CLINICAL STUDY PROTOCOL

Study Code: COST-PCCT-CCS Trial
Cost
Outcome
Study of
Computed **T**omography –
Photon
Counting
Compared with
Traditional (EID) in
Chronic
Coronary
Syndrome

Title: Randomized Prospective Trial on the Cost-Effectiveness of Photon-Counting CT Versus Energy-Integrating Detector CT in Suspected Chronic Coronary Syndrome

Principal Investigator: Antonio Esposito

CLINICAL STUDY PROTOCOL

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Study Code	COST-PCCT-CCS Trial
Other Protocol Identifiers	To be registered in ClinicalTrial.gov
Version	1.2
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Sponsor	Università Vita Salute San Raffaele (UNISR)
Authorized Sponsor Representative	Antonio Esposito, MD Professore di Radiologia, Università Vita-Salute San Raffaele Direttore Programma Strategico Imaging Cardio-Toraco-Vascolare e della Prevenzione con Tecnologie Avanzate, Ospedale San Raffaele
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1. KEY STUDY CONTACTS

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Funding source(s)	Siemens Healthineers.
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2. SYNOPSIS

Study Code	COST-PCCT-CCS Trial
Study Title	Randomized Prospective Trial on the Cost Effectiveness of Photon Counting CT Versus Energy Integrating Detector CT in Suspected Chronic Coronary Syndrome
Protocol Version and Date	Version 1.2 date 02/07/26
Sponsor	Università Vita-Salute San Raffaele (UNISR) Via Olgettina, 58 20132 – Milano, Italy
Funding Source(s)	Siemens Healthineers
Principal Investigator	Antonio Esposito
Study Description	Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality worldwide. Coronary computed tomography angiography (CCTA) is the first-line imaging test for patients with suspected obstructive CAD. However, its main limitation is the relatively low and variable specificity and positive predictive value across different studies, especially in patients with high calcified coronary plaque burden due to blooming and beam-hardening artifacts that can lead to the overestimation of the degree of coronary artery stenosis, reduced specificity, and, consequently, increased rate of downstream functional imaging tests or diagnostic invasive coronary angiography (ICA). Photon-Counting Detector–Computed Tomography (PCD-CT) represents an important evolution in the CT technology introduced in the clinical practice in the last years, but still with a limited diffusion due to the high purchase cost of the scanners. In the context of CAD evaluation, the two modalities differ in spatial resolution, blooming artifacts, and electronic noise levels, representing distinct technical approaches to diagnostic imaging accuracy. Recent studies demonstrate that these technical advantages may translate into a higher diagnostic accuracy of PCD-CT in differentiating functional significant stenosis from non-significant stenosis, with a lower rate of false positive results and higher overall diagnostic accuracy. This increase in diagnostic accuracy with reduction in false positive results may be associated to a reduction in downstream functional tests performed after a PCD-CT CCTA compared with an EID-CT CCTA, as well as a decrease in unnecessary invasive coronary angiographies resulting from false-positive CCTA findings. Moreover, a more precise diagnosis may also translate into more appropriate treatment decisions and potential prognostic benefits.

	These potential advantages may ultimately lead to a reduction in downstream healthcare expenditures when using PCD-CT CCTA. However, the impact of these differences on clinical decision-making and healthcare resource utilization remains to be fully established in real-world settings. Thus, we propose to compare the diagnostic performance of PCD-CT performed with a NAEOTOM Alpha photon-counting CT scanner (Siemens Healthineers, Germany) and EID-CT performed with a SOMATOM Definition Flash; (Siemens Healthineers, Germany) in the identification and quantification of CAD. Moreover, we aim to assess the cost-effectiveness and the prognostic impact of PCD-CT compared to EID-CT in CAD diagnosis and management according to 2024 ESC Guidelines, collecting all index data related to the patients' clinical history from the day of the CCTA examination up to two years afterward, and estimating healthcare costs according to the national and regional reimbursement tariffs of the public health system for all healthcare services delivered.	
Study Design	Single-center, randomized interventional study on a diagnostic procedure, including remote follow-up via telephone or teleconsultation	
Primary Objective To compare the positive predictive value (PPV) of coronary computed tomography angiography (CCTA) performed using PCD-CT versus EID-CT, when used according to the clinical indications defined by the 2024 ESC Guidelines for the management of chronic coronary syndromes.	**Primary Endpoint** Positive predictive value (PPV) of CCTA for the detection of obstructive CAD, using ICA as the reference standard.	**Time point(s)** Baseline diagnostic workup
Secondary Objectives To evaluate the cost-effectiveness cost-effectiveness comparing two CT platforms implemented in routine clinical practice in the diagnostic workup of suspected chronic coronary syndromes, according to the 2024 ESC Guidelines.	**Secondary Endpoints** Incremental cost-effectiveness ratio (ICER), expressed as cost per correctly diagnosed patient based on healthcare resource utilization and diagnostic outcomes. For the calculation of the ICER true negative will be considered all patients with negative CCTA without events (MACEs) over the 3 years FU.	**Time point(s)** Follow-up analysis.
Exploratory Objective 1 Comparing accuracy of CT-based FFR between PCD-CT and EID-CT in the subgroup of participants who will undergo ICA and/or functional tests for clinical reasons	**Other** Sensitivity, specificity, PPV and NPV of vessel CT-based FFR in defining functional significance of stenosis considering FFR < 0.8 as threshold of significance.	**Time point(s)** 1st and 2nd year
Exploratory Objective 2 Comparing long-term clinical outcomes between the two study	**Other** Occurrence of major adverse cardiovascular events (MACEs) including death from coronary heart	**Time point(s)** 36-month follow-up

