type 1, 2 or 4 Amplatzer ™ plug. The type 4 plugs are available up to 8 mm in diameter, can be introduced using diagnostic 0.038 inch light catheters, but the passage of a 8 mm diameter plug can be very difficult, if not impossible, when there is significant arterial tortuosity. Type 1 or 2 plugs require the insertion into the artery of a 6F guide catheter or a long valve hydrophilic 5F pre-bent introducer, which can only be envisaged when the origin of the celiac trunk is not too oblique and the splenic artery is only moderately tortuous. The splenic artery may also be occluded by coils of 8 to 8 mm in diameter. Rigid coils of 0.035 inch are preferred so as to reduce the risk of emboli migration. The use of microcoils should be avoided and the use of glue, gelatin fragments or microparticles prohibited. Proximal embolization is preferred for high grade lesions without a vascular abnormality. This is a preventive embolization which, by lowering the splenic perfusion pressure reduces the risk of bleeding[61]. It is also used when there are multiple vascular abnormalities. Indeed, it would be too time-consuming and deleterious to be selective in each pathological artery, so we will prefer proximal embolization. Embolization is complete on complete occlusion of the treated artery at the "bundle" level. It must persist during a recovery in downstream arterial flow by collaterals thus ensuring splenic perfusion and limiting ischemia.

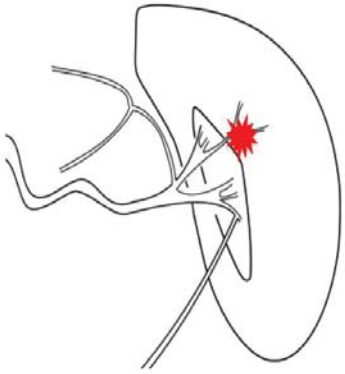
Proximal embolization



IV-2-2-2-2: Distal Embolization

This is an intra-parenchymal embolization, at the level of the segmental branches of the splenic artery. This embolization implies terminal vascularization and is therefore ischemic62. It must therefore only concern a limited vascular territory. It will be preferred in patients with isolated vascular abnormalities. This is an embolization of hemostasis. In most cases the embolization requires the use of a microcatheter. Embolization is done by microcoils or gelatin fragments. The use of glue or microparticles is strongly discouraged as it runs the risk of non-targeted embolization.

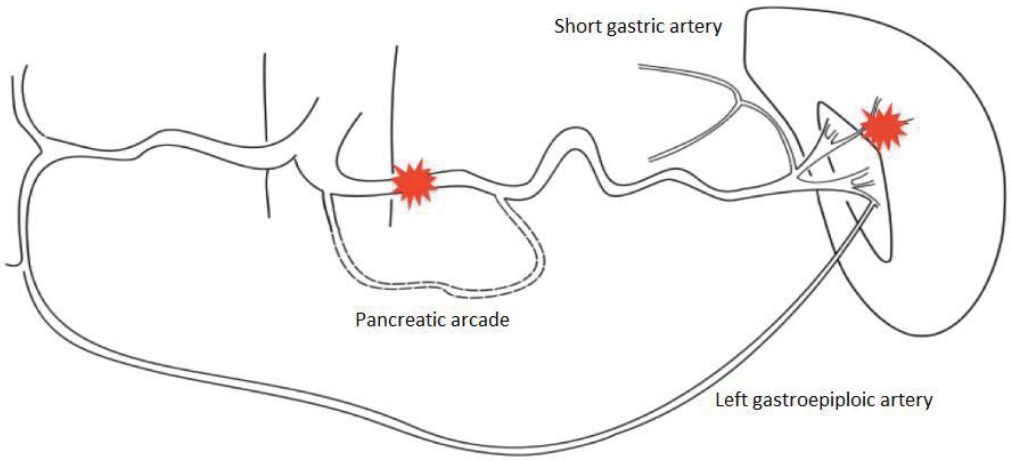
Distal Embolization



IV-2-2-2-3: Combined Embolization

This technique combines a proximal embolization with a distal embolization. It is reserved for isolated vascular abnormalities associated with high-grade AAST trauma or an abundant hemoperitoneum.

Combined Embolization



Whenever possible splenic artery occlusion will be achieved using a plug-type device of 6 to 10 mm in diameter inserted through a valve introducer or a guide catheter. The occlusion should involve the proximal, middle or distal segment (before the splenic hilum), but ideally be located in the middle part of the splenic artery, between the first large pancreatic artery (dorsal pancreatic artery) and the last one (magna pancreatic artery). When the splenic artery has a superior polar branch of early origin, the occlusion will preferentially be performed upstream of this collateral. In case of difficulty or foreseeable technical impossibility to achieve occlusion by plug, the occlusion will be done by means of coils of 0.035 or 0.018 inch, with controlled or uncontrolled detachment.

Temporary emboli, liquid agents and microparticles should not be used in this trial.

If a distal vascular lesion is found that was not detected on the pre-operative CT scan, it could be subject to targeted occlusion in addition to the proximal embolization.

The arteriographic assessment will include at least a splenic or celiac arteriogram with selective catheterization before and after embolization, with an analyzable splenic parenchymography.

The amount of contrast medium and its concentration, the total dose delivered in gray.cm² and the total time of the procedure "from skin to skin" will be recorded.

In order to avoid any classification bias, it is planned that all initial CTs will be read “blinded” by two independent senior radiologists.

IV-2-2-3 Visit at D5 (+/- 3 days).

The effectiveness of the embolization, if it was performed and the verification of the absence of complication development of embolization is measured by a postoperative CT scan which is done in the majority of cases on the 5th day post-admission (+ /- 3 days). For non-embolized patients, the 5-day CT allows to verify the absence of complications of the trauma (infarction, pseudo-aneurysm, arteriovenous fistula) and to authorize patient discharge. CT examinations will include at least one series after opacification acquired at a parenchymal time. Imaging data will be archived.

During the post-procedure biological assessment, which is carried out systematically, the various immunological assays of markers of vascular reconstruction (kininoformation) and the following immunosuppression assays will be performed:

- Peripheral lymphocyte populations: evaluation of standard lymphocyte populations (CD4 and CD8 T, B, NK) among total lymphocytes and extensive immunophenotyping of B and T lymphocytes (with evaluation of naive and memory cell subpopulations among B cells, TCD4 or TCD8).
- Circulating VE-cadherin,
- Plasma proteases

IV-2-2-4 Visit at D30

The primary endpoint (intact spleen or spleen with at least 50% parenchyma vascularized at arterial CT time by CT) will be evaluated by the surgeon at the one-month consultation. This one-month postoperative consultation with CT but without abdominal injection is common practice, and will be performed regardless of the group to which the patient was randomized, to look for sequelae of splenic involvement: pseudo-aneurysm, arteriovenous fistula, pseudo-aneurysm cysts, or zones of necrosis. For patients with a pseudo-aneurysm, or an arteriovenous fistula a radiological opinion will be requested and a splenic embolization performed if the embolization criteria are retained by the team.
A telephone consultation at one month and after the CT scan has been sent to the surgeon, is also common practice in centers that routinely deal with traumas related to seasonal sports (skiing, mountaineering, water sports, etc) because a non-negligible proportion patients were on vacation at the time of the trauma. For patients living more than 200 km from the center, this examination will be prescribed at discharge, addressed to the referring surgeon and the consultation will be done by a telephone interview organized by the referring surgeon. In the event of the discovery of lesions requiring radiological or surgical treatment, the patient will be summoned to one of the centers participating in the study closest to his home.

In order to avoid any misjudgment of the primary endpoint, it is expected that all CTs at D30 will be read blinded to the study arm by a committee composed of two independent senior radiologists.

During the biological assessment systematically performed before CT (creatinemia), the levels of various immunological markers of vascular reconstruction (kininoformation) and the following markers of immunosuppression will be assayed.

- Peripheral lymphocyte population: measurement of standard lymphocyte populations (CD4 and CD8 T, B, NK) among total lymphocytes and extensive immunophenotyping of B and T lymphocytes (with evaluation of naive and memory cell subpopulations among B cells, TCD4 or TCD8).
- Circulating VE-cadherin,
- Plasma proteases.

IV-2-2-5 Visit at D180

During the consultation at one month a second consultation at 6 months after the trauma, with prescription for an injected abdominal CT will be organized. This examination is to detect late pseudoaneurysms and arteriovenous fistulas. For the splenectomized patients, during this consultation an assessment of the vaccinations received will be made and the patient reminded about the risks involved in splenectomy.

In centers wishing to participate, an immunological assessment will be done.
Immunological assessment will be performed in a systematic manner with the various immunological assays that are markers of vascular reconstruction (kininoformation) as well as the following markers of immunosuppression:

- Peripheral lymphocyte population: measurement of standard lymphocyte populations (CD4 and CD8 T, B, NK) among total lymphocytes and extensive immunophenotyping of B and T lymphocytes (with evaluation of naive and memory cell subpopulations among B cells, TCD4 or TCD8).
  Circulating VE-cadherin,
- Plasma proteases

