STUDY NUMBER: PCa Restaging- PET/MR

STUDY TITLE: Phase II prospective monocentric study on prostate cancer restaging by using PET/MR with innovative radiotracers

VERSION NUMBER: 2

DATE: 31 October 2019

COMPOUNDS:

- Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)] (68Ga-PSMA)
- Bombesin receptor antagonist (68Ga-Bombesin)

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Principal Investigator: Maria Picchio, MD, U.O. Medicina Nucleare, IRCCS Ospedale San Raffaele

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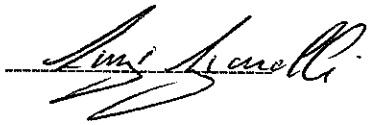

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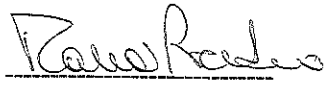
Signature Principal Investigator **date**



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1. SYNOPSIS

COMPOUNDS:
- Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)] (68Ga-PSMA)
- Bombesin receptor antagonist (68Ga-Bombesin)

Study number: PCa Restaging – PET/MR

TITLE: Phase II prospective monocentric study on prostate cancer restaging by using PET/MR with innovative radiotracers	
TRIAL LOCATION U.O. Medicina Nucleare, IRCCS Ospedale San Raffaele / PI: Prof.ssa Maria Picchio	
STUDY OBJECTIVE(S)	Overall goal: To provide an innovative approach to restage patients with biochemical recurrence of prostate cancer by using hybrid PET/MR with innovative radiotracers (68Ga-PSMA and 68Ga-Bombesin) Primary endpoint: - To evaluate the diagnostic accuracy of 68Ga-PSMA PET/MR to identify the site of recurrence in patients with biochemical relapse of PCa after primary treatment and comparison with the performances of 68Ga-Bombesin PET/MR Secondary endpoint - To correlate 68Ga-PSMA PET/MR and 68Ga-bombesin-PSMA PET/MR imaging with clinical and pathological features. - To evaluate the results of a lesion-targeted approach in terms of biochemical-recurrence-free survival and clinical recurrence-free survival. A particular effort will be made in order to identify patients that might benefit most from this approach in terms of predictors of both positive imaging findings as well as response to local treatment of metastatic sites with both surgery and radiation therapy.
STUDY DESIGN	Prospective monocentric study, 60 total patients enrolled. Phase II, open, uncontrolled study. After exclusion of patients with contraindications to PET/MR examinations (See inclusion/exclusion criteria), the 60 enrolled patients will be submitted to both 68Ga-PSMA PET/MR and 68Ga-bombesin PET/MR imaging at our Institution. Each PET/MR study will have a duration of approximately 2 hours (including approximately 1 hour of waiting time and 1 hour of execution of 68Ga-PSMA or 68Ga-Bombesin PET/MR study). To correlate 68Ga-PSMA PET/MR and 68Ga-bombesin-PSMA PET/MR imaging with clinical and pathological features, the following variables will be tested: - Age - Pre-operative PSA - Pathological Gleason score - Pathological stage - Time to biochemical recurrence

	- PSA slope - PSA doubling time Patients with the diagnosis of local recurrence will be submitted to standard clinical work-up procedures.
STUDY POPULATION Main selection criteria: Prostate cancer patients who experienced biochemical recurrence after primary treatment. Total expected number of patients: 60	Inclusion criteria: 1. Patients with histological proven diagnosis of prostate cancer. 2. Patients treated with radical therapy (RP o EBRT, with or without further adjuvant therapies), who present rising serum PSA values ≥ 0.2 ng/mL. 3. Age ≥ 18 years-old. 4. Willing to provide a signed informed consent. Exclusion criteria 1. Age < 18 years-old. 2. Previous and/or concomitant androgen deprivation therapy will be excluded. 3. Any additional medical condition that may significantly interfere with study compliance. 4. Contraindications to MR study (i.e. Pacemaker)

INVESTIGATIONAL PRODUCT(S)

Formulation(s):

1. Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)] (68Ga-PSMA)

Route(s) of administration: intravenously

Dose regimen: 160±50 MBq

2. Bombesin receptor antagonist (68Ga-Bombesin)

Route(s) of administration: intravenously

Dose regimen: 140±50 MBq

EFFICACY CRITERIA: 68Ga-PSMA PET/MR and 68Ga-Bombesin PET/MR findings will be assessed as follow :

1) histology (when deemed necessary by the clinician as expected under the normal care pathway) obtained by echographically-guided biopsy in suspected local recurrence in the prostate lobe or during pelvic and/or extraperitoneal lymph node dissection in the event of suspected nodal recurrence

2) Clinical and laboratory data of the same patients (i.e. serum PSA assay) foreseen within the normal clinical work-up.