groups over a 36-month follow-up period.	disease or non-fatal myocardial infarction.	
Study Population	Patients undergoing clinically indicated coronary CTA for suspected CAD	
Inclusion Criteria	1) Patients with clinical indication to perform CCTA for CAD assessment according to 2024 ESC Guidelines	
Exclusion Criteria	1) Refusal to participate in the study 2) Age <18 years old	
Intervention(s)		
Intervention(s)	Randomization	
Comparator	PPV of CCTA performed using EID-CT (n=315) will be compared with CCTA performed using PCD-CT (n=315). CCTA will always perform according to routine and normal clinical practice.	
Safety Criteria	Diagnostic procedures (CCTA) are performed according to the 2024 ESC Guidelines for the management of CCS and represent standard-of-care clinical practice. No additional examinations, radiation exposure, or contrast administration beyond routine clinical management are required by the study protocol. Patient safety will therefore be ensured through adherence to institutional imaging protocols and current clinical guidelines, including radiation dose optimization principles and standard monitoring for contrast-related adverse events. All adverse events will be recorded according to routine clinical practice.	
Efficacy Criteria	The primary efficacy criterion is the PPV of CCTA for the detection of obstructive CAD, (defined as a functionally significant coronary stenosis), using functional imaging tests (e.g. stress CMR, SPECT or stress-Echo) or invasive coronary angiography (ICA) as the reference standard. Secondary efficacy criteria include the evaluation of diagnostic accuracy metrics (sensitivity, specificity, accuracy) and the Incremental Cost-Effectiveness Ratio (ICER), calculated based on healthcare resource utilization, downstream testing, and diagnostic outcomes. Finally, the prognostic outcomes over 36 months, defined as death from coronary heart disease or non-fatal myocardial infarction will be evaluated as exploratory endpoint.	

Sample Size	A total of 630 subjects will be included in the study, with a randomization ratio of 1:1 between the two groups.
Statistical Design	This is a prospective, randomized, single-center interventional study with a 1:1 allocation ratio between PCD-CT and EID-CT groups (315 patients per arm, total N=630). Descriptive statistics of the study population and of the two groups will be calculated. Comparisons of diagnostic performance will be performed using appropriate statistical tests (chi-square or Fisher's exact test for categorical variables; t-test or Mann–Whitney U test for continuous variables). Positive predictive value will be calculated with 95% confidence intervals. Cost-effectiveness analysis will be conducted using standard health economic methods. For survival analysis, we will use the Cox proportional hazards (Cox PH) regression model to estimate the risk of MACE at 36 months and log-rank test will be used for comparison. Standard Kaplan-Meier curves will be computed to visualize event-free survival.
Duration of the Study	Duration of enrollment: enrollment of patients will last 12 months from the beginning of the study (month 0) Duration of subject participation: 36 months] Duration of treatment: NA Duration of total follow-up: each patient will be followed up for 36 months from the date of the CCTA Duration of total study period: total prospective study duration will be 54 months (last patient enrolled at month 12 + 36 months of follow-up + 6 months for data analysis)

3. ABBREVIATIONS AND DEFINITIONS

3.1. Abbreviations

CAD	Coronary artery disease
CCS	chronic coronary syndromes
CCTA	Coronary Computed Tomography Angiography
EID-CT	Energy-integrating detector-CT
ICA	Invasive coronary angiography
MACE	Major adverse cardiovascular events
PCD-CT	Photon-counting detector-CT
PPV	Positive predictive value
PH	Proportional Hazards

4. BACKGROUND AND RATIONALE

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality worldwide.
Coronary computed tomography angiography (CCTA) is recommended as a first-line diagnostic test for patients with suspected chronic coronary syndrome at low-to-moderate pre-test probability of obstructive CAD, according to the 2024 ESC Guidelines (doi:10.1093/eurheartj/ehae177), the American Heart Association (AHA) (doi: 10.1161/CIR.0000000000001168) and Italian Guidelines (doi: 10.1007/s11547-021-01378-0).
Although CCTA serves as an effective and safe initial diagnostic tool and gatekeeper for invasive coronary angiography (ICA) due to its very high negative predictive and, hence, very high safety in excluding significant CAD, one of the main limitations is its relatively low and variable specificity and positive predictive value across different studies.
A recent meta-analysis by Knuuti et al. (doi: 10.1093/eurheartj/ehy267) reported a sensitivity of 97% but a specificity of 78% for diagnosing obstructive CAD of CCTA using ICA as the reference standard. These data are derived from studies of the last years, all based on the use of energy Integrating Detector–Computed Tomography (EID-CT) scanners. EID-CT represents the currently most diffused technology used for CCTA over the world; however, its diagnostic accuracy may be limited by image noise, blooming artifacts from coronary calcifications, and limited spatial resolution, which can lead to the overestimation of coronary artery stenosis, and to an increased rate of downstream diagnostic ICA (doi:10.1556/ 1647.2020.00011.; doi: 10.1148/rg.2016160079; doi: 10.1016/j.jcct.2023.11.079.). A recent meta-analysis showed that the specificity of CCTA for diagnosing obstructive CAD significantly dropped with a high total CAC score (doi: 10.1016/j.jcmg.2018.07.022.)
Photon-Counting Detector–computed tomography (PCD-CT) is a recent technological development in CT imaging, with technical differences compared to conventional energy-integrating detector CT (EID-CT), associated to improved spatial resolution, reduced electronic noise, and decreased blooming artifacts (doi: 10.3348/kjr.2022.0377.). However, the impact of these differences on clinical decision-making and healthcare resource utilization remains to be fully established in real-world settings.
These technical advances could potentially provide a more accurate and detailed assessment of coronary arteries stenosis and atherosclerotic plaque features, making it very promising in the cardiovascular imaging field (doi: 10.1186/s12880-025-02038-9; doi: 10.1148/radiol.230160). Indeed, a recent study showed that PCD-CT improved image quality and diagnostic confidence of physicians reading CT images for assessing CAD compared with EID-CT (doi: 10.1148/radiol.211780).

A few recent retrospective studies have suggested the potential advantage of PCD-CT over EID-CT in the diagnostic accuracy of CAD, improving the evaluation of luminal stenosis in the presence of calcified plaques (doi: 10.1117/12.2613019.) and resulting in a reduced number of subsequent ICA (doi: 10.1016/j.jcct.2023.11.079.; doi: 10.1016/j.jacc.2024.10.069. Epub 2024 Oct 28. PMID: 39466216). In particular, retrospective evaluation by Sakai et al. (doi: 10.1016/j.jacc.2024.10.069) compared patient outcomes after CCTA on EID-CT and PCD-CT. The authors observed that the PCD-CT group had lower referral rates to subsequent ICA, a higher frequency of revascularization among referred patients, and a reduced rate of unnecessary diagnostic angiographies.