IV-2-3 Summary of visits and examinations

Visit	Investigation Procedure	Embolization Group: Information to collect	Surveillance Group: Information to collect	Person in charge of data collection
Admission	Clinical examination and preoperative CT with contrast medium Measurement of subpopulations of B and T lymphocytes and kininogen activity	Clinical status, eligibility of the patient	Clinical status, eligibility of the patient	Investigator : resuscitator or surgeon (or delegated to interns)
Randomization no later than 48 hours after the trauma		Free and informed consent	Free and informed consent	Investigator : resuscitator or surgeon (or delegated to interns)
Intervention / Control no later than 48 hours after the trauma	Embolization or surveillance	Terms of realization Evolution of the clinical state of the patient	Evolution of the clinical state of the patient	Investigator / Clinical research assistant
Hospitalisation D0-D5	Additional interventions or explorations	- Complications specific to embolization - Necessity for splenectomy - Evolution of the clinical state of the patient - WOMAC auto questionnaire on physical activity. before the trauma.	- Necessity for splenectomy - Evolution of the clinical state of the patient - WOMAC auto questionnaire on physical activity. before the trauma.	Investigator / Clinical research assistant
D5+/- 3 days	D5 CT scan Measurement of B and T lymphocyte sub-populations	-Result of embolization, - Evolution of the clinical state of the	Evolution of the clinical state of the patient	Investigator / Clinical research assistant

	kininogene activity	patient		
Discharge home D6-		State of patient at discharge ; prescribed treatments	State of patient at discharge ; prescribed treatments - Is there an indication for embolization (pseudo-aneurysm, AVF): scheduling of embolization.	Investigator / Clinical research assistant
Surgical consultation at D30	Clinical examination D30 CT scan Measurement of B and T lymphocyte sub-populations kininogene activity	State of patient at discharge; secondary complications Tests and prescribed treatments WOMAC auto questionnaire on physical activity.	State of patient at discharge; secondary complications Tests and treatments prescribed If indication for embolization (pseudo-aneurysm, AVF) scheduling of embolization. WOMAC auto questionnaire on physical activity	Investigator / Clinical research assistant
Surgical consultation at 6 months	Clinical examination D180 CT scan Measurement of B and T lymphocyte sub-populations kininogene activity	State of patient secondary complications Tests and treatments prescribed; Patients with splenectomy : vaccination and information -WOMAC auto questionnaire on physical activity	State of patient; secondary complications Tests and treatments prescribed; Patients with splenectomy: vaccination and information -WOMAC auto questionnaire on physical activity	Investigator / Clinical research assistant

IV-3 Provisional timetable for the study

Expected date of start of inclusions: June 2013

Expected date of completion of inclusions: December 2017

Duration of participation for a subject: 6 months

Time required for data analysis and communication of results: 6 months

Total duration of the study: 66 months

IV-4 Study sites and investigators

The 12 centers participating in the study are all public institutions located throughout France. The inclusion of centers of different size is intended to give a recruitment of patients who are as varied as possible in order to avoid selection bias on the one hand and to achieve optimum study size on the other hand.

	Site	**Innovarc team number**	**Surgeon**	**Re-animator**	**Radiologist**

1	**CHU A Michallon, Grenoble**	**1**	**Pr C ARVIEUX Coordinating Investigator**	Dr P BOUZAT Co-investigator (Team 13)	Dr F THONY Co-investigator (Team 12)
2	**CHU Pellegrin, Bordeaux**	**2**	**Dr V DUBUISSON**	Dr M BIAIS	Dr Yann LE BRAS
3	**CHU Lyon-Sud, Pierre-Bénite**	**3**	**Pr JS DAVID**	Dr E VOIGLIO	Pr PJ VALETTE
5	**CHU La Timone, Marseille**	**5**	**Dr BEGE**	Pr M LEONE	Pr K CHAUMOITRE
6	**CHU St Eloi, Montpellier**	**6**	Dr F GUILLON	Dr CHARBIT JONATHAN	**Dr Valerie Monnin-Bares**
7	**Centre d'Instruction des Armées Percy-Val de grâce**	**7**	**Emmanuel Hornez**	Jean Louis Daban	Dr TERIITEHAU
8	**CHU Nîmes**	**8**	**Dr LE MOINE DONY marie christine**	Dr Laurent Muller	Pr Jean Paul BEREGI
10	**Hôpital H Mondor, A P H Paris**	**10**	**Pr Philippe Compagnon**	?	Pr H KOBEITER Pr A LAURENT
11	**Centre Hospitalier Régional de Valence**	**11**	**Dr** Christophe Henry	Dr P Patrice Frenandez	**Dr Thomas Martinilli**
12	**Centre Hospitalier Régional d'Annecy**	**12**	**Dr MESTRALLET**	Dr A LEVRAT Dr SIRODOT	Dr C DARAGON Dr A MARIE Dr O SEGALL
13	**CHU D'Angers**	**13**	**Dr LERMITE EMILIE**	Dr Guillaume Bouhours	Dr Antoine Bouvier
14	**CH de Chambéry**	**14**	**Dr Michoud Marie**	Dr Jean-Marc Thouret	Dr Al naasan Irchid
15	**CHU de Nantes**	**15**	Dr Sylvie Métairie	Dr Raphaël Cinotti	**Dr Frederic DOUANE**
17	**HIA Sainte-Anne - Toulon**	**17**	**Dr Tristan MONCHAL**	Dr Bertrand Prunet	Pr Charles Arteaga
18	CHRU de Lille	**18**	Dr Jean-Robert NZAMUSHE-LEPAN-MABLA	Dr Delphine Garrigue	Dr Marc Haberlay
19	**Hôpital de la Pitié-Salpêtrière**	**19**	**Pr Christophe TRESALLET**	Dr Mathieu RAUX	Pr Philippe CLUZEL

IV-5 Random allocation method

The randomization list will be drawn up by the CRO Clininfo (Lyon) before the start of study and held by them (people not involved in patient monitoring and data review) throughout the study until freezing the database.

Randomization will be centralized with stratification by center and blocks of random sizes.

It will be performed by the investigating physician via the e-CRF. After inclusion and collection of written consent, the investigator will randomize the patient directly using the e-CRF. The treatment arm will then be assigned associated with a randomization number.

Once the randomization number has been allocated, it will be considered as assigned to an included patient, even if the latter prematurely discontinues participation in the trial (eg withdrawal of consent)

V- Treatments and care to be compared

Care of admitted patients will be according to current practices in each center from admission to inclusion in the trial. The biological, radiological and clinical follow-up of the patients will be carried out according to the recommendations of good practice of the Learned Societies of each specialty (Visceral surgery, Imaging and interventional radiology, Resuscitation).

VI- Variables to be measured and methods of measurement

VI-1 Variables

Clinical and paraclinical variables measured from inclusion to 6 months postoperative will be as follows :

- Age and sex of patient
- Glasgow neurological Score
- Revised Trauma Score (RTS)
- New overall score of Trauma severity (NISS)
- Moore Score of splenic injury severity
- Type of secondary intervention performed gesture (total splenectomy, partial splenectomy, splenic preservation, embolization)
- Immunological data (blood, plasma and cells)
- Type of embolization (proximal or distal)
- Embolization material used
- Postoperative complications (up to 30 jours)
- Duration of hospitalisation
- Time off work
- Death
- Evaluation of physical activity (WOMAC)

Samples required

Whole blood will be collected by venipuncture of the forearm into three 4.5 ml tubes (13.5 ml) at T1 (before the initial scan - at randomization) and at D5, D30 and D180 after the procedure. In total, for each patient included in the study, 54 ml of peripheral venous blood will be collected in 4 punctures. Given the need for serum creatinine testing before each CT scan, inclusion in the study will not impose additional venipuncture on the patient.

Samples can be taken at the CH and CHU sites: 4.5 ml citrated tubes 4.5(light blue cap color code), 4.5 ml EDTA tubes (purple cap color code), 4.5 ml tubes without anticoagulant (red cap color code).

Collection and transport of samples

The transfer of biological samples is the responsibility of the Grenoble University Hospital. The organization of the transport of samples from the investigative site to Grenoble CHU will be provided by the general services. The samples will be collected by an authorized driver (BIOMNIS) and transported at 20 C ° to the angioedema exploration center on the 6th floor - Unit E, Hôpital Michallon, CHU de Grenoble. CS 10207 38043 Grenoble cedex 9. The transporter must respect the temperature constraint of 20°C; the must be transported without non-centrifugation (whole blood) and within less than 48 hours.

Future of the samples at the end of the clinical trial

Samples will be stored for the purposes of the SPLASH clinical trial (archival number recorded witht the CNIL and the biosample bank register: DC-2008-634). Samples will be stored at -80ºC. The data will be kept on behalf of the promoter in their secured filing system (secure office) for a period of 15 years.

Main outcome criterion:

This corresponds to the spleen salvage rate in the embolization and surveillance groups, defined as the maintenance of an immunocompetent spleen at one month after the trauma with:

• Intact spleen

• Splenic preservation by surgical methods (all hemostasis processes that do not devascularize

the spleen, perisplenic mesh, partial splenectomy leaving at least 50% splenic tissue volume)
• Splenic necrosis of less than 50% of spleen volume

VI-2 Measurement methods

VI-2-1 Evaluation of the lesional grade on the initial CT examination:

- The surface of a subcapsular hematoma is measured on an axial section in the middle part of the spleen;
- the involvement of hilar or segmental vessels in grade IV lesions corresponds to a complete fracture of the spleen, reaching the division of branches from the splenic artery (lobar and then segmental arteries) before their penetration into the splenic parenchyma. The involvement of trabecular vessels in grade III lesions corresponds to an incomplete parenchymal fracture, in which the first intra- parenchymal arteries may be damaged.

VI-2-2 Evaluation of a hemoperitoneum by CT examination:

A hemoperitoneum is considered as minimal when it is located in the peri-splenic and right inter-hepatorenal space; moderate when it reaches parietal-colonic channels and major when it is visible at the pelvic level.

VII- Data collection and management

VII-1 Data collection

All the interrogation and clinical examination data must be recorded in the patient's medical file, which can be consulted by the sponsor, and which will constitute the source data.
The collection of data will be done through an electronic observation booklet (e-crf) which allows real time quality control of the data (control at data entry plus immediate checking by a clinical research assistant with fast correction requests if necessary). This electronic observation booket is managed by Clininfo (Lyon).
The electronic observation notebook also allows a very precise monitoring of the inclusions and thus a close piloting of the study (relaunch of centers if necessary).
By agreeing to participate the investigator undertakes strict compliance with the experimental protocol, "Good Clinical Practices" and the legislation in force. He/she vouches for the authenticity of the data collected within the framework of the study and accepts the legal provisions authorizing the promoter of the study to carry out quality controls.

Statistical analysis will only be performed after verification of data entry and consistency and on completion of the database freezing procedure.

The source documents are:
The demographic data, the main data from the medical interrogation and the clinical examination, the data from the examinations, and the dates of the visits of the patients. Adverse events and the arm of the study be recorded in a separate file, bearing the protocol reference number as well as the patient number. This document constitutes the source file.

