National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Everolimus, lanreotide, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression

Response to consultee and commentator comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultees	Comments [sic]	Action
Appropriateness	Imaging Equipment	Yes this topic is appropriate for NICE appraisal as there are limited treatment options for patients with this rare disease. Over the past three years, there has been a high level of national and international support for Lu-177 DOTATATE. This is demonstrated by the endorsement of Lu-177 DOTATATE as a therapeutic option by the European Neuroendocrine Tumour Society (ENETS), the British Society of Gastroenterology and the European Society for Medical Oncology (ESMO) in their treatment guidelines (Öberg et al. 2012, Pavel et al. 2016, Ramage et al. 2012). [redacted]	Comments noted.
	Ipsen	The topic is appropriate for NICE appraisal.	Comment noted.

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	Novartis	The topic is highly appropriate given that neuroendocrine tumours (NETs) are rare cancers that have not been previously assessed by NICE. There is urgency for the institute to review this topic to ensure that patients receive access to effective medicines in an area where there is a clear unmet clinical need. SOMATOSTATIN ANALOGUES We believe that it is not appropriate to appraise the somatostatin analogues (lanreotide Autogel and octreotide-LAR) as part of this MTA (ID 858) or STA (ID 961). Both lanreotide Autogel and octreotide LAR have been licensed since 2001 and 1998 respectively and are now considered the standard of care in NETs as a first-line therapy[1] Additionally; both analogues are available in the UK with no access issues. We believe that it is not an efficient use of NICE's resources to appraise treatments that are now established first line therapies and have been so for almost two decades. We therefore propose that NICE do not assess the somatostatin analogues and remove them from this MTA. If NICE do wish to appraise the somatostatin analogues, we would recommend that **both are assessed as interventions.** It should be noted that: 1. BSC defined today may not reflect the standard of care that was in place before the introduction of the first long acting analogue (octreotide- LAR) in 1998. It should also be noted that the current definition of BSC may vary between treating Centres of Excellence. 2. Although octreotide-LAR & lanreotide Autogel are used to treat NETs in current clinical practice; the patient populations in the respective trials (PROMID[2] and CLARINET[3]) are not comparable. PROMID recruited functioning and non-functioning gastrointestinal (GI) NET patients with progressive disease. CLARINET recruited non-functioning GI and pancreatic NET patients with clinically confirmed stable disease. Therefore a clinically meaningful indirect comparison cannot be made.	Comment noted. We acknowledge that lanreotide and octreotide have been licensed for a long time. However, the anti-tumour indication for lanreotide (which is the indication being considered in this appraisal) is a newly licensed indication. Consultees did not discuss the inclusion of octreotide as an intervention for this MTA for progressed disease during the first consultation and the scoping workshop for this MTA. However, they discussed whether it should be included as an intervention in the

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			upcoming STA of lanreotide for non-progressive disease. Given that there was no clear agreement among the consultees on whether to include octreotide as an intervention in the STA for non-progressive disease and in the absence of any comment on its inclusion for the progressed disease; a referral was not sought for octreotide as an intervention. However, octreotide has been included as a comparator in the final scope in line with the comments from Consultees during the post-referral consultation.

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		TARGETED THERAPIES It should be noted that GI, Lung and pancreatic NETs are distinct in clinical practice. The diseases present differently, are treated differently and it is not uncommon that they are managed by different clinicians in the same institutions. We disagree with the inclusion of everolimus for the [redacted] in the draft scope for this MTA. There is an unmet medical need for patients with Lung NETs, and patients with GI NETs who have progressed following current therapy, since there are no currently licensed treatments available for either of these populations. The RADIANT 4 trial (a randomised, double-blind placebo controlled phase III trial of everolimus in adults with advanced progressive well-differentiated, non-functional NETs of lung or gastrointestinal origin) showed superior progression free survival compared to best supportive care (hazard ratio 0.48 95% CI 0.35 – 0.67)[4] While the institute has decided an MTA in NETs is necessary, the inclusion of everolimus risks an avoidable delay for patients to the availability of an effective and innovative targeted cancer therapy. Everolimus is the only targeted therapy to show efficacy in the lung and GI NET patient populations. As per the principles laid out in the new reimbursement process of the cancer drug fund presented to the NHSE Board on 25th February 2016, all new licensed cancer drugs and indications should be referred to NICE for appraisal. This faster NICE process should enable a draft recommendation before marketing authorisation and final guidance within 90 days of marketing authorisation. This process should apply to topics that are eligible for a NICE appraisal after 1st April 2016 We request that the institute considers reviewing the new indication (anticipated date of CHMP positive opinion [redacted] through the STA process, under the new reimbursement process. Please note that FDA has already approved the use of everolimus in this indication (February 2016).	Please note that this topic was referred for appraisal before April 2016, when the new process for cancer topics came into place. However, NICE is still committed (as we were previously) to publishing guidance as quickly as possible following marketing authorisation, whilst also balancing the needs and efficiency of the TA work programme and what the NHS requires from NICE in this area. Removing everolimus from the MTA at this point, will not necessarily result in earlier

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			publication of final guidance for everolimus, as it would need to be allocated a slot in the work programme which is under increasing demand. Also please note that an MTA will still allow the committee to consider whether a drug could be recommended in the context of the Cancer Drugs Fund.
	Pfizer	Pfizer consider it appropriate for this topic to be referred to NICE for appraisal.	Comment noted.

