The effectiveness and cost-effectiveness of everolimus, lanreotide, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression; a systematic review and economic evaluation.

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1 Title of the project

The clinical effectiveness and cost-effectiveness of everolimus, lanreotide, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression; a systematic review and economic evaluation.

2 Name of TAR team and project 'lead'

TAR Team Peninsula Technology Assessment Group (PenTAG), Evidence Synthesis and Modelling for Health Improvement (ESMI), University of Exeter Medical School

3 Name **Marcela Haasova**

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4 Plain English Summary

The aim of this project is to review the clinical effectiveness and cost effectiveness of everolimus, lanreotide, lutetium-177 DOTATATE, and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression in a multiple technology appraisal. The medical benefits and risks associated with these treatments will be assessed and compared across the treatments and against available standard treatments.

5 Decision problem

5.1 Purpose of the decision to be made

This project will review and appraise the evidence presented to the National Institute of Health and Care Excellence (NICE) on the clinical effectiveness and cost-effectiveness of everolimus, lanreotide, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression.[1]

5.2 Background

Neuroendocrine tumours constitute a heterogeneous group of rare tumours. These tumours develop from neuroendocrine cells of the pancreas, gastrointestinal tissue (from diffuse neuroendocrine cells distributed throughout the gut), the lung (neuroendocrine cells within the respiratory epithelium) and thyroid.[1] Data from the UK, Sweden and Switzerland suggest that the incidence of neuroendocrine tumours of the gastrointestinal tissue is between 2 and 3 per 100,000 of the population per year; using USA datasets the incidence of pancreatic neuroendocrine tumours was estimated to be less than 0.2 per 100,000 of the population per year.[2]

Neuroendocrine tumours of the gastrointestinal tract are classified according to their point of origin, into tumours of the foregut (stomach, gall bladder, and proximal duodenum), mid-gut (distal duodenum, jejunum, ileum, caecum and appendix, ascending, and right two thirds of transverse colon) and hindgut (left one third of transverse colon, and rectum). Pancreatic neuroendocrine tumours (also known as pancreatic islet cells tumours) develop from pancreatic islet cells. Neuroendocrine tumours of the lung are classified according to their histology and clinical outcome into typical carcinoid lung tumour and atypical carcinoid lung tumour.[1] In England and Wales, the 5-year survival rates for stomach, small intestine, pancreatic and colon well-differentiated tumours were 52%, 59%, 39% and 65%, respectively.[2]

The current widely used WHO 2010 tumours classifications is based on histology (as measured by Ki-67index or mitotic count) and differentiate neuroendocrine tumours into grade 1 (low grade), grade 2 (intermediate grade) and grade 3 tumours (high grade; Table

1).[3] The 5-year survival rates for grades 1, 2 and 3 tumours reported by a German study are 96%, 73% and 28%, respectively.[4]

Most neuroendocrine tumours are 'well differentiated' (mainly grades 1 and 2) with a smaller proportion being 'poorly differentiated tumours' (mainly grade 3). Differentiation relates to how well/little the tumour looks like the normal tissue/tissue of origin. Well-differentiated cancer cells look more like normal cells and tend to grow and spread more slowly than poorly differentiated cells.

Based on the site-specific tumour size, lymph node status, and distant metastasis status, the TNM (tumour-node-metastasis) classification defines the stage of the tumour in relation to the extent of tumour spread (stages 0-IV). Advanced neuroendocrine tumours fall within stages III (locally advanced and/or has spread to regional lymph nodes) and IV (distant metastasis has occurred).[1] The 5-year survival rate for stages III and IV reported by a German study ranged from 55% to 79%.[4]

Table 1 WHO 2010 Classification of Tumours of the Digestive System[3]

Type	Grade	Ki-67 index[a,b]	Mitotic Count [a]
Neuroendocrine tumours (Carcinoids)	**Grade 1**	≤2%	<2 mitoses per 10 HPF
Neuroendocrine tumours	**Grade 2**	3-20%	2-20 mitoses per 10 HPF
Neuroendocrine carcinoma	**Grade 3**	>20%	>20 mitoses per 10 HPF

Key: HPF, high-power field of 2 mm^2; WHO, World Health Organisation.

