European Registry of Next Generation Imaging in Advanced Prostate Cancer
Version 5.3
13th June 2024

Sponsor	Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau (Barcelona, Spain)
Supporters	J&J Innovative Medicine (ex Janssen) – funder EAU Research Foundation – scientific support and endorsement
Coordinator site	Fundació Puigvert
Version Number	5.3
Protocol number	RG01-01
Date	13th June 2024

This study will be conducted by the protocol, Good Clinical Practice (GCP), and any other applicable regulatory requirements, including the archiving of essential documents.

INVESTIGATOR AGREEMENT
RING study
RG01-01: European Registry of Next Generation Imaging in Advanced Prostate Cancer

I have read and understand this protocol and agree that it contains all the details for the study as described. I will conduct this protocol as outlined therein and will make all reasonable efforts to complete the study within the designated time.

I agree to conduct this trial according to the Declaration of Helsinki, the International Conference on Harmonization (ICH), the Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements.

I understand that the study may be terminated, or enrolment suspended at any time by the Sponsor, with or without cause, or by me, if it becomes necessary to do so in the best interests of the study subjects.

_____
Investigator's Name (print)

_____ _____
Investigator's Signature Date

Invited investigators and clinical site

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PROTOCOL AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

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Clinical study
"European Registry of Next Generation Imaging in Advanced Prostate Cancer"

Abbreviations

AE	Adverse Event
APC	Advanced Prostate Cancer
CRO	Contract Research Organization
CT	Computed Tomography
DSS	Disease-Specific Survival
EAU	European Association of Urology
EAU RF	EAU Research Foundation
eCRF	electronic Case Report Form
EPCCE	European Association of Urology Prostate Cancer Centres of Excellence
EU	European Union
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HA	Health Authorities
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
IT	Information Technology
mHSPC	metastatic Hormone-Sensitive Prostate Cancer
MRI	Magnetic Resonance Imaging
NGI	Next-Generation Imaging
OS	Overall Survival
PCWG	Prostate Cancer Working Group
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PSA	Prostatic Specific Antigen
PSA-DT	PSA Doubling Time
PSMA	Prostate-Specific Membrane Antigen
RECIST	Response Evaluation Criteria in Solid Tumor
RedCap	Research electronic data Capture
RING	Registry of Next Generation Imaging
SD	Standard Deviation
SSE	Symptomatic Skeletal-related events
SUV	Standardized Uptake Value
WB-MRI	Whole-Body MRI

Summary

Study title	"European Registry of Next Generation Imaging in Advanced Prostate Cancer"
Acronym	RING
Protocol number and protocol version	RG01-01; V_5.2
Sponsor name	Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau (Barcelona, Spain)
Study Design	No-profit, non-interventional, multicentre, international, prospective, investigator-initiated registry enrolling patients with histologically proven prostate cancer at high risk of harbouring metastasis (either as treatment naïve patients or recurrent disease in patients with former local treatment) who require imaging staging. The registry is planned to be run in two stages: 1) Stage 1: cross-sectional observation of patients recruited according to selection criteria. 2) Stage 2: longitudinal observation of patients recruited and in follow-up.
Study treatments or interventions	Standard of care. Drugs, treatments, and/or interventions are routinely administered to patients per local standards. Treatment decisions will be made at the treating physician's discretion, per routine clinical practice.
Eligibility Criteria	<u>Inclusion criteria</u>: 1. Adult male patients (≥18 years with no upper age limit). 2. Histologically proven prostate cancer. 3. Patients who require imaging exploration (conventional, Next-Generation Imaging (NGI), or their combination) at high risk for harbouring metastatic deposits at the hormone-sensitive stage, either at the diagnostic workout of a "naïve" patient or at biochemical relapse/progression after local treatment. 4. Patients who authorize their participation in the study by signing a written informed consent form (ICF). <u>Exclusion criteria:</u> 1. Patients participating in other interventional or non-interventional study which requires NGI as a triage test for metastatic assessment.

