SERVICE SPECIFICATION FOR THE PROVISION OF A NEUROENDOCRINE TUMOUR PEPTIDE RECEPTOR RADIONUCLIDE TREATMENT (PRRT) SERVICE

Service	Specification for the delivery of Peptide Receptor Radionuclide Treatment (PRRT) for the treatment of patients with advanced Neuroendocrine Tumours (NETs), following failure of somatostatin analogue therapy .
Commissioner Lead	NCCP
Provider Lead	St Vincent's University Hospital

1 Scope

1.1 Specialised Service description

Peptide Receptor Radionuclide Therapy (PRRT) is a form of molecular targeted therapy which involves the systemic administration of a radiolabelled peptide that is designed to target receptors that are overexpressed on tumours.

PRRT can be used to treat neuroendocrine tumours (NETs) by using radiolabelled somatostatin receptor agonist lutetium (^{177}Lu) oxodotreotide. This treatment has been successfully used to treat patients with metastatic or inoperable NETs expressing somatostatin receptor subtype 2. PRRT can result in a complete or partial response in up to 30% of patients. Patients who have a higher tumour receptor expression show better responses leading to longer survival and improved quality of life. Lutetium (^{177}Lu) oxodotreotide (Lutathera®) is a radiolabelled somatostatin receptor agonist, the evidence for lutetium (^{177}Lu) oxodotreotide is compelling with a 79% reduction in the risk of progression or death seen. Further analysis from the NETTER 1 study also demonstrated a significant quality of life benefit in patients treated with lutetium (^{177}Lu) oxodotreotide compared to high dose octreotide. Lutetium (^{177}Lu) oxodotreotide has been licensed by the European Medicines Agency (EMA), and was approved for reimbursement by the HSE in February 2021. While St Vincent's University Hospital has been

designated the PRRT centre for NETS, at present, patients need to travel abroad to access this treatment, so the launch of an Irish PRRT service is a significant priority for healthcare staff and patients with NETs alike.

There are no specific guidelines in place in Ireland for treatment of NETs, however the most applicable guidelines used in the Irish setting are the European Neuroendocrine Tumour Society (ENETS) Guidelines as per Table 1. The National NET Service in St. Vincent's University Hospital (SVUH) in addition to both satellite groups in Galway and Cork rigidly follow the ENETS guidelines.

TABLE 1: TREATMENT PATHWAY FOR ADVANCED GI AND P-NETS – ENETS GUIDELINE

	Advanced, metastatic GI-NETs	Advanced, metastatic P-NETs
First line	Somatostatin Analogues (SSAs) for symptom control Midgut: SSAs (preferably if Ki67 is ≤10%) Systemic chemotherapy if G3	Somatostatin Analogues (SSAs) for symptom control Lanreotide (Ki67 ≤10%) Systemic chemotherapy in progressive or bulky P-NETs, or G3 STZ-based chemotherapy in G1/G2
Second line	IFN if functional, as add on to SSAs for symptom control PRRT after failure of medical therapy Everolimus after failure of SSA	IFN if functional, as add on to SSAs for symptom control Everolimus or sunitinib after failure of SSA or chemotherapy PRRT after failure of medical treatment including SSA, chemotherapy or novel targeted drugs
Additional options	PRRT can be used third line after failure of everolimus, or everolimus can be used third line after failure of PRRT in patients with mid-gut NETs Sequencing of everolimus/PRRT as second or third-line treatment will also depend on other issues including accessibility and appropriateness of PRRT in the individual patient (SSTR expression, hepatic/bone disease level, kidney function)	Optimal sequencing with targeted drugs and/or chemotherapy needs to be defined in P-NET when data from prospective randomised trials in pancreatic NET become available Potential increasing toxicity, e.g., after prior chemotherapy or targeted therapy needs to be considered and might justify earlier use of PRRT in selected patients

1.2 Principles

The principles underpinning the specification are:

- This treatment is currently only available for Irish patients with NETs through the HSE Treatment Abroad Scheme (TAS), however, lutetium (^{177}Lu) oxodotreotide has been approved for reimbursement in Ireland and the launch of a national PRRT service is pending.

