Title: Clinical Investigation Plan. HYROS (HYbrid RObotic Surgery in urology)		
Standards and applying chapters: **According to IF-PR01-022 Bitrack_Applicable Regulation and IF-PR01-023_A8 Bitrack Aplicable standards**		
Protocol Nr: **PL-PR01-027**	Revision Nr: **A2**	Date of issue: **04-OCT-2022**
Project Code: **PR01**		Author: **AKRN Scientific Consulting**

REVIEW HISTORY

Reviewed Edition	Date	Section	Rationale	List of Changes
A1	05-Sep-2022	NA	Initial document release	NA
A2	04-Oct-2022	NA	Response to EC comments	Update the version of CIP and date of issue
		4		[redacted]
		4.1		[redacted]
		7.1.1		[redacted]
		10.4.1		[redacted]
		13.1		[redacted]

SUMMARY OF CHANGES

Revision	Summary of Changes
1.0	Document release
2.0	Response to EC comments

CONTACT INFORMATION

SPONSOR AND LEGAL MANUFACTURER
Rob Surgical Systems, S.L.
Autovia de Castelldefels C-31 km 190.5, El Prat de Llobregat (Barcelona, Spain), 08820
[redacted]

Central CRO:
AKRN Scientific Consulting S.L.
[redacted]

SITE PRINCIPAL INVESTIGATOR:
Hospital Clinic de Barcelona
[redacted]

CLINICAL INVESTIGATION PLAN (CIP) SUMMARY

Version Number	2.0
Date	04-October-2022
Sponsor	Rob Surgical Systems, S.L. Autovia de Castelldefels C-31, km 190.5 El Prat de Llobregat (Barcelona, Spain), 08820
Clinical Investigation Identification	HYROS
Title	HYbrid RObotic Surgery in urology
Objectives	The purpose of this early feasibility clinical investigation is to evaluate the safety and feasibility of the Bitrack System and its corresponding ESE and NESE instruments [redacted] in patients with the indication of a robot assisted laparoscopic radical/simple nephrectomy. [redacted]
Device Under Investigation	Bitrack System along with its ESE/NESE instruments
Number of Subjects Required for Clinical Investigation	3 subjects shall be included in this early feasibility clinical investigation
Planned Number of Sites	1 investigational site located in Spain
Clinical Investigation Design	This is a single-center, early feasibility, and first in human (FIH) clinical investigation with a single arm, open label and non-randomized design
Primary Endpoints	The primary safety and performance endpoints of this early feasibility investigation are: 1) Evaluation of the safety of the Bitrack 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/simple nephrectomy. 2) Evaluation of the performance of the investigational devices by means of its ability to access and reach the target zone, perform all relevant surgical tasks and to be withdrawn efficiently without conversion to MIS or open surgery. The performance of the Bitrack System and the ESE/NESE instruments will be analyzed through the conversion rate to conventional laparoscopy/open surgery.

Secondary Endpoints	The secondary endpoints planned for this clinical investigation are listed below:
	• All AE(s) events during the procedure and through the 30 days post-procedure will also be assessed, and therefore relationship with the investigational device and/or procedure will be examined by the principal investigator and reported to Rob Surgical.
	  ○ Timeframe: Procedure, discharge, 14 days and 30 days follow-up
	• Individual safety (i.e., absence of unwanted injure of any tissue) and performance (VAS scale 0-10 following the subjective surgeon's opinion, being 0 a non-functional tool and 10 an instrument that works exactly equivalent to the surgeon/s hands) for each instrument surgical function.
	  ○ Timeframe: Procedure
	• Blood Loss defined as estimated mL of blood loss, transfusion rates and use of hemostasis agents.
	  ○ Timeframe: Procedure
	• Operative Time Procedure measurement for the different tasks.
	  ○ Timeframe: Procedure
	• To evaluate post-operative pain in patients through the Cumulative Analgesic Consumption Score (CACS) during the first week (7days) post-procedure.
	  ○ Timeframe: Discharge
	• To assess the duration of subject's hospitalization as the Length of Stay (LoS) in hospital calculated from day of admission to day of discharge.
	  ○ Timeframe: Discharge
	• Patient pain assessment via VAS. Patient interview questions.
	  ○ Timeframe: Discharge, 14- and 30-days post-procedure
	• Post-procedure complication rates, including the measurement of the comprehensive complication index (CCI) on a scale from 0 (no complications) to 100 (death), and the Clavien-Dindo classification, which consists 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.
	  ○ Timeframe: Discharge,14 and 30 days follow-up

Subject Follow-up	Subjects will have a 14-days in clinic visit and a 30-days post-procedure remote clinical follow-up visit
Inclusion Criteria	1. Adult subjects between 18 and 90 years old