	2. Patients with evidence of any other clinically significant disease or condition which in the opinion of the investigator discourages their participation in the study. 3. Patients who will not be able to complete the study.
Sample Size	An average of 35 patients/year per centre (for a minimum of 12 centres involved) was estimated, with an overall number of 600 patients recruited in the 1.5 years of the study's recruitment period (whichever comes first). Patients will be consecutively selected in the outpatient clinics, and those who sign the informed consent will be included in the registry.
Study Procedures	Patients will provide the ICF before the enrolment in the study and at the start of data collection. Patients must meet all the inclusion criteria and do not meet any of the exclusion criteria. Patients will be managed according to the local usual clinical practice. The study will consist of two stages: 1) landscape analysis, and 2) follow-up analysis. The data will be extracted from patient's medical records and recorded in the RedCap (Research Electronic Data Capture) Registry DataBase. The registry is going to be developed according to the recommendations on the design, implementation, governance, and long-term sustainability of disease registries in the European Union (EU). The responsible investigators will ensure that the data collection process strictly complies with the guiding principles of the applicable laws and regulations in the country where this prospective non-interventional registry is being carried out. A Contract Research Organization (CRO) will be responsible for data management: review, cleaning up, queries, etc. Timely updated reports will be sent to the participating centres.
Study Objectives	<u>Stage 1: cross-sectional observation</u> 1. To identify the proportion of patients for whom, an imaging work-up with NGI at baseline may result beneficial, according to physician criteria. 2. Assess management prompted by NGI vs. conventional imaging in usual clinical practice. 3. To identify the proportion of patients for whom conventional imaging is considered informative enough for making a clinical decision, according to physician criteria. 4. Stratification of metastatic prostate cancer patients by the number, volume, and location of deposits, according to the different imaging tools employed. 5. Reclassification of HSPC (M0 vs low vs. high volume) based on NGI respect to CI when both imaging modalities are used.

	Stage 2: longitudinal observation 1. Evaluation of survival outcomes and their relationship with the imaging pathway undertaken. 2. Identification of prognostic factors related to treatment response and disease progression.
Study Endpoints	Stage 1: landscape analysis 1. Proportion of patients requiring NGI, conventional imaging, or a combination of both imaging tools. 2. Clinical variables associated to each imaging pathway. 3. Proportion of patients with a change of treatment determined by the imaging test result. Stage 2: follow-up analysis 1. Progression-free survival (PFS) (biochemical, clinical and radiologic) or need for change of treatment (overall and per imaging subgroups) 2. Disease-specific survival (DSS) (overall and per imaging subgroups). 3. Symptomatic skeletal-related events (SSE) and SSE-free survival (overall and per imaging subgroups). 4. Imaging biomarkers related to treatment response and disease progression [SUV, type of tracer, scoring system used and relevant scores, etc.].
Recruitment period	18 months.
Follow up	For the purpose of Stage 2 of the project, a minimal mean follow-up time of 24 months is needed to satisfy the main survival outcome (progression-free survival/need for change of treatment).
Central IEC/IRB	Fundació Puigvert, Barcelona, Spain.
Statistical analysis	Different analyses have been planned by using the information collected at baseline and during follow-up. A description of the collected data will be performed. Qualitative variables will be described with absolute frequencies and percentages. The description of quantitative variables will be performed using the mean, standard deviation (SD), median, and inter-quartile ranges. The Kolmogorov-Smirnov test will be used to assess the normality of distributions.
Financing resources	Stage 1 of the registry is supported by the contribution of Janssen. Additional fund raising will be undertaken to carry out phase 2 of the study