- PRRT is a relatively novel treatment in Ireland, although it is well established and long-studied internationally. As a result, standardised protocols and guidelines exist for therapeutic indications as well as the management of toxicities and responses.
- The number of patients requiring this treatment annually is relatively small, therefore in the first instance a single national centre, St Vincent's University Hospital, will provide the service with the potential to open additional sites in the future should the need arise. This allows the concentration of expertise necessary to provide this treatment safely and responsibly to patients who need it.
- Selected providers (initially designated at St Vincent's University Hospital) will need to:
    - Evidence appropriate accreditation
    - Evidence previous experience of PRRT
    - Evidence effective implementation of standard operating procedures and risk management arrangements for successfully providing PPRT and handling of radiopharmaceuticals
- All necessary regulatory approvals (HIQA, EPA) are also pre- requisites for service provision at the selected providers. In the absence of the HIQA regulatory process, individual patient justification will be utilised.
- This specification will be reviewed annually or at earlier intervals as service experience and patient need requires.
- The primary clinicians involved in prescribing PRRT for NETs and managing patients on treatment will be consultants in the NET clinic with support from their clinical teams. Evidence of accreditation/training for clinicians will be required prior to being approved to prescribe PRRT. Handling of the radiopharmaceuticals will be performed by trained nuclear medicine/PET staff, according to standard operating procedures developed at the treating site. Additional clinical support from haematology or other medical specialties will be provided in the management of treatment-related toxicities, and these supports must be in place at the treating site.
- It is expected that PRRT for other indications in NETs and other cancers may be approved at a later date; this is beyond the scope of this document but the basic infrastructure for administration would be common to PRRT for all cancers.

2 Care Pathway and Clinical Dependencies

2.1 Current Care Pathway

PRRT is not currently available in Ireland. According to TAS, 27 patients travelled abroad for PRRT in 2018, 30 in 2019, data to be included for 2020.2021 and 2022 of available. The cohort of patients currently referred is restricted to those patients fit for travel rendering those patients unfit to travel unable to access PRRT.

For those patients eligible for PRRT abroad, delays with the referral process can result in several months' wait for treatment. Both the wait time and the burden of travel can lead to heightened anxiety for the patient. In addition, it is likely that given the barriers to this treatment some patients who would benefit are currently not being referred. Patients clinical status may not allow them to travel and several patients have refused to travel for various reasons; the latter highlighted during the COVID-19 pandemic. Equity of access to internationally recognised best standards of therapy is required.

Other treatment options (see table 1) would include systemic therapies following failure of somatostatin analogues, such as everolimus or cytotoxic chemotherapy; these are considered less effective and more toxic than PRRT for the appropriate patient population. Treatment pathways vary based on primary site of disease (pancreatic/small bowel/lung) and on grade of tumour. Locoregional treatments are also incorporated where appropriate, including surgical resection, radiotherapy, chemoembolization and radiofrequency ablation.

2.2 Decision to Treat

The pending PRRT service will be centralised in NET centres (initially SVUH). All patients considered for PRRT would be discussed at a NET-specific multidisciplinary team meeting (MDM). Currently there are three NET Centres with MDMs focusing on NET patients and a PRRT treatment pathway has been validated via the NCCP PRRT National Advisory Group sub group. The decision to prescribe PRRT would be balanced with the patient's comorbid medical conditions, alternative treatment options, and the likelihood of benefit from PRRT. The NCCP national chemotherapy regimen details the relevant inclusion and exclusion criteria.

Following discussion at MDM and approval to consider PRRT, the patient's primary clinician in collaboration with other clinicians in the NET MDT are responsible for:

- Confirming patient eligibility in line with the manufacturers licence and the trials on which the licence is based with regard to age, fitness, disease and treatment stage, including direct review of tissue and radiological diagnostics and staging and fitness for treatment.
- Confirming patients (and/or their carers) have been informed and understand the potential benefits, risks and complications of treatment as part of shared decision-making and psychological support is available.
- Assessing patients prior to treatment preparation and initiation
- Managing the treatment, post treatment management and follow up in line with the approved and accredited SOP

- Undertaking reporting, data analysis and audit – this may include engagement with manufacturers as required.

2.3 Initial Admission

Although it is possible for PRRT to be administered as an outpatient, it may be necessary to admit patients overnight following their treatment based on factors such as distance from hospital to home. A dedicated infusion suite will be needed, including a toilet reserved for the patient post treatment. A site-specific SOP will be developed for preparation of the room prior to each patient's treatment. On initial treatment, baseline blood tests will be drawn and a clinical examination will be performed to assess the patient's eligibility for treatment. Prior to treatment, patients will be educated on radiation risks and methods to protect themselves and others.

2.4 Product Preparation / Manufacture

The radiopharmaceutical will be prepared as per the product SPC and according to site-specific protocols for radiation safety.