	2. Subjects must provide written informed consent prior to any clinical investigation related procedure 3. Subjects who have been scheduled for a laparoscopic radical/simple nephrectomy surgery 4. Ability and willingness to comply with all study requirements to be evaluated for each study visit
Exclusion Criteria	1. Pregnant or breastfeeding women at the time of the surgery 2. Inability to adhere to study-related procedures 3. Subject has known allergy to some of the device components (i.e., stainless steel, etc.) 4. Subjects who participate in another trial which may affect the outcome data on this study or the ability to complete the follow up requirements 5. Subjects not suitable to undergo MIS/MIRS, according to medical criteria 6. Subjects with life expectancy inferior to 3 months 7. Subjects with a BMI ≥ 40. 8. Subjects with severe cardiopulmonary or coronary artery disease, bleeding disorders or that have been submitted to multiple prior operations. 9. Subjects with abuses of active substances or with uncontrolled psychiatric disorders. 10. Subjects scheduled for surgeries intended to be in direct contact with the heart, the central circulatory system or the central nervous system 11. Subjects with any contraindication for the use of the Bitrack System and the ESE/NESE instruments, as specified in the Instructions For Use
Electronic Data Capture	[redacted]
Expected Duration of the Study	[redacted]

INVESTIGATOR PROTOCOL SIGNATURE PAGE

[redacted]

[redacted]

Investigator Signature

04-Oct-2022

Date (DD-MMM-YYYY)

[redacted]

Investigator Printed Name

Investigator

Study Role

Hospital Clínic de Barcelona

Investigational Site Name

SPONSOR SIGNATURE PAGE

COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, ISO 14155:2020 standards, EU Regulation 2017/745 (MDR) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Ethics Committee (EC) of the respective clinical site and as specified by local regulations. Any additional requirement imposed by the EC will be followed.

CONFIDENTIALITY STATEMENT

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent Ethics Committees or Competent Authorities. The contents of this document shall not be disclosed to others without written authorization from the Sponsor unless it is necessary to obtain informed consent from potential study participants.

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[redacted]

[redacted]

1. INTRODUCTION

Laparoscopy is defined as 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 video-camera system to help the surgeons perform the surgery[1,2]. [redacted]

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 by a console, a robotic unit and an embedded software.

[redacted]

The primary objective of this clinical investigation is to evaluate the safety and performance of the Bitrack System in patients indicated with robotic assisted laparoscopic Radical/simple nephrectomy surgery. [redacted]

This clinical investigation is sponsored by Rob Surgical Systems (Barcelona, Spain) and will be conducted in accordance with this CIP. [redacted]

1.1. Background

Laparoscopic surgeries have become the gold standard for many surgical procedures as they allow minimally invasive surgery (MIS) to be performed, thus providing a benefit over an open procedure, including, among others, a reduction in post-operative pain, a decrease in the length of hospital stays, a faster return to daily activities and improved cosmesis, which increases patients' quality of life[4]. New surgical tools, such as the development of robotic-assisted surgery (RAS), have been designed to improve the effectiveness of the process, minimizing the ergonomic and visualization deficiencies of laparoscopy while preserving the advantages of minimally invasive surgery[3].

During minimally invasive robotic surgery (MIRS) procedures, the robots employed are not considered autonomous, [redacted] Nevertheless, decades of continued improvement [redacted] have significantly increased the potential for these robots to assist during minimally invasive surgeries[6].

[redacted] One of the main concerns for surgeons is the absence of haptic sensation; however, RAS permits fine and precise movements, as well as the elimination of tremor, which is argued to compensate the aforementioned disadvantage. Besides, the robotic platforms used in RAS offer the possibility to reduce ergonomic issues by providing a comfortable seating or neutral posture position, avoiding forced unnatural movements and delegating the torquing forces to the robotic arms, decreasing the burden on surgeon's muscles in the sensitive areas like the neck, shoulders, and upper back[7].

Medical application of laparoscopic procedures includes a wide range of surgical processes, among which the most frequent are gastrointestinal complications, bariatric and metabolic surgeries, and gynecological and

urological applications[3,4]. [redacted] The European Association of Urology indicates that robotic and laparoscopic procedures, such as prostatectomy and partial nephrectomy (RNP), are equivalent, [redacted] it has been also determined that the use of RAS may improve the precision of movements and reduce the risk of damage to the cavernous nerves to maintain erectile function by mechanical trauma, traction or thermal energy[8,9].