Section 1: Introduction

Next-generation imaging (NGI) is going to revolutionize the management of prostate cancer patients at all stages of the disease process.
The advent of magnetic resonance imaging (MRI) and positron emission tomography / computed tomography (PET/CT) technologies in advanced prostate cancer (APC) is already impacting both the disease diagnosis pathways as well as the treatment follow-up. In particular, whole-body MRI (WB-MRI) and PET/CT with new tracers (F/Ga-PSMA, 18F-fluciclovine, etc.) have been adopted in multiple centres because of their increased accuracy in the assessment of the metastatic dissemination of prostate cancer and/or of response to systemic treatments (new antiandrogen agents, chemotherapy, theranostic, etc) than traditional CT and bone scans, commonly referred to as conventional imaging (1).
The Prostate Cancer Working Group 3 (PCWG3) and the response evaluation criteria in solid tumour (RECIST)-v1.1 criteria only define the progression of metastases based on conventional imaging findings; nevertheless, they do not define a positive benefit of treatment, instead relying on prostatic specific antigen (PSA) changes which are known to be inaccurate in response assessment settings for hormone sensitivity and castration-resistant disease state (2,3).
In the proPSMA trial, the PET-CT PSMA for high-risk prostate cancer patients has been shown to prompt management change more frequently than conventional imaging before curative treatment in 28% vs. 15% of the cases, respectively (4).
In patients with biochemical recurrence after primary treatment, MRI and PET/CT-PSMA are the tools of preference according to the latest version of the EAU Guidelines on prostate cancer, with MRI especially useful to guide biopsy of the prostate for salvage treatment after primary radiotherapy, and PET/CT-PSMA to differentiate local vs distant recurrent disease after local treatment(5).
Accordingly, more precise detection of metastatic disease as well as of the detection of non-responsiveness of known disease to systemic therapy may help promote patient health by allowing timely adjustments of treatments. On the other hand, it is not yet clear whether earlier shifts of systemic therapies are beneficial, although accumulating data strongly suggests that lower volume/risk patients have improved prognoses(6). These are unmet clinical needs, as previously highlighted by the European Association of Urology (EAU) Guidelines on Prostate Cancer for the lack of evidence in this regard(5).
Few clinical trials are investigating the impact of NGI in the setting of advanced prostate cancer (7,8). Those reporting such studies are usually undertaken in highly specialized centres, with small sample sizes of very highly selected patients.
International registries may have the advantage of providing complementary evidence by capturing real-life data to better define the clinical utility of NGI technologies in centres that have already adopted them for routine patient care.
We aim to understand when, which, and why NGI investigations are undertaken in the assessment of real-life APC populations, to:

- Better identify patients who potentially benefit from an earlier/finer assessment of metastatic prostate cancer at baseline with NGI.
- Better identify patients for whom conventional imaging is informative enough for making a clinical decision.
- Assess change of management prompted by NGI vs. conventional imaging in usual clinical practice.

Section 2: The RING Registry

2.1 Study Objectives

This registry is intended to collect real-world data on patient demographics, medical history, clinical endpoints, histological tumour characteristics and imaging explorations of the patients with prostate cancer at high risk for harbouring metastatic deposits at the hormone-sensitive stage, who require imaging exploration (conventional, NGI, or their combination) either at the diagnostic workup of a "naïve" patient or at biochemical relapse/progression after local treatment.

Stage 1: cross-sectional observation

1. To identify the proportion of patients for whom an imaging work-up with NGI at baseline may result beneficial, according to physician criteria.
2. Assess management prompted by NGI vs. conventional imaging in usual clinical practice.
3. To identify the proportion of patients for whom conventional imaging is considered informative enough for making a clinical decision, according to physician criteria.
4. Stratification of metastatic prostate cancer patients by the number, volume, and location of deposits, according to the different imaging tools employed.
5. Reclassification of HSPC (M0 vs low vs. high volume) based on NGI respect to CI when both imaging modalities are used.

Stage 2: longitudinal observation

1. Evaluation of survival outcomes and their relationship with the imaging pathway undertaken (overall and per subgroup of imaging modality).
2. Identification of prognostic factors related to treatment response and disease progression.

2.2 Study Endpoints

Stage 1: landscape analysis

1. Proportion of patients requiring NGI, conventional imaging, or a combination of both imaging tools.
2. Clinical variables associated to each imaging pathway.
3. Proportion of patients with a change of treatment determined by the imaging test result, when multiple imaging tests have been realized.

Stage 2: Follow-up analysis

1. Progression-free survival (PFS) (biochemical, clinical and radiologic) or need for change of treatment (overall and per imaging subgroups)
2. Disease-specific survival (DSS) (overall and per imaging subgroups).
3. Symptomatic skeletal-related events (SSE) and SSE-free survival (overall and per imaging subgroups).
4. Imaging biomarkers related to treatment response and disease progression [SUV, type of tracer, scoring system used and relevant scores, etc.].

2.3 Design of study to establish RING patient database.

This is a no-profit, non-interventional, multicentre, international, prospective, investigator-initiated registry designed to establish a database of demographics, medical history, clinical endpoints, and tumour characteristics at histology and imaging explorations from patients with histologically proven prostate cancer at high risk of harbouring metastasis (either as treatment naïve patients or recurrent disease in patients with former local treatment) who require imaging staging.

