Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Application Number: 2023-001

Lutetium oxodotreotide for the treatment of metastatic or inoperable gastroenteropancreatic neuroendocrine tumours (GEP-NETs):

Evidence synthesis to support a generic justification decision

Date of Publication 20 April 2023

About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.

- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.

- **Regulating health services —** Regulating medical exposure to ionising radiation.

- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.

- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.

- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

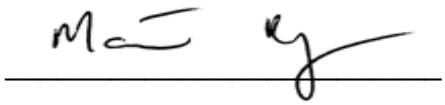
Foreword

The European Union Basic Safety Standards for the Protection Against Dangers from Medical Exposure to Ionising Radiation (Euratom) were initially transposed into Irish law under SI 256 in January 2019.(1) These Regulations named HIQA as the competent authority for medical exposure to ionising radiation. One requirement under the Regulations is that new practices involving medical exposures must be justified by HIQA before they are generally adopted – this is known as generic justification.

Peptide receptor radionuclide therapy (PRRT) with lutetium (^{177}Lu) oxodotreotide is licensed as a treatment option for gastroenteropancreatic neuroendocrine tumours (GEP-NETs). As this treatment has not been available in Ireland to date, eligible patients with metastatic or inoperable GEP-NETs have been referred for treatment abroad, typically through the Health Service Executive (HSE) Treatment Abroad Scheme. St. Vincent's University Hospital in collaboration with the National Cancer Control Programme (NCCP) wish to repatriate this service to the Republic of Ireland. However, this practice first requires generic justification to verify that there is a net benefit to the health of an individual, compared to the available alternatives, including those that involve less or no ionising radiation, before it is generally adopted in Ireland.

This report sets out a review of prior evidence syntheses which provides the evidence base to inform HIQA's generic justification decision. The report also includes the consideration of this evidence by HIQA's multidisciplinary Medical Exposure to Ionising Radiation Expert Advisory Group which is formally reported using an evidence to decision framework. The review considers the net benefit for this patient population in the context of the medical exposure to ionising radiation; the potential for occupational and public exposure is also considered.

This review was undertaken by the Ionising Radiation Evidence Review Team from the HTA Directorate in HIQA and was supported by HIQA's Medical Exposure to Ionising Radiation Expert Advisory Group who advised on the preparation of this report and participated in the evidence-to-decision exercise. HIQA would like to thank the Evidence Review Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.



Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

Acknowledgements

HIQA would like to thank all of the individuals and organisations who provided their time, advice and information in support of this report. Particular thanks are due to the members of the Medical Exposures to Ionising Radiation (MEIR) Expert Advisory Group (EAG) who provided advice and information, and to the Norwegian National Institute of Public Health for providing translated versions of their protocols and reports and permitting the reproduction of tables from their report.

The findings of the evidence review prepared by HIQA informed the deliberations of the MEIR EAG in completing the evidence to decision framework, with the output of the framework reached through consensus.

Expert advisory group membership

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Key: * Not a member of the standing Expert Advisory Group, but attended as an ad hoc member for the meeting where this practice was discussed.

Members of the Evidence Review Team

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Not all members of the Evidence Review Team are involved in the evidence synthesis to support each generic justification decision.

Conflicts of interest

None declared.

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List of abbreviations used in this report

AMSTAR-2	assessing the methodological quality of systematic reviews-2
EAG	expert advisory group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPA	Environmental Protection Agency
EPAR	European public assessment report
ERT	Evidence Review Team
FDA	Food and Drug Administration
GRADE	grading of recommendations, assessment, development and evaluation
GEP-NETs	gasteroenteropancreatic neuroendocrine tumours
HIQA	Heath Information and Quality Authority
HRQoL	health-related quality of life
HTA	health technology assessment
HSE	Health Service Executive
^{177}Lu	Lutetium-177
MEIR	medical exposure to ionising radiation
MEN	multiple endocrine neoplasia
MeV	mega electron volt
NCCP	National Cancer Control Programme
NNIPH	Norwegian National Institute of Public Health
PET	positron emission tomography
PRISMA	preferred reporting items for systematic reviews and meta-analysis
PRRT	peptide receptor radionuclide therapy/peptide receptor radiotherapy
RCT	randomised controlled trial
SI	statutory instrument
SSTR2	somatostatin subtype-2 receptors
WHO	World Health Organization
^{90}Y	Yttrium-90

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Plain Language Summary

Neuroendocrine tumours (NETs) are rare compared to other cancers and can develop almost anywhere in the body. They mostly occur in the lungs, appendix, small intestine, rectum and pancreas. A radionuclide known as ^{177}Lutetium (^{177}Lu) oxodotreotide is one of the treatment options for some patients who have NETs in the gut, that cannot be removed by surgery or have spread to other parts of the body. A radionuclide is a cancer medicine that emits a small amount of radioactivity, which causes damage to tumour cells. This type of treatment is only for NETs that have a particular type of receptor on the surface of their cells, called somatostatin receptors.

Until recently, patients in Ireland could only get ^{177}Lu oxodotreotide if they travelled abroad. This was typically funded through the Health Service Executive (HSE) Treatment Abroad Scheme. However, the HSE and the National Cancer Control Programme now wish to give this treatment in hospitals in the Republic of Ireland.

Under Irish law, any new practices which involve the exposure of patients to ionising radiation must be justified by the Health Information and Quality Authority (HIQA). Justification means making sure that the benefits of the practice outweigh the risks involved for the kind of patients undergoing this treatment. To decide if this practice is justified, HIQA have reviewed the available evidence in the medical literature, and sought input from a group of experts, including patient representatives. HIQA have also considered the occupational and public radiation safety issues in this review.

The available evidence indicates that ^{177}Lu oxodotreotide is a safe and effective treatment for this group of patients. Data from a clinical trial with 231 patients showed that ^{177}Lu oxodotreotide helps to slow down the progression of NETs in the gut. This trial also indicated that patients who were treated with ^{177}Lu oxodotreotide had better quality of life than those treated using a combination of best supportive care and another drug. Other evidence from observational studies that followed patients receiving the treatment over time supported the findings of this clinical trial. The most common side effects of this treatment include nausea and vomiting, which may be caused by an infusion which is given as part of this treatment to protect the kidneys. Other common side effects include low blood counts (for example, low white blood cells, which make it harder for someone to fight infection), feeling tired and low appetite. There is also a small risk of more severe side effects, such as damage to the kidneys and liver, and developing blood cancers. However, overall, the benefits of this treatment, which involves an exposure to ionising radiation, seem to outweigh the risks.

Key Points

- Application
  - This review was conducted in response to an application submitted by St. Vincent's University Hospital in conjunction with the National Cancer Control Programme for the generic justification of lutetium (^{177}Lu) oxodotreotide for gasteroenteropancreatic neuroendocrine tumours (GEP-NETs).
  - ^{177}Lu oxodotreotide is a peptide receptor radionuclide therapy (PRRT) marketed for the treatment of metastatic or inoperable GEP-NETs.
- Summary of evidence synthesis process
  - In accordance with HIQA's Methods for generic justification of new practices in ionising radiation, the evidence review team conducted a review of prior evidence syntheses to establish the evidence base for this new type of practice.
  - In total, 41 systematic reviews, health technology assessments (HTAs) and guidelines were identified. All 41 publications identified had favourable conclusions for ^{177}Lu oxodotreotide.
  - A 2018 HTA published by the Norwegian National Institute of Public Health (NNIPH) was identified as the most recent summary of evidence relevant to the research questions posed.
  - A further 66 publications and 30 ongoing trials were identified by the Evidence Review Team (ERT) since the NNIPH conducted its review.
- Clinical efficacy evidence
  - The body of evidence was largely underpinned by the findings of a single randomised control trial (RCT), the NETTER-1 trial, which had a primary outcome of progression free survival (PFS).
  - Final results from the NETTER-1 trial demonstrated improvements in PFS (HR = 0.18, 95% CI 0.11 – 0.29) when measured from the pre-randomisation baseline scan.
  - Differences in overall survival were not statistically significant (HR = 0.84, 95% CI 0.60 – 1.17), likely due to methodological issues, patient-cross over and treatment switching in NETTER-1.
  - NETTER-1 found that 18% of patients treated with ^{177}Lu oxodotreotide had either partial (17%) or full (1%) response compared with only 3% in the control group, representing a difference of 15% (95% CI 7.5 – 22.5%).
  - NETTER-1 also assessed health-related quality of life using the EORTC QLQ-C30-GHS/QoL (Global Health Status/Quality of Life) questionnaire. Time to deterioration was significantly longer in the ^{177}Lu oxodotreotide

arm in a number of domains, while observational studies supported the findings of improved quality of life.

- Adverse Events and Safety Evidence
  - Compared with high dose octreotide, ^{177}Lu oxodotreotide was associated with significantly more adverse events (RR=2.8, 95% CI 2.1 – 3.7) and severe adverse events (RR=9.9, 95% CI 1.3 – 75.9). No significant difference was noted in terms of withdrawals due to adverse events.
  - Late effects resulting from exposure to ionising radiation were not evident from NETTER-1. However, various estimates of secondary myelodysplastic syndrome (MDS) and leukaemia were reported in observational studies, with one study estimating a 6.7% long-term risk of MDS / leukaemia.
- Certainty of the evidence
  - The certainty of the evidence in the NNIPH report was found to be low particularly for safety outcomes and overall survival. Only the outcomes of PFS, tumour response and a select few adverse events had estimates that were considered to be of moderate certainty.
  - Downgrading of the certainty of the evidence was predominantly on the basis that the participants and researchers were not blinded in the only RCT.
- Medical Exposure to Ionising Radiation Expert Advisory Group (MEIR EAG)
  - Informed by the review of the above evidence, the MEIR EAG completed judgements under a modified evidence-to-decision making framework to arrive at a recommendation to HIQA on the generic justification of ^{177}Lu oxodotreotide for GEP-NETs.
  - The MEIR EAG judged that there was a small benefit in terms of overall survival and health-related quality of life and a moderate benefit for progression free survival.
  - The majority of adverse events were considered predictable and manageable. The incidence of MDS / leukaemia was noted to be low and clinically acceptable by the MEIR EAG in the context of the treatment indication, that is, adults with metastatic or inoperable GEP-NETs. The overall potential for harm was considered small in the context of this particular population.
  - In terms of the potential for public and occupational exposure, the MEIR EAG agreed that risk is likely to be low, provided appropriate radiation protection safeguards are in place.
  - The MEIR EAG, on consideration of the balance between the benefits and harms, recommended that this practice be generically justified for the treatment of adults with metastatic or inoperable GEP-NETs.
- Decision making

- Having considered the application, the evidence review and the recommendation from the MEIR EAG, HIQA is satisfied that on consideration of the balance between the benefits and harms, this practice should be generically justified.
- The new practice of lutetium oxodotreotide for the treatment of adults with metastatic or inoperable gastroenteropancreatic neuroendocrine tumours is generically justified under SI 256/2018.
- The generic justification of this practice is effective from 20 April 2023.

1 Introduction

1.1 Background to the application

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu oxodotreotide is authorised by the European Medicine's Agency as a treatment option for gastroenteropancreatic neuroendocrine tumours (GEP-NETs).(2) As this treatment has not been available in Ireland, to date, eligible patients with metastatic or inoperable GEP-NETs have been referred for treatment abroad, typically through the Health Service Executive (HSE) Treatment Abroad Scheme. Those unable to travel abroad or ineligible for this scheme are offered alternative treatments such as somatostatin analogues, everolimus, sunitinib, temozolomide with or without capecitabine, radiotherapy, or cytotoxic chemotherapy. A retrospective study found a median waiting time of 84 days for Irish patients referred abroad for ^{177}Lu oxodotreotide treatment, with a range of 8 to 209 days.(3)

The HSE and the National Cancer Control Programme (NCCP) wish to repatriate this service to the Republic of Ireland. The use of ^{177}Lu oxodotreotide for NETs would represent a new practice in Ireland. Therefore, consistent with the requirements under the European Union Basic Safety Standards for the Protection Against Dangers from Medical Exposure to Ionising Radiation (Euratom), which were transposed into Irish law under SI 256 in January 2019, it requires generic justification before it can be generally adopted.

^{177}Lu oxodotreotide is an established treatment in other countries. Topic exploration performed by HIQA in advance of developing this report indicated that a number of evidence syntheses have already been conducted in relation to its use for NETs. For these reasons, and in accordance with HIQA's Methods for generic justification of new practices in ionising radiation, a 'Review of prior evidence syntheses' was undertaken.(4) This review has three review questions (RQs) which focus on clinical effectiveness, quality of life, safety and adverse events. Reference is also made to the potential for public and occupational exposure to ionising radiation arising from the use of ^{177}Lu oxodotreotide.

1.2 Overall approach

A standing multidisciplinary MEIR expert advisory group (EAG) has been convened by HIQA comprising representation from key stakeholders. A full list of the membership of the EAG is available in the acknowledgements section of this report. The terms of reference for the EAG are published on the HIQA website.

This review of prior evidence syntheses was prepared to provide an evidence base to inform the discussions of the MEIR EAG and its recommendation-making process as

well as the subsequent decision-making by the Director of Health Technology Assessment (HTA). The following summarises the steps taken:

- A review of prior evidence syntheses was performed to provide the evidence base for a generic justification decision.
- This review systematically identified relevant evidence which related to the efficacy, health related-quality of life and safety of ^{177}Lu oxodotreotide for the treatment of adults with metastatic or inoperable GEP-NETs.
- A draft report summarising the benefits and harms associated with this practice was produced and was circulated to the MEIR EAG for review.
- Following a meeting of the MEIR EAG, the final draft of the report was amended as appropriate and was circulated to MEIR EAG for review.
- Having considered the application, the evidence review and the recommendation from the MEIR EAG, HIQA is satisfied that on consideration of the balance between the benefits and harms, this practice should be generically justified.
- The new practice of ^{177}Lu oxodotreotide for the treatment of adults with metastatic or inoperable gastroenteropancreatic neuroendocrine tumours is generically justified under SI 256/2018.
- The generic justification of this practice is effective from 20 April 2023.
- Following HIQA's decision, the final report and generic justification decision were published on the HIQA website.

2 Description of the technology

^{177}Lu oxodotreotide is a radiopharmaceutical which may be administered as a form of peptide receptor radionuclide therapy (PRRT) for the treatment of GEP-NETs. In 2018, ^{177}Lu oxodotreotide, also known as ^{177}Lu dotatate and ^{177}Lu DOTA-octreotate, was authorised by the European Medicines Agency and placed on the market under the brand name Lutathera®.(5) Lutathera® is a ready-to-use radiopharmaceutical medicinal product which is for intravenous, single-use only. The product consists of a 370MBq/mL solution which should only be handled and administered in accordance with regulatory requirements. Overexpression of somatostatin subtype-2 receptors (sstr2) is a common feature of GEP-NETs. ^{177}Lu oxodotreotide takes advantage of the overexpression of somatostatin receptors, sstr2, by binding to the receptor and concentrating in tumour cells. ^{177}Lu has a half-life of 6.647 days and decays via β-emission to stable Hafnium (^{177}Hf), and the electron produced causes damage to the DNA of tumour cells and surrounding tissues. The average energy of this electron is 0.130MeV, with a maximum energy of 0.497MeV.

As with the introduction of other radionucleotides, ^{177}Lu oxodotreotide PRRT requires additional training of staff. Low energy gamma radiation is also emitted, which requires additional shielding in the physical infrastructure of the planned nuclear medicine site. Licensing by the Environmental Protection Agency (EPA) is required in order to carry out this practice.

2.1 Current diagnostic and treatment pathway

The only potentially curative treatment for NETs is surgery; all other treatments are undertaken primarily to reduce symptoms and or prolong life.(6) Given the heterogeneous nature of GEP-NETs, signs and symptoms may differ greatly. Many of these GEP-NETs are diagnosed incidentally when people are undergoing investigation or treatment for an unrelated illness.(7)

PRRT with ^{177}Lu oxodotreotide is indicated for adults with metastatic or inoperable progressive, well-differentiated (G1 and G2), somatostatin receptor positive-GEP-NETs in adults aged 18 years and older.(2) The overexpression of the somatostatin receptors, sstr2, in the tumour tissue must be confirmed to determine eligible candidates for ^{177}Lu oxodotreotide.(8) This is typically confirmed using either somatostatin receptor scintigraphy or a ^{68}Ga-labelled somatostatin analogue PET scan, with a requirement that the tumour uptake should be at least as high as normal liver uptake. ^{177}Lu oxodotreotide is typically considered as a second-line treatment and therefore, this cohort of patients may have received a variety of other treatments prior to being considered for PRRT with ^{177}Lu oxodotreotide.

The applicant has indicated that PRRT with ^{177}Lu oxodotreotide is part of the established treatment pathway for advanced gastrointestinal and pancreatic NETs, referring to joint European Association of Nuclear Medicine (EANM), Society of Nuclear Medicine and Molecular Imaging (SNMMI) and International Atomic Energy Agency (IAEA) guidelines.(9) In Ireland, patients for whom this treatment is indicated have been referred abroad in the past as the facilities required to administer the treatment were not in place. The applicant has indicated that the HSE previously funded patients through its Treatment Abroad Scheme to receive this treatment in locations such as London (England), Uppsala (Sweden) and Rotterdam (the Netherlands).

^{177}Lu oxodotreotide generally involves four treatment cycles, which typically occur eight weeks apart. A slow infusion of 7.4GBq of ^{177}Lu oxodotreotide is administered at each treatment cycle over approximately 30 minutes, along with an amino acid infusion to protect the kidneys. An anti-emetic is injected at least 30 minutes prior to the commencement of the amino acid infusion. ^{177}Lu oxodotreotide uptake and distribution is confirmed by post-therapy imaging. According to the applicant, the mean effective dose for the treatment is 370mSv; however, this varies among patients depending on their tumour burden and somatostatin avidity. The ^{177}Lu oxodotreotide vial is stored in either a polymethyl methacrylate container (a radioprotective container which allows visualisation of the vial) or a lead container.

3 Epidemiology

NETs are relatively rare compared to other cancers and can occur almost anywhere in the body.[10] They are a diverse group of tumours which mostly occur in the lungs, appendix, small intestine, rectum and pancreas.[11] Although their exact cause is not known, the risk of NETs is relatively higher in people with inherited genetic syndromes such as multiple endocrine neoplasia (MEN) 1, MEN 2, and neurofibromatosis.[12]

GEP-NETs can be grouped by where the tumour starts in the body (foregut, midgut or hindgut), whether they are functional or non-functional (based on whether or not they produce hormones and cause hormone-related symptoms) and whether they are indolent or aggressive (slow growing versus fast growing and more likely to spread).

For the purpose of this report, GEP-NETs are defined as any histological subtypes and classifications of NETs, as outlined in the World Health Organization (WHO) classification guide, occurring in the foregut (stomach, duodenum, and pancreas) or midgut/hindgut (ileum, jejunum, ascending colon and proximal two-thirds of transverse colon, distal third of transverse colon, descending colon, sigmoid colon and rectum).[13-15]

There has been a steady increase in the incidence of invasive NETs in Ireland, with an annual percentage increase of 8% between 1994 and 2010.[7] According to the most recent publication from the National Cancer Registry in Ireland (NCRI), the incidence of invasive NETs was 4.6 cases per 100,000 persons (4.4 in females and 5.0 in males) in 2013.[7] Exact figures for the incidence of adults with metastatic or inoperable disease were not included in this report; however, the NCRI indicated that approximately 36% of upper gastrointestinal NETs, 55% of pancreatic NETs, 55% of appendicular NETs, 65% of colorectal NETs, and 70% of small intestinal NETs are advanced (stage T3 or greater) at diagnosis.[7] The applicant has estimated that between 50 and 60 adult patients will be treated per year in St Vincent's University Hospital using PRRT with ^{177}Lu oxodotreotide.

4 Clinical efficacy, effectiveness and safety

4.1 Methodology

The generic justification process is informed by three review questions (RQs). RQ1 and RQ2 consider progression-free survival, overall survival, quality of life and symptom control while RQ3 considers adverse events and toxicity. In Ireland, public and occupational exposure is primarily the responsibility of the Environmental Protection Agency. However, the Regulations require HIQA to consider public and occupational exposure as part of the justification of medical exposures.(1) The approach taken to this issue and the three RQs is outlined in the following sections.

4.1.1 Review questions 1, 2 and 3

This evidence review to inform decision-making on generic justification comprised three distinct RQs:

RQ1 In patients with metastatic or inoperable GEP-NETs, does the use of ^{177}Lu oxodotreotide lead to improved overall survival and progression-free survival compared with other available treatments?

RQ2 In patients with metastatic or inoperable GEP-NETs, does the use of ^{177}Lu oxodotreotide lead to improved health-related quality of life or symptom control compared with other available treatments?

RQ3 In patients with GEP-NETs, what is the risk of adverse events and toxicity associated with the ^{177}Lu oxodotreotide compared with other available treatments?

Table 1 outlines the PICOS for RQ1, RQ2, and RQ3.