Bitrack System is a surgical robot indicated to be used during urological surgical procedures, general abdominal laparoscopic surgical procedures, and gynecological laparoscopic surgical procedures. This robot is intended to assist in the accurate control of endoscopic instruments and accessories for visualization and endoscopic manipulation. RAS systems and equipment such as Bitrack System are intended for use in invasive surgical procedures, during which patients are potentially most vulnerable to physical harm. [redacted]

[redacted]

[redacted]

1.3. Rationale for Conducting this Clinical Investigation

Traditional laparoscopic surgery has been associated with ergonomic issues due to prolonged operative times, unnatural body postures, and positioning of trocars. Robotic platforms have been introduced as an option to decrease some of these issues. Bitrack System is presented as an open robotic platform designed to improve efficiency with regards to current robotic systems, reducing limitations of conventional laparoscopy and robotic surgery while maintaining its advantages over the open approach. Additionally, enabling fine and precise movements of the surgical instruments results in accurate control of their corresponding endoscopic surgical instruments in case of urologic laparoscopic surgical procedures carried out by means of an abdominopelvic approach.

[redacted].

2. MEDICAL DEVICE OVERVIEW

[redacted]

2.1. Device Under Investigation

Bitrack System is an Open Robotic Platform designed to universalize high precision surgery and improve the efficiency on current robotics solutions.

Hybrid surgery is a new surgical approach that allows for combining minimally invasive surgery (MIS) and minimally invasive robotic surgery (MIRS) in the same procedure and to move quickly from MIS to MIRS.

[redacted]

Finally, in tele-assisted mode, through the console unit, the console user can take control of the system. The system reproduces the user maneuvers (position and orientation) from the console unit manipulators to the instrument end-effectors. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]
).

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

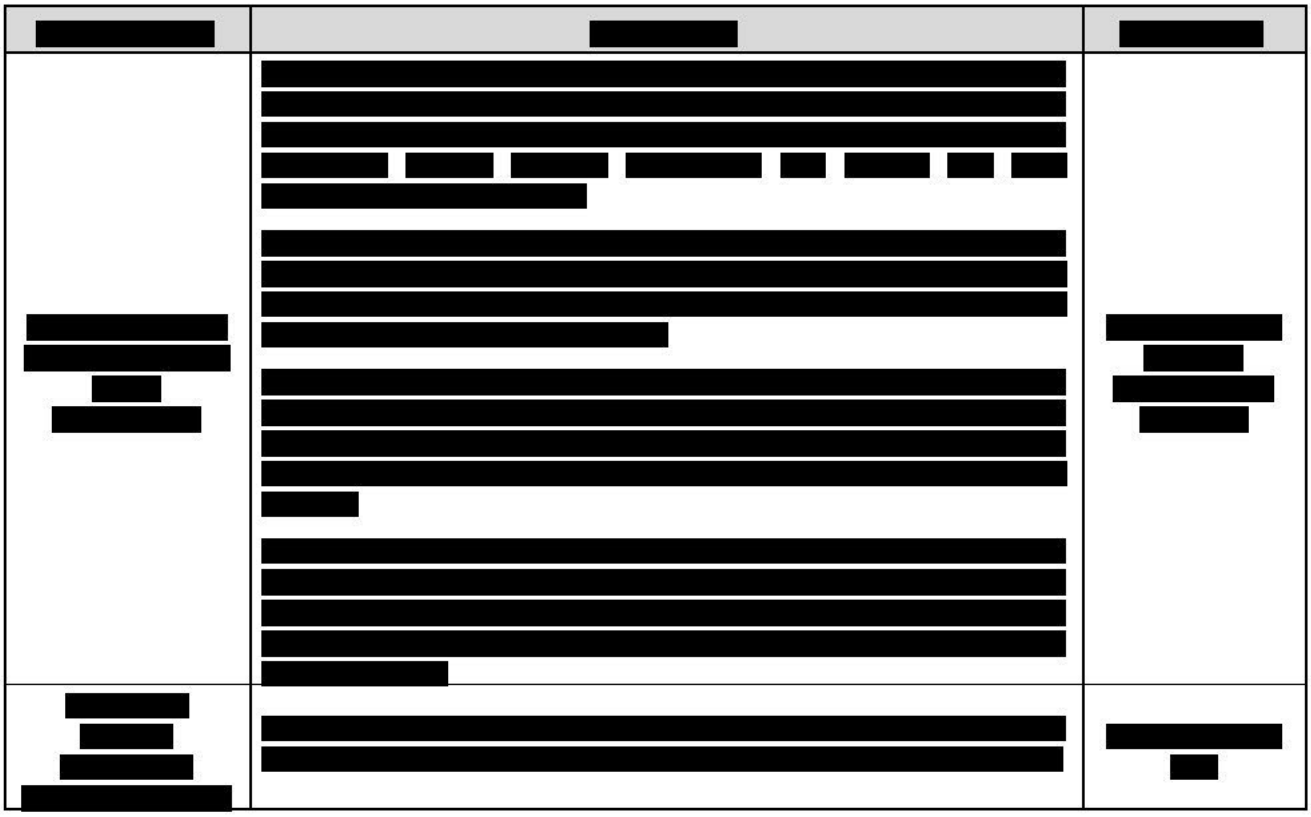
Intended purpose: Mechanical cutting and blunt dissection.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Characteristic	Description	References
Description of the device	[redacted]	Investigator's Brochure