3) Conventional imaging modalities performed to assess disease status as part of the routine clinical work-up including CT, pelvic mp-MR, MR and bone scintigraphy.

4) A comparison between the two modalities will be also performed.

SAFETY CRITERIA: data concerning safety and the registration of adverse events will be collected.

STUDY PROCEDURES

Sixty consecutive patients with biochemical recurrence (PSA≥0.2 ng/ml), previously treated with radical prostatectomy for organ confined prostate cancer will be enrolled during the whole duration of the study (36 months). Patients with previous and/or concomitant androgen deprivation therapy will be excluded from enrolment.
All patients will undergo both 68Ga-PSMA PET/MR and 68Ga-Bombesin PET/MR imaging at San Raffaele Scientific Institute in two different days (> 48 hours between the two studies) and within one month one from the other; all clinical and pathological variables available at the time of PET/MR studies will be recorded for each patient. PET/MR results will be compared to other imaging procedures performed and available in the course of routinely work-up evaluation.

PATIENTS TREATMENT AND PROCEDURES

Treatment approach will be based on all available clinical and instrumental data, including 68Ga-PSMA and 68Ga-Bombesin PET/MR, evaluated during multidisciplinary sessions including expert Urologists, Nuclear Medicine and Radiologist physicians. Patients with local recurrence will be candidate to salvage radiation therapy (sRT).

Patients presenting only LN recurrence will be proposed to be submitted to salvage lymph node (LN) dissection (sLND) or sRT; alternatively, conventional androgen deprivation therapy will be performed in those patients who will not be willing to undergo secondary surgery or radiation therapy. To assess the diagnostic accuracy of 68Ga-PSMA and 68Ga-Bombesin PET/MR, images will be validated with: 1) histology (when deemed necessary by the clinician as expected under the normal care pathway) obtained by echographically-guided biopsy in suspected local recurrence or during sLND in the event of suspected nodal recurrence; 2) biochemical response after tailored treatment in patients submitted to sRT for local or LN recurrence 3) conventional imaging modalities performed to assess disease status as part of the routine clinical work-up. The validation procedures reported in point 1), 2) and 3) will be performed according the timing required by the routine clinical work-up of the patient and so they could be performed at any time during the course of the study. 68Ga-PSMA and 68Ga-Bombesin PET/MR will be correlated with available clinical and pathological features. To assess the impact of 68Ga-PSMA PET/MR and 68Ga-Bombesin PET/MR in changing patients' management, patients will be followed-up after the execution of PET/MR studies. Patients will be followed-up until the end of the study period.	
STATISTICAL CONSIDERATIONS	The sample size was computed based on sensitivity analysis for PET/MR in predicting lymph node metastasis. Assuming an average prevalence of lymph node metastasis of 35%, a total sample size of 60 patients is sufficient for evaluating a sensitivity of 80% with an absolute precision of 18% (at 95% confident level). 8Ga-Bombesin PET/MRI and68Ga-PSMA PET/MRI will be compared. Sixty patients treated with radical prostatectomy with biochemical recurrence of prostate cancer (PSA < 0.2 ng/ml and raising) will be evaluated and recruited in the study. They will be submitted to both 68Ga-PSMA PET/MR and 68Gabombesin PET/MR. Clinical and pathological variables will be recorded for each patient. The exact sites of recurrence as well as the size of all lesions will be recorded for all patients at both imaging procedures. A direct comparison between the two tracers will be performed using Chi-square test for categorical variables. Univariable and multivariable logistic regression analyses will be used in order to identify the predictors of positive imaging at both 68Ga-PSMA PET/MR and 68Ga-bombesin PET/MR. In patients with evidence of local recurrence submitted to salvage radiation therapy the biochemical response to radiotherapy will be used as confirmation of the positivity of imaging. In patients with nodal only recurrence, a salvage pelvic and/or retroperitoneal lymph node dissection according to the site of the positive nodes will be proposed. For patients undergoing nodal dissection, a direct comparison between PET studies and histopathological examination in terms of site and size of the recurrent nodes will be performed. The performance characteristics of both 68Ga-PSMA PET/MR and 68Ga-bombesin PET/MR will be evaluated and compared through accuracy, sensitivity, specificity, positive and negative predictive value in a patient-based as well as in a lesion-based approach. For the evaluation of the response to lesion-targeted treatments Kaplan-Meier analyses as well as univariable and multivariable Cox regression analyses will be performed.
DURATION OF STUDY PERIOD	Total duration of the study: 3 years. Each patient will perform two PET/MRI studies in two different days. Each study will last

	approximately 2 hours (including approximately 1h of waiting time and 1 hour of execution of PET/MRI study). If available, patients will be followed up until the end of the study period.

