STATISTICAL ANALYSIS PLAN

TRIAL FULL TITLE	HYbrid RObotic Surgery in Partial, Radical nephrectomy and Prostatectomy
Acronym	**HYROS-PRnP**
SPONSOR	Rob Surgical Systems S.L.
SAP PROTOCOL #	PL-PR01-119
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We the undersigned, certify that we read this SAP and approved it as adequate in the scope of the main analyses of the HYROS-PRnP clinical investigation

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Abbreviations and Definitions

AE: Adverse Event

BMI: Body Mass Index

CACS: Cumulative Analgesic Consumption Score

CCI: Comprehensive complication index

CIP: Clinical Investigation Plan

COPD: Chronic Obstructive Pulmonary Disease

CRA: Clinical Research Associate

EC: Ethics Comittee

eCRF: electronical Case Report Form

EHS: Erectile Hardness Score

ESE/NESE: electrosurgical and non-electrosurgical endoscopic instruments

HYROS-PRnP: HYbrid RObotic Surgery in Partial, Radical nephrectomy and Prostatectomy

IRB: Institutional Review Board

ITT: Intention-to-treat

LoS: Length of Stay

MIS: Minimally Invasive Surgery

MIRS: Minimally Invasive Robotic Surgery

PI: Principal Investigator

PN: Partial Nephrectomy

PP: Per protocol

PRAE: Procedure-Related Adverse Event

PSA: Prostate-specific antigen

RN: Radical Nephrectomy

RP: Radical Prostatectomy

SAE: Serious Adverse Event

SAP: Statistical Analysis Plan

VAS: Visual Analog Scale

1 PREFACE

This statistical analysis plan (SAP) describes the intended statistical analyses to be performed on data collected in the HYROS-PRnP study:

HYbrid RObotic Surgery in Partial, Radical nephrectomy and Prostatectomy (HYROS-PRnP)

The following documents were reviewed in the preparation of this SAP:

- Clinical Investigation Plan (CIP) Version PL-PR01-076_A2, 15-May-2024

The analyses described within this document relate to the main analyses to assess the medical devices under investigation in this study. If other analyses are performed, they will be documented separately. The SAP is intended to be a document that stands alone from the study protocol to which it will adhere in the main points of analysis. However, the SAP can undergo revision outside of the protocol.

2 AMENDMENTS FROM PREVIOUS VERSION (S)

Versions changes registry		
Versions	Dates	Changes
1	02 Jan 2024	Not Applicable

A2	19 Apr 2024	- Document has been added to QMS of the Sponsor with the following reference: PL-PR01-119_A2_Safety Analysis Plan.
		
		- In the whole document adding information when corresponding about:
		  - *"Camera Adapter"* as an accessory device required for the Bitrack System performance
		  - *"Lysis of Adhesions"* and *"Lymphadenectomy"* as part of the urological surgical procedures indicated for use of the Bitrack System, according to the IFU ES-PR01-156
		
		- At section 3: "Study Objective", the following clarification has been added: *"in a minimally invasive robotic hybrid surgery"*.
		- At section 4.1: "Overall study design", the following clarification has been added: *"An estimation of 150 measurements of performance of the Bitrack System with his accessory Camera Adapter and each ESE/NESE instrument and function during the surgical procedures performed in 15 patients"*

		- At section 4.3: "Intervention" a clarification about the concept of *"Hybrid Surgery"* has been included.
		
		- At section 4.4.2: "Secondary Endpoints" the following clarification has been added about the variable *"Length of Stay (LoS)": "a corrected LoS should be calculated: from day of intervention to discharge. Admission use to be 1 day before the surgery."*
		
		- At section 4.5.1 "Primary variables":
		  - the primary variable has been corrected according to the wording of the Clinical Investigation Plan: *"Occurrence of a Serious Adverse Event during the intervention, related to the use of the medical devices under investigation, when devices are all used according to the respective Instructions for use"*
		  - all the instruments have been listed for further detail.
		  - a clarification has been added about the simultaneous use of similar instruments that will be evaluated separately.
		  - a clarification about Hybrid Surgery has been added: *"Furthermore, since Bitrack System allows to perform Hybrid surgery, some of these steps could be done using MIS surgery instead of MIRS, without implying any kind of protocol deviation. As explained previously, Hybrid surgery is a new surgical approach that allows to combine the minimally invasive surgery (MIS) and minimally invasive robotic surgery (MIRS) in the same procedure and Bitrack System is the unique robotic platform that allows to move quickly from MIS to MIRS."*
		
		- At section 4.5.3:"Exploratory variables" the following information has been added to correct the last exploratory variable: *"Staff training effectiveness (times of: setup, draping and intervention) »*
		
		- At section 4.6: "Sample Size" the following sentence: *"The main performance hypothesis will be that verification units will be ≥ 3 **for each unit** of the Bitrack System"* has been modified for *"The main performance hypothesis will be that verification units will be ≥ 3 **for the** Bitrack System"* to clarify the section.

		- At section 6.2: "Final statistical analysis and reporting" the following clarification has been added: *"The analyses of the primary endpoints will be performed on the discharge of patient 15 (or any number equivalent to last patient in)"*; - At section 7.2: "General Statistical considerations" the following information has been added: *"Furthermore, this statistical approach will also be used to assess the performance specifically for each instrument, but also for any additional performance assessments (such as global score assessed for each surgery or performance score assessed by each surgical procedure or step, including lysis adhesions and lymphadenectomies)."* - At section 7.4 "Safety Analysis", a correction has been done changing ITT per PP in the following explanation: *"Safety analyses for the primary safety endpoint will be performed on the ITT cohort, as primary safety analysis, and on the PP cohort."* - At section 7.5: "Deviations from the CIP" the following sentences have been deleted: *"No waivers for CIP deviations will be granted by the Sponsor"* and *"Investigators will inform their EC or equivalent committee of all CIP deviations in accordance with their specific EC or equivalent committee reporting policies and procedures" to avoid possible confusion.* - At section 7.9: "Clinical variables collected": - *"Occurrence of Serious Adverse Events related to Bitrak System"* has been corrected to *"Occurrence of Serious Adverse Events related to devices under investigation (Y/N)"* - the sentence *"Only when applicable"* has been added to *"N. Lymph nodes resected (histopathology)"* - At section 7.10 "Analysis for the Primary Endpoints" The expression "As a whole " has been added in the following explanation: The main hypothesis, i.e. assessing if the performance score is higher or equal to 3, will be initially evaluated using a one-sample T-test (or

		Wilcoxon test as adequate) for the Bitrack System (as a whole) and the ESE/NESE instruments separately.
A3	31 May 2024	- At front page and preface updating CIP version to PL-PR01-076_A2, 15-May-2024 - At section 7.2 "General Statistical considerations", the sentence "Visual representations such as bar plots or histograms will be performed when adequate." has been added. - At 6.2 the obligatoriety to report post-hoc analisis in a separate statistical analysis report was removed. - At section 4.4.2 Secondary endpoinds the following definitions were changed to match those of CIP rev.A2 - For Length of Stay (LoS) in hospital:" calculated from day of admission" was corrected to "calculated from surgerydDay to homogenize with CIP rev A2. - "To evaluate post-operative pain in patients through the CAC8 during the first week (7 days) post-procedure" was corrected to "To evaluate post-operative pain in patients through the CACS postprocedure while the patient is hospitalized" - At 4.4.2 secondary endpoints are presented separately distinguishing between safety and performance. - At 7.2 the sentence "95% confidence intervals will also be provided" has been added.

Background

Laparoscopy is a surgical technique that allows surgical procedures to be performed while minimizing trauma to the body. These procedures require a small incision in the body, which permits the introduction of a laparoscopic-camera system to assist surgeons in performing the surgery[1,2]. Currently, new surgical tools are being developed to improve the effectiveness of laparoscopy[3]. Bitrack System is a tele-assisted surgical robot intended to assist in the accurate control of the exclusive Bitrack System-compatible range of ESE/NESE (electrosurgical and non-electrosurgical endoscopic) instruments. The Bitrack System is composed of a console, a robotic unit and embedded software. In addition, Bitrack System needs a Camera Adapter coupled to one of its robotics arms in order to perform a robotic surgery. The intended purpose of the camera adapter is to hold and sense the laparoscopic camera during MIRS (Minimally Invasive Robotic Surgery) interventions carried out by the Bitrack System for an accurate visualisation of the target anatomical area and precise control of surgical endoscopic instruments.

In this document, the statistical analysis plan associated to a clinical investigation, named HYbrid RObotic Surgery in Partial, Radical nephrectomy and Prostatectomy (HYROS-PRnP), that will assess the safety and performance of the Bitrack System along with ESE/NESE instruments and the Camera Adapter accessory in patients eligible for robotic assisted laparoscopic nephrectomy and prostatectomy, is presented.

HYROS-PRnP is an open label, single-center, non-randomized clinical investigation with a single arm. HYROS-PRnP is a confirmatory study having as objectives: (1) to evaluate the performance of the Bitrack system and its corresponding ESE/NESE instruments and the Camera Adapter accessory in patients with the clinical indication for a Radical Nephrectomy (RN), Partial Nephrectomy (PN) or Radical Prostatectomy (RP) along with lysis adhesions and lymphadenectomy when it applies and (2) to assess the safety of the Bitrack System also of the ESE/NESE instruments. The hypothesis is that Bitrack System with Camera Adapter coupled using the ESE/NESE instrument performs as intended by the surgeon *(performance score scale ≥ 3)* during the intervention without causing any particular Serious Adverse Event (SAE) related to the use of medical devices under investigation. A total of 15 patients will be included in the clinical investigation, selecting those eligible for robotic assisted laparoscopic RN, PN or RP procedures and when it applies for Lysis of adhesions during a PN, RN or Prostatectomy, to cut the adhesion and gain access to the organ. During a Prostatectomy when it applies a Lymphadenectomy could also be performed after the prostatectomy with the aim to surgically remove the lymph nodes. *The expected duration of the subject's participation is 30 days post-procedure for the three indications under evaluation, and the expected duration of the whole trial is four months (3 months of enrolment plus 1 month of follow-up).*

3 STUDY OBJECTIVE

The purpose of this clinical investigation is to evaluate the safety and performance of the Bitrack System, its corresponding ESE and NESE instruments and the Camera Adapter accessory in a minimally invasive robotic hybrid surgery patients with the indication of a robot assisted laparoscopic Radical/simple nephrectomy (RN), Partial nephrectomy (PN) or Radical Prostatectomy (RP) and also lysis adhesions and lymphadenectomy , as applicable.

4 STUDY METHODS

4.1 Overall study design

HYROS-PRnP is an open label, single-center non-randomized confirmatory clinical investigation with a single arm. A total of 15 patients between 18 and 90 years will be included. The clinical investigation will be conducted at the *Hospital Clinic de Barcelona* (Barcelona, Spain).

4.2 Selection of study population

4.2.1 Inclusion criteria

Subjects who meet all the following criteria will be considered to be included in this clinical investigation:

1. Adult subjects between 18 and 90 years old who have provided written informed consent before any clinical investigation-related procedure.
2. Subjects who have been scheduled for a laparoscopic Radical Nephrectomy, Partial Nephrectomy or Radical Prostatectomy.
3. Ability and willingness to comply with all study requirements to be evaluated for each study visit.

4.2.2 Exclusion criteria

Subjects who meet at least one of the following criteria will be excluded from this clinical investigation:

1. Pregnant or breastfeeding women at the time of the surgery
2. Subjects with severe concomitant illness that, at PI´s discretion, increases risk of therapeutic interventions or that have been submitted to multiple prior surgeries.
3. Subjects admitted to the hospital due to an emergency situation.
4. Subjects with untreated active infection
5. Subject with known allergy to some of the device components (i.e., stainless steel, etc.)
6. Subjects not suitable to undergo MIS/MIRS, according to medical criteria.
7. Subjects with a life expectancy inferior to 3 months
8. Subjects with a BMI ≥ 40
9. Subjects with any contraindication for the use of the Bitrack System and the ESE/NESE instruments, as specified in the Instructions For Use
10. Subjects with abuses of active substances or with uncontrolled psychiatric disorders
11. Subjects with severe cardiopulmonary or coronary artery disease, bleeding disorders or that have been submitted to multiple prior operations.
12. Subjects scheduled for surgeries intended to be in direct contact with the heart, the central circulatory system or the central nervous system.
13. Inability to adhere to study-related procedures.
14. Subjects who participate in another trial which may affect the outcome data on this study or the ability to complete the follow-up requirements.

4.3 Intervention

Radical nephrectomy, partial nephrectomy and radical prostatectomy with minimally invasive robotic surgery using the Bitrack System along with the accessory Camera Adapter and its corresponding ESE/NESE instruments. Under the scope of these three procedures, lysis of adhesions or a lymphadenectomy (after a prostatectomy) can also be performed during the surgical procedure when applicable.

In addition, all these procedures could be performed in the context of an Hybrid surgery. This is a new surgical approach that allows to combine the minimally invasive surgery (MIS) and minimally invasive robotic surgery (MIRS) in the same procedure. There is not state of the art about this new surgical approach since Bitrack System is the unique robotic platform that allows to move quickly from MIS to MIRS.

4.4 Study endpoints

4.4.1 Primary endpoint

The primary performance and safety endpoints of this clinical investigation are (1) the performance of the Bitrack System to assist in the accurate control of its compatible ESE/NESE instrument as assessed by the surgeon and (2) the occurrence of any particular SAE related to the use of the medical devices under investigation.

For the performance evaluation, the surgeon will determine the adequacy of the Bitrack System (in which already has been coupled camera adapter) using a 1 to 5 Likert scale. The Surgeon Performance Scale Score has been designed to evaluate the performance of the Bitrack System in each surgery as a whole procedure but also specifically for each ESE/NESE instrument in all the steps defined for each surgery. The score ranges of the Surgeon Performance Scale Score have been defined as:

1. Failure: If the "Bitrack System" or "ESE/NESE instruments" evaluated do not perform the intended function.
2. Unacceptable: If the "Bitrack System" or "ESE/NESE instruments" evaluated perform the intended function with too much difficulty.
3. Satisfactory[1]: If the "Bitrack System" or "ESE/NESE instruments" evaluated perform the intended function with some effort and some repetition.
4. Good[2]: If the "Bitrack System" or "ESE/NESE instruments" evaluated perform the intended function easily.
5. Excellent[3]: If the "Bitrack System" or "ESE/NESE instruments" evaluated perform the intended function comfortably.

This clinical investigation hypothesizes that the average performance score will be ≥ 3, defining this threshold as an acceptance criterion. In addition, these criteria will only be accepted if the use of the Bitrack System (containing all auxiliary devices and accessories) does not cause any particular SAE related to the use of the medical devices under investigation to any of the patients included in the trial. The occurrence of SAEs will be assessed during the procedure, at discharge, at 14 days follow-up and at 30 days follow-up.

[1] Satisfactory also means Acceptable.
[2] Good: that it means to performs its intended function without effort.
[3] Excellent: that it means to performs its intended function easily.

4.4.2 *Secondary Endpoints*

The secondary performance and safety endpoints of this clinical investigation for the three indications are:

1) Safety secondary endpoints:

- Assessment of the surgical success rate, defined as a procedure completed without conversion to open surgeries and without re-operations due to intraoperative complications during the hospitalization.
- Evaluation of the safety of the Bitrack System (as a whole system) by measuring the occurrence of Procedure-Related Adverse Events (PRAEs) and Serious Adverse Events (SAEs) during the procedure and through the 30 days post-procedure period of enrolled patients indicated for robot-assisted laparoscopic Radical Nephrectomy, Partial nephrectomy and Radical Prostatectomy.
- Assessment of all Adverse Events (AEs) analyzing the number of subjects reporting an AE and the frequency of each AE reported. Relationship with the investigational device and or procedure will be examined by the principal investigator and reported to Rob Surgical. The timeframe period for this Advetse Events AE(s) assessment will be during the procedure, discharge, 14 days and through the 30 days post-procedure for the three indications.
- Blood Loss defined as estimated mL of blood loss, transfusion rates and use of hemostasis agents during the surgery.
- Post-procedure complication rates.
- Comprehensive complication index (CCI, on a scale from 0/no complications to 100/death).
- Clavien-Dindo classification (7 grades, I, II, IIIa, IIIb, Iva, Ivb and V, the first one indicating any deviation from the normal postoperative course, the highest grade indicating death at discharge and 30-day follow-up).

2) Performance secondary endpoints:

- Procedure Times per each surgery and type measurement for the different tasks/steps from room setting through the surgical procedure until postoperative room restoration.
  - Set up for surgery, Initiation time, Draping, Coupling and Docking.
  - Operative Time, critical manoeuvres and total time.
  - System withdrawn times, Undocking, uncoupling and Undraping time in minutes.

- Length of Stay (LoS) in the hospital calculated from surgery day to discharge day.
- Patient pain assessment via VAS at Discharge, 14 and 30 days post-procedure Patient survey.
- Post-operative pain in patients through the Cumulative Analgesic Consumption Score (CACS) post-procedure while the patient is hospitalized.

In addition, for Partial Nephrectomy:

- Warm ischemic time (period in which the kidney has no blood supply)
- Positive surgical margins after surgery collected at 30 days.

In addition, for Radical Prostatectomy

- PSA test
- N. Lymph nodes resected (histopathology)
- Positive surgical margins after surgery collected at 30 days

4.5 Variables

4.5.1 Primary variables

- Surgeon Performance Scale Score (Likert scale from 1 to 5: 1-Failure/2-Unaceptable/3-Satisfactory/ 4-Good / 5-Excellent)
- Occurrence of a Serious Adverse Event during the intervention related to the use of the medical devices under investigation, when devices are all used according to the respective Instructions for use.

The Surgeon Performance scale will be assessed by the surgeon, assessing the Bitrack System with the Camera Adapter coupled in each surgery (1) as a whole procedure but also, more specifically, (2) at the different surgical procedure steps, separately for each ESE/NESE instrument used, within each intervention. The performance scale will be assessed using the categories as described below.

	5	Excellent	Perform the intended function comfortably.
	4	Good	Perform the intended function easily
	3	Satisfactory	Perform the intended function with some effort and some repetition.
	2	Unacceptable	Perform the intended function with too much difficulty
	1	Failure	Does not perform the intended function

(1) About the global assessment, the global performance evaluation of the Bitrack System will be assessed in the following 9 items separately.

1. *Ability to reach the target zone.* Easy to reach intended trocar setting (1 to 5)
2. *Ability to reach the target zone.* Feasibility to reach the surgical target zone (1 to 5)
3. *Ability to reach the target zone.* Feasibility to access to the patient by table patient surgeon (1 to 5)
4. *Ability to perform all relevant surgical tasks.* Feasibility to perform intended surgery (1 to 5)

5) *Ability to perform all relevant surgical tasks.* Feasibility to precisely wrist the ESE/NESE instruments (1 to 5)
6) *Ability to perform all relevant surgical tasks.* Feasibility of conversion between operation modes during the surgery (if applicable) (1 to 5)
7) *Console unit.* Movement of manipulators (1 to 5)
8) *Console unit.* Finger grip grasping and movement (1 to 5)
9) *Ability to withdrawal system / instruments efficiently.* Easy to undock and uncouple the ESE/NESE instruments (1 to 5)

A **global score** averaging all 9 items for each surgery will be computed and considered as the main endpoint for assessing the global performance of the Bitrack System on a scale from 1 to 5. Therefore, this averaged score assumes the same weights for all items considered.

(2) About the specific assessment, each of the following ESE/NESE instruments (, Hook, Monopolar Round scissors and Bipolar Maryland Forceps, Forceps, microforceps) will be specifically assessed (i) in each surgery procedure step and (ii) at each specific intended purpose of the surgery separately each time they are used within the intervention. (Note that in cases where two similar instrument can be used simultaneously- each instrument will be evaluated separately).

The different procedure steps that can be used by type of surgery and different laparoscopic intended purposes assigned to each ESE/NESE instrument are described in the tables below.

Procedure steps by surgical indication		
Radical Nephrectomy	*Partial Nephrectomy*	*Radical Prostatectomy*
1. Liberation of the colon *2. Identification of the ureter* *3. Liberation of the upper renal pole* *4. Luxation of the lower pole* *5. Dissection of the renal vein* *6. Dissection of the renal artery dissection* *7. Section of the vascular pedicle* *8. Liberation of the parenchyma* *9. Removal of kidney into a laparoscopic retrieval bag*	*1. Liberation of the colon* *2. Identification of the ureter and liberation of the lower pole* *3. Liberation of the upper renal pole* *4. Dissection of the vascular pedicle* *5. Liberation of the renal parenchyma, identification of the renal tumor and placing the kidney in adequate position for tumor resection* *6. Clamping of the renal artery* *7. Tumor resection*	*1. Identification and exposure of Prostate* *2. Separation of the vesico-prostate plane until the identification of the seminal vessels* *3. Dissection of the seminal vessels* *4. Section of the proximal prostatic vascular pedicle* *5. Liberation of the posterior aspect of the prostate* *6. Liberation of the lateral aspects of the prostate*

10. Checking of haemostasia of the surgical bed (surgical area)	8. Suture of the surgical bed of the kidney. 9. Removal of the clamp and checking of haemostasia 10. Removal of the tumor using an endobag	(neurovascular bundle preservation if indicated) 7. Liberation of the anterior aspect of the prostate (section of puboprostatic ligaments and vein plexus) 8. Section of the urethra and haemostasia check 9. Vesicourethral anastomosis 10. Removal of the prostate using an endoscopic bag and final checking of the surgical result.

It should be taken into account that in the first step of each surgery, the surgeon could need to perform a "Lysis of adhesion" if the patient had undergone a previous surgery adhesions around the intra-abdominal space can occurred surrounding the colon and/or any other abdominal organ, blocking the access to the surgical target.

In addition, at the end of a Radical Prostatectomy, a lymphadenectomy could be also performed. It is an often surgical procedure used to assess and potentially remove nearby lymph nodes in the pelvic region. This is done to determine whether prostate cancer has spread beyond the prostate gland.

Furthermore, since Bitrack System allows to perform Hybrid surgery, some of these steps could be done using MIS surgery instead of MIRS, without implying any kind of protocol deviation. As explained previously, Hybrid surgery is a new surgical approach that allows to combine the minimally invasive surgery (MIS) and minimally invasive robotic surgery (MIRS) in the same procedure and Bitrack System is the unique robotic platform that allows to move quickly from MIS to MIRS.

Therefore, the performance surgeon score (1 to 5) will be observed for each of the three indications (RN, PN and RP) and also, when it applies, for the lysis of adhesions and lymphadenectomy, then for each of the steps according to the indication, and then for each of the ESE/NESE instruments used according to the step and intended purpose. Thus, the variable will be observed within each surgery in a repeated measures framework considering 10 steps × 3-5 instruments × 3-5 intended purposes in a nested experimental design.

Instrument	Intended purpose	Score	Comments

							If "≤2": provide an explanation
Monopolar Round Scissors	Mechanical cutting	1	2	3	4	5	
	Electrical cutting	1	2	3	4	5	
	Blunt dissection	1	2	3	4	5	
	Coagulation	1	2	3	4	5	
	Manipulation of tissue	1	2	3	4	5	
Bipolar Maryland Forceps	Grasping	1	2	3	4	5	
	Coagulation	1	2	3	4	5	
	Manipulation of tissue	1	2	3	4	5	
Forceps	Grasping	1	2	3	4	5	
	Ligation	1	2	3	4	5	
	Suturing	1	2	3	4	5	
	Manipulation of tissue	1	2	3	4	5	
Microforceps	Grasping	1	2	3	4	5	
	Ligation	1	2	3	4	5	
	Suturing	1	2	3	4	5	
	Manipulation of tissue	1	2	3	4	5	
Monopolar hook	Electrical cutting	1	2	3	4	5	
	Blunt dissection	1	2	3	4	5	

	Coagulation	1	2	3	4	5	
	Manipulation of tissue	1	2	3	4	5	

4.5.2 Secondary variables

- Surgical success (procedure completed without conversion to open surgeries and without re-operations due to intraoperative complications during the hospitalization).
- Occurrence of Procedure-Related Adverse Events (PRAEs) during the procedure, discharge and through the 14 and 30 days post-procedure
- Occurrence of Serious Adverse Events (SAEs) during the procedure, discharge and through the 14 and 30 days post-procedure
- Occurrence of Adverse Events (AEs) during the procedure, discharge and through the 14 and 30 days post-procedure
- Blood Loss (mL), transfusion rates and use of hemostasis agents during the surgery
- Procedure Times per each surgery and type measurement for the different tasks: Set up for surgery: Initiation time, Draping, Coupling and Docking.
- Operative Time: critical manoeuvres, including warm ischemic time for partial nephrectomy, and total time.
- System withdrawn times: Undocking, uncoupling and Undraping time in minutes
- Length of Stay (LoS) in the hospital calculated from the day of admission to discharge day.
- Patient pain assessment via VAS at Discharge, 14 and 30 days post-procedure Patient survey.
- Cumulative Analgesic Consumption Score (CACS) during the first week (7 days) post-procedure (as opportune, the average consumption per day will also be computed).
-
- Post-procedure complication rates
  - Comprehensive complication index (CCI) on a scale from 0 (no complications) to 100 (death)
  - Clavien-Dindo classification, consisting of 7 grades (I, II, IIIa, IIIb, Iva, Ivb and V), the first one indicating any deviation from the normal postoperative course, the highest grade indicating death at discharge and 30-day follow-up.

4.5.3 Exploratory variables

- Indication (RP, NP or RP and when it applies lysis adhesions and lymphadenectomy).

- Sex (Male/Female)
- Age (years)
- Weight (kg), Height (cm) and BMI (kg/m2)
- Medical history (previous diagnosis)
- 0, 14, 30 days monitoring (trends)
- Staff training effectiveness(times of : setup, draping and intervention)

4.6 Sample size

To evaluate the performance of the Bitrack System, and also the ESE/NESE instruments and Camera Adapter, in surgical interventions (PN,RN and RP) the scores measuring the specific performance (as verification units from 1-failure to 5-excellent as assessed by the surgeon) will be considered. The main performance hypothesis will be that verification units will be ≥ 3 for the Bitrack System during the intervention without causing any particular device-related SAE, which will be considered to be the acceptance criteria.

A previous investigation with animals showed that the performance of each ESE/NESE instrument was significantly equal to or higher than 3 in verification units. It should be noticed that, in terms of statistical units, verification is undergone several times within each intervention ranging from 0 to an undetermined number of times, therefore repeated measures were considered within each individual. Results from this previous analysis showed that an average of 9.89 (rounded to 10) measurements in each intervention were observed.

The inclusion of 15 subjects, leading to the measurement of the performance scores a total of 150 times (assuming that 10 measurements will be undergone in each intervention, as previously described), will be enough to ensure 90% of statistical power to assess the acceptance criteria (verification units ≥ 3; Ho=2.5 vs H1=3), using for this purpose a one-sided t-test with alpha=0.05 and Cohen's d=0.25 (mu0=2.5, mu1=3 and standard deviation=2, i.e. d=(3-2.5)/2). The exact required sample size is 138.38 which will be increased up to 150 to consider the potential attrition (11 additional measurements, 7.3%). Analysis will be made on the PP population, as stated in the CIP. Indeed, patients in the PP population correspond to those that have completed the surgical procedure with the Bitrack System without any major protocol deviation.

5 RANDOMIZATION

No randomization will be undergone in this clinical investigation. Patients satisfying the inclusion criteria will be recruited on a first-patient-in basis.

6 SEQUENCE OF PLANNED ANALYSES

6.1 Interim analyses

No interim analyses are planned.

6.2 Final statistical analysis and reporting

The analyses of the primary endpoints will be performed on the discharge of patient 15 (or any number equivalent to last patient in).

Secondary endpoints and exploratory variables will be performed once the 30-day follow-up is achieved for all patients recruited, using the PP population. At this moment, a review will be conducted, and final changes will be eventually made to this SAP. The final analysis will be conducted hereafter.

Any post-hoc, exploratory analyses which are not identified in this SAP will be labelled explicitly as such. Any further future analyses not specified in the analysis protocol will be considered exploratory.

7 STATISTICAL ANALYSIS

7.1 Analysis software

All analyses will be performed using the software R V4.0.1 or later versions for the final analyses.

7.2 General statistical considerations

Continuous variables will be summarized using descriptive statistics including mean and standard deviation if normally distributed or median and interquartile range for skewed distributions; minimum and maximum values, and quantiles will also be considered. Categorical variables will be summarized using absolute frequencies and relative percentages. Percentages given in these tables will be rounded, and therefore, may not always sum to 100%. Percentages will be calculated using non-missing data as the denominator. If applicable, the number of patients with missing information for a specific variable will be displayed. All variables (primary endpoints, secondary endpoints and exploratory variables) will be summarized using these univariate descriptive statistics. Visual representations such as bar plots or histograms will be performed when adequate.

To assess the main performance of Bitrack System with the Camera Adapter coupled and each ESE/NESE instrument, T-tests (and Wilcoxon test as adequate) will be undergone to evaluate whether the performance is higher than 3 in terms of verification units. Heat maps showing the raw data to visually assess whether the performance is higher than 3 (using a scale colour from red to yellow and green) will be additionally developed. Chi-square tests (and Binomial exact test as adequate) for one proportion will also be used to assess the remaining performance but also the safety endpoints. 95% confidence intervals will also be provided. In addition, generalized mixed linear models will also be used to adjust for the within-individual variability, taking into account the nested structure of repeated measures (steps within indication × laparoscopic instrument × function). Furthermore, this statistical approach will also be used to assess the performance specifically for each instrument, but also for any additional performance assessments (such as global score assessed for each surgery or performance score assessed by each surgical procedure or step, including lysis adhesions and lymphadenectomies). The occurrence of any SAEs, PRAEs

and AEs will be reported with their absolute frequency. All analyses will be made using the statistical program R, setting the threshold for significance at α=0.05.

7.3 Population under analysis

The following analysis sets are defined:

- The intention-to-treat population (ITT) will include all adult humans eligible for a laparoscopic RN, PN or RP surgery using Bitrack System and its sterile endoscopic ESE/NESE instruments medical devices, in whom treatment using the device under investigation is attempted but not achieved.

- The per-protocol population (PP) will include all subjects who fulfil the inclusion criteria, do not meet any exclusion criteria, have signed the informed consent form (ICF), and have undergone a robotically assisted RN, PN or RP using Bitrack System medical device and corresponding ESE/NESE instruments.

- Performance analysis set: all analyses for the primary and secondary efficacy endpoints will be performed on the PP population. As a secondary analysis, this will be repeated in the ITT population to support the primary results.

- Safety analysis set: analysis of the primary and secondary safety endpoints will be performed on the ITT population. As a secondary analysis, this will be repeated in the PP population to support the primary results.

Demographic and baseline characteristics will be summarized for PP and ITT populations.

7.4 Methods for missing data and outliers

As anticipated in the clinical investigation plan (CIP) , the amount of missing data will be minimal in the present study and only expected for secondary variables. No imputation methods will be used, and missing data will be only reported in terms of statistical description.

Outliers will be queried during data collection and statistical analysis. Unless confirmed as data entry errors, outliers will not be excluded from the analysis.

7.5 Deviations from CIP

Participants with a major clinical investigation plan deviation will be excluded from PP analysis and only considered within ITT populations.

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing.

All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of CIP deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, Sponsor may terminate the investigator's participation in the clinical investigation.

7.6 Data transformations

No data transformations are planned.

7.7 Data Quality Assurance

All entries in the electronic case report form (eCRF) will be stored in a database. The structure of the database is based on the division into sections and entry fields defined in the eCRF. To improve and ensure data quality, data checks will be performed automatically in the eCRF directly on electronic entry at the study site and manually by the monitory data management team.

Plausible value ranges for numerical data entries and logical data and list entries will be filled in the eCRF. The tests for consistency and completeness based on this will be performed during entry in the eCRF. The validity of the recorded data will therefore be ensured by the validations incorporated in the documentation system, which highlight incorrect or implausible entries to the data entry responsible if corrections are necessary after the data are saved, these will be documented in an audit trail.

A quality assurance audit/inspection of this study may be conducted by the study's designees or by the Institutional Review Board (IRB)s/Ethics Committee (EC)s or regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

All tables, figures and data listings to be included in the report will be checked for consistency, integrity and in accordance with standard procedures for analysis and reporting.

7.8 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IRB / EC review and regulatory inspection, providing direct access to all related source data/documents. Electronic medical records and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the clinical study monitor, auditor and inspection by health authorities The clinical research associate (CRA)/on-site monitor and auditor may review all eCRFs, and written informed consents (if applicable).

7.9 Clinical variables collected

All clinical variables that will be collected (at baseline visit, in hospital and during follow-up) are listed below:

1. Baseline visit variables:

- Intervention (RN/PN/RP) + Lysis adhesions and lymphadenectomy
- Age (years)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Medical history
  - Cardiovascular history (Y/N)
    - Ischemic heart disease (Y/N)
    - Hypertension (Y/N)
    - Stroke (Y/N)
    - Coronary artery disease (Y/N)
    - Peripheral vascular disease (Y/N)
    - Other (text)
  - Bleeding disorder (Y/N
  - Coagulopathy (Y/N)
  - Hematologic Disease (Y/N)
  - Pulmonary disease (Y/N)
    - Lung fibrosis (Y/N)
    - Respiratory failure (Y/N)
    - Chronic obstructive pulmonary disease (COPD) (Y/N)
    - Asthma (Y/N)
    - Other (text)
  - Renal disease (Y/N)
  - Gastrointestinal disease (Y/N)
  - Hyperlipidemia (Y/N)

- Diabetes (Y/N)
- Connective tissue disorder (Y/N)
- Cancer (Y/N)
  - Gastrointestinal malignancies (text)
  - Other (text)
- History of allergy/hypersensitivity (text)
- Other relevant medical conditions (text)
- Urinary Incontinence (Y/N) *Only for Radical Prostatectomy*
- EHS (Erectile Hardness Score) (Y/N) *Only for Radical Prostatectomy*
- PSA (ng/ml) *Only for Radical Prostatectomy*

2. Procedure (in hospital) variables:

- Blood loss (ml)
- Need for blood transfusion (Y/N)
- Use of hemostasis agents (Y/N)
- Warm ischemic time (mm:ss) O*nly for Partial Nephrectomy*
- Total Operative Laparoscopy procedure time (mm:ss)
- Performance global score
- Global score assessing the performance of the Bitrack system (including camera adapter accessory) (1 to 5), corresponding to the average of the following 10 variables:

  1. *Ability to reach the target zone.* Easy to reach intended trocar setting (1 to 5)
  2. *Ability to reach the target zone.* Feasibility to reach the surgical target zone (1 to 5)
  3. *Ability to reach the target zone.* Feasibility to access to the patient by table patient surgeon (1 to 5)
  4. *Ability to perform all relevant surgical tasks.* Feasibility to perform intended surgery (1 to 5)
  5. *Ability to perform all relevant surgical tasks.* Feasibility to precisely wrist the ESE/NESE instruments (1 to 5)
  6. *Ability to perform all relevant surgical tasks.* Feasibility of conversion between operation modes during the surgery (if applicable) (1 to 5)
  7. *Console unit.* Movement of manipulators (1 to 5)
  8. *Console unit.* Finger grip grasping and movement (1 to 5)
  9. *Ability to withdrawal system / instruments efficiently.* Easy to undock and uncouple the ESE/NESE instruments (1 to 5)

- Performance Scale Score assessed on each ESE/NESE instrument and function:

  1. *Monopolar Round Scissors*. Mechanical cutting (1 to 5)
  2. *Monopolar Round Scissors.* Electrical cutting (1 to 5)
  3. *Monopolar Round Scissors.* Blunt dissection (1 to 5)
  4. *Monopolar Round Scissors.* Coagulation (1 to 5)
  5. *Monopolar Round Scissors.* Manipulation of tissue (1 to 5)
  6. *Bipolar Maryland Forceps*. Grasping (1 to 5)
  7. *Bipolar Maryland Forceps.* Coagulation (1 to 5)
  8. *Bipolar Maryland Forceps.* Manipulation of tissue (1 to 5)

9. *Forceps*. Grasping (1 to 5)
10. *Forceps*. Ligation (1 to 5)
11. *Forceps*. Suturing (1 to 5)
12. *Forceps*. Manipulation of tissue (1 to 5)
13. *Microforceps*. Grasping (1 to 5)
14. *Microforceps*. Ligation (1 to 5)
15. *Microforceps*. Suturing (1 to 5)
16. *Microforceps*. Manipulation of tissue (1 to 5)
17. *Monopolar hook*. Electrical cutting (1 to 5)
18. *Monopolar hook*. Blunt dissection (1 to 5)
19. *Monopolar hook*. Coagulation (1 to 5)
20. *Monopolar hook*. Manipulation of tissue (1 to 5)

- Occurrence of Adverse Events (Y/N)
- Occurrence of Serious Adverse Events (Y/N)
- Occurrence of Serious Adverse Events related to devices under investigation (Y/N)

3. Discharge (in hospital) variables:

- *WHO pain relief ladder(day 1, day 2 and day 3)*
- *CACS score (day 1, day 2 and day 3)*
- Pain level (VAS scale from 0 to 10)
- Comprehensive Complication Index, CCI (from 0 to 100)
- Clavien-Dindo classification (I, II, IIIa, IIIb, Iva, Ivb or V)
- Occurrence of Adverse Events (Y/N)
- Occurrence of Serious Adverse Events (Y/N)
- Occurrence of Serious Adverse Events related to devices under investigation (Y/N)

4. Follow-up visit (14 days) variables:

- *PSA (ng/ml) Only for Radical Prostatectomy*
- *Urinary Incontinence (Y/N) Only for Radical Prostatectomy*
- *EHS (Erectile Hardness Score) (Y/N) Only for Radical Prostatectomy*
- Pain level (VAS scale from 0 to 10)
- Comprehensive Complication Index, CCI (from 0 to 100)
- Clavien-Dindo classification (I, II, IIIa, IIIb, Iva, Ivb or V)
- Occurrence of Adverse Events (Y/N)
- Occurrence of Serious Adverse Events (Y/N)
- Occurrence of Serious Adverse Events related to the devices under investigation (Y/N)

5. Follow-up visit (30 days) variables:

- *PSA (ng/ml) Only for Radical Prostatectomy*
- *Urinary Incontinence (Y/N) Only for Radical Prostatectomy*

- *EHS (Erectile Hardness Score) (Y/N) Only for Radical Prostatectomy*
- Pain level (VAS scale from 0 to 10)
- Comprehensive Complication Index, CCI (from 0 to 100)
- Clavien-Dindo classification (I, II, IIIa, IIIb, Iva, Ivb or V)
- *Tumor margins (positive/negative) Only when applicable*
- *N. Lymph nodes resected (histopathology) Only when applicable*
- Occurrence of Adverse Events (Y/N)
- Occurrence of Serious Adverse Events (Y/N)
- Occurrence of Serious Adverse Events related to devices under investigation (Y/N)

7.10 Analysis of the primary endpoints

Performance score will be considered as a continuous variable, which will be summarized by computing mean (and standard deviation), median (and interquartile range), and minimum and maximum values (and quantiles). Performance scores will be described globally, for the Bitrack System (including camera adapter) and for the ESE/NESE instruments, but also specifically for each item assessed. In addition, several heatmaps showing the raw data will be produced to visually inspect the results obtained. Therefore, the performance score will be visualized using a scale colour from red to green (red, orange, yellow, light green and dark green corresponding to a performance score of 1 to 5, respectively). This representation will serve to visually inspect whether the performance is higher than 3, that is with a predominance of yellow and green colours and may describe, if any, particular patterns. Heatmaps will be used to describe the performance score globally on the Bitrack System but also for the ESE/NESE instruments. The main hypothesis, i.e. assessing if the performance score is higher or equal to 3, will be initially evaluated using a one-sample T-test (or Wilcoxon test as adequate) for the Bitrack System (as a whole) and the ESE/NESE instruments separately. Furthermore, mixed linear models accounting for the within-individual variability and nested repeated measures (steps within indication × laparoscopic instrument × intended purpose) will also be performed to assess the main hypothesis. Finally, statistical assessment will also be performed marginally for each item or ESE/NESE instrument. The threshold for statistical significance will be set at α=0.05, 95% confidence intervals will be produced, and statistical tests will be one-sided.

Occurrence of Serious Adverse Events related to the medical device during the surgical intervention will be considered as a dichotomous variable. Frequency, using absolute and relative values, will be used to describe it.

7.11 Analysis of the secondary endpoints

Blood loss, procedure times , operative time, system withdrawn time, LoS, pain assessed with VAS, CACS and CCI will be considered as continuous variables and described using mean and standard deviation if normally distributed or median and interquartile range for

skewed distributions, minimum and maximum values, and quantiles will also be considered. Clavien-Dindo will be considered as a categorical variable and absolute frequencies and relative percentages will be calculated for each of its 7 grades. Surgical success and other safety variables (AEs and SAEs at discharge, 14 and 30-day follow-up visits) will be considered as dichotomous variables and will be summarized using absolute frequencies and relative percentages. Statistical analysis will be eminently descriptive.

7.12 Analysis for exploratory variables and subgroup analysis

The remaining variables will be considered as exploratory and described as continuous or categorical as adequate. Bivariate analysis by intervention type (RN, PN and RP) will be considered and eventually explored, even though this is not the goal of this investigation. However, we assume that levels of efficacy and safety do not differ among the three surgical indications and, therefore, the presented study does not warrant statistical power to assess associations of efficacy/safety with indication.

7.13 Deviations from the Statistical Plan

In case of a deviation from the original statistical plan, the sponsor will be notified and a description will be added in the final study report.

7.14 Safety analysis

Safety analyses for the primary safety endpoint will be performed on the ITT cohort, as primary safety analysis, and on the PP cohort, as secondary safety analysis. Safety analyses for the secondary safety endpoints will be performed as well on the ITT cohort, as primary safety analysis, and on the PP cohort, as secondary safety analysis.

As specified in the CIP adverse event reporting will comply with worldwide standards and guidelines on clinical investigation adverse event reporting. An adverse event (AE) will be considered in case of 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 medical device under investigation. A Serious Adverse Avent (SAE) will be considered if, in addition, any of the following criteria are met:

a) Death

b) 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 hospitalization or prolongation of existing 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.

5. chronic disease

c) Fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

Any relationship between the occurrence of the AE or SAE and the medical device with be determined by the investigator. Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE or SAE is to be determined by the Investigator and recorded on the appropriate CRF form. Determination should be based on an assessment of temporal relationships, evidence of alternative aetiology, medical/biologic plausibility, and patient condition (pre-existing condition).

Several tables will be produced to describe the occurrence of AEs, SAEs and their relation will the medical device, described below.

7.14.1 Adverse event

Tables with the absolute frequency and percentage of adverse events (AEs) for all the patients in the study will be presented, reporting specifically those observed during the surgical procedure, at discharge or 14/30-day follow up visits and whether they were related to the medical device under investigation.

7.14.2 Serious adverse event

Tables with the absolute frequency and percentage of Serious Adverse Events (SAEs) for all the patients in the study will be presented, reporting specifically those observed during the surgical procedure, at discharge or 14/30-day follow-up visits and whether they were related to the medical device under investigation.

7.14.3 Deaths

If any, a by-subject list of deaths will be provided indicating the specific cause, time (during surgery, before discharge or during follow-up) and any other variable of clinical interest.

8 REFERENCES

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[2] Ahmed, I. & Paraskeva, P. A clinical review of single-incision laparoscopic surgery. Surgeon vol. 9 341–351 Preprint at https://doi.org/10.1016/j.surge.2011.06.003 (2011).

[3] Greaves, N. & Nicholson, J. Single incision laparoscopic surgery in general surgery: A review. Annals of the Royal College of Surgeons of England vol. 93 437–440 Preprint at https://doi.org/10.1308/003588411X590358 (2011).

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Divulgación de firma y Registro electrónicos: Aceptado: 04/06/2024 18:16:16 ID: 3892217d-7a8f-4136-9b4c-fda141481d0e		
Jaume Amat jaume.amat@robsurgical.com Nivel de seguridad: Correo electrónico, Autenticación de cuenta (ninguna)	DocuSigned by: 5105BC2EA4AB4DC... Adopción de firma: Dibujada en dispositivo Utilizando dirección IP: 217.150.213.160	Enviado: 04/06/2024 18:16:33 Visto: 05/06/2024 12:40:02 Firmado: 05/06/2024 12:40:10
Divulgación de firma y Registro electrónicos: Aceptado: 28/11/2023 13:31:42 ID: 0641cbeb-79f1-4795-85b5-6527bd69ba74		

Eventos de firmante en persona	Firma	Fecha y hora

Eventos de entrega al editor	Estado	Fecha y hora

Eventos de entrega al agente	Estado	Fecha y hora

Eventos de entrega al intermediario	Estado	Fecha y hora

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Eventos de copia de carbón	Estado	Fecha y hora
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Eventos del testigo	Firma	Fecha y hora

Eventos de notario	Firma	Fecha y hora

Resumen de eventos del sobre	Estado	Marcas de tiempo
Sobre enviado	Con hash/cifrado	04/06/2024 11:02:22
Certificado entregado	Seguridad comprobada	05/06/2024 12:40:02
Firma completada	Seguridad comprobada	05/06/2024 12:40:10
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