2.2. Intended purpose

Bitrack System is intended to assist in the accurate control of endoscopic instruments and accessories for visualization and endoscopic manipulation of tissue including grasping, mechanical and monopolar cutting, dissection and blunt dissection, approximation, ligation, bipolar coagulation, suturing, and delivery, placement and tracking of endoscopic assistance instruments and/or manual instruments. Bitrack System is indicated for use during urological surgical procedures, general laparoscopic surgical procedures, and gynecological laparoscopic surgical procedures. The patient target population of Bitrack System is adults. The intended users are trained physicians in an operating room environment in accordance with the Instructions for Use.

2.3. Intended Indication for Use

Bitrack System is a robotic surgical system indicated for urologic, general laparoscopic and gynecologic laparoscopic surgical procedures. The recommended procedures are listed as follows:

- Urology
  - Partial/radical nephrectomy
  -
  -
  - Radical prostectomy
  -
  - Lysis of Adhesions
  - Lymphadenectomy
  -

[redacted]

[redacted]

2.5. Description of the Control Device(s) or Historic Control

No Control Devices or Historic Control are applicable to this study, since there is no direct comparison to other competitor devices.

2.6. Device Handling

[redacted]

ESE/NESE instruments will be handled according to the approved Instructions For Use. Prior to use of the device, there is a non-sterile manipulation of the devices to remove them from third and secondary packages, [redacted]

Traceability of all components involved will be present in the corresponding device labels.

3. CLINICAL INVESTIGATION OBJECTIVE

The purpose of this early feasibility clinical investigation is to evaluate the safety and performance of the Bitrack System and its corresponding ESE and NESE instruments and accessories in patients with the indication of a robot assisted laparoscopic radical/simple nephrectomy.

[redacted]

4. CLINICAL INVESTIGATION DESIGN

The study will be conducted as an early feasibility clinical investigation with a single arm, open-label, and non-randomized design, and will include 3 subjects candidate to a standard of care laparoscopic surgery.

The clinical investigation will be conducted in 1 center in Spain. Therefore, this clinical investigation will be considered as monocentric. The site investigation details are provided below:

Hospital Clinic de Barcelona

[redacted]

The objective of the study is to make a preliminary and exploratory evaluation of the safety and performance of the Bitrack System device and its laparoscopic instruments for the first time in humans, [redacted] Since the study does not include a formal hypothesis and it is an Early Feasibility Study (EFS) as described by Annex I of EN ISO 14155:2020 on Clinical research with medical devices, the statistical analysis of the sample population is not considered applicable.

[redacted]

4.1. Clinical Investigation Procedures and Follow-up Schedule

The Clinical Investigation visits will occur as in-clinic visits at Baseline, Procedure, Discharge, 14 and 30-days follow-up.

The Flow Chart and the Follow-up phases of this clinical investigation are described in Figure 4-1 below.

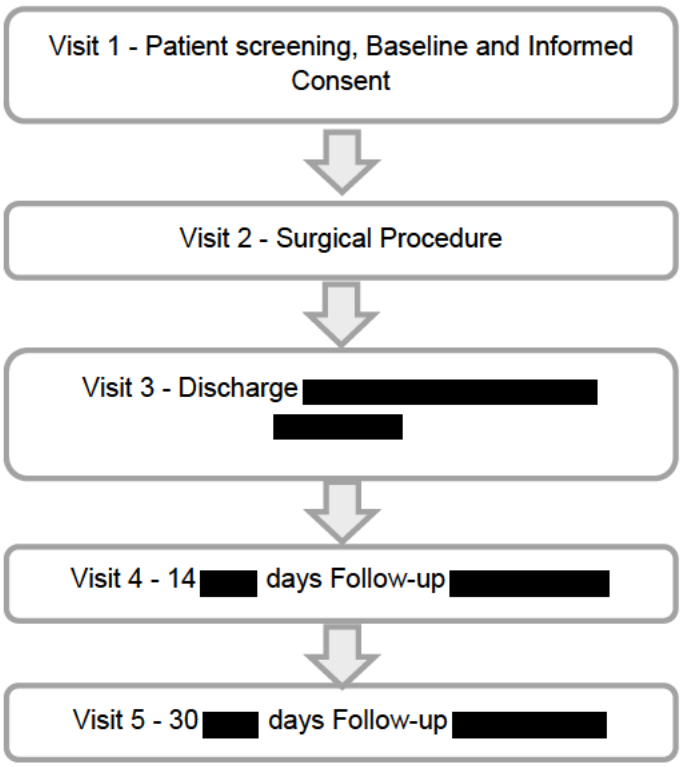


Figure 4-1. Flowchart of the clinical investigation schedule

The scheduling of the clinical investigation visits will include the following:

Baseline visit (Visit 1)

During the baseline visit, the patient will be informed about the clinical study and provide signed informed consent form if surgeon decides that the patient is eligible as applicable. In case of pregnancy, the patient will withdraw of the study a .