2.5 Administration

Administration of PRRT will be performed by trained medical, physics and nursing staff. Intravenous access will be secured, and administration of a renoprotective amino acid will commence prior to the PRRT infusion and will continue until after its completion. Administration of PRRT will be performed according to a site-specific protocol for infusion, following best practices for safety.

Following treatment, patients may be discharged home or admitted overnight if needed for monitoring or to ensure radiation safety. Infusions of PRRT are administered every 8 weeks for a total of four infusions (with the possibility of repeat courses in cases of later relapse). Patient monitoring on treatment should occur every 4 weeks and include blood tests including blood counts, electrolytes, renal and liver function tests, as well as clinical assessment (in person or by phone). The safety of each treatment cycle should be assessed by treating clinicians on or prior to the scheduled treatment date, and delays in treatment for toxicity are permitted.

2.6 Interdependence with other Services

All designated PRRT providers must be able to demonstrate they have the required protocols, clinical facilities, staffing, medical supervision and care, training and education, accreditation and governance to address the following:

2.7 Regulatory

Accredited Quality Management System, SOPs and Protocols and Risk Evaluation and Mitigation Strategy capable of demonstrating a high quality, safe treatment pathway capable of effectively managing all side effects including those that are life threatening is required.

2.9 Clinical management

The clinical management of patients should be detailed in local hospital SOPs and should include procedures for the clinical monitoring of patients, the requirement for access to specialist diagnostic services and ambulatory care procedures. Careful liaison between primary NET treating physician and primary care physician to be implemented.

2.10 Management of toxicities and critical care

These should be detailed in the local hospital SOPs and should include reference to toxicities.

2.11 Training

The nuclear medicine physicians and nuclear physicists in SVUH have previously attended training courses in London and all NET specialist, nurses and nuclear medicine physicians will receive updated training; there are several courses provided by the EANM several times a year.

2.12 Patient / data registry[1]

There is a current patient registry as part of the SVUH NET Centre, and patients treated with PRRT would have their information collected as part of this registry for the purposes of adverse event monitoring/reporting and audit/quality improvement.

3 Population Covered and Population Needs

These have been considered in the health technology assessments completed by the NCPE.

4 Outcomes and Applicable Quality Standards

4.1 Quality Statement – Aim of Service

The aim is to detail the expected requirements of providers who will oversee the clinical delivery of PRRT to eligible patients.

The specification will ensure that:

- Patient access is secured at a national level.

[1] The data registry has been deemed compliant with the relevant legislation by the SVUH Data Protection Officer (DPO).

- Best practice for the safe and effective delivery of PRRT.
- Clinical dependencies are addressed and secured.
- Traceability and tracking and best practice for patient follow-up and data capture is secured.

The main aim of this service specification is to support the interim introduction and delivery of PRRT as clinically recommended.

Provider centres will support research activity and where appropriate be willing to support future phased adoption across the HSE. There is a need for shared learning between teams regarding these new technologies and their toxicities.

4.2 Quality Assurance

Selected providers are required to participate in annual quality assurance and collect and submit data to support the assessment of compliance with the service specification as agreed (INAB).

5 Applicable Service Standards

5.1 Regulatory Approval Requirements

A licence application to the Environmental Protection Agency (EPA) will need to be prepared and submitted. This will require risk assessments, preparing radiations safety procedures, drafting SOPs and patient information leaflets.

In addition, the submission of a new procedure application to HIQA is also needed to obtain generic justification approval for PRRT nationally. HIQA have indicated an application/notification would be required 3 months in advance of starting the service. However, the application process function has not yet been established by HIQA for new procedures/treatments involving ionising radiation. In the absence of this process, individual patient justification will be utilised.

6. Designated Providers (if applicable)

The NCCP has designated St. Vincent's University Hospital as the initial designated PRRT provider centres in Ireland.

7. Abbreviation and Acronyms Explained

The following abbreviations and acronyms have been used in this document:

PRRT	Peptide Receptor Radionuclide Treatment
NET	Neuroendocrine tumour
GI	Gastrointestinal
ENETS	European Neuroendocrine Tumour Society
MDM	Multidisciplinary Team Meeting
EPA	Environmental Protection Agency
HIQA	Health Information and Quality Authority
SOPs	Standard Operating Procedures
NCPE	National Centre for Pharmacoeconomics
TAS	Treatment Abroad Scheme
DPO	Data Protection Officer