2. FLOW CHART

	T0	T1	T2*
Inclusion/exclusion criteria evaluation	X		
Informed consent administration	X		
68Ga-PSMA or 68Ga Bombesin PET/MR study		X	
68Ga-PSMA or 68Ga Bombesin PET/MR study			X

* ≥ 48 hours ≤ 1 month from T1

3. GLOSSARY

PET: Positron Emission Tomography

MR: Magnetic Resonance Imaging

PSA: Prostate specific antigen

RP: radical prostatectomy

EBRT: External beam radiation therapy

4. INTRODUCTION AND RATIONALE

Medical imaging requires innovation to support personalized care. This need is particularly emerging in the setting of prostate cancer (PCa) recurrence, a condition that affects up to 50% of patients treated with radical prostatectomy (RP) or external-beam radiotherapy (EBRT) as primary treatment for clinically localized disease.(1) When biochemical recurrence (BR) is detected, an accurate identification of location and extent of cancer recurrence is mandatory in order to address patients to directed therapies with prolonged intervals of cancer-free survival (e.g. surgical resection and/or radiation treatment on the specific site of recurrence), thus avoiding systemic treatments, including androgen deprivation therapy.(2)
Imaging plays a key role in identifying local or distant recurrence when Prostate-Specific Antigen (PSA) level is rising.(3)
Positron Emission Tomography/Computed Tomography (PET/CT) by using Choline radiolabeled with either 11C or 18F is the most established imaging modality in PCa restaging; however, its low detection rate for low PSA values hampers the real usefulness of this imaging modality within this specific therapeutic window of opportunity.(4,5) The limitation related to low PSA values might be due both to the integration of CT into PET/CT scanner, which is not the best morphological imaging modality to detect local PCa relapse, and to the low sensitivity of Choline as radiotracer.
The recent introduction of integrated PET/Magnetic Resonance Imaging (MR) paves the way to a completely innovative imaging approach for PCa recurrence, by overcoming several limitations of the currently available imaging modalities. The combined simultaneous acquisition of PET and multiparametric MR (mp-MR) provides metabolic, structural and functional imaging information regarding prostate cancer status in a whole-body single session examination, with better soft tissue contrast and reduced radiation exposure in comparison to PET/CT.(6,7) Although some evidence regarding the clinical value of the individual component of this imaging modality have been reported so far, very few data on the incremental value of combined PET/MR in PCa recurrence are currently available.
Moreover, differently from CT, MR imaging consists of several sequences that can be applied depending on the specific clinical questions that need to be addressed and on the anatomical region that requires to be evaluated. Nowadays, there is still no consensus regarding the optimal acquisition protocols that should be performed to accurately restage PCa.(8)
Along with technological advances, alternative radiotracers have been proposed to overcome the limitations of Choline.
New molecular probes targeting the Prostate-Specific Membrane Antigen (PSMA) have been developed, showing high expression in PCa cells.(9) Among the available tracers and ligands to image PSMA-expressing tumours, Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)] (68Ga-PSMA) is currently one of the most successful and promising PSMA radioligands for PCa, improving the detection rate of metastases in patients with biochemical recurrence, even at low serum PSA values.(10) Encouraging results have been also achieved with 68Ga-labeledDOTA-4-amino-1- carboxymethyl-piperidine-DPhe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu NH2 (68Ga-Bombesin) radiotracer, a synthetic bombesin receptor antagonist targeting gastrin-releasing peptide receptors (GRPr), which are overexpressed in 63%–100%

of human prostate cancer tissue; this radiotracer has been proposed as a new promising molecular probe for PET imaging in biochemical recurrence of PCa with.(11-14) However, very limited data are currently available on its role in this clinical setting.
A well-suited technology such as PET/MR, combining mp-MR together with PET metabolic imaging by using radiotracers alternative to Choline and potentially more specific, represents an innovative powerful diagnostic tool that will surely have a burning impact on the diagnostic workflow of patients with PCa recurrence and therefore on personalized treatment.