Procedure – (Visit 2)

The study population consists of subjects that provided signed ICF, met all inclusion criteria and none of the exclusion criteria, and successfully undergo surgery with the Bitrack System and its corresponding ESE/NESE instruments. These patients will be followed up until 30 days post-procedure. On the other hand, those subjects

in whom robot assisted laparoscopic radical/simple nephrectomy is attempted but not achieved will be followed-up for 30 days, but not included as population for analysis.

[redacted]

For research purposes, we will consider the start of the procedure at the moment of docking, meaning the moment when the camera of the robot is introduced insider the trocar. Therefore, all procedures that started but do not proceed with the use of the Bitrack system or are converted into a conventional laparoscopic/open surgery are included under the Intent-to-treat (ITT) population. Any robot assisted surgery converted to conventional laparoscopic/open surgery due to reasons different than the failure of the Bitrack System and its corresponding sterile endoscopic surgical instruments will be excluded from the endpoint analysis. [redacted] This event will be considered a procedure failure.

[redacted]

[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Discharge (Visit 3)

Subject´s discharge will be completed following site´s standard of care practices and always when it is safe for the subject. At the time of discharge, subject´s clinical information will be collected to assess the post-operative pain, together with the rate of post-procedure complications.

14-Days follow-up visit (Visit 4)

The objective of this visit is to collect data on AEs related to the device and the procedure. [redacted]

30-Days follow-up visit (Visit 5)

[redacted] The objective of this follow-up visit will be to collect data about any AE related to the device, the procedure or both. Additionally, information about the patient pain evaluation will also be gathered.

[redacted]

4.2. Measures Taken to Avoid and Minimize Bias

The following steps will be taken to minimize bias in the conduct of the clinical study:

4.2.1. Subject requirement

Patients of both genders will be considered as anatomy does not influence the surgical approach.

A[redacted]

4.2.2. Safety monitoring

Measures taken to avoid bias related to safety includes 100% of source data verification related to AEs documented in the Monitoring Plan.

4.2.3. [redacted]

[redacted]

5. ENDPOINTS

5.1. Primary Endpoint

The primary safety and performance endpoints of this early feasibility investigation are:

1. Evaluation of the safety of the Bitrack 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/simple nephrectomy.
2. Evaluation of the performance of the investigational devices by means of its ability to access and reach the target zone, perform all relevant surgical tasks and to be withdrawn efficiently without conversion to MIS or open surgery. The performance of the Bitrack System and the ESE/NESE instruments will be analyzed through the conversion rate to conventional laparoscopy/open surgery.

5.2. Secondary Endpoints

The secondary endpoints planned for this clinical investigation are listed below:

- All AE(s) events during t**he** procedure and through the 14- and 30-days post-procedure will also be assessed, and therefore relationship with the investigational device and/or procedure will be examined by the principal investigator and reported to Rob Surgical
    - Timeframe: Procedure, discharge, 14- and 30 -days follow up visits
- Individual safety (i.e., absence of unwanted injure of any tissue) and performance (VAS scale 0-10 following the subjective surgeon´s opinion, being 0 a non-functional tool and 10 an instrument that works exactly equivalent to the surgeon´s hands) for each instrument surgical function.
    - Timeframe: Procedure
- Blood Loss defined as estimated mL of blood loss, transfusion rates and use of haemostasis agents
    - Timeframe: Procedure
- Operative Time Procedure measurement for the different tasks.
    - Timeframe: Procedure
- To evaluate post-operative pain in patients through the Cumulative Analgesic Consumption Score (CACS) during the first week (7days) post-procedure.
    - Timeframe: Discharge
- To assess the duration of subject's hospitalization as the Length of Stay (LoS) in hospital calculated from day of admission to day of discharge.
    - Timeframe: Discharge
- Patient pain assessment via VAS. Patient interview questions
    - Timeframe: Discharge, 14- and 30-days post-procedure
- Post-procedure complication rates, including the measurement of the comprehensive complication index (CCI) on a scale from 0 (no complications) to 100 (death), and the Clavien-Dindo classification, which consists 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
    - Timeframe: Discharge,14 and 30 days follow-up

6. SUBJECT SELECTION AND WITHDRAWAL

6.1. Subject Population

This clinical investigation will enroll male and female subjects between 18-90 years old candidates to a radical/simple laparoscopic nephrectomy for benign/malignant pathology.

[redacted]

6.1.1. Number of Subjects

A total of 3 subjects will be enrolled in the clinical investigation.