The registry is planned to be run in two stages:

1) Stage 1: cross-sectional observation of patients recruited according to selection criteria.
2) Stage 2: longitudinal observation of patients recruited and in follow-up.

2.4 Study Setting

This is a multicentre study conducted in specialist prostate cancer centres in tertiary/university hospital settings fulfilling EPCCE criteria.
The planned sites are (pending confirmation upon contract negotiation):

Fundació Puigvert, Barcelona, Spain
Skane University Hospital, Malmö, Sweden
IRCCS AOU Bologna - Policlinico Sant´Orsola, Alma Mater Studiorum University of Bologna, Italy
University Hospital, Dresden, Germany
München LMU, LMU-University Clinic, München, Germany
UniversitätsklinikTübingen, Germany
Hospices Civils de Lyon, Lyon, France
University Hospital La Pitié-Salpêtrière, Paris, France
University Hospital of Bern, Bern, Switzerland
ERASMUS MC /Franciscus Hospital, Rotterdam, the Netherlands /
UZ Leuven, Leuven, Belgium
AOUC Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy
IRCCS Ospedale San Raffaele, Milan, Italy
Jagiellonian University Medical College, Kracow, Poland

Each site should submit the protocol and ICF to the relevant IEC/IRB. The CRO will support sites Investigators on this regard, and the IRB of the Coordinator site will be provided to facilitate the process.

2.5 Study plan and procedures

As a non-interventional study, patients will be managed according to their local procedures and policies. The registry will be developed in collaboration with those prostate cancer centres with high quality standards in clinical practice, research, investigation, and training in prostate cancer, as identified by the European Prostate Cancer Centres of Excellence.

2.6 Screening participants and informed consent

Participants will be selected in outpatient clinical attendance and will be screened for eligibility according to the inclusion and exclusion criteria as already defined in this protocol. A screening log will be kept tracking details of subjects invited to participate in the study. The log will also ensure that potential participants are approached only once.
If patients are eligible for inclusion, they will be provided with a copy of the ICF containing details of the registry aims the type of clinical information collected, and the way these latter will be managed. As soon as the patient has got sufficient time for them to process the information and to make a decision and eventual questions will be appropriately addressed and discussed by/with the involved site staff (as per the delegation log, including medical staff and research nurses), the patients will be invited to provide written informed consent by signing and dating the study consent form. Written informed consent will always be obtained before study-specific procedures/investigations. Patients who decline their participation should be reported in the screening log and reported as screening failure.
The original signed consent form will be retained in the Investigator Site File (ISF), and the participant will receive a copy of the ICF. Alternatively, where electronic medical records are in use then the investigator will comply with local consent policy at their site. The right to refuse to participate without giving reasons will be respected. Participants will be informed and will be required to agree to their medical records being inspected by the Sponsor or their delegate, if required, but understand that their confidential details will not be disclosed outside the research team.

2.7 Withdrawal Procedures

Patients will be considered as included in the study once they have signed the ICF.
Participants have the right to withdraw from the study at any time for any reason, and without giving a reason. Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible in the Registry DataBase (RedCap).

2.8 Inclusion and exclusion criteria

The inclusion criteria are broad, and the exclusion criteria are deliberately sparse to allow the inclusion of a large and varied population representative of real-life prostate cancer management across Europe.

Inclusion Criteria
Consecutive patients referred with prostate cancer meeting the following inclusion criteria will be recruited:

1. Adult male patients (≥18 years with no upper age limit).
2. Histologically proven prostate cancer.
3. Patients who require imaging exploration (conventional, NGI, or their combination) are at high risk for harbouring metastatic deposits at the hormone-sensitive stage, either at the diagnostic workout of a “naïve” patient or at biochemical relapse/progression after local treatment.
4. Patients who authorize their participation in the study by signing a written ICF.

Exclusion criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Patients participating in other interventional or non-interventional study which requires NGI as a triage test for metastatic assessment.
2. Patients with evidence of any other clinically significant disease or condition which in the opinion of the investigator discourages their participation in the study.
3. Patients who will not be able to complete the study.

2.9 Data Collection

The recruited centres will form a local team of investigators, which will include one urologist and one imaging expert (radiologist or nuclear medicine physician) and led by a Principal Investigator (PI) of their choice.