Moreover, recent studies estimated the cost-effectiveness of PCD-CT compared to EID-CT in clinical practice by developing decision and simulation models using Monte Carlo simulations:

results suggested that PCD-CT has the potential to reduce the financial burden on healthcare systems and procedure-related complications for stable chest pain patients when compared to EID-CT (doi: 10.1016/j.jcct.2024.10.011. doi: 10.1016/j.ejrad.2025.112245.), although these results coming from simulation need to be confirmed on prospectively collected real data,

In fact, prospective comparative real-world data about the potential impact of PCD-CT in clinical practice on PPV, healthcare costs, and eventually prognosis, are still lacking.

This study is designed as a pragmatic, real-world comparison between two CT platforms used in routine clinical practice at the participating institution, the EID-CT which represents a clinically established dual-source high performance CT system routinely used for CCTA, and the PCD-CT, a novel platform promising higher spatial resolution and native spectral sensitivity, in patients with suspected chronic coronary syndromes undergoing clinically indicated CCTA according to ESC guidelines.

The objective is to evaluate the overall clinical performance, downstream diagnostic pathways, and associated costs as observed in real-life implementation conditions, hence, the results are expected to provide clinically relevant evidence to support technology adoption decisions and optimize diagnostic strategies in contemporary CAD care.

5. RISK/BENEFIT ASSESSMENT

This study involves patients with suspected chronic coronary syndrome undergoing clinically indicated CCTA according to the 2024 ESC Guidelines. Both imaging modalities (Photon Counting CT and Energy Integrating Detector CT) are approved technologies routinely used as standard procedures in clinical practice, although the PCD-CT scanner have limited diffusion due to the high cost.
The study does not have associated risks. Patient safety, and well-being are ensured through adherence to established clinical guidelines and institutional imaging protocols.
Benefit for the patients: Participation in the study will be offered to patients who already have an appointment for coronary CT angiography on our institution's EID-CT scanner. Following 1:1 randomization, half of the patients who will express voluntary and informed consent to participate in the study, will be allocated to the PCD-CT arm and will therefore undergo their examination on the PCD-CT system instead of the EID-CT they would have received outside the study. Although all the patients will receive the examination according to the current internal clinical practice and in compliance with the current international and national guidelines, is already known as the use of PCD-CT provides advantages for patients. This technology enables coronary imaging with higher spatial resolution with equal ore reduced radiation exposure and contrast medium amount (doi: 10.1186/s12880-025-02038-9). As a result, participants randomized to the PCD-CT arm may directly benefit from these improved imaging conditions. Hence, the participation to the study as no risk and is associated to potential benefits for enrolled participants.

5.1. Known Potential Risks

The study does not introduce any additional risk to the standard-of care clinical practice.

Thus, the only risks associated with participation in this study are consistent with those of standard-of-care CCTA, in particular:

- Contrast Media Reactions: Potential for allergic or hypersensitivity reactions to iodinated contrast media, ranging from mild (nausea, flushing) to severe (anaphylaxis).
- Contrast-Induced Nephropathy (CIN): Risk of renal function impairment, which will be mitigated by screening patients' eGFR prior to the procedure.
- Extravasation: Potential for contrast media to leak at the injection site.
- Radiation Exposure: Both scanners involve exposure to ionizing radiation within the limits requested for the examination.

5.2. Known Potential Benefits

PCD-CT is known for potential differences in performance compared to EID-CT, such as improved spatial resolution, reduced electronic noise, and decreased blooming artifacts. Recent studies demonstrated that PCD-CT offers improved image quality providing a more accurate and detailed assessment of coronary arteries stenosis, resulting in increased diagnostic confidence of radiologists and reduced number of patients referred to non-necessary ICA (doi: 10.1016/j.jacc.2024.10.069.; doi: 10.1016/j.jcct.2023.11.079; doi: 10.1148/radiol.211780.).
Thus, the participants randomized to the PCD-CT arm may benefit from optimized diagnostic accuracy (higher PPV) and potentially reduced non-necessary ICA, reducing the risk of procedural complications and radiation exposure.
The main long-term benefit would be to optimize clinical management and long-term prognosis based on a more detailed characterization of coronary plaques and stenosis severity.

5.3. Assessment of Risks and Benefits ratio

The risks to participants are reasonable and minimized by the study design, as both diagnostic procedures are performed according to the 2024 ESC Guidelines for chronic coronary syndromes. No experimental interventions are introduced. Risks are minimized through guideline-based patient selection, optimized imaging protocols, and standard safety monitoring.
The potential for PCD-CT to significantly improve the Positive Predictive Value (PPV) and reduce the burden of false-positive results provides a high value of information.

6. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints	Time point(s)
Primary Objective To compare the positive predictive value (PPV) of coronary computed tomography angiography (CCTA) performed using PCD-CT versus EID-CT, when used according to the clinical indications defined by the 2024 ESC Guidelines for the management of chronic coronary syndromes.	**Primary Endpoint** Positive predictive value (PPV) of CCTA for the detection of obstructive CAD, using ICA as the reference standard.	**Time point(s)** Baseline diagnostic workup

Secondary Objectives	Secondary Endpoints	Time point(s)
To evaluate the cost-effectiveness comparing two CT platforms implemented in routine clinical practice in the diagnostic workup of suspected chronic coronary syndromes, according to the 2024 ESC Guidelines.	Incremental cost-effectiveness ratio (ICER), expressed as cost per correctly diagnosed patient based on healthcare resource utilization and diagnostic outcomes. For the calculation of the ICER true negative will be considered all patients with negative CCTA without events (MACEs) over the 3 years FU.	Follow-up analysis.