6.2. Subject Screening and Informed Consent

6.2.1. Subject Screening

Potential patients presenting at the clinical sites will be fully informed about the clinical investigation, following the established Informed Consent process (described in **section 6.2.2**). The Principal Investigator or designee previously trained to the CIP will revise patient´s eligibility according to the inclusion/exclusion criteria. Patients meeting general inclusion criteria and no exclusion criteria will be asked to sign an Informed Consent form if they agree to participate in the clinical investigation.

[redacted]

Subject data will be collected following enrollment into the clinical investigation.

6.2.2. Informed Consent

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's EC. [redacted]

Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject's legal rights. Financial incentives will not be given to the subject. [redacted]. The subject shall have adequate time to review, ask questions, and consider participation. [redacted] If the subject agrees to

participate, the Informed Consent form must be signed and dated by the subject and thereafter by the person obtaining the consent prior to any clinical investigation-specific procedures. [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

6.3. Eligibility Criteria

6.3.1. General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. If some of the clinical and laboratory tests are not included in site standard tests, they must be done but after written informed consent is obtained. Patients must meet ALL of the inclusion criteria to be considered for the clinical investigation. If ANY of the exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled.

6.3.2. Inclusion Criteria

1. Adult subjects between 18 and 90 years old
2. Subjects must provide written informed consent prior to any clinical investigation related procedure
3. Subjects who have been scheduled for a laparoscopic radical/simple nephrectomy
4. Ability and willingness to comply with all study requirements to be evaluated for each study visit

6.3.3. Exclusion Criteria

1. Pregnant or breastfeeding women at the time of the surgery
2. Inability to adhere to study-related procedures
3. Subject has known allergy to some of the device components (i.e., stainless steel, etc.)

4. Subjects who participate in another trial which may affect the outcome data on this study or the ability to complete the follow up requirements
5. Subjects not suitable to undergo MIS/MIRS, according to medical criteria
6. Subjects with life expectancy inferior to 3 months
7. Subjects with a BMI ≥ 40.
8. Subjects with severe cardiopulmonary or coronary artery disease, bleeding disorders or that have been submitted to multiple prior operations.
9. Subjects with abuses of active substances or with uncontrolled psychiatric disorders.
10. Subjects scheduled for surgeries intended to be in direct contact with the heart, the central circulatory system or the central nervous system.
11. Subjects with any contraindication for the use of the Bitrack System and the ESE/NESE instruments, as specified in the Instructions For Use

6.4. Subject Enrollment

[redacted]For the HYROS study, a patient is considered enrolled in the clinical investigation from the moment they provide written informed consent, has been confirmed to meet all inclusion criteria and none of the exclusion criteria and has been successfully treated with the Bitrack System.

[redacted]

6.5. Subject Withdrawal

Each enrolled subject shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

6.6. Expected Duration of the Participants in the Clinical Investigation

[redacted] Subjects´ participation in the clinical investigation will be finalized at the conclusion of their 30 days follow-up visit. [redacted].

6.6.1. Suspension or Early Termination of the Clinical Investigation

While no formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined, the Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- Unanticipated adverse device effect (e.g.,UADE) occurs and it presents an unreasonable risk to the participating subjects.
- An oversight committee (e.g., Steering/Executive Committee, Data Monitoring Committee) makes a recommendation to stop or terminate the clinical investigation (such as higher frequency of anticipated adverse device effects).
- Further product development is cancelled.

Should the clinical investigation be discontinued by the Sponsor, subjects will be followed per routine hospital practice with device-related AEs reported to the Sponsor as per vigilance/commercial reporting requirements.

[redacted]

7. TREATMENT AND EVALUATION OF ENDPOINTS

7.1. Baseline

7.1.1. Baseline Clinical Assessments

During the baseline visit, in those subjects who have signed the informed consent form and meet all the inclusion and none of the exclusion criteria, the following medical assessments will be performed, as required by the clinical investigation design:

- [redacted]

7.2. Randomization

No randomization process will take place in this clinical investigation.

7.3. Blinding

This is an open-label clinical investigation. Investigators and subjects will not be blinded to the procedure assignment.

7.4. Index Procedure

The robotic assisted laparoscopic radical/simple nephrectomy surgery will be performed a maximum of 4 weeks after Baseline visit and up to the surgeon criteria and patient´s agreement. The dates of the following visits are calculated starting from the day this visit took place.

[redacted]

7.4.1. Procedures Involved in the Use of the Devices Under Investigation

For further information about the investigational devices, their components and their intended use and applications, refer to the IFU.

7.4.2. [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

7.5. [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]					
[redacted]	[redacted]		[redacted]			
[redacted]		[redacted]				
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]		[redacted]				
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[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]			
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						[redacted]

[redacted]

8. ADVERSE EVENTS

[redacted].

8.1. Definition

8.1.1. Adverse Event

An adverse event (AE) is 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.