Table 1 PICOS table for RQ1, RQ2 and RQ3

PICOS	Description
Patient/Problem:	Adults aged 18 years and older with metastatic or inoperable sstr2-positive GEP-NETs
Intervention:	Lutetium (^{177}Lu) oxodotreotide
Comparison:	Treatments used as part of current care in Ireland (for example, octreotide, lanreotide, everolimus, sunitinib, temozolomide, best supportive care, no treatment)
Outcomes:	• overall survival • progression-free survival • response rate

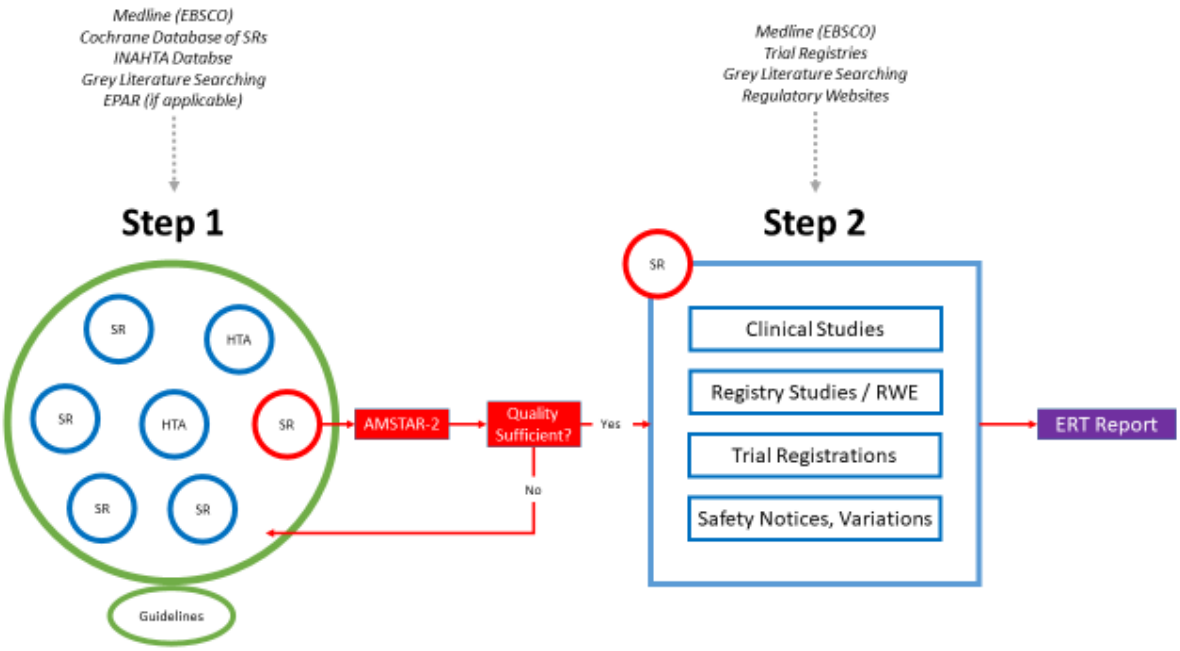
PICOS	Description
	• symptom control • adverse events • health-related quality of life measured using a validated instrument*
Study Design:	Only human studies will be included. Step 1: For identification of prior evidence syntheses: • systematic reviews • clinical guidelines • HTAs. Step 2: For identification of primary evidence published after the documented search date in the selected prior evidence synthesis: • randomised and non-randomised control trials • cohort studies • case-control studies • self-controlled case series. Case reports, and cross-sectional studies will be excluded.
Languages:	Only articles for which an adequate English translation can be obtained will be included.

Key: GEP-NETs - gasteroenteropancreatic neuroendocrine tumours; HTA - health technology assessment; sst2r - somatostatin receptor 2.
* For example, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)

4.1.2 Search strategy

Figure 1 outlines the two-step process used to identify evidence to inform the Evidence Review Team (ERT) report using a prior evidence synthesis methodology. The full search strategy can be found here: https://doi.org/10.5281/zenodo.7565139

Figure 1: Process for identifying evidence using a review of prior evidence synthesis methodology



Step 1 Identifying prior evidence syntheses

This step involved identifying all relevant systematic reviews, HTAs and guidelines.

Electronic searches were conducted in Medline (EBSCO), and the Cochrane Database for Systematic Reviews, and supplemented by a grey literature search. The full search strategy and a list of grey literature sites are presented in Appendix 1. The search was undertaken on 23 November 2022. All citations were entered into the online systematic reviewing software Covidence. European Public Assessment Reports (EPARs) for marketed forms of this drug were reviewed.

Systematic reviews and HTAs were compiled and ordered in accordance with their relevance to the review questions and the recency of the searches they performed. After checking for consistency of findings across all prior evidence syntheses identified, the most relevant and recent evidence synthesis was selected and appraised with Assessing the Methodological Quality of Systematic Reviews-2 (AMSTAR-2), a critical appraisal tool for systematic reviews.[16] Network meta-analyses were not considered for selection due to concerns about the clinical heterogeneity of the general GEP-NET cohort.

Clinical guidelines provide evidence that a practice is currently being undertaken in another country and can provide useful recommendations around the practice. For this reason, clinical guidelines identified as part of Step 1 were compiled and presented in the results section and in Appendix 1.

Step 2: Identifying new evidence

Electronic searches were conducted in Medline (EBSCO) and supplemented by a grey literature search. The search strategy was identical to that of Step 1, with the exception that the filter for systematic reviews was replaced with a filter for randomised control trials, cohort studies and case-control studies. The search was limited to May 2017 onwards as this was the last search date used in the evidence synthesis selected in Step 1. The number of records received/screened and the date of the search were recorded.

A grey literature search was conducted on Google, Google Scholar and selected relevant websites (presented in Appendix 1). This search included a search of clinical trial databases for ongoing and unpublished trials and a search for safety notices, signal reports and variations to the marketing authorisation. Forward citation searching had been planned in the project protocol, but was not undertaken for the selected evidence synthesis from Step 1 due to the lack of a digital object identifier (DOI).

4.1.3 Study selection

Step 1 and Step 2

Returned citations from the collective search were added to Covidence. All citations (titles and abstracts) were screened independently by two reviewers as per the inclusion criteria. Full-text screening was conducted by one reviewer, with the second reviewer checking agreement in 20% of citations. Any disagreements were resolved by discussion. Reasons for exclusion following full-text review were documented and summarised in the PRISMA Flowchart (see Figure 2 and Figure 3).

4.1.4 Data extraction and management

Step 1 and Step 2

Standardised data extraction templates were developed and piloted prior to undertaking data extraction. Data extraction was performed by one reviewer. The second reviewer checked 20% of the records. A few minor disagreements were resolved by discussion.

4.1.5 Risk of bias assessment

Step 1

AMSTAR-2 was used to assess the risk of bias in the selected systematic review.

Step 2

As the aim of this step was only to identify if any new studies contradicted what had been found in step 1, no formal risk of bias assessment was carried out on these studies.

4.1.6 Data synthesis

Data obtained from Step 1 and Step 2 were narratively synthesised. Findings from Step 1 were presented and complimented by evidence identified in Step 2 that may highlight evidence gaps or discordant findings.

4.1.7 Grading of Recommendations Assessment, Development and Evaluation (GRADE)

A summary of findings table, including the certainty of the evidence for the primary outcomes, was extracted from the systematic review selected in Step 1. This was conducted using GRADEpro and was performed to help populate the evidence-to-decision table for generic justification that is outlined in HIQA's methods document.[4, 17]

4.1.8 International practice and guidelines

An overview of current international practice is provided based on the findings of the topic exploration exercise conducted by the ERT and the search in Step 1 for guidelines. The grey literature search included a search of national public health organisations, and of the websites of governmental departments and relevant agencies for countries where the applicant or literature suggested this practice was already in place. Any guidelines found and the associated recommendations are summarised in Table A. in Appendix 1.

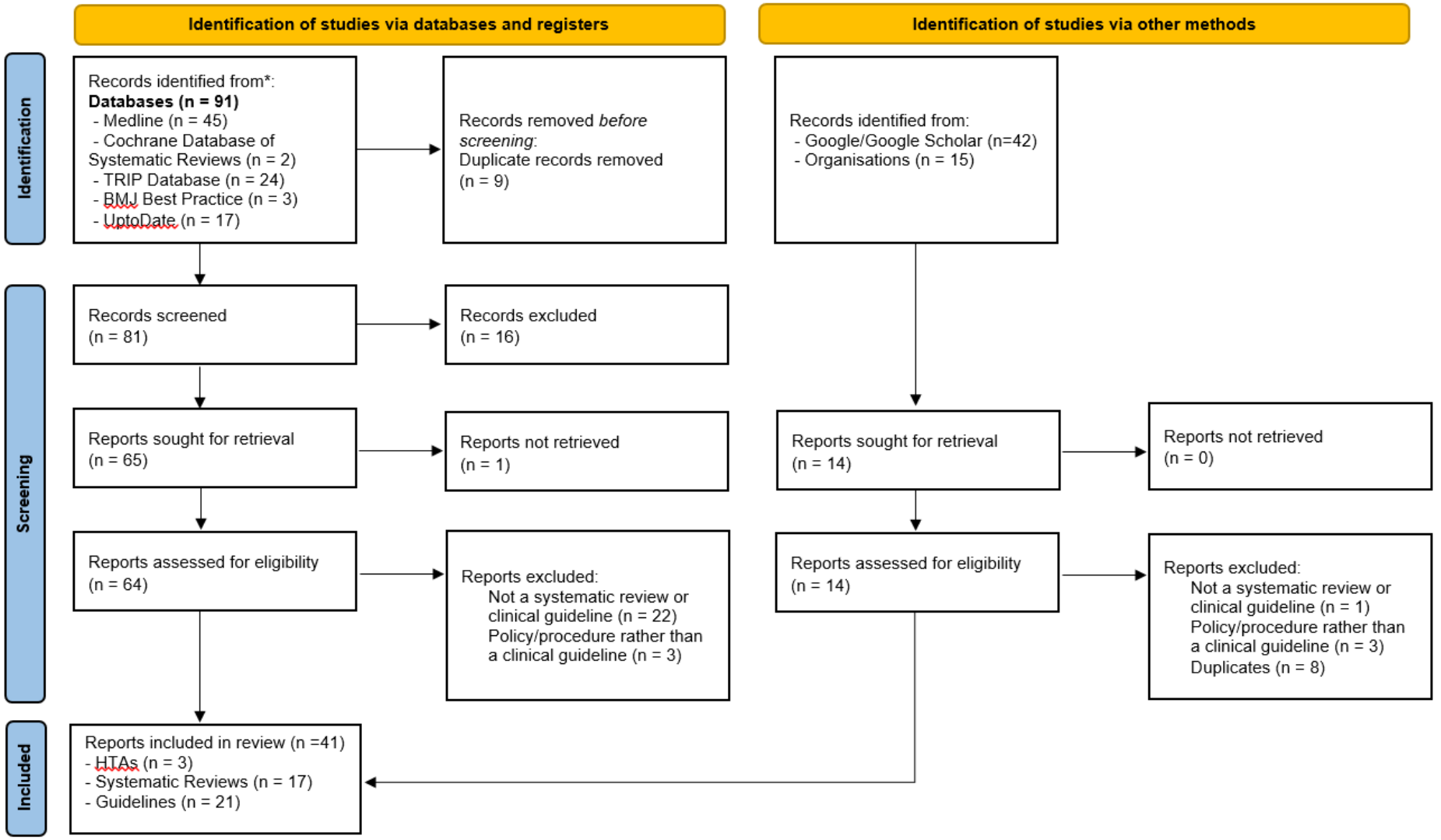
4.2 Results

4.2.1 Search results RQ1, 2 and 3

Step 1: Identifying Prior evidence syntheses

The systematic search of the literature identified 81 unique records from databases and registers and a further 57 from the grey literature search. After screening, 20 prior evidence syntheses and 21 guidelines were identified as shown in Figure 2.

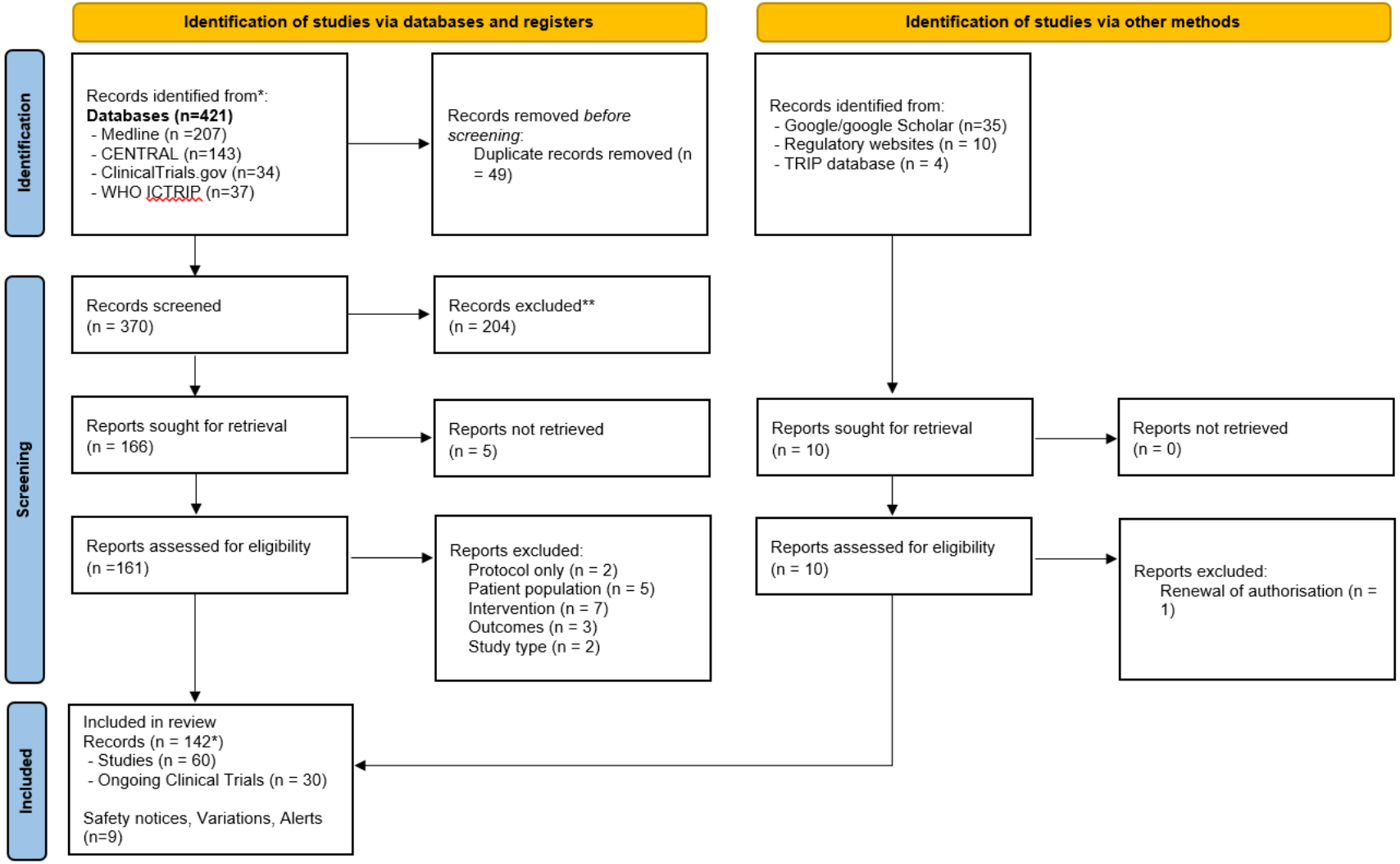
Figure 2. PRISMA flow diagram for step 1



Step 2: Identifying new evidence

A systematic search of the literature identified 370 unique records from databases and clinical trial registers. After screening, 142 records were identified. As multiple records referred to the same study or trial, this resulted in 66 completed publications and 30 registrations of ongoing unpublished trials since the prior evidence synthesis as shown in Figure 3. A full list of publications and ongoing trials can be found in Table A.4. and A.5 of Appendix 1.

Figure 3. PRISMA flow diagram for step 2.



*A number of the records referred to the same studies, therefore of 142 separate records, there were 60 completed studies and 30 ongoing studies.

4.2.2 Review selection, study characteristics and quality appraisal

Step 1

The 41 prior evidence syntheses reports identified comprised HTAs (n=3), systematic reviews (n=17) and guideline documents (n=21), a brief summary of which are provided in Tables A.1 to A.3 of Appendix 1. All those identified concluded that using ^{177}Lu oxodotreotide was beneficial.

In accordance with the methods outlined in Section 4.1.3, a systematic review conducted as part of a 2018 HTA performed by the Norwegian National Institute of Public Health (NNIPH) was selected due to its relevance to the review questions and the recency of its search (May 2017).[18] This NNIPH HTA focused on nine studies: one randomised controlled trial (RCT) (NETTER-1) and eight observational studies. Not all studies contained every outcome of interest or were relevant to all RQs. All nine studies concluded that ^{177}Lu oxodotreotide was beneficial and or safe.

The quality of the systematic review used in the NNIPH HTA was assessed using AMSTAR-2 (Appendix 2). Areas of potential weakness in the systematic review included a lack of detail on the doses of the intervention, limited appraisal of possible confounding in non-randomised studies, and no discussion of the impact of bias on the results. While the AMSTAR-2 tool indicated that, based on the latter two weaknesses, the review would be considered of 'critically low' quality, it was noted that in all other domains of the AMSTAR-2 checklist, the systematic review in the NNIPH HTA performed well. The limited discriminatory capacity of AMSTAR-2 has been described elsewhere,[19] and having carefully considered the possible weaknesses that were identified through AMSTAR-2, the review was deemed to be an acceptable quality to inform decision-making. The above-mentioned weaknesses were explored further by the ERT and are reconciled in the discussion section of this report.

Step 2

All of the 66 new studies identified since May 2017 were found to have favourable conclusions for the application of ^{177}Lu oxodotreotide in terms of benefits and or safety. These studies were largely observational studies and case series, with the exception of a publication of final follow-up results from the NETTER-1 study. Some explored ^{177}Lu oxodotreotide as part of novel combination therapies, maintenance or salvage treatments. In these applications, some imprecision and inconsistency of findings were noted. Details on ongoing trials and publications since the prior evidence synthesis are laid out in Table A.4. and A.5 of Appendix 1.

In keeping with the protocol for this review, studies published since the last search performed in the prior evidence synthesis were not quality assessed as there were

limited discordant findings. The exception to this was the final results of the NETTER-1 RCT which reported no statistically significant improvement in overall survival; this contrasted with the findings in the earlier interim analysis.

4.2.3 Data synthesis

The NNIPH synthesised the findings of nine studies on the clinical effectiveness and safety of ^{177}Lu oxodotreotide. These studies are presented in Table 2.

Table 2 Studies included in the Norwegian National Institute of Public Health's synthesis of clinical effectiveness and safety

Author	Study Design	Population	Intervention/ Comparator	Follow-up	Outcomes
Strosberg 2017[20]	Randomised Control Trial N = 229	100% GEP-NETs (>90% small intestine)	^{177}Lu oxodotreotide (N = 116) Vs High Dose Octreotide (N = 113)	20 month	OS, PFS, TRR, AE (general symptoms and toxicity)
Hörsch 2016[21]	Registry study (partly prospective) N = 450 of which 241 treated with ^{177}Lu DOTATATE	At least 80% GEP-NETs (approx. 38% pancreas, 30% small bowel, 19% unknown primary, 4% bronchial system)	^{177}Lu oxodotreotide	24 months	OS, PFS, TRR, AE (toxicity)
Kwekkeboom 2008[22]	Cohort Study (prospective) N = 504, of which 310 followed up on current outcomes	At least 90 % GEP-NETs (approx. 60% carcinoid, 20 % pancreatic cancer and 10% unknown origin)	^{177}Lu oxodotreotide	48 months (median)	OS, PFS, TRR, TTP, AE (general symptoms and toxicity)
Bodei 2015[23]	Register study (retrospective) N = 807, of which 333 treated with	At least 75 % GEP-NETs (approx. 35% small intestine, 40% pancreas), 15% bronchial and 10% unknown origin)	^{177}Lu oxodotreotide	30 months (median)	AE (toxicity)

	^{177}LuDOTATATE				
Bergsma(a) 2016[24]	Cohort Study (prospective) N = 324	Approx. 90 % NET (NETs unspecified)	^{177}Lu oxodotreotide	6 months (minimum)	AE (short term toxicity)
Bergsma(b) 2016[25]	Cohort Study (prospective) N = 554, of which 323 followed up on current outcomes	Approx. 90 % NET (NETs unspecified)	^{177}Lu oxodotreotide	27 months	AE (toxicity)
Sabet 2013[26]	Cohort Study (retrospective) N = 203	At least 95 % GEP-NETs (approx. 60% intestine, 35% pancreas and 5% unknown origin)	^{177}Lu oxodotreotide	31 months (median)	AE (toxicity)
De Keizer 2008[27]	Cohort Study (prospective) N = 479	At least 80% GEP-NETs (approx. 50% gut, 30% pancreas, 5% bronchial and 15% other and unknown origin)	^{177}Lu oxodotreotide	48 months (median)	AE (symptoms: hormonal crises)
Khan 2011[28]	Cohort Study (prospective) N = 265	At least 90% GEP-NETs (approx. 60% carcinoid, 30% pancreatic cancer and 10% unknown origin)	^{177}Lu oxodotreotide	48 months (median)	AE (general symptoms) and HRQoL

Key: AE – adverse events; GEP-NETs – gasteroenteropancreatic neuroendocrine tumours; HRQoL – health-related quality of life; OS – overall survival; PFS – progression-free survival; TRR – tumour response rate.

RQ1: Overall survival and progression-free survival

The NNIPH HTA considered evidence from one randomised controlled trial (RCT) (NETTER-1) with 229 patients and from eight observational studies (n=1,200). Based on synthesis and appraisal of the data within the included studies, NNIPH concluded that ^{177}Lu oxodotreotide probably reduces overall mortality and is likely to increase both overall and progression free survival (PFS). However, they highlighted that the effect on overall survival and PFS was highly uncertain and dependent on the type of NET.

Midgut NETs are the most common GEP-NET.[29] The NETTER-1 study randomly assigned patients with well-differentiated, metastatic midgut NETs to either ^{177}Lu oxodotreotide plus best supportive care including 30mg long-acting octreotide, or to treatment with high dose (60mg) long-acting octreotide only. Data from the primary analysis at 20 months informed the estimates in the HTA. ^{177}Lu oxodotreotide was associated with a significant reduction in mortality (RR 0.52, 95% CI 0.29 – 0.95; HR = 0.4, p=0.004). Based on GRADE criteria, this estimate was assessed to be of low certainty, that is, the authors had limited confidence in the estimate. Downgrading of the certainty of the evidence was on the basis of there being one study only and because the participants were not blinded. The HTA identified three observational studies that reported mortality data, all three of which supported the findings of the RCT. While acknowledging substantial uncertainty, on the basis of these observational studies, the HTA concluded that ^{177}Lu oxodotreotide possibly leads to an increase in overall survival of between 40 and 70 months.

Assessment of PFS was based on the NETTER-1 RCT and four observational studies. There was RCT evidence of a significant difference in the proportion of survivors without disease progression at 20 months with 65.2% (95% CI 50% – 76.8%) in the ^{177}Lu oxodotreotide group versus 10.8% (95% CI 3.5% – 23%) in the control arm (MD = 54.4%, 95% CI 43.1% – 65.7%). In terms of disease progression or death, the authors of the RCT reported a HR of 0.21 (95% CI 0.13 – 0.33) in favour of the intervention group, corresponding to an estimated 79% reduction in risk. This estimate was assessed to be of moderate certainty based on GRADE criteria. While the certainty of the evidence was downgraded because the participants were not blinded, it was noted that while there was only one study, no further downgrading should occur due to the large effect size seen. The median PFS was 8.4 months in the control group and had not yet been reached in the ^{177}Lu-oxodotreotide group. Evidence from the observational studies supported the RCT findings with the HTA concluding that ^{177}Lu-oxodotreotide leads to an increase in PFS of between 20 and 50 months.

A number of studies relevant to overall survival and PFS were identified in Step 2, the update (performed by the ERT) of the NNIPH HTA search. The majority of those identified were retrospective cohort studies or case series. The main discordant result identified in Step 2 was the updated and final analysis of overall survival in NETTER-1.[30] This final analysis, which was published in December 2021, was pre-specified to happen either after 158 deaths had occurred or five years after the last patient was randomised, whichever occurred first. The authors reported that the analysis was based on the overall survival five years after all of the patients were randomised. Based on these data, it was noted that ^{177}Lu-oxodotreotide did not lead to a significant improvement in median overall survival (HR = 0.84, 95% CI 0.60 – 1.17; two-sided p=0.30). Median overall survival was 48.0 months (95% CI 37.4 –

55.2) in the ^{177}Lu-oxodotreotide group and 36.3 months (95% CI 25.9 – 51.7) in the control group. There was a large amount of cross-over with 41 patients (36%) in the control arm receiving PRRT in total, and 23% had crossed over within 24 months of randomisation. During long-term follow-up, 55 (24%) of 231 patients in both groups were documented as receiving other antineoplastic agents, including everolimus in 17 (15%) of 117 patients in the ^{177}Lu-oxodotreotide group and 20 (18%) of 114 patients in the control group. These factors limited the analysis that could be undertaken, particularly with proportional hazard models.(30) Additionally, the interim result for PFS included in the NNIPH report (HR = 0.21, 95% CI 0.13 – 0.33; p<0.001) was subsequently updated and included in the final NETTER-1 results found in Step 2. Reassessment included pre-randomisation baseline scans, rather than use of scans before treatment if there had been a delay. This led to a slightly different estimate of PFS (HR = 0.18, 95% CI 0.11 – 0.29; p<0.0001).

As noted, the majority of studies identified in the Step 2 search were retrospective cohort studies and case series, most of which were based on small study numbers. Of note was one large retrospective, multicentre Italian study (records from 25 oncology centres; n=508 patients). It concluded that in patients with NETs who had experienced disease progression on somatostatin analogue (SSA) treatment, ^{177}Lu oxodotreotide was associated with significantly improved survival outcomes compared with upfront chemotherapy or targeted therapy.(31)

It is relevant to note that, since the publication of the NNIPH HTA, one further RCT (NETTER-2, NCT03972488) remains active.(32) The aim of NETTER-2 is to determine if ^{177}Lu oxodotreotide in combination with long-acting octreotide, when used as a first-line treatment, prolongs PFS in GEP-NET patients with high proliferation rate tumours (G2 and G3), compared to treatment with high dose (60 mg) long-acting octreotide.

Tumour response rate

The objective response rate to treatment (tumour response rate) was considered as an outcome in the NNIPH HTA. Response was assessed based on the same studies as for PFS and used the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. The NNIPH HTA concluded based on the NETTER-1 RCT that ^{177}Lu oxodotreotide was associated with a significantly higher tumour response rate; 18% of patients treated with ^{177}Lu oxodotreotide had either partial (17%) or full (1%) response compared with only 3% in the control group, representing a difference of 15% (95% CI 7.5 – 22.5%). The authors had moderate certainty in these findings. Data from the observational studies supported the findings of the RCT; these reported a higher effect size for ^{177}Lu oxodotreotide, but there was considerable uncertainty around the estimates.

RQ2: Symptom control and health related quality of life (HRQoL)

The NNIPH HTA examined an observational study of 265 patients, which measured health-related quality of life (HRQoL) using the EORTC QLQ-C30-GHS/QoL (Global Health Status/Quality of Life) questionnaire. These findings indicated an improvement in HRQoL following ^{177}Lu oxodotreotide for some domains related to emotional and social functioning. However, the study was deemed low quality and the NNIPH HTA authors concluded that there was a high degree of uncertainty associated with the results.

A number of studies were identified that reported improvements in HRQol or symptom control associated with ^{177}Lu oxodotreotide use. One study reported HRQoL data from NETTER-1, which used the EORTC QLQ-C30-GHS/QoL questionnaire. Time to deterioration was significantly longer in the ^{177}Lu oxodotreotide arm in a number of domains including global health status (HR = 0.41, 95% CI 0.24 – 0.69), physical functioning (HR = 0.52, 95% CI 0.30 – 0.89), role functioning (HR = 0.58, 95% CI 0.35 – 0.96), fatigue (HR = 0.62, 95% CI 0.40 – 0.96), pain (HR = 0.57, 95% CI 0.34 – 0.94), diarrhoea (HR= 0.47, 95% CI 0.26 – 0.85), disease-related worries (HR = 0.57, 95% CI 0.36 – 0.91), and body image (HR = 0.43, 95% CI 0.23 – 0.80).[33]

Additional studies identified in the Step 2 search included a publication on patient diaries from the NETTER-1 study, which reported a reduction in abdominal pain, diarrhoea, and flushing, constituting the core symptoms of patients with progressive midgut neuroendocrine tumours, compared with high dose octreotide.[34]

Another study found during Step 2 further concluded that in a case series of insulinomas, ^{177}Lu oxodotreotide achieved hypoglycaemia symptomatic control and reported improvements in quality of life.[35, 36]

The effect on ^{177}Lu oxodotreotide on the control of carcinoid syndrome (characterised by diarrhoea, shortness of breath, flushing and itching) was not reported in the NNIPH HTA. However, one retrospective cohort study identified in Step 2, which included 22 patients with metastatic midgut NETs experiencing carcinoid syndrome, concluded that ^{177}Lu oxodotreotide may provide some symptomatic control.[37]

RQ3: Adverse events

In terms of adverse events, the NNIPH HTA authors noted that all included studies (one RCT and eight observational studies) measured adverse events, representing a combined population of approximately 1,200 patients. Estimates relating to adverse events were assessed to be of either low or very low quality, meaning that they had limited or very little confidence in the estimates based on GRADE criteria.

Estimates for an overall adverse event rate and severe adverse event rate were taken from the NETTER-1 RCT. Compared with high dose octreotide, ^{177}Lu oxodotreotide was associated with significantly more adverse events (RR=2.8, 95% CI 2.1 – 3.7) and severe adverse events (RR=9.9, 95% CI 1.3 – 75.9). No significant difference was noted in terms of withdrawals due to adverse events.

The NNIPH HTA compiled the evidence on the risk of haematological toxicity from their included studies. The authors noted that not all studies broke down haematological toxicity by grade, and estimates of relative risk were characterised by large confidence intervals. Across the included studies, estimates relating to haematological toxicity were assessed to be of either low or very low quality. Estimates from the NETTER-1 RCT indicated that the risk of haematological toxicity was significantly higher in patients receiving ^{177}Lu oxodotreotide, including a significantly higher risk of thrombocytopenia (RR=27.8, 95% CI 3.8 – 200.4), anaemia (RR=2.6, 95% CI 1.1 – 6.5), lymphopenia (RR=9.9, 95% CI 2.4 – 41.4), and leukopenia (RR=10.9, 95% CI 1.43 – 83.0); no significant difference was reported with respect to neutropenia (RR=6.0, 95% CI 0.7 – 48.6). Six of the eight observational studies included in the NNIPH HTA reported subacute haematological toxicity associated with ^{177}Lu oxodotreotide use. Estimated incidence of severe (grade 3 and 4) haematological toxicities ranged from 3% to over 11%.[23-26] Haematological toxicity in these patients was reported to be persistent (>six months), with up to half requiring blood transfusions. With respect to long term bone marrow suppression, studies variably reported that this occurred after one, two and three years in 1.2%, 2.2% and 3% of patients treated with ^{177}Lu oxodotreotide or that normal blood counts were restored after an average of 12 months in all patients (range 3 to 22 months).[26] Evidence identified in Step 2 seemed to indicate a low incidence of haematological toxicity, and studies such as those by de Vries-Huizing et al. indicated that severe cases were rarely observed, and that adaptation of dosages and postponement of administrations could still allow many to complete their treatment.[38]

Secondary myelodysplastic syndrome (MDS) and leukaemia are of particular concern in patients treated with ^{177}Lu oxodotreotide. The NNIPH HTA found no RCT evidence of leukaemia, but identified one case of MDS that was considered possibly attributable to ^{177}Lu oxodotreotide. Estimates from the included observational studies suggested incidences of MDS ranging from 1% to 2.4% and of 0% to 1.1% for leukaemia. The higher of these estimates was based on a study of heterogeneous PRRT interventions including ^{90}Yttrium (^{90}Y) DOTATOC alone or in combination with ^{177}Lu oxodotreotide. Step 2 identified additional data with respect to haematological toxicity. The final results of the NETTER-1 RCT noted that 2% (2 of 11 patients) developed MDS, one of whom died 33 months post randomisation, but that no new cases of MDS or leukaemia occurred during long-term follow-up.[30]

Estimates from observational studies (some of which were in the context of salvage PRRT) varied. Using data from four phase 2 clinical trials, one retrospective study of long term toxicity (n=104 patients, median follow-up 68 months) reported a 6.7% long-term risk of MDS / leukaemia.[39] Another estimated the incidence of persistent hematologic dysfunction (defined as MDS, acute myeloid leukaemia (AML), myeloproliferative neoplasm (MPN), MDS/MPN, or otherwise unexplained cytopenia for >6 months) in 274 GEP-NETs, as 4% with a median latency of 41 months.[40] Others have estimated the incidence of MDS to occur in <1% of patients, which may in part be due to insufficient follow-up.[41]

RCT data on nephrotoxicity were immature (median duration of follow-up 14 months) at the time of the NNIPH HTA, which noted no reports of renal damage with ^{177}Lu oxodotreotide when administered concomitantly with a renal-protective agent. A relatively low incidence of grade 3 or higher nephrotoxicity (~0.3%) was noted in observational studies; low grade toxicity (grade 1 and 2) was more common, although estimates varied (for example, from 4% to 27% with grade 1 subacute nephrotoxicity).[23, 24] Long-term data from one observational study indicated that the annual reduction in renal function was less than 10% in 98% of patients. Evidence identified during Step 2 confirmed a finding of limited long-term nephrotoxicity. The final results of the NETTER-1 study reported grade 3 or worse nephrotoxicity, regardless of causality, in six (5%) of 111 patients in the ^{177}Lu oxodotreotide group and four (4%) of 112 patients in the control group. Additionally, a single-centre retrospective analysis (n=33) found that this treatment was well tolerated in patients with pre-existing stage 3 chronic kidney disease, with a low incidence of permanent major nephrotoxicity.[42]

The NNIPH HTA reviewed one observational study which examined acute hormonal crisis (that is, the massive release of hormones from the tumour tissue, which becomes necrotic as a result of ^{177}Lu oxodotreotide). Six patients (1%) developed this condition and recovered after treatment with high doses of octreotide, intravenous fluids and general support therapy, but three of them had a new crisis when treatment was resumed with the next dose of ^{177}Lu oxodotreotide. One smaller observational study (n=34) identified in Step 2, which included patients with metastatic functional pancreatic NETs, reported that hormonal crises were relatively common (9%), such that preventive therapy should be considered before and or during PRRT.[43]

Tumour flare was not well reported in the literature, however one study identified (Step 2) reported a 12-person case series in which five patients experienced this phenomenon. Two of these five patients experienced pain due to their bony metastases, two experienced bowel dysfunction due to soft tissue metastases, and one experienced pain due to a liver metastasis.[44]

Other adverse events noted by the authors of the NNIPH HTA in those treated with ^{177}Lu oxodotreotide, based on RCT evidence from the NETTER-1 trial, included a statistically significant increase in nausea (RR=5.0, 95% CI 2.9 – 8.5), vomiting (RR = 4.7, 95% CI 2.6 – 8.5), fatigue (RR=1.6, 95% CI 1.1 – 2.3), headaches (RR=3.6, 95% CI 1.4 – 9.3), alopecia (RR=6.0, 95% CI 1.4 – 26.0), and a decreased appetite (RR=2.2 95% CI 1.1 – 4.6). No significant difference was reported for a range of other adverse events: diarrhoea (RR=1.5, 95% CI 0.9 – 2.5), cough (RR=2.0, 95% CI 0.8 – 5.1), oedema (RR=2.0, 95% CI 0.9 – 4.4), muscle and skeletal pain (RR=1.4, 95% CI 0.9 – 2.3), dizziness (RR=2.0, 95% CI 0.8 – 5.1) and flushing (RR=1.4, 95% CI 0.6 – 3.0). These estimates were all assessed to be of low quality, that is, there is limited confidence in the estimates based on the GRADE criteria.

The NNIPH HTA concluded that there are generally few serious adverse events and side effects associated with this treatment. Bone marrow suppression and kidney function were thought to be the most important adverse events, alongside general side effects, such as nausea, stomach pain and hair loss. In most cases, normal bone marrow function is restored.

Several variations, updates to labelling, and updates to packaging were found from a targeted search of the US Food and Drug Administration's (FDA) and European Medicines Agency's (EMA) websites. Some updates related to changes to dosing, administration, and new information emerging from longer follow-up with phase II and phase III studies. Others related to adverse events, including updates to labelling and information related to one case of acute kidney injury due to tumour lysis syndrome, one case of angioedema, the incidence rate of secondary MDS based on the ERASMUS study (covered above), and data on hypersensitivity and anaphylactic reactions.

4.2.4 GRADE

The NNIPH HTA appraised outcomes using GRADE. Their summary of findings table was extracted and is reproduced in its entirety in Table 3.

Table 3. GRADE summary of findings table produced in the Norwegian National Institute of Public Health's HTA

Patient or population: neuroendocrine tumours
Setting: assessed at 20 months after randomisation
Intervention: 177Lu-DOTATATE + Octreotide
Comparison: Octreotide only

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Octreotide only	Risk with 177Lu-DOTA-TATE + Octreotide			
Deaths 20 months after randomisation (assessed in number of events)	230 per 1,000	120 per 1,000 (67 to 219)	RR 0.52 (0.29 to 0.95)	229 (1RCT)	⨁⨁◯◯ LOW [a,b]
Overall survival (assessed in months)	Not reported	Not reported		229 (1RCT)	
Progression-free survival 20 months after randomisation (assessed in %) Scale from: 0 to 100 %		The mean percentage of progression-free survival 20 months after randomisation in the intervention group was 54.4% more (43.1 more to 65.7 more)		229 (1RCT)	⨁⨁⨁◯ MODERATE a,c
Progression-free survival (assessed in months)	Not reported	Not reported		229 (1RCT)	
Tumour response rate (RECIST) 20 months after randomisation (assessed in %). Scale from: 0 to 100 %		The mean tumour response rate (RECIST) in the intervention group was 15 % more (7.5 more to 22.5 more)		201 (1 RCT)	⨁⨁⨁◯ MODERATE [a,c]
Adverse events (all types)	318 per 1,000	881 per 1,000 (668 to 1,000)	RR 2.77 (2.10 to 3.65)	221 (1 RCT)	⨁⨁◯◯ LOW [a,c,d]
Haematotoxic side-effects of all grades (thrombocytopenia)	9 per 1,000	252 per 1,000 (35 to 1,000)	RR 27.75 (3.84 to 200.40)	221 (1 RCT)	⨁⨁◯◯ LOW [a,c,e]

Haematotoxic side-effects of all grades (anaemia)	55 per 1,000	144 per 1,000 (58 to 355)	RR 2.64 (1.07 to 6.50)	221 (1 RCT)	⊕⊕◯◯ LOW [a,b]
Haematotoxic side-effects of all grades (lymphopenia)	18 per 1,000	180 per 1,000 (43 to 753)	RR 9.91 (2.37 to 41.39)	221 (1 RCT)	⊕⊕◯◯ LOW [a,c,e]
General side-effects of all grades (nausea)	118 per 1,000	585 per 1,000 (344 to 999)	RR 4.95 (2.91 to 8.45)	221 (1 RCT)	⊕⊕⊕◯ MODERATE [a,c]
General side-effects of all grades (vomiting)	100 per 1,000	468 per 1,000 (258 to 849)	RR 4.68 (2.58 to 8.49)	221 (1 RCT)	⊕⊕⊕◯ MODERATE [a,c]
General side-effects of all grades (abdominal pain)	264 per 1,000	261 per 1,000 (169 to 406)	RR 0.99 (0.64 to 1.54)	221 (1 RCT)	⊕⊕◯◯ LOW [a,b]
General side-effects of all grades (fatigue)	255 per 1,000	397 per 1,000 (267 to 588)	RR 1.56 (1.05 to 2.31)	221 (1 RCT)	⊕⊕◯◯ LOW [a,b]

*The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Participants not blinded
b. One study only
c. One study only, but not further downgraded (for example due to large effect size)
c. Composite outcome
d. Wide confidence interval

4.2.5 Public and occupational exposure

The NNIPH HTA contained a chapter outlining considerations in relation to level two or generic justification from the perspective of the Norwegian regulations. In addition to the review of clinical effectiveness and safety, the following factors were considered:

- the radiation properties of [177]Lu
- the approval status for importation and shipment
- the training and competencies required at a hospital level for the safe preparation
- administration and disposal of [177]Lu
- safeguards against the exposure of staff and members of the public

- and the licensing process for this kind of nuclear medicine activity.

Based on the information in the NNIPH HTA, Norway concluded that ^{177}Lu oxodotreotide could be generically justified for this indication.

In summary, ^{177}Lu has a half-life of 6.647 days and emits β-particles and small amounts of γ-photons. β-particles, which are responsible for the therapeutic effect of this radionuclide, have a maximum energy of 490keV and a limited range of about 2mm in tissue, which minimises the potential for damage in normal tissue surrounding the tumour. However, more penetrative γ-photons are also emitted in the decay process, with an energy of 113keV and 208keV. Therefore, the administration of ^{177}Lu oxodotreotide results in risk of exposure of staff and members of the public. While noting that it was current clinical practice in Norway for patients to spend one night in hospital after completion of treatment, the NNIPH HTA concluded that ^{177}Lu oxodotreotide is safe for use on an outpatient basis provided the equivalent dose rate at one metre (EDR-1m) from the patient is less than 25 μSv/h and that the patient, after an individual assessment, is willing and able to follow recommended strict restrictions on close contact with household members. The main possible sources of contamination associated with this practice are through blood and urine, given that ^{177}Lu oxodotreotide is mainly excreted through the kidneys.[45] Radioactive waste, (for example, syringes, needles, paper contaminated with residue of ^{177}Lu oxodotreotide) should be disposed of appropriately.[45]

In the context of the Republic of Ireland, it is thought that exposure to staff, the public, carers and comforters can be minimised through a carefully considered prospective risk assessment and use of a well-developed quality management system. Such risk assessments are reviewed as part of the Environmental Protection Agency's authorisation procedure for undertakings offering ^{177}Lu oxodotreotide. It should also be noted that some publications since the NNIPH report may also help inform local policies, procedures, protocols and guidelines on ^{177}Lu oxodotreotide therapy.[46-48] Local policies, procedures and guidelines must be in place to protect staff and members of the public, and ensure that dose limitations set out in the Regulations (Section 2, SI 30 of 2019) are adhered to.[1, 49] Information on the dose constraints for carers and comforters, and individuals participating in medical or biomedical research is also available in guidance issued by HIQA.[50]

4.2.6 Alternative interventions and treatment regimes

The following comparators and alternative interventions were identified in the literature:

- everolimus

- sunitinib
- somatostatin analogues (SSAs) (for example octreotide, lanreotide)
- chemotherapies including capecitabine, temozolomide and the combination regimen FOLFOX (leucovorin, fluorouracil and oxaliplatin).
- PRRT with alternative radio nucleotides/radio ligands
- Yttrium-90 radioembolisation
- 131I-mIBG (Iodine-131 metaiodobenzylguanidine) therapy.

The pivotal NETTER-1 study assessed by the NNIPH HTA compared ^{177}Lu oxodotreotide to high-dose SSAs. The other possible interventions are noted from observational studies. The use of therapies that are administered concurrently, adjuvant or neo-adjuvant with ^{177}Lu oxodotreotide is an emerging area, such as the concurrent addition of capecitabine and temozolomide (CAPTEM) to treatment with ^{177}Lu oxodotreotide.(51) This is also being explored as "sandwich" chemo-PRRT, where ^{177}Lu oxodotreotide is given, followed by capecitabine and then further PRRT.(52)

Evidence on the precise timing of PRRT, and the benefits and or safety when combined with other therapies, is largely based on observational data with some discordant conclusions noted between studies.(51, 53-56) The benefit-risk ratio in patients pre-treated with other therapies therefore remains unclear; however, one prospective study was identified that reported that it was not able to find an influence of pre-treatment with everolimus or sunitinib on the subacute haematotoxicity of ^{177}Lu oxodotreotide.(56) There is also some emerging evidence on the use of different combinations of radionucleotides for PRRT (e.g., ^{90}Y/177Lu oxodotreotide). However, this would represent a different type or class of practice and is outside the scope of this report.(57)

4.2.7 Additional benefits or harms

Some additional evidence was found in Step 2 which indicated that ^{177}Lu oxodotreotide may have a role in the treatment of a subgroup of patients with resistant, refractory and progressive GEP-NETs. Additional cycles of ^{177}Lu oxodotreotide in progressive disease appears to confer some additional benefit, however are caveated with possible additional adverse events and toxicity.(58-61) A 2021 publication from the NETTER-1 study noted that during long-term follow-up, approximately 14 patients (12%) in the ^{177}Lu oxodotreotide trial arm received additional cycles of PRRT (either ^{177}Lu oxodotreotide or ^{90}Y DOTACTOC). Estimates on incidence of MDS, leukaemia and renal toxicity varied.

There is also some evidence from Step 2 regarding the importance of dose for efficacy and safety. A 10-year follow-up from a non-comparative open label phase II trial indicated that dose was an important modifying factor. The observed median

OS was 71.0 months (95% CI 46.1 – 107.3) in the group who received 18.5 GBq and 97.6 months (95% CI 64.3 – not reached) in the group treated with 27.5 GBq (P = 0.22).[62] One non-randomised study identified in Step 2 found that in patients with a cumulative activity of less than 29.6GBq, ^{177}Lu oxodotreotide was less efficacious with poorer tumour responses and overall survival observed.[63] Conversely, it was concluded elsewhere that a reduced dose per cycle (mean 5.92 GBq/cycle) and prolonged duration (over 5 cycles and 1.5 years) in metastatic NETs proved equally efficacious and was better tolerated with less toxicity.[64] Two studies identified in Step 2 investigated the use of personalised dosimetry in this area, and suggested a favourable effect on effectiveness and/or adverse events.[65, 66] However, there are conflicting reports in this regard with one other study identified in step 2 failing to demonstrate a tumour dose-response relationships for NETs originating in the small intestine.[67]

Finally, a recent study by Chiapponi et al. and Parghane et al. also noted the possible role of ^{177}Lu oxodotreotide in the conversion of borderline unresectable cases into surgical candidates, which may confer additional survival benefits.[68, 69]

4.3 International practice and guidelines

The Step 1 search identified 21 guidelines relating to the treatment of NETs using ^{177}Lu oxodotreotide from 18 organisations (both official and informal) and groups. There did not appear to be a systematic evidence synthesis component to these guidelines, and the guidelines did not indicate the strength of their recommendation. Many of the guidelines were formed based on consensus or expert opinion. Therefore, the nature of the guidelines varied and included clinical recommendations, procedures, policies, and work instructions.

Guidelines released before the publication of the NETTER-1 RCT (January 2017) and the approval of ^{177}Lu oxodotreotide by the FDA and EMA (January 2018) indicated that ^{177}Lu oxodotreotide was a promising, although experimental treatment. However, there is good international agreement in later guidelines (2017 onwards) that ^{177}Lu oxodotreotide is an effective second-line treatment for progressive GEP-NETs, following discussion of individual patients by a multi-disciplinary team. A full list of guidelines identified and their recommendations are outlined in Appendix 1.

5 Discussion

For the purposes of this report and the generic justification of ^{177}Lu oxodotreotide, the ERT has compiled systematic reviews relevant to the three main RQs, identified a suitable prior evidence synthesis (a 2018 HTA by NNIPH) which addresses these questions, and appraised this systematic review using a validated tool. The ERT

subsequently undertook a search for additional studies published since the NNIPH literature search and reported on same.

Based on this evidence identified, and noting that GEP-NETs are a heterogeneous group of malignancies, ^{177}Lu oxodotreotide generally demonstrated good efficacy compared to the available alternatives and appears to have generally few serious adverse events and side effects. However, the exact effect size of many of these outcomes, particularly safety outcomes, remains uncertain. Using GRADE criteria, the certainty of the evidence for all outcomes was downgraded due to the fact that study participants in the only RCT identified (NETTER-1) were not blinded. Given the radiation protection requirements associated with administration of ^{177}Lu oxodotreotide, blinding would have been challenging. The search for emerging evidence since the systematic search was conducted in the HTA (i.e., Step 2) identified very limited discordant conclusions in recently published literature. Where identified, these mainly related to overall survival estimates from the NETTER-1 RCT, which were not statistically significant on the final analysis (discussed in more detail below), and small variations in the estimates of risk and relative risk of adverse events. Furthermore, one small study (identified in Step 2) of Irish patients referred abroad for ^{177}Lu oxodotreotide treatment concluded that the treatment is an effective second-line therapy for metastatic well-differentiated NETs, echoing the positive outcomes reported elsewhere. However, the authors also highlighted the need for further research on the effect of prior targeted therapies on ^{177}Lu oxodotreotide treatment outcomes.(3)

While the evidence synthesis methodology here relies heavily on prior efforts to synthesise the evidence, the lack of discordant findings between reviews, guidelines and HTAs suggests an appropriate application of this methodology. It is unlikely that a full systematic review or rapid review would have revealed any additional evidence which would have altered confidence in findings.

Meta-analyses and network meta-analyses were not selected for Step 1 due to the clinical heterogeneity of GEP-NETs. Such studies already include disease from the foregut, midgut and hind gut in different proportions, with patients having received a wider variety of prior treatments or no prior treatment at all. They also include a wide variety of histological types, and both functioning and non-functioning tumours. When demographic differences are also considered, it was thought to be unlikely that an overall estimate from a meta-analytic technique would produce data that are representative of any particular person or cohort. This decision was also underpinned by the lack of certainty in many outcomes.

The ERT was of the opinion that the possibility of confounding in non-randomised studies was often overlooked in systematic reviews and studies. In particular, it is possible that 'confounding by disease severity' is present in some places. This is

where patients who receive PRRT might do so because their disease is not as severe as other patients, and hence these patients appear to do better than patients on other treatments. It is possible that if such confounding is present, the effect on OS and PFS is overestimated, and the frequency and/or severity of adverse events is underestimated.

Long-term follow-up (five years after the last patient was randomised) from NETTER-1 did not show a statistically significant difference in overall survival (OS) in the group that received ^{177}Lu oxodotreotide plus best supportive care (including long-acting octreotide) compared to those receiving treatment with high dose long-acting octreotide.[30] However, over a third of patients in the control arm received one form of PRRT and treatment switching was a common occurrence. This finding should be considered in the context of these methodological issues, and the consistently favourable outcomes seen across other studies. The primary endpoint of the NETTER-1 study was progression-free survival (PFS) which was reported in terms of the interim analysis only and was in favour of ^{177}Lu oxodotreotide. The relationship between PFS and OS in GEP-NETs is therefore not clear from the evidence synthesised.

A number of emerging investigational areas were identified by the ERT. Dose appears to play a role in modulating both efficacy and safety outcomes, and personalised dosimetry was seen as an emerging area of investigation in the literature.[62-66] Personalised dosimetry or dose-finding techniques represent an example of treatment optimisation which may allow practitioners and medical physicists to keep the dose as low as reasonable achievable. Such practices may also affect the benefit-risk balance and require care, however they themselves do not require generic justification. Practitioners and medical physicists should be cautious when employing such techniques and working towards better treatment optimisation, as the findings from the literature and the NNIPH HTA may not be generalisable to those receiving more personalised therapy.

Finally, it is important to note that the addition of non-ionising therapies to an existing practice involving ionising radiation does not represent a new class or type of practice requiring generic justification; however, practitioners involved in the individual justification of such therapies should be aware that such changes may dramatically change the benefit-risk balance. The exact sequencing of treatments, establishment of treatment regimes, and use of additional cycles or maintenance PRRT may also affect this balance.

6 Evidence to decision

A draft of this report was submitted to the MEIR EAG for their consideration and feedback. Following this, a discussion was held in which the evidence synthesis and additional contextual factors were considered. As per the HIQA Methods for generic justification of new practices in ionising radiation, a modified version of the GRADE evidence to decision (EtD) framework was used to support the MEIR EAG in coming to a recommendation regarding the generic justification of ^{177}Lu oxodotreotide for metastatic or inoperable GEP-NETs.[4]

6.1 Overview of MEIR EAG GRADE EtD discussion

The full EtD framework including a summary of the panel discussion and the final judgements can be found in Appendix 3 and Table 4, respectively. The MEIR EAG discussed the outcomes relevant to the benefits of this intervention (progression-free survival (PFS), overall survival (OS), tumour response rate and health related-quality of life (HRQoL)) and concluded that the benefit was moderate for PFS based on the evidence provided, but was possibly small for OS and HRQoL. Therefore, the decision of the EAG was to mark the judgement for this criteria as 'varies'.

In terms of potential undesirable effects, there was general agreement among the MEIR EAG that the incidence of nephrotoxicity was small and while there was potential for haematological toxicity (for example, thrombocytopenia, neutropenia), this was manageable and anticipated in the context of a cohort that may have received prior chemotherapy. Secondary myelodysplastic syndrome (MDS) and leukaemia are of particular concern in patients treated with ^{177}Lu oxodotreotide. However, the incidence of these was noted to be small and was considered acceptable by the MEIR EAG in the context of the treatment indication, that is, for adults with metastatic or inoperable progressive GEP-NETs. It was noted that the patient cohort is typically heavily pre-treated and while there may be improvements in survival, the treatment is primarily palliative. It was also noted that the NETTER-1 RCT compared ^{177}Lu oxodotreotide plus best supportive care (consisting of 30mg octreotide every four weeks for symptom control) with high dose octreotide (60mg every four weeks). This double dose of octreotide in the control arm may have had a positive effect on symptom control in some patients, with the potential for bias with respect to the higher relative risk of gastrointestinal side-effects with ^{177}Lu oxodotreotide that was observed. The risk of occupational and public exposure was also considered small as long as appropriate radiation protection safeguards are in place. Overall the undesirable effects of the intervention were judged to be 'small'. As a number of the critical outcomes had low to moderate certainty of evidence (Table 3), in accordance with GRADE criteria, the overall certainty of the evidence in relation to effect was considered to be 'low' (Table 3).

Although there was no evidence for the value patients placed on the outcomes presented, the MEIR EAG discussed whether there was likely to be important uncertainty or variability in how people valued these outcomes. It was stated that considering the population being treated, HRQoL may be of particular importance to these patients. It was felt that the schedule for delivery of ^{177}Lu oxodotreotide treatment may be preferred by patients as ^{177}Lu oxodotreotide involves four treatment cycles about eight weeks apart, whereas other treatments such as octreotide treatment involve attending hospital every two weeks. The judgment of the panel for this criterion was that there was 'probably no important uncertainty or variability'.

For the final EtD criteria, the balance of effects, the MEIR-EAG judged that the balance between benefits and harms 'probably favours the intervention'.

On the basis of the above discussion, the MEIR-EAG have recommended to HIQA that ^{177}Lu oxodotreotide for the treatment of GEP-NETs should be generically justified.

Table 4: Modified evidence to decision table for the generic justification of [177]Lu oxodotreotide for GEP-NETs

Criteria	Summary of Judgements*					
Desirable Effects	Trivial	Small	Moderate	Large	**Varies**	Don't Know
Undesirable Effects	Large	Moderate	**Small**	Trivial	Varies	Don't Know
Certainty of Evidence	Very Low	**Low**	Moderate	High	No Included Studies	
Values	Important Uncertainty or Variability	Possibly Important Uncertainty or Variability	**Probably no Important Uncertainty of Variability**	No Important Uncertainty or Variability		
Balance of Effects	Favours the Comparison	Probably Favours the Comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't Know

* Completed by the MEIR EAG based on the evidence identified within this report and considering broader contextual factors.

6.2 HIQA Decision

Having considered the application, the evidence review and the recommendation from the MEIR EAG, HIQA is satisfied that on consideration of the balance between the benefits and harms, this practice should be generically justified.

The new practice of lutetium oxodotreotide for the treatment of adults with metastatic or inoperable gastroenteropancreatic neuroendocrine tumours is generically justified under SI 256/2018.

The generic justification of this practice is effective from 20 April 2023.Under the Regulations, HIQA may review the generic justification of this practice if new and important evidence about the practice emerges.(1) HIQA may also review this practice if new and important evidence about alternative techniques and technologies (including non-ionising practices) emerges. Should this occur, HIQA will endeavour to update its website and inform stakeholders and the public of its intention to review the generic justification of this practice.

7 References

1. European Union (Basic Safety Standards for Protection Against Dangers Arising from Medical Exposure to Ionising Radiation) Regulations 2018 as amended. Dublin: The Stationary Office (2019).
2. European Medicines Agency. Assessment Report: LUTATHERA United Kingdom: 2018.
3. Almeamar H, Cullen L, Murphy DJ, Crowley RK, Toumpanakis C, Welin S, et al. Real-world efficacy of lutetium peptide receptor radionuclide therapy in patients with neuroendocrine tumours. Journal of neuroendocrinology. 2022;34(6):e13138.
4. Health Information & Quality Authority (HIQA). Methods for Generic Justification of New Practices in Ionising Radiation. 2022.
5. European Medicines Agency. Lutathera 2022 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/lutathera.
6. Uri I, Grozinsky-Glasberg S. Current treatment strategies for patients with advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Clinical Diabetes and Endocrinology. 2018;4(1):16.
7. National Cancer Registry Ireland. Cancer Trends No 18. Neuroendocrine Tumours 2013 [Available from: https://www.ncri.ie/sites/ncri/files/pubs/CancerTrendsNo.18-NeuroendocrineCancers.pdf
8. Advanced Accelerator Applications. Radioligand therapy (RLT) with LUTATHERA® 2022 [Available from: https://www.global.lutathera.com/about-lutathera/index.htmlh
9. Herrmann K, Giovanella L, Santos A, Gear J, Kiratli PO, Kurth J, et al. Joint EANM, SNMMI and IAEA enabling guide: how to set up a theranostics centre. Eur J Nucl Med Mol Imaging. 2022;49(7):2300-9.
10. Das S, Dasari A. Epidemiology, Incidence, and Prevalence of Neuroendocrine Neoplasms: Are There Global Differences? Curr Oncol Rep. 2021;23(4):43.
11. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Neuroendocrine and Adrenal Tumors. 2022 Contract No.: Version 1.2022.
12. Leoncini E, Carioli G, La Vecchia C, Boccia S, Rindi G. Risk factors for neuroendocrine neoplasms: a systematic review and meta-analysis. Annals of Oncology. 2016;27(1):68-81.
13. Rindi G, Mete O, Uccella S, Basturk O, La Rosa S, Brosens LAA, et al. Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. Endocrine Pathology. 2022;33(1):115-54.
14. Rindi G, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Archiv : an international journal of pathology. 2006;449(4):395-401.
15. Rindi G, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Archiv : an international journal of pathology. 2007;451(4):757-62.

16. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017:j4008.
17. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022. [Available from: https://gradepro.org
18. Frønsdal KB LU, Skår Å, Lund Håheim L, Unhjem JF, Grøvan A, Stoinska-Schneider A, Hafstad E, Fure B, Juvet LK. 177Lutetium-based peptide receptor radionuclide therapy for treating neuroendocrine tumours: a health technology assessment. Norway: 2023.
19. Li L, Asemota I, Liu B, Gomez-Valencia J, Lin L, Arif AW, et al. AMSTAR 2 appraisal of systematic reviews and meta-analyses in the field of heart failure from high-impact journals. Systematic reviews. 2022;11(1):147.
20. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. New England journal of medicine. 2017;376(2):125 - 35.
21. Hörsch D, Ezziddin S, Haug A, Gratz KF, Dunkelmann S, Miederer M, et al. Effectiveness and side-effects of peptide receptor radionuclide therapy for neuroendocrine neoplasms in Germany: A multi-institutional registry study with prospective follow-up. Eur J Cancer. 2016;58:41-51.
22. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. Journal of clinical oncology. 2008;26(13):2124 - 30.
23. Bodei L, Kidd M, Paganelli G, Grana CM, Drozdov I, Cremonesi M, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging. 2015;42(1):5-19.
24. Bergsma H, Konijnenberg MW, Kam BL, Teunissen JJ, Kooij PP, de Herder WW, et al. Subacute haematotoxicity after PRRT with (177)Lu-DOTA-octreotate: prognostic factors, incidence and course. Eur J Nucl Med Mol Imaging. 2016;43(3):453-63.
25. Bergsma H, Konijnenberg MW, van der Zwan WA, Kam BL, Teunissen JJ, Kooij PP, et al. Nephrotoxicity after PRRT with (177)Lu-DOTA-octreotate. Eur J Nucl Med Mol Imaging. 2016;43(10):1802-11.
26. Sabet A, Ezziddin K, Pape UF, Ahmadzadehfar H, Mayer K, Pöppel T, et al. Long-term hematotoxicity after peptide receptor radionuclide therapy with 177Lu-octreotate. J Nucl Med. 2013;54(11):1857-61.
27. de Keizer B, van Aken MO, Feelders RA, de Herder WW, Kam BL, van Essen M, et al. Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3]octreotate. Eur J Nucl Med Mol Imaging. 2008;35(4):749-55.
28. Khan S, Krenning EP, van Essen M, Kam BL, Teunissen JJ, Kwekkeboom DJ. Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0,Tyr3]octreotate. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2011;52(9):1361-8.
29. Campana D, Tomassetti P. Incidence, Epidemiology, Aetiology and Staging, Classification, Clinical Presentation/Signs and Symptoms, Diagnosis, Staging

Procedures/Investigation. In: Ambrosini V, Fanti S, editors. PET/CT in Neuroendocrine Tumors. Cham: Springer International Publishing; 2016. p. 1-5.
30. Strosberg JR, Caplin ME, Kunz PL, Ruszniewski PB, Bodei L, Hendifar A, et al. 177Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. The lancet Oncology. 2021;22(12):1752 - 63.
31. Pusceddu S, Prinzi N, Tafuto S, Ibrahim T, Filice A, Brizzi MP, et al. Association of Upfront Peptide Receptor Radionuclide Therapy With Progression-Free Survival Among Patients With Enteropancreatic Neuroendocrine Tumors. JAMA network open. 2022;5(2):e220290.
32. Advanced Accelerator Applications SA. Study to Evaluate the Efficacy and Safety of Lutathera in Patients With Grade 2 and Grade 3 Advanced GEP-NET (NETTER-2) 2019 [Available from: https://clinicaltrials.gov/ct2/show/NCT03972488h
33. Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with177lu-dotatate in the phase III netter-1 trial. Journal of clinical oncology. 2018;36(25):2578 - 84.
34. Strosberg JR, Srirajaskanthan R, El-Haddad G, Wolin EM, Chasen BR, Kulke MH, et al. Symptom Diaries of Patients with Midgut Neuroendocrine Tumors Treated with 177Lu-DOTATATE. Journal of nuclear medicine. 2021.
35. Veltroni A, Cosaro E, Spada F, Fazio N, Faggiano A, Colao A, et al. Clinico-pathological features, treatments and survival of malignant insulinomas: a multicenter study. European journal of endocrinology. 2020;182(4):439-46.
36. Magalhães D, Sampaio IL, Ferreira G, Bogalho P, Martins-Branco D, Santos R, et al. Peptide receptor radionuclide therapy with (177)Lu-DOTA-TATE as a promising treatment of malignant insulinoma: a series of case reports and literature review. J Endocrinol Invest. 2019;42(3):249-60.
37. Zandee WT, Brabander T, Blažević A, Minczeles NS, Feelders RA, de Herder WW, et al. Peptide Receptor Radionuclide Therapy With 177Lu-DOTATATE for Symptomatic Control of Refractory Carcinoid Syndrome. The Journal of clinical endocrinology and metabolism. 2021;106(9):e3665-e72.
38. de Vries-Huizing DMV, Versleijen MWJ, Sinaasappel M, Walraven I, Geluk-Jonker MM, Tesselaar MET, et al. Haematotoxicity during peptide receptor radionuclide therapy: Baseline parameters differences and effect on patient's therapy course. PLoS One. 2021;16(11):e0260073.
39. Kennedy KR, Turner JH, MacDonald WBG, Claringbold PG, Boardman G, Ransom DT. Long-term survival and toxicity in patients with neuroendocrine tumors treated with 177 Lu-octreotate peptide radionuclide therapy. Cancer. 2022;128(11):2182-92.
40. Bergsma H, van Lom K, Raaijmakers M, Konijnenberg M, Kam B, Teunissen JJM, et al. Persistent Hematologic Dysfunction after Peptide Receptor Radionuclide Therapy with (177)Lu-DOTATATE: Incidence, Course, and Predicting Factors in Patients with Gastroenteropancreatic Neuroendocrine Tumors. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2018;59(3):452-8.

41. Alsadik S, Gnanasegaran G, Chen L, Quigley A-M, Mandair D, Toumpanakis C, et al. Single centre retrospective review of outcome of 177 Lu-DOTATATE peptide receptor radionuclide therapy in the treatment of progressive metastatic neuroendocrine tumours: Survival, toxicity, and prognostic factors. Journal of neuroendocrinology. 2022;34(11):e13210.
42. Alsadik S, Gnanasegaran G, Chen L, Mandair D, Toumpanakis C, Caplin M, et al. Safety of Peptide Receptor Radionuclide Therapy with 177 Lu-DOTATATE in Neuroendocrine Tumor Patients with Chronic Kidney Disease. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2022;63(10):1503-8.
43. Zandee WT, Brabander T, Blažević A, Kam BLR, Teunissen JJM, Feelders RA, et al. Symptomatic and Radiological Response to 177Lu-DOTATATE for the Treatment of Functioning Pancreatic Neuroendocrine Tumors. The Journal of clinical endocrinology and metabolism. 2019;104(4):1336-44.
44. Salner AL, Blankenship B, Dunnack H, Niemann C, Bertsch H. Lutetium Lu-177 Dotatate Flare Reaction. Advances in Radiation Oncology. 2021;6(1).
45. Hope TA, Abbott A, Colucci K, Bushnell DL, Gardner L, Graham WS, et al. NANETS/SNMMI Procedure Standard for Somatostatin Receptor-Based Peptide Receptor Radionuclide Therapy with (177)Lu-DOTATATE. J Nucl Med. 2019;60(7):937-43.
46. Heads of the European Radiological protection Competent Authorities (HERCA). 131I therapy: Patient release criteria 2010.
47. Levart D, Kalogianni E, Corcoran B, Mulholland N, Vivian G. Radiation precautions for inpatient and outpatient 177Lu-DOTATATE peptide receptor radionuclide therapy of neuroendocrine tumours. EJNMMI Physics. 2019;6(1):7.
48. Nelson KL, Sheetz MA. Radiation Safety Observations Associated with 177Lu Dotatate Patients. Health physics. 2019;117(6):680-7.
49. Radiological Protection Act 1991 (Ionising Radiation) Regulations 2019 as amended. Dublin: The Stationary Office (2019). .
50. Health Information and Quality Authority (HIQA). Guidance on Dose Constraints for Carers and Comforters and Individuals Participating in Medical and Biomedical Research Involving Medical Exposures to Ionising Radiation. 2020.
51. Ostwal V, Basu S, Bhargava P, Shah M, Parghane RV, Srinivas S, et al. Capecitabine-Temozolomide in Advanced Grade 2 and Grade 3 Neuroendocrine Neoplasms: Benefits of Chemotherapy in Neuroendocrine Neoplasms with Significant 18FDG Uptake. Neuroendocrinology. 2021;111(10):998-1004.
52. Parghane RV, Ostwal V, Ramaswamy A, Bhandare M, Chaudhari V, Talole S, et al. Long-term outcome of "Sandwich" chemo-PRRT: a novel treatment strategy for metastatic neuroendocrine tumors with both FDG- and SSTR-avid aggressive disease. European journal of nuclear medicine and molecular imaging. 2021;48(3):913-23.
53. Yordanova A, Ahrens H, Feldmann G, Brossart P, Gaertner FC, Fottner C, et al. Peptide Receptor Radionuclide Therapy Combined With Chemotherapy in Patients With Neuroendocrine Tumors. Clinical nuclear medicine. 2019;44(5):e329-e35.

54. Plante A, Baudin E, Do Cao C, Hentic O, Dubreuil O, Terrebonne E, et al. Patient-reported tolerance in treatments approved in neuroendocrine tumors: A national survey from the French Group of Endocrine Tumors. Clinics and research in hepatology and gastroenterology. 2018;42(2):153-9.
55. Fröss-Baron K, Garske-Roman U, Welin S, Granberg D, Eriksson B, Khan T, et al. 177Lu-DOTATATE Therapy of Advanced Pancreatic Neuroendocrine Tumors Heavily Pretreated with Chemotherapy: Analysis of Outcome, Safety, and Their Determinants. Neuroendocrinology. 2021;111(4):330-43.
56. Medaer E, Verslype C, Van Cutsem E, Dekervel J, Clement PM, Nackaerts K, et al. Influence of pretreatment with everolimus or sunitinib on the subacute hematotoxicity of 177 Lu-DOTATATE PRRT. Acta oncologica (Stockholm, Sweden). 2020;59(6):644-51.
57. Kunikowska J, Zemczak A, Kołodziej M, Gut P, Łoń I, Pawlak D, et al. Tandem peptide receptor radionuclide therapy using 90Y/177Lu-DOTATATE for neuroendocrine tumors efficacy and side-effects - polish multicenter experience. European Journal of Nuclear Medicine and Molecular Imaging. 2020;47(4):922-33.
58. Kalshetty A, Ramaswamy A, Ostwal V, Basu S. Resistant functioning and/or progressive symptomatic metastatic gastroenteropancreatic neuroendocrine tumors: efficacy of 177Lu-DOTATATE peptide receptor radionuclide therapy in this setting. Nuclear medicine communications. 2018;39(12):1143-9.
59. Minczeles NS, van Eijck CHJ, van Gils MJ, van Velthuysen M-LF, Nieveen van Dijkum EJM, Feelders RA, et al. Induction therapy with 177 Lu-DOTATATE procures long-term survival in locally advanced or oligometastatic pancreatic neuroendocrine neoplasm patients. European journal of nuclear medicine and molecular imaging. 2022;49(9):3203-14.
60. Yordanova A, Mayer K, Brossart P, Gonzalez-Carmona MA, Strassburg CP, Essler M, et al. Safety of multiple repeated cycles of 177 Lu-octreotate in patients with recurrent neuroendocrine tumour. European journal of nuclear medicine and molecular imaging. 2017;44(7):1207-14.
61. Yordanova A, Wicharz M, Mayer K, Brossart P, Gonzalez-Carmona M, Strassburg C, et al. Efficacy of adding somatostatin analogues to [177lu]lu-octreotate as a combination and maintenance therapy in metastatic neuroendocrine tumors. Neuroendocrinology. 2018;Conference: 15th Annual ENETS Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease. Spain. 106(Supplement 1):265.
62. Paganelli G, Sansovini M, Nicolini S, Grassi I, Ibrahim T, Amadori E, et al. 177 Lu-PRRT in advanced gastrointestinal neuroendocrine tumors: 10-year follow-up of the IRST phase II prospective study. European journal of nuclear medicine and molecular imaging. 2021;48(1):152-60.
63. Minczeles NS, de Herder WW, Feelders RA, Verburg FA, Hofland J, Brabander T. Long-Term Outcomes of Submaximal Activities of Peptide Receptor Radionuclide Therapy with 177 Lu-DOTATATE in Neuroendocrine Tumor Patients. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2023;64(1):40-6.
64. Sitani K, Parghane R, Talole S, Basu S. The efficacy, toxicity and survival of salvage retreatment PRRT with 177 Lu-DOTATATE in patients with

progressive NET following initial course of PRRT. The British journal of radiology. 2022;95(1137):20210896.
65. Del Prete M, Buteau F-A, Arsenault F, Saighi N, Bouchard L-O, Beaulieu A, et al. Personalized 177 Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: initial results from the P-PRRT trial. European journal of nuclear medicine and molecular imaging. 2019;46(3):728-42.
66. Del Prete M, Buteau F-A, Beauregard J-M. Personalized 177 Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: a simulation study. European journal of nuclear medicine and molecular imaging. 2017;44(9):1490-500.
67. Jahn U, Ilan E, Sandström M, Garske-Román U, Lubberink M, Sundin A. Lu-DOTATATE Peptide Receptor Radionuclide Therapy: Dose Response in Small Intestinal Neuroendocrine Tumors. Neuroendocrinology. 2020;110(7-8):662-70.
68. Chiapponi C, Lürssen N, Cremer B, Wahba R, Drebber U, Faust M, et al. Peptide receptor radionuclide therapy as a two-step strategy for initially unresectable liver disease from neuroendocrine tumors: a single-center experience. Endocrine. 2020;70(1):187-93.
69. Parghane RV, Bhandare M, Chaudhari V, Ostwal V, Ramaswamy A, Talole S, et al. Surgical Feasibility, Determinants, and Overall Efficacy of Neoadjuvant ¹⁷⁷Lu-DOTATATE PRRT for Locally Advanced Unresectable Gastroenteropancreatic Neuroendocrine Tumors. Journal of Nuclear Medicine. 2021;62(11):1558.
70. Gosain R, Gupta M, Roy AM, Strosberg J, Glaser KM, Iyer R. Health-Related Quality of Life (HRQoL) in Neuroendocrine Tumors: A Systematic Review. Cancers. 2022;14(6).
71. Ronde EM, Heidsma CM, Eskes AM, Schopman JE, Nieveen van Dijkum EJM. Health-related quality of life and treatment effects in patients with well-differentiated gastroenteropancreatic neuroendocrine neoplasms: A systematic review and meta-analysis. European journal of cancer care. 2021;30(6):e13504.
72. Ricci C, Lamberti G, Ingaldi C, Mosconi C, Pagano N, Alberici L, et al. Treatment of Advanced Gastro-Entero-Pancreatic Neuro-Endocrine Tumors: A Systematic Review and Network Meta-Analysis of Phase III Randomized Controlled Trials. Cancers. 2021;13(2).
73. Strosberg J, Leeuwenkamp O, Siddiqui MK. Peptide receptor radiotherapy re-treatment in patients with progressive neuroendocrine tumors: A systematic review and meta-analysis. Cancer treatment reviews. 2021;93:102141.
74. Walter MA, Nesti C, Spanjol M, Kollár A, Bütikofer L, Gloy VL, et al. Treatment for gastrointestinal and pancreatic neuroendocrine tumours: a network meta - analysis. Cochrane Database of Systematic Reviews. 2021(11).
75. Sonbol MB, Halfdanarson TR, Hilal T. Assessment of Therapy-Related Myeloid Neoplasms in Patients With Neuroendocrine Tumors After Peptide Receptor Radionuclide Therapy: A Systematic Review. JAMA oncology. 2020;6(7):1086-92.
76. Zhang J, Song Q, Cai L, Xie Y, Chen Y. The efficacy of 177 Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) in patients with metastatic

neuroendocrine tumours: a systematic review and meta-analysis. Journal of cancer research and clinical oncology. 2020;146(6):1533-43.
77. Stolniceanu CR, Nistor I, Bilha SC, Constantin V, Simona V, Matovic M, et al. Nephrotoxicity/renal failure after therapy with 90Yttrium- and 177Lutetium-radiolabeled somatostatin analogs in different types of neuroendocrine tumors: a systematic review. Nuclear medicine communications. 2020;41(7):601-17.
78. Wang L-F, Lin L, Wang M-J, Li Y. The therapeutic efficacy of 177Lu-DOTATATE/DOTATOC in advanced neuroendocrine tumors: A meta-analysis. Medicine. 2020;99(10):e19304.
79. Satapathy S, Mittal BR. 177Lu-DOTATATE peptide receptor radionuclide therapy versus Everolimus in advanced pancreatic neuroendocrine tumors: a systematic review and meta-analysis. Nuclear medicine communications. 2019;40(12):1195-203.
80. Saravana-Bawan B, Bajwa A, Paterson J, McEwan AJB, McMullen TPW. Efficacy of 177Lu Peptide Receptor Radionuclide Therapy for the Treatment of Neuroendocrine Tumors: A Meta-analysis. Clinical nuclear medicine. 2019;44(9):719-27.
81. Pozzari M, Maisonneuve P, Spada F, Berruti A, Amoroso V, Cella CA, et al. Systemic therapies in patients with advanced well-differentiated pancreatic neuroendocrine tumors (PanNETs): When cytoreduction is the aim. A critical review with meta-analysis. Cancer treatment reviews. 2018;71:39-46.
82. Dannoon SF, Alenezi SA, Elgazzar AH. The efficacy of the available peptide receptor radionuclide therapy for neuroendocrine tumors: a meta-analysis. Nuclear medicine communications. 2017;38(12):1085-93.
83. Kim S-J, Pak K, Koo PJ, Kwak JJ, Chang S. The efficacy of (177)Lu-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: a meta-analysis. European journal of nuclear medicine and molecular imaging. 2015;42(13):1964-70.
84. Pusceddu S, De Braud F, Festinese F, Bregant C, Lorenzoni A, Maccauro M, et al. Evolution in the treatment of gastroenteropancreatic-neuroendocrine neoplasms, focus on systemic therapeutic options: a systematic review. Future oncology (London, England). 2015;11(13):1947-59.
85. Gulenchyn KY, Yao X, Asa SL, Singh S, Law C. Radionuclide therapy in neuroendocrine tumours: a systematic review. Clinical oncology (Royal College of Radiologists (Great Britain)). 2012;24(4):294-308.
86. Ludwig Boltzmann Institut Health Technology Assessment. Radiopeptidtherapie. 90Yttrium und 177Lutetium Somatostatinanaloga zur Behandlung von inoperablen neuroendokrinen Tumoren. Wien: 2010.
87. National Comprehensive Cancer Network. Neuroendocrine and Adrenal Tumors [Internert]. 2022 [cited 2022 Nov 22]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
88. Love C, Desai NB, Abraham T, Banks KP, Bodei L, Boike T, et al. ACR-ACNM-ASTRO-SNMMI Practice Parameter for Lutetium-177 (Lu-177) DOTATATE Therapy. American journal of clinical oncology. 2022;45(6):233-42.
89. Japan Neuroendocrine Tumor Society (JNETS). Clinical practice guidelines for gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN), [Internet]. 2019 [cited 2022 22 Nov]. Available from: http://jnets.umin.jp/.

90. Pavel M, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2020;31(7):844-60.
91. Hope TA, Bodei L, Chan JA, El-Haddad G, Fidelman N, Kunz PL, et al. NANETS/SNMMI Consensus Statement on Patient Selection and Appropriate Use of (177)Lu-DOTATATE Peptide Receptor Radionuclide Therapy. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2020;61(2):222-7.
92. Indian Council of Medical Research (ICMR). Indian Council of Medical Research (ICMR): Consensus document for management of neuroendocrine tumours (GEP-NETs) [Internet]. 2019 [cited 2022 Nov 22]. Available from: https://main.icmr.nic.in/sites/default/files/guidelines/Consensus_2.pdf
93. Hicks RJ, Kwekkeboom DJ, Krenning E, Bodei L, Grozinsky-Glasberg S, Arnold R, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogues. Neuroendocrinology. 2017;105(3):295-309.
94. Riechelmann RP, Weschenfelder RF, Costa FP, Chaves Andrade A, Bersch Osvald A, Quidute ARP, et al. Guidelines for the management of neuroendocrine tumours by the Brazilian gastrointestinal tumour group. ecancermedicalscience. 2017;11.
95. Strosberg JR, Halfdanarson TR, Bellizzi AM, Chan JA, Dillon JS, Heaney AP, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors. Pancreas. 2017;46(6):707-14.
96. Singh S, Asa SL, Dey C, Kennecke H, Laidley D, Law C, et al. Diagnosis and management of gastrointestinal neuroendocrine tumors: An evidence-based Canadian consensus. Cancer treatment reviews. 2016;47:32-45.
97. Scottish Neuroendocrine Tumour Group (SCONET). Scottish Neuroendocrine Tumour Group (SCONET): Consensus guidelines for the management of patients with neuroendocrine tumours [Internet]. 2015, updated 2018 [cited 2022 Nov 22]. Available from: https://www.woscan.scot.nhs.uk/managed-clinical-networks/neuroendocrine-tumour/guidelines/.
98. Singh S, Dey C, Kennecke H, Kocha W, Maroun J, Metrakos P, et al. Consensus Recommendations for the Diagnosis and Management of Pancreatic Neuroendocrine Tumors: Guidelines from a Canadian National Expert Group. Annals of Surgical Oncology. 2015;22(8):2685-99.
99. Bodei L, Mueller-Brand J, Baum RP, Pavel ME, Hörsch D, O'Dorisio MS, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. European journal of nuclear medicine and molecular imaging. 2013;40(5):800-16.
100. Government of South Australia (SA Health). South Australian Gastroenteropancreatic Neuroendocrine Tumour Pathway [Internet]. 2013 [cited 2022 Nov 22]. Available from: https://www.sahealth.sa.gov.au/wps/wcm/connect/14b9c8804178964697b2ff67a94f09f9/GEPTNETs+Cancer+Pathway+FINAL+2015.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-14b9c8804178964697b2ff67a94f09f9-niPWFrz

101. Cancer Care Ontario. Radionuclide Therapy for Patients with Neuroendocrine Tumors (NETs) in Ontario: Expert Panel Report [Internet]. 2011 [cited 2022 Nov 22]. Available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/3171
102. García-Carbonero R, Salazar R, Sevilla I, Isla D. SEOM clinical guidelines for the diagnosis and treatment of gastroenteropancreatic neuroendocrine tumours (GEP NETS). Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2011;13(8):545-51.
103. Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut. 2012;61(1):6.
104. Boudreaux JP, Klimstra DS, Hassan MM, Woltering EA, Jensen RT, Goldsmith SJ, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. Pancreas. 2010;39(6):753-66.
105. Clinical Oncology Society of Australia. COSA:NETs guidelines [Internet]. 2014 [cited 2022 Nov 22]. Available from: https://wiki.cancer.org.au/australia/COSA:NETs_guidelinesh
106. Clement D, Navalkissoor S, Srirajaskanthan R, Courbon F, Dierickx L, Eccles A, et al. Efficacy and safety of 177 Lu-DOTATATE in patients with advanced pancreatic neuroendocrine tumours: data from the NETTER-R international, retrospective study. European journal of nuclear medicine and molecular imaging. 2022;49(10):3529-37.
107. Demirci E, Kabasakal L, Toklu T, Ocak M, Şahin OE, Alan-Selcuk N, et al. 177Lu-DOTATATE therapy in patients with neuroendocrine tumours including high-grade (WHO G3) neuroendocrine tumours: response to treatment and long-term survival update. Nuclear medicine communications. 2018;39(8):789-96.
108. Frilling A, Clift AK, Frampton AE, Bomanji J, Kaemmerer D, Al-Nahhas A, et al. A combination of surgery, theranostics, and liquid biopsy - a personalised oncologic approach to treatment of patients with advanced metastatic neuroendocrine neoplasms. International journal of medical sciences. 2021;18(10):2166-75.
109. Garske-Román U, Sandström M, Fröss Baron K, Lundin L, Hellman P, Welin S, et al. Prospective observational study of 177 Lu-DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. European journal of nuclear medicine and molecular imaging. 2018;45(6):970-88.
110. Genc CG, Klümpen HJ, van Oijen MGH, van Eijck CHJ, Nieveen van Dijkum EJM. A Nationwide Population-Based Study on the Survival of Patients with Pancreatic Neuroendocrine Tumors in The Netherlands. World journal of surgery. 2018;42(2):490-7.
111. Goncalves I, Burbury K, Michael M, Iravani A, Ravi Kumar AS, Akhurst T, et al. Characteristics and outcomes of therapy-related myeloid neoplasms after peptide receptor radionuclide/chemoradionuclide therapy (PRRT/PRCRT) for

metastatic neuroendocrine neoplasia: a single-institution series. European journal of nuclear medicine and molecular imaging. 2019;46(9):1902-10.
112. Hagmarker L, Svensson J, Rydén T, Gjertsson P, Bernhardt P. Segmentation of Whole-Body Images into Two Compartments in Model for Bone Marrow Dosimetry Increases the Correlation with Hematological Response in 177 Lu-DOTATATE Treatments. Cancer biotherapy & radiopharmaceuticals. 2017;32(9):335-43.
113. Hamiditabar M, Ali M, Bolek L, Vahdati G, Tworowska I, Delpassand ES. Safety and Effectiveness of 177Lu-DOTATATE Peptide Receptor Radionuclide Therapy After Regional Hepatic Embolization in Patients With Somatostatin-Expressing Neuroendocrine Tumors. Clinical nuclear medicine. 2017;42(11):822-8.
114. Hamiditabar M, Ali M, Roys J, Wolin EM, O'Dorisio TM, Ranganathan D, et al. Peptide Receptor Radionuclide Therapy With 177 Lu-Octreotate in Patients With Somatostatin Receptor Expressing Neuroendocrine Tumors: six Years' Assessment. Clinical nuclear medicine. 2017;42(6):436-43.
115. Hayes AR, Mak IYF, Evans N, Naik R, Crawford A, Khoo B, et al. Understanding the Treatment Algorithm of Patients with Metastatic Pancreatic Neuroendocrine Neoplasms: A Single-Institution Retrospective Analysis Comparing Outcomes of Chemotherapy, Molecular Targeted Therapy, and Peptide Receptor Radionuclide Therapy in 255 Patients. Neuroendocrinology. 2021;111(9):863-75.
116. Katona BW, Roccaro GA, Soulen MC, Yang Y-X, Bennett BJ, Riff BP, et al. Efficacy of Peptide Receptor Radionuclide Therapy in a United States-Based Cohort of Metastatic Neuroendocrine Tumor Patients: Single-Institution Retrospective Analysis. Pancreas. 2017;46(9):1121-6.
117. Kipnis ST, Hung M, Kumar S, Heckert JM, Lee H, Bennett B, et al. Laboratory, Clinical, and Survival Outcomes Associated With Peptide Receptor Radionuclide Therapy in Patients With Gastroenteropancreatic Neuroendocrine Tumors. JAMA network open. 2021;4(3):e212274.
118. Kobayashi N, Wild D, Kaul F, Shimamura T, Takano S, Takeda Y, et al. Retrospective study of peptide receptor radionuclide therapy for Japanese patients with advanced neuroendocrine tumors. Journal of hepato-biliary-pancreatic sciences. 2021;28(9):727-39.
119. Kong G, Hicks RJ. PRRT for higher-grade neuroendocrine neoplasms: What is still acceptable? Current opinion in pharmacology. 2022;67:102293.
120. Kovan B, Özkan ZG, Demir B, Tunçman D, Işik EG, Şimşek DH, et al. An Analysis for Therapeutic Doses of Patients with Neuroendocrine Tumor Treated with Lutetium 177 (177 Lu)-DOTATATE. Cancer biotherapy & radiopharmaceuticals. 2022;37(1):17-22.
121. Kudo A, Tateishi U, Yoshimura R, Tsuchiya J, Yokoyama K, Takano S, et al. Safety and response after peptide receptor radionuclide therapy with 177 Lu-DOTATATE for neuroendocrine tumors in phase 1/2 prospective Japanese trial. Journal of hepato-biliary-pancreatic sciences. 2022;29(4):487-99.
122. Lin E, Chen T, Little A, Holliday L, Roach P, Butler P, et al. Safety and outcomes of 177 Lu-DOTATATE for neuroendocrine tumours: experience in New South Wales, Australia. Internal medicine journal. 2019;49(10):1268-77.

123. Liu AJ, Ueberroth BE, McGarrah PW, Buckner Petty SA, Kendi AT, Starr J, et al. Treatment Outcomes of Well-Differentiated High-Grade Neuroendocrine Tumors. The oncologist. 2021;26(5):383-8.
124. Löser A, Schwarzenböck SM, Heuschkel M, Willenberg HS, Krause BJ, Kurth J. Peptide receptor radionuclide therapy with 177Lu-DOTA-octreotate: dosimetry, nephrotoxicity, and the effect of hematological toxicity on survival. Nuclear medicine communications. 2018;39(3):236-46.
125. Magalhães D, Sampaio IL, Ferreira G, Bogalho P, Martins-Branco D, Santos R, et al. Peptide receptor radionuclide therapy with 177 Lu-DOTA-TATE as a promising treatment of malignant insulinoma: a series of case reports and literature review. Journal of endocrinological investigation. 2019;42(3):249-60.
126. Marinova M, Mücke M, Fischer F, Essler M, Cuhls H, Radbruch L, et al. Quality of life in patients with midgut NET following peptide receptor radionuclide therapy. European journal of nuclear medicine and molecular imaging. 2019;46(11):2252-9.
127. Mejia A, Vivian E, Nwogu C, Shah J, Longoria R, Vo A, et al. Peptide receptor radionuclide therapy implementation and results in a predominantly gastrointestinal neuroendocrine tumor population: A two-year experience in a nonuniversity setting. Medicine. 2022;101(9):e28970.
128. Mollazadegan K, Skogseid B, Botling J, Åkerström T, Eriksson B, Welin S, et al. Poor outcome after systemic therapy in secondary high-grade pancreatic neuroendocrine tumors. Endocrine connections. 2022;11(3).
129. Naveed Ahmad JA, Schroeder BB, Ruhoy SM, Kennecke HF, Lin BS. Severe Thrombocytopenia in Patients With Advanced Neuroendocrine Tumor Treated With Peptide Receptor Radioligand Therapy. Clinical nuclear medicine. 2022;47(5):409-13.
130. Partelli S, Bertani E, Bartolomei M, Perali C, Muffatti F, Grana CM, et al. Peptide receptor radionuclide therapy as neoadjuvant therapy for resectable or potentially resectable pancreatic neuroendocrine neoplasms. Surgery. 2018;163(4):761-7.
131. Prasad V, Srirajaskanthan R, Toumpanakis C, Grana CM, Baldari S, Shah T, et al. Lessons from a multicentre retrospective study of peptide receptor radionuclide therapy combined with lanreotide for neuroendocrine tumours: a need for standardised practice. European journal of nuclear medicine and molecular imaging. 2020;47(10):2358-71.
132. Sitani K, Parghane RV, Talole S, Basu S. Long-term outcome of indigenous 177 Lu-DOTATATE PRRT in patients with Metastatic Advanced Neuroendocrine Tumours: a single institutional observation in a large tertiary care setting. The British journal of radiology. 2021;94(1117):20201041.
133. Sundlöv A, Gleisner KS, Tennvall J, Ljungberg M, Warfvinge CF, Holgersson K, et al. Phase II trial demonstrates the efficacy and safety of individualized, dosimetry-based 177 Lu-DOTATATE treatment of NET patients. European journal of nuclear medicine and molecular imaging. 2022;49(11):3830-40.
134. Thang SP, Lung MS, Kong G, Hofman MS, Callahan J, Michael M, et al. Peptide receptor radionuclide therapy (PRRT) in European Neuroendocrine Tumour Society (ENETS) grade 3 (G3) neuroendocrine neoplasia (NEN) - a

single-institution retrospective analysis. European journal of nuclear medicine and molecular imaging. 2018;45(2):262-77.
135. Thiis-Evensen E, Poole AC, Nguyen H-TT, Sponheim J. Achieving objective response in treatment of non-resectable neuroendocrine tumors does not predict longer time to progression compared to achieving stable disease. BMC cancer. 2020;20(1):466.
136. Vaghaiwalla T, Ruhle B, Memeh K, Angelos P, Kaplan E, Liao C-Y, et al. Response rates in metastatic neuroendocrine tumors receiving peptide receptor radionuclide therapy and implications for future treatment strategies. Surgery. 2021;169(1):162-7.
137. van der Zwan WA, Brabander T, Kam BLR, Teunissen JJM, Feelders RA, Hofland J, et al. Salvage peptide receptor radionuclide therapy with [177 Lu-DOTA,Tyr 3]octreotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumours. European journal of nuclear medicine and molecular imaging. 2019;46(3):704-17.
138. Yadav MP, Ballal S, Bal C. Concomitant 177 Lu-DOTATATE and capecitabine therapy in malignant paragangliomas. EJNMMI research. 2019;9(1):13.
139. Yordanova A, Wicharz MM, Mayer K, Brossart P, Gonzalez-Carmona MA, Strassburg CP, et al. The Role of Adding Somatostatin Analogues to Peptide Receptor Radionuclide Therapy as a Combination and Maintenance Therapy. Clinical cancer research : an official journal of the American Association for Cancer Research. 2018;24(19):4672-9.
140. Zhang J, Kulkarni HR, Singh A, Niepsch K, Müller D, Baum RP. Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms: Safety and Survival Analysis in 69 Patients. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2019;60(3):377-85.
141. Zhang-Yin J, Guilabert N, Kiffel T, Montravers F, Calais P, Lumbroso J, et al. Patient external dose rate after 177 Lu-DOTATATE therapy: factors affecting its decrease and predictive value. International journal of medical sciences. 2021;18(12):2725-35.

Appendix 1

Table A.1 Health technology assessments identified in Step 1.

Year	Title (Organisation)	Date of Search	PICO (where explicitly reported)	Number of studies included for each RQ	Conclusions of HTA
2018	Scottish Medicines Consortium Assessment of ^{177}Lu Oxodotreotide (Scottish Medicines Consortium)	Unknown	N/R	3 studies included RQ1: 2 studies RQ2: 1 study RQ3: 1 study	^{177}Lu oxodotreotide is accepted for use within NHS Scotland for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), SSTR2 positive GEP-NETs in adults.

2018	Everolimus, lutetium-177 DOTATATE and sunitinib for advanced, unresectable or metastatic neuroendocrine tumours with disease progression: a systematic review and cost-effectiveness analysis (NIHR)	May 2016	N/R	56 studies included RQ1: 35 studies RQ2: 0 studies RQ3: 1 study	High degree of uncertainty regarding the clinical effectiveness and cost-effectiveness of everolimus, ^{177}Lu oxodotreotide and sunitinib in the treatment of advanced, progressive GEP-NETs. Uncertainty is due to the lack of mature overall survival data and treatment switching by patients with disease progression in some studies. Long term data on HRQoL which is specific to these agents is not available, e.g. towards end of life.
2018	Peptide receptor radionuclide therapy based on ^{177}Lutetium for the treatment of neuroendocrine cancer (Norwegian National Institute of Public Health)	Mar 2017	**P:** Peptide receptor radionuclide therapy based on ^{177}Lu for the treatment of neuroendocrine cancer I: ^{177}Lu – the branded somatostatin analogue **C:** No treatment or other systemic tumour-directed therapy such as interferon alpha, somatostatin analogues (lanreotide, octreotide), mTor inhibitors	9 studies included RQ1: 4 studies RQ2: 1 study RQ3: 9 studies	Evidence is not sufficient to draw any definitive conclusions but ^{177}Lu oxodotreotide probably reduces overall mortality and increases both OS and PFS. Tumour response rates, assessed using RECIST, are likely to improve with ^{177}Lu oxodotreotide. The rate of myelodysplastic syndrome and acute leukaemia following ^{177}Lu oxodotreotide in uncertain, but may be about 1%. ^{177}Lu oxodotreotide, is considered to be justified, providing the radiation protection regulations are followed.

			(everolimus), tyrosine kinase inhibitors (sunitinib), chemotherapy or best supportive care. Excluded as comparators: surgery, ablation therapy or conventional radiotherapy (which are 1st line treatments). O**:** For clinical efficacy: overall survival, progression-free survival, time to progression, symptom control, quality of life and response rate in terms of tumour inhibition/reduction in tumour size: stable disease, partial response, full response. For side effects and adverse events: treatment-related morbidity, complications during or after treatment, adverse effects and adverse effects or events for the patient, close contacts and personnel or the environment due to radiation.		

			Study design: For clinical efficacy: SRs and HTAs of high quality, prospective studies with control group (initially RCTs, but if not available, non-randomised studies). If the latter is not available, cohorts and case series, but not case studies. For safety: same as for clinical efficacy, but in addition retrospective studies including registry studies.		

Key: GEP-NETs: gastroenteropancreatic neuroendocrine tumours; HR-QoL: health related quality of life; HTA: health technology assessment; NHS: National Health Service; N/R: not reported; OS: overall survival; PFS: progression free survival; RECIST: response evaluation criteria in solid tumours; RQ: review question; SSTR-2: somatostatin receptor sub-type-2

Table A.2. Systematic reviews, not in the context of health technology assessments, identified in Step 1

Author	Study & Year	Date of Search	PICO (where explicitly reported)	Number of Articles included for each review question	Authors conclusions
Gosain et al.[70]	Health-Related Quality of Life (HRQoL) in Neuroendocrine Tumors: A Systematic Review (2022)	May 2019	N/R	61 studies included RQ1: 0 studies RQ2: 2 studies RQ3: 0 studies	Time to QoL deterioration (TTD) was defined as the time from randomisation to first deterioration >/10 points on a 100-point scale for that domain. Side effects that may affect HRQoL, (diarrhoea, abdominal pain, flushing) were slightly higher in the ^{177}Lu oxodotreotide group, but this was not statistically significant. The rate of grade 3 and grade 4 side effects was similar in both groups. The TTD was statistically longer in the PRRT arm for a number of domains including global health (HR 0.41, $p < 0.001$), role functioning (HR = 0.58, $p = 0.03$), physical functioning (HR 0.52, $p = 0.15$), disease-related worries (HR 0.57, $p = 0.018$), body image (HR = 0.43, $p = 0.006$), diarrhoea 0.47 ($p = 0.01$), pain (HR 0.57, $p = 0.025$), and fatigue (HR 0.62, $p = 0.03$). Median TTD was statistically significant for PRRT for the global health domain (22.7-month difference) and physical functioning domain (13.7-month difference).

Ronde et al.[71]	Health-related quality of life and treatment effects in patients with well-differentiated gastroenteropancreatic neuroendocrine neoplasms: A systematic review and meta-analysis (2021)	Jun 2021	P: ≥18 years of age Well-differentiated GEPNENs I: Any treatment of the primary tumour C: Any comparator (or none) O: HRQoL measured using the EORTC QLQ-C30 (preferably with GINET21 module) Treatment effect outcomes (e.g., tumour response, survival, adverse events)	11 studies included RQ1: 1 study RQ2:1 study RQ3:1 study	SSA therapy, PRRT, chemotherapy and targeted therapies showed stable global HRQoL and disease stabilisation in patients with well-differentiated GEP-NETs. High-quality HRQoL reporting was lacking and the best sequence of treatment after progression on SSAs is unknown. Patients' subjective experience of health and QoL prospects may be decisive in treatment-related decision-making. HRQoL should be investigated along with survival outcomes. EORTC QLQ-C30 questionnaire with the QLQ-GINET21 module should be used in all studies with GEP-NET patients.

Ricci et al.[72]	Treatment of Advanced Gastro-Entero-Pancreatic Neuro-Endocrine Tumors: A Systematic Review and Network Meta-Analysis of Phase III Randomized Controlled Trials (2021)	01-Oct-2020	P: patients having non-resectable GEP–NENs I: any nonsurgical therapy C: placebo arm O: all studies reporting at least PFS and grade 3–4 toxicity S: all phase III RCTs included at least two arms	9 studies included RQ1: 1 study RQ2: 0 studies RQ3: 1 study	SSAs alone remain the best choice for well-differentiated GEP–NETs. [177]Lu oxodotreotide plus SSA is a valid alternative for midgut NENs but has a higher risk for toxicity. [177]Lu oxodotreotide plus SSA had the highest probability (99.6 %) of being associated with the longest PFS, followed by sunitinib use (64.5%), IFN-α plus SSA one (53.0%), SSA alone (46.6%), bevacizumab plus SSA one (45.0%), and everolimus ± SSA one (33.6%). The placebo administration had the lowest probability of being associated with the longest PFS (7.6%). Placebo or bevacizumab use has the highest probability of being the safest (73.7% and 76.7%), followed by SSA alone (65.0%), IFN-α plus SSA (52.4%), 177Lu-Dotatate plus SSA (49.4%), and sunitinib alone (28.8 %). The everolimus-based approach had the lowest probability of being the safest (3.9%).

Strosberg et al.[73]	Peptide receptor radiotherapy re-treatment in patients with progressive neuroendocrine tumors: A systematic review and meta-analysis (2021)	22-Mar-2020	P: Adults (≥18 years) with progressive NETs previously treated with PRRT I: Re-treatment with 177Lu-DOTATATE/DOTATOC and/or 90Y-PRRT C: Any comparison or none O: Efficacy and safety outcomes: PFS, ORR, and OS Safety as fatigue, endocrine syndrome, renal toxicity, and bone marrow toxicity Administered dosage and number of cycles Impact of various dosing regimens Prognostic factors	13 studies included (9 related to [177]Lu oxodotreotide) RQ1: 7 studies RQ2: 0 studies RQ3: 7 studies	Encouraging median PFS and DCR in conjunction with re-treatment involving [177]Lu oxodotreotide in patients with progressive GEP-NETs who were previously treated with PRRT. Re-treatment with PRRT did not adversely affect the safety profile of initial PRRT.

Walter et al. 2021[74]	Treatment for gastrointestinal and pancreatic neuroendocrine tumours: a network meta-analysis (2021)	11 Dec 2020	P: Patients with GI-NET I: 177-Lu-DOTATATE + SSA, bevacizumab + SSA, everolimus, everolimus + SSA, interferon, interferon + SSA, SSA, streptozocin + 5-FU, surufatinib C: Placebo O: disease control after 12 months, progression-free survival	11 studies included (1 related to ^{177}Lu oxodotreotide) RQ1: 1 study RQ2: 0 studies RQ3: 1 study	NET therapies have a broad range of risk for adverse events and effects on quality of life, but these were reported inconsistently. Evidence from this network meta-analysis (and underlying RCTs) does not support any particular therapy (or combinations of therapies) with respect to patient-centred outcomes (e.g., overall survival and quality of life).
Sonbol et al.[75]	Assessment of therapy-related myeloid neoplasms in patients with neuroendocrine tumors after peptide receptor radionuclide therapy: a systematic review (2020)	01 Apr 2019	N/R	28 studies included RQ1: 0 studies RQ2: 0 studies RQ3: 27 studies	The risk for development of therapy-related myeloid neoplasms is small, but not insignificant. Close monitoring is recommended to identify patients at an early stage of the disease.

Zhang et al.[76]	The efficacy of ^{177}Lu -DOTATATE peptide receptor radionuclide therapy (PRRT) in patients with metastatic neuroendocrine tumours: a systematic review and meta-analysis (2020)	18 Jan 2019	N/R	15 studies included RQ1: 15 studies RQ2: 0 studies RQ3: 15 studies	^{177}Lu oxodotreotide is effective and safe for the treatment of NETs. No unified standard for the dose or frequency of delivery and no data on dosage standards or long-term adverse reactions are available. Additional ^{177}Lu oxodotreotide clinical data from Asian samples are required. High-quality original research, especially RCTs, are needed to provide more evidence for the clinical application of ^{177}Lu oxodotreotide.
Stolniceanu et al.[77]	Nephrotoxicity/renal failure after therapy with 90Yttrium- and 177Lutetium-radiolabeled somatostatin analogs in different types of neuroendocrine tumors: a systematic review (2020)	Nov 2018	N/R	34 studies included RQ1: 0 studies RQ2: 0 studies RQ3: 34 studies	Patients with NETs treated with PRRT can develop potentially serious long-term nephrotoxicity, despite kidney protection. RCTs with a long follow-up period (at least 5 years), using a personalized dosimetry-based PRRT approach, with BED limits, and renal function quantified by direct GFR measurements should be conducted.

Wang et al. (78)	The therapeutic efficacy of 177Lu-DOTATATE/DOTATOC in advanced neuroendocrine tumors: A meta-analysis (2020)	30 April 2019	P: Adults with NETs I: 177Lu-DOTATATE/DOTATOC PRRT C: Single arm trials, comparator is before therapy O: Dose response rate (complete response + partial response) and Disease control rates (complete response + partial response + stable disease)	22 studies included RQ1: 22 studies RQ2: 0 studies RQ3: 0 studies	In advanced NETs patients, DRRs and DCRs were significantly improved in patients advanced NETs, after initial treatment with ^{177}Lu oxodotreotide. This treatment is beneficial and promising for advanced or inoperable NETs patients.

Satapathy et al.[79]	177Lu-DOTATATE peptide receptor radionuclide therapy versus everolimus in advanced pancreatic neuroendocrine tumors: a systematic review and meta-analysis (2019)	01 Jun 2019	N/R	27 studies included (15 related to [177]Lu oxodotreotide) RQ1: 12 studies RQ2: 0 studies RQ3: 3 studies	[177]Lu oxodotreotide showed better therapeutic efficacy and caused fewer adverse effects compared to everolimus in patients with advanced pancreatic NET. [177]Lu oxodotreotide may be considered as first-line treatment for progressive disease over other alternatives.

Saravana-Bawan et al. [80]	Efficacy of 177Lu Peptide Receptor Radionuclide Therapy for the Treatment of Neuroendocrine Tumors: A Meta-analysis (2019)	04 Jun 2018	N/R	18 studies included RQ1: 18 studies RQ2: 0 studies RQ3: 0 studies	4 treatments using ^{177}Lu oxodotreotide is an effective way of treating unresectable metastatic NETs. The optimal treatment regimen (indication, activity, duration) require further investigation.
Pozzari et al. [81]	Systemic therapies in patients with advanced well-differentiated pancreatic neuroendocrine tumors (PanNETs): when cytoreduction is the aim. A critical review with meta-analysis.	10 April 2018	N/R	17 studies included RQ1: 0 studies RQ2: 1 Study (Chemo + PRRT Response Rate) RQ3: 0 studies	Multi-agent chemotherapy (various regimens) appear to be the best cytoreductive treatment. PRRT combined with chemotherapy and sunitinib appeared promising in pancreatic NETs with a homogeneous and high functional SSTR expression. PRRT seems a good candidate for clinical trials in locally advanced/oligometastatic potentially resectable SSTR positive pancreatic NETs.

Dannoon et al. [82]	The efficacy of the available peptide receptor radionuclide therapy for neuroendocrine tumors: a meta-analysis (2017)	Dec 2016	N/R	14 studies included RQ1: 6 studies RQ2: 0 studies RQ3: 0 studies	PRRT of NETs should be planned specifically for each patient depending on their well-being, the size of their tumours/metastasis, and their previous treatments. Some patients might benefit from ^{177}Lu-PRRT, whereas others might require ^{90}Y-PRRT, followed by ^{177}Lu-PRRT. Clinical investigation of this treatment is still underexplored and more trials are warranted. The pooled effects of this study were in favour of the tandem-PRRT compared with ^{90}Y-only or ^{177}Lu-only therapies.
Kim et al.[83]	The efficacy of 177Lu-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: a meta-analysis (2015), NA	Sep 2014	N/R	6 studies included RQ1: 0 studies RQ2: 6 studies RQ3: 2 studies	Although the treatment protocols are not standardized and the treatment effects should be further verified through prospective randomized controlled trials, ^{177}Lu-labelled PRRT is an effective treatment option for patients with inoperable or metastatic NETs, based on this meta-analysis of the published data.

Pusceddu et al.[84]	Evolution in the treatment of gastroenteropancreatic-neuroendocrine neoplasms, focus on systemic therapeutic options: a systematic review (2015)	Unknown	N/R	Not specified RQ1: 4 studies RQ2: 0 studies RQ3: 0 studies	The combination of radionuclides with different physical properties, such as ^{90}Y and ^{177}Lu, could be advantageous in patients with lesions of different sizes. A Phase II pilot study using a tandem protocol with ^{90}Y and ^{177}Lu was conducted in patients with NEN, refractory to conventional therapy. This approach induced a complete response in 7.7% of patients, a partial response in 34.6% and SD in 42.3%. Global OS estimated at 24 months was 78.1%, while median PFS was 25.0 months (interquartile range: 10.6–34.3 months). A symptomatic response with an improvement in quality of life was observed in the majority of patients.
Gulenchyn et al. [85]	Radionuclide therapy in neuroendocrine tumours: a systematic review	04 Nov 2010	N/R	32 studies RQ1: 2 studies RQ2: 1 study RQ3: 1 study	No strong conclusion can be made that one therapeutic radiopharmaceutical of PRRT is more effective than others for malignant NET patients. It seems that 177Lu-DOTATATE is more effective than ^{111}In and ^{90}Y from the comparisons with historical controls. However, the results from these comparisons should be interpreted with caution.

Ludwig Boltzmann Institute for HTA[86]	Radiopeptide therapy 90Yttrium and 177 Lutetium somatostatin analogues for the treatment of unresectable neuroendocrine tumors. Systematic review (2010)	04 02 2010	P: Patients with metastatic or inoperable somatostatin receptor-positive NETs. I: 90Y and/or 177Lu labelled somatostatin analogues. Control intervention A non-labelled somatostatin analogues (2) Interferon-alpha (3) Chemotherapy O: (target variables) tumour reduction, quality of life, complications during or after surgery, mortality S: For efficacy: all prospective studies (n≥50). For safety: all studies (n≥50).	8 studies included in total RQ1: 3 studies RQ2: 0 studies RQ3: 0 studies	Inclusion in the benefit catalogue is recommended with reservations. The existing evidence suggests a net benefit of the evaluated intervention, but new studies may have an important influence on the estimation of the effect. A re-evaluation of the evidence at a later date is recommended.

Key: BED: biological effective dose; DCR: disease control rate; DRR: disease response rate; EORTC-QLQ: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; GI-NETs: gastrointestinal NETs; GEP-NETs: gastroenteropancreatic neuroendocrine tumours; GFR: glomerular filtration rate; HR: hazard ratio; HR-QoL: health related quality of life; IFN-α; interferon- α; NEN: neuroendocrine neoplasms; N/R: not reported; OS: overall survival; PFS: progression free survival; PRRT: peptide receptor radionuclide therapy; RCT: randomised controlled trial; RQ: review question; SSA: somatostatin analogues; TTD: time to deterioration; 5-FU: 5-flurouracil.

Table A.3. Guidelines and practice parameters identified in Step 1

Year	Guideline title	Organisation	Recommendation
2022	NCCN Guidelines Version 2.2022 Neuroendocrine and Adrenal Tumours[11, 87]	National Comprehensive Cancer Network	Recommends PRRT with ^{177}Lu oxodotreotide as a treatment option for GEP-NETs patients with advanced and/or metastatic disease or progression on octreotide and lanreotide. Tumours should be SSR positive on imaging.
2022	ACR-ACNM-ASTRO-SNMMI Practice Parameter for Lutetium-177 (Lu-177) DOTATATE Therapy[88]	Developed collaboratively by the ACR, the American College of Nuclear Medicine (ACNM), the American Society for Radiation Oncology (ASTRO), and the Society of Nuclear Medicine	^{177}Lu oxodotreotide is an effective therapy for adult patients with inoperable, locally advanced, or metastatic GEP-NETs, including fore gut, midgut, and hindgut NETs that progress on conventional treatments.
2021	JNETS clinical practice guidelines for gastroenteropancreatic neuroendocrine neoplasms: diagnosis, treatment, and follow-up: a synopsis[89]	The Japanese Society of Gastroenterology	Patients for whom other treatments have proved ineffective should be prioritised for PRRT. PRRT only recently covered by insurance in Japan. Facilities for the administration of PRRT need to be built in Japan.

2020	Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[90]	European Society of Medical Oncology	PRRT is recommended as second-line therapy in patients with midgut NETs with disease progression on SSAs. PRRT is recommended after failure of approved therapies for pancreatic NETs.
2020	NANETS/SNMMI Consensus Statement on Patient Selection and Appropriate Use of 177Lu-DOTATATE Peptide Receptor Radionuclide Therapy[91]	The North American Neuroendocrine Tumor Society & The Society of Nuclear Medicine and Molecular Imaging	^{177}Lu oxodotreotide should be considered when treating GEP-NETs, and tumours of unknown origin, generally after progression on somatostatin analogues. Decision to initiate ^{177}Lu oxodotreotide should take place following a multidisciplinary discussion.
2019	Consensus Document for Management of Neuroendocrine Tumours[92]	Indian Council of Medical Research	Individual patients should assessed to determine which treatment is appropriate: chemotherapy, targeted therapy, PRRT or best supportive care. Refers to NETTER-1 data.
2017	ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogues[93]	European Neuroendocrine Tumour Society	PRRT appears to be a highly effective therapy. Clinicians and patients should be aware of the risk of some rare life-threatening events. Treatment should be adapted to the circumstances of individual patients and to local experience and conditions.

2017	Guidelines for the management of neuroendocrine tumours by the Brazilian gastrointestinal tumour group[94]	Brazilian gastrointestinal tumour group	^{177}Lu oxodotreotide is recommended for progressive well differentiated midgut NETs. Most effective timing has not been established but improved PFS has been demonstrated as a second line treatment. Recommended after other systemic therapies have failed as there is limited data on delayed safety analysis of this treatment. ^{177}Lu oxodotreotide is recommended for patients with an advanced well differentiated pancreatic or hindgut NET whose disease progressed with somatostatin analogues, locoregional and/or systemic therapy. SSTR2 expression should be confirmed prior to PRRT.
2017	The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors[95]	The North American Neuroendocrine Tumour Society	^{177}Lu oxodotreotide recommended as a second-line treatment for SSTR2 positive mid-gut NETs. Need more data regarding optimal sequence and long-term toxicity for current treatment options, including the cumulative radiation dose from liver radioembolisation and PRRT.
2016	Diagnosis and management of gastrointestinal neuroendocrine tumors: An evidence-based Canadian consensus[96]	Canadian National Expert Group	^{177}Lu oxodotreotide should be considered in patients with well-differentiated, SSR-positive midgut NETs with Ki-67 index 62% who have progressed on standard dose SSA therapy. ^{177}Lu oxodotreotide is also an option for other GI-NETs. The role of internal dosimetry to optimise therapeutic response and limit renal and myelotoxicities deserves further evaluation.

2015	Consensus guidelines for the management of patients with neuroendocrine tumours[97]	Scottish Neuroendocrine Tumour Group	^{177}Lu oxodotreotide is now approved for the treatment of GEP-NETs with significant disease shown on SST scintigraphy and acceptable renal function.
2014	Consensus recommendations for the diagnosis and management of pancreatic neuroendocrine tumors.[98]	Canadian National Expert Group	^{177}Lu oxodotreotide is an option for patients with good to excellent performance status, adequate renal, hepatic and bone marrow function, at least moderately bulky disease and those with progressive disease despite consideration of attempt with less toxic therapies. Toxicity should be an important consideration because bone marrow toxicity and treatment related myelodysplastic syndrome may limit future treatment options.
2013	The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours[99]	IAEA, EANM, SNMMI	Despite the large body of evidence regarding efficacy and clinical safety, PRRNT is still considered an investigational treatment. Treatment with PRRNT should be delivered by an experienced multidisciplinary team. PRRNT may be beneficial as a neoadjuvant therapy in order for patient to become suitable for surgery. Suitable candidates include those with GEP tumours with positive SSTR2 expression.

2013	South Australian Gastroenteropancreatic Neuroendocrine Tumours Pathway[100]	Statewide Cancer Clinical Network	Suitable patients include inoperable, locally-advanced or unresectable metastatic NETs with significant SSR expression and high Ki-67 (>10%) or intense FDG uptake. Patients should have hormone-related symptoms uncontrolled by SSA and at least one of these criteria: - Symptoms related to hormonal secretion or tumour burden (including pain, weight loss or organ dysfunction), not controlled by conventional therapy. - Evidence of disease progression within the last 12 months.
2011	Radionuclide therapy for patients with neuroendocrine tumors (NETs) in Ontario: Expert Panel Report[101]	Cancer Care Ontario	PRRT for NETs should offered as part of a province-wide clinical trial. The recommended PRRT agent for clinical trials is ^{177}Lu oxodotreotide.

2011	SEOM clinical guidelines for the diagnosis and treatment of gastroenteropancreatic neuroendocrine tumours (GEP NETS)[102]	Spanish Society of Medical Oncology	Patients with SSTR positive, advanced disease may be considered for PRRT. The appropriate timing of this therapeutic intervention or the relative long-term benefit-risk ratio compared to other treatment options is not yet clear.

2011	Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs)[103]	British Society of Gastroenterology, the Society for Endocrinology, the Association of Surgeons of Great Britain and Ireland (and its Surgical Specialty Associations), the British Society of Gastrointestinal and Abdominal Radiology and others	Access to some form of radionuclide therapy should be made available to centres treating patients with NETs.
2010	The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors[104]	The North American Neuroendocrine Tumor Society	Imaging to assess SSTR update are required prior to treatment with PRRT. Further studies with PRRT are required.
2010	COSA:NETs guidelines/Radionuclide Therapy[105]	Clinical Oncology Society of Australia	The preferred agent for PRRT is ^{177}Lu oxodotreotide. The major Australian clinical experience with ^{177}Lu-octreotate to date comprises approximately 200 GEP-NET patients treated at Peter MacCallum Cancer Centre, Melbourne and Fremantle Hospital, Perth since 2005. Experience in Australia with approximately 200 GEP-NET patients in Melbourne and Perth is consistent with outcomes of the large retrospective series from Europe.

Key: FDG: fluorodeoxyglucose; GEP-NETs: gastroenteropancreatic neuroendocrine tumours; PRRT: peptide receptor radionuclide therapy; SSR: somatostatin receptor; SSTR-2: somatostatin receptor sub-type-2.

Table A.4. Ongoing trials identified in Step 2

Study: Reference (name), country	Design	Control & Intervention	Number of participants	Started (date)	Planned study completion date	Status
NCT03972488 (NETTER-2) USA, Canada, France, Germany, Italy, Republic of Korea, Netherlands, Spain, UK	RCT	^{177}Lu + octreotide vs. octreotide	222	Jan 2020	Jul 2027	Active, not recruiting
NCT02358356 (CONTROL-NETS) Australia	RCT	^{177}Lu vs. capecitabine + temozolomide Vs. ^{177}Lu + capecitabine + temozolomide	75	Nov 2015	Oct 2021	Closed to recruitment
NCT03049189 (COMPETE) USA, Australia, Belgium, Czechia, France, Germany, Italy, Netherlands, Poland, South Africa, Spain, Switzerland, UK	RCT	^{177}Lu vs. everolimus	300	Feb 2017	Jun 2029	Active, not recruiting
NCT04919226 (COMPOSE)	RCT	^{177}Lu vs. best standard of care (investigator's choice of capecitabine/everolimus/FOLFOX)	202	Dec 2021	Sept 2026	Recruiting

USA, Australia, France, India, Italy, Netherlands, Spain, Sweden, UK						
NCT04917484 Denmark	RCT	^{177}Lu standard dose vs. ^{177}Lu individualised dose	100	Feb 2020	Dec 2025	Recruiting
CTRI/2020/01/022636 India	RCT	^{177}Lu vs. ^{177}Lu + capecitabine	50	Jan 2020	Unknown	Recruiting
NCT04234568 USA	Phase 1	^{177}Lu + triapine	29	Jan 2020	Jan 2023	Recruiting
NCT03691064 USA, France, Portugal, UK,	Post-authorisation safety study	^{177}Lu	1000	Nov 2018	Nov 2028	Recruiting
NCT02230176 (OCCLURANDOM) France	RCT	^{177}Lu vs. cunitinib	80	Feb 2015	Oct 2023	Recruiting
CTRI/2019/07/02038 India	RCT	^{177}Lu vs. ^{177}Lu + capecitabine + temozolomide	162	Aug 2019	Unknown	Recruiting

EUCTR2019-001562-15-DE Brazil, Canada, China, France, Germany, Italy, Republic of Korea, Netherlands, Spain, UK, USA	RCT	^{177}Lu + best supportive care (octreotide) vs. best supportive care (octreotide)	222	Unknown	Unknown	Authorised – recruitment may be ongoing or finished
ACTRN12611000207910 2011 (NETTLE) Australia	Phase 1	^{177}Lu + different doses of everolimus	16	May 2011	Completed	Completed
NCT04727723 (REAL-Lu) Italy	Observational study	^{177}Lu	164	Mar 2021	Apr 2025	Active, not recruiting
NCT04614766 (SPORE-3) USA	Non randomised interventional study	^{177}Lu + iobenguane 131 vs. ^{177}Lu	50	Dec 2023	Oct 2025	Not yet recruiting
EUCTR2021-001306-30-FR/NCT04954820 (Re-LUTH) France	RCT	^{177}Lu (2 cycles vs. 4 cycles)	146	Sep 2021	Unknown	Unknown
EUCTR2014-003067-38-IT Italy	RCT	^{177}Lu + capecitabine vs. ^{177}Lu	176	Mar 2016	Unknown	Unknown
EUCTR2015-004727-31-IT/NCT03454763 (LUTHREE)	RCT	^{177}Lu given every 5 weeks or every 8-10 weeks	618	May 2016	May 2021	Recruiting

Italy						
EUCTR2020-006068-99-PL Poland	RCT	^{177}Lu – personalized vs. standard treatment	92	Sept 2019	Unknown	Unknown
NCT05387603 (START-NET) Sweden	RCT	^{177}Lu – personalized vs. standard treatment	300	Jun 2022	Oct 2025	Not yet recruiting
NCT01237457 USA	Phase 2	^{177}Lu	144 [60 on ct.gov but seems to have been extended]	Oct 2010	Aug 2015	Active, not recruiting
NCT04915144 Canada	RCT	^{177}Lu – personalized vs. standard treatment	200	Jan 2023	Dec 2027	Not yet recruiting
NCT05359146 Switzerland	Phase 1, Randomised crossover study	^{177}Lu vs. ^{161}Terbium	16	Dec 2022	Dec 2025	Not yet recruiting
NCT05247905 USA	RCT	^{177}Lu vs. ^{177}Lu + capecitabine + temozolomide	198	Mar 2022	Mar 2028	Recruiting
NCT05610826 USA	RCT	Cytoreductive surgery vs. Preoperative ^{177}Lu	52	Feb 2023	Feb 2027	Not yet recruiting

NCT05459844 China	RCT	^{177}Lu vs. octreotide long acting release	196	Aug 2022	Dec 2024	Recruiting
USA	RCT	^{177}Lu + low dose telotristat vs. ^{177}Lu + high dose telotristat	70	Jul 2021	Jun 2034	Recruiting
NCT03478358 China	RCT	^{177}Lu + amino acids vs. ^{177}Lu (different activities)	60	Apr 2017	Dec 2022	Recruiting
NCT04544098 USA	Phase I	^{177}Lu given intravenously vs. ^{177}Lu given through hepatic intra-arterial infusion	10	Sep 2020	Sept 2024	Recruiting
NCT04750954 USA	Phase I	^{177}Lu + peposertib	29	Jun 2021	Jun 2023	Recruiting
NCT05249114 USA	Phase I	^{177}Lu + cabozantinib	90	Jun 2022	Dec 2027	Recruiting
NCT05178693 UK	Phase I	^{177}Lu + cedazuridine 100mg + 35mg decitabine	27	Apr 2022	Dec 2025	Recruiting

Key: RCT: randomised controlled trial; UK: United Kingdom; USA: United States of America

Table A.5. Relevant publications identified in Step 2

Author	Year	RQ	Authors conclusions
Almeamar et al.[3]	2022	RQ1, RQ3	^{177}Lu oxodotreotide is an effective second-line treatment for metastatic WD-NETs. Lu-PRRT may cause a rare and devastating side effect of leukaemia. Prior use of targeted therapies therefore needs to be evaluated.
Alsadik et al.[42]	2022	RQ1, RQ2, RQ3	^{177}Lu oxodotreotide appears to be generally safe in NET patients with pre-existing chronic kidney disease (CKD) stage 3. Low incidence of grade 3/4 haematological toxicity (9%) and permanent major nephrotoxicity (3%). Average annual estimated glomerular filtration rate loss was estimated at 2.5%. No significant risk factors for patients developing reduced renal function. ^{177}Lu oxodotreotide appears to have a good therapeutic effect with progression free survival of 42 months and overall survival of 47 months. Most patients also had an improvement in their quality of life.
Alsadik et al.[41]	2022	RQ1, RQ3	^{177}Lu oxodotreotide is an effective therapeutic modality for SSR expressing NETs with a moderate or large tumour burden. ^{177}Lu oxodotreotide resulted in disease control rate of 86% and median progression free survival (PFS) and overall survival at 33 and 46 months, respectively. Ki-67, chromogranin A and body mass index are independent predictive factors of PFS on multivariate analysis. ^{177}Lu oxodotreotide was generally well-tolerated, with grade 3 or 4 toxicity renal toxicity <1%, grade 3 or 4 bone

Author	Year	RQ	Authors conclusions
			marrow toxicity at 8% and myelodysplastic syndrome recorded in <1%.
Bergsma et al. [40]	2018	RQ 3	The prevalence of therapy-related persistent haematologic dysfunction (PHD) after PRRT with ^{177}Lu DOTATATE in GEP NET patients was 4%, implying a relative risk of 2.7. The median latency time to disease development was 41 months. In the group of GEP NET patients, no risk factors could be identified for the development of therapy-related PHD. Anaemia combined with a rise in mean corpuscular volume occurred in half the patients with PHD related to PRRT with ^{177}Lu-DOTATATE.
Chiapponi et al.[68]	2020	RQ1, RQ3	^{177}Lu oxodotreotide represents an option for primarily unresectable neuroendocrine liver disease for conversion into resectabilty. Can also be repeated in case of disease relapse or combined with a variety of other treatments.
Clement et al.[106]	2022	RQ1	Overall, this retrospective real-world study conducted across sites in three countries supports recommendations in guidelines for ^{177}Lu oxodotreotide use and reinforces the role of ^{177}Lu-DOTATATE for the treatment of patients with SSTR-positive pancreatic NETs, a disease area with limited therapeutic options and an unmet need for novel treatments.
de Vries-Huizing et al.[38]	2021	RQ3	PRRT in our hospital is safe therapy with low incidence of severe haematological toxicity using an extensive screening program and haematological monitoring, and 96/100 patients were not restricted in treatment continuation by haematological toxicity. No differences in baseline parameters (haematological, somatostatin receptor positive tumour volume and general patient characteristics) between none/mild, moderate and severe haematological toxicity were identified. Persistent moderate to severe haematological toxicity was rarely observed, but after adapting dosages and/or postponed administrations, many patients still could complete their treatment course.

Author	Year	RQ	Authors conclusions
Del Prete et al.[65]	2019	RQ1, RQ3	Preliminary results of our ongoing prospective study of personalized PRRT, confirm the feasibility of delivering a prescribed renal dose by personalizing the injected activity based on dosimetry. This approach appears safe and allows to significantly increase tumour irradiation. Initial efficacy results are suggestive of enhanced therapeutic response, particularly in patients with pancreatic NET, as well as a positive impact on the quality of life.
Del Prete et al.[66]	2017	RQ1, RQ3	Devised a practical, dosimetry-based ^{177}Lu oxodotreotide protocol wherein the absorbed dose to the kidney is controlled and standardized. PRRT personalization offers the prospect of significantly increasing absorbed dose to the tumour, and thus the likelihood of therapeutic benefits, while limiting the risk of toxicity by keeping the renal absorbed dose within the threshold limit adopted by many for the induction course.
Demirci et al.[107]	2018	RQ1	^{177}Lu oxodotreotide significantly contributes to the survival rate in patients with SSTR-2-positive metastatic NETs including grade III tumours with a high expression of somatostatin receptors. The response rates, progression free survival and overall survival rates of ^{177}Lu oxodotreotide treatment in our cohort are significantly higher than alternative treatment methods.
Frilling et al.[108]	2021	RQ1, RQ3	Combining molecular imaging, surgery, and targeted molecular therapy provides a promising and safe approach for treatment of patients with well-differentiated metastasised small bowel NETs. The multianalyte biomarker NETest seems to be a promising tool for detection of neuroendocrine disease.
Frösss-Baron et	2021	RQ1, RQ3	^{177}Lu oxodotreotide therapy was feasible and highly effective, with a median progression free survival (PFS) of 24 months and a median overall survival (OS) of 42 months, in patients with advanced, inoperable pancreatic NETs

Author	Year	RQ	Authors conclusions
al.[55]			heavily pre-treated with chemotherapy. More than one line of chemotherapy constituted a therapy-related independent risk factor for shorter PFS and OS. Patients with morphological response achieved PFS and OS benefits. Dosimetry-based therapy was feasible and patients receiving the number of cycles required to reach 23 Gy absorbed dose to the kidneys achieved better morphological response than those who did not.
Garske-Román et al.[109]	2018	RQ1 & RQ3	Dosimetry-based therapy with ^{177}Lu oxodotreotide is feasible. Patients in whom the absorbed dose to the kidneys reached 23 Gy had a longer overall survival (OS) than those in whom it did not. Patients with complete response/partial response had a longer OS than those with stable disease. Bone marrow dosimetry did not predict toxicity.
Genc et al.[110]	2018	RQ1	Surgical resection shows favourable outcome for all pancreatic NET tumours, including indolent tumours and tumours with distant metastases. Prospective trials are needed confirm these results. Patients who underwent surgery had the highest 5-year survival (86%) compared to PRRT (33%), chemotherapy (21%), targeted therapy and somatostatin analogues (24%) (all p=0.001).
Goncalves et al.[111]	2019	RQ3	The diagnosis of therapy-related myeloid neoplasms (t-MN) after PRRT/chemoradionuclide therapy is an infrequent but serious complication with poor overall survival. Most patients present with thrombocytopenia; unfavourable genetic mutations have a poor response to t-MN

Author	Year	RQ	Authors conclusions
			treatment. Prospective data are needed to explore potential pre-existing genetic factors and predictive biomarkers to minimise the risk of t-MN.
Hagmarker et al.[112]	2017	RQ3	Compared to whole-body dosimetry, stronger correlation was found between absorbed dose to bone marrow (BM) and haematological response using the two-compartment method. The two-compartment method has potential as a valuable image based alternative to blood-based BM dosimetry.
Hamiditabar et al.[113]	2017	RQ1 & RQ3	Treatment with ^{177}Lu oxodotreotide did not show clinically or statistically significant toxicity in chemoembolization and radionuclide hepatic embolization (CRHE). CRHE patients regardless of frequency of embolization or time interval between embolization and first PRRT. Results suggested a statistically significant higher response rate in patients with a history of CRHE. A prior history of CRHE is not a contraindication to subsequent PRRT.
Hamiditabar et al.[114]	2017	RQ1 & RQ3	^{177}Lu oxodotreotide has shown promising potential as a safe and effective targeted therapy in inoperable, well to moderately differentiated metastatic NETs. This study concurs with the results of the multicentre randomised clinical trial conducted in US and Europe.
Hayes et al.[115]	2021	RQ1	This study suggests that PRRT is associated with superior clinical outcomes relative to other systemic therapies for G2 metastatic pancreatic NETs. Prospective studies are required to confirm these observations.
Jahn et	2020	RQ 3	It was not possible to demonstrate a tumour dose-response relationship in SI-NET metastases, with the applied

Author	Year	RQ	Authors conclusions
al. [67]			dosimetry method, contrary to what was previously shown for pancreatic NETs.
Kunikowska et al.[57]	2020	RQ3	These results of a multicentre trial indicate that tandem radioisotope 90Y/^{177}Lu-DOTATATE therapy for patients with metastatic neuroendocrine tumours (G1 and G2) is highly effective and safe, with limited side effects. The data demonstrate statistically significant favourable outcomes of tandem 90Y/^{177}Lu-DOTATATE therapy in patients with NET G1 compared to NET G2.
Kalshetty et al.[58]	2018	RQ1	The data support the evidence that PRRT could be potentially beneficial in resistant, refractory, and progressive symptomatic groups of GEP-NETs with functional disease burden. The use of a multidimensional response evaluation should be adopted (rather than only anatomical–functional imaging) and needs to be considered while managing this subset of patients.
Katona et al.[116]	2017	RQ1 & 3	PRRT is an effective therapy in a US population. Progression-free survival and overall survival were better in grade I/II NETs and when PRRT was sequenced prior to systemic chemotherapy.
Kennedy et al.[39]	2022	RQ1 & 3	^{177}Lu oxodotreotide remains an efficacious and well tolerated treatment in long-term follow-up. For clinicians deciding on the timing of PRRT for individual patients, the 6.7% long-term risk of myelodysplastic syndrome/leukaemia needs to be balanced against the 21% progression free survival at 10 years.
Kipnis et al.[117]	2021	RQ1 & 3	This cohort study of patients with metastatic NETs found that PRRT was associated with laboratory-measured toxic effects during treatment for most patients and an overall median progression free survival (PFS) of 21.6 months. Patients with small bowel NETs had longer PFS after PRRT compared with patients with pancreatic NETs.

Author	Year	RQ	Authors conclusions
			These findings suggest that PRRT may be a useful treatment for NETs in US-based populations. The study found that patients with small bowel NETs have significantly longer PFS compared with patients with pancreatic NETs.
Kobayashi et al.[118]	2021	RQ1 & RQ3	PRRT was effective and safe for Japanese patients with advanced NETs. PRRT was equally effective as front-line and late-line treatment.
Kong et al.[119]	2019	RQ1 & 3	Our results indicate high efficacy and morphologic responses with minimal toxicity and very encouraging survival from PRRT in patients with metastatic rectal NEN despite the adverse prognostic features of this cohort. Further prospective PRRT trials are warranted in this subgroup.
Kovan et al.[120]	2022	RQ3	The critical organs that seem to affect the treatment scheme in PRRT with ^{177}Lu oxodotreotide are kidney and bone marrow. Although there are established threshold levels, derived from radiotherapy experience, more studies are needed to clarify these dose limits in systemic radionuclide therapies such as PRRT.
Kudo et al.[121]	2022	RQ1 & RQ3	^{177}Lu oxodotreotide demonstrated remarkable tumour shrinkage and tolerability in Japanese patients with advanced NETs.
Lin et al.[122]	2019	RQ1 & RQ3	^{177}Lu oxodotreotide is a promising treatment for advanced NETs. Superior survival in patients who met selection criteria emphasise the importance of protocol adherence.
Liu et al.[123]	2021	RQ1	Among patients with NET G3, capecitabine/temozolomide was the most commonly used treatment with clinically meaningful efficacy and disease control.

Author	Year	RQ	Authors conclusions
			FOLFOX or PRRT are other potentially active treatment options. Etoposide/Platinum has some activity in NET G3, but responses appear to be short-lived. Prospective studies evaluating different treatments effects in patients with NET G3 are needed to determine an optimal treatment strategy.
Löser et al.[124]	2018	RQ1, RQ3	The findings indicate that ^{177}Lu oxodotreotide is a safe and effective treatment method for patients with NETs. Moreover, these data strongly suggest that haematological parameters may affect survival so a further re-evaluation in prospective studies is warranted.
Magalhães et al.[125]	2019	RQ1, RQ3	After the start of ^{177}Lu oxodotreotide all patients achieved hypoglycaemia symptomatic control and had evident improvement of their quality of life. Three patients showed imagological improvement suggesting reduced tumour load.
Marinova et al.[126]	2019	RQ2	Our study confirmed an equally positive effect of PRRT on quality of life in midgut NET patients with high or moderate functional status in terms of increasing global health, functional status, and alleviating symptoms
Medaer et al.[56]	2020	RQ3	In a patient cohort with NET pre-treated with everolimus and/or sunitinib, we could not demonstrate a significant effect of prior/pretreatment with everolimus and/or sunitinib on the sub-acute haematological toxicity of ^{177}Lu oxodotreotide.
Mejia et al.[127]	2022	RQ1 & RQ3	^{177}Lu oxodotreotide was well tolerated in patients with GEP-NET. Additional studies are needed to examine long-term clinical and patient-reported outcomes associated with GEP-NET treatment as well as financial considerations for hospitals embarking on a PRRT program.

Author	Year	RQ	Authors conclusions
Minczeles et al.[63]	2023	RQ1	In NET patients treated with a cumulative activity less than 29.6 GBq ^{177}Lu oxodotreotide, PRRT was less efficacious in terms of tumour response and survival compared to patients who received 29.6 GBq.
Minczeles et al.[59]	2022	RQ1	Early administration of PRRT followed by surgery is associated with favourable long-term outcomes in patients with locally advanced or oligometastatic pancreatic NEN and can be considered for selected patients with vascular involvement and/or increased risk of recurrence.
Mollazadegan et al.[128]	2022	RQ1	In conclusion, this hypothesis-generating study failed to identify any promising treatment alternatives for patients with secondary pancreatic NET-G3. This demonstrates the need for both improved biological understanding of this particular NET entity and for designing prospective studies to further assess its treatment in larger patient cohorts
Naveed et al.[129]	2022	RQ3	Severe refractory thrombocytopenia after PRRT is rare and may result from numerous known causes, including radiation-induced myelotoxicity, myelodysplastic syndrome, and tumour bone marrow (BM) infiltration. We present 3 cases of thrombocytopenia related to persistent or progressive BM metastasis. Although known bone metastasis is not a contraindication to PRRT, thrombocytopenia may be a manifestation of tumour progression and should be considered when making decisions about continuation of therapy.
Ostwal et al.[51]	2021		Capecitabine/Temozolomide (CAPTEM), alone or concurrent with PRRT, has significant activity in grade 2 and grade 3 NENs with dual SSTR and 18FDG expression. A Ki67 index >5% predicts strongly for inferior outcomes and should be further explored as a prognostic cut-off in grade 2 NETs. Early initiation of CAPTEM should be considered in this group of tumours with significant baseline 18FDG

Author	Year	RQ	Authors conclusions
			expression. Both regimens were well tolerated.
Paganelli et al.[62]	2021	RQ1 & RQ3	Long-term follow-up shows that Lu-PRRT is a safe and effective therapy for patients with advanced GI-NET, the most important prognostic factor being tumour burden, hepatic lesions, and age. We believe that ^{177}Lu oxodotreotide should be offered to patients with early-stage disease.
Parghane et al.[52, 69]	2021	RQ1, RQ2, RQ3	Favourable response rates with effective control of symptoms and longer progression free survival and overall survival without high-grade or life threatening toxicities were important observations in NET patients with aggressive, both FDG- and SSTR-avid, metastatic progressive disease. The study results indicate the potential role of "sandwich chemo-PRRT" in future therapeutic algorithms of aggressive, both SSTR- and FDG-positive subset of neuroendocrine tumours.
Parghane et al.[69]	2021	RQ3	In a moderate fraction of GEP-NET patients whose primary tumour was unresectable because of vascular involvement — either without liver metastases or with potentially resectable liver metastases—the unresectable primary tumour became resectable after ^{177}Lu oxodotreotide. This neoadjuvant therapy can be useful in such patients. ^{177}Lu oxodotreotide can be considered safe; it does not have a high incidence of major hematologic or renal toxicity and would likely be helpful in reducing the overall morbidity and mortality associated with surgery or other treatment modalities. There was a favourable imaging response in most patients, who became symptom-free after ^{177}Lu oxodotreotide. The success rate of tumour resectability after PRRT depends on the site of the primary tumour, the presence or absence of regional lymph node involvement, the size of the primary tumour, the size and number of liver metastases in those patients who have them, and the intensity of 18F-FDG uptake in the primary tumour.

Author	Year	RQ	Authors conclusions
Partelli et al.[130]	2018	RQ1 & RQ3	Neoadjuvant peptide receptor radionuclide therapy for resectable or potentially resect able pancreatic neuroendocrine neoplasms in patients with high-risk features of recurrence seems to be beneficial, but well-designed and much larger prospective trials are needed to confirm the safety and the oncologic value of this approach.
Plante et al.[54]	2018	RQ2 & RQ3	Our retrospective analysis suggests that perceived tolerance differ in between therapeutic options and may help physicians to sequence the therapeutic strategy. EORTC QLQ-30 global health status/quality of life and fatigue score demonstrated a significant benefit to everolimus. PRRT had the lowest relative perceived tolerance; none of the nine patients treated by PRRT reported poor perceived tolerance. Patients may be not aware of potential long-term haematological and renal toxicities of PRRT that remain asymptomatic for a long duration of time, in comparison with other side effects such as diarrhoea, vomiting, fatigue, or anorexia, commonly described with cytotoxic chemotherapy or targeted therapies.
Prasad et al.[131]	2020	RQ1 & RQ3	Effectiveness data were encouraging in this selected population, highlighting the potential usefulness and feasibility of lanreotide combined with and after PRRT in patients with GEP NETs. The study also identified challenges associated with evaluating clinical practice in a rare-disease setting and highlighted the need for standardisation of PRRT procedures.
Puscedd u et al.[31]	2022	RQ1	Treatment with upfront PRRT in patients with enteropancreatic neuroendocrine tumours who had experienced disease progression with SSA treatment was associated with significantly improved survival outcomes compared with upfront chemotherapy or targeted therapy. Further research is needed to investigate the correct strategy, timing, and optimal specific sequence of these

Author	Year	RQ	Authors conclusions
			therapeutic options.
Salner et al.[44]	2021	RQ 3	Tumour flare reactions are common with the use of ^{177}Lu oxodotreotide in the management of GEP-NETs. In this series of 12 patients, 2 had flare reactions characterized by bony metastasis causing spine pain and cranial nerve dysfunction due to skull base metastasis. An additional 3 patients had flare reactions due to soft tissue metastasis causing pain due to liver metastasis in one and bowel dysfunction in 2. All flare reactions were manifested in the first of 4 administrations. Management with a short course of corticosteroids and appropriate analgesics was generally successful. Use of such strategy for the 3 subsequent courses was helpful, as was close monitoring of the patient in the week after therapy to determine what interventions might be helpful.
Sitani et al.[64]	2022	RQ1, RQ3	With limited therapeutic options available for progressive NET after initial PRRT and in the absence of high grade toxicity after ^{177}Lu oxodotreotide salvage PRRT, retreatment with PRRT may be considered as a relatively safe therapeutic option for these patients.
Sitani et al.[132]	2021	RQ1, RQ3	The present results demonstrate that ^{177}Lu oxodotreotide improved symptoms and biochemical markers substantially in most of the NET patients, with disease stabilisation on both anatomical and molecular imaging in majority and response in a sizeable fraction. Additionally, the therapeutic protocol with lesser dose per cycle (mean 5.92 GBq/cycle) and prolonged duration (over 5 cycles and 1.5 years) in a metastatic NET setting proved equally efficacious (with superior PFS and OS rates) and relatively better tolerated with minimal toxicity.
Strosberg et al.[30]	2021	RQ1, RQ3	Treatment with 177Lu-Dotatate did not lead to a significant improvement in overall survival versus high-dose long-acting octreotide; however, an arguably clinically relevant difference in median overall survival of 11.7 months with 177Lu-Dotatate was recorded, and was accompanied by a favourable long-term safety profile, in patients with

Author	Year	RQ	Authors conclusions
			advanced, progressive, well-differentiated, grade 1 and grade 2 midgut NETs. Along with the significantly reduced risk of disease progression or death and the associated quality-of-life benefits, these data further support the use of ^{177}Lu-Dotatate in this patient population with disease progression on somatostatin analogues.
SundlÃv et al.[133]	2022	RQ1, RQ3	Individualized treatment with ^{177}Lu oxodotreotide based on renal dosimetry is clearly feasible with low toxicity and promising efficacy, showing the potential to further improve outcome beyond the standard approach, and should be further assessed in randomized trials.
Thang et al.[134]	2018	RQ1, RQ3	RT achieves clinically relevant disease control with acceptable toxicity in G3 NETs.
Thiis-Evensen et al.[135]	2020	RQ1	We found no treatment benefit with regard to time to progression for our patients that experienced objective response compared to those who achieved stable disease.
Vaghaiwalla et al.[136]	2021	RQ1	Patients with unresectable advanced or metastatic pancreatic neuroendocrine tumours may benefit from a full course of peptide receptor radionuclide therapy, whereas other neuroendocrine tumours appear less likely to respond. Large prospective studies are needed to confirm these findings.
van der Zwan et al.[137]	2019	RQ1, RQ3	A cumulative dose of up to 60.5 GBq salvage with ^{177}Lu oxodotreotide is safe and effective in patients with progressive disease (relapse-PD) following PRRT with ^{177}Lu oxodotreotide. Safety appears similar to that of initial PRRT as no higher incidence of acute myeloid leukaemia or myelodysplastic syndrome was observed. No grade III/IV renal toxicity occurred after retreatment.

Author	Year	RQ	Authors conclusions
Veltroni et al.[35]	2020	RQ1	Our study includes the largest series of patients with malignant insulinoma reported to date. The hypoglycaemic syndrome may occur after years in initially non-functioning NETs or be misunderstood with delayed diagnosis of NETs. Surgical treatment and Ki67 ≤10% are prognostic factors associated with better survival. PPRT proved to be effective in the control of hypoglycaemia in majority of cases.
Yadav et al.[138]	2019	RQ1	Our data confirm that ^{177}Lu oxodotreotide-capecitabine therapy is effective in achieving an objective response in 28% and symptomatic response in 43% patients. There was no great advantage of concomitant therapy; however, it could be due to under-powered study. We recommend a large randomized trial to prove or disprove the utility of capecitabine as a radiosensitiser for PRRT in patients with paraganglioma.
Yordanova et al.[53]	2019	RQ1, RQ3	According to different imaging modalities, the combination of PRRT and temozolomide +/− capecitabine led to disease control in 38% to 55% of the progressive NETs after PRRT or chemotherapy alone failed. The overall survival in this extensively pre-treated group of patients was nearly 25 months. The majority of patients did not experience any serious adverse events.
Yordanova et al.[60]	2017	RQ1, RQ3	Therapy with eight or more cycles of ^{177}Lu oxodotreotide was well tolerated and led to a survival benefit in patients with recurrent NET.
Yordanova et	2018	RQ1	SSA may play a significant role in tumour control in patients with NET, who underwent a PRRT, especially as a

Author	Year	RQ	Authors conclusions
al.[139]			maintenance therapy.
Zandee et al.[43]	2019	RQ1, RQ2, RQ3	PRRT with ^{177}Lu oxodotreotide for the treatment of functioning pancreatic NET is safe, but prevention of hormonal crises should be considered. Furthermore, it results in a symptomatic response in a high percentage of patients with a substantial increase of quality of life. Radiological response seems comparable with non-functioning pancreatic NETs.
Zandee et al.[37]	2021	RQ1, 2, 3	PRRT with ^{177}Lu oxodotreotide for symptomatic control of refractory carcinoid syndrome is a viable, safe, and effective option for patients with stable and recently diagnosed advanced midgut NETs.
Zhang et al.[140]	2019	RQ1, RQ3	PRRT was tolerated well, without significant adverse effects, and was efficacious in G3 NETs; the clinical outcome was promising, especially in patients with a Ki-67 index of less than or equal to 55% and even in patients for whom chemotherapy had failed. Baseline 18F-FDG along with SSTR molecular imaging was useful for stratifying G3 NET patients with high uptake on SSTR PET/CT and no or minor 18F-FDG avidity—a mismatch pattern that was associated with a better long-term prognosis.
Zhang-Yin et al.[141]	2021	N/A*	All patients could have been discharged 3 hours after administration according to the criterion EDR-1m <40 µSv/h. Using EDR-1m <25 µSv/h as criterion, an extended hospital stay beyond 3 hours would have been necessary in around one-third of the PRRT treatments and could be anticipated based on creatinine clearance ≤96 mL/min/1.73m2. EDR-1m <25 µSv/h at 180 min during the first PRRT yielded a strong predictive value on the patient's survival at two years, a finding that should be confirmed in future studies.

Key: CRHE: chemoembolisation & radionuclide hepatic embolisation; CKD: chronic kidney disease; FDG: flurodeoxyglucose; NET: neuroendocrine tumour; PFS: progression-free survival; PHD: persistent haematologic dysfunction; PRRT: peptide receptor radionuclide therapy; RQ: review question; SI-NETs: small intestine neuroendocrine tumours; SSR: somatostatin receptor. * relates to public & occupational exposure

Appendix 2

Table A.6. AMSTAR-2 Checklist

AMSTAR 2 checklist item	NNIPH HTA (2018)
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
Did the review authors use a comprehensive literature search strategy?	Yes
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
Did the review authors describe the included studies in adequate detail?	Partial Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
Did the review authors report on the sources of funding for the studies included in the review?	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Not Applicable
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Not Applicable
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Not Applicable
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
Quality outcome	**Critically low**

Key: NNIPH – Norwegian National Institute of Public Health; HTA – Health Technology Assessment; ROB: risk of bias; PICO: Population, Intervention, Comparison, Outcome.

Appendix 3

Evidence to Decision Framework **Desirable Effects** How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	**Overall survival:** From NNIPH HTA (1 RCT at 20 months): Favours intervention, mortality RR 0.52 (95% CI: 0.29 to 0.95) (Low certainty) Observational studies, 3 studies supported this finding. Overall survival possibly between 40 and 70 months. Recent studies (step 2): Studies identified agreed with HTA, only discordant result was final analysis of NETTER-1 trial with no significant improvement in median overall survival (HR = 0.84, 95% CI 0.60–1.17; two-sided p=0.30, 48.0 months for intervention group and 36.3 months for control group). - Authors reported large amount of crossover, with 36% of control patients receiving PRRT, as well as both arms receiving antineoplastic agents. **Progression Free Survival:** From NNIPH HTA (1 RCT at 20 months): 65.2% (95% CI: 50% – 76.8%) in intervention vs 10.8% (95% CI: 3.5% – 23%) in control arm (mean difference 54.4%; 95% CI: 43.1% – 65.7%, HR 0.4, p=0.004). (Moderate certainty) Observational studies: 4 studies, supported the finding from RCT. PFS of between 20 and 50 months In terms of disease progression or death, authors of RCT reported a 79% reduction in risk for the intervention group **Tumour Response rate:** From NNIPH HTA (1 RCT at 20 months): 18% in intervention group had partial (17%) or full (1%) response, compared to 3% in control group. Difference of 15% (95% CI: 7.5% – 22.5%). (Moderate certainty)	

	Observational studies: 4 studies; supported finding from RCT. **Health Related Quality of Life (HRQoL):** From NNIPH HTA (1 observational study, using EORTIC QoL): Improvement in HRQoL, but high degree of uncertainty associated with results. Recent studies (step 2): NETTER 1 using EORTIC QoL, reported time to deterioration in a number of domains was significantly longer with intervention. NETTER 1 also reported a reduction in symptoms such as abdominal pain, diarrhoea and flushing compared to control arm. Other studies identified suggested the intervention improved some symptoms of carcinoid syndrome and could improve QoL.	

Panel discussion:

The panel considered the evidence for the four outcomes listed, both in terms of the magnitude of the effect and the certainty of the evidence. It was suggested that the benefit could be considered 'moderate' for PFS, but for the final analysis of OS and HRQoL the benefit may be considered 'small'. It was also noted that the NETTER-1 RCT was designed around the PFS outcome not overall survival. A judgement of 'varies' was recorded by the EAG for this criteria as the benefit was considered to vary between 'small' and 'moderate' benefit depending on the outcome considered.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	**Ionising radiation dose** From NETTER-1 RCT identified through NNIPH HTA NETTER-1 RCT: patients received 7.4 GBq (200 mCi) of 177Lu-Dotatate four infusions every 8 weeks (cumulative radioactivity, 29.6 GBq [800 mCi]) **Adverse Events:** From NNIPH HTA (1 RCT, 8 observational studies): NETTER-1 RCT noted significantly more adverse events in intervention arm RR 2.8 (95% CI: 2.1 – 3.7) (Low certainty)	**Occupation and public exposure** Lu177: half-life of 6.647 days Emits β-particles & γ-photons β-particles responsible for therapeutic effect

	Risk of haematological toxicity was significantly higher in intervention group (thrombocytopenia (RR = 27.8, 95% CI 3.8 – 200.4), anaemia (RR = 2.6, 95% CI: 1.1 – 6.5), lymphopenia (RR = 9.9, 95% CI: 2.4 – 41.4), and leukopenia (RR = 10.9, 95% CI: 1.43 – 83.0); no significant difference was reported with respect to neutropenia (RR = 6.0, 95% CI: 0.7 – 48.6) (All low certainty)). NETTER-1 RCT: No nephrotoxicity. Other adverse events included significant increase in risk of nausea (RR = 5.0, 95% CI: 2.9 – 8.5), vomiting (RR = 4.7, 95% CI: 2.6 – 8.5), fatigue (RR = 1.6, 95% CI: 1.1 – 2.3), headaches (RR = 3.6, 95% CI: 1.4 – 9.3), alopecia (RR=6.0, 95% CI: 1.4 – 26.0), and a decreased appetite (RR = 2.2 95% CI: 1.1 – 4.6) (Low to moderate certainty). <u>From NNIPH HTA</u> Observational studies, 6 out of 8 reported subacute haematological toxicity associated with the intervention. Estimated incidence of severe (grade 3 and 4) haematological toxicities ranged from 3% to over 11%. Secondary myelodysplastic syndrome (MDS) incidence 1% to 2.4%; leukaemia incidence 0% to 1.1%. Low incidence of grade 3 or higher nephrotoxicity (~0.3%). Variable incidence for lower grade nephrotoxicity (for example 4% to 27% for subacute grade 1). One study suggested 1% developed acute hormonal crisis, but recovered from this. <u>Recent studies (step 2):</u> Final results from NETTER-1 RCT: 2% developed MDS. Other studies have suggested 6.7% risk for MDS/Leukaemia. Studies identified confirmed a finding of limited long-term nephrotoxicity. The final results of the NETTER-1 study reported grade 3 or worse nephrotoxicity, regardless of causality, in 5% intervention group and 4% in the control group. One observational study suggested up to 9% of patients with functional metastatic pancreatic nets developed acute hormonal crisis with intervention. One case series of 12 patients suggested 42% experienced tumour flare.	β-particles: maximum energy of 490keV & limited range of ~2mm in tissue γ-photons: energy of 113keV and keV This means there is a risk of exposure of staff and members of the public. However, this is mitigated when the appropriate radiation protection safeguards are in place. NNIPH report: ^{177}Lu is safe for use on an outpatient basis.

Panel discussion:

The panel considered the evidence for the outcomes listed, both in terms of the magnitude of the effect and the certainty of the evidence. The potential for secondary malignancies secondary to the ionising radiation exposure was discussed. The incidence of myelodysplastic syndrome / leukaemia was noted to be low and clinically acceptable in the context of treatment indication, that is, for adults with unresectable or metastatic progressive GEP-NETs. In terms of the potential for public and occupational exposure it was agreed doses were likely to be very low and that the risks were low provided appropriate radiation protection safeguards are in place. It was noted that the control arm of NETTER-1 received double the dose of octreotide compared to the intervention arm (60mg versus 30mg), and that this higher dose may have had a positive effect on symptom control for the control arm. In clinical practice, management of the acute side effects associated with ^{177}Lu treatment have also been optimised, e.g., acute nausea associated with the amino acid infusion given to protect the kidneys is generally effectively managed by prophylactic antiemetic medications. The low incidence of renal toxicity was also noted. It was noted the haematological toxicity associated with ^{177}Lu is confounded

by the fact that this population may have received previous chemotherapy, so may be more susceptible to haematological toxicity. Haematological toxicity was noted to be predictable and manageable. It was suggested that the harms could be considered as 'small' or even 'trivial' in the context of this particular population – following discussion it was decided that 'small' was the most appropriate judgement for this outcome.

Certainty of the evidence

What is the overall certainty of the evidence of effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence for outcomes is Low or Moderate - Overall the certainty of the evidence is **Low.**	Reasons for certainty of evidence to be marked down included: -Participants of RCT not blinded -Only one study included -Composite outcome -Wide confidence interval

Panel discussion:

No panel discussion around this criteria.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability		

○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		

Panel discussion:

It was suggested that this group of patients may value improvements in HRQoL and PFS over improvements in OS. [177]Lu involves 4 cycles of treatment given at 8-weekly intervals – this contrasts with attending the hospital every two weeks for octreotide treatment. It was felt that from the patient's perspective that [177]Lu might be preferable for this reason. It was suggested that the most appropriate judgement would be 'probably no important uncertainty or variability'. This was agreed upon.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either		

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Risk with usual treatment	**Risk with 177Lu oxodotreotide**			
	Study population				

the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Mortality follow-up: 20 months	230 per 1,000	**120 per 1,000** (67 to 219)	**RR 0.52** (0.29 to 0.95)	229 (1 RCT)	⊕⊕◯◯ Low[a,b]		
	Progression Free Survival (PFS) follow-up: 20 months		MD **54.4 % higher** (43.07 higher to 65.73 higher)	-	229 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]		
	Tumour response rate		MD **15 % more** (7.48 more to 22.52 more)	-	201 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]		
	Adverse Events (all) (AE)	Study population		**RR 2.77** (2.10 to 3.65)	201 (1 RCT)	⊕⊕◯◯ Low[a,c,d]		
		340 per 1,000	**942 per 1,000** (714 to 1,000)					
	Haematotoxic side-effects of all grades (thrombocytopenia)	Study population		**RR 27.75** (3.84 to 200.40)	221 (1 RCT)	⊕⊕◯◯ Low[a,d]		
		9 per 1,000	**252 per 1,000** (35 to 1,000)					
	Haematotoxic side-effects of all grades (anaemia)	Study population		**RR 2.64** (1.07 to 6.50)	221 (1 RCT)	⊕⊕◯◯ Low[a,b]		
		55 per 1,000	**144 per 1,000** (58 to 355)					
	Haematotoxic side-effects of all grades (lymphopenia)	Study population		**RR 9.91** (2.37 to 41.39)	221 (1 RCT)	⊕⊕◯◯ Low[a,d]		
		18 per 1,000	**180 per 1,000** (43 to 753)					
	Nausea	Study population		**RR 4.95** (2.91 to 8.45)	221 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]		
		118 per 1,000	**585 per 1,000** (344 to 999)					
	Vomiting	Study population						

	100 per 1,000	**468 per 1,000** (258 to 849)	**RR 4.68** (2.58 to 8.49)	221 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]	
Abdominal pain	Study population		**RR 0.99** (0.64 to 1.54)	221 (1 RCT)	⊕⊕◯◯ Low[a,b]	
	264 per 1,000	**261 per 1,000** (169 to 406)				
Fatigue	Study population		**RR 1.56** (1.05 to 2.31)	221 (1 RCT)	⊕⊕◯◯ Low[a,b]	
	255 per 1,000	**397 per 1,000** (267 to 588)				

Panel discussion:

A short discussion around whether to judge this criteria as 'favours the intervention' or 'probably favours the intervention' – due to the variability of the benefits and the certainty of the evidence it was decided that 'probably favours the intervention' was the most appropriate judgement.

Recommendation

On the basis of the above discussion, and in the context of this intervention typically being considered a second-line treatment in a cohort of patients that have progressive disease having previously received a variety of other treatments, the MEIR-EAG, on consideration of the balance between the benefits and harms, found that the intervention is probably favoured over the other treatment types considered. The MEIR-EAG have recommended to HIQA that [177]Lu oxodotreotide should be generically justified for the treatment of adults with unresectable and or metastatic GEP-NETs.

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