Exploratory Objective 1	Other Exploratory Endpoints	Time point(s)
Comparing accuracy of CT-based FFR between PCD-CT and EID-CT in the subgroup of participants who will undergo ICA and/or functional tests for clinical reasons	Sensitivity, specificity, PPV and NPV of vessel CT-based FFR in defining functional significance of stenosis considering FFR < 0.8 as threshold of significance.	1st and 2nd year

Exploratory Objectives 2	Other Exploratory Endpoints	Time point(s)
Comparing long-term clinical outcomes between the two study groups over a 36-month follow-up period.	Occurrence of major adverse cardiovascular events (MACEs) including death from coronary heart disease or non-fatal myocardial infarction.	36-month follow-up

7. STUDY DESIGN

Today, the non-invasive characterization and quantification of coronary plaque and stenosis with CCTA have become essential for implementing highly personalized preventive strategies aimed at improving patient prognosis and avoiding overtreatment. CCTA is the standard of care for CAD assessment and is commonly acquired using conventional EID-CT scanners. CCTA acquired on a EID-CT scanner has a very high negative predictive value, but a suboptimal positive predictive value which is cause of unnecessary downstream functional imaging examinations and invasive coronary angiography procedures. The recent introduction of PCD-CT offers the opportunity to overcome most of these limitations, enabling a more precise and detailed evaluation of coronary stenosis and atherosclerotic plaque morphology, potentially improving the positive predictive value.

We believe that integrating PCD-CT into clinical practice may enhance the diagnostic accuracy of CCTA for detecting obstructive CAD compared with EID-CT, particularly by increasing PPV and thereby reducing the number of unnecessary invasive procedures. Consequently, PCD-CT implementation may improve cost-effectiveness and have a favorable long-term impact on patient prognosis. Moreover, PCD-CT, providing anatomical images of the coronary arteries characterized by superior spatial resolution, may allow a more precise and reliable extraction of CT-based FFR compared to EID-CT.

This is a single-center, open-label, randomized study that includes remote follow-up through telephone calls or teleconsultations of patients undergoing clinically indicated CCTA for the evaluation of atherosclerotic CAD.

Eligible participants will be randomized in a 1:1 ratio to undergo PCD-CT (Group B, n = 315) or EID-CT (Group A, n = 315). Randomization will be performed centrally through a computer-generated, unstratified allocation sequence. Imaging procedures are unblinded. Bias will be minimized through random allocation, standardized acquisition protocols, guideline-based patient selection, and uniform image interpretation.

Patients will be identified and randomized to PCD-CT performed with a NAEOTOM Alpha photon-counting CT scanner (Siemens Healthineers, Germany) or EID-CT performed with a SOMATOM Definition Flash; (Siemens Healthineers, Germany) before the time of their clinically indicated CCTA. All subsequent evaluations and procedures will follow routine clinical practice. Therefore, decisions regarding additional diagnostic or therapeutic interventions will remain entirely independent of study participation. In particular, ICA will be performed when clinically indicated according to current guidelines and the treating physician's judgment.

Aside from randomization, the only study-related procedures will be periodic telephone calls or teleconsultations (maximum interval of 3 months for the first year, 1 time/year after) to collect follow-up data throughout a 36-month period.

Patients' data (e.g., data related to demographics, risk factors and clinical-instrumental visits) will be collected to achieve the study objectives. All data collected will be treated in agreement with the current legislation.

7.1. Study duration

Duration of enrollment: enrollment of patients will last 12 months.
Duration of treatment/procedure: 1 day (single session)

Duration of total follow-up: each patient will be followed up for 36 months from the date of the CCTA.
Duration of total study period: total prospective study duration will be 50 months (last patient enrolled at month 12 + 36 months of follow-up + 2 months for data analysis).

8. STUDY POPULATION

8.1. Study Participants

The study will enrol 630 adult patients with suspected chronic coronary syndromes referred for clinically indicated CCTA according to the 2024 ESC Guidelines.
Participants will be recruited consecutively from patients presenting to the study hospital and meeting eligibility criteria. All subjects will provide written informed consent prior to inclusion.

8.2. Inclusion Criteria

- Patients with clinical indication to perform CCTA for CAD assessment according to 2024 ESC Guidelines

8.3. Exclusion Criteria

- Refusal to participate in the study
- Age <18 years old
- Severe reduction in eGFR (<30 mL/min)

8.4. Screening Failures

Screening failures are defined as participants who provide informed consent but do not meet one or more eligibility criteria during the screening process and therefore are not randomized. Basic demographic data and the reason for screening failure will be recorded to allow transparent reporting. No further study-related data will be collected from screening failures.
Participants who fail screening due to potentially modifiable or transient conditions (e.g., temporary renal function impairment, uncontrolled heart rate, or temporary contraindications to CCTA) may be rescreened at the discretion of the investigator once the condition has resolved. Rescreened participants will retain the same screening identification number.
Participants who fail screening due to non-modifiable criteria (e.g., known obstructive coronary artery disease or permanent contraindications to contrast media) will not be rescreened.
Screening failures will not undergo any study-specific procedures and will continue to receive standard clinical care.

9. STUDY INTERVENTIONS

9.1. Intervention description

Participants will undergo clinically indicated CCTA according to the 2024 ESC Guidelines for the management of chronic coronary syndromes. Both imaging scanners used in this study are CE-

marked within the same CE-marked product family (Medical and electromedical apparatus and equipment, in particular computed tomography scanners) and routinely employed in clinical practice.

Two randomized study groups are defined:

- Group A: CCTA performed using Energy Integrating Detector CT (EID-CT).
- Group B: CCTA performed using Photon Counting CT (PCD-CT).

Both PCD-CT and EID-CT examinations constitute standard-of-care diagnostic procedures and follow identical clinical indications and patient preparation. Both protocols need contrast administration, ECG-gated acquisition, and provide radiation dose optimization strategies.
The procedure is performed at baseline after patient enrollment and randomization. If the scan is positive for obstructive CAD and clinically indicated, the reference standard (Invasive Coronary Angiography) will be scheduled within routine clinical timeframes.
Hence, the clinically indicated CCTA is not a study-related intervention, both for participants randomized in the Group A and in the Group B, as well as the entire clinical pathway that the participants will follow after the CCTA. Therefore, aside from the scheduled telehealth follow-up that is already part of the study design, the only additional intervention beyond routine clinical care will be the structured recording of study-specific data in a dedicated electronic Case Report Form (eCRF). No further diagnostic tests, imaging procedures, or therapeutic actions beyond standard practice will be introduced."