VII-2 Monitoring

Data monitoring will be carried out on all data by a Clinical Research Assistant (CRA) from the coordination center or subcontracted to a free-lance CRA under the responsibility of the coordination center. 100% of the consent forms of the patients included in the study will be verified, as well as inclusion/non-inclusion criteria, and serious adverse events.

The monitoring of clinical data will be on 20% of the case report booklets selected at random.

A monitoring report will be written by the CRA and kept in the study file (sponsor + investigator).

VIII- Statistical Analysis

VIII-1 Calculation of the number of subjects needed

With an alpha risk set at 5% and a power of 80%, 60 subjects per group will be needed to demonstrate an increase in the splenic rescue rate from 40% in the surveillance group (60% expected splenectomy) to 90% in the embolization group (10% expected splenectomy).

This number of 120 patients over two years is sufficient for a risk assessment of embolization, under the assumption of a complication rate, in particular pleural effusion, of 30% in the embolization group versus 10% in the surveillance group

This number of 60 patients to be included per year is reasonable considering the emergency context in which the refusal of patients to participate is possible:
- Number of Centers: 12 Centers have already confirmed their participation;
- with 3-6 patients per year per center (5 on average);
- this corresponds to 100-130 eligible patients per year as calculated previously: the centers admit an average of 30 splenic traumas per year that can benefit from non-operative treatment, of which 25-50% would be eligible for the study (8-15 patients per center on average).

Considering that 10% of patients will probably not complete the study (absence of CT scan on day 30), we propose to randomize 140 patients.

VIII-2 Data analysis strategy

The analysis will be done in intention to treat in order to evaluate the risks / benefits of the strategy of carrying out a prophylactic embolization compared to simple surveillance. Analysis will be done for the main criterion after freezing the whole database. It will be the same for all the secondary criteria.

In view of the hypothesis, no interim analysis is planned.

The analysis of the primary endpoint (spleen rescue rate at 1 month) will be done by a Chi-square test, as will the analysis of qualitative secondary criteria.

The search for prognostic factor(s) favoring of spleen rescue at 1 month will use a univariate and then multivariate analysis by a logistic regression model. The absence of interaction between a prognostic factor and the treatment arm will be sought. All variables with an observed p value <0.2 in univariate analysis and without interaction with the treatment under study, will be introduced in the multivariate analysis.

All statistical tests will be at the usual alpha threshold of 5%. The evaluation of the prevalence of splenic salvage will be presented with a 95% confidence interval according to binomial law tables. The different measures of association between treatment and standard judgment criteria for therapeutic trials (relative risk and 95% CI, relative risk reduction and its 95% CI, number of patients needed to avoid an event) will also be presented.

VIII-3 Persons in charge of analyzes

Writing the statistical analysis plan and performing the analyzes: statistician and epidemiologist of the Clinical Research Center (CIC) of Grenoble University Hospital (CHUG).

VIII-4 Site of data analyzes and software used

Data management, statistical analyses and archiving of the database (after the database freezing procedure) will be the responsibility of the CIC Statistician and Epidemiologist. The statistical analysis will be done with STATA version XI for OS X (StataCorp LP 4905 Lake Walk Drive Station, Texas 77845, USA).

IX- Safety

IX-1 Expected adverse events

A new event may also be may be: the unexpected frequency of an expected serious adverse event; a serious adverse event related to the trial procedure, insufficient efficacy (of treatment) in life-threatening diseases, a non-clinical event.

Adverse event: Any harmful event occurring in a person participating in biomedical research, this event is related or not to the research or the product to which this research relates (Article R. 1123-39 1 ° of the French Code of Public Health (CPH).

Adverse Effect: Any adverse and unwanted reaction to a product or medical device or any incident that could have caused this reaction if appropriate action had not been taken, in a person participating in biomedical research or to the user of a medical device (Article R1123-39 4 ° of the CPH). Any unwanted event due to the research.

Serious adverse event or reaction: Serious adverse event or reaction, any adverse event or effect that causes death, endangers the life of a person who participates in the research, requires hospitalization or prolongation of hospitalization (except hospitalization <12h, hospitalization planned before the patient's participation in the study), causes a major or long-term disability or handicap, or leads to an abnormality or a congenital malformation (Article R. 1123-39 6 ° of the CPH) or any other manifestation considered serious by the investigator and / or the sponsor

IX-2 Unexpected adverse effect

Any adverse effect of which the nature, the severity or the evolution does not concord with the information relating to the product (reference document), acts practiced and methods used during the research (Article R. 1123-39 8 ° of the PHC).

For research on a medical device or an in vitro diagnostic medical device, the information should be given in the instruction leaflet or the instructions for use when it is CE labelled, and in the protocol or the brochure for the investigator when the device has not obtained of such labelling (Article R. 1123-39 7 ° of the CSP).

An adverse effect is unexpected when it is not listed below.

IX-3 List of expected adverse events

IX-3.1 List of expected adverse effects related to splenic trauma

General complications related to trauma
Many complications can occur depending on the affected organs and the resuscitation performed.

Specific complications of splenic trauma
Pleural effusion
Splenic necrosis> 50%
Splenic hemorrhage
Pancreatitis
Digestive perforation
Thrombosis of the splenic and / or portal vein
Splenic pseudocyst
Septic syndrome

The expected adverse effects related to prophylactic embolization are:

Complications related to arterial puncture:
- Hematoma at the point of puncture
- Abscess at the point of puncture
- Thrombosis of the femoral artery, dissection, or emboli downstream of the puncture site
- False aneurysm or arteriovenous fistula

Complications related to catheterization:
- Dissection of the iliac axis
- Dissection of the celiac trunk or splenic artery with downstream ischemia
- Rupture of the celiac trunk or splenic artery with locoregional hematoma or increase in the hemoperitoneum

Complications related to embolization:
- Post embolization syndrome (feve ≥38°C and severe pain (EVA≥5)
- Migration of coils
- Thrombosis of the splenic and/or portal vein
- Splenic necrosis greater than 50% of the parenchyma
- Splenic abscess
- Diffuse or localized ischemic pancreatitis
- Inflammatory pleuritis
- Non-targeted embolization, outside the trunk of the splenic artery.

***Expected** adverse effects due to surveillance are:*
-Splenectomy
Complications: wall abscess, deep abscess, hemorrhage, pancreatitis, digestive fistula, peritonitis, occlusion, infections, septicemia, Thrombosis of the splenic and/or portal vein.

Death due to trauma outside the context of the splenic lesion

IX-3.2 List of expected adverse effects related to contrast agents

See SPC of contrast products used.

IX-4 SAE validation committee (Data and Safety monitoring board)

Any expected or unexpected serious adverse event will be validated by the Event Validation Committee/Data and Safety monitoring board. This validation will, among other things, confirm whether the adverse event is related to the pathology or to the treatment. All information regarding these cases, including reports of examinations and/or hospitalization will be retrieved by the coordination center, anonymized and presented during regular Event Validation Committee/ Data and Safety monitoring board meetings. A report will be written by the Event validation committee and sent to Dr Edith SCHIR (Vigilance Service CHUG).

IX-5 Adverse event Detection and documentation procedures

It is the responsibility of the investigators of the study to document all adverse events in the table provided for this purpose in the CRF observation booklet.
The investigator evaluates each adverse event in terms of its severity (non-serious or serious with at least one specified severity criterion). It also assesses the causal relationship of each adverse event with the study procedure(s), along with any other suspected potential treatments, and consulting the patient's medical history if necessary. The investigator sends this assessment to the sponsor. Adverse events should be documented and monitored until they are resolved or stabilized (during or after the study).

IX-6. Reporting of serious adverse events to the ethics committee (CPP) and the health authorities (ANSM)

As soon as the investigator becomes aware of a Serious Adverse Event (SAE), and or a new happening, they must declare it within 24 hours using a notification form for this purpose which will be faxed to the coordination center and to the sponsor. The investigator is required to send detailed supplementary reports to document the evolution of the event or to update missing data. If an SAE related to the study treatment is reported by the investigator after the last protocol visit, this SAE will be spontaneously reported to the sponsor with no time limit.
For biomedical research, the sponsor declares any suspicion of **an unexpected serious adverse reaction** (USAE) that occurred in France within 7 days from the day the sponsor became aware of it.
In the case of a serious adverse reaction, the relevant **additional information** should be notified within a further period of eight days from the seven-day period referred to in the second subparagraph

Expected adverse effects related to the product or the pathology or the act will also be reported to the ANSM (competent authority) and the CPP

All serious adverse events will be reported to the Clinical Studies Vigilance Service of Grenoble University Hospital (Dr Edith SCHIR, Dr Marylaure GVARD, Dr Sophie LOGEROT, vigilance-essaiscliniques@chu-grenoble.fr, tel : 33 (0)4 76 76 68 21, fax : 33 (0)4 76 83 54) using the report form in appendix 8 of the protocol.

IX-7 In-utero exposure

If a woman becomes pregnant whilst participating in the research, the pregnancy must be reported to the sponsor within 24 hours of becoming aware of it.
The investigator informs the sponsor's vigilance service through a standard "collection of initial pregnancy data" sheet. This form must contain the predicted date of delivery, the contact information of the obstetrician and the maternity ward for delivery if the pregnancy continues.
The investigator must follow the woman until the end of the pregnancy or its termination and notify the outcome to the sponsor through a standard "outcome of pregnancy" form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (spontaneous abortion with hospitalization, fetal death, congenital anomaly, etc) the investigator must follow the procedure for declaration of a SAE.

IX-8 Annual safety report

On the on annual anniversary date of the first inclusion, the sponsor writes a safety report including:
The list of serious adverse reactions that may be related to the experimental product of the trial, including unexpected and expected serious effects.
A concise and critical analysis of the safety of subjects participating in the research.
This report may be submitted to the coordinating investigator for approval
This report is sent to the competent authorities (ANSM) and the ethics committee (CPP) within 60 days of the anniversary date of the first inclusion.