Note 1: This definition includes events related to the medical device under investigation or the comparator.

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 medical devices under investigation.

8.1.2. Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death,

b) Led to a serious deterioration in 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) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

8.1.3. Device Deficiency/Device Malfunction

Device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Note: Performance specifications include all claims made in the labeling of the device.

A device malfunction is the failure of a device to meet its performance specifications or otherwise perform as intended, when used in accordance with the instructions for use or CIP.

8.2. Device Relationship

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

8.2.1. Unanticipated (Serious Adverse) Device Effect [U(S)ADE]

Unanticipated serious adverse device effect (USADE) refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.3. Adverse Event and Device Deficiency/Device Malfunction Reporting

8.3.1. Adverse Event Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical investigation. [redacted] All adverse event data, [redacted], will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information with regard to an adverse event should be updated within the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

[redacted]

SAE Reporting

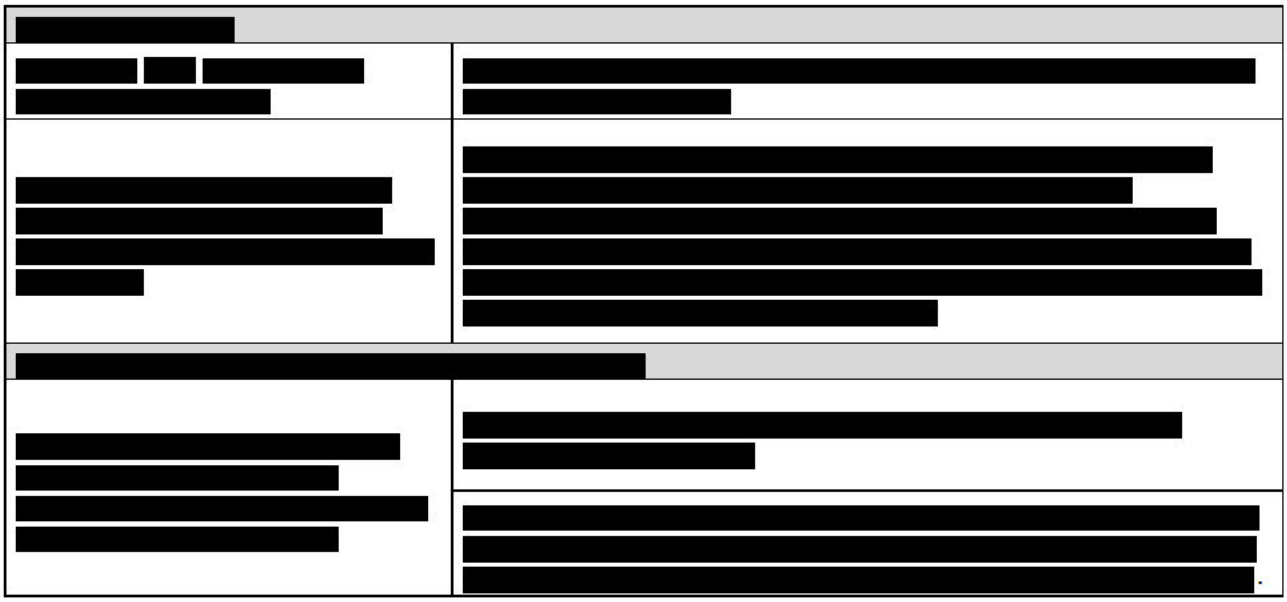
The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Table 8-1. (S)AEs reporting

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 24 hours from the day the site personnel became aware of the event [redacted]

[redacted]

[redacted]



8.3.2. Determination of Adverse Events related to device and/or procedure

As detailed in Section 5.1, the primary endpoint of the study is to measure the safety and performance of Bitrack System. Among the ratios to be measured, the rate of death occurrence (SAE) during the surgery related directly to the use of the Bitrack System and the rate of any adverse event (AE) occurrence during the surgery directly related with the procedure and/or device under investigation will be determined.

8.3.3. Unanticipated Serious Adverse Device Effect Reporting to Sponsor and EC

The Sponsor requires the Investigator to report any USADE to the Sponsor within 24 hours of the investigator's knowledge of the event, unless local requirements are more stringent, and to the EC per EC requirements.

8.3.4. Device Deficiency/Malfunction Reporting

[redacted]

Clinical Sites	Reporting timelines
All Sites	Device deficiencies/malfunctions must be reported to the Sponsor no later than 24 hours from the day the site personnel became aware of the event [redacted]

[redacted]

[redacted]

9. DATA AND DATA ANALYSIS: STATISTICAL CONSIDERATIONS

[redacted]

9.1. Analysis Populations

9.1.1. Intent-to-treat Population (ITT)

The intent-to-treat population (ITT) includes all adult humans derived for a robot assisted laparoscopic Radical/simple nephrectomy surgery using Bitrack System and its sterile endoscopic surgical instruments medical devices, in whom treatment using the device under investigation is attempted but not achieved.