9.2. Method for Assigning Subjects to Treatment/Intervention Groups

Eligible participants will be randomized in a 1:1 ratio to either PCD-CT-CCTA or EID-CT CCTA. Randomization will be performed centrally using a computer-generated allocation sequence. Assignment will occur after confirmation of eligibility and informed consent. Allocation will be communicated to the imaging team prior to the scheduled examination.

Randomization 1:1, is managed via REDCap platform. In particular, the randomization list is prepared by the Clinical Trial Center (CTC) and uploaded on REDCap platform. The Investigator will randomize the participant, upon communication and request by the sub-Investigators.

9.3. Blinding of treatment/procedure

Due to the nature of the imaging procedures, blinding of participants and operators is not feasible.

9.4. Preparation, Administration and Accountability of the study Treatments

This study does not introduce any investigational medicinal product, investigational device modification, or therapeutic intervention. Both imaging modalities evaluated in the study—Photon-Counting Detector CT (PCD-CT) and Energy-Integrating Detector CT (EID-CT)—are CE-marked, clinically approved CT systems used in routine coronary computed tomography angiography (CCTA). Therefore, all diagnostic examinations included in the protocol are

performed strictly according to standard clinical practice, institutional guidelines, and manufacturer instructions for use.

9.4.1. Preparation of the Study Imaging Procedures

Preparation for CCTA examinations (both PCD-CT and EID-CT) follows **routine clinical workflow**, including:

Patient identification and eligibility confirmation.

Standard pre-CCTA preparation (e.g., heart rate control, sublingual nitrates when clinically appropriate, fasting status, IV access).

Verification of renal function, contrast media contraindications, and known allergies as per institutional and ESC guidelines.

No additional preparation steps are required for study purposes.

9.4.2. Administration of Imaging Procedures

The imaging protocol (contrast administration, scanning parameters, reconstruction techniques) remains identical to routine diagnostic CCTA protocols already implemented at the participating institution. The study does not alter clinical decision-making, image acquisition, or post-processing parameters beyond standard practice.

The study does not mandate any additional pharmacologic agents, radiation exposure, contrast dose, or variant protocol beyond what is clinically indicated.

9.4.3. Follow-Up and Study-Specific Procedures

The only procedure introduced by the study in addition to routine care is:

A scheduled telehealth follow-up, included in the study design to assess downstream healthcare utilization up to one year and clinical outcomes up to three years after the index CCTA.

This telehealth follow-up does not involve physical visits, imaging, laboratory testing, or therapeutic interventions. It consists solely of structured remote assessment of the participant's clinical status and healthcare utilization.

9.4.4. Accountability and Documentation

Because no investigational treatment is administered, accountability relates exclusively to:

Documentation of clinical and imaging data derived from routine care in a **dedicated electronic Case Report Form (eCRF)**.

The eCRF provider is REDcap, a clinical electronic data capture system specifically developed around HIPAA-Security guidelines; more information on the consortium and system security is available at https.//www.projectredcap.org/.
The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement of a user ID and password to enter or change data. These user ID and password transmitted by OSR to study sites staff are personal and confidential. The list of individuals who are authorized to enter or correct data is available to the PI in REDCap. All data entry and corrections are recorded in the audit trail (date of data entry/correction, name of person, type of action).

Secure and complete entry of CCTA parameters, ICA findings (when clinically performed), downstream tests, healthcare utilization data, and follow-up outcomes.

Ensuring data accuracy, traceability, and audit readiness.

No investigational product tracking, drug accountability logs, or device accountability procedures are required.

9.4.5. Responsibilities of the Study Team

The Principal Investigator ensures that all imaging procedures are performed per standard clinical protocols.

Radiographers and radiologists follow institutional standard operating procedures for CCTA.

Study personnel trained in data management are responsible for the timely and accurate completion of the eCRF.

All personnel must comply with GDPR and institutional data protection policies.

9.5. Compliance with study treatment

Adherence to the study protocol will be assessed and verified for each of the following key phases:

- CCTA Procedure Compliance: Verified by the successful execution of the randomized CT scan (PCD-CT or EID-CT) and the availability of diagnostic-quality images in the institutional PACS. Non-compliance is defined as the inability to perform the scan.
- Reference Standard (ICA) Compliance: For patients with a positive CCTA and clinically indicated ICA, adherence will be verified by the performance of the Invasive Coronary Angiography within the clinically recommended timeframe. The study team will monitor the clinical records to ensure that all patients indicated for ICA actually receive the procedure, as this is essential for the primary endpoint (PPV) calculation.
- Follow-up Compliance: Adherence to the 36-month prognostic follow-up will be verified by the completion of scheduled telephone/telehealth interviews.

9.6. Concomitant Medication

All concomitant medications relevant to cardiovascular status will be recorded at baseline and at follow-up.
Routine cardiovascular therapies will not be restricted and will be managed according to standard clinical practice.
No study-related medication restrictions are imposed.

9.7. Other Interventions

Not applicable. No additional investigational interventions are included in this study. Invasive coronary angiography and subsequent treatments may occur only when clinically indicated and are not mandated by the study protocol.

10. EFFICACY AND SAFETY CRITERIA

10.1. Efficacy Criteria

Efficacy will be assessed through imaging, clinical, and economic outcomes.
Primary efficacy endpoint:

- Positive predictive value (PPV) of CCTA for detection of obstructive coronary artery disease, using invasive coronary angiography as reference standard.

Secondary efficacy endpoints:

- Cost-effectiveness expressed as incremental cost-effectiveness ratio (ICER) per correct diagnosis and per avoided clinical event.
- Downstream resource utilization (additional testing, invasive procedures).

Exploratory efficacy endpoints:

- Sensitivity, specificity, PPV and NPV of vessel CT-based FFR in defining functional significance of stenosis considering FFR < 0.8 as threshold of significance.
- Composite of death from coronary heart disease or non-fatal myocardial infarction during 36-month follow-up.

Imaging data will be collected from institutional PACS systems. Clinical outcomes will be obtained from electronic medical records and follow-up visits. Economic data will be derived from hospital administrative databases.