X- Scientific committees

X-1 Safety Monitoring Committee

An independent safety monitoring committee will meet in case of occurrence of unexpected serious adverse events (USAE or SUSAR), or in case of unusual frequency of SAEs or of an unusual difference between the 2 randomization groups (20% increase (absolute difference) in SAE in the embolization group compared to the surveillance group; or at the request of the sponsor via the pharmacist responsible for vigilance and/or the coordinating investigator.

This committee may propose to the sponsor and to the coordinating investigator, the stop of this research or a modification of the protocol if the safety of the subjects participating in the study does not seem to her/him be sufficient.

X-2 Committee of experts in Radiology

Among the radiologists participating in the study, two will constitute a committee of experts. These are the Doctors:

- Valérie Monnin (Radiologist CHU de Montpellier).
- Julien Frandon (Radiologist CHU de Nîmes)

Self-evaluation phase of the radiologists:

Since reading CT scans at inclusion and attributing a Moore grade is potentially a source of discordance between radiologists, each investigation center will be provided with a hard-copy atlas. This atlas will include concrete cases illustrated by images and reading instructions to help classify the splenic involvement in grades 1 to 5 and the extent of low, medium or high hemoperitoneum. The atlas will be prepared by Dr. Frédéric Thony and his colleagues.
Before starting the study, each participating radiologist will be asked to perform a self-evaluation based on the interpretation of 5 CTs on a website dedicated to the study. The opening of the investigative centers will be conditioned by the participation and the satisfactory results of this self-evaluation by the radiologists.

Second reading of inclusion CT

CDs containing CT scans at inclusion will be sent to the 2 expert radiologists by post.

These scans will not mention the identity of the center or the grade attributed by the investigator. Each of the 2 expert radiologists will examine the scans within 3 days of patient inclusion, and will report to the Clinical Research Center (CIC) of Grenoble University Hospital. This second reading could modify the Moore score attributed and maintain or not the inclusion of the patient in the study:
- if this rating (Moore grade and hemoperitoneum) is homogeneous between the 2 expert radiologists and the investigator, the inclusion is maintained with an unchanged grading;
- if this score is discordant for 1 of the 2 expert radiologists, 1 of the 2 experts being in agreement with the investigator, the inclusion is maintained with an unchanged grading ;
- If this rating by the two radiologists is discordant, regardless of the judgment of the investigator, the grading and inclusion of the patient will be specifically discussed

CT reading at one month (primary endpoint):

The 1-month CT scan will be interpreted by 2 expert radiologists in Nîmes and Montpellier. The CDs will be sent by post.
Scans will be read blind to the study arm and the center. Although embolization is identifiable on the images, it could be either an initial embolization, in the embolization arm, or a secondary embolization in the surveillance arm. Estimating the proportion by volume of vascularized splenic tissue may require the use of angiographic images to determine the initial volume of the spleen.

XI End or premature termination of the research

XI-1 Criteria for stopping participation in the research

Subject withdraws consent to participate

XI-2 Premature stop of treatment by a subject

The investigating physician is free to discontinue the patient's treatment. In the case of this research, this includes stopping simple surveillance if a secondary embolization or surgery is required.

The schedule for monitoring these patients remains unchanged

XI-3 Stop of study by the sponsor

The sponsor may stop the study at any time for the following reasons:

- Inability of the investigator to include patients according to schedule.
- Absence of signed consent.
- Major violations to the protocol.
- Incomplete or erroneous data.
- In the event of an adverse event deemed severe by the investigator and potentially threatening the health of the patient, the investigator, in agreement with the sponsor, may decide withdraw the patient from the study. Patients whose treatment has been terminated prematurely will not be replaced.

A patient will be considered lost to follow-up when, at the end of a test center's participation in the trial, it was not possible to obtain information about the patient despite documented searches by the investigator.

XII. Financial Aspects

Funding for this project has been obtained through a national Hospital Clinical Research Project (PHRC) call for tenders.

Apart from costs related to the organization of the study and data collection, additional costs were estimated for:

- Consultations and contrast injected abdominal CT scans at 6 months,
- Blinded double reading of CT images of included patients (initial CT, D5, M1 and M6); and costs of postage.

On the other hand, no additional costs related to the realization of the embolization have been planned as the participating centers are centers expert centers in interventional radiology and their participation in the will probably decrease their practice of embolization during the duration of the study.

XIII Regulatory and legal aspects

XIII-1 Ethical rules and good clinical practices

This trial will be carried out in accordance with the Declaration of Helsinki (1964), its successive revisions (Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset 1996, Edinburgh 2000, Washington 2002, Tokyo 2004), Good Clinical Practices and the law of 9 August 2004 on public health policy and the decrees implementing it.

XIII-2 Ethics committee: "Comité de protection des personnes" (CPP)

Before starting any biomedical research involving humans, the sponsor must submit the project to an ethics committee competent for the place where the coordinating investigator practices his activity. She/he can solicit only one opinion per research project. She/he is legally required to wait for a written favorable opinion from the etiics committee and authorization from the competent authorities (the ANSM) before starting the clinical research.

XIII-3 National Agency for the Safety of Medicines and Health Products (ANSM)

Before starting a biomedical research project involving humans, the sponsor is required to apply for research authorization to the competent authorities (ANSM).

XIII-4 Patient Information and written informed consent

In accordance with Good Clinical Practices and the legislation in force, any preselected subject will be informed beforehand by the investigator of the objectives of the study, its methodology, its duration, its constraints and foreseeable risks, possible therapeutic alternatives, and modalities of medical care provided at the end of the research, including in the case of discontinuation of the study before its term. In particular, it will be made clear to the patient that he is entirely free to refuse to participate in the study or to withdraw his consent at any time without incurring any liability or prejudice thereby. A document summarizing the information given by the investigator will be provided (Appendix 1).
After ensuring that the information provided has been understood by the patient, the investigator will check the patient's availability and will seek his/her written consent to participate in the study. If he agrees, the patient will sign the consent form (Appendix 2) prior to inclusion in the study.

The law states that in the case of biomedical research to be carried out in emergency situations that do not permit the prior consent of the person to be obtained, the protocol presented to the ethics committee may stipulate that the consent of that person is not sought and that only the consent of close members of his/her family or that of a person of trust as defined in Article L. 1111-6 is requested under the conditions set out in Article L. 1122-1-1, if present (see Appendix 3).
Given the fact that this study is involves patients with spleen trauma. Therefore, after ensuring that the information provided is clear, the Investigating Physician will seek the written consent of a close family member or a person of trust on behalf of the patient to participate in the study. If they agree, they will sign the consent form (see Appendix 4) for the patient's participation in the study.
The patient will be informed as soon as possible and his/her consent will be sought for his/her participation in the continuation of the research (see Appendix 1). The patient or person of trust may also refuse the use of his or her data as part of this research.

Patients can only be included in the study after written consent has been given. Due to the extreme emergency and possible impossibility for them to receive information from a doctor explaining the purpose of the study, the duration of participation, procedures, benefits, risks, and confidentiality, two situations are possible:
- the patient is not conscious but is accompanied by a close family member or person of trust. The information notice is given to this person who must sign the consent form in duplicate (see Appendix 4). As soon as the patient can, his consent will be sought (Appendix 2).
- the patient is not conscious, and he is not accompanied by a close family member or person of trust. The Investigating Physician will sign the "Investigator Statement" (see Appendix 5). As soon as the patient or a close family member or the person of trust can, the consent form will be signed.

All the above information is summarized in the patient information notice; a copy will be given to the patient and the investigator must keep the second copy for at least 15 years. At the request of the patient, withdrawal of consent can be exercised at any time without jeopardizing the quality of care.

XIII-5 Professional secrecy and confidentiality

The investigator is bound by professional secrecy. The data collected, including the results of the analyzes, will be anonymized by any appropriate means. The sponsor and his representatives are subject to the same obligations of professional secrecy as the investigator.
This document and its annexes are given to the investigator on a confidential basis and should only be handed in or disclosed to the persons specifically named in the trial, with the agreement or at the request of the coordinator.

XIII-6 Insurance Contrat

It should be pointed out that the non-respect of the legal conditions of the research (lack of written consent of the included persons, absence of approval by an ethics committee (CPP) or of authorization by the competent authorities (ANSM), continuation of halted or prohibited research) are exclusion clauses of the insurance

XIII-7 Protocol amendements

Any substantial modification of the protocol will be the subject of an amendment submitted by the sponsor for approval by the ethics committee (CPP) and/or authorization by the competent authorities (ANSM).

XIII-8 Anonymity of the subjects participating in the study

The data collection is done through an electronic case report book, the computer file (medical data) will be anonymized; it will not include the surname, the first name, or the date of birth (simply the age and sex), nor any indication of the address of patients. The anonymization of the patient will include a center number (assigned at the beginning of the study to each investigator), a patient inclusion number (automatically attributed at inclusion in the electronic report system) and the initials of the patient (first 2 letters of the surname, first letter of the first name).
The coordinates (name, address, telephone number, etc) of the patient, of a close family member or person of trust, will be sent to the coordination center by fax (CIC-CHU de Grenoble). In no circumstances must this personal and nominative information be computerized. It will only be used by the coordination center to contact the patient for follow-up purposes.

The computer file (medical data) will be the subject of a declaration to the French French Data Protection Authority (Commission Nationale Informatique et Libertés, CNIL).

XIII-9 Quality Assurance

The clinical part of the study will be performed in accordance with Good Clinical Practice. Quality assurance audits may be performed by an independent service provider, the sponsor, or any Health Authority during the study or after its completion.

XIII-10 Indemnities for subjects participating in the research

No compensation for patients is planned

XIII-11 Authorization of research site(s)

According to L1121-13 of the French Code of Public Health (CSP), no site authorization is required for this study; it does not require acts other than those usually performed by the investigating physicians.
Moreover, the persons who are suitable for the study do not present a clinical condition distinct from those for which these research sites are competent

XIII-12 Exclusion period

Exclusion period: Subjects participating in this study will not be able to simultaneously participate in other biomedical research.
No exclusion period is necessary following this study.

XIII-13 Study sponsor

Department of Clinical Research and Innovation Department (DCRI), CHU Grenoble, 38043 GRENOBLE CEDEX 09

XIII-14 Publications

This protocol will be registered on the Website: www.clinicaltrial.gov.

All data collected during this research are the property of the sponsor of the study and must not be communicated to a third party under any circumstances without the written consent of the investigator.
Any publication or communication (oral or written) will respect international recommendations:
"Uniform Requirements for Manuscripts Submitted to Biomedical Journals"
http://www.cma.ca/publications/mwc/uniform.htm

XIII-15 Archiving

All the files of the study will be archived for a period of 15 years, under the responsibility of the sponsor.

The source documents, the originals of the consent forms, and the signed protocol must be kept by the investigator for a minimum of 15 years from the end of the study in a locked room.
The sponsor must organize, at least during the shelf life of any products, the storage of the following documents in appropriate premises (European Directive 91/501 / EEC):
- Protocol with annexes, amendments;
- Backups of the database on a server;
- Clinical study follow-up documents: reports of monitoring, and clinical study, and all administrative documents and correspondence related to the study.
- Study report.

Signature of the Sponsor and the Coordinating Investigator:

I have read all the pages of the clinical study protocol for which the Grenoble University Hospital (CHU de Grenoble) is the promoter.

I confirm that it contains all the information necessary for the conduct of the study. I undertake to carry out the study respecting the protocol and the terms and conditions defined therein. I commit myself to carry out the study respecting:

- the International and French rules and recommendations of Good Clinical Practices (Good Clinical Practice Guidelines for biomedical research).
- The Code of Public Health ,
- the national legislation and regulations in force for clinical studies.

I also agree that other qualified members of my team will have access to copies of this protocol and documents related to the proper conduct of the study to enable them to work in compliance with the provisions contained in these documents.

Coordinating Investigatr:
Pr Catherine ARVIEUX

For the Sponsor :
Mme Jacqueline HUBERT
General Director

XIV Appendixes

Appendix I. Patient information

PATIENT INFORMATION LETTER	
Study Title: "Benefit of prophylactic embolization on splenic rescue in traumatized patients at high risk of splenectomy"	
Coordinating Investigator: Pr Catherine ARVIEUX Address: **Digestive Surgery and Emergency Clinic** CHU de Grenoble – CS 10217 38043 Grenoble cedex 09 Tél : + 33 (0)4 76 76 92 60 ; Fax : + 33 (0)4 76 76 58 02 e-mail : CArvieux@chu-grenoble.fr	Sponsor: Grenoble University Hospital Address: Clinical Research and Innovation Administration CHU de Grenoble – CS 10217 38043 Grenoble cedex 09. Tél : + 33 (0)4 76 76 84 55 ; Fax + 33 (0)4 76 76 52 21

Dear Patient,
Dr. .... proposes that you participate in a biomedical research study. It is organized by Grenoble Alpes University Hospital. The purpose of this study is to determine whether spleen embolization is of interest in preventing splenectomy (removal of the spleen) in people with trauma of the spleen compared to usual post-traumatic surveillance.

You are free: - to accept
- or to refuse to participate in this study.
You may withdraw your consent at any time. You will not incur any liability or prejudice as a result.
To help you make your decision, here is some information about this research.

1. TITLE OF THE STUDY

"Benefit of prophylactic embolization on splenic rescue in traumatized patients at high risk of splenectomy"

2. AIM AND PROCEDURE OF THE STUDY

The purpose of this study is to determine whether it is beneficial to perform spleen embolization to prevent splenectomy (removal of the spleen) in people with spleen trauma rather than conventional surveillance. Indeed, the removal of the spleen has possible complications (pancreatitis, infection, venous thrombosis) and especially it leads to a decrease in immunity, i.e. your resistance to certain infections. This means that splenectomized patients should have vaccinations against pneumococcal and possibly meningococcal and *Haemophilus*, treatment with antibiotics (penicillin G) for at least two years after splenectomy followed by antibiotics in the event of any fever during the rest of their lives, as well as taking particular precautions (during travel ,with pets).

In view of your clinical condition there are two possible strategies, immediate embolization or surveillance. In order to objectively find out which is the best strategy, this study is randomized. Randomization is the best method to make this type of comparison. The doctor who takes care of you will draw lots to determine which strategy you will follow, according to a list made before the start of the study.

You will be either in the group:
-Surveillance: Embolization will be performed only in case of hemorrhage "curative embolization"
- Embolization: this will be carried out from the outset as a preventive measure "prophylactic embolization"

Splenic arterial embolization (SAE) is already used routinely when the spleen shows signs of active bleeding or disrupted vessels due to trauma, because it avoids splenectomy and its consequences. We know that this has its own complications (10%), the main ones being: hematoma, injury to the wall of the femoral artery (related to the puncture of the femoral artery), a low risk of kidney failure or intolerance to iodine (related to the contrast

product that is injected) and a risk linked to the embolization of the spleen itself: partial or complete necrosis, abscess, migration of the embolization material to another organ. SAE can also be ineffective in around 10% of cases.

After discharge from the hospital you will be followed-up as usual with a consultation with the surgeon and an abdominal CT scan one month after the trauma. The clinical examination and radiological examination results will be communicated to you as well as any action to be taken. A second consultation at 6 months with a new CT scan, with an injected contrast agent, is planned as part of the study. Your travel expenses for this consultation will be refunded.

3. DURATION OF THE STUDY

You will be included in the study for a period of 6 months
You will not be able to participate in another clinical study during your participation in this study.

4. BENEFITS AND RISKS RELATED TO THE STUDY

Your participation in this study will not incur any additional costs for you.

You will benefit from increased medical surveillance and a prolonged follow-up at 6 months.

The expected adverse effects related to prophylactic embolization are those usually associated with this technique

Vascular complications
- Hematoma or abscess at the point of puncture
- involvement of the femoral artery (dissection, embolus downstream of the puncture site, false aneurism or arteriovenous fistula)
- Complications related to catheterization (dissection or rupture of the iliac axis, or celiac trunk)

Complications related to embolization:
- Post embolization syndrome (fever ≥38 °C and severe pain (≥5 on a scale of 1 to10)
- Migration of the embolization coils
- Thrombosis of the splenic and / or portal vein
- Splenic necrosis greater than 50% of the parenchyma
- Splenic abscess
- Diffuse or localized ischemic pancreatitis,
- Inflammatory pleuritis
- Non-targeted embolization, outside the trunk of the splenic artery
- Allergy or intolerance to the contrast product
- Renal failure

Expected side effects of surveillance only are:
- Splenectomy

For both groups the expected complications are:
- wall abscess,
- deep abscess,
- bleeding,
- pancreatitis,
- digestive fistula,
- peritonitis,
- occlusion,
- infections
- septicemia,
- thrombosis of the splenic and / or portal vein

These risks are not specific to the study but to the initial trauma and its usual care.

5. PROTECTION OF PEOPLE PARTICIPATIN IN BIOMEDICAL RESEARCH STUDIES

This study has received approval from the Committee for the Protection of Persons “Sud-Est V” on 12/06/2013. It was authorized by the National Agency for the Safety of Medicines and Health Products on 27/06/2013. Grenoble University Hospital has taken all the measures provided for by the law for the protection of persons participating in research (insurance contract SHAM No. 135 751, 18, rue Edouard Rochet, 69372 Lyon Cedex

08).
A copy of this information sheet is for you.
To participate in this study you must be affiliated to a social security scheme.
At the end of this study you can be informed of its overall results, if you ask the surgeon in a letter.

6. CONFIDENTIALITY OF DATA RELATING TO YOU

As part of the biomedical research study in which the surgeon proposes you participate, your personal data will be stored and processed by computer. This will allow the results of the study to be analyzed in terms of the objective of the study. For this, the data collected about you will be transmitted to:
- the sponsor of the study
- or to persons or companies acting on their behalf, in France.

This data will be identified only by a number and your initials. They may also be transmitted to:
- French or foreign health authorities,
- other departments of Grenoble University Hospital.

This will be done under conditions ensuring confidentiality and with written agreement of the study sponsor.
In accordance with the Data Protection Act of January 6, 1978 (CNIL), you have a right of access and rectification. You also have the right to object to the transmission of information covered by medical secrecy that may be used in this research and be processed.
You can also access to all of your medical data either:
- directly,
- or through a doctor of your choice.

This complies with the provisions of Article L 1111-7 of the Public Health Code. These rights are to be exercised with the doctor who follows you as part of the research. Only he/she knows your identity.

7. CONSTITUTION OF A BLOOD SAMPLE COLLECTION

During this study, blood samples will be taken for your usual follow-up. A peripheral venous blood sample of three additional tubes of 4.5 ml will be taken at the time of your initial CT scan, then three samples at D5 and D30 at the same time as the CT scans. Another sample of 3 x 4.5ml will be taken by the nurse during the postoperative consultation and we will ask you to come back for an additional consultation and a CT scan at 6 months after the trauma, when a last sample of 3 x 4.5 ml will be taken. Thus samples of your blood will be kept throughout the duration of the study in the sample collection of the angioedema exploration laboratory at Grenoble University Hospital.
These samples will not be kept after the end of this study.

IN SUMMARY

At the practical level, your participation in this study will include:

Two consultations with abdominal CT scans: 1 month and 6 months after the trauma. If you live more than 100 km from the hospital that initially took care of you this consultation will take place by phone once the surgeon who follows you has received the CT scans.

Four peripheral venous blood samples will be taken during your hospitalization (at the same time as the initial CT scan and on D5)
Another at the same time as the CT scan of the postoperative consultation (D30), and a last sample at the time of the 6 month consultation.