9.1.2. Per-Protocol Population (PP)

Per-Protocol Population (PP) includes all subjects who fulfill the inclusion criteria, do not meet any exclusion criteria, have signed the informed consent form (ICF), and have undergone to a robotic assisted radical/simple nephrectomy surgery using Bitrack System medical device. [redacted].

9.2. Statistical Analyses

9.2.1. Primary Safety and Feasibility Endpoint Analyses

The primary safety and performance endpoints of this early feasibility investigation are:

1) Evaluation of the safety of the Bitrack System by measuring the occurrence of Procedure-Related Adverse Events (PRAEs) and Serious Adverse Events (SAEs) during the procedure and through the 14-days and 30-days post-procedure period of enrolled patients indicated for robot assisted laparoscopic Radical/simple nephrectomy surgery.

2) Evaluation of the performance of the investigational devices by means of its ability to access and reach the target zone, perform all relevant surgical tasks and to be withdrawn efficiently without conversion to MIS or open surgery.

Considering the low number of subjects, no formal hypothesis has been defined for this clinical investigation. [redacted]

9.3. Sample Size Calculation and Assumptions

HYROS is a feasibility study performed as an exploratory clinical investigation, to determine the limitations and advantages of Bitrack System, to capture information in order to freeze the design of the medical device and to progress to the validation stage. In this sense, only three patients are considered for this clinical investigation and consequently statistical considerations do not apply [redacted]

[redacted]

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. [redacted]

10.2. Clinical Investigation Finances and Agreements

The clinical investigation will be financed by Rob Surgical Systems, S.L. [redacted]

10.4. Training

10.4.1. Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Over-the-phone or self-training may take place as required. [redacted]

10.4.2. Training Required for the Use of the Device

Bitrack System is to be used by professionals who have been previously trained in MIS procedures. [redacted]

10.5. Monitoring

Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification. This monitoring plan will be a separate document that can be updated during the curse of the study.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

10.6. Deviations from CIP

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.

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.1. Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

[redacted]

The Sponsor requires the investigational sites to transfer into Sponsor's data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such as the patient's medical condition, treatment, dates of treatment, etc. [redacted]

[redacted]

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2. Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data entry and collection. Data review and data cleaning, and issuing, resolving data discrepancies and methods for data base lock. [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

11.4. Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and CRF completion. [redacted]

[redacted]

[redacted]

[redacted]

11.5. Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements, but at least for 15 years. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.4. Steps Taken to Control or Mitigate Risks

Risks associated with the use of surgical robots are well established and can be extensively minimized by the use of a good technique and experience/training.

12.5. Benefit to Risk Rationale

[redacted]

[redacted]

[redacted].

The benefit that the device provides overweight the residual risks, at this stage of the design.

[redacted]

[redacted]

[redacted]

[redacted]

13. ETHICAL CONSIDERATION

13.1. Ethics Committee and AEMPS Review and Approval

Ethics Committee (EC) and Spanish Agency of Medicines and Medical Products (AEMPS) approval for the CIP and ICF/other written information provided to the patient will be obtained at each investigational site prior to consenting and enrolling patients in this clinical investigation. The approval letter must be received prior to the start of this clinical investigation and a copy must be provided to the Sponsor.

[redacted]

14. CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- Site is closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure.

[redacted]

15. PUBLICATION POLICY

The data and results from the clinical investigation are the sole property of the Sponsor. [redacted]

[redacted]

APPENDIX I: ABBREVIATIONS AND ACRONYMS

Abbreviation/acronym	Words
APS	Acute Procedural Success
CCI	Comprehensive Complication Index
CIP	Clinical Investigation Plan
CRF	Case Report Form
CT	Computed Tomography
DMP	Data Management Plan
DOF	Degree Of Freedom
EC	Ethics Committee
EDC	Electronic Data Capture
EKG	Electrocardiogram
ESE	Electrosurgical Endoscopic Instruments
FIH	First In Human
HYROS	Hybrid Robotic Surgery In Urology
ICF	Informed Consent Form
IFU	Instructions For Use
ITT	Intent-To-Treat Population
MIRS	Minimally Invasive Robotic Surgery
MIS	Minimally Invasive Surgery
MRI	Magnetic Resonance Imaging
NESE	Non-Electrosurgical Endoscopic Instruments
PP	Per protocol
PRAEs	Procedure-Related Adverse Events
RAS	Robotic Assisted Surgery
RCC	Renal Cell Carcinoma
RN	Radical Nephrectomy or Radical/simple Nephrectomy
SAEs	Serious Adverse Events
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
US	Ultrasound
VAS	Visual Analogue Scale

[redacted]