10.2. Safety Criteria

Adverse events will be collected according to routine clinical practice and documented in the study database. No additional laboratory or physical examinations beyond standard care are required. Participants experiencing adverse events will receive appropriate medical management according to institutional standards.

11. STUDY PROCEDURES

	Screening	Baseline	Study Visit (ICA if positive)	Follow-Up Visit	Follow-Up Visit	Follow-Up Visit
Day **Procedures**	-1 month to 0	Month 0	Within 6 months	+12 months	+24 months	+36 months
Informed consent	R					
Demographics	R					
Medical history	R					
Eligibility assessment	R					
Randomization / Allocation						
Physical examination (including height and weight)	C	C				
Vital signs	C	C				
Study procedure administration (CCTA)		C				
Additional Imaging assessment (ICA)*			C			
Collection of MACEs information				R	R	R

* Invasive coronary angiography (ICA), when required, is performed after CCTA according to standard clinical practice and is not mandated by the study protocol

11.1. Informed Consent

Informed consent will be obtained by the Principal Investigator or a designated sub-investigator prior to any study-specific procedures. The process includes a verbal explanation of the study's randomized nature, the comparison of CT technologies, and the long-term follow-up.
Consent forms describing in detail the study objectives, procedures, potential risks, benefits, and data handling will be provided to participants.
A copy of the signed informed consent will be archived, and the patient will be considered enrolled in the study. The clinician will inform the patient that participation to the study is voluntary and refusal to participate will not impact in any way on diagnostic or therapeutic procedures.

11.2. Subject Recruitment and Screening

Participants will be consecutively recruited among patients referred for clinically indicated CCTA at the participating centre.

The target sample size is of 630 participants, including adult men and women aged ≥18 years.
This is a monocentric study, with all participants enrolled at a single tertiary-care hospital.
Participants will be identified among patients scheduled for CCTA on EID-CT scanner as part of routine clinical care.
Potentially eligible participants will be approached by a member of the study team prior to the imaging procedure and provided with study information. Written informed consent will be obtained before enrolment.
After confirmation of eligibility and informed consent, participants will be randomized in a 1:1 ratio to undergo either PCD-CT or EID-CT.
Because follow-up is required for outcome assessment, retention will be supported through review of electronic medical records and, when necessary, telephone contact.

No vulnerable populations are specifically targeted in this study.

11.3. Subject Identification

Starting from the signature of the informed consent by the patient, the subject is considered enrolled in the study.

11.4. Randomization and Blinding

Participants will be randomly assigned (1:1) to one of the two CT scanners.
Randomization will be performed using the Clinical Trial Randomization Tool provided by the National Institutes of Health (NIH).
The randomization sequence will be generated centrally through the NIH Clinical Trial Randomization Tool and will not be accessible to investigators involved in participant enrollment prior to assignment, ensuring allocation concealment.

Randomization will occur after informed consent and confirmation of eligibility, immediately prior to the scheduled CT examination.

11.5. Baseline Assessments

Baseline assessment will be performed at the time of enrollment, including demographic data, risk factors, symptoms, current medications, clinical-instrumental tests results, clinical indication to perform CCTA, physical examination and vital signs.
Ad hoc electronic Case Report Forms (CRF) will be designed on RedCap to standardize data collection and thus facilitate subsequent analyses.
The data of patients who provided the informed consent will be treated in accordance to the pseudonymization procedures.
Collected data will be stored on a dedicated archive within the boundaries of the Promoter
Imaging baseline assessment will include CCTA data performed with either PCD-CT or EID-CT according to randomization, including imaging parameters (radiation dose metrics), presence, location, features and severity of coronary artery disease.

In patients with positive or clinically relevant CCTA findings, ICA may be performed according to standard clinical practice. ICA findings will be recorded.

Baseline economic data related to diagnostic resource utilization (imaging procedure type, additional testing, and immediate downstream procedures) will also be collected.

11.6. Visits and Follow Up

Patients will be contacted every 3 months via a telephone call or teleconsultation for the first year and every 12 months for the following 2 years.

11.7. Definition of End of Study

The end of the study will be defined as the completion of all the data analysis procedures.

12. DISCONTINUATION AND WITHDRAWAL

12.1. Discontinuation of study Intervention

Because this is a diagnostic imaging study and both coronary CT angiography techniques (PCD-CT and EID-CT) are performed as part of standard clinical care, discontinuation of the study intervention refers to inability to complete the assigned CCTA examination.

Reasons for discontinuation may include, but are not limited to participant withdrawal of consent, technical failure or inability to complete image acquisition, development of acute clinical conditions preventing completion of CCTA.

Participants who are unable to complete the assigned CCTA examination for any reason will be withdrawn from the study and excluded from follow-up analyses. These participants will continue

their diagnostic and therapeutic pathway according to standard clinical practice, regardless from study participation.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the CCTA may be replaced. Subjects who sign the informed consent form and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will also be replaced.
A participant will be considered lost to follow-up if he or she is unable to be contacted by the study site staff even after more than one telephone call or after a certified letter to the participant's last known mailing address.
Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

13. SAMPLE HANDLING

Not applicable.

14. PATIENT SAFETY

Randomization does not introduce any additional risk for participants. Both the CT scanner technologies (EID-CT and PCD-CT) are approved and routinely used in clinical practice and represent standard of care diagnostic procedures.
All imaging examinations will be performed according to institutional protocols and ESC guideline recommendations. Therefore, participation in the study does not expose patients to risks.
Telephone or tele-health follow-up does not introduce any additional risk to participants.

15. DATA MANAGEMENT

The information relating to the subjects of the study will be kept confidential and managed according to the relevant provisions (Legislative Decree 196/30 June 2003 and subsequent amendments and EU regulation 679/2016; Guidelines of the Privacy Guarantor of 24/07/2008).
The data of patients who provided the informed consent will be treated in accordance to the procedures described in the document attached to the study protocol.
Each patient will be assigned an identification code and the data collected during the study, with the exception of the name, will be recorded, processed and stored together with this code, age at diagnosis and all other data. Only the clinician of the study and the authorized subjects will be able to link the code to the name and will not provide third parties with the data of the patients included in the study.