5. STUDY OBJECTIVES

5.1 Primary

To provide an innovative approach to restage patients with biochemical recurrence of prostate cancer by using hybrid PET/MR with innovative radiotracers (68Ga-PSMA and 68Ga-Bombesin)

5.2 Primary and secondary specific aims

Primary aim
To evaluate the diagnostic accuracy of 68Ga-PSMA PET/MR to identify the site of recurrence in patients with biochemical relapse of PCa after primary treatment and comparison with the performances of 68Ga-Bombesin PET/MR

Secondary aims
- To correlate 68Ga-PSMA PET/MR and 68Ga-bombesin-PSMA PET/MR imaging with clinical and pathological features.
- To evaluate the results of a lesion-targeted approach in terms of biochemical-recurrence-free survival and clinical recurrence-free survival. A particular effort will be made in order to identify patients that might benefit most from this approach in terms of predictors of both positive imaging findings as well as response to local treatment of metastatic sites with both surgery and radiation therapy.

6. STUDY DESIGN

6.1 Description of the protocol

Prospective monocentric study (Phase II study).
Sixty consecutive patients with biochemical recurrence (PSA≥0.2 ng/ml), previously treated with radical prostatectomy for organ confined prostate cancer will be enrolled; patients with previous and/or concomitant androgen deprivation therapy will be excluded from enrolment.
All patients will undergo both 68Ga-PSMA PET/MR and 68Ga-Bombesin PET/MR imaging at San Raffaele Scientific Institute in two different days; all clinical and pathological variables available at the time of PET/MR studies will be recorded for each patient.
PET/MR results will be compared to other imaging procedures performed and available in the course of routinely work-up evaluation. Treatment approach will be based on all available clinical and instrumental data, including 68Ga-PSMA and 68Ga-Bombesin PET/MR, evaluated during multidisciplinary sessions including expert Urologists, Nuclear Medicine and Radiologist physicians. Patients with local recurrence will be candidate to salvage radiation therapy (sRT). Patients presenting only LN recurrence will be proposed to be submitted to salvage lymph node (LN) dissection (sLND) or sRT; alternatively, conventional androgen deprivation therapy will be performed in those patients who will not be willing to undergo secondary surgery or radiation therapy.
To assess the diagnostic accuracy of 68Ga-PSMA and 68Ga-Bombesin PET/MR, images will be validated with: 1) histology (when deemed necessary by the clinician as expected under the normal care pathway) obtained by echographically-guided biopsy in suspected local recurrence or during sLND in the event of suspected nodal recurrence; 2) biochemical response after tailored treatment in patients submitted to sRT for local or LN recurrence 3) conventional imaging modalities performed to assess disease status as part of the routine clinical work-up. 68Ga-PSMA and 68Ga-Bombesin PET/MR will be

correlated with available clinical and pathological features. To assess the impact of 68Ga-PSMA PET/MR and 68Ga-Bombesin PET/MR in changing patients' management, patients will be followed-up after the execution of PET/MR studies. Patients will be followed-up until the end of the study period.

6.2 Duration of study

Total duration of the study: 3 years.
For each patient the time of patient direct involvement will be approximately 2 hours for each PET/MR study (duration: approximately 1h after i.v. administration and approximately 1h for the duration of each PET/MR examination).
The patients will be followed-up up to until the end of the study period.

7. SELECTION OF PATIENTS

7.1 Number of patients planned

- 60 prostate cancer adult patients: the enrolled patients will undergo to 68Ga-PSMA PET/MR and 68Ga-Bombesin PET/MR 68Ga-PSMA PET/CT.

7.2 Inclusion criteria

1. Patients with histological proven diagnosis of prostate cancer.
2. Patients treated with radical therapy (RP o EBRT, with or without further adjuvant therapies), who present rising serum PSA values ≥ 0.2 ng/mL.
3. Age ≥ 18 years-old.
4. Willing to provide a signed informed consent.

7.3 Exclusion criteria

1. Age < 18 years-old.
2. previous and/or concomitant androgen deprivation therapy will be excluded.
3. Any additional medical condition that may significantly interfere with study compliance.
4. Contraindications to MR study (i.e. Pacemaker)
5. Known hypersensitivity to

8. TREATMENTS

In addition to the execution of 68Ga-PSMA PET/MR and 68Ga-Bombesina PET/MR scans, all the other imaging procedures and treatment strategies performed will be in the course of routine work-up patient management.