The informed consent form should be signed at the baseline visit before data will be recorded in the database. All the relevant patients' information will be collected according to the electronic Case Report Form (eCRF) and fed into the information technology (IT) platform of the registry; for the stage 2 phase, the number of visits and modality of follow-up will be according to the usual clinical practice. Clinical data will be included in the eCRF by using a pseudonymised process, by de-identifying patients name(s) and surname(s) with a local site code followed by a progressive number, according to screening sequence.

Recruitment will be open for 18 months.

Stage 1: "Landscape" visit will take place 4 to 6 weeks after the baseline visit, or as soon as the diagnostic work up is completed, and a decision is made for the type of treatment the patient will undertake.

Stage 2: Follow-up monitoring will take place according to local protocol schedule, and data will be collected every 3 months concerning the closest visit to each time-point. A minimum follow-up time of 24 will be required to get a sufficient number of expected events to satisfy the main survival outcome (progression-free survival/need for a change of treatment), even though the ideal follow-up time to collect the >50% of most the survival events should be 3 to 5 years, and 5 to 10 years for the overall survival.

The following domains are covered: demographics, clinical variables, tumour characteristics at histology, and imaging explorations.

The relevant data will be recorded in the Registry DataBase (RedCap).

It is important to note that the imaging explorations to be performed are those planned by usual clinical practice. The participation in this study does not imply a modification in the pattern of imaging explorations use.

It is the site investigator's responsibility to ensure adequate source documentation for all collected data. Designated investigator staff will enter the data required by the protocol into the eCRFs. The investigator must certify that the data are complete and accurate by entering a password. After being reviewed for completeness, plausibility, and correctness by the monitor, the data are locked. At 1 year an interim analysis will be conducted to verify conditions to extend recruitment and/or follow-up to satisfy the primary endpoints.

A CRO will be responsible for data management (review, cleaning up, query, etc.); timely updated reports will be sent to the participating centres.

Study calendar**:**
All patients included should be evaluated according to the evaluation calendar presented below:

Evaluation	**Baseline visit**	**Interval time for baseline imaging diagnostic work up**	**Landscape visit** (4-6 weeks from baseline, or as soon as a treatment decision is made)	**Interim analysis** (1 year)	**Follow-up visits** (every 3 months, covering a minimum of 24 months from baseline)
Informed Consent Form	√				
Selection criteria	√				
Socio-demographic data (age, family history of prostate, breast, or ovarian cancer)	√				
Past medical history (other than prostate cancer)	√				
Tumour characteristics (prostate cancer), including diagnosis date	√				
Imaging explorations (NGI, conventional or combination)		√			√
Relevant information from imaging explorations			√		√
Patients with treatment decision (determined by the of imaging test)			√		
PSA / PSA DT	√				√
Events (biochemical/radiological/clinical progression)					√
Relevant concomitant treatments			√		√

2.10 Data monitoring, quality control, and assurance

In this study, monitoring will be done remotely, by videoconference and/or email correspondence. The Investigator and institutions involved in this study will agree to allow study monitors from the Sponsor or its designee direct access (through the computer) to all source data, and documents, including a subject's complete medical record if necessary. eCRFs will be checked by the monitor remotely and queries will be created if there is any inconsistency with the patient source documents. The number of monitoring visits will depend on the course of the study/patient recruitment. Direct access must also be granted to authorized auditors, IRB/IEC reviewers, and all applicable regulatory bodies as necessary.
Monitoring of the study will be arranged by the Sponsor or its designee (e.g., CRO). The study site may also be subject to quality assurance audits by the Sponsor or its designee (e.g., CRO), as well as inspection by the appropriate regulatory agencies. The site investigator and their relevant personnel must be available during the monitoring visits and any scheduled audits, and study-related records must be made available, and sufficient time must be devoted to the monitoring process.
The completion of the study involves the collection and processing of personal data. All processing of personal data at the clinic and by the Sponsor must be carried out by national legislation concerning the protection of personal data. The site Investigator is responsible for the subject's privacy, as well as for the quality of data collected. On the eCRF or other documents submitted to the Sponsor, subjects will be identified by a subject identification code only. Documents that are not submitted to the Sponsor (e.g., signed ICF) should be kept in a strictly confidential file by the Investigator (ISF). As part of the required content of the ICF, subjects will be informed that their records may be reviewed by the Sponsor or its designee and by regulatory agencies. Should access to medical records require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.
All monitoring findings will be reported and followed up with the appropriate persons promptly.