15.1. Definition of source data and source documents

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies). Any

data recorded directly on the CRFs (i.e., no prior written or electronic record of data), is considered to be source data.
Source Documents: Original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; subjects' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies, subject files, or records)

A record of patient screen failures will be maintained for patients who do not qualify for enrollment, including the reason for the screen failure.

15.2. Documentation of data in Case Report Forms (CRFs)

All relevant data collected during the study for all of the patients enrolled in the study will be entered in the CRF by the responsible investigator or someone authorized by the investigator in a timely manner (as soon as possible after the information is collected. The physician will confirm the completeness, correctness, plausibility, and compliance with the ICH guidelines and the institutional SOPs of the data by dated signature. An explanation must be provided for any and all missing data. The duly
completed CRF will remain on the test site.

All study data, which include tabular data collected within CRFs and pseudonymized image data, will be stored on a cloud archive with regulated access within the IT boundaries of Università Vita-Salute San Raffaele.

15.3. Data Recording and Record Keeping

The investigator shall arrange for the retention of Essential Documents for the Conduct of a Clinical study (according to Chapter 8 of GCP ICH E6(R2) (e.g., patient files, other source data, and the Trial Master File/Investigator Site File) after the completion or discontinuation of the study according to institutional procedures and applicable laws.

15.4. Data Protection

The Investigator undertakes to:
- use the data only for the purposes of the foreseen analyses and within the limits established by the study and approved by the competent EC;
- store data in a secure network system;
- prohibit unauthorised third parties from accessing, even partially, data.
- guarantees to limit access to and processing of data only to its employees and collaborators who, upon appointment as an authorized person:
    1. need to process the data in order to carry out their work in relation to the study;
    2. have undertaken to maintain the confidentiality of the Data and of any information deriving from it or that is communicated to them.

If, within the context of the Study, the Investigator needs to make use of its own suppliers, the latter undertakes to appoint these subjects as Data Processors /Responsabili dei Trattamenti with a specific agreement or other legal act suitable for this, before the start of any data processing by them, according to Regulation (EU) n. 2016/679, art. 28.

The Investigator also undertakes to adopt suitable measures to facilitate the exercise of the rights of the subject provided for by Regulation (EU) n. 2016/679, art. 15 – 22, including the rights of access, rectification, cancellation, limitation, opposition and portability, within 30 days of receiving the relative request.

16. STATISTICS

Statistical analyses will be performed locally and not by a Contract Research Organization (CRO).
The statistical analysis plan is designed to address the primary, secondary, and tertiary objectives of the study, including diagnostic performance, cost-effectiveness, and long-term clinical outcomes.
The primary hypothesis is that coronary CT angiography performed with PCD-CT provides a higher PPV for the detection of obstructive CAD compared with EID-CT.
Secondary hypotheses include improved cost-effectiveness of PCD-CT compared with EID-CT and differences in long-term prognosis between groups.
Analyses will be conducted on the intention-to-diagnose population, defined as all randomized participants who complete the assigned CCTA examination. Participants who do not complete the assigned CCTA will be excluded from efficacy and follow-up analyses.

16.1. Description of Statistical Methods

The primary endpoint is the PPV of CCTA for obstructive CAD, using ICA as the reference standard when available. PPV will be calculated for each group and compared using chi-square or Fisher's exact test, as appropriate. Ninety-five percent confidence intervals will be reported.
Secondary endpoints include cost-effectiveness and long-term clinical outcomes. Cost-effectiveness will be evaluated by calculating the incremental cost-effectiveness ratio (ICER), defined as the difference in mean costs between PCCT and EID-CT divided by the difference in diagnostic effectiveness.
The tertiary endpoint (death from coronary heart disease or non-fatal myocardial infarction) will be analysed over a 36-month follow-up period using Kaplan–Meier survival curves and compared between groups using the log-rank test. Cox proportional hazards regression may be used to adjust for baseline covariates.
Continuous variables will be expressed as mean ± standard deviation or median with interquartile range, as appropriate. Categorical variables will be presented as frequencies and percentages. Between-group comparisons will be performed using Student's t-test or Mann–Whitney U test for continuous variables and chi-square test for categorical variables.
All statistical tests will be two-sided, and a p-value <0.05 will be considered statistically significant.
Statistical analyses will be performed using standard statistical software (Python).

16.2. Sample Size Determination

The sample size was calculated based on the primary endpoint, defined as the PPV of CCTA for detecting obstructive coronary artery disease at the patient level, using ICA as reference when available.

Published vessel-level PPV value (10.1016/j.jacc.2024.10.069) was assumed to be approximately 0.63 for EID-CT and 0.83 for PCD-CT. To convert vessel-level PPV to patient-level PPV, an effective number of diseased vessels per positive patient (K_{eff} = 1.4), derived from published literature, was applied using the following relationship:

$PPV_{patient} = 1 - (1 - PPV_{vessel})^{(Keff)}$

This resulted in estimated patient-level PPV values of approximately 0.75 for EID-CT and 0.92 for PCD-CT.

Assuming a two-sided alpha of 0.05 and 80% statistical power, the minimum detectable difference between these proportions corresponds to a required sample size of 79 CCTA-positive patients per group.

To account for potential missing coronary angiography data or incomplete datasets, a 10% inflation factor was applied, yielding 88 CCTA-positive patients per group.

To estimate the total number of patients to be randomized, the expected prevalence of positive CCTA examinations was derived from institutional data, showing that approximately 28% of patients present with ≥50% coronary stenosis.

Based on this prevalence, approximately 315 patients per group are required to obtain the necessary number of positive cases.

Therefore, the total planned sample size is 630 patients (315 per group).

A sensitivity analysis assuming 90% statistical power results in an estimated total sample size of approximately 836 participants.

16.3. Analysis Populations

All randomized participants who undergo CCTA will be included in the primary analysis according to the intention-to-treat (ITT) principle, based on assigned imaging modality (EID-CT or PCD-CT).

A per-protocol analysis will also be performed including all participants who complete the assigned CCTA examination and, when clinically indicated, invasive coronary angiography, without major protocol deviations.