Thank you for reading this document

Appendix II. Patient consent form

PATIENT CONSENT TO PARTICIPATE	
Study Title: "Benefit of prophylactic embolization on splenic rescue in traumatized patients at high risk of splenectomy"	
Coordinating Investigator: Pr Catherine ARVIEUX Address: **Digestive Surgery and Emergency Clinic** CHU de Grenoble – CS 10217 38043 Grenoble cedex 09 Tél : + 33 (0)4 76 76 92 60 ; Fax : + 33 (0)4 76 76 58 02 e-mail : CArvieux@chu-grenoble.fr	Sponsor: Grenoble University Hospital Address: Clinical Research and Innovation Administration CHU de Grenoble – CS 10217 38043 Grenoble cedex 09. Tél : + 33 (0)4 76 76 84 55 ; Fax + 33 (0)4 76 76 52 21

I, the undersigned
Mrs, Miss, Mr. ..... freely and voluntarily accepts to participate in the biomedical research study entitled:

"Benefit of prophylactic embolization on splenic rescue in traumatized patients at high risk of splenectomy "

The physician signing this document has informed me orally and in writing about the study's purpose, its course, the possible advantages and disadvantages, as well as the potential risks.

I have read and understood the patient information sheet for the above mentioned study. I have received answers to all my questions about my participation in this study. I have had enough time to think about it before making my decision.

I have received a copy of the patient information letter and my written consent statement.

I have been told that this clinical research study was approved by the "CPP Sud Est V" on 12/06/2013, and was authorized by the ANSM on 27/06/2013. I understand that Grenoble UniversityHospital has taken all the measures provided for by the law with regard to the protection of persons participating in clinical research (insurance contract SHAM No. 135 751, 18, rue Edouard Rochet, 69372 Lyon Cedex 08).

I participate voluntarily in this research. I am free at any time to interrupt this participation. I will report this to the doctor in charge of this study. In this event I shall not incur any responsibilityand my decision shall not prejudice to the quality of care that will be provided to me. I will then tell the doctor who follows me if I oppose the use of the data collected up until the moment of my decision.

I agree to the computerized processing of my personal data and access to it by the study sponsor and authorized staff.

The data that concerns me will remain strictly confidential. I authorize their consultation only by persons subject to professional secrecy and collaborating in this research for the sponsor.

I **freely** agree to participate in this clinical research study under the conditions specified above.

Person participating in the study	Investigating surgeon or doctor
Date: First name and family name: Signature	Date: First name and family name: Signature

Appendix III. Information for close relative or person of trust

INFORMATION FOR PATIENT PROXY	
Study Title: "Benefit of prophylactic embolization on splenic rescue in traumatized patients at high risk of splenectomy"	
Coordinating Investigator: Pr Catherine ARVIEUX Address: **Digestive Surgery and Emergency Clinic** CHU de Grenoble – CS 10217 38043 Grenoble cedex 09 Tél : + 33 (0)4 76 76 92 60 ; Fax : + 33 (0)4 76 76 58 02 e-mail : CArvieux@chu-grenoble.fr	Sponsor: Grenoble University Hospital Address: Clinical Research and Innovation Administration CHU de Grenoble – CS 10217 38043 Grenoble cedex 09. Tél : + 33 (0)4 76 76 84 55 ; Fax + 33 (0)4 76 76 52 21

Dear Madame/Sir,

You are acting as proxy for a relative or close friend who is the victim of spleen trauma. We want to include this patient in a research protocol, ie to participate in a clinical study.
The purpose of this document is to provide you with the information necessary to understand the objectives of this study. Do not hesitate to ask for additional explanations, especially if certain terms do not seem clear to you.

You are free: - to accept
- or to refuse that your relative or close friend participates in this study.
You, or the patient, may withdraw consent at any time. He/she will not incur any liability or prejudice as a result.
To help you make your decision, here is some information about this research.

1. TITLE OF THE STUDY

"Benefit of prophylactic embolization on splenic rescue in traumatized patients at high risk of splenectomy"

2. AIM AND PROCEDURE OF THE STUDY

The purpose of this study is to determine whether it is beneficial to perform spleen embolization to prevent splenectomy (removal of the spleen) in people with spleen trauma rather than conventional surveillance. Indeed, the removal of the spleen has possible complications (pancreatitis, infection, venous thrombosis) and especially it leads to a decrease in immunity, i.e. ones resistance to certain infections. This means that splenectomized patients should have vaccinations against pneumococcal and possibly meningococcal and *Haemophilus*, treatment with antibiotics (penicillin G) for at least two years after splenectomy followed by antibiotics in the event of any fever during the rest of their lives, as well as taking particular precautions (during travel, with pets).

In view of your relative or friend's clinical condition there are two possible strategies, immediate embolization or surveillance. In order to objectively find out which is the best strategy, this study is randomized. Randomization is the best method to make this type of comparison. The doctor who takes care of your relative or close friend will draw lots to determine which strategy to follow, according to a list made before the start of the study.

Your relative or close friend will be either in the group:
- Surveillance: Embolization will be performed only in case of hemorrhage "curative embolization"
- Embolization: this will be carried out from the outset as a preventive measure "prophylactic embolization"

Splenic arterial embolization (SAE) is already used routinely when the spleen shows signs of active bleeding or disrupted vessels due to trauma, because it avoids splenectomy and its consequences. We know that this has its own complications (10%), the main ones being: hematoma, injury to the wall of the femoral artery (related to the puncture of the femoral artery), a low risk of kidney failure or intolerance to iodine (related to the contrast product that is injected) and a risk linked to the embolization of the spleen itself: partial or complete necrosis, abscess, migration of the embolization material to another organ. SAE can also be ineffective in around 10% of cases.

After discharge from the hospital your relative or close friend will be followed-up as usual with a consultation with the surgeon and an abdominal CT scan one month after the trauma. The clinical examination and radiological examination results will be communicated to him/her as well as any action to be taken. A second consultation at 6 months with a new CT scan, with an injected contrast agent, is planned as part of the study. The travel expenses for this consultation will be refunded.

3. DURATION OF THE STUDY

Your relative or close friend will be included in the study for a period of 6 months
He/she will not be able to participate in another clinical study during his/her participation in this study.

4. BENEFITS AND RISKS RELATED TO THE STUDY

Your relative or close friend's participation in this study will not incur any additional costs for him/her.

He/she will benefit from increased medical surveillance and a prolonged follow-up at 6 months.

The expected adverse effects related to prophylactic embolization are those usually associated with this technique

Vascular complications
- Hematoma or abscess at the point of puncture
- involvement of the femoral artery (dissection, embolus downstream of the puncture site, false aneurism or arteriovenous fistula)
- Complications related to catheterization (dissection or rupture of the iliac axis, or celiac trunk)

Complications related to embolization:
- Post embolization syndrome (fever ≥38 °C and severe pain (≥5 on a scale of 1 to10)
- Migration of the embolization coils
- Thrombosis of the splenic and / or portal vein
- Splenic necrosis greater than 50% of the parenchyma
- Splenic abscess
- Diffuse or localized ischemic pancreatitis,
- Inflammatory pleuritis
- Non-targeted embolization, outside the trunk of the splenic artery
- Allergyor intolerance to the contrast product
- Renal failure

Expected side effects of surveillance only are:
- Splenectomy

For both groups the expected complications are:
- wall abscess,
- deep abscess,
- bleeding,
- pancreatitis,
- digestive fistula,
- peritonitis,
- occlusion,
- infections
- septicemia,
- thrombosis of the splenic and / or portal vein

These risks are not specific to the study but to the initial trauma and its usual care.

5. PROTECTION OF PEOPLE PARTICIPATIN IN BIOMEDICAL RESEARCH STUDIES

This study has received approval from the Committee for the Protection of Persons "Sud-Est V" on 12/06/2013. It was authorized by the National Agency for the Safety of Medicines and Health Products on 27/06/2013. Grenoble University Hospital has taken all the measures provided for by the law for the protection of persons participating in research (insurance contract SHAM No. 135 751, 18, rue Edouard Rochet, 69372 Lyon Cedex 08).
A copy of this information sheet is for you and another copy will be given to the patient in due course.

To participate in this study your relative or close friend must be affiliated to a social security scheme.
At the end of this study your relative or close friend can be informed of its overall results, if he/she asks the surgeon in a letter.

6. CONFIDENTIALITY OF DATA RELATING TO THE PATIENT

As part of the biomedical research study in which the surgeon proposes your relative or close friend participates, his/her personal data will be stored and processed by computer. This will allow the results of the study to be analyzed in terms of the objective of the study. For this, the data collected about him/her will be transmitted to:
- the sponsor of the study
- or to persons or companies acting on their behalf, in France.

This data will be identified only by a number and his/her initials. They may also be transmitted to:
- French or foreign health authorities,
- other departments of Grenoble University Hospital.

This will be done under conditions ensuring confidentiality and with written agreement of the study sponsor.
In accordance with the Data Protection Act of January 6, 1978 (CNIL), your relative or close friend has a right of access and rectification. He/she also has the right to object to the transmission of information covered by medical secrecy that may be used in this research and be processed.
He/she can also access to all of his/her medical data either:
- directly,
- or through a doctor of his/her choice.

This complies with the provisions of Article L 1111-7 of the Public Health Code. These rights are to be exercised with the doctor who follows him/her as part of the research. Only the doctor knows your relative or friend's identity.

7. CONSTITUTION OF A BLOOD SAMPLE COLLECTION

During this study, blood samples will be taken for your relative or friend's usual follow-up. A peripheral venous blood sample of three additional tubes of 4.5 ml will be taken at the time of his/her initial CT scan, then three samples at D5 and D30 at the same time as the CT scans. Another sample of 3 x 4.5ml will be taken by the nurse during the postoperative consultation and we will ask your relative or friend to come back for an additional consultation and a CT scan at 6 months after the trauma, when a last sample of 3 x 4.5 ml will be taken. Thus samples of his/her blood will be kept throughout the duration of the study in the sample collection of the angioedema exploration laboratory at Grenoble University Hospital.
These samples will not be kept after the end of this study.

IN SUMMARY

At the practical level, your relative or close friend's participation in this study will include:

Two consultations with abdominal CT scans: 1 month and 6 months after the trauma. If he/she lives more than 100 km from the hospital that initially took care of him/her then this consultation will take place by phone once the surgeon who follows him/her has received the CT scans.

Four peripheral venous blood samples will be taken during his/her hospitalization (at the same time as the initial CT scan and on D5)
Another at the same time as the CT scan of the postoperative consultation (D30), and a last sample at the time of the 6 month consultation.

Thank you for reading this document

Appendix IV. Consent form for close relative or person of trust

CONSENT TO PARTICIPATE MADE BY THE PATIENT'S PROXY	
Study Title: "Benefit of prophylactic embolization on splenic rescue in traumatized patients at high risk of splenectomy"	
Coordinating Investigator: Pr Catherine ARVIEUX Address: **Digestive Surgery and Emergency Clinic** CHU de Grenoble – CS 10217 38043 Grenoble cedex 09 Tél : + 33 (0)4 76 76 92 60 ; Fax : + 33 (0)4 76 76 58 02 e-mail : CArvieux@chu-grenoble.fr	Sponsor: Grenoble University Hospital Address: Clinical Research and Innovation Administration CHU de Grenoble – CS 10217 38043 Grenoble cedex 09. Tél : + 33 (0)4 76 76 84 55 ; Fax + 33 (0)4 76 76 52 21

I, the undersigned
Mrs, Miss, Mr *(cross out the inappropriate titles) (first name, family name*) ……
as a parent, a person of trust * or a close friend ** (*cross out the useless mentions*) **accepts freely and voluntarily** that Mrs., Miss, Mr. (*cross out the inappropriate titles) (first name, family name*.)..... .....
..participates in the biomedical research study entitled:

"Benefit of prophylactic embolization on splenic rescue in traumatized patients at high risk of splenectomy "

The physician signing this document has informed me orally and in writing about the study's purpose, its course, the possible advantages and disadvantages, as well as the potential risks.

I have read and understood the information sheet for patients' proxies for the above mentioned study. I have received answers to all my questions about my relative or close friend's participation in this study. I have had enough time to think about it before making my decision.

I have received a copy of the information sheet for patient proxies and my written consent statement.

I have been told that this clinical research study was approved by the "CPP Sud Est V" on 12/06/2013, and was authorized by the ANSM on 27/06/2013. I understand that Grenoble UniversityHospital has taken all the measures provided for by the law with regard to the protection of persons participating in clinical research (insurance contract SHAM No. 135 751, 18, rue Edouard Rochet, 69372 Lyon Cedex 08).

I agree that blood samples will be kept for the duration of the study.

I accept that my relative or close friend participates in this study. I or my relative or close friend is free at any time to interrupt this participation. I or he/she will report this to the doctor in charge of this study. In this event the neither myself nor the patient shall incur any responsibility and my or his/her decision shall not prejudice the quality of care that will be provided to him/her. I or the patient will then tell the doctor who follows him/her if he/she opposes the use of the data collected up until the moment of this decision.

I agree to the computerized processing of my relative or close friend's personal data and access to it by the study sponsor and authorized staff.

The data that concerns my relative or close friend will remain strictly confidential. I authorize their consultation only by persons subject to professional secrecy and collaborating in this research for the sponsor.

I **freely** agree that my relative or close friend participates in this clinical research study under the conditions specified above.

Proxy for the person participating in the study

Date:
First name and family name:
Signature

Investigating surgeon or doctor

Date:
First name and family name:
Signature

Appendix V. Investigator's Declaration

INVESTIGATOR STATEMENT

Study Title: Benefit of prophylactic embolization on splenic rescue in trauma patients at high risk of splenectomy - SPLASH

Coordinating investigator: Pr Catherine ARVIEUX
Digestive and Emergency Surgery Clinic, Grenoble University Hospital.

Tel: 04 76 76 92 60 Fax: 04 76 76 58 02 E-mail: CArvieux@chu-grenoble.fr

Sponsor's representative: Mme H. Sabbah Guillaume,
Grenoble University Hospital, CS10 217, 38043 Cedex 09.
Tel: 04.76.76.84.55

I, the undersigned, Professor, Doctor ....., investigating physician, declare that the patient's condition and the absence of a family member or a person of trust designated by the patient do not allow them to currently receive information about the objectives, methods, risks and constraints of the clinical study that I propose the patient participates in.

Until I can obtain written consent signed by the patient, a family member or a person of trust designated by the patient I am including the patient in this study.
In the event of a subsequent refusal/withdrawal of consent to participate by the patient, in my role as investigator I undertake to destroy all data concerning the patient.
The patient has the right to refuse that any data collected are used.

Name and first name of the patient ……

Name of investigator …….....

Statement made at ……....

Date … ./… ./….

Signature

Appendix VI- References

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Appendix VII: The WOMAC questionnaire:

There are 2 systems of scoring the answers to questions:
The Lickert scale with 5 possible answers: null = 0; minimal = 1; moderate = 2; severe = 3; extreme = 4
Or a visual analogue scale (VAS) of 100 mm. It is possible to calculate the scores for each domain or for the whole WOMAC

WOMAC Pain domain:
How great is the pain?
1. When you are walking on a flat surface?
2. When you go up or down the stairs?
3. At night when you are in bed?
4. When you get up from a chair or sit down?
5. When you stand up

WOMAC Stiffness Domain:
1. How stiff are your joints when you get up in the morning?
2. How stiff are your joints when you move after sitting, lying or resting during the day ?

WOMAC Functions Domain:
How great is the difficulty you experience when you:
1. Descend stairs?
2. Go upstairs?
3. Get up from a sitting position?
4. Stand up?
5. Lean forward?
6. Walk on flat ground?
7. Get in and out of a car?
8. Do your shopping?
9. Put on tights or socks?
10. Get out of bed?
11. Remove your tights or socks?
12. Lie down on the bed?
13. Get in or out of a bathtub?
14. Sit down?
15. Sit down and get up from the toilet?
16. Do housework "thoroughly" in your home?
17. Do daily care of your home

Reference: Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stit LWJ. Validation of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1995; 15: 1833-40

Appendix VIII: Severe Adverse Event form

CHU Grenoble	**RAPPORT D'EVENEMENT INDESIRABLE GRAVE** **Procédure expérimentale HPS** CRPV-FOR-02	CRPV-Direction de la Recherche CHU de Grenoble Pavillon E 38 043 Grenoble cedex 09 Tel : 04 76 76 51 45 Fax : 04 76 76 56 55

A transmettre par fax 04 76 76 56 55 ou par mail vigilance-essaiscliniques@chu-grenoble.fr

n° promoteur: 12PHN01……	Titre de l'étude : SPLASH
idRCB n° : 2013-A00409-36	
Nom et N° du centre :……..	

Rapport initial : ☐ Rapport de suivi : ☐ N° base Safety : *(réservé PV : n° de suivi ……..)*

1) Informations sur le patient :
Date d'inclusion : ……
N° unique d'inclusion :……..
Bras de traitement: ……
Initiales du sujet : _ _ / _ _
Sexe : M ☐ F ☐ Date de naissance : ……./……../……
Poids : ……..kg Taille : ……cm

2) Antécédents significatifs (médicaux, chirurgicaux, allergie connues)
……
……
……
……

3) Evènement indésirable *: (description, symptômes et **diagnostic retenu**)
Date de début : ……./……../……..
Description :……
……
……
……
Diagnostic retenu : ……
Intensité de l'événement (entourer) : légère / modérée / sévère
Durée de l'événement (du point de vue clinique) :……
Evénement attendu ☐ **inattendu** ☐

Evolution :
☐ Amélioration en cours
☐ Résolution sans séquelle ☐, avec séquelles ☐ Date de résolution…./……/……
☐ Sans changement
☐ Décès
☐ Inconnu

Gravité de l'évènement :
Effet grave depuis le : ……/……/……..

☐ Mise en jeu du pronostic vital.
☐ Hospitalisation :
Du ……/……../…….. au……/……../……..
☐ Séquelles ou invalidité.
Préciser : ……
……
☐ Médicalement significatif.
☐ Anomalie congénitale. Préciser :……
……
……. ;….
☐ Décès. Date du Décès : …../……./……
Précisez la (les) cause(s) du décès :
……

4) Procédure expérimentale et médicaments concomitants : Noter tous les traitements (expérimentaux et concomitants) pris par le patient avant la survenue de l'événement. Ne pas noter les médicaments pris pour corriger les évènements indésirables.
Si applicable : Levée d'aveugle : ☐ **Oui** ☐ **Non**

Nom (préciser les spécialités) Voie d'administration	**Indication**		**Date de randomisation**		**Actions prises**	**Imputabilité**
Embolisation Artérielle Splénique OU						☐Effet lié à la procédure expérimentale ☐Non lié à la procédure ☐ Ne peut conclure
Surveillance						☐Effet lié ☐Non lié ☐ Ne peut conclure
Médicaments concomitants	posologie	Indication	Date de début	Date de fin		☐Effet lié ☐Non lié ☐ Ne peut conclure
						☐Effet lié ☐Non lié ☐ Ne peut conclure
						☐Effet lié ☐Non lié ☐ Ne peut conclure

Commentaires : ……
……

5) Conclusion : Selon l'investigateur, l'événement indésirable semble plutôt lié : :
☐ à la procédure expérimentale
☐ autre(s) traitement(s) concomitant(s)
☐ au protocole de l'essai (en dehors de la procédure à l'essai) :
Préciser :……
……
☐ à une atteinte associée : Préciser……..
☐ autre(s) maladie(s)concomitante(s) : Préciser : ……
☐ autre(s) Préciser : ……

6) Auteur de la déclaration :
Investigateur ☐ Autre ☐
Nom du déclarant :

Tel / Fax :
Mail :

Date et signature de l'investigateur :

* **Joindre le(s) compte-rendu(s) d'hospitalisation et examens biologiques et d'imagerie**

Remplace CRPV –FOR-001 Date d'application : 8 mars 2012

Appendix IX: SPLASH Study - Amendments to Protocol

Protocol	N° 10.0 of 08.11.2016
Patient information letter	N° 2.0 of 28.05.2013
Patient Consent	N° 2.0 of 28.05.2013

N°1	Ethics committee (CPP) and health authority (ANSM) informed: 30 Aug 2013 Modifications: - Modification of a secondary objective: impact on physical activity instead of impact on quality of life and modification of its corresponding endpoint: evaluation of physical activity (WOMAC) instead of evaluation of quality of life; because the questionnaire used is a questionnaire of about physical activity and not about quality of life. -Detail the measurements of B and T lymphocyte counts in order to better explain to the analytical laboratory the measurements needed. (No change from the previous version of the protocol)
N°2	Approved by Ethics committee (CPP) : 19 Mars.2014 Health authority (ANSM) informed: 10 Apr 2014 The addition of 2 study centers/sites : CHU Nantes: Frédéric DOUANE Associated Investigators: Dr Sylvie METAIRIE Dr Raphaël CINOTTI CHU Toulouse: Pr Philippe OTAL Associated Investigator: Dr Jean-Pierre DUFFAS
N°3	Approved by Ethics committee (CPP): 16 Apr 2014 Health authority (ANSM) informed: 09 May 2014 The addition of 1 study center/site: CH Chambéry : Dr Marie MICHOUD
N°4	Approved by Ethics committee (CPP): 03 Sep 2014 Health authority (ANSM) informed: 22 Sep14 The addition of a non-inclusion criterion: Patient with acquired hemostasis (anticoagulant therapy) or innate abnormality in hemostasis.
N°5 (22.09.2014)	Approved by Ethics committee (CPP): 15 Oct 2014 Health authority (ANSM) informed : 3 Nov 14 The addition of 1 study center/site: Hôpital d'Instruction des Armées Sainte Anne- Toulon. Principal Investigator: Dr Tristan MONCHAL Associated Investigators: Dr Bertrand PRUNET Pr Charles ARTEAGA
N°6	Approved by Ethics committee (CPP): 09 Dec 2015 Health authority (ANSM) informed : 18 Dec 15 The addition of 1 study center/site: CHRU de Lille. Principal Investigator: Dr Jean-Robert NZAMUSHE-LEPAN-MABLA Associated Investigators: Dr Delphine GARRIGUE Dr Marc HABERLAY - Prolongation of the length of the study. - Change in sponsor's representative: Madame Jacqueline HUBERT – General Director of Grenoble University Hospital - Update of the chapter on independent monitoring committee (DSMB)
N°7	- Approved by Ethics committee (CPP): 06 Jul 2016 - Health authority (ANSM) informed: 12 Jul 2016 - The addition of 1 study center/site: - Hôpital de la Pitié-Salpêtrière

	- Principal Investigator: Pr Christophe TRESALLET - Addition of 2 co-investigators at Chambéry and Marseille - Closure of 3 centers, Toulouse, Clermont Ferrand and Dijon that have not included any patients. - Reduction of Radiology expert committee from 3 to 2 radiologists - Modification of coordinating center and project manager: Fatah TIDADINI Digestive and Emergency Surgery Clinic replaces Mme Carole ROLLAND Clinical Investigation Center – Inserm 003 - In the section: adverse events change " medical device" to "procedure" and "effect" to "event", and update the delay for reporting SUSAR (unexpected serious adverse events or reactions) - Delete sections IX-7 and IX-8 now obsolete due to above modification.
N°8	- Approved by Ethics committee (CPP): 07 Dec 2016 - Health authority (ANSM) informed: 23 Dec2016 - Increase the number of patients to include from 120 to 140 patients (due to withdrawals and absence of CT scans at D30 for technical reasons) - The duration of the study is increased by 12 months until 31 Dec 2017.

SPLASH Statistical analysis plan

Translated from the original version in French by Dr. Alison FOOTE (Grenoble-Alpes University Hospital) - February, 2019

0. Calculation of the number of subjects needed.

With an alpha risk of 5% and a power of 80%, 60 subjects per group will be needed to demonstrate 90% splenic salvage in the pSAE group (10% expected splenectomy) against 40% in the group with surveillance only (60% expected splenectomy).

This number of 120 patients is sufficient for assessment of the risks linked to embolization, assuming a maximum complication rate of 30% in the embolization group versus 10% in the surveillance group and occurrence of splenic vascular events of 5% in the SAE group and 30% in the surveillance group.
This number of 60 patients included per year is reasonable given the emergency context with the likelihood of patients to refusing to participate:

- Number of Centers: 16 Centers
- or 3-6 patients per year and per center (5 on average)
- corresponding to the 60 eligible patients per year (which was calculated earlier: indeed the centers admit an average of 30 splenic trauma cases per year eligible for non-operative treatment, thus 25-50% of which are eligible for the study (8 -15 patients per center on average).

Considering that 10% of patients might not complete the study (no CT scan at D30), we propose to randomize 140 patients.

1. General methods of analysis.

The normality of the quantitative parameters will be determined by graphical verification of the symmetry of the distribution.
The Chi2 test for categorical parameters will be used when the “Cochran 1954” criterion is met: the theoretical value of each cell must be greater than or equal to 1, and 80% of the cells must have a theoretical value greater than or equal to 5.
Non-parametric tests will be carried out when the conditions of application of parametric tests is not met.
The alpha threshold used for all analyzes is 0.05. There is no provision for adjusting the threshold.
Post-inclusion visits occurred on day 5 (5-9 days after inclusion), day 30 (20-60 days after inclusion), and day 180 (between 150 and 210 days after inclusion.

2. Descriptive analyses

The quantitative parameters will be expressed as means with standard deviations if the normality is confirmed, and medians with interquartiles if the normality is not met.
The categorical parameters will be expressed as numbers and percentages.
The population will be described after validation of the flow chart by the principal investigator (final analysis population) for the main parameters collected at the time of inclusion. In accordance with the usual recommendations for randomized trials (Schulz et al., CONSORT 2010 Statement: updated

guidelines for reporting parallel group randomized trials », BMJ, 2010), a statistical test comparing the two populations will not be performed.

For the study criteria, a comparison between randomization arms, of the descriptive parameters will be based on a comparison of the means for the quantitative parameters where normality has been confirmed, or by a Mann-Whitney test for parameters whose normality has not been confirmed. For descriptive categorical parameters, a comparison between the randomization arms will be done using a Chi2 test if the conditions of application conditions are confirmed and otherwise by a Fisher's exact test.

3. Other analyses.

No intermediate analyses are planned.

No subgroup analyzes are planned except for any subpopulations resulting from available data for the secondary endpoint analyzes.

4. Missing data.

The replacement of missing data by imputation of the main analysis criterion will be put in place if they represent between 5% and 15% of the data.

5. Analysis of the main objective.

The primary endpoint will be constructed by combining the variables related to necrosis, vascularization and rescue of the spleen on day 30 by the center and the experts. A overall variable for splenic rescue (yes / no) will be created.

Analysis of the primary endpoint will be done by implementing a Chi2 test after verification of the application criteria. If the criteria of application are not respected, the analysis of the principal criterion of judgment will be done using an exact test of Fisher.

The analysis will be in intention to treat (ITT). There is no provision for per protocol analysis.

6. Analysis of secondary objectives.

The analysis of the spleen rescue rate at 6 months will be done using a Chi2 test if the conditions for its use are confirmed, otherwise using an exact test of Fisher. Spleen rescue at 6 months will be established by combining variables related to necrosis, vascularization and spleen rescue at that time.

Any vascular complications will be analyzed using a Chi2 if the conditions of application are met, otherwise using an exact test of Fisher. The different vascular complications will be analyzed separately. An analysis of the combined variable "vascular complication: yes / no" may also be done. The notion of occurrence of splenic vascular events will be constructed from the following variables (already foreseen in the secondary objectives): need for splenic re-embolization in the SAE group or need for splenic embolization in the surveillance group, haemorrhage, pseudoaneurysm or splenic arteriovenous fistula during the course of follow-up.

The number of transfused RBC units linked to a hemorrhagic complication will be analyzed by a Chi2 test if the application conditions are met, or otherwise by a Fisher exact test.

Any deaths will be analyzed using a Chi2 test if the conditions of application are met, or by a Fisher exact test, if not.

The duration of hospitalization (in days) will be compared using a Student test if the normality of the data is confirmed and otherwise by a Mann-Whitney test. The length of hospital stay will be calculated by comparing the dates of admission and discharge from the hospital.

The need for re-hospitalization will be analyzed by a Chi2 test if the application conditions are met, or by an exact Fisher test if not. Re-hospitalization will be determined by analyzing the severity of the reported adverse events.

The impact on the professional activity will be analyzed by studying the duration of work being off work and compared using a Student test if the normality is met, otherwise a Mann-Whitney test will be used. The duration of time off work will be calculated by comparing the date of resumption of the work and the date of occurrence of the trauma. This analysis will be carried out only for the subgroup of "active" patients on D0.

The evaluation of physical activity will be analyzed by a Student test if normality is met, if not by a Mann-Whitney test.

The immunological assays (spontaneous kininogenase activity and B lymphocyte count) will be analyzed using a Student's test if the normality is met or a Mann-Whitney test if not.

Complications related to embolization will be analyzed separately by a Chi2 if the conditions of use are met, if not by an exact Fisher test if not. These complications are hematoma and thrombosis, as well as renal failure and allergy to contrast agents. Complications associated with to any new embolization will also be analyzed using the same methodology.

The analysis of complications specific to embolization will be performed only on the subpopulation of embolized patients.

7. Place and persons in charge of statistical analyses.

Statistical analyzes will be carried out after freezing the database, by a statistician of the Grenoble Alpes University Hospital (CHUGA) Data-Stat cell, under the responsibility of Prof. Jean-Luc Bosson, in accordance with the good practices put in place by the Quality Unit of the Clinical Research Administration (DRCI) of CHUGA. The analyses will be performed using the Stata 15 software.

The final statistical analysis report will be written according to the recommendations of the "CONSORT Statement for Randomized Trials of Non-pharmacological Treatments".