2.11 Adverse event monitoring and documenting

This is a low-risk study and there are no unexpected adverse reactions from the study procedures as they are part of standard care. Any intervention is expected to be aligned to standard care. Any adverse event related to the ongoing treatment, and/or to the imaging exploration, and/or to any intervention should be reported by the site Investigator to the local authorities according to the relevant regulations in place, as by usual clinical practice.

Definitions
Adverse event (AE)
Any untoward medical occurrence in a subject to whom a study intervention or procedure has been administered, including occurrences that are not necessarily caused by or related to that intervention. An AE, therefore, does not necessarily have a causal relationship with a new initiated treatment
Product Quality Complaint (PQC):
Any complaint for a medical product that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or delivery system is considered a PQC. Not all PQCs involve a patient.

The notification of undesirable effects related to the use of medical devices will be carried out in accordance with the provisions of European law.

2.12 Final report, publication, and data-sharing policy

All study information is considered confidential and the property of the Sponsor until publication. The results or conclusions of this study may be sent to scientific conferences and medical journals. The investigator agrees to keep this information strictly confidential and will not use it for any other purpose without written permission from the Sponsor.

Once the study has been completed and the statistical analysis performed, the Sponsor will prepare the final report of the study. This report will contain a description of the objectives and methodology of the study as well as the results and conclusions. It will be sent to the IEC/IRB and Health Authorities (HA) if requested.

2.13 Data Security Arrangements

The database will be held and administered by the Sponsor. The database administrators have considerable experience in managing large databases for oncology diseases. Database management will require regular review of cases with feedback to site investigators to clarify data inconsistencies and to address missing or incomplete data. An audit of the informed consent process and source data verification will be conducted on a sampling basis.

2.14 Compliance with the Data Protection Act

All data entered will be anonymized and will be processed according to the General Data Protection Regulation (GDPR) - Regulation (EU) 2016/679. This will be the responsibility of the Host institution. Each participating centre will need to ensure they are in line with GDPR guidance and that they are satisfied with processes before data entry. The information included in the RING database will be only accessible to the data manager and the members of the Steering Committee, for both monitoring and statistical analysis. The site investigator and the sponsor are jointly responsible for the treatment of patients' personal data.

2.15 Ethical approval and good clinical practice

The investigator will ensure that the study is conducted in compliance with the study protocol, the ethical principles contained in the latest version of the Declaration of Helsinki developed by the World Medical Association, the principles of GCP, and the long-term sustainability of disease registries in the EU. Each partner site will obtain the IEC/IRB approval. Additionally, any other necessary approvals required by partner sites will be obtained before the commencement of the study at the site. All patients must provide written informed consent to participate. It is the responsibility of the investigator at individual sites to obtain the appropriate approvals and to ensure that informed consent is in place. ~~The site investigator and the sponsor are jointly responsible for the treatment of patients' personal data.~~

2.16 Sponsorship, Stakeholders, and Funding Arrangements

The Sponsor is defined as the organization responsible for the administration and management of the study. In this case, the sponsoring organization will be the Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau (Barcelona, Spain).
The project has received the endorsement and scientific support from the EAU-Research Foundation.
The study and network activities may be funded by educational and research grants from the pharmaceutical industry, academic funders, professional societies, or charities as appropriate.
In the Stage 1 part of the study, will be supported by the contribution of Janssen. Further fund raising will apply to undertake the Stage 2 e part of the project. In each case, the investigators will discuss and agree on a research contract with individual funding bodies to cover:
- The work to be undertaken
- The financial contribution and payment terms
- The share of technical, commercial, and economic risks for each part
- The right to publication of results
- Ownership of work and access rights to data
- Agreed liabilities and indemnities

2.17 Study Management:

Principal investigator responsibilities:

- Ensuring that no participant is recruited into the study until all relevant regulatory permissions and approvals have been obtained.
- Obtaining written informed consent from participants before any study-specific procedures.
- Familiarity with the study procedures.
- Compliance with the protocol, documentation of AE of Grade 3 and 4.
- Study conducts and the welfare of study subjects.
- Screening and recruitment of subjects.
- Provision of adequate medical care in the event of an adverse event.
- Compliance with the Declaration of Helsinki developed by the World Medical Association, the principles of GCP, the long-term sustainability of disease registries in the EU, and any other relevant legislation and regulatory guidance.
- The PI shall be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial. S/he shall provide a current signed & dated curriculum vitae as evidence for the Trial Master File.
- Ensuring Study Site team members are appropriately qualified by education, training, and experience to undertake the conduct of the study.
- Availability for Investigator meetings, monitoring visits, and in the case of an audit.
- Maintaining study documentation and compliance with reporting requests.
- Maintaining a site file, including copies of study approval, list of subjects, and their signed informed consent forms.
- Documenting appropriate delegation of tasks to other study personnel e.g., research nurse, co-investigator (s), trial coordinators, and data managers.
- Ensuring data collected is accurate, timely & complete.
- Providing updates on the progress of the trial.
- Ensuring subject confidentiality is maintained during the project and archival period.
- Ensuring archival of study documentation for a minimum of 15 years following the end of the study unless local arrangements require a longer period.

Protocol amendments, deviations, and breaches

Amendments to the current registry study protocol should be made only after consultation between an authorized representative of the Sponsor and the investigator. Amendments to the protocol must be prepared by a representative of the Sponsor and reviewed and approved initially by the Sponsor's medical team and a biostatistician.

All substantial amendments to the protocol should be sent to the same IEC/IRB for approval by local requirements. Approval must be expected before any changes are made, except those necessary to eliminate immediate risks to trial patients. A record of non-substantial amendments (when the change/s involves only logistical or administrative aspects in the study, e.g., change of telephone number, change of monitor, must be kept.

Study documentation

The investigator is responsible for maintaining an ISF during and after the study. A representative of the Sponsor is responsible for establishing the file. The study monitor will deliver it to the investigator and instruct the investigator on the appropriate use of the file. The relevant contents and completeness of the file will be monitored. The Investigator's file includes the correspondence, copy of the final signed protocol including appendices and amendments, ethics committee approval and other correspondence with the ethics committee, agreements, copy of the notification to the regulatory authority, signed copies of ICFs, information to study team members, patient identification list, final study report, source data other than those archived in the hospital records, investigator's copies of completed eCRFs and study termination form.

The investigator is responsible for retaining the ISF for at least 5 years to allow for audit or inspection after terminating the study. The investigator should ensure that the patient's files (patient's medical history) can be archived for at least 15 years in the hospital.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

2.18 Study Duration/end of study

The planned start date will be in 2024. The study recruitment period will be 18 months.
During the study, the investigator will collect data from the patient´s medical records, necessary to complete the eCRF.

The end of the study is defined as data entry for the last patient visit. The Sponsor or Steering Committee has the right at any time to terminate the study for clinical or administrative reasons. The end of the study will be reported to the Sponsor and the appropriate IEC/IRB within appropriate local and/or national timelines by individual Sites. Individual Sites will be responsible for ensuring appropriate follow-up and information to participants in the event of premature termination of the study.

2.19 Statistical Analysis

Data collection and data analysis

The investigator must include the required data in an eCRF according to standard procedures. At the end of the study, a statistical report will be performed with all tables, lists, and figures as per the statistical analysis plan.

Statistical Analysis Plan and Statistical Methods

This collection of cases has the main objective to analyse the clinical management of the APC population in a real-life context. Different analyses have been planned by using the information collected at baseline and during follow-up.

A description of the collected cases will be performed. Qualitative variables will be described with absolute frequencies and percentages. The description of quantitative variables will be performed using the mean, SD, median, and quartiles. The Kolmogorov-Smirnov test will be used to assess the normality of distributions.

Sample size calculation

In the context of a registry, there is no sample size required to be calculated. However, given the prevalence of the targeted stage disease and the mean volume of the centres involved, an average of 35 consecutive patients/year per centre was estimated, with an overall number of 600 patients recruited in the 1.5 years of the study's recruitment period (whichever comes first). Baseline visits will be done coinciding with any of the routine follow-up visits of the patient, without any alteration of the standard clinical practice of the site.

Section 3: References

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