Participants who do not complete the CCTA examination for technical or clinical reasons will be excluded from efficacy analyses but will be reported descriptively.

16.4. Interim Analysis

An interim analysis is planned to address the primary objective of the study: the comparison of the positive predictive value (PPV) between PCD-CT and EID-CT CCTA, using invasive coronary angiography as reference when available. The interim analysis is performed for descriptive purposes only and is not intended for sample size re-estimation or protocol modifications. No stopping rules for efficacy or futility are planned, and the study will continue as outlined in the protocol until completion. Comparison of PPV between EID-CT and PCD-CT will be derived with an interim analysis of the results within 18 months from the beginning of the enrollment.

16.5. Stopping Rules

No formal stopping rules for efficacy or futility are planned, as both imaging modalities are part of standard clinical practice and no experimental treatment is administered.

The study may be terminated prematurely in case of regulatory authority request or operational reasons, at the discretion of the investigators.

17. ETHICAL AND REGULATORY CONSIDERATIONS

This clinical study will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments established by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice.
This clinical study will be conducted in compliance with all international laws and regulations; national laws and regulations of the country in which the clinical study is performed; as well as any other applicable guidelines.

17.1. Responsibilities of the Investigator(s)

The Investigator(s) undertake(s) the responsibility to perform the study in accordance with this Protocol, Good Clinical Practice, and the applicable regulatory requirements. The Investigator is required to ensure compliance with the investigational product schedule, visits schedule, and procedures required by the protocol. The Investigator agrees to provide all information requested in the Case Report Form (CRF) in an accurate and legible manner. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior EC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted. The investigator must have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the study to conduct the study properly and safely.

17.2. Ethics Committee (EC) Approvals

This clinical study protocol as well as the Informed Consent are to be submitted to the appropriate Ethics Committee, and it is mandatory to obtain the written and dated approval, signed by the chairman with Ethics Committee(s) composition.
The clinical study the documents reviewed, the list of voting members and their qualifications, and the date of the review should be clearly stated on the written Ethics Committee approval.

18. GENDER MEDICINE IN RESEARCH PROTOCOL

Both male and female participants will be eligible for inclusion in this study, without discrimination based on sex or gender. Sex will be recorded for all participants and considered as a biological variable in baseline characteristics and descriptive analyses.
Enrollment will reflect the real-world population undergoing clinically indicated CCTA.
Inclusion and exclusion criteria are not sex-specific and are based solely on clinical indications for CCTA.
No specific gender-related interventions are planned. This study focuses on diagnostic imaging performance; therefore, no differential risks related to sex or gender are anticipated.

19. QUALITY ASSURANCE AND QUALITY CONTROL

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations, and standard operating procedures. Investigators involved in the study will permit

study-related monitoring, audits, EC review, and regulatory inspections by providing direct access to all study records.
The Investigator will notify the CTC promptly of any inspection scheduled by any regulatory authorities and will promptly forward copies of any inspection reports received.

19.1. Monitoring

Regular monitoring will be performed, according to the Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

19.2. Deviation from study protocol

A deviation from the protocol is an unintended departure from the procedures or processes approved by the Sponsor and the EC.
The Investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from the protocol to eliminate an immediate hazard to study patients without prior IEC approval. As soon as possible after such an occurrence, the implemented deviation, the reasons for it, and any proposed protocol amendments should be submitted to the EC for review and approval, and to the regulatory authorities, if required.
Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Investigators will be notified by the monitor of deviations. As required by local regulatory authorities, the Investigator will notify the EC of any applicable protocol deviations in a timely manner.
Every deviation from the study protocol must be specified and documented separately for each patient. The investigator must consult with the monitor and discuss the type and extent of deviation as well as the possible consequences for further participation of the patient in the study. If the evaluability of a patient is questionable, the coordinating investigator will be consulted.

19.3. Data and Safety Monitoring Board

Not applicable. No Data and Safety Monitoring Board (DSMB) is planned for this study due to its low-risk and the use of standard-of-care procedures.

19.4. DSMB roles and responsibilities

Not applicable.

20. FINANCE AND INSURANCE

20.1. Funding

The study has a non-profit nature, having no purpose of economic exploitation of the data and the results of the experiment itself.

Università Vita-Salute San Raffaele will receive a funding granted by Siemens Healthineers (10.000 euros) to support the data collection and the statistical analysis.

20.2. Patient Insurance

No specific insurance policy has been activated for this study, as it involves only standard-of-care procedures and does not introduce additional risks beyond routine clinical practice.

21. END OF CLINICAL STUDY

In accordance with applicable regulation, ICH GCP and SOPs, the PI shall notify the end of the clinical study within 15 days from the end of the clinical study.
The PI shall notify a temporary halt of a clinical study for reasons not affecting the benefit-risk balance within 15 days from the temporary halt of the clinical study and shall include the reasons for such action. When a temporarily halted clinical study is resumed the PI shall notify within 15 days from the restart of the temporarily halted clinical study. If a temporarily halted clinical study is not resumed within two years, the expiry date of this period or the date of the decision of the PI not to resume the clinical study shall be deemed to be the date of the end of the clinical study. In the case of early termination of the clinical study, the date of the early termination shall be deemed to be the date of the end of the clinical study. In the case of early termination of the clinical study for reasons not affecting the benefit-risk balance, the PI shall notify the reasons for such action and, when appropriate, follow-up measures for the subjects.

Upon completion or termination of the study, the study monitor will conduct site closure activities with the Investigator or site staff (as appropriate).

21.1. Summary of the results of the clinical study

Irrespective of the outcome of a clinical study, within six months from the end of a clinical study, the PI shall submit a summary of the results of the clinical study to Ethical Committee and Clinical Trial Center.

22. INTELLECTUAL PROPERTY

Not applicable.

23. PUBLICATION POLICY

The results of the study will be made public anonymously through conference presentations and scientific publications. In no case is the publication of data that allow the patient to be recognized.

The results of this study will be submitted to international scientific journals; posters and oral communications will be submitted to national and international scientific meetings. All publications and communications regarding the study will be approved in advance by the PI.

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