Notes: a, if the mitotic count and Ki-67 index are both used and differ, the higher of the two is used; b, Ki-67 index: % of 500–2000 cells in "hot spot areas" stained positive for MIB-1 antibody.

The WHO 2010 classification[3] superseded the WHO 2000 classification[5] that divided neuroendocrine tumours into well-differentiated endocrine tumours, well-differentiated endocrine carcinoma, and poorly differentiated endocrine carcinoma. However, the previous WHO 2000 classification[5] do not directly match to the current WHO 2010 Grade 1-3 classification.[3]

Most neuroendocrine tumours express somatostatin receptors and are somatostatin receptor positive (SSR+); somatostatin receptors are present in 75-95% of neuroendocrine tumours.[2] Tumours not expressing somatostatin receptors are somatostatin receptor negative (SSR-). A tumour that is releasing hormones is identified as a functioning tumour. For example pancreatic tumours releasing gastrin are known as gastrinomas, while carcinoid syndrome is caused by the gastrointestinal tumours secreting serotonin. The hormone release will often cause symptoms which frequently need a specific treatment (tumours can be divided into symptomatic and non-symptomatic).[1] Tumours that are not releasing hormones are known as non-functioning tumours. However, non-functional tumours can also cause non-specific symptoms such as intestinal or bronchial obstruction and abdominal pain.[1]

Surgery is the only curative treatment for neuroendocrine tumours. For people who are unable to have surgery, or where surgery has been unsuccessful or curative surgery was not an option because of the advanced stage of the disease, the choice of treatment depends

on the symptoms, stage of disease, histological features of the tumour, and the performance status of the patient.[1]

5.3 Interventions

- **Everolimus (Afinitor, Novartis)** is an oral inhibitor of the mammalian target of rapamycin (mTOR) protein, a central regulator of tumour cell division and blood vessel growth in cancer cells. It has a marketing authorisation in the UK for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease. It does not currently have a marketing authorisation in the UK for the treatment of advanced neuroendocrine tumours of gastrointestinal or lung origin. It has been studied in clinical trials compared with placebo in adults with advanced unresectable or metastatic neuroendocrine tumours of gastrointestinal or lung origin.[1]
- **Lanreotide (Somatuline Autogel, Ipsen)** is an inhibitor of various endocrine, neuroendocrine, exocrine and paracrine functions. It is an analogue of natural somatostatin which binds to human somatostatin receptors which are present in the majority (75-95%) of neuroendocrine tumours. Lanreotide is administered by deep sub-cutaneous injection. It has a marketing authorisation in the UK for treating grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of mid-gut or pancreatic or unknown origin where hindgut sites of origin have been excluded in adult patients with unresectable locally advanced or metastatic disease. The exact mechanism of action of lanreotide in delaying progression of gastroenteropancreatic neuroendocrine tumours is not well understood.[1]
- **Lutetium-177 DOTATATE (Lutathera, Imaging Equipment)** is a radio-labelled analogue of somatostatin designed to deliver radiation to the cells. It kills tumour cells by binding to a specific type of somatostatin receptor, called sst2 receptors, which are overexpressed by the malignant cells. It does not currently have marketing authorisation in the UK for any indication. It has been studied in a clinical trial in people with inoperable, locally advanced or metastatic somatostatin receptor positive mid-gut neuroendocrine tumours (Ki67 index ≤ 20%) with or without disease progression compared with octreotide long acting release (LAR). It has also been studied in a single arm study in people with gastrointestinal or pancreatic neuroendocrine tumours with or without disease progression. Lutetium-177 DOTATATE is administered by intravenous infusion.[1]
- **Sunitinib (Sutent, Pfizer)** is a protein kinase inhibitor that works by preventing tumour proliferation and inhibiting blood vessel growth, leading to cancer cell death. It has a marketing authorisation for treating unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults. Sunitinib is administered orally.[1]

5.4 Place of the interventions in the treatment pathway

- **Everolimus** is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.[7]

Everolimus was removed from the Cancer Drug Fund on 12th March 2015; it was available for the treatment of progressive unresectable or metastatic well differentiated neuroendocrine tumour of the pancreas.

- **Lanreotide** is indicated for the treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours of mid-gut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease. Lanreotide is also indicated for the treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours. Lanreotide is not recommended for use in children and adolescents due to lack of data on safety and efficacy.[8]
- **Lutetium-177 DOTATATE** is not currently licensed in the EU for any indication. Lutetium-177 is currently in phase III clinical trials comparing its effect on progression free survival against treatment with long-acting release formulation of octreotide.[1]

  Lutetium-177 was delisted from the Cancer Drug fund on 4th November 2015; it was available for treatment of advanced neuro-endocrine tumours after Sunitinib/chemotherapy, for mid-gut carcinoid, after octreotide/somatostatin therapies.
- **Sunitinib** is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults; limited experience of sunitinib as first-line treatment was noted. The safety and efficacy of sunitinib in patients below 18 years of age have not been established.[9]

  In 2011, the Scottish Medicines Consortium advised (SMC Drug ID 698/11) that Sunitinib is accepted for use within NHS Scotland for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.

  Sunitinib is currently available on the Cancer Drug Fund for the treatment of pancreatic neuroendocrine carcinomas where all the following criteria are met:

  1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy;
  2. biopsy proven well differentiated pancreatic neuroendocrine tumour;
  3. a) 1st line indication, OR, b) 2nd line indication, OR, c) 3rd line indication; and
  4. no previous vascular endothelial growth factor targeted therapy.

  The NICE multiple technology appraisal will determine whether sunitinib should be recommended for routine commissioning, not recommended, or whether its use within the Cancer Drugs Fund should continue.

5.5 Comparators

The interventions should be compared with each other, where appropriate, and with:

- octreotide (long-acting release formulation);
- interferon alpha;

- chemotherapy regimens (including but not restricted to combinations of streptozocin, 5-FU, doxorubicin, temozolomide, capecitabine); and
- best supportive care.[1]

5.6 Population and relevant sub-groups

The population of interest to the current appraisal is people with progressive unresectable or metastatic neuroendocrine tumours. All tumour locations as covered by the existing or anticipated marketing authorisations of the individual interventions will be considered.[1]

In addition, if evidence allows the following subgroups will be considered:

- location of tumour;
- grade/degree of differentiation;
- stage of tumour;
- secretory profile; and
- number of previous treatments.[1]

5.7 Outcomes to be addressed

Evidence on the following outcomes will be considered:

- overall survival;
- progression-free survival;
- response rates;
- symptom control;
- adverse effects of treatment; and
- health-related quality of life (HRQL).[1]

5.8 Other considerations

Some of the drugs being appraised do not currently have an existing marketing authorisation at the time of developing the protocol (i.e. lutetium-177 DOTATATE, everolimus for tumours of gastrointestinal or lung origin). The anticipated timings for regulatory approval for these drugs are confidential and cannot be reported in the protocol.

This technology appraisal only considers lanreotide for the treatment of unresectable or metastatic gastroenteropancreatic neuroendocrine tumours with disease progression; the treatment of unresectable or metastatic neuroendocrine tumours without disease progression is outside the scope of this appraisal and is subject to ongoing NICE appraisal (ID961).[1]

Finally, this technology appraisal only considers lutetium-177 for the treatment of unresectable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours with disease progression; the treatment of unresectable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours without disease progression is outside the scope of this appraisal and is subject to ongoing NICE appraisal (ID857).[1]

6 Report methods for synthesis of evidence of clinical effectiveness

A systematic review of clinical effectiveness will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.[10]

6.1 Search strategy

The searches will be developed by an information specialist. Searches will be run from database inception.

The search strategy will comprise the following main elements:

- Searching of bibliographic and ongoing trials databases; and
- scrutiny of bibliographies of retrieved papers.

The following electronic databases will be searched: MEDLINE (Ovid); MEDLINE-in-Process (Ovid); EMBASE (Ovid); CENTRAL (The Cochrane Library, Wiley Interface), Web of Science (including conference proceedings citation index; Thomson Reuters).

The following trials registries will be searched:

- Current Controlled Trials;
- ClinicalTrials.gov;
- FDA website; and
- EMA website.

The following websites will be searched for conference proceedings:

- The European Neuroendocrine Tumour Society (http://www.enets.org/); and
- The UK and Ireland Neuroendocrine Tumour Society (http://www.ukinets.org/).

Studies included on full-text will be forwards (using Web of Science) and backwards citation chased (i.e. manually scanning the each study's reference list).

In addition, studies that are included in the manufacturers' submissions and that meet our inclusion criteria will also be considered for inclusion in the review.

All references will be exported into Endnote X7 (Thomson Reuters) where automatic and manual de-duplication will be performed.

6.2 Study selection and inclusion and exclusion criteria

Studies retrieved from the searches will be selected for inclusion through a two-stage process according to the inclusion/exclusion criteria specified in Table 2. First, abstracts and titles returned by the search strategy will be screened for inclusion independently by two researchers. Disagreements will be resolved by discussion, with involvement of a third reviewer when necessary. Full texts of identified studies will be obtained and screened in the same way. At each step studies which do not satisfy those criteria will be excluded;

abstract-only studies will be included provided sufficient methodological details are reported to allow critical appraisal of study.

The review of clinical effectiveness will include any RCT reporting at least one of the outcomes of interest. However, if any outcomes of interest are lacking RCT evidence or if the RCTs do not provide an adequate length of follow-up, we will extend our inclusion criteria to non-randomised comparative trials.

Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of the results to be undertaken. Systematic reviews and clinical guidelines will be included as sources of references for finding further RCTs and to compare with our systematic review.

For the purpose of this review, a systematic review will be defined as one that has:

- a focused research question;
- explicit search criteria that are available to review, either in the document or on application;
- explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest;
- a critical appraisal of included studies, including consideration of internal and external validity of the research; and
- a synthesis of the included evidence, whether narrative or quantitative.

Table 2 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	People with progressed unresectable or metastatic neuroendocrine tumours; according to the specific locations covered by the existing and anticipated marketing authorisations of the interventions.	Children.
Interventions	1. Everolimus (Afinitor®, Novartis) for the treatment of NETs of gastrointestinal, pancreatic or lung origin. 2. Lanreotide (Somatuline Autogel ®, Ipsen Ltd) for the treatment of NETs of mid-gut, pancreatic or unknown origin (where hindgut sites are excluded). 3. Lutetium-177 DOTATATE (Lutathera, Imagining Equipment) for the treatment of NETs of gastrointestinal or pancreatic origin. **4.** Sunitinib (Sutent; Pfizer Ltd) for the treatment of NETs of pancreatic origin.	1. Votubia®, Novartis; Certican®, Novartis; Zortress (USA) 2. Lanreotide (Somatuline LA ®, Ipsen Ltd)
Comparators	The technologies listed above will be compared with each other, where appropriate, octreotide (Sandostatin LAR®, Novartis), interferon alpha, chemotherapy regimens, and best supportive care.	Ablation therapy, radiotherapy.
Outcomes	Overall survival, progression free survival, response rates, symptom control, adverse events and HRQL.	
Design	RCTs	

Key: HRQL, health-related quality of life; NETs, neuroendocrine tumours**;** RCTs, randomised clinical trials.

6.3 Data extraction strategy

Included full papers will be split between two reviewers for the purposes of data extraction using a standardised data specification form, and checked independently by another. Information extracted and tabulated will include details of the study's design and methodology, baseline characteristics of participants and results including any adverse events if reported. Where there is incomplete information on key data, we will attempt to contact the study's authors to gain further details. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary. Where multiple publications of the same study are identified, data will be extracted and reported as a single study.

6.4 Quality assessment strategy

The methodological quality of each included study will be assessed by one reviewer and checked by a second reviewer, using criteria based on those proposed by the NHS Centre for Reviews and Dissemination for RCTs (Table 3).[10]

Table 3 Quality assessment

Treatment allocation	1. Was the assignment to the treatment groups really random?
	2. Was treatment allocation concealed?
Similarity of groups	3. Were the groups similar at baseline in terms of prognostic factors?
Implementation of masking	4. Were the care providers blinded to the treatment allocation?
	5. Were the outcome assessors blinded to the treatment allocation?
	6. Were the participants blinded to the treatment allocation?
Completeness of trial	7. Were all a priori outcomes reported?
	8. Were complete data reported, e.g. was attrition and exclusion (including reasons) reported for all outcomes?
	9. Did the analyses include an ITT analysis?
Generalisability	10. Are there any specific limitations which might limit the applicability of this study's findings to the current NHS in England?

Key: ITT, intention-to-treat; NHS, National Health Service
Source: Centre for Reviews and Dissemination (University of York), 2009[10]

6.5 Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. If appropriate (i.e., if a number of studies which report data relating to a given outcome are comparable in terms of key features such as their design, populations, and interventions), meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention-to-treat analyses.

Where appropriate, meta-analysis will be carried out using STATA and/or WinBUGS software, with the use of fixed and/or random-effects appropriate to the assembled datasets. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for

homogeneity and the I^2 statistic. In addition, if data allows, a network meta-analysis will be considered.

If evidence allows, the subgroups defined in 5.6 will be considered in the analyses.

We will investigate the likelihood of publication bias (using funnel plots if there are sufficient included studies) and other reporting bias as recommended by the Cochrane Handbook.[11]

7 Report methods for synthesising evidence of cost-effectiveness

A review of published cost-effectiveness studies will be undertaken.

7.1 Review of economic studies relevant to the decision problem

The aims of the review of economic studies are to:

- Gain insights into the key drivers of cost-effectiveness in this disease area;
- get an overview of the alternative modelling approaches that have been adopted in this disease and treatment area; and
- provide a summary of the findings of previous relevant cost-utility, cost-effectiveness, and cost-benefit studies generalisable to the UK.

7.1.1 Search strategy

The searches will be developed by an information specialist. Search filters will be used to limit the searches to economic or health utilities studies as appropriate. Searches will be run from database inception.

The search strategy will comprise the following main elements:

- Searching of bibliographic and ongoing trials databases; and
- scrutiny of bibliographies of retrieved papers.

The following databases will be searched for economic studies: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); NHS EED (via Cochrane Library); EconLit (EBSCO) and Web of Science (Thomson Reuters).

A supplementary search for health utilities will be run in the following databases: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); PsycINFO (Ovid); Web of Science (Thomson Reuters); and ScHARR Health Utilities Database.

In addition, studies that are included in the company submissions and that meet our inclusion criteria will also be considered for inclusion in the review.

All references will be exported into Endnote X7 (Thomson Reuters) where automatic and manual de-duplication will be performed.

7.1.2 Study selection and inclusion and exclusion criteria

The inclusion and exclusion criteria for the systematic review of economic evaluations will be identical to those for the systematic review of clinical effectiveness (Table 2), except:

- Non-randomised studies will be included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies).
- Full cost-effectiveness analyses, cost–utility analyses, cost–benefit analyses and cost–consequences analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be calculated from the published data.)
- Studies that measure only costs but not health benefits will be excluded except for stand alone cost analyses from the perspective of the UK NHS.

Based on the above inclusion/exclusion criteria, study selection will be made by two reviewers.

7.1.3 Quality assessment strategy

The quality of identified cost–utility analyses will be assessed using the checklist developed by Evers et al. (2005)[12] by one reviewer. Where studies are based on decision models they will be further quality assessed using the checklist developed by Philips et al. (2004; 2006).[13, 14]

7.1.4 Data synthesis

Economic studies will be summarised and synthesised using tabulated data and narrative synthesis.

7.2 Economic Modelling

A new cost-effectiveness analysis will be carried out from the perspective of the UK NHS and personal social services (PSS) using a decision analytic model. The aims of the economic modelling are to:

- Estimate the base case lifetime incremental QALYs and incremental costs of the defined comparators according to NICE reference case methods (or with only limited deviations from NICE reference case methods due to deficiencies in available data), and assess the cost-effectiveness of the various interventions in the NHS;
- describe and explore the impact of structural and parameter uncertainty on the estimates of cost-effectiveness; and
- compare the cost-utility estimates between the company's economic analyses and those by us, the assessment group.

The evaluation will be constrained by available evidence. The evaluation will produce estimates of incremental cost per QALY gained (see 7.2.1 for more details).

Model structure will be determined on the basis of available research evidence and clinical expert opinion on the health states that drive costs, mortality and health related quality of life outcomes. The model will be implemented in Microsoft Excel 2013. Depending on the evidence and expert opinion a single model structure or multiple model structures will be developed. We will draw on the expertise of our two clinical experts: Consultant Medical Oncologist Dr Mark Napier from the Royal Devon Hospital in Exeter and Consultant Clinical Oncologist Dr David Sherriff from the Derriford Hospital in Plymouth.

The sources of parameter values that determine the effectiveness of the interventions being compared will be obtained from our own systematic review of clinical effectiveness or other relevant research literature. If required parameters are not available from good quality published studies in the relevant patient group, we may use data from the company submissions to NICE or from other unpublished data, or where no clinical data are available, from expert opinion.

The resource use associated with different health states or clinical events will be obtained or estimated either from trial data, company submissions, other published sources, or – where published sources are unavailable – relevant expert contacts or NHS Trusts. Unit cost data will be identified from national NHS and PSS reference cost databases for the most recent year, or, where these are not relevant, extracted from published work and/or company submissions to NICE. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts.

Analysis of uncertainty will focus on the effect of varying parameters on the estimate of incremental cost per QALY gained or, if this estimate cannot be obtained, on the alternative primary measure used to synthesise cost and benefits. Uncertainty will be explored through one way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). In addition to the probabilistic mean ICER estimate, the outputs of PSA will be presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves or cost-effectiveness acceptability frontiers if more than one comparator is present.

ICERs estimated from company models will be compared with the respective ICERs from our model, and reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

7.2.1 Methods for measuring and valuing health effects

Ideally, measures of health-related quality of life (HRQL) should be obtained directly from patients. The EQ-5D will be the preferred measure of HRQOL for the purposes of estimating QALYs. [15] In the absence of reliable EQ-5D profile data from relevant trials or patient groups, the use of alternative quality of life classification systems for health states will be informed by the NICE Guide to the methods of technology appraisal (2013).[15]

The value of patients' HRQOL outcomes, that is, utilities, should be based on public preferences for health profiles elicited from a representative sample of the UK population using a choice-based method. [15] In selecting utility estimates for the AG analyses we will, therefore, prefer those derived from UK population valuations over non-UK population valuations, and representative samples over samples not representative of the general public. Non-UK population valuation will only be considered in the absence of valuations from UK ones.

7.2.2 Time horizon, perspective and discounting

The time horizon of our analysis will be sufficiently long to reflect any differences in costs and outcomes between the technologies being compared. In principle, it may cover the patient's lifetime but shorter lengths may be adopted to reflect the state of the evidence base on long-term treatment effects and disease course in this area.

The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%.[15]

8 Handling the company submission(s)

All data submitted by the companies will be considered if received by NICE no later than 5pm on 13th September 2016. Data arriving after this date may not be considered.

The company submissions will be:

- Critically appraised for integrity and quality of evidence;
- used as a source of data, to identify studies not located by the searches and that meet the review inclusion criteria; and
- used to compare the results of analyses based on any submitted company model(s) with our independent economic assessment.

Any economic evaluations included in the company submission will be assessed against the NICE Guide to the methods of technology appraisal[15] and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. We will compare the structure, parameter values and results between the company models and our model.

Tabulated summaries and technical commentaries on the economic models used in the company submissions will be provided. This will not be a full critique as for a single technology appraisal but will be used to reflect on the results from the PenTAG model and to discuss any differences.

Any 'commercial in confidence' data provided by companies, and specified as such, will be highlighted in blue and underlined in our assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by companies, and specified as such, will be highlighted in yellow and underlined in our assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

9 Details of TAR team

Name	Institution	Expertise
Chris Cooper	PenTAG, ESMI, University of Exeter Medical School	Information specialist.
Marcela Haasova	PenTAG, ESMI, University of Exeter Medical School	Project management and systematic reviewing.
Martin Hoyle	PenTAG, ESMI, University of Exeter Medical School	Economic modelling and economic evaluation. Project director and guarantor.
Stefano Lucherini	University of York, Department for Economics and Related Studies.	Health economist.
Ruben Mujica-Mota	PenTAG, ESMI, University of Exeter Medical School	Health economics, cost effectiveness review and economic evaluation.
Mark Napier	Royal Devon Hospital, Exeter	Consultant Medical Oncologist.
David Sherriff	Derriford Hospital, Plymouth	Consultant Clinical Oncologist.
Irina Tikhonova	PenTAG, ESMI, University of Exeter Medical School	Economic modelling and economic evaluation.
Joanna Varley-Campbell	PenTAG, ESMI, University of Exeter Medical School	Systematic reviewing.

Key: ESMI, Evidence Synthesis and Modelling for Health Improvement; PenTAG, Peninsula Technology Assessment Group.

Other PenTAG resources: Depending on the agreed scope of work we will draw on other researchers from PenTAG as required.

9.1 About PenTAG

The Peninsula Technology Assessment Group (PenTAG) is part of the University of Exeter Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme, systematic reviews and economic analyses for the NICE Centre for Public Health Excellence, as well as for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Institute of Health Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

Recent health technology assessment projects include:

- The effectiveness and cost-effectiveness of immunosuppressive therapy for kidney transplantation in children adolescents: a systematic review and economic model (in progress).
- The effectiveness and cost-effectiveness of immunosuppressive therapy for kidney transplantation in adults: a systematic review and economic model (in progress).
- The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142): a systematic review and economic model (2014).
- Bosutinib for previously-treated chronic myeloid leukaemia: a single technology appraisal (2013).
- A systematic review and economic evaluation of intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer (2013).
- Dasatinib and Nilotinib for the 1st line treatment of chronic phase chronic myeloid Leukaemia (CML): a systematic review and economic model (2012).
- Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate: a single technology appraisal (2011).
- The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model (2011).
- Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma: a single technology appraisal (2011).
- Bevacizumab, Cetuximab, and Panitumumab for in colorectal cancer (metastatic) after failure of 1st line chemotherapy: a systematic review and economic model (2010).
- Ofatumumab (Arzerra®) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab: a single technology appraisal (2010).
- The clinical and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours: a single technology appraisal (2009).
- The clinical- and cost effectiveness of lenalidomide for multiple myeloma in people who have received at least one prior therapy: a single technology appraisal (2009).
- The Effectiveness and Cost-Effectiveness of Methods of Storing Donated Kidneys from deceased donors: A Systematic Review and Economic Model (2009).
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10 Competing interests of authors

None.

11 Timetables

Action	Expected due date
Draft protocol	11/05/2016
Final protocol	02/06/2016
Company submissions from NICE	13/09/2016
Progress report due	27/09/2016
Submit draft report to NICE	22/11/2016
Submit final report to NICE	16/12/2016
1st committee meeting	28/02/2017
2nd committee meeting	26/04/2017

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Appendix 1. Draft search strategy

Sample Clinical effectiveness

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Host: OVID

Data parameters: 1946 to Present

Date searched: Thursday May 19th 2016

Searcher: CC

Hits: 1334

#	Searches	Results
1	exp Neuroendocrine Tumors/	146579
2	Carcinoma, Neuroendocrine/	2939
3	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	46552
4	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	52214
5	(((low$ or intermediate) adj3 grade) or ("grade 1" or "grade 2")).ti,ab,kw.	70454
6	1 or 2 or 3 or 4 or 5	292693

7	(everolimus or afinitor or affinitor or VOTUBIA or Zortress or CERTICAN or xience or RAD001 or "RAD 001" or SDZ RAD or SDZ-RAD or SDZRAD or 159351-69-6).ti,ab,kw. or Everolimus/	4765
8	(Lanreotide or Somatuline or ITM-014 or 108736-35-2).ti,ab,kw.	701
9	(Lutetium-177 DOTATATE or lutecium or Lutetium 177 or Lutetium-177 or Lutetium177 or 177LU or 177 LU or Lu177 or LU 177 or Lutathera or 14265-75-9).ti,ab,kw.	969
10	(Sunitinib or sutent or SU011248 or "SU 011248" or SU11248 or SU 11248 or su011248 or su010398 or "su 010398" or su010398 or pha 290904oad or pha290904oad or 557795-19-4).ti,ab,kw.	4011
11	7 or 8 or 9 or 10	9910
12	6 and 11	1334

Sample Cost-effectiveness

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Host: OVID

Data parameters: 1946 to Present

Date searched: Thursday May 19th 2016

Searcher: CC

Hits: 123

#	Searches	Results
1	exp Neuroendocrine Tumors/	146579
2	Carcinoma, Neuroendocrine/	2939
3	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	46552
4	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	52214
5	(((low$ or intermediate) adj3 grade) or ("grade 1" or "grade 2")).ti,ab,kw.	70454
6	1 or 2 or 3 or 4 or 5	292693
7	(everolimus or afinitor or affinitor or VOTUBIA or Zortress or CERTICAN or xience or RAD001 or "RAD 001" or SDZ RAD or SDZ-RAD or SDZRAD or 159351-69-6).ti,ab,kw. or Everolimus/	4765
8	(Lanreotide or Somatuline or ITM-014 or 108736-35-2).ti,ab,kw.	701
9	(Lutetium-177 DOTATATE or lutecium or Lutetium 177 or Lutetium-177 or Lutetium177 or 177LU or 177 LU or Lu177 or LU 177 or Lutathera or 14265-75-9).ti,ab,kw.	969
10	(Sunitinib or sutent or SU011248 or "SU 011248" or SU11248 or SU 11248 or	4011

	su011248 or su010398 or "su 010398" or su010398 or pha 2909040ad or pha2909040ad or 557795-19-4).ti,ab,kw.	
11	7 or 8 or 9 or 10	9910
12	exp Economics/	526611
13	ec.fs.	363988
14	economics, medical/	8869
15	Economics, Nursing/	3937
16	Economics, Pharmaceutical/	2619
17	Economics, Hospital/	10680
18	(economic* or price or prices or pricing or priced or discount or discounts or discounted or discounting or ration* or expenditure or expenditures or budget* or afford* or pharmacoeconomic or pharmaco-economic*).tw.	502094
19	(cba or cea or cua).ti,ab.	29189
20	exp "Fees and Charges"/	28197
21	(fee or fees or charge* or preference*).tw.	304749
22	(fiscal or funding or financial or finance).tw.	102276
23	exp "Costs and Cost Analysis"/	197689
24	exp Health Care Costs/	52041
25	cost*.tw.	433649
26	exp decision support techniques/	66124
27	exp Models, Economic/	11688
28	exp Statistical Model/	314512
29	markov*.tw.	17327
30	markov chains/	11224
31	monte carlo.tw.	36521
32	monte carlo method/	22617
33	(decision adj2 (tree* or analy* or model*)).tw.	15053
34	(survival adj3 analys*).tw.	34011
35	"Deductibles and Coinsurance"/	1525
36	exp Health expenditures/	17233
37	uncertain*.tw.	118654
38	uncertainty/	8052
39	(quality adj3 life).tw.	191145
40	quality of life/	137192
41	value of life/	5500
42	Quality-adjusted life years/	8422
43	(qol* or qoly or qolys or hrqol* or qaly or qalys or qale or qales).tw.	41092
44	(sensitivity analys* or discrete event or "willingness to pay" or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc*).tw.	28468

45	utilit*.tw.	147802
46	valu*.tw.	1601201
47	exp hospitalization/	181928
48	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47	3893099
49	6 and 11 and 48	299