<u>68Ga-PSMA PET/MR and 68Ga-Bombesin PET/MR study</u>:

Tracers synthesis will be performed in our Department following IMPD. 68Ga-PSMA PET/MR study will start 60 minutes after the administration of 160±50 MBq of 68Ga-PSMA and 68Ga-Bombesin study will start 45 minutes after the administration of 140±50 MBq of 68Ga-Bombesin. For both scans the following protocol will be applied:

- localizer MR scans to define the number of table positions (PET-FOV) to acquire (4-min/table position); specific attenuation correction and anatomical localization MR sequences at each PETFOV; pelvic multi-parametric MR protocol according to European Society of Urogenital Radiology (ESUR) guidelines.
  Gadolinium-based paramagnetic contrast agent will be injected intravenously with a dose of 0.1mmol/kg and an injection rate of 4 ml/sec. The MR protocol may be modified according to specific clinical requirements.

- PET-acquisition will start from the mid-thigh to the base of the skull base to exploit the reduced ^{68}Ga-PSMA and 68Ga-Bombesin ligand uptake in the urinary system after pre-scan voiding. Acquisition should proceed from the lower end of the axial field of view cranially in order to minimize misalignment for the urinary bladder which tends to fill up during the time of the examination. PET scans will be acquired in three-dimensional (3D) mode with an acquisition time of usually 2–4 min per bed position. Overall, PET coverage will be identical to the anatomical MR scan range.

8.1 Investigational Medicinal Product (IMP)

68Ga-PSMA dossier: see attached file (IMP dossier).
68Ga-Bombesin dossier: see attached file (IMP dossier).

8.2 Responsibilities

The investigator or other personnel allowed to dispense Investigational Products is responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified and in accordance with the applicable regulatory requirements. The Investigational Products are to be used as directed by this clinical trial protocol.

8.3 IMP accountability and compliance

All IMP shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued is maintained.

9. STUDY PROCEDURES

9.1 Efficacy

Positive PET/MR findings will be compared to :

1) histology (when deemed necessary by the clinician as expected under the normal care pathway) obtained by echographically-guided biopsy in suspected local recurrence in the prostate lobe or during pelvic and/or extraperitoneal lymph node dissection in the event of suspected nodal recurrence

2) Clinical and laboratory data of the same patients (i.e. serum PSA assay) foreseen within the normal clinical work-up.

3) Conventional imaging modalities performed to assess disease status as part of the routine clinical work-up including CT, pelvic mp-MR, MR and bone scintigraphy.

4) A comparison between the two modalities will be also performed.

9.2 Safety

Data concerning safety and the registration of adverse events will be collected.

10. PATIENT SAFETY

10.1 Safety instructions

The PET tracers are well tolerated and safe without reported clinically significant adverse events. Allergic reactions could occur in a very low percentage of patients as in routine clinical practice, due to the injection of gadolinium-based paramagnetic contrast medium during PET/MR examinations.
The assessment of the safety of the experimental examination will consist in monitoring and recording adverse events and serious adverse events.

10.2 Definitions of Adverse Event, Adverse Drug Reaction and Serious Adverse Event, Serious Adverse Reaction

Adverse events
Information about all adverse events, whether spontaneously reported by the subject, or those experienced by physician specific questions, such as those highlighted by the patient's physical examination, laboratory or other investigations, will be collected, registered on the Case Report Form (CRF) and followed as appropriate.
An event is defined as any sign, symptom or unplanned clinical condition occurring after the PET/MR examination, although there is no causal relationship between the event and the radiotracer administered.

Information about all serious adverse events will be collected and recorded on the Sample Adverse Event Reporting Module. To ensure patient safety, all serious adverse events must be reported within 24 hours of the researcher who is aware of it.

Severe Events are defined as those adverse events that:
• are fatal;
• put the patient in danger of life;
• require patient admission or prolong hospital stay;
• they involve significant and persistent disability / inability but not necessarily permanent;
• they are significant from the medical point of view in the sense that they can harm the patient and require medical or surgical intervention to prevent the above listed situations.

10.3 Pharmacovigilance Procedure

Information about all serious adverse events will be collected and recorded on the Sample Adverse Event Reporting Module. To ensure Patient safety, all serious adverse events must be reported within 24 hours of the researcher who is aware of it.

11. TEMPORARY OR DEFINITIVE TREATMENT DISCONTINUATION

The patient can withdraw from the study at any time without giving reasons and he will not be in any way disadvantaged by this.

After 68Ga-PSMA and 68Ga-Bombesin PET/MR imaging, in case patients won't be available to be followed-up, 68Ga-PSMA PET/MR and 68Ga-Bombesin PET/MR imaging data will be evaluated and data will be equally used in order to assess the diagnostic accuracy of 68Ga-PSMA PET/MR and 68Ga-Bombesin PET/MR for the detection of the site/s of relapse (aim 1); to correlate 68Ga-PSMA PET/MR and 68Ga-bombesin-PSMA PET/MR imaging with clinical and pathological features (aim2) and to evaluate the results of a lesion-targeted approach in terms of biochemical-recurrence-free survival and clinical recurrence-free survival (aim 3).

12. STATISTICAL CONSIDERATIONS

12.1 Determination of sample size

The sample size was computed based on sensitivity analysis for predicting lymph node metastasis. Assuming an average prevalence of lymph node metastasis of 35%, a total sample size of 60 patients is sufficient for evaluating a sensitivity of 80% with an absolute precision of 18% (at 95% confident level).

12.2 Statistical Methods

Clinical and pathological variables will be recorded for each patient. The exact sites of recurrence as two tracers will be performed using Chi-square test for categorical variables.

Univariable and multivariable logistic regression analyses will be used in order to identify the predictors of positive imaging at both 68Ga-PSMA PET/MRI and 68Ga-bombesin PET/MRI.

In patients with evidence of local recurrence submitted to salvage radiation therapy the biochemical response to radiotherapy will be used as confirmation of the positivity of imaging.

In patients with nodal only recurrence, a salvage pelvic and/or retroperitoneal lymph node dissection according to the site of the positive nodes will be proposed.

For patients undergoing nodal dissection, a direct comparison between PET studies and histopathological examination in terms of site and size of the recurrent nodes will be performed.

The performance characteristics of both 68Ga-PSMA PET/MRI and 68Ga-bombesin PET/MRI will be evaluated through accuracy, sensitivity, specificity, positive and negative predictive value in a patient-based as well as in a lesion-based approach.

For the evaluation of the response to lesion-targeted treatments Kaplan-Meier analyses as well as univariable and multivariable Cox regression analyses will be performed.

13. ETHICAL AND REGULATORY CONSIDERATIONS

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

13.1 Informed Consent

All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand. Prior to a patient's participation in the clinical trial, he MUST sign the written Informed Consent Form.

It must also be made clear to the patient that he can withdraw from the study at any time without giving reasons and that he will not be in any way disadvantaged by this. Any Informed Consent will be part of Investigator's file and retained with it. A copy of the signed and dated written Informed Consent Form must be provided to the patient.

The letter to the treating physician is not necessary as the patients included in the study are selected and followed up by Medical Doctors of San Raffaele Hospital.

13.2 Responsibilities of the investigator(s)

The investigator (according to applicable regulatory requirements), or a person designated by the investigator, and under the investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial.

13.3 Responsibilities of the sponsor/promoter

The promoter or a person designated by the investigator, and under the investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial.

14. DATA MANAGEMENT

14.1 Source Documents

According to the ICH /Good Clinical Practice, the monitoring team must check the Case Report Form entries against the source documents.

14.2 Data Management

Personnel designated by the principal Investigator must report the information required by the protocol on the Case Report Form (CRF). The Clinical Monitor, chosen by the Promoter, as qualified personnel, will be responsible for monitoring of the study progression.

14.3 Case Report Forms (CRFs)

It is the responsibility of the investigator to maintain adequate and accurate CRFs (according to the technology used). All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.
Should a correction be made, the information to be modified must not be overwritten. The corrected information should be transcribed by the authorized person next to the previous value, initialed and dated.
The Investigator is responsible for storing and storing the essential documents of the study before, during, and after the completion or termination of the study, in accordance with the time required by the applicable laws and GCPs.
The data collected on the CRF will be strictly anonymous and the subject will be uniquely identified with a number and initials.
The researcher will have to keep the patient's original data and a copy of the signed written informed consent. For some data, it is possible to establish, before the study begins, that they are written directly to the CRF, which will then act as the original data.

15. DATA PROTECTION

The researcher will have to keep the patient's original data and a copy of the signed written informed consent. The files will be kept in a locked closet in Nuclear Medicine Department.

16. CLINICAL TRIAL RESULTS

The Promoter will be responsible for preparing a Clinical Study Report monitoring the study progression and obtained results

17. BIBLIOGRAPHIC REFERENCES

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