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	The NET Patient Foundation	The writer of the scoping exercise document has perhaps misunderstood some of the issues with regard to diagnosis and treatment of NETs, which is both strongly multimodal and multidisciplinary, as reflected by the detailed requirements for achievement of European Neuroendocrine Tumour Society Centre of Excellence status (http://www.enets.org/coe.html).	Comment noted. Consultees will also have the opportunity to discuss the decision problem in more detail at the Stakeholder information meeting and in their written submission.
	British Nuclear Medicine Society	Yes. This treatment is widely used in the UK and Europe. The principle of treating patients when they are fitter rather than when they have deteriorated and sometimes more significantly is a recognised issue in clinical practice.	Comment noted.
	Royal College of Pathologists	Yes this is appropriate for a technology appraisal	Comment noted.

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	UK and Ireland NET Society	This response is coordinated on behalf of UKINETS, the only multi-professional society representing NET cancers in UK and Ireland. The timing of this scoping exercise is clearly very important given the 3 clinical trials presented at ESMO in 2015 [Radiant 4, TELSTAR and NETTER-01]. Whilst we accept the need for NICE to consider undertaking a scoping exercise, the process brings together four different treatments used in very different clinical situations, and only occasionally will these be overlapping. In most situations these will be used either for specific indications or in sequence as patients progress from one category to another as their tumour progresses. The writer of the scoping exercise document has perhaps misunderstood some of the issues with regard to diagnosis and treatment of NETs, which is both strongly multimodal and multidisciplinary, as reflected by the detailed requirements for achievement of European Neuroendocrine Tumour Society Centre of Excellence status (http://www.enets.org/coe.html).	Comment noted. Consultees will have the opportunity to nominate experts to attend the committee meetings. Consideration would be given to the knowledge/ experience of the nominated experts. Please see the Guide to the process of Technology Appraisals for further details. Consultees will also have the opportunity to discuss the decision problem in more detail at the Stakeholder information meeting and in their written submission.

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		The UKINETS would anticipate that the coordinators of the scoping exercise would invite recognised experts in the field to advise on the process, given the complexities and challenges of managing NETs. There are many differences between NETs and the common cancers and these must be taken into account. Furthermore the term NETs embraces a substantial number of tumour types, arising from the oral pharynx through to anus but with the predominant sites being in the lung, pancreas, small bowel, appendix and caecal areas. Traditionally they were divided into foregut, midgut and hindgut but now it is more usual to classify according to the anatomical site of origin. There is sometimes confusion over the definition and interpretation of the term functional which most commonly equates to carcinoid syndrome or symptoms due to specific hormones such as insulin. It may also be interpreted as meaning that the tumour stains positive for hormonal markers on immunocytochemistry or is somatostatin receptor positive as demonstrated by Octreotide Scan or 68Gallium-dotatate PET/CT. Categorisation into functional or non-functional is appropriate but other parameters are taken into account including loco-regional versus metastatic disease. Localised or loco-regional disease has a very high chance of long-term remission or cure. Even oligo-metastatic disease in the liver may be suitable for resection or ablation with very long term remissions. In addition, the introduction of the newer targeted agents and peptide receptor radiotherapy (PRRT) has seen long term remissions in patients with advanced metastatic disease that is not amenable to surgery. Thus the scoping exercise is very timely given the introduction of these new drugs/therapies which will become available over the next 12-18 months.	

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		Furthermore it should be recognised that while this scoping exercise is predominantly looking at tumours that are of lower grades G1 and G2, (excluding high-grade/G3), some G3 tumours can be well differentiated and thus behave more like G2 and therefore understanding the biology of NETs is important in the decision making process. It should be recognised that these treatments will often be given in sequence in NET patients according to their functional status and disease progression. For example in functional tumours somatostatin analogues will be the treatment of choice initially, and patients will then move on to alternative treatments such as PRRT, chemotherapy, new targeted agents, embolisation or ablative therapies according to their symptoms, availability of treatment, pattern of disease and SSTR receptor expression. It should be noted that chemotherapy has little role in G1/2 small intestinal NETs whereas there is stronger evidence for PRRT. Chemotherapy however, is significantly more active and effective in progressive pancreatic G1/2 NETs. Octreotide [s.c and long acting release (LAR)] and Lanreotide Autogel are confirmed treatments for NET patients with neuroendocrine tumours of lung and gastro-entero-pancreatic origins that are causing hormone related symptoms/syndromes. New data as referenced below has shown that for patients with progressive but asymptomatic disease, there is now evidence for improved progression free survival indicating an anti-proliferative effect. Everolimus and sunitinib are well-established in the treatment of pancreatic NETs and have been accepted by the Scottish Medicines Consortium (SMC). It should be recognised that progression of disease in this tumour should include progression of symptoms, biochemistry and decline in QoL. The ENETs guidelines were updated for publication in 2016 and are a timely reminder of current European standards of care (Neuroendocrinology, Karger 2016)	

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	Healthcare Improvement Scotland	This response is coordinated on behalf of SMC and HIS and reflects the needs for Scottish health care. The document should recognise there are variations in accessing medicines in the devolved nations but that there should be equity of care across the UK. The timing of this scoping exercise is clearly very important given the 3 clinical trials presented at ESMO in 2015 [Radiant 4, TELSTAR and NETTER-01]. Whilst we accept the need for NICE to consider undertaking a scoping exercise, the process brings together four different treatments used in very different clinical situations, and only occasionally will these be overlapping. In most situations these will be used either for specific indications or in sequence as patients progress from one category to another as their tumour progresses. The writer of the scoping exercise document has perhaps misunderstood some of the issues with regard to diagnosis and treatment of NETs, which is both strongly multimodal and multidisciplinary, as reflected by the detailed requirements for achievement of European Neuroendocrine Tumour Society Centre of Excellence status (http://www.enets.org/coe.html). We would anticipate that the coordinators of the scoping exercise would invite recognised experts in the field to advise on the process, given the complexities and challenges of managing NETs. There are many differences between NETs and the common cancers and these must be taken into account. Furthermore the term NETs embraces a substantial number of tumour types, arising from the oral pharynx through to anus but with the predominant sites being in the lung, pancreas, small bowel, appendix and caecal areas. Traditionally they were divided into foregut, midgut and hindgut but now it is more usual to classify according to the anatomical site of origin.	Comment noted. Consultees will have the opportunity to nominate experts to attend the committee meetings. Consideration would be given to the knowledge/ experience of the nominated experts. Please see the Guide to the process of Technology Appraisals for further details. Consultees will also have the opportunity to discuss the decision problem in more detail at the Stakeholder information meeting and in their written submission.

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		There is sometimes confusion over the definition and interpretation of the term functional which most commonly equates to carcinoid syndrome or symptoms due to specific hormones such as insulin. It may also be interpreted as meaning that the tumour stains positive for hormonal markers on immunocytochemistry or is somatostatin receptor positive as demonstrated by Octreotide Scan or 68Gallium-dotatate PET/CT. Categorisation into functional or non-functional is appropriate but other parameters are taken into account including loco-regional versus metastatic disease. Localised or loco-regional disease has a very high chance of long-term remission or cure. Even oligo-metastatic disease in the liver may be suitable for resection or ablation with very long term remissions. In addition, the introduction of the newer targeted agents and peptide receptor radiotherapy (PRRT) has seen long term remissions in patients with advanced metastatic disease that is not amenable to surgery. Thus the scoping exercise is very timely given the introduction of these new drugs/therapies which will become available over the next 12-18 months. Furthermore it should be recognised that while this scoping exercise is predominantly looking at tumours that are of lower grades G1 and G2, (excluding high-grade/G3), some G3 tumours can be well differentiated and thus behave more like G2 and therefore understanding the biology of NETs is important in the decision making process. It should be recognised that these treatments will often be given in sequence in NET patients according to their functional status and disease progression. For example in functional tumours somatostatin analogues will be the treatment of choice initially, and patients will then move on to alternative treatments such as PRRT, chemotherapy, new targeted agents, embolisation or ablative therapies according to their symptoms, availability of treatment, pattern of disease and SSTR receptor expression.	

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	Peninsular Technology Assessment Group	No comments	Response noted.
Wording	Imaging Equipment	Yes the remit broadly does reflect the intended license.	Comment noted.
	Ipsen	The wording of the remit is appropriate.	Comment noted.

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	Novartis	The wording of the remit is appropriate ie unresectable or metastatic neuroendocrine tumours with disease progression. Pancreatic NETs is the only indication with comparable evidence available to inform an MTA (ie everolimus (RADIANT-3 5) vs. sunitinib (SUN-1116).	Comment noted.

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	Pfizer	People with unresectable or metastatic neuroendocrine tumours and whose disease has progressed represent a heterogeneous population (1). It is now accepted that pancreatic neuroendocrine tumours (NETs) and non-pancreatic NETs (often termed 'carcinoid') should be regarded as separate clinical entities, despite sharing many characteristics. Grade 3 pancreatic NETS are further deemed by the clinical community as a separate tumour type, not covered in the clinical data/marketing authorisation for either everolimus or sunitinib. Furthermore, the marketing authorisations of both everolimus and sunitinib are restricted to the subpopulation of patients with pancreatic NETs only of Grade 1 and 2 as per WHO classification (or Ki67<20% (a marker of tumour proliferation) (2, 3). Therefore, Pfizer recommend the remit reflects the need to differentiate treatment of pancreatic NETs from carcinoid tumours as follows: "To appraise the clinical and cost effectiveness of everolimus, lanreotide, lutetium-177 DOTATATE and sunitinib within their marketing authorisation for treating unresectable or metastatic neuroendocrine tumours of pancreatic or non-pancreatic origin with disease progression and Ki67 <20%"	Comment noted. This topic has been referred for appraisal with the current remit. The current remit is broad and does not exclude any possible population or indication for the treatments being appraised. The population has been amended to clarify that the appraisal will take into account the specific locations covered by the marketing authorisations of the interventions.

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	The NET Patient Foundation	No comments	Comment noted.
	British Nuclear Medicine Society	No. Nuclear Medicine resources must be costed	Comment noted.
	Royal College of Pathologists	Yes although my opinion this technology should be considered as part of a much wider technology appraisal for all NETs both gastropancreatic and arising elsewhere in the intestine, although I realise that this may not be practical	Comment noted. The appraisal will only cover the indications covered by the marketing authorisations of the interventions.

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	UK and Ireland NET Society	The wording of the scoping remit is intermittently flawed probably due to the complexity of managing these tumours and suggests some misunderstandings about the management of neuroendocrine tumours. Other treatments such as ablation therapy, embolisation, [including SIRT] and long-acting release octreotide are frequently used. However newer indications have emerged from the data from the PROMID study with long acting octreotide which have shown that patients with metastatic small bowel NETs had significantly slower disease progression rates compared to those on placebo. Similarly in the CLARINET study, Lanreotide Autogel demonstrated improvement in progression free survival in pancreatic as well small bowel NETs. Interferon alpha is only occasionally used in the United Kingdom.	Although the remit is broad, it states that the listed technologies will be appraised within their marketing authorisations. Consultees will have the opportunity to discuss the decision problem in more detail at the Stakeholder information meeting

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	Healthcare Improvement Scotland	The wording of the scoping remit is intermittently flawed probably due to the complexity of managing these tumours and suggests some misunderstandings about the management of neuroendocrine tumours. Other treatments such as ablation therapy, embolisation, [including SIRT] and long-acting release octreotide are frequently used. However newer indications have emerged from the data from the PROMID study with long acting octreotide which have shown that patients with metastatic small bowel NETs had significantly slower disease progression rates compared to those on placebo. Similarly in the CLARINET study, Lanreotide Autogel demonstrated improvement in progression free survival in pancreatic as well small bowel NETs. Interferon alpha is only occasionally used in the United Kingdom.	Although the remit is broad, it states that the listed technologies will be appraised within their marketing authorisations. Consultees will have the opportunity to discuss the decision problem in more detail at the Stakeholder information meeting.

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	Peninsular Technology Assessment Group	The remit states: "To appraise the clinical and cost effectiveness of everolimus, lanreotide, lutetium-177 DOTATATE and sunitinib within their marketing authorisation for treating unresectable or metastatic neuroendocrine tumours with disease progression." However, some of the drugs being appraised would not have been used within their MA.	Comment noted. The wording of the remit covers both existing and anticipated marketed authorisations of the interventions. The wording of the population has been amended to clarify this.
Timing Issues	Imaging Equipment	Patient with unresectable or metastatic neuroendocrine tumours with disease progression have no curative treatment options, and functioning GEP-NETs are associated with debilitating clinical symptoms. Currently, there are no interventions which have undergone appraisal by NICE. Therefore, this appraisal should be reviewed by NICE, so that guidance is available to the NHS in a timely manner. A diagnosis of GEP-NET and subsequent treatment impacts on patients and their families in many ways. Symptoms associated with NET hormonal hypersecretion may impair patients' QoL and in some instances can be life-threatening (e.g. severe diarrhoea and hypokalaemia in VIPomas) (Ramage et al. 2012). GEP-NETs are often at an advanced stage at the time of diagnosis and are often deemed incurable. Historically, treatments often improved symptoms but not always overall survival, and although the development of new treatments has improved progression-free survival it has also increased toxicity.	Comment noted.

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	Ipsen	The licence extension for Somatuline (lanreotide) Autogel in the UK for the treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease was received in February 2015. Therefore use within the new indication is established across England and Wales.	Comment noted.
	Novartis	Given the high unmet need in patients with lung NETs, and patients with GI NETs who have progressed following current therapy, it is important that NICE ensures timely guidance. Including everolimus in an MTA for GI and lung NETs is not consistent with the institutes' remit to ensure that all NHS patients have equitable access to the most clinically - and cost-effective treatments, and to provide guidance in a timely fashion. We believe it more appropriate and request everolimus in GI and lung NETs is appraised via the **STA process, under the new reimbursement process.**	Comment noted. Please see the previous response on why a separate STA for this indication was not considered appropriate.
	Pfizer	No comments	Response noted.
	The NET Patient Foundation	No comments	Response noted.
	British Nuclear Medicine Society	Urgent. The number of treatments for adult neuroendocrine tumours has increased from 130 to 355 pa from 32007 to 2012 in the UK (Rojas et al Nuc Med Commun 36(8):761-765) and continues to increase. Cancer survival statistics support the concept of improving quality of life and this technology lends itself directly to such an approach.	Comment noted.

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	Royal College of Pathologists	Relatively urgent both in progressed and non-progressed GI NETs	Comment noted.
	UK and Ireland NET Society	The timing is highly relevant given the recent presentations at ESMO 2015, Vienna on PRRT and Everolimus (as well as Telotristat which is not included in the scoping exercise). Lutetium dota-octreotate PRRT has been delisted by the CDF, having previously been listed for past 4 years, but now the data is available to confirm its activity in metastatic progressive small bowel carcinoids. The results from the clinical trial are quite remarkable and show a substantial clinical benefit for those patients who received PRRT compared to those receiving high-dose octreotide LAR. The confirmatory data from Radiant 4 study showed a significant benefit for Everolimus in both small intestinal and bronchial neuroendocrine tumours. Efficacy of Everolimus for treatment of pancreatic neuroendocrine tumours had previously been demonstrated by the Radiant 3 trial. Patients, doctors and the charities are all very keen to see approval for these agents in neuroendocrine tumours. These are widely available throughout much of Europe and North America and patients in the United Kingdom are being deprived of treatments which have potential to prolong their lives and improve the quality-of-life	Comment noted.

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	Healthcare Improvement Scotland	The timing is highly relevant given the recent presentations at ESMO 2015, Vienna on PRRT and Everolimus (as well as Telotristat which is not included in the scoping exercise). Lutetium dota-octreotate PRRT has been delisted by the CDF, having previously been listed for past 4 years, but now the data is available to confirm its activity in metastatic progressive small bowel carcinoids. The results from the clinical trial are quite remarkable and show a substantial clinical benefit for those patients who received PRRT compared to those receiving high-dose octreotide LAR. The confirmatory data from Radiant 4 study showed a significant benefit for Everolimus in both small intestinal and bronchial neuroendocrine tumours. Efficacy of Everolimus for treatment of pancreatic neuroendocrine tumours had previously been demonstrated by the Radiant 3 trial. Radiant 4 study showed a significant benefit for Everolimus in both small intestinal and bronchial neuroendocrine tumours. Efficacy of Everolimus for treatment of pancreatic neuroendocrine tumours had previously been demonstrated by the Radiant 3 trial. Patients, doctors and the charities are all very keen to see approval for these agents in neuroendocrine tumours. These are widely available throughout much of Europe and North America and patients in the United Kingdom are being deprived of treatments which have potential to prolong their lives and improve the quality-of-life.	Comment noted.
	Peninsular Technology Assessment Group	No comments	Response noted.
Additional comments on the draft remit	Imaging Equipment	No comments	Response noted.
	Ipsen	No comments	Response noted.
	Novartis	No comments	Response noted.

Section	Consultees	Comments [sic]	Action
	Pfizer	No comments	Response noted.

Section	Consultees	Comments [sic]	Action
	The NET Patient Foundation	Any additional comments on the remit As an organisation we are in total symmetry with the comments sent by UKINETs but would state very strongly that there is a need for an expert NET consultant to sit on the appraisal panel due to the complexity of this cancer type and to ensure that no errors are made within this important MTA. Whilst we welcome the opportunity to review the treatments available for neuroendocrine tumours, and the need for an urgent update on management guidelines, the document is in danger of mixing very different clinical indications. The final outcome will need to reflect these different clinical scenarios which require separate management protocols. It is essential these are made clear in the final document. It is also vital to consider the impact of progression on the patient. A disease where they may have stability for some time but in the knowledge that any change in symptoms, biochemistry or radiological imaging, indicates the start of a difficult journey. Patients talk about 'the Sword of Damocles' hanging over them day after day. We need to be able to offer appropriate and timely treatments to a cancer population that have been disregarded for too long.	Comments noted. Consultees will have the opportunity to nominate experts to attend the committee meetings. Consideration would be given to the knowledge/ experience of the nominated experts. Please see the Guide to the process of Technology Appraisals for further details. Consultees will also have the opportunity to discuss the decision problem in detail at the Stakeholder information meeting and in their written submission.

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	British Nuclear Medicine Society	No comments	Response noted.
	Royal College of Pathologists	No comments	Response noted.

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	UK and Ireland NET Society	Any additional comments on the remit Whilst we welcome the opportunity to review the treatments available for neuroendocrine tumours, and the need for an urgent update on management guidelines, the document is in danger of mixing very different clinical indications. The final outcome will need to reflect these different clinical scenarios which require separate management protocols. It is essential these are made clear in the final document.	Comment noted. The population has been amended to clarify that the appraisal will take into account the specific locations covered by the existing and anticipated marketing authorisations of the interventions. Consultees will have the opportunity to discuss the decision problem in more detail at the Stakeholder information meeting and in their written submission.

Section	Consultees	Comments [sic]	Action
	Healthcare Improvement Scotland	Whilst we welcome the opportunity to review the treatments available for neuroendocrine tumours, and the need for an urgent update on management guidelines, the document is in danger of mixing very different clinical indications. The final outcome will need to reflect these different clinical scenarios which require separate management protocols. It is essential these are made clear in the final document.	Comment noted. The population has been amended to clarify that the appraisal will take into account the specific locations covered by the existing and anticipated marketing authorisations of the interventions. Consultees will have the opportunity to discuss the decision problem in more detail at the Stakeholder information meeting and in their written submission.

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	Peninsular Technology Assessment Group	No comments	Response noted.

Comment 2: the draft scope

Section	Consultees	Comments [sic]	Action
Background information	Imaging Equipment	The Chemotherapies listed in the draft scope including, dacarbazine, 5-fluorouracil and doxorubicin are not recommended in the treatment algorithm for G1 or G2 GEP-NETs (Ramage et al., 2012).	Comment noted. The scope describes these treatments as options. Attendees at the scoping workshop stated that chemotherapy regimens were possible comparators for progressed disease. No changes have been made.
	Ipsen	The background information states that the technology appraisal considers lanreotide for the treatment of unresectable, somatostatin receptor-positive GEP-NETs with disease progression. Confirmation of somatostatin receptor positivity via current methods such as use of an Octreoscan or 68Gallium DOTATATE PET/CT is not required within the Somatuline Autogel licence, nor is it routine clinical practice to obtain this confirmation before initiating therapy with Somatuline Autogel. This differs to the situation with lutetium-177 DOTATATE where this is indeed indicated to confirm that sufficient uptake would occur on administration of the radionuclide.	Comment noted. The scope has been amended accordingly.

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	Novartis	The background information is described accurately. We note that clinical practice is individualisedfor this disease area which is heterogeneous in nature. In addition, clinical practice does not necessarily reflect the available evidence base as there is a paucity of data in this area. We recommend that NET clinical experts who practice in ENETs approved Centres of Excellence are consulted in this appraisal.	Consultees will have the opportunity to nominate experts to attend the committee meetings. Consideration would be given to the knowledge/ experience of the nominated experts. Please see the Guide to the process of Technology Appraisals for further details.
	Pfizer	No comments	Response noted.
	The NET Patient Foundation	No comments	Response noted.
	British Nuclear Medicine Society	Yes	Comment noted.

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	Royal College of Pathologists	The basic pathological assessment for gastrointestinal NETs is relatively standardised with the use of the FRCPath minimum dataset for gastrointestinal NETs; https://www.rcpath.org/resourceLibrary/g081_datasetgiendocrine_sep12-pdf.html with assessment of morphology, basic stains for neuroendocrine phenotype e.g. chromogranin, CD 56 and assessment of proliferation fraction using Ki 67. The introduction of these new drugs creates additional diagnostic dilemmas as it may not always be feasible to identify the primary site of a neuroendocrine tumour; there are some differences in the immunohistochemical assessment of pancreatic NETs compared to non-pancreatic NETs as pancreatic NETs tend to express ISL 1, see also Maxwell JE et al Surgery 2014 (6); 156; 1359-66. Most UK laboratories the moment do not have the immunohistochemical expertise to accurately separate pancreatic and non-pancreatic NETs using immunohistochemistry techniques so this would require some additional investment if these drugs were only to be used for pancreatic NETs as the primary site of an annuity may not be certain despite careful imaging assessment. EUS cytology/core biopsy is also important in the diagnosis of pancreatic tumours and there may only be limited amounts of material available for immunohistochemical assessment from cell blocks.	Comment noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal.
	UK and Ireland NET Society	NETs are very challenging tumours to treat due to the complexity and variety of clinical behaviours of the tumours included within this family. It must be recognised that their behaviour can vary greatly, depending upon their site of origin and functionality. Furthermore it is important to remember that these are not alternative treatments but are often used sequentially over many years as these patients may live for 10 years or more with their disease.	Comment noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal.

Section	Consultees	Comments [sic]	Action
	Healthcare Improvement Scotland	NETs are very challenging tumours to treat due to the complexity and variety of clinical behaviours of the tumours included within this family. It must be recognised that their behaviour can vary greatly, depending upon their site of origin and functionality. Furthermore it is important to remember that these are not alternative treatments but are often used sequentially over many years as these patients may live for 10 years or more with their disease.	Comment noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal.
	Peninsular Technology Assessment Group		-
The technology/ intervention	Imaging Equipment	The description of the technology is accurate, however the following text is suggested for inclusion: Mechanism of action / Pharmacodynamic effects: Lu-177 DOTATATE has a high affinity for subtype 2 somatostatin receptors (sst2). It binds to malignant cells which overexpress sst2 receptors. Lu-177 DOTATATE is a β- emitting radionuclide with a maximum penetration range in tissue of 2.2 mm (mean penetration range of 0.67 mm), which is sufficient to kill targeted tumour cells with a limited effect on non-target cells. Lutetium-177 has been studied in many clinical trials in people with unresectable or metastatic neuroendocrine tumours, with two trials used to support the regulatory submission. [redacted] The second, NETTER-1, is in advanced or metastatic somatostatin receptor positive midgut neuroendocrine tumours (Ki67 ≤ 20%) with disease progression compared with octreotide long acting release (LAR).	Comment noted. This section of the scope aims to provide a brief description of the technology; additional details may be included in the company's evidence submission, at the time of the appraisal. However, the scope has been amended to state that the treatment is designed to deliver radiation to the cells.

Section	Consultees	Comments [sic]	Action
	Ipsen	The description of the technology is accurate, except for the statement 'the exact mechanism of action of lanreotide in delaying progression of gastroenteropancreatic neuroendocrine tumours is not known'. The mechanisms by which lanreotide exerts its anti-tumour effect have been elucidated, and include cell-cycle inhibition, a proapoptotic effect, angiogenesis inhibition and immune system modulation. In addition, the intervention details for lanreotide are not entirely consistent with the licence. Within the licensed indication, Somatuline Autogel is for use in patients with GEP-NETs of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded. The intervention is listed more broadly to include neuroendocrine tumours of midgut, pancreatic or unknown origin).	Comments noted. The sentence has been amended to 'the exact mechanism of action of lanreotide in delaying progression of gastroenteropancreatic neuroendocrine tumours is not well understood'. The intervention details have been updated in the scope.

Section	Consultees	Comments [sic]	Action
	Novartis	The interventions are defined appropriately in accordance with their respective marketing authorisations for tumour control. However as mentioned previously, we do not believe the somatostatin analogues should be considered in this MTA. The planned marketing authorisation for everolimus should be updated for the new indications with the following wording: [redacted] It should also be noted that everolimus is administered orally. The NETTER-17 trial for lutetitum-177 DOTATATE + octreotide 30mg does not include pancreatic patients and thus lutetitum-177 DOTATATE should be excluded from the review of pancreatic NETs in progressive patients in this MTA	Comments noted. Information marked as commercial in confidence cannot be included in the scope. However, the population has been amended to clarify that the appraisal will take into account the specific locations covered by the existing and anticipated marketing authorisations of the interventions. The scope described everolimus as an 'oral' inhibitor of mTOR protein. We note that there are other trials of lutetium-177 that include pancreatic NETs. Please note that the interventions will be appraised according the locations specified in their marketing authorisations. No changes required.
	Pfizer	Pfizer note that the long-acting formulation of lanreotide (Somatuline Autogel) has been specified in this section. Pfizer recommend that the appropriate lanreotide formulation is specified throughout the scope, since licensed indications for other formulations differ.	Comment noted. The technology section clearly describes the formulation and indication that will be covered in the appraisal. No changes have been made at this time.

Section	Consultees	Comments [sic]	Action
	The NET Patient Foundation	No comments	Response noted.
	British Nuclear Medicine Society	Not sufficient. The statement '[Lu-177 DOTATATE] kills tumour cells by binding to a specific type of somatostatin receptor, called sst2 receptors, which are overexpressed by the malignant cells' does not mention that the treatment delivers radiation to these cells. As such, the effectiveness of treatment depends on the radiation dose delivered and therefore the level localisation.	Comment noted. The scope has been amended to state that the treatment is designed to deliver radiation to the cells.
	Royal College of Pathologists	Yes	Response noted.
	UK and Ireland NET Society	Everolimus and sunitinib are already accepted as standard of care for metastatic progressive pancreatic NETs and approved for usage by SMC. Data for PRRT are very fresh and awaiting publication but it is anticipated that PRRT with lutetium dota-octreotate will be licensed during 2016. It is seen as a longstanding standard of care in Europe and had been previously funded by the CDF in England. Everolimus is now shown to be an active drug in lung and small intestinal NETs and again is likely to be licensed in Europe in 2016.	Comments noted.
	Healthcare Improvement Scotland	Everolimus and sunitinib are already accepted as standard of care for metastatic progressive pancreatic NETs and approved for usage by SMC. Data for PRRT are very fresh and awaiting publication but it is anticipated that PRRT with lutetium dota-octreotate will be licensed during 2016. It is seen as a longstanding standard of care in Europe and had been previously funded by the CDF in England. Everolimus is now shown to be an active drug in lung and small intestinal NETs and again is likely to be licensed in Europe in 2016.	Comments noted.

Section	Consultees	Comments [sic]	Action
	Peninsular Technology Assessment Group	We would like to note that Lanreotide (Somatuline LA ®, Ipsen Ltd) is not in the scope; this is just a clarification point. Secondly, we would like to ask if we are considering Lutetium-177 DOTATATE, should Y90 DOTA-TOC be also considered?	Comments noted. The appraisal will only consider Somatuline Autogel. Y90 DOTA-TOC is not included in the remit of this appraisal, therefore it will not be considered.
Population	Imaging Equipment	Yes the population has been accurately defined.	Comment noted.
	Ipsen	The population is considered appropriate, although it should be noted that the Somatuline Autogel licence also includes patients with locally advanced disease, in addition to metastatic disease.	Comment noted. The wording of the population has been summarised briefly to cover all the stages of disease specified in the different marketing authorisations. Therefore patients with locally advanced disease are not excluded.
	Novartis	The population is defined appropriately; in patients with unresectable or metastatic neuroendocrine tumours whose disease has progressed. Due to the complexity of the disease, it should be noted that there are many ways of reviewing this population. The population may be further categorised according to tumour functional status, as functioning and non-functioning patients may have distinct diagnosis and treatment pathways.	Comment noted. The population has been amended to clarify that the appraisal will take into account the specific locations covered by the marketing authorisations of the interventions. In addition, further population categories are included as possible subgroups in the scope.

Section	Consultees	Comments [sic]	Action
	Pfizer	Please refer to comments on the draft remit above. Pfizer recommend the population differentiate patients with tumours of pancreatic origin from non-pancreatic as follows: "People with unresectable or metastatic neuroendocrine tumours of pancreatic or non-pancreatic origin and whose disease has progressed and Ki67 <20%".	Comment noted. The population has been amended to clarify that the appraisal will take into account the specific locations covered by the existing and anticipated marketing authorisations of the interventions.
	The NET Patient Foundation	No comments	Response noted.
	British Nuclear Medicine Society	The likely primary site for the metastatic neuroendocrine tumours is not defined. The primary site could be bowel related; pancreas related or lung. A significant number also have an unknown or uncharacterised primary. One piece of guidance covering all these different behaviours is ambitious and perhaps needs some careful consideration.	Comment noted. The population has been amended to clarify that the appraisal will take into account the specific locations covered by the existing and anticipated marketing authorisations of the interventions.
	Royal College of Pathologists	Yes	Response noted.

Section	Consultees	Comments [sic]	Action
	UK and Ireland NET Society	Previous comments have addressed the issues about populations and definitions. Many of these tumours fall into Orphan status category (approximate incidence 3-5 per 105 population). It is important to separate the functional/syndromic patients from the non-functional patients with stable disease as there are clear differences determining intervention. However for non-functional/syndromic patients with progressive disease, previously there had been no effective therapeutic options and now there are several active treatment options available	Comment noted. The population has been amended to clarify that the appraisal will take into account the specific locations covered by the marketing authorisations of the interventions. In addition, further population categories are included as possible subgroups in the scope.
	Healthcare Improvement Scotland	Previous comments have addressed the issues about populations and definitions. Many of these tumours fall into Orphan status category (approximate incidence 3-5 per 105 population). It is important to separate the functional/syndromic patients from the non-functional patients with stable disease as there are clear differences determining intervention. However for non-functional/syndromic patients with progressive disease, previously there had been no effective therapeutic options and now there are several active treatment options available.	Comment noted. The population has been amended to clarify that the appraisal will take into account the specific locations covered by the marketing authorisations of the interventions. In addition, further population categories are included as possible subgroups in the scope.
	Peninsular Technology Assessment Group	No comments	Response noted.

Section	Consultees	Comments [sic]	Action
Comparators	Imaging Equipment	The draft scope should define what constitutes best supportive care (BSC). BSC includes somatostatin analogue aimed at providing symptomatic relief associated with hormonal overproduction and not slowing underlying disease progression. (Öberg K, 2000, 2002; Rinke A et al., 2009). BSC is not considered to be an option in guidelines for progressive patients (Pavel et al. 2016, Ramage et al. 2012). The Chemotherapies listed in the draft scope including dacarbazine, 5-fluorouracil and doxorubicin are not recommended in the treatment algorithm for G1 or G2 GEP-NETs (Ramage et al., 2012).	Comments noted. Attendees at the scoping workshop stