Clinical Investigation Plan:

Safety and Performance of Metastatic Tumor Cell Trap Device in Patients with Advanced Ovarian Cancer

Protocol Number:	MTRAP-2016-01
Version Number :	3.0
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Sponsor	MTrap, Inc. [redacted] Vice President, Regulatory, Quality & Clinical Affairs Telephone: [redacted] Email: [redacted]

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SPONSOR

Person or organization that takes responsibility for the initiation and / or the implementation of a clinical investigation:

Name: MTrap, Inc.

Contact: [redacted], VP Regulatory, Quality and Clinical Affairs

Address: [redacted]

Phone number:

Email: [redacted]

Legal Representative:

Name: [redacted], MTrap Board Member

Address: [redacted]

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CLINICAL INVESTIGATION ORGANIZATION

Clinical Research Organization

Person designated by the sponsor to verify the progress of a clinical investigation, i.e., verify that it is conducted, recorded and communicated according to the clinical investigation plan, the written procedures, the ISO 14155 standard and the applicable requirement(s):

Name: [redacted]

Address: [redacted]

Phone number: [redacted]

Fax number: [redacted]

PROTOCOL SIGNATURE PAGE

Protocol number: MTRAP-2016-01

Safety and Performance of Metastatic Tumor Cell Trap Device in Patients with Advanced Ovarian Cancer

I have read the Clinical Investigation Plan mentioned above and agree to adhere to its requirements.

I have received a copy of the most current version of the Investigator's Brochure.

I will provide copies of the protocol and access to all information furnished by the Sponsor, MTRAP, to the study personnel under my supervision and involved in carrying out the study. I will discuss this material with them to ensure that they are fully informed about the investigational device and the conduct of the study.

I have read the Confidentiality Statement of this protocol. The contents of this protocol may not be used in any other clinical study and may not be disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by law or regulation, for example submission to an Ethics Committee; however, I will give prompt notice to the Sponsor of any such disclosure.

Site Number/Name: _____

Printed Name of Investigator: _____

Date: _____ Signature:

Printed Sponsor Name & Title: [redacted], VP Regulatory, Quality and Clinical Affairs

Date: _____ Signature:

Printed Legal Representative Name for the Sponsor: [redacted], MTrap Board Member

Date: _____ Signature:

PROTOCOL SYNOPSIS

Title:	Safety and Performance of Metastatic Tumor Cell Trap Device in Patients with Advanced Ovarian Cancer
Protocol Number:	MTRAP-2016-01
Medical Device:	Metastatic Tumor Cell Trap Device (M-Trap)
Intended Use:	M-Trap is an implantable medical device designed to capture disseminated tumor cells (DTCs). It is intended for use in advanced-stage ovarian cancer patients.
Surgical Use:	Up to three (3) M-Trap devices will be surgically implanted via laparotomy in the right and left paracolic (pelvic) gutters and behind segment 6 of the liver within the peritoneal cavity of the patient at the time of surgical resection. Patients will receive standard chemotherapy with carboplatin and paclitaxel. After completion of chemotherapy, M-Trap devices will be removed via minimally invasive surgery (laparoscopy) following the device removal protocol.
Study Design:	Prospective, multi-center, non-blinded, single-arm study. Safety and performance study conducted in accordance with ISO 14155.
Study Objective(s):	The study objective is to assess the safety and the performance of the MTrap device. Safety objectives: The primary objective is to demonstrate that the safety of M-Trap, as measured by freedom from device- and procedure-related major adverse events through 6-months post-implantation, is non-inferior to historical controls. The secondary objective is to collect long-term safety data to support device safety and post-market surveillance. Safety will be evaluated to demonstrate acceptable levels of device-related and procedure-related complications. Performance objective: The primary objective is to confirm M-Trap performance, as determined by histological evidence of tumor cell capture. The secondary objective is to assess disease focalization with use of the M-Trap device.
Primary Endpoints:	Safety endpoints: The primary safety endpoint is incidence of device- and procedure-related major adverse events through 6-months post-implantation, including shock, cardiac arrest, myocardial infarction, pulmonary embolism, prolonged intubation, unplanned reintubation, or adverse events leading to removal of the device, including infection, seroma formation, mesh migration, bowel obstruction, adhesions, and local cancer progression through the abdominal wall at M-Trap suture sites. Performance endpoints: The primary performance endpoint is histopathologic evidence of tumor cell capture. Histopathology will be performed after device explant.
Secondary Endpoints:	Safety endpoints: Secondary safety endpoints include incidence of other device-related adverse events and all other adverse events long-term. Patients will be evaluated by physical examination, CT scan, ultrasound, and biomarker cancer antigen CA-125. Performance endpoints: Secondary performance endpoints include semi-quantitative scoring of disease focalization based on direct visual assessment, CT scan and

	ultrasound at the time of device removal. In additon, a microscopic assessment will be performed during explant, including cytologic assessment of any ascites present, cytologic assessment of peritoneal washings, if indicated, and a minimum of two (2) peritoneal biopsies from designated locations, if indicated.
Participating Sites:	The study will be conducted at eight (8) sites in Spain.
Study Population:	Stage IIIC or Stage IV ovarian cancer patients with the following outcomes after debulking surgery: • Stage IIIC primary debulking surgery patients with residual visible tumor ≤1 cm, OR • Stage IIIC or Stage IV interval debulking surgery patients with complete resection or residual visible tumor ≤1 cm. Up to 22 patients will be treated to have 20 evaluable patients.
Study Approach:	This study will be conducted in two phases: (1) The first phase will enroll five (5) patients. Safety data at the 1-month timepoint will be collected, including physical examination, ultrasound, adverse events, and concomitant medications. (2) The second phase will enroll the remaining seventeen (17) patients and will commence upon approval by AEMPS to proceed with a continuation of the study.
Inclusion Criteria:	Patient will be included if all of the following criteria are met: 1. Is a female ≥18 years old. 2. Presents with a diagnosis of Stage IIIC or Stage IV ovarian cancer. 3. Presents with high-grade serous carcinoma. 4. Has one of the following: a. Stage IIIC disease and visible residual tumor ≤1 cm after primary tumor debulking surgery. b. Stage IIIC or Stage IV disease and three or four cycles of neoadjuvant chemotherapy and complete resection after interval tumor debulking surgery. c. Stage IIIC or Stage IV disease and three or four cycles of neoadjuvant chemotherapy and visible residual tumor ≤1 cm after interval tumor debulking surgery. 5. ECOG performance status of 0 or 1. 6. Is willing to comply with required follow-up study visits. 7. Is willing and able to provide written informed consent.
Exclusion Criteria:	Patient will not be included if any one of the following conditions exists: 1. Has a life expectancy of <3 months. 2. Is pregnant, as confirmed through a blood test prior to any study procedure, planning on becoming pregnant during the study, or is lactating. 3. Will be receiving intraperitoneal chemotherapy. 4. Has undergone prior treatment with abdominal and/or pelvic radiotherapy. 5. Has significant active concurrent medical illnesses including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

	6. Presence of central nervous system or cerebral metastases. 7. Recurrent ovarian cancer. 8. Complete resection with no residual tumor after primary tumor debulking surgery. 9. Suboptimal resection with >1 cm residual tumor after primary or interval tumor debulking surgery. 10. Is simultaneously enrolled in another investigational study. 11. Has a history of cancer within 5 years other than in-situ uterine cervix cancer or non-melanoma skin cancer. 12. Has a known hypersensitivity to carboplatin or paclitaxel. 13. Is concurrently using other antineoplastic agents.
Estimated Timelines:	Estimated duration for enrollment: Nine (9) months. Estimated total duration for study: Thirty-six (36) months. Duration of participation for each subject: patients will be evaluated pre-operatively, at time of surgery, at 1 month, 3 months, 6 months, 9 months, 12 months, 15 months and 18 months post-surgery.
Clinical Study Organization:	**Sponsor:** MTrap, Inc. [redacted]
	EU Study Principal Investigator: Antonio Gil Moreno, MD Hospital Vall D'Hebron, Barcelona, Spain
	DSMB Chair: Luis Chiva, MD University of Navarre, Pamplona, Spain
	Monitor: [redacted] [redacted]
	A Data Safety Monitoring Board (DSMB) will review study data from all patients after the first five (5) patients have reached the 1-month time point. The DSMB will then meet semi-annually until all patients are enrolled, and annually thereafter. The recommendations of the DSMB will guide continuation of enrollment during the enrollment phase of the study, as well as continuation of the study once enrollment is done.

Schedule of Assessments / Flow Chart:

Examination/Assessment	Visit 0 Screening Within 21 days	Visit 1 Procedure (D0)	Visit 2 1 Month (± 1 week)	Visit 3 3 Months[1] (± 2 weeks)	Visit 4 6 Months[2] (± 2 weeks)	Visit 5 9 Months (±1 month)	Visit 6 12 Months (±1 month)	Visit 7 15 Months (±1 month)	Visit 8 18 Months (±1 month)
Signed Informed Consent	X								
Eligibility criteria check	X	X							
Demographics, medical history	X								
Physical examination	X	X	X	X	X	X	X	X	X
Biomarker CA-125	X			X	X	X	X	X	X
CT scan	X			X	X	X	X	X	X
Ultrasound		X	X	X	X	X	X	X	X
PCI[3]	X	X							
Cytology/biopsy									X[4]
Pathology (explant)									X[4]
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X

[1] 3M visit must occur after the final chemotherapy infusion in interval debulking patients. The 3M CT scan will serve as the baseline for assessing disease progression for purposes of device removal.
[2] 6M visit must occur after the final chemotherapy infusion in primary debulking patients. The 6M CT scan will serve as the baseline for assessing disease progression for purposes of device removal.
[3] Peritoneal Carcinomatosis Index.
[4] To be performed at time of device removal. Device removal may occur earlier if conditions for device removal described in Section 6.2 are met.

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1. INTRODUCTION – STUDY RATIONALE

1.1. Epidemiology

Cancer is one of the leading causes of mortality in the world and accounts for 8 million deaths annually. Each year, 14 million new cases are diagnosed and cancer rates are predicted to increase. Metastatic disease remains the primary cause of morbidity and mortality in cancer, accounting for more than 90% of cancer-related deaths. Despite substantial advances in diagnosis, surgical techniques, and therapeutic treatments, metastatic disease remains the major cause of death from cancer.

Ovarian cancer accounts for 4% of all cancers in women, with 239,000 new cases diagnosed worldwide in 2012, and is the leading cause of death from gynecologic malignancies. Ovarian cancer often has no symptoms at the early stages, so the disease is generally advanced (stage III or IV) when it is diagnosed. Approximately 75% of diagnosed women have Stage III or Stage IV.[1]

Primary cytoreductive surgery, to reduce or eliminate intraabdominal tumor burden, followed by platinum-taxane based chemotherapy is the standard therapy in advanced ovarian cancer, i.e., cancer classified as Stage III to IV by the International Federation of Gynecology and Obstetrics (FIGO).[2] As an alternative, neoadjuvant chemotherapy followed by interval debulking surgery can be carried out. This approach is mainly considered as an option for patients who are unlikely to be optimally cytoreduced, as well as for patients who are not medically suitable to undergo primary surgery due to the extent of disease or comorbidities.

Despite radical surgery and chemotherapy, most patients with ovarian cancer develop recurrence and die due to progressive disease.[3,4] The 5-year survival rate of women with ovarian cancer ranges from approximately 30-50%.[5] The greater the residual disease after the surgery, the poorer the prognosis, with a 5-year survival rate of 28.6% for patients with a residual tumor of 0.1-1 cm diameter and 21.3% when residual disease is greater than 1 cm.[2]

A comprehensive literature review was performed to evaluate survival outcomes in the target population for the M-Trap device, including patients with disease that is unlikely to or cannot be optimally reduced during surgery. For the targeted patient population, median overall survival and progression-free survival vary from 24-50 months[6,7,8,9,10,11,12,13]**Error! Bookmark not defined.** and 12-21 months[6,7,8,10], respectively. This compares to median overall survival and progression-free survival in patients with complete resection after primary debulking surgery (patient population with the best prognosis) of 69 months and 29 months, respectively.[14] Based on the poor survival outcomes in the target M-Trap population, there is a clear unmet clinical need for therapeutic options beyond standard-of-care for high-risk patients with advanced ovarian cancer.

1.2. Novel Therapeutic Strategy

The M-Trap Device (Metastatic Tumor Cell Trap Device) represents a breakthrough therapeutic strategy that provides a preferential site for the capture of disseminating tumor cells, transforming a systemic disease into a focalized disease where surgery, radiation, and chemotherapy have proven efficacy. M-Trap is an implantable surgical

mesh comprised of a non-resorbable, polycarbonate polyurethane (PCPU) scaffold with a Type I collagen coating.

M-Trap is intended to be implanted into the peritoneal cavity during the tumor debulking procedure to capture disseminating tumor cells. Up to three (3) M-Trap devices will be surgically implanted via laparotomy in the right and left paracolic (pelvic) gutters and behind segment 6 of the liver within the peritoneal cavity of the patient at the time of surgical resection. Patients will receive standard platinum-based chemotherapy. If the cancer is diagnosed to have recurred, M-Trap devices with captured tumor cells will be removed via minimally invasive surgery (laparoscopy).

1.3. Study Clinical Justification

Based on the complete literature review, clinical studies highlight the poor prognosis in the target population, such as patients with disease that unlikely to or cannot be optimally reduced during surgery. A significant unmet clinical need exists for options beyond current standard-of-care in these high-risk patients with advanced ovarian cancer who demonstrate poor survival outcomes. Clinical case studies support the concept of using a mesh to capture cancer cells in the abdominal cavity. M-Trap provides a preferential site for the capture of disseminating tumor cells, transforming a systemic disease into a focalized disease where directed treatment such as surgery, radiation, and chemotherapy have proven efficacy. M-Trap is expected to deliver a clinical benefit to patients for a life-threatening medical condition for which current medical alternatives are insufficient and carry significant risks.

1.4. Available Results with M-Trap Device

M-Trap non-clinical testing was designed to demonstrate the safety and efficacy of the device in the context of its intended use. Complete details are included in the Investigator Brochure. The preclinical testing for M-Trap falls into six categories:

1. ISO 10993 biocompatibility testing demonstrated safety of the final, sterile device.
2. Preclinical mode-of-action studies established the non-pharmacological mode-of-action of the device.
3. Preclinical studies assessed the risk of tumor proliferation and tumor cell dissemination from the M-Trap device, and these risks were determined to be negligible.
4. Histologic evaluation of the host tissue response to the device in a clinically relevant murine model of peritoneal dissemination demonstrated an initial inflammatory response that is progressively transformed into a dense fibrotic response, an expected response to porous synthetic biomaterials. Histology also verified the durability of the device to capture disseminated tumor cells after one-year of implantation.
5. Preclinical performance studies in an ovarian cancer murine model validated that the device functions as intended to capture disseminating tumor cells. These studies demonstrated that the device captures relevant cell lines of ovarian cancer tumors in clinically relevant models, the device performance is maintained over time and in the presence of chemotherapy, and focalization of the disease by the device results in significant improvements in survival outcomes.
6. Preclinical studies in a large animal model assessed device usability (i.e., implantation and laparoscopic removal with lack of complications at 30 days),

and no issues affecting the risk evaluation were noted. This study confirmed device safety during implantation and removal.

There have been no previous clinical investigations or clinical usage with this device.

1.5. Study Design Justification

This study is a prospective, multi-center, non-blinded, single arm study to evaluate the safety of the M-Trap device in Stage IIIC ovarian cancer patients in comparison to historical controls. Device performance will be verified based on histological evidence of tumor cell capture.

A single-arm cohort study is appropriate for this study because there is extensive information in the literature regarding the outcomes for these patients with current available treatments. Safety will be evaluated in the context of this published literature to demonstrate acceptable levels of complications in comparison to historical controls.

A non-inferiority design is being utilized based on a risk assessment supporting low risk and high benefit. As a surgical mesh comprised of two components with regulatory approval for use in the intended implant location, M-Trap does not pose any new risks in terms of materials of construction, method of sterilization, implant location, or function. However, the potential benefits are significant, due to the high unmet clinical need. Recurrence rates in women with advanced ovarian cancer are high, with ~40%-50% of the targeted patient population progressing at the 12-month time point after surgery and standard chemotherapy.[6,7] Extensive preclinical testing on the device has validated M-Trap performance benefits. In light of the low risk / high benefit balance, the M-Trap clinical study is designed to prove the hypothesis that M-Trap does not decrease the rate of freedom from device- and procedure-related major adverse events (AEs) compared to standard-of-care through 6 months post-cytoreductive surgery.

Published literature supports major adverse event rates of 10% for advanced ovarian cancer patients undergoing cytoreductive surgery. In a comprehensive analysis of 30-day post-operative complications in 2,870 patients undergoing surgery for ovarian cancer between 2005-2012, Patankar et. al. demonstrated a rate of severe complications of 6.8% and a rate of any complications of 11.9%, depending on the number of procedures performed during the cytoreductive surgery, as shown in **Table A** below.[15] Any complication was defined as a composite measure if the patient was noted to have any of the following postoperative complications: pneumonia, acute renal failure, urinary tract infection, cerebrovascular accident, coma, sepsis, shock, cardiac arrest, myocardial infarction, pulmonary embolism, deep venous thrombosis, prolonged mechanical ventilation, unplanned re-intubation, or progressive renal insufficiency. Severe complications were analyzed based on Clavian class IV complications and included shock, cardiac arrest, myocardial infarction, pulmonary embolism, prolonged intubation or unplanned reintubation.

Table A: Perioperative Outcomes Stratified by Number of Procedures Performed

	0 procedures	1 procedure	2 procedures	≥3 procedures	Total
Total patients (n)	1,352	1,214	254	50	2,870
Any complications					
Number (n)	99	156	72	15	342
Rate (%)	7.3%	12.9%	28.3%	30.0%	**11.9%**
Wound complications					
Number (n)	68	80	36	9	193
Rate (%)	5.0%	6.6%	14.2%	18.0%	**6.7%**
Severe complications					
Number (n)	51	92	44	9	196
Rate (%)	3.8%	7.6%	17.3%	18.0%	**6.8%**

Using a success rate of 90% (freedom from device- and procedure-related major adverse events), a non-inferiority margin of 25%, >85% power, and one-sided alpha=0.05, a sample size of n=20 patients is needed to demonstrate that M-Trap is as safe as current standard-of-care through 6-months post-surgery. Assuming a 10% dropout rate, up to 22 patients will be treated to have 20 evaluable patients.

2. INVESTIGATIONAL DEVICE

The M-Trap (Metastatic Tumor Cell Trap) device is comprised of a non-resorbable, polycarbonate polyurethane scaffold matrix with a Type I collagen coating. The M-Trap device is provided sterile for single use and is intended to capture metastatic tumor cells in advanced-stage ovarian cancer patients.

The M-Trap scaffold is a biostable, reticulated (possessing interconnected and intercommunicating open pores), polycarbonate polyurethane-urea matrix. The reticulated matrix permits tissue ingrowth and proliferation into the implant. The matrix has a void content greater than 90%, with average cell sizes measuring in the range of 250 to 500 microns. The M-Trap collagen coating is comprised of a [redacted] Type I collagen that is [redacted] cross-linked for in-vivo durability.

M-Trap devices are manufactured under GMP conditions. Devices are individually packaged in moisture-resistant pouches and sterilized using gamma irradiation. M-Trap is available in an oval configuration of 15 mm (width) x 50 mm (length) x 5 mm (thickness). The device has been demonstrated to be biocompatible and biostable per ISO-10993 testing for a permanent, tissue/bone-contacting implant.

M-Trap is intended to be implanted into the peritoneal cavity during the tumor debulking procedure to capture disseminating tumor cells. Up to three (3) M-Trap devices will be surgically implanted via laparotomy in the right and left paracolic (pelvic) gutters and behind segment 6 of the liver within the peritoneal cavity of the patient at the time of surgical resection. Patients will receive standard platinum-based chemotherapy. If the cancer is diagnosed to have recurred, M-Trap devices with captured tumor cells will be removed via minimally invasive surgery (laparoscopy).

3. STUDY DESIGN

This study is a prospective, multi-center, non-blinded, single arm study to evaluate the safety of the M-Trap device in Stage IIIC ovarian cancer patients in comparison to historical controls.

Up to eight (8) sites located in Spain will participate in this study.

Patients with one of the following outcomes after debulking surgery will be targeted in this study:

- Residual visible tumor ≤1 cm after primary debulking or
- Complete resection or residual visible tumor ≤1 cm after interval debulking surgery.

Up to twenty-two (22) patients will be treated in the clinical investigation to obtain twenty (20) evaluable patients.

Once patients have received the study treatment, they will be evaluated at 1 month, 3 months, 6 months, 9 months, 12 months, 15 months, and 18 months post-operatively.

This study will be conducted in a two-phase approach, as follows:

(1) The first phase will enroll five (5) patients. Safety data at the 1-month timepoint will be collected, including physical examination, ultrasound, adverse events, and concomitant medications.

(2) The second phase will enroll the remaining seventeen (17) patients and will commence upon approval by AEMPS to proceed with a continuation of the study.

4. STUDY OBJECTIVE(S) AND ENDPOINTS

The study objective is to assess the safety and the performance of the MTrap device in the capture of metastatic tumor cells in Stage IIIC ovarian cancer patients to support CE-marking of the device.

<u>Safety objectives</u>:
The primary objective is to demonstrate that the safety of M-Trap, as measured by freedom from device- and procedure-related major adverse events through 6-months post-implantation, is non-inferior to historical controls.

The secondary objective is to collect long-term safety data to support device safety and post-market surveillance. Safety will be evaluated to demonstrate acceptable levels of device-related and procedure-related complications.

<u>Performance objective</u>:
The primary objective is to confirm M-Trap performance, as determined by histological evidence of tumor cell capture.

The secondary objective is to assess disease focalization with use of the M-Trap device.

4.1. Primary Endpoint(s)

4.1.1. Primary Safety Endpoint(s)

The primary safety endpoint is incidence of device- and procedure-related major adverse events, defined as severe complications based on Clavian Class IV complications[15], through 6-months post-implantation, including shock, cardiac arrest, myocardial infarction, pulmonary embolism, prolonged intubation, unplanned reintubation, or adverse events leading to removal of the device, including infection, seroma formation, mesh migration, bowel obstruction, adhesions, and local cancer progression through the abdominal wall at M-Trap suture sites.

4.1.2. Primary Performance Endpoint

The primary performance endpoint is histopathologic evidence of tumor cell capture. Histopathology will be performed after device explant.

4.2. Secondary Endpoints

4.2.1. Secondary Safety Endpoints

Secondary endpoints include incidence of other device-related adverse events and all other adverse events long-term. Patients will be evaluated by physical examination, CT scan, ultrasound, and biomarker cancer antigen CA-125. Please also refer to Section 7 (anticipated or potential adverse events).

4.2.2. Secondary Performance Endpoints

Secondary performance endpoints include semi-quantitative scoring of disease focalization based on direct visual assessment, CT scan and ultrasound at the time of device removal. In addition, a microscopic assessment will be performed during explant, including cytologic assessment of any ascites present, cytologic assessment of peritoneal washings, if indicated, and a minimum of two (2) peritoneal biopsies from designated locations, if indicated.

5. SUBJECT SELECTION

5.1. Inclusion Criteria (IC)

Candidates for the study must meet ALL of the following inclusion criteria:

1. Is a female ≥18 years old.
2. Presents with a diagnosis of Stage IIIC or IV ovarian cancer.
3. Presents with high-grade serous carcinoma.
4. Has one of the following:
    a. Stage IIIC disease and visible residual tumor ≤1 cm after primary tumor debulking surgery.
    b. Stage IIIC or Stage IV disease and three or four cycles of neoadjuvant chemotherapy and complete resection after interval tumor debulking surgery.
    c. Stage IIIC or Stage IV disease and three or four cycles of neoadjuvant chemotherapy and visible residual tumor ≤1 cm after interval tumor debulking surgery.
5. ECOG performance status of 0 or 1.
6. Is willing to comply with required follow-up study visits.

7. Is willing and able to provide written informed consent.

5.2. Exclusion Criteria (EC)

Candidates for this study will be excluded if ANY of the following conditions are present:

1. Has a life expectancy of <3 months.
2. Is pregnant, as confirmed through a blood test prior to any study procedure, planning on becoming pregnant during the study, or is lactating.
3. Will be receiving intraperitoneal chemotherapy.
4. Has undergone prior treatment with abdominal and/or pelvic radiotherapy.
5. Has significant active concurrent medical illnesses including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
6. Presence of central nervous system or cerebral metastases.
7. Recurrent ovarian cancer.
8. Complete resection with no residual tumor after primary tumor debulking surgery.
9. Suboptimal resection with > 1 cm residual tumor after primary or interval tumor debulking surgery.
10. Is simultaneously enrolled in another investigational study.
11. Has a history of cancer within 5 years other than in-situ uterine cervix cancer or non-melanoma skin cancer.
12. Has a known hypersensitivity to carboplatin or paclitaxel.
13. Is concurrently using other antineoplastic agents.

5.3. Subject Accountability

5.3.1. Enrolled Subjects

The point of enrollment starts when the subject provides written informed consent and agrees to participate in the clinical investigation. Subject for whom consent was not obtained prior to participation in the study will not be considered enrolled. No data collected from this “subject” will be included in any analysis.

5.3.2. Screen Failures

A screen failure subject is an enrolled subject who withdraws consent prior to index procedure or is unsuitable for index procedure following the debulking procedure. This subject will be exited from the study once screen failure is confirmed. Screen failure subjects will be recorded in Enrollment and Screening Log. Their signed informed consent forms will be kept in the site’s administrative files.

5.3.3. Treated Subjects

A treated subject is an enrolled subject who meets all eligibility criteria, and has been treated. This subject will be followed in accordance with the protocol requirements.

6. STUDY PROCEDURES AND ASSESSMENTS

Schedule of Assessments / Flow Chart:

Examination/ Assessment	Visit 0 Screening Within 21 days	Visit 1 Procedure (D0)	Visit 2 1M (±1W)	Visit 3 3M[5] (±2W)	Visit 4 6M[6] (±2W)	Visit 5 9M (±1M)	Visit 6 12M (±1M)	Visit 7 15M (±1M)	Visit 8 18M (±1M)
Signed Informed Consent	X								
Eligibility criteria check	X	X							
Demographics, medical history	X								
Physical examination	X	X	X	X	X	X	X	X	X
Biomarker CA-125	X			X	X	X	X	X	X
CT scan	X			X	X	X	X	X	X
Ultrasound		X	X	X	X	X	X	X	X
PCI[7]	X	X							
Cytology/biopsy									X[8]
Pathology (explant)									X[8]
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X

6.1. Screening and Baseline Assessments

6.1.1. Informed Consent Process

Investigators will not ask subjects to sign the Informed Consent Form until the clinical investigation has been fully approved by the institution's Ethics Committee (EC) and the Sponsor or their CRO representative has received and reviewed the specific EC-approved Informed Consent form.

When the Investigator has determined the eligibility of a specific subject to enter the clinical investigation, the Investigator will provide an informed consent form to the subject. The Investigator or designee, will discuss and explain the clinical investigation with the subject as follows:

- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- do not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

[5] 3M visit must occur after the final chemotherapy infusion in interval debulking patients. The 3M CT scan will serve as the baseline for assessing disease progression for purposes of device removal.
[6] 6M visit must occur after the final chemotherapy infusion in primary debulking patients. The 6M CT scan will serve as the baseline for assessing disease progression for purposes of device removal.
[7] Peritoneal Carcinomatosis Index.
[8] To be performed at time of device removal. Device removal may occur earlier if conditions for device removal described in Section 6.2 are met

The Investigator will obtain the signed informed consent form from the subject before performing the implant procedure or any protocol-specific tests. The Investigator will provide subjects with a copy of their signed informed consent form. The Investigator will maintain a copy of the EC-approved Informed Consent Form along with a copy of each subject's signed Informed Consent Form in a designated study file.

If during the debulking procedure, the subject is found not to be eligible for inclusion in the study, the subject should be notified. Reason for ineligibility will be accounted for as "screen failure" and will be documented as such in the Enrollment & Screening log. If the subject has signed the informed consent form, but is found not eligible for inclusion in the study prior to or during the procedure, the subject should receive the appropriate treatment as identified by the clinical investigator.

6.1.2. Screening/Baseline Assessments

The following screening assessments and tests will be completed within 21 days before the index procedure for those study subjects who continue to be eligible. This set of examinations and tests will be considered the study subject's baseline evaluations:

- Obtain written informed consent. No procedures will be performed without informed consent.
- Check eligibility criteria, inlcuding a pregnancy test, if applicable.
- Obtain demographic information.
- Obtain complete medical history.
- Conduct physical examination.
- Collect Biomarker CA-125 level.
- Perform a baseline CT scan of the abdomen, pelvis, and chest.
- Determine Peritoneal Carcinomatosis Index (PCI), if available.
- Record any adverse events.
- Collect concomitant medications information.

6.2. Procedure

The following assessments and tests will be completed on the day of procedure, prior to the procedure:

- Conduct physical examination.
- Check eligibility criteria Determine Peritoneal Carcinomatosis Index (PCI) pre- and post-debulking.

The following assessments and tests will be completed prior to discharge:

- Perform an abdominal ultrasound (within 24 hours of implant).
- Record any adverse events.
- Collect concomitant medications information.

6.2.1. Debulking Procedure

Debulking will be performed following the institution's standard protocols. A PCI must be documented pre- and post-debulking. In addition, all residual tumor will be documented on the Case Report Form. If possible, photographs should be taken, documenting the residual tumor.

6.2.2. Implant Procedure

Three M-Trap devices will be implanted following the completion of a standard debulking procedure performed following the institution's standard protocols. The three devices will be implanted in the following locations:

- right paracolic (pelvic) gutter;
- left paracolic (pelvic) gutter;
- and behind segment 6 of the liver within the peritoneal cavity.

Prior to use, each M-Trap mesh will be removed from the sterile pouch. Each implant must be submerged completely and soaked for 2 minutes in sterile normal saline in a sterile dish large enough to accommodate the device. The mesh will be placed in the target location and secured using six (6) points of surgical attachment such that the mesh lays flat against the lateral parietal wall, with no wrinkling, dead space, gaps, or other placement deficiencies. A non-absorbable suture, size 2-0, should be used. The suture bite into the mesh should be a minimum of ~0.5 cm from the edge of the mesh. The device should be oriented as necessary to contour to the target anatomy.

Surgery will be completed following the institution's standard protocols. An ultrasound must be performed within 24 hours post-surgery to confirm device placement. Each patient will receive an implant card.

6.2.3. Device Removal Procedure

Following completion of chemotherapy treatment, M-Trap devices will be removed under one of following scenarios, whichever occurs first:

(1) In the event of an adverse event necessitating device removal.
(2) After disease progression as defined by objective RECIST 1.1 and CA-125 criteria. Both criteria must be met as follows:
   RECIST 1.1 criteria[16]
   i. Compared to baseline* (or lowest sum while on study if less than baseline), a 20% increase in the sum of the diameters of baseline target lesions with an absolute increase of at least 5 mm, or
   ii. Any new lesions (measurable or non-measurable), or
   iii. Unequivocal increase in non-target disease, defined as an overall level of substantial worsening in non-target disease such that the overall tumor burden merits discontinuation of therapy.
   Gynecological Cancer Intergroup criteria[17]
   i. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart, or
   ii. Patients with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value on 2 occasions at least 1 week apart, or
   iii. Patients with CA-125 in the reference range before treatment must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.
(3) At the final 18-month post-implantation time point.

* Baseline is defined as the follow-up time point following completion of chemotherapy treatment.

Device removal will be performed via minimally invasive surgery (laparoscopy) following the institution's standard protocols. To remove the device, M-Trap device(s) will be located, carefully segregating the device with any captured tumor cells from the surrounding tissues. Next, a single-use specimen retrieval system (Endobag™ container) will be placed to recover the extracted M-Trap device through the 15mm trocar cannula of the laparoscopic port, maintaining the integrity of the device for histological analysis.

The laparoscopy will be completed following the institution's standard protocols. An assessment of the device removal procedure will occur at the time of explant, including ease of locating and removing the M-Trap device and the occurrence of any device- or procedural-related AEs during the removal procedure. If for some reason the device(s) cannot be explanted through laparoscopy, the surgeon should proceed using best clinical judgement, including a potential conversion to laparotomy.

Semi-quantitative scoring of disease focalization based on direct visual assessment, CT scan and ultrasound will be performed at the time of device removal, using the following scale:

Degree of Disease Focalization	Definition
I	Approximately 100% of recurrent disease contained in M-Trap devices
II	Approximately 75% of recurrent disease contained in M-Trap devices
III	Approximately 50% of recurrent disease contained in M-Trap devices
IV	Approximately 25% of recurrent disease contained in M-Trap devices
V	No obvious recurrent disease contained in M-Trap devices

Following device removal, mark the side of the device that faced outward into the peritoneal cavity with an "X" using a surgical suture. Place each explanted device in a separate, labelled container prepared per standard institution protocol. Labels shall include institution name, protocol number (MTRAP-2016-01), study subject identification number, date of explant, and location of explant (i.e., right paracolic gutter, left paracolic gutter, liver). The hospital laboratory must follow Appendix 1 to prepare the explant for shipping to the core laboratory. After standard pathological analysis at the institution, samples shall be shipped following the institution's protocols for shipment of biological samples to the core laboratory for histology evaluation:

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All patients will be followed through 18 months, regardless of whether or not the device was removed at an earlier time point.

6.3. Post-Operative Care

Post-operative care will follow the institution's standard rehabilitation protocol.

6.4. Follow-Up Assessments

At each follow-up visit at 1 month ± 1 week, 3 months ± 2 weeks, 6 months ± 2 weeks , 9 months ± 1 month, 12 months ± 1 month, 15 months ± 1 month and 18 months ± 1 month, the patient will undergo the following assessments and tests:

- Conduct physical examination.
- Collect Biomarker CA-125 level. (except at 1 month visit)
- Perform an abdominal ultrasound.
- Perform a CT scan of the abdomen, pelvis, and chest. (except at 1 month visit)
- Record any adverse events.
- Collect concomitant medications information.
- In addition, if device removal is planned:
    - Record data regarding device removal.
    - Perform pathology of the explanted device.

6.5. Medication Regimen

Use of all medications will be recorded in the patient's CRF. This will include all prescription and OTC drugs. Any changes in medications also will be recorded in the patient's CRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the principal investigator to ensure that details regarding the medication are recorded in full on the CRF.

6.6. Summary of Required Assessments

6.6.1. Demographic Data/Medical History

Demographic data and a complete medical history will be collected at screening. The medical history will include a complete history of the patient's cancer and any prior treatments. The medical history will be used to ensure that the patient does not meet any of the exclusion criteria. A review of medical history will be conducted at the screening visit.

6.6.2. Physical Examination

A pre-op general physical examination will occur at the screening visit. A specific pelvic (gynecologic) examination to manually examine the abdomen and pelvic area for any nodules or bumps, as indicated in the CRF, will be conducted at the screening visit and at each follow-up visit.

6.6.3. Biomarker CA-125

Cancer antigen 125 (CA-125) is best known as a biomarker to monitor epithelial ovarian cancer and for the differential diagnosis of pelvic masses. A CA-125 test measures the amount of the CA-125 in a person's blood. This test can be used to monitor the effectiveness of treatment and cancer recurrence. A CA-125 test will be performed at the screening visit and at each follow-up visit.

6.6.4. CT Scan

Computed tomography (CT) scan is one of the most commonly used tools for the screening, diagnosis and treatment of cancer. A CT scan is an X-ray procedure that uses a computer to produce three-dimensional, cross-sectional images of inside the body. A CT scan of the abdomen, pelvis, and chest will be performed at the screening visit and at each follow-up visit. Observations based on CT findings will be documented on the CRF with images appended for review and confirmation by the Data Safety Monitoring Board.

6.6.5. Ultrasound

Ultrasound (US) is a non-invasive method for evaluation of the abdominal cavity. US will be used precisely locate the position of a tumor, monitor M-Trap performance and assess tumor recurrence. Abdominal US will be performed within 24 hours of the implant procedure (post-implant) and at each follow-up visit. Observations based on real-time ultrasound findings will be documented on the CRF with still images appended for review and confirmation by the Data Safety Monitoring Board.

6.6.6. Peritoneal Carcinomatosis Index (PCI)

The Peritoneal Carcinomatosis Index (PCI) is used to assess the extent of peritoneal cancer throughout the peritoneal cavity. For this purpose, the peritoneal cavity is divided in 13 well-defined regions. In each of the 13 regions, the size of the largest tumor nodule is measured. If no tumor is visualized, a score of “0” is given to that region. If the largest tumor nodule is smaller than 0.5 cm, the score is “1”. For tumors measuring between 0.5 cm and 5 cm, the score is “2”. For lesions larger than 5 cm, the score is “3”. If there is layering or a confluence of multiple small tumor nodules, the score is “3”. The PCI is calculated by adding the scores of all 13 regions together with a maximum score of 39 (13×3). Determination of PCI will be made at time of diagnostic laparoscopy (if available) and at time of surgical debulking (pre- and post-procedure).

6.6.7. Pathology

Pathology analysis will be done on explanted M-Trap devices to evaluate the host tissue response to the device, assess the cellular immune response, and characterize the tumor cells captured by the device.

Each device will be excised, fixed in 10% neutral-buffered formalin, and embedded in paraffin. Tissue samples will be sectioned (3-5 μm), hematoxylin and eosin (H&E) stained and histologically evaluated. Masson Trichrome stain will also be used to evaluate collagen deposition.

Tumor size will be determined by measuring the longest diameter (length) and width. Immunohistochemistry (IH) against CD3, CD20 and CD68 will be performed to assess the cellular immune response. Immunohistochemistry (IH) against CKAE1/AE3, CK7, ER and P53 will be performed to characterize tumor cells captured by the device. Immunohistochemical results will be evaluated semi-quantitatively, by considering percentage of positively stained cells. All the findings will be documented and images from a microscope will be obtained. Advanced analysis may be performed, if available.

6.6.8. Cytology/biopsy

At the time of device removal, additional miscroscopic data will be collected following a modfied, laparoscopic second-look procedure (Gynecologic Oncology Group Surgical Procedures Manual, rev Jan 2010).

Ascites: If ascites are present, a sample will be collected for cytologic assessment.

Peritoneal Washings: If ascites are not present, prior to device removal peritoneal washings will be performed in the following locations:

a) Pelvis
b) Right and left paracolic gutters, and
c) Subdiaphragmatic space.

The three specimens will be combined and analyzed cytologically as a single specimen.

Biopsies: If no visual tumors are seen, a minimum of two (2) biopsies should be obtained from the following locations after device removal and will be analyzed as separate specimens:

a) Right and left sidewall,
b) Cul-de-sac and vesical peritoneum,
c) Right and left abdominal gutter peritoneum,
d) Undersurface of the right diaphragm,
e) Residual omentum,
f) Adhesive bands, abnormally scarred areas, and
g) Retroperitoneum.

6.7. Withdrawals or Discontinuation

6.7.1. Lost to Follow-Up Subject

A subject will be considered “lost to follow-up” and terminated from the study when all of the following criteria have been met.

- Failure to complete 3 consecutive visits without due cause (after 30 days).
- Documentation of three (3) unsuccessful attempts, one of which must be in written communication, by the Investigator or his/her designee to contact the subject or next of kin.
- A letter from the Investigator to Sponsor reporting subject as lost to follow up.

6.7.2. Withdrawal and Replacement of Subjects

Subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. Patients still implanted at the time of intent of withdrawal will undergo the device removal procedure and associated assessments before being exited from the trial. The reason for withdrawal will be recorded (if given) in all cases of withdrawal. The investigator may discontinue a subject from participation in the study if the investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject. Data that have already been collected on withdrawn subjects will be retained and used for analysis but no new data will be collected after withdrawal.

Withdrawn subjects will not be replaced.

7. RISK-BENEFIT ANALYSIS

7.1. Risks Assessment and Risk Mitigation

A risk analysis has been conducted, in accordance with ISO 14971:2012 “Application of risk management to medical devices.” The risks associated with this investigational device have been identified and been minimized through appropriate design control, which was confirmed by bench testing and pre-clinical animal testing presented in the Investigator’s Brochure.

During the conduct of the clinical study, the existing risk analysis will be reviewed to identify if additional hazards have been introduced. If any new hazards were introduced, the associated risk(s) shall be re-assessed and addressed.

7.1.1. Anticipated or Potential Adverse Events

The list below provides anticipated or potential adverse events that may occur during the study.

Adverse events that may be associated with a general surgical procedure are:

- Allergic reactions or hypersensitivity to medication, including anesthesia
- Anesthesia complications
- Bleeding
- Death
- Deep vein thrombosis
- Delayed or impaired wound healing
- Infection

Adverse events that may be associated with the surgical debulking procedure are: [10, 11, 12, 13, 14, 15, 16]

- Abdominal collection requiring drainage
- Abscess
- Acute cardiopulmonary failure
- Acute renal failure
- Anastomotic leak or failure
- Anemia
- Bowel / intestinal obstruction
- Cardiac failure / cardiac arrest / myocardial infarction
- Cardiac dysrhythmia
- Cerebrovascular accident
- Coma
- Death
- Deep vein thrombosis
- Diarrhea
- Fever
- Fistula
- Hematoma
- Hemoperitoineum
- Hemorrhage / bleeding
- Hypotension

- Ileus
- Infection
- Nausea
- Pain
- Pancreatitis
- Pancreatic leak
- Perforation
- Pericardial effusion
- Peritonitis
- Pleural effusion
- Pleuresia
- Pneumonia
- Pneumonitis
- Pneumothorax requiring placement of a chest tube
- Prolonged mechanical ventilation
- Prolonged or unplanned reintubation
- Pulmonary embolism
- Renal insufficiency or failure
- Reoperation
- Respiratory complication
- Respiratory distress syndrome
- Sepsis
- Seroma formation
- Shock
- Surgical site infection
- Thromboembolism
- Trauma
- Urethral obstruction
- Vomiting
- Wound dehiscence

Additional adverse events that may be associated with the device removal and cytology/biopsy laparascopy procedure are:

- Adhesions
- Anesthesia-related complications
- Bruising
- Conversion to laparotomy
- Cyst rupture
- Hematoma
- Incisional hernia
- Injury to blood vessels of the abdominal wall or those of the lower abdomen and pelvic sidewall
- Peritonitis
- Port-site metastases
- Tumor cell peritoneal dissemination (seeding)
- Urinary tract or bowel injury
- Wound infection

Adverse events that may be associated specifically with the M-Trap device are:

- Adhesions
- Bleeding
- Fistula
- Hematoma
- Infection including abscess formation
- Inflammation
- Local cancer progression through the abdominal wall at M-Trap suture sites
- Mesh migration
- Obstruction
- Organ or bowel injury resulting from device removal procedure
- Pain
- Perforation
- Seroma formation

7.1.2. Risk Management

All adverse events will be reviewed by the study sponsor and the Data Safety Monitoring Board.

Additional efforts to minimize risks associated with performing the procedure include the following:

- Selection of qualified Investigators as described above.
- Comprehensive investigator training to ensure that investigators have a thorough knowledge of the CIP and the proper technique for implantation and removal of the M-Trap device.

7.2. Benefit Assessment

There is a significant unmet clinical need for options beyond current standard-of-care in high-risk patients with advanced ovarian cancer who demonstrate poor survival outcomes. The potential benefit of disease focalization so that it can be easily treated using directed surgery is significant. Published studies have shown significant improvements in survival outcomes for patients undergoing secondary cytoreduction who are cytoreduced to microscopic disease.[18,19,20,21] Preclinical studies have clearly demonstrated focalization of the disease with use of M-Trap, and the survival study demonstrated that removal of the M-Trap upon capture of tumor cells, similar to the planned use of the device in clinical practice, resulted in minimal residual disease and a substantial improvement of >3.3X in mean overall survival (6/8 animals survived through the 1-year endpoint).

M-Trap is expected to deliver a clinical benefit to patients for a life-threatening medical condition for which current medical alternatives are insufficient and carry significant risks. While M-Trap also carries risks, namely those associated with a porous surgical mesh and its removal, these risks are well-known and understood and are less severe than the risks associated with advanced ovarian cancer.

8. ADVERSE EVENT MANAGEMENT

8.1. Event Definitions

Subjects will be carefully monitored during the study for possible Adverse Events (AEs) from the time the Subject signs the Patient Informed Consent form to the completion of their participation in the study. Any AE observed will be fully investigated by the Investigator and classified in line with the definitions of the ISO 14155:2011 below.

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

NOTE 1 This definition includes events related to the investigational medical device.
NOTE 2 This definition includes events related to the procedures involved.
NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

Device Deficiency: Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Adverse Device Effect (ADE): Adverse event related to the use of an investigational medical device.

NOTE 1 This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2 This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Event (SAE):

a) led to death,
b) led to serious deterioration in the health of the subject, that either resulted in
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function, or
    3) in-patient or prolonged hospitalization, or
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) led to fetal distress, foetal death or a congenital abnormality or birth defect

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE): Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

8.2. Severity Definitions

Event severity is classified as follows:

Mild: awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae.

Moderate: interferes with the patient's usual activity and/or requires symptomatic treatment.

Severe: symptom(s) causing severe discomfort and significant impact on the patient's usual activity and requires treatment.

8.3. Causality Relationship

The investigator will assess the causality of all adverse events in relation to the research, i.e., the relationship between the AE / SAE and the investigational treatment or any other study-related procedures.

Each event will be classified according to five different levels of causality:

Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

8.4. Investigator Reporting Responsibilities

The investigator should report to the sponsor the following events, whether expected or not, in the corresponding sheet of the CRF, with the exception of AEs / SAEs detected before the patients has signed the patient consent form.

- AE
- SAE
- Device Deficiencies that did not, but might have, led to a SAE if:
    - Suitable action has not been taken or
    - Intervention had not been made or
    - If circumstances had been less fortunate
- New findings/updated in relation to already reported events

If an AE / SAE is present at the beginning of study prior to the subject providing signed consent to participate in the study, only its worsening should be reported.

The investigator shall notify the sponsor immediately and not later than 24 hours after the investigator has become aware of a SAE or device deficiency that might have led to a SAE.

The investigator must ensure that all additional relevant information that becomes available is also forwarded to the sponsor immediately after the initial notification.

The investigator shall transmit to the sponsor all relevant supporting documents related to the SAE (i.e., copy of laboratory exams, hospitalization reports indicating the SAE) ensuring anonymization of the documents and indicating the identification number of the subject in the trial

The investigator will report to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports. Device malfunctions and use errors should also be reported without unjustified delay.

All Serious Adverse Events including all device deficiencies should be reported to the Sponsor within **24 hours** of awareness of an event via the Adverse Event electronic Case Report Form in the study's electronic database, as that will trigger an immediate e-notification to the Sponsor and CRO.

The investigator will document all AEs on the Adverse Event Form, including (at a minimum) a description of the event, date of onset, severity, relationship to the investigational device and/or procedure, required interventions, duration, and outcome. The investigator will monitor all AEs until they are resolved, determined to be a chronic condition or the subject is lost to follow-up. The investigator will report all AEs regardless of whether it is anticipated or unanticipated and regardless of classification, seriousness, intensity, outcome or causality.

8.5. Reporting to Ethic Committee / Competent Authority

Depending on the local requirements or following agreement between both parties, the sponsor or the principal investigator will be responsible for performing safety reporting to the Ethics Committee according to the relevant local regulatory requirements.

The sponsor will be responsible for reporting to the National Competent Authority according to national requirements and in line with MEDDEV 2.7/3 and/or MEDDEV 2.12-1, as applicable.

9. STUDY COMMITTEES

9.1. Data Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board (DSMB) is a group of independent professionals, experienced in clinical care and clinical research, assembled to provide additional safety oversight to the clinical study. The DSMB will include three members with at least one medical oncologist and two surgeons experienced in diagnosing and treating ovarian cancer.

The DSMB will review study data from all patients after the first five (5) enrolled patients have reached the 1-month time point. The DSMB will then meet face-to-face or by web-assisted conferencing semi-annually until all patients are enrolled, and annually thereafter. The recommendations of the DSMB will guide continuation of enrollment during the enrollment phase of the study, as well as continuation of the study once enrollment is done. Each meeting will be documented in minutes and reported directly to M-Trap. The DSMB Charter further describes the composition and activity of the DSMB.

10. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

10.1. Sample Size Determination

The primary objective is to demonstrate that the safety of M-Trap, as measured by freedom from device- and procedure-related major adverse events (see Primary Endpoint for definition) through 6-months post-implantation, is non-inferior to historical controls. Using a success rate of 90% (freedom from device- and procedure-related major adverse events), a non-inferiority margin of 25%, >85% power, and one-sided alpha=0.05, a sample size of n=20 patients is needed to demonstrate that M-Trap is as safe as current standard-of-care through 6-months post-surgery. Assuming a 10% dropout rate, up to 22 patients will be treated to have 20 evaluable patients.

10.2. Analysis Sets

In this study two analysis sets will be defined.

- The Intent-to-Treat (ITT) population will comprise all subjects who signed their informed consent, have been judged suitable for index procedure and are compliant with all inclusion/exclusion criteria.
- The As-Treated population will comprise all subjects from the ITT population implanted with at least one (1) M-Trap device.

10.3. Analysis Methods

The number of patients in all study populations, as well as the distribution by site will be presented. The reasons for interruption of patient follow-up will be listed and the average time of patient follow-up will be given. Descriptive statistical data will be used to summarize the characteristics of subjects at the time of inclusion (demographics, baseline and procedure data).

Quantitative parameters will be described using the following summary descriptive statistics at each time point: number of non-missing values, mean, standard deviation, median, first and third quartiles, and minimum and maximum values. Qualitative parameters will be described overall using frequencies and percentages. Percentages will be calculated on the number of non-missing observations. In order to provide unbiased and informative findings, no replacement of missing values is planned for any parameters. In all applicable cases, reported analysis will mention the number of missing values for each outcome relatively to the considered analysis set.

Analysis of safety will be performed on the ITT population and the As-Treated population. The primary safety endpoint will be analyzed using a unilateral one sample test for binomial proportion at the 5% level. In addition, the exact bilateral 95% confidence interval will also be given. The statistical test for the primary safety endpoint is given by:

- H0: M-Trap freedom MAE incidence <= 90% - Non inferiority margin (25%) Versus
- HA: M-Trap freedom MAE incidence > 90% - Non inferiority margin (25%)

The primary performance endpoint is the percentage of recurrent patients with histological evidence of tumor cell capture in at least one M-Trap device. The secondary performance endpoints are the percentages of recurrent patients with disease focalization scores of: 1) I, 2) I or II, 3) I, II or III, and 4) I, II, III or IV. Analysis of performance will be performed on the As-Treated population. The primary performance and secondary endpoints will be assessed with exact one-sided 90% confidence intervals.

A medical coding will be done on the adverse events using the MedDRA dictionary. All adverse events (AEs) will be categorized by system organ class (SOC) and preferred term (PT). A complete description will be done: total number of AEs, device related AEs, serious AEs, device deficiencies, SADEs, USADEs, and number of subjects with at least one of the respective categories: AEs, SAEs, etc. The causality relationship will be presented for all AEs.

Data will be locked and summarized for each DSMB meeting. An interim analysis will be performed after all patients reach the 6-month time point to support the CE-marking application.

11. GENERAL STUDY CONSIDERATIONS

11.1. Ethical and Regulatory Considerations

The study will be performed in accordance with the standard EN ISO 14155 on clinical investigations with medical devices on human subjects and recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions.

The clinical investigational plan, informed consent, any other specific study documents and all amendments to these study documents will be reviewed and approved by the appropriate Ethics Committees (ECs) and Competent Authority/ies (CAs) before enrollment of any patient. In addition, the sponsor will keep the regulatory authorities informed of any SAEs throughout the study course.

11.2. Supplemental Applications - Amendments

As appropriate, the Sponsor will submit changes in the clinical investigational plan to Investigators to obtain EC re-approval to implement the changes.

11.3. Protocol Compliance

The investigator is required to conduct the study in accordance with the signed investigator agreement and the clinical protocol. The Principal Investigator shall immediately notify the Sponsor after significant deviation from the study plan, to protect the life or physical well-being of a subject in an emergency.

When specific tasks are delegated by the Principal Investigator, included but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

11.3.1. Protocol Violations

Protocol violations are defined as instances where the protocol requirements and/or regulatory guidelines were not followed and are generally more serious in nature. Protocol violations are considered to potentially affect the scientific soundness of the study and/or the rights, safety or welfare of subjects:

- Failure to obtain signed informed consent
- Unapproved (by sponsor and EC) investigator implanting the investigational device for the study purposes
- Subject inclusion/exclusion violations and protocol requirement violations that affect the primary endpoints of the study design

All protocol violations should be recorded by the Investigator in the appropriate page of the CRF, and documented by a Note to File by the investigator that can be filed in Site File.

Deviations will be reviewed and evaluated on an ongoing basis by the Sponsor and the Monitor. And, as necessary, appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) will be put into place by the Sponsor and/or designee.

11.3.2. Protocol Deviations

Protocol deviations are defined as instances where the protocol requirements are not followed in such a manner whereby data is unusable or unavailable. Protocol deviations are less serious in nature as long as they do not have an effect on the rights, safety or welfare of the study subject.

Protocol deviations include, but are not limited to:

- Examinations/test/assessment not performed within the allowed follow-up window
- Required data not obtained

The study site should report the protocol deviation on the applicable CRF page.

Both protocol deviations and violations will be reported in progress reports to CA and EC where applicable and within regulatory timelines.

11.4. Training

The Sponsor is responsible for providing site personnel with the information and training they need to conduct the study properly and in accordance with the training plan. Study-specific training and education is required for all site staff with roles in this trial. The Sponsor is responsible for maintaining documentation of attendance at each of the training sessions provided.

The Sponsor personnel will provide training and technical support to the Investigator and other health care personnel as needed during any procedures and testing required by the protocol. In addition, the Sponsor personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy.

11.5. Device Accountability

The investigational devices will be provided by the Sponsor to the clinical sites. This will occur only after the site has been initiated and all regulatory approvals as well as required documentation have been collected from the site.

The devices shall be securely maintained, controlled, and used only in this clinical study. Additionally, the study personnel must follow the instructions related to the storage of the devices as noted in the Instructions For Use (IFU). Device Accountability Logs will be provided to the sites and will be used to track subjects and device allocations during the study.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigating sites until return or disposal.

Records shall be kept at each study site to document the physical location and conditions of storage of all investigational devices. Sites must not dispose of any devices for any reason at the site unless instructed to do so by the Sponsor. Any device that is disposed of at the site must be recorded in the Device Accountability Log. The Principal Investigator must document the reasons for any discrepancy noted in device accountability.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include the following:

- Date of receipt
- Identification of each investigational device
- Expiry date, as applicable
- Date of use
- Subject identification
- Date on which the investigational device was returned/explanted from subject, if applicable
- Date of return of unused, expired, or malfunctioning investigational devices, if applicable

This accounting will be verified by the Sponsor or its designee during regular visits on site, and copy of the Device Accountability Logs will be made.

11.6. Data Handling and Record Keeping

11.6.1. Data Collection, Processing and Review

Subject data will be recorded in a limited access secure electronic data capture (EDC) system. The clinical database will reside on a production server hosted by [CRO] SAS. All changes made to the clinical data will be captured in an electronic audit trail and be available for review by the Sponsor or its representative. The software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate eCRFs in compliance with local regulations.

Manual and/or automatic queries will be created in the EDC system and will be issued to the center for appropriate response. Site staff will be responsible for resolving all queries in the database.

11.6.2. Data Retention

Sponsor and Investigator will maintain the clinical investigation documents for a minimal period of fifteen (15) years after the clinical investigation is completed, or longer depending on national requirements. They will take measures to prevent accidental or premature destruction of these documents and ensure these are filed in a secure place. Investigator or Sponsor may transfer custody of records to another person or party and document the transfer at the investigation site, or at the Sponsor's facility.

11.7. Monitoring

Monitoring will be performed during the study according to the monitoring plan to assess continued compliance with the protocol and applicable regulations. In addition, the monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Investigator/institution guarantees direct access to original source documents by the Sponsor, their designees, and appropriate regulatory authorities.

The study site may also be subject to a quality assurance audit by the Sponsor or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

11.8. Insurance

Subjects who participate in this study will be insured against study related injury.

The Sponsor has obtained clinical trial insurance with appropriate coverage for the continuation of the entire study.

11.9. Suspension or Termination

11.9.1. Premature Termination

The Sponsor reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

11.9.2. Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following:

- Under the direction of AEMPS, after review of the safety data collected on the first five (5) patients through 30 days.
- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of the Sponsor to suspend or discontinue development of the device.

11.9.3. Criteria for Suspending/Terminating a Study Site

The Sponsor reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all study devices and testing equipment, as applicable, will be returned to the Sponsor unless this action would jeopardize the rights, safety or well-being of the subjects. The EC and regulatory authorities, as applicable, should be notified. All subjects enrolled in the study at the site will continue to be followed per this protocol. The Principal Investigator at the site must make provision for these follow-up visits unless the Sponsor notifies the investigational center otherwise.

11.10. Publication Policy

Following completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Principal Investigator will be responsible for manuscript preparation and submission. The Sponsor shall be notified of any planned presentations or publications and shall have the opportunity to review any such materials. The Sponsor has final approval authority over all such issues.

Data, as well as any derivative works and intellectual property, arising from this clinical investigation are the exclusive property of the Sponsor. Data cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

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APPENDIX 1 M-TRAP DEVICE EXPLANT PROCESSING PROTOCOL

Please follow this processing protocol after receiving a tissue specimen containing an M-Trap device.

1. Take high-resolution, clear photographs of the gross specimen. Please, establish the block identification key in a copy of the picture. (see step 4).
2. Measure and record tissue dimensions (length, width and thickness).
3. Identify the side that faced outward into the peritoneal cavity (marked with a surgical suture thread (X)) (Fig 1).

   Fig 1:

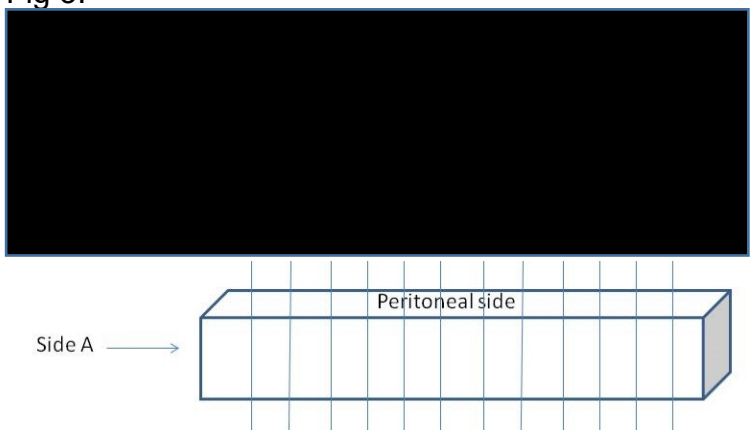
4. Paint with ink (Indian ink) the side that was sutured against the abdominal wall and the surgical resection margins (Fig 2).

   Fig 2:

5. Perform serial sectioning (10 sections of 0.3 cm) (the entire sample). For large samples (more than 3 cm width), include an additional cassette for each additional 1 cm of greatest dimension (Fig 3).

   Fig 3:

6. Prepare blocks facing the side identified as A (Fig 4A, 4B).

Fig 4A:

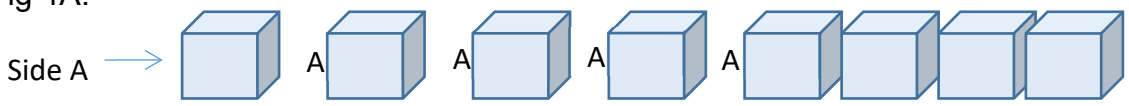
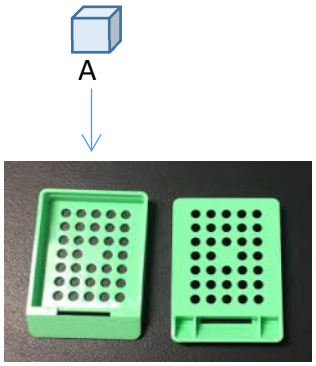


Fig 4B:



7. Label the blocks with site number, patient code, M-Trap device code and the block number, from left to right: 1, 2, 3, 4…10.
   a. Example: 03 01 A1, where 03 refers to the site number, 01 refers to the patient number, A refers to the M-Trap device code (*see below) and 1 refers to the first block.
      * A: Right paracolic gutter
        B: Left paracolic gutter
        C: Liver segment (VI)
8. Fix the tissue in neutral buffered formalin for 16-24h at room temperature.
9. Process the tissue and embedded in paraffin following the department's pathology protocols.
10. Stain sections with Hematoxilin-Eosin.
11. Send the paraffin blocks, along with all photographs and the measurements of the tissue specimens, to the reference laboratory.

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