

## STUDY PROTOCOL

- Title:** Exploratory phase IV randomized single blind study evaluating the efficacy and tolerability of Hemopatch in improving time of hemostasis and preventing post-operative complications after hepatic resection.
- Protocol No.:** PAC-HEM-16-001
- Protocol version:** Amendment I - version 2..0, 1 April 2017
- Protocol Phase:** IV
- Coordinating Investigator:** Prof. Fabio Pacelli  
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### AMENDMENT APPROVAL

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*Prof. Fabio Pacelli*

## PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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### DECLARATION OF PRINCIPAL INVESTIGATOR

I confirm that I have read and understood this protocol, and agree to conduct the study as outlined in the protocol and other information supplied to me. I agree to conduct the study in compliance with all local legal and regulatory requirements, Good Clinical Practice, the International Conference on Harmonization (ICH) document and the Declaration of Helsinki. I will also appropriately direct and assist the staff who will be involved in the conduct of the study at the trial site.

\_\_\_\_\_  
Principal Investigator (Signature)

\_\_\_\_\_  
Date (dd/mm/yyyy)

\_\_\_\_\_  
Principal Investigator (Print Name and Surname)

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## 1. GENERAL INFORMATION

### 1.1 List of abbreviations

ACM	Acellular Collagen Matrix
ACRO	Academic Contract Research Organization
AE	Adverse Event
ALT	Alanine Transaminase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
CST	Common Surgical Techniques
CTC	Clinical Trial Center
ECG	Electrocardiogram
EMA	European Medicines Agency
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
INR	International Normalized Ratio
NHS-PEG	Pentaerythritol Polyethylene Glicol Ether Tetra-Succinimidyl Glutarate
PI	Principal Investigator
PT	Prothrombin Time
TBS	Target Bleeding Site

## 1.2 Synopsis

<b>TITLE</b>	Exploratory phase IV randomized single blind study evaluating the efficacy and tolerability of Hemopatch in improving time to hemostasis and preventing postoperative complications after hepatic resection
<b>PROTOCOL ID</b>	PAC-HEM-16-001
<b>VERSION</b>	Amendment I, version 2.0, 1 April 2017
<b>SPONSOR</b>	Prof. Fabio Pacelli
<b>TRIAL TYPE</b>	Phase IV
<b>TRIAL DESIGN</b>	Randomized, single blind study evaluating the efficacy and tolerability of Hemopatch
<b>INDICATION</b>	Patients undergoing hepatic resection
<b>TRIAL Medical Device</b>	HEMOPATCH, surgical sealant for hemostasis
<b>PATIENT INVOLVEMENT IN THE STUDY</b>	8,5 weeks (about 9 weeks)
<b>RECRUITMENT DURATION</b>	18 months
<b>TOTAL STUDY DURATION</b>	24 months (up to the Clinical Study report completion)
<b>MEDICAL DEVICE APPLICATION</b>	Post surgical resection
<b>COUNTRY AND NUMBER OF SITES</b>	Italy, 1 site. Within the site 3 Surgical Departments will contribute to the patient population: the Department of Emergency Surgery, the Department of General and Hepatobiliary Surgery and the Department of General and Transplantation Surgery.
<b>TRIAL POPULATION</b>	Patients undergoing liver resection for any underlying disease and with resectable mass. Information relevant to underlying acceptable diseases are reported in the inclusion criteria section (Synopsis and Protocol).
<b>STUDY RATIONALE</b>	<ul style="list-style-type: none"> <li>• Previous <i>in vitro</i> and <i>in vivo</i> studies detected the HEMOPATCH Sealing Hemostat® to be a new versatile, self-adhering hemostatic sealing pad consisting of a polyethylene glycol-coated collagen [10-13].</li> <li>• Initial study assessed that HEMOPATCH Sealing Hemostat® can be applied to seal almost any bleeding surface encountered during a range of procedures [12]. The Authors shown that the device is eminently capable in both via laparotomy and laparoscopic approaches, and in patients with impaired coagulation or highly variable anatomies. They support the ease-of-use, application, and immediate hemostatic effect of the patch across a broad range of surgical settings and clinical applications, including solid organ, gastrointestinal, biliopancreatic, endocrine, cardiovascular, and urologic surgeries.</li> <li>• In a recent published case report [14] the authors reported the feasibility in using HEMOPATCH Sealing Hemostat® for the management of a myocardial wound, performing the procedure on cardiopulmonary bypass, which meant the patient had to be heparinized. Despite these major risk factors for bleeding HEMOPATCH Sealing Hemostat® managed to contain bleeding and seal the wound without needing any suture.</li> </ul>

<p><b>TRIAL OBJECTIVES</b></p>	<p><b>Primary Objectives</b> To explore whether Hemopatch can improve time to hemostasis</p> <p><b>Secondary objectives</b> To explore whether Hemopatch can:</p> <ul style="list-style-type: none"> <li>• reduce the post-operative complications</li> <li>• shorten the use of drainage tube after hepatic resection</li> </ul>
<p><b>ENDPOINTS</b></p>	<p><b>Primary</b> Evaluated comparing the achievement of hemostasis within 3 minutes from the application of the patch in two groups:</p> <ol style="list-style-type: none"> <li>1. common surgical techniques + Hemopatch</li> <li>2. common surgical techniques</li> </ol> <p><b>Secondary</b> Evaluated comparing the following outcomes:</p> <ul style="list-style-type: none"> <li>• the total drainage volume</li> <li>• the timing of drainage removal</li> <li>• the measurement of total volume of transfused blood products</li> <li>• the bile leaks</li> <li>• any adverse event</li> <li>• the length of hospital stay</li> <li>• rate of post-operative mortality</li> </ul>
<p><b>INCLUSION CRITERIA</b></p>	<ul style="list-style-type: none"> <li>• Signed and dated Informed Consent obtained prior to the inclusion in the trial</li> <li>• Men and women of any ethnic origin aged 18-75 years</li> <li>• Women with childbearing potential willing not to start a pregnancy during the course of the study (at least within the time period foreseen for the patch absorption, i.e. 6-8 weeks from the application of Hemopatch)</li> <li>• Men having relationships with women with childbearing potential willing not to procure a pregnancy during the course of the study (at least within the time period foreseen for the patch absorption, i.e. 6-8 weeks from the application of Hemopatch)</li> <li>• Patients undergoing liver resection for any underlying disease and with resectable mass. The list of the underlying diseases is the following (but might not be limited to):             <ul style="list-style-type: none"> <li>➤ Hepatocellular carcinoma</li> <li>➤ Hilar cholangiocarcinoma</li> <li>➤ Adrenal cancer metastasis</li> <li>➤ Breast cancer metastasis</li> <li>➤ Colorectal cancer metastasis</li> <li>➤ Ovarian cancer metastasis</li> <li>➤ Biliary carcinoma</li> <li>➤ Hemangioma</li> <li>➤ Hepatic adenoma</li> <li>➤ Focal nodular hyperplasia</li> <li>➤ Unilocular hydatid cyst</li> <li>➤ Multilocular hydatid cyst</li> </ul> </li> </ul>



<p><b>EXCLUSION CRITERIA</b></p>	<ol style="list-style-type: none"> <li>1. Trauma surgery</li> <li>2. Active sepsis around the liver</li> <li>3. Documented history of cirrosis</li> <li>4. Pregnant or nursing women</li> <li>5. Severe coagulopathy (defined as an International normalized ratio INR &gt;2.0)</li> <li>6. Severe Liver disfunction, as per clinical assessment</li> <li>7. Previous liver transplantation</li> <li>8. Laparoscopic procedure</li> <li>9. Any other intraoperative finding, which defines the no eligibility of the patient for liver resection</li> <li>10. Known hypersensitivity to bovine proteins or brilliant blue</li> <li>11. Mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study</li> </ol>
<p><b>MAIN PARAMETERS OF EFFICACY</b></p>	<p>Timing of intra-operative hemostasis</p>
<p><b>MAIN PARAMETERS OF SAFETY</b></p>	<p>All adverse events will be recorded starting from the Informed Consent Signature. In particular, adverse events potentially occurring with the use of Hemopatch during the study will be appropriately recorded and documented to follow-up on the safety profile.</p>
<p><b>STUDY TREATMENTS</b></p>	<p><b>ARM A Standard Technique:</b></p> <ul style="list-style-type: none"> <li>• Common surgical techniques (CST)</li> </ul> <p><b>ARM B Experimental Technique:</b></p> <ul style="list-style-type: none"> <li>• Hemopatch in addition to Common surgical techniques (CST)</li> </ul>
<p><b>STUDY PROCEDURES</b></p>	<p>Patients will perform a total of 8 visits including a Follow-up at 30 days after the surgery (<math>\pm</math> 2 days) and an End of Study Visit at 6-8 weeks after surgery. For the details relevant to the procedures requested at each visit please refer to the study flow chart hereafter reported.</p>

## FLOW CHART

Study Period	Screening	Baseline	Surgery	+1 day after Surgery	+2 days after Surgery	+3 to 6 days after Surgery	Follow-up at 30 days	END of STUDY VISIT
Visit No.	V1	V2	V3	V4	V5	V6	V7	V8
(Days ± days)	Day -90 to -1	Day 0	Day 1	Day 2	Day 3	Day 4 to Day 6	Day 30 (± 2 days)	6-8 weeks (from surgery)
<b>PROCEDURES</b>								
Informed Consent	X							
Inclusion/Exclusion Criteria (verification and confirmation)	X	X						
Vital Signs (BP, HR)/Physical Examination	X							
Medical History	X							
Pregnancy Test (note 1)	X							
Hematology (note 2)	X			X	X	X	X	X
ECG	X							
Pulmonary Slab (note 13)	X							
Liver Function Test (note 3)	X			X	X	X	X	X
Viral Titres (note 4)	X							
Laboratory Test Results verification (note 5)		X						
Randomization (note 6)		X						
Medical device accountability			X					
Appropriate target bleeding site			X					
Bleeding site characteristics (note 7)			X					
Intraoperative details (note 8)			X					
Output and characteristics of the perihaptic drains (note 9)				X	X	X	X	X
Bilirubin concentration in the perihaptic drains (note 10)					X			
Abdominal ultrasound to detect the presence of any perihaptic collection (note 10)					X			
Timing of abdominal drainage removal (note 11)						X	X	
Concomitant medications	X	X	X	X	X	X	X	X
Adverse Event (note 12)	X	X	X	X	X	X	X	X

**Notes:**

- note 1: pregnancy test (by serum or urine determination, according to Principal Investigator or his delegates decision) for women of childbearing potential or with amenorrhea  $\leq 2$  years.
- note 2: hematology includes: glucose, urea nitrogen, , creatinine, sodium, potassium, calcium, total cholesterol, HDL and LDL, triglyceride, , alkaline phosphatase, LDH, complete blood cell counts with differential and platelet counts, APTT, PT, INR, fibrinogen, VES, PCR.  
During the hospitalization (from day 2 to day 6) the panel of the blood tests could be modified.
- note 3: the assessment of liver function includes: ALT, AST ALP, bilirubin and total protein, gamma-GT.  
During the hospitalization (from day 2 to day 6) the panel of the liver function could be modified.
- note 4: viral titres include: Hepatitis B and C. Tests to be performed only if not yet available within the medical history of the patient or if the previous results available have to be confirmed. HIV test is performed according to Principal Investigator or hisdelegates decision.
- note 5: hematology, the assessment of liver function, the determination of the viral titres and the pregnancy test, if applicable, will be evaluated by the Principal Investigator (PI) and/or his delegates and recorded first in the patient's medical record and then in the eCRF. The Principal Investigator and/or his delegates will check the laboratory test results vs. the inclusion/exclusion criteria. In case any result shows an out of range parameter judged to have an impact on the Inclusion/Exclusion criteria, this will be repeated before the confirmation for randomization.
- note 6: randomization will be performed by an independent statistician who will maintain it during the entire period of the study.
- note 7: the Principal Investigator and/or his delegates will record, first in the patient's medical record and then in the eCRF, the following information: source of bleeding, bleeding severity using "oozing" or "moderate", approximate area of bleeding.
- note 8: the Principal Investigator and/or his delegates will record, first in the patient's medical record and then in the eCRF, the following information: hepatic parenchyma characteristics, intraoperative measurement of total volume of transfused blood products, duration of the surgery, type of the hepatic resection, the estimated intraoperative blood loss, the use of Pringle's maneuver.
- note 9: the Principal Investigator and/or his delegates will record, first in the patient's medical record and then in the eCRF, the output (in ml) and the characteristics of the perihepatic drains (drain pigmentation, i.e.biliary bloody clear ). These information will be recorded by the Principal Investigator and/or his delegates from day 1 after surgery to the End of Study Visit if the drainage is still in place.
- note 10: these evaluations will be performed to detect the presence of any perihepatic collection and recorded by the Principal Investigator and/or his delegates first in the patient's medical record and then in the eCRF.
- note 11: removal of the abdominal drainage will be done at visit 6 only if applicable.
- note 12: Adverse Event (AE) will be monitored starting from the screening visit, immediately after the Informed Consent signature, up to the End of Study Visit and at least until the completion of the Hemopatch absorption period. The follow-up monitoring period of the AE could be different upon Investigator judgement, who should appropriately document the relevant decision
- note 13: in case the patient has performed a CT scan or RMN (because of the routinary assessment of the progression of the underlying disease) within at least 2 months from the ICF signature, the pulmonary slab will not be performed

<p><b>STATISTICAL CONSIDERATIONS</b></p>	<p>All the variables will be descriptively analyzed by treatment and visit (mean, median, standard deviation, minimum and maximum for continuous variables, frequency distribution for categorical variables). All the analyses will be detailed in the Statistical Analysis Plan (SAP) which will be finalized in Version 1.0 before the Data Base freezing.</p> <p>The proportion of responder patients (i.e. patients who achieve hemostasis after 3 min – see Section 11.5) measured at treatment end (i.e. visit 3) will be the primary endpoint. The treatment comparison will be performed by a <math>\chi^2</math> test.</p>
<p><b>PLANNED SAMPLE SIZE</b></p>	<p>Based on previous studies of hemostatic product it was estimated that 66% of patients receiving the hemostatic agent and 34% of those receiving standard care alone achieve hemostasis after 3 min. To show a difference between the two treatment options at a power of 90% with a significance level of 5%, a sample size of 98 patients was required for this trial.</p>
<p><b>TOTAL NUMBER OF CENTERS</b></p>	<p>1</p>
<p><b>ENROLLMENT AND DATA MANAGEMENT</b></p>	<p>98 patients will be enrolled. The source data, recorded in the appropriate source documentation, will be reported by the Investigator or a designee in a web-based Data Base (eCRF) provided by CMV-Stat. The data cleaning will be performed by CMV-Stat Data Management team who will provide the Investigator with the list of the detected inconsistencies. The validation of the inconsistencies (change or acceptance) will be made by the Investigator. Before the data freezing, CMV-Stat will code the medical terms, they will also be in charge of the Data Base freezing. CMV-Stat Data Manager will provide the Biostatistics Unit with the cleaned Data Base for the Statistical Analyses</p>
<p><b>CONTACT FOR SCIENTIFIC ISSUES</b></p>	<p>Prof. Fabio Pacelli Unità Operativa di Chirurgia D’Urgenza Fondazione Policlinico Universitario Agostino Gemelli</p>
<p><b>CONTACT FOR COORDINATION AND ADMINISTRATIVE ISSUES</b></p>	<p>Dr. Betty Polikar Head of the ACRO, Clinical Trial Center Fondazione Policlinico Universitario Agostino Gemelli</p>

## 2. INTRODUCTION

### 2.1 Background information

Advances in surgical techniques have reduced the occurrence of postoperative complications following liver resection and resulted in low surgical mortality and morbidity rates in high-volume centers.

Although partial liver resections for primary or secondary hepatic malignancies are considered standard interventions, intraoperative blood loss remains a risk factor associated with major complications in liver surgery [1–3]. There are several methods for reduction of blood loss, including meticulous resection technique along anatomical planes, reduction of central venous pressure during transection of the liver parenchyma [4], and vascular occlusion techniques (i.e., inflow occlusion and total vascular occlusion) [5–7]. In addition, specific instruments were devised for liver transection, such as the ultrasonic dissector, water jet, and other, more recent developments (e.g., focal radiofrequency ablation) that allow sealing of small vessels during transection [8, 9].

In order to control diffuse bleeding and to prevent intraperitoneal complications attributed to bleeding, various topical products are used when the conventional methods, such as suture, ligation, or argon beam coagulation, fail. Currently, there are numerous products on the market which are promising a successful outcome for hemostasis. These products include gelatin, collagen, oxidized regenerated cellulose, fibrin sealant glues, and synthetic glues.

### 2.2 Literature review on the use of Hemopatch

Previous *in vitro* and *in vivo* studies detect the HEMOPATCH Sealing Hemostat® to be a new versatile, self-adhering hemostatic sealing pad consisting of a polyethylene glycol-coated collagen [10-13].

Initial study assesses that HEMOPATCH Sealing Hemostat® can be applied to seal almost any bleeding surface encountered during a range of procedures. The Authors show that the device is eminently capable in both via laparotomy and laparoscopic approaches, and in patients with impaired coagulation or highly variable anatomies. They document the ease-of-use, application, and immediate hemostatic effect of the patch across a broad range of surgical settings and clinical applications, including solid organ, gastrointestinal, biliopancreatic, endocrine, cardiovascular, and urologic surgeries [12].

In a recent published case report the authors reported the feasibility in using HEMOPATCH Sealing Hemostat® for the management of a myocardial wound, performing the procedure on cardiopulmonary bypass, which meant the patient had to be heparinized. Despite these major risk factors for bleeding HEMOPATCH Sealing Hemostat® managed to contain bleeding and seal the wound without needing any suture [14].

These initial results lead up to future randomized clinical trials with more extensive follow-up to assess which is the real contribution of HEMOPATCH Sealing Hemostat to reduce postoperative bleeding complications in cases where mechanical or energy-driven hemostasis is not possible or insufficient.

### **3. STUDY OBJECTIVES**

#### **3.1 Primary Objectives**

To explore whether Hemopatch can improve time to hemostasis.

#### **3.2 Secondary Objectives**

To explore whether Hemopatch can:

- reduce the post-operative complications
- shorten the use of drainage tube after hepatic resection

### **4. EXPERIMENTAL DESIGN**

#### **4.1 Study endpoints**

##### **Primary Endpoint**

The primary endpoint of the study is to compare the achievement of hemostasis in the two arms. The patients in the ARM A will receive common surgical techniques while those in the ARM B will receive Hemopatch in addition to common surgical techniques within 3 minutes.

##### **Secondary Endpoint**

The secondary endpoints of the study are to compare the following outcomes:

- the total drainage volume
- the timing of drainage removal
- the measurement of total volume of transfused blood products
- the bile leaks
- any adverse event
- the length of hospital stay
- rate of post-operative mortality

#### **4.2 Design of the study**

A phase IV, exploratory prospective, comparative, single blind, randomized trial on the addition of Hemopatch compared to standard techniques to achieve bleeding control after hepatic surgical procedures.

Patients will be randomly assigned to common surgical techniques (ARM A) or assigned to Hemopatch in addition to common surgical techniques (ARM B) in a 1:1 ratio. The study endpoint is the time interval to obtain hemostasis.

Details of the randomization procedure will be specified in an ad hoc separate document of the study.

## 5. STUDY PROCEDURES AND VISIT SCHEDULING

### 5.1 Study flow-chart (continues on the next two pages)

Study Period	Screening	Baseline	Surgery	+1 day after Surgery	+2 days after Surgery	+3 to 6 days after Surgery	Follow-up at 30 days	END of STUDY VISIT
Visit No.	V1	V2	V3	V4	V5	V6	V7	V8
(Days $\pm$ days)	Day -90 to -1	Day 0	Day 1	Day 2	Day 3	Day 4 to Day 6	Day 30 ( $\pm$ 2 days)	6-8 weeks(from surgery)
<b>PROCEDURES</b>								
Informed Consent	X							
Inclusion/Exclusion Criteria (verification and confirmation)	X	X						
Vital Signs (BP, HR)/Physical Examination	X							
Medical History	X							
Pregnancy Test (note 1)	X							
Hematology (note 2)	X			X	X	X	X	X
ECG	X							
Pulmonary Slab (note 13)	X							
Liver Function Test (note 3)	X			X	X	X	X	X
Viral Titres (note 4)	X							

Study Period	Screening	Baseline	Surgery	+1 day after Surgery	+2 days after Surgery	+3 to 6 days after Surgery	Follow-up at 30 days	END of STUDY VISIT
Visit No.	V1	V2	V3	V4	V5	V6	V7	V8
(Days ± days)	Day -90 to -1	Day 0	Day 1	Day 2	Day 3	Day 4 to Day 6	Day 30 (± 2 days)	6-8 weeks (from surgery)
<b>PROCEDURES</b>								
Laboratory Test Results verification (note 5)		X						
Randomization (note 6)		X						
Medical device accountability			X					
Appropriate target bleeding site			X					
Bleeding site characteristics (note 7)			X					
Intraoperative details (note 8)			X					
Output and characteristics of the perihepatic drains (note 9)				X	X	X	X	X
Bilirubin concentration in the perihepatic drains (note 10)					X			



Study Period	Screening	Baseline	Surgery	+1 day after Surgery	+2 days after Surgery	+3 to 6 days after Surgery	Follow-up at 30 days	END of STUDY VISIT
Visit No.	V1	V2	V3	V4	V5	V6	V7	V8
(Days ± days)	Day -90 to -1	Day 0	Day 1	Day 2	Day 3	Day 4 to Day 6	Day 30 (± 2 days)	6-8 weeks (from surgery)
<b>PROCEDURES</b>								
Abdominal ultrasound to detect the presence of any perihepatic collection (note 10)					X			
Timing of abdominal drainage removal (nota 11)						X	X	
Concomitant medications	X	X	X	X	X	X	X	X
Adverse Event (note 12)	X	X	X	X	X	X	X	X

**Notes:**

note 1: pregnancy test (by serum or urine determination, according to Principal Investigator or his delegates decision) for women of childbearing potential or with amenorrhea ≤ 2 years.

note 2: hematology includes: glucose, urea nitrogen, , creatinine, sodium, potassium, calcium, total cholesterol, HDL and LDL, triglyceride, , alkaline phosphatase, LDH, complete blood cell counts with differential and platelet counts, APTT, PT, INR, fibrinogen, VES, PCR.

During the hospitalization (from day 2 to day 6) the panel of the blood tests could be modified.

note 3: the assessment of liver function includes: ALT, AST ALP, bilirubin and total protein, gamma-GT,.

During the hospitalization (from day 2 to day 6) the panel of the liver function could be modified.

- note 4: viral titres include: Hepatitis B and C. Tests to be performed only if not yet available within the medical history of the patient or if the previous results available have to be confirmed. HIV test is performed according to Principal Investigator or his delegates decision.
- note 5: hematology, the assessment of liver function, the determination of the viral titres and the pregnancy test, if applicable, will be evaluated by the Principal Investigator (PI) and/or his delegates and recorded first in the patient's medical record and then in the eCRF. The Principal Investigator and/or his delegates will check the laboratory test results vs. the inclusion/exclusion criteria. In case any result shows an out of range parameter judged to have an impact on the Inclusion/exclusion criteria, this will be repeated before the confirmation for randomization.
- note 6: randomization will be performed by an independent statistician who will maintain it during the entire period of the study.
- note 7: the Principal Investigator and/or his delegates will record, first in the patient's medical record and then in the eCRF, the following information: source of bleeding, bleeding severity using "oozing" or "moderate", approximate area of bleeding.
- note 8: the Principal Investigator and/or his delegates will record, first in the patient's medical record and then in the eCRF, the following information: hepatic parenchyma characteristics, intraoperative measurement of total volume of transfused blood products, duration of the surgery, type of the hepatic resection, the estimated intraoperative blood loss, the use of Pringle's maneuver.
- note 9: the Principal Investigator and/or his delegates will record, first in the patient's medical record and then in the eCRF, the output (in ml) and the characteristics of the perihepatic drains (drain pigmentation, i.e. biliary bloody clear ). These information will be recorded by the Principal Investigator and/or his delegates from day 1 after surgery to the End of Study Visit if the drainage is still in place.
- note 10: these evaluations will be performed to detect the presence of any perihepatic collection and recorded by the Principal Investigator and/or his delegates first in the patient's medical record and then in the eCRF.
- note 11: removal of the abdominal drainage will be done at visit 6 only if applicable.
- note 12: Adverse Event (AE) will be monitored starting from the screening visit, immediately after the Informed Consent signature, up to the End of Study Visit and at least until the completion of the Hemopatch absorption period. The follow-up monitoring period of the AE could be different upon Investigator judgement, who should appropriately document the relevant decision.
- note 13: in case the patient has performed a CT scan or RMN (because of the routinary assessment of the progression of the underlying disease) within at least 2 months from the ICF signature, the pulmonary slab will not be performed

## 5.2 Visit procedures

Below is a detailed description of each visit planned for the study. The Principal Investigator and/or his delegates will record each information first in the patient's medical record (or appropriate source document) and then in the eCRF.

### Visit 1 (Screening): Day -90 to -1

- Informed Consent procedure completion, which has to be implemented before any trial procedures is performed
- Inclusion and exclusion criteria verification and confirmation
- Complete medical history, vital signs (BP, HR) collection and physical examination
- Pregnancy test (by serum or urine determination, according to Principal Investigator or hisdelegates decision) for women of childbearing potential or with amenorrhea  $\leq$  2 years
- Hematology examinations, which include: glucose, urea nitrogen, , creatinine, sodium, potassium, calcium, total cholesterol, HDL and LDL, triglyceride, , alkaline phosphatase, LDH, complete blood cell counts with differential and platelet counts, APTT, PT, INR, fibrinogen, VES, PCR
- ECG
- Pulmonary slab. In case the patient has performed a CT scan or RMN (because of the routinary assessment of the progression of the underlying disease) within at least 2 months from the ICF signature, the pulmonary slab will not be performed Liver function test includes: ALT, AST, ALP, bilirubin and total protein, Gamma-GT
- The determination of viral titres include: hepatitis B and C,. Tests to be performed only if not yet available within the medical history of the patient or if the relevant results need to be confirmed. HIV test is performed according to Principal Investigator or his delegates decision
- Concomitant medications recordings
- Adverse event assessment and recording

### Visit 2 (Baseline):– Day 0

- Laboratory test results evaluation
- Check and confirmation of the inclusion and exclusion criteria vs. the laboratory test results
- Randomization of the patient, according to the specific procedure implemented for the study
- Concomitant medications recordings
- Adverse event assessment and recording

### Visit 3 (Surgery):Day 1

- Evaluation of the appropriate target bleeding site in the hepatic parenchyma (“oozing” or “moderate”)
- Recording of bleeding site characteristics (source of bleeding, bleeding severity using “oozing” or “moderate”, approximate area of bleeding site)
- Recording of intraoperative details (hepatic parenchyma characteristics, intraoperative measurement of total volume of transfused blood products, duration of the surgery, type of hepatic resection, the estimated intraoperative blood loss and the use of Pringle’s maneuver) Concomitant medications recordings
- Adverse event (intraoperative and not-intraoperative) assessment and recording

The patients randomized to Common Surgical Techniques (CST) will be treated conventionally while the patients randomized to experimental technique (CST + Hemopatch) will be treated conventionally with the adjunct of Hemopatch.

For patients included in ARM B Hemopatch is applied upon the verification made by the surgeon of the presence of an appropriate target bleeding (oozing or moderate) site in the hepatic parenchyma. At the time point of application a stopwatch starts simultaneously (time zero). Time to hemostasis is defined as the time required to obtain successful haemostasis in a single bleeding site. This time will be recorded by the operator delegated by the Principal Investigator and according to the surgeon’s observation. At 3 minutes the inspection will be made and, if haemostasis is not

achieved, the treatment is considered failed and the Principal Investigator and/or his delegates is allowed to use additional haemostatic measures (including other topical haemostatic agents).

The time to haemostasis will be recorded before in the patient's medical record and then in the eCRF. The bleeding site will be observed for 1 additional minute (after the first 3 minutes) at the end of the haemostatic procedure and at the end of the surgery, in order to confirm the achievement of haemostasis. At the end of surgery at least one perihepatic Jackson-Pratt drain will be left near the site of resection.

Patients allocated to ARM A, will undergo the conventional hemostatic procedures and therefore also these patients will end up with a perihepatic Jackson-Pratt drain, which will be left near the site of resection.

#### **Visit 4 (+1 day after Surgery): Day 2**

- Hematology examinations, which includes: glucose, urea nitrogen, creatinine, sodium, potassium, calcium, total cholesterol, HDL and LDL, triglyceride, alkaline phosphatase, LDH, complete blood cell counts with differential and platelet counts, APTT, PT, INR, fibrinogen, VES, PCR
- Liver function test examinations, which include: ALT, AST, ALP, bilirubin and total protein, gamma-GT
- Output (in ml) and characteristics of the perihepatic drains (drain pigmentation, i.e. biliary bloody clear)
- Concomitant medications recordings
- Adverse event assessments and recording

During the hospitalization the panel of the blood tests and of the liver function could be modified

#### **Visit 5 (+2 days after Surgery): Day 3**

- Hematology examinations, which includes: glucose, urea nitrogen, creatinine, sodium, potassium, calcium, total cholesterol, HDL and LDL, triglyceride, alkaline phosphatase, LDH, complete blood cell counts with differential and platelet counts, APTT, PT, INR, fibrinogen, VES, PCR
- Liver function test examinations, which include: ALT, AST, ALP, bilirubin and total protein, gamma-GT
- Output (in ml) and characteristics of the perihepatic drains (drain pigmentation, i.e. biliary bloody clear)
- Bilirubin concentration in the perihepatic drains, to detect the presence of any perihepatic collection
- Abdominal ultrasound, to detect the presence of any perihepatic collection
- Concomitant medications recordings
- Adverse Event assessment and recording

During the hospitalization the panel of the blood tests and of the liver function could be modified.

#### **Visit 6 (+3 to 6 days after Surgery): Day 4 to 6**

- Hematology examinations, which includes: glucose, urea nitrogen, creatinine, sodium, potassium, calcium, total cholesterol, HDL and LDL, triglyceride, alkaline phosphatase, LDH, complete blood cell counts with differential and platelet counts, APTT, PT, INR, fibrinogen, VES, PCR
- Liver function test examinations, which include: ALT, AST, ALP, bilirubin and total protein, gamma-GT.
- Output (in ml) and characteristics of the perihepatic drains (drain pigmentation, i.e. biliary bloody clear)
- Timing of abdominal drainage removal, if applicable
- Concomitant medications recordings
- Adverse Event assessment and recording

During the hospitalization the panel of the blood tests and of the liver function could be modified.

**Visit 7 (Follow-up at 30 days ± 2 days): Day 30**

A follow-up visit is scheduled for each patient and it will be done after 30 days from the day of the surgery, with an acceptable time-window of ±2 days.

- Hematology examinations, which includes: glucose, urea nitrogen, creatinine, sodium, potassium, calcium, total cholesterol, HDL and LDL, triglyceride, alkaline phosphatase, LDH, complete blood cell counts with differential and platelet counts, APTT, PT, INR, fibrinogen, VES, PCR
- Liver function test examinations, which include: ALT, AST, ALP, bilirubin and total protein, gamma-GT.
- Output (in ml) and characteristics of the perihepatic drains (drain pigmentation, i.e. biliary bloody clear ), if the drainage is still in place
- Timing of abdominal drainage removal, if applicable
- Concomitant medications recordings
- Adverse Event assessment and recording

**Visit 8 (6-8 weeks after Surgery): End of Study Visit**

- Hematology examinations, which includes: glucose, urea nitrogen, creatinine, sodium, potassium, calcium, total cholesterol, HDL and LDL, triglyceride, alkaline phosphatase, LDH, complete blood cell counts with differential and platelet counts, APTT, PT, INR, fibrinogen, VES, PCR
- Liver function test examinations, which include: ALT, AST, ALP, bilirubin and total protein, gamma-GT.
- Output (in ml) and characteristics of the perihepatic drains (drain pigmentation, i.e. biliary bloody clear ), if the drainage is still in place
- Concomitant medications recordings
- Adverse Event assessment and recording

**6. TRIAL POPULATION****6.1 Inclusion criteria**

1. Signed and dated Informed Consent, obtained prior to the inclusion in the trial
2. Men and women of any ethnic origin aged 18-75 years
3. Women with childbearing potential willing not to start a pregnancy during the course of the study (at least within the time period foreseen for the patch absorption, i.e. 6-8 weeks from the application of Hemopatch)
4. Men having relationships with women with childbearing potential willing not to procure a pregnancy during the course of the study (at least within the time period foreseen for the patch absorption, i.e. 6-8 weeks from the application of Hemopatch)
5. Patients undergoing liver resection for any underlying disease and with resectable mass. The list of the underlying diseases is the following (but might not be limited to):
  - Hepatocellular carcinoma
  - Hilar cholangiocarcinoma
  - Adrenal cancer metastasis
  - Breast cancer metastasis
  - Colorectal cancer metastasis
  - Ovarian cancer metastasis
  - Biliary carcinoma
  - Hemangioma
  - Hepatic adenoma
  - Focal nodular hyperplasia
  - Unilocular hydatid cyst
  - Multilocular hydatid cyst

## 6.2 Exclusion criteria

1. Trauma surgery
2. Active sepsis around the liver
3. Documented history of cirrosis
4. Pregnant or nursing women
5. Severe coagulopathy (defined as an International normalized ratio INR >2.0)
6. Severe Liver disfunction, as per clinical assessment
7. Previous liver transplantation
8. Laparoscopic procedure
9. Any other intraoperative finding, which defines the non eligibility of the patient for liver resection
10. Known hypersensitivity to bovine proteins or brilliant blue
11. Mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study

## 6.3 Withdrawal procedures

Patients have the right to withdraw from the trial on their request or at the discretion of the Principal Investigator and or his delegates.

The discontinuation from the study is foreseen in the following conditions:

- ✓ patient's request (also not motivated);
- ✓ principal investigator's decision (motivated) if considered as necessary, in own judgment, for the interest of the patient;
- ✓ occurrence of new diseases clinically relevant, not related to the study treatment;
- ✓ occurrence of particularly important adverse reactions;
- ✓ occurrence, in the course of the study, of one or more of the situations listed in the "exclusion criteria".

Patients withdrawn because of Hemopatch's failure, should be monitored for safety until the end of the study (please refer to the section 9.1).

## 7. STUDY TREATMENT

### 7.1 Treatment in study

Hemopatch is an EMA approved sealant for hemostasis. It consists of a soft, thin, pliable, flexible pad of collagen derived from bovine dermis, coated with NHS-PEG. The white, tissue-facing side is covered with a thin layer of NHS-PEG that provides firm tissue attachment, thus sealing the bleeding surface and inducing hemostasis simultaneously. Due to its flexible structure, the application of Hemopatch to the site where hemostasis is desired is easily controlled. For differentiation, the non-coated side is marked with blue squares of a biocompatible colorant.

Hemopatch will be supplied in the following size:

- Hemopatch 45 x 90 mm

Hemopatch is intended as an haemostatic device for surgical procedures when control of bleeding by pressure, ligature or conventional procedures is either ineffective or impractical.

In contact with blood, collagen induces aggregation of platelets. Platelets deposit in large numbers on the collagen structure, degranulate, and release coagulation factors that, together with plasma factors, enable the formation of fibrin. The structure of Hemopatch provides a three dimensional matrix for the additional mechanical strengthening of the clot. The NHS-PEG coating of this device, when in contact with blood, enhances its tissue adhesion properties and seals the bleeding surface. When applied as recommended, Hemopatch is resorbed in 6 – 8 weeks with little tissue reaction.

Hemopatch is not intended to be used in pulsatile, severe bleedings. The use of Hemopatch is not recommended in the presence of an active infection. Hemopatch is not intended as a substitute for meticulous surgical technique and the proper application of ligatures or other conventional procedures for hemostasis. Hemopatch should be maintained dry prior to application [15].

### **7.1.1 Application of Hemopatch**

The investigator will select the appropriate size of the pad so that it overlaps the margins of the bleeding surface by about 1 cm. The pad may be cut to the desired size and shape. Dry gloves and surgical instruments (forceps, scissors) should be used to handle, cut and apply Hemopatch. Multiple pads may be used for larger bleeding surfaces. The investigator will apply the dry Hemopatch with the non-marked white surface contacting the bleeding area. A dry gauze or patty will be used and will be held in place with gentle, uniform pressure over the entire pad surface for 2 minutes. When applying Hemopatch, the investigator should minimize contact with bloody surgical instruments, gauzes or gloves due to the affinity of collagen to blood. After 2 minutes, the investigator should gently remove the gauze or patty from the pad; gentle irrigation may also help in removing the gauze or patty without dislodging Hemopatch from the bleeding site. If the bleeding has not been satisfactorily controlled, Hemopatch can be removed, without tissue damage, up to 3 minutes from the time of the initial tissue contact. The investigator should not try to forcefully remove the pad.

The target bleeding site is defined as a bleeding site that, after 30 seconds of firm manual compression, has persistent bleeding requiring immediate attention. The investigator, an experienced hepatic surgeon, will define the bleeding source (arterial, venous, capillary), bleeding severity (oozing, middle or spurting) and the approximate area of bleeding site (cm<sup>2</sup>, mean).

### **7.1.2 Packaging, storage, labelling and accountability**

Hemopatch will be used with size 45X90 mm and will be provided to the site with the standard packaging. Nevertheless, the standard packaging will be specifically labelled in order to comply with the need to trace the assignment to the patient within this clinical trial. The identification of the packages assigned will be managed through the randomization procedure and will be reconciled within the accountability procedures that will be put in place for the purposes of the trial.

## **7.2 Randomization**

A phase IV randomized comparative design with specific statistical tests will be carried out. Patients will be randomly assigned to standard (ARM A) or experimental (ARM B; Hemopatch in addition to common surgical techniques) with a 1:1 ratio. The study endpoint is the time interval to obtain hemostasis.

Assigned treatment ARM will remain unknown to the patients, while physicians will use the treatment assigned according to the randomization list.

The randomization will be performed at the visit 2 - baseline, before surgery. Details on the randomization process managing and possible stratification factors to be considered will be included in a specific document, which will be finalized before the study starting.

## **7.3 Concomitant medications**

No contraindications to the use of any concomitant medication during the course of the study.

## 8. VIGILANCE REQUIREMENTS

### 8.1 Incidents and near incidents

#### Definitions

##### Incident

Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or USER or of other persons or to a serious deterioration in their state of health.

##### Fatal incident

Incident where the Medical Device (MD) determined (or contributed to determine) the patient death (or user death). Factors such as potential risks in use of MD, characteristics of MD, patient health condition, etc. should be considered to assess the causality relationship between the MD and the death. The evaluation of the health professional who witnessed the fatal event should be also taken into account.

**Incident in which the MD has caused a serious deterioration** in the health condition of a patient or user or third person is to be intended as:

- an illness or life-threatening injury;
- an impairment of a body function;
- a condition requiring medical or surgical intervention to prevent an impairment of a body function or impairment of a body structure;
- a condition requiring hospitalization or prolongation of hospitalization.

##### Near Incident

Near Incident is to be intended as:

- the condition where any malfunction or deterioration in the characteristics or performances, as well as any inadequacy in the labeling or instructions for use could result, if the MD had been used, a worsening of health condition or death of the patient or user , or
- the condition where any malfunction or deterioration in the characteristics or performances, as well as any inadequacy or in the labeling or instructions for use could cause during the procedure of use or following, if health personnel had not intervened, a worsening of health condition or death of the patient or user.

##### Complaint

Health care professionals should report only to the manufacturer or authorized representative or distributor any non-compliance and / or events that are not listed above, concerning the use or pre-use procedures, related to a MD.

##### Investigator Regulatory Obligations

The Investigator should submit to the Regulatory Authority (Ministero della Salute), to the EC and possibly also to the manufacturer/ authorized representative/distributor every incident and near incident, as defined above.

Such submissions must be performed:

- within 10 calendar days by occurrence for incidents;
- within 30 calendar days by occurrence for near incidents.



The form provided in Appendix I (in Italian) is to be used to report incidents and near incidents. It must be filled in with all the available information, dated and signed.

Upon request by the Regulatory Authorities, the Investigator must complete his report with all available follow-up information.

Reports on complaints must be transmitted to the manufacturer/ authorized representative/distributor within 30 calendar days by event occurrence.

The MD involved in the notified incident/near incident, if still available, must be kept at the Pharmacy of FPG and, unless otherwise specified by Ministero della Salute, delivered to the concerned company within 10 calendar days from the submission date of relevant incident or within 30 calendar days from the submission date of relevant near incident.

### Transfer Of Regulatory Obligations

The regulatory obligations are delegated by the Investigator to the Clinical Trial Center – FPG, ACRO Unit.

If the Investigator becomes aware of an incident/near incident/complaint as defined above, he must immediately report (**not later than 24 hours from the knowledge**) to the Clinical Trial Center – FPG by filling in the dedicated form (Appendix I). The form should be compiled in Italian. The reference contacts are reported in the table hereafter.

<b>Clinical Trial Center</b> <b>Fondazione Policlinico Universitario A. Gemelli Università Cattolica del Sacro Cuore</b> <b>L.go A. Gemelli, 8 – 00168 Roma</b>	
FORM Transmission (incident/near incident/complaint) e-mail Fax number (to be used just in case of electronic mail crash)	<b>fv.clinicaltrialcenter@rm.unicatt.it</b>  <b>06.888.055.67</b>
Contact Person Phone Mobile e-mail	Dr Elena Carafelli 06.888.055.66 328-3125259 elena.carafelli@policlinicogemelli.it

### Safety Follow-up

The safety information will be recorded starting from the date of the Informed Consent signature by the patient and will end-up at the End of Study Visit. This approach will apply also to those patients who were dropped out from the study because of failure of Hemopatch effect (and therefore treated with a rescue therapy), but who were left Hemoptach on the resection site because of difficulty in removing it. Those patients will be requested to return to the site to perform regularly from Visit 4 to Visit 8.

## **9. QUALITY CONTROL PROCEDURES**

### **9.1 Data documentation and reporting**

Electronic case report forms (eCRFs) will be used for study documentation. eCRF entries will be transcribed from source documents. Assessments for which source documents are usually available include laboratory data, medical history, physical examination, *etc.*. The Principal Investigator and/or his delegates should place all source documents in the patient's medical record.

Details of the eCRF completion will be explained to the Principal Investigator and/or his delegates during the Site Initiation Visit (SIV) by the statistician. All entries in the eCRF must be made in English language. The Principal Investigator and/or his delegates must give a reasonable explanation for all missing data. Each delegate of the clinical staff needs to register for eCRF entries with an individual user name and password. The eCRFs must be updated after each visit provided by the clinical study. If corrections are made to entries in the eCRF by the Principal Investigator or his delegates, the automated audit trail will keep track of all changes.

### **9.2 Study monitoring**

Accredited study monitors appointed by the Clinical Trial Center (CTC) of the Fondazione Policlinico Universitario A. Gemelli will carry out the monitoring of the clinical study. The eCRF will be reviewed on site and checks will be made against source documents. The Principal Investigator and/or his delegates must ensure that the medical records will be available for direct verification of source data. To this end, the Principal Investigator or his delegates agree to allow regular visits (frequency depending on enrollment) by the study monitors and to ensure they have adequate access to study personnel and documents.

### **9.3 Inspections**

The PI and/or his delegates must allow the Regulatory Authority to conduct Inspections.

The inspection conducted by the Regulatory Authority consists of an official review of the documents, facilities, records and any other resource considered by the Authority to be connected with the study.

## **10. DATA MANAGEMENT**

The data collection will be carried out at site. The data will be entered by the Investigator or a designee in a web-based Data Base provided by CMV-Stat. The electronic system will include the data entry pages prepared on the basis of the study flow-chart (section 5.1).

The data cleaning will be performed by CMV-Stat Data Management team who will provide the Investigator with the list of the detected inconsistencies on each group of data analyzed. The validation of the inconsistencies (change or acceptance) will be made by the Investigator. Before the data freezing, CMV-Stat will code the medical terms according to the following dictionaries (a Validation Coding Report will be prepared by CMV-Stat Biologist in charge and approved by the Sponsor or his delegates):

- MedDRA for the pathologies and the Adverse Events
- WHO-ATC for the drugs

At the end of the study, CMV-Stat will be in charge of the Data Base freezing. The Data Manager in charge will provide the Biostatistics Unit with the cleaned Data Base for the Statistical Analyses.

## 11. STATISTICAL METHODS

### 11.1 Sample size

Based on previous studies of hemostatic product [16,17] it was estimated that 66% of patients receiving the hemostatic agent and 34% of those receiving standard care alone achieve hemostasis after 3 min. To show a difference between the two treatment options at a power of 90% with a significance level of 5%, a sample size of 98 patients (49 per arm) are required for this trial.

### 11.2 Analysis populations

For this study, two populations will be considered:

Safety population defined as all patients who signed the Informed Consent. This population will be used for the safety and tolerability analyses.

Intention-To-Treat (ITT) population defined as all the randomized patients who received the assigned treatment. This population will be used for the efficacy analyses.

### 11.3 Methods

The analyses will be performed with SAS version 9.4. All the variables will be descriptively analyzed by treatment and visit (mean, median, standard deviation, minimum and maximum for continuous variables, frequency distribution for categorical variables).

All the analyses to be carried out will be detailed in the Statistical Analysis Plan (SAP) which will be finalized in Version 1.0 before the Data Base freezing. Version 2.0 of the SAP will be prepared after the Data Review Meeting (in which the protocol violations will be evaluated) and will include the list of the patients belonging to the defined populations and the randomization list.

### 11.4 Treatment comparison at study entry

A descriptive analysis for demographic data and baseline characteristics will be carried out in order to verify the treatment balance at study entry.

### 11.5 Efficacy analyses

#### Responder definition

A patient is defined as “Responder” if he/she achieves hemostasis after 3 min. Time to haemostasis is defined as the time required to obtain successful haemostasis in a single bleeding site. At 3 min, the inspection will be made and, if haemostasis is not achieved, the treatment is considered failed and the patient will be defined as “Non-Responder”. A patient assigned to the experimental arm (Hemopatch) for whom was not possible, for any reason, to proceed with the assigned treatment (i.e. has to be treated with the standard care) will be considered as “Randomization failure” and excluded from the ITT population.

In accordance with the primary objective of the study, the proportion of responder patients measured at treatment end (i.e. visit 3) will be the primary endpoint.

The treatment comparison will be performed by a  $\chi^2$  test.

The test will be two-sided and conducted at the standard 0.05 significance level

### 11.6 Safety analyses

The Safety population will be used to evaluate safety and tolerability data.

Physical examinations, vital signs, laboratory tests, adverse events and concomitant medications will be considered for the safety and tolerability evaluation.

Categorical variables (physical examination normality, etc.) will be analyzed with shift tables (baseline vs. last visit), while continuous variables (laboratory parameters, vital signs, etc.) by descriptive summaries.

Laboratory data will also be analysed with shift tables (baseline vs. last visit), considering each value as being normal/abnormal with respect to the appropriate normal ranges.

Baseline conditions and adverse events will be coded using the MedDRA dictionary. All the data related to the baseline conditions and adverse events will be listed by patient. Descriptive statistics will be performed classifying the events by system organ class and preferred term; they will also be classified by seriousness and relationship with the study treatment.

Prior and concomitant medications will be summarized using the WHO coding system.

## **12. ETHICAL ISSUES**

### **12.1 Ethical approvals**

Before the start of the study, the written information to be provided to the patients and the Informed Consent form must be submitted to the review and approval of the local Ethics Committee of the Fondazione Policlinico Universitario A. Gemelli, together with the protocol.

The Informed Consent must be requested, obtained and documented by the Principal Investigator in accordance with applicable legislation, with the Good Clinical Practice and with the ethical principles which derive from the Declaration of Helsinki and subsequent revisions (Appendix II).

### **12.2 Amendments to the protocol**

An amendment can be substantial and non-substantial. A substantial amendment is defined as an amendment to the terms of the application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- ✓ the safety or physical or mental integrity of the subjects of the study;
- ✓ the scientific value of the study;
- ✓ the conduct or management of the study; or
- ✓ the quality or safety of any investigational medicinal product used in the trial.

The substantial amendments should be submitted in order to make visible changes. To this end, the Principal Investigator must submit both a version with tracked changes and a version clean. The version clean must have a new numbering and dated. A copy of the previous version must be archived.

Substantial amendments must be submitted to the evaluation of the local Ethics Committee and notified to the Regulatory Authority. Only if the local Ethics Committee has not expressed objections, the amendment can be applied. Non-substantial amendments are changes to the detail of the study which do not have a significant impact either on the subjects enrolled in the trial or the conduct, management or scientific value of the trial. Non-substantial amendments must only be notified to the local Ethics Committee.

### **12.3 Informed Consent**

The Principal Investigator and/or his delegates must explain to each patient the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect her subsequent medical treatment or relationship with physician. The informed consent will be given by means of standard written statement, written in non-technical language. The patient should read and consider the statement before signing and dating it, and should be given a copy of the signed document. No patient can enter the study before his informed consent has been obtained. Confirmation that the Informed Consent was obtained will also be documented in the patient's medical record and in the eCRF. If a protocol amendment is made and also the Informed Consent may need to be revised, after the Ethics Committee has

approved changes, it is responsibility of the PI and/or his delegates to inform all active patients affected by changes, and to receive their written and dated “new” Informed Consent for continuation in the study.

### **13. ADMINISTRATIVE PROCEDURES**

#### **13.1 Possible changes in the clinical trial or in the analysis planned**

Once the protocol is signed by the Principal Investigator, approved by the local Ethics Committee and notified to the Regulatory Authority, the protocol cannot be modified. Any change made to the protocol must be approved by local Ethics Committee after presenting an amendment and notified to the Regulatory Authority.

#### **13.2 Archiving of study records**

Essential documents should be retained for a minimum of 7 years after the end of the study. However, documents should be retained for a longer period if required by the terms of the clinical trial authorization.

#### **13.3 Use of the information and publication of the results**

The Principal investigator and his study staff involved in the clinical study are responsible for publishing the results of the study and for their sharing with the Regulatory Authority/ies.

#### **13.4 Insurance coverage and civil liability**

The Sponsor has activated an insurance coverage for the trial, as per GCP and local laws pertaining the management of clinical trials requirements.

### **14. PRINCIPAL INVESTIGATOR RESPONSIBILITIES**

The Principal Investigator is aware of his responsibility for all the actions delegated by him to other members of his study staff assigned to the conduct of the study. The Principal Investigator and his staff are obliged to conduct the study in compliance with the study protocol and in adherence to the Good Clinical Practice and with the principles of the Declaration of Helsinki (1964) and successive revisions (Appendix II) as well as in respect of applicable legislation. Being the study referencing a Medical Device, compliance will be ensured also to applicable sections of the MEDDEV 2.7/3, December 2010, (Guideline on Medical Devices) and MEDDEV 2.12-1, rev 8, January 2013 (Guideline on a Medical Devices Vigilance System).

#### **14.1 Direct access to original documents**

The Principal Investigator and/or his delegates must allow the Regulatory Authority/ies and individuals delegated by the Independent Ethics Committee to have free access to and to conduct the relevant verification of all the original documentation of the study, including the informed consent forms signed by the patients enrolled into the study, the relevant patient files and/or out-patient files. Those individuals who are given free access to the documentation must take every reasonable precaution to keep the identity of the patients as reserved information, in accordance with applicable legislation.

### **15. REPORT OF THE END OF THE STUDY**

A final clinical study report will be produced by the Principal Investigator on the basis of the statistical report.

## 16. APPENDIX

### 16.1 Appendix I

#### Form to be used to report incidents and near incidents with the medical device

Segnalazione Iniziale

Follow Up

Dati Generale sull'Indagine Clinica

Centro	
Denominazione della struttura	
Protocollo di studio	

#### Dati relativi al Dispositivo Medico

Fabbricante (nome, ragione sociale e indirizzo)	
Fornitore (nome, ragione sociale e indirizzo)	
Nome commerciale ed eventuale modello del dispositivo	
Descrizione del dispositivo medico	
N. codice del dispositivo assegnato dal fabbricante	
Numero di lotto o di serie	
Data di scadenza	
Codice Classificazione unica nazionale dispositivi medici (CND)	
Dispositivo su misura <input type="checkbox"/> Se Sì, specificare il campo di applicazione, la tipologia e l'origine del materiale	
Sistemi o kit <input type="checkbox"/>	
Prodotto sterile <input type="checkbox"/> Non sterile <input type="checkbox"/>	
Dispositivo monouso <input type="checkbox"/> pluriuso <input type="checkbox"/>	

**Dati Relativi All'evento**

L'episodio ha coinvolto: il paziente  l'operatore

ID Paziente: \_\_\_\_\_

**Nel caso di dispositivo impiantato**

Data dell'impianto (se conosciuta) \_\_\_\_\_

**Dati sull'utilizzo del dispositivo**

Il dispositivo è stato utilizzato	Sì	<input type="checkbox"/>	No	<input type="checkbox"/>
Motivo per il quale è stato utilizzato (o si intendeva utilizzare) il dispositivo; per i dispositivi impiantabili, indicare anche la specifica diagnosi:				
_____				
_____				
_____				
_____				
Nel caso di effettivo utilizzo del dispositivo: procedura diagnostica, clinica, chirurgica, contatto con il paziente, tempo di permanenza, durata della procedura, etc.:				
_____				
_____				
_____				
_____				
_____				

**Descrizione dell'Incidente/Mancato Incidente**

_____
_____
_____
_____
_____
_____
_____
_____



**Esito**

Risolto  Data risoluzione: \_\_\_\_\_

Risolto con sequelae  Data risoluzione: \_\_\_\_\_

Ongoing

Morte

Data di morte: \_\_\_\_\_

**L'evento è giudicato correlato al DM in sperimentazione?**

SI  NO

**Argomentare il giudizio di correlazione**

.....  
.....  
.....  
.....

Il DM ("specifico pezzo") coinvolto è disponibile:

Sì

No

Se sì, dove: .....

**Azioni intraprese**

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.....  
.....



**Ulteriori commenti e dettagli**

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**Dati del segnalatore**

Nome e cognome: \_\_\_\_\_

Firma: \_\_\_\_\_ Data: \_\_\_\_\_

Data di avvenuta conoscenza da parte del Segnalatore: \_\_\_\_\_

## 16.2 APPENDIX II Declaration of Helsinki

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964  
and amended by the:  
29th WMA General Assembly, Tokyo, Japan, October 1975  
35th WMA General Assembly, Venice, Italy, October 1983  
41st WMA General Assembly, Hong Kong, September 1989  
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996  
52nd WMA General Assembly, Edinburgh, Scotland, October 2000  
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)  
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)  
59th WMA General Assembly, Seoul, Republic of Korea, October 2008  
64th WMA General Assembly, Fortaleza, Brazil, October 2013

### Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

### General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

#### **Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

### **Vulnerable Groups and Individuals**

**19.** Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

**20.** Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

### **Scientific Requirements and Research Protocols**

**21.** Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

**22.** The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

### **Research Ethics Committees**

**23.** The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

**Privacy and Confidentiality**

**24.** Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

**Informed Consent**

**25.** Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

**26.** In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

**27.** When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

**28.** For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

**29.** When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

**30.** Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been

approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

**31.** The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

**32.** For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

#### **Use of Placebo**

**33.** The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

#### **Post-Trial Provisions**

**34.** In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

#### **Research Registration and Publication and Dissemination of Results**

**35.** Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

**36.** Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**Unproven Interventions in Clinical Practice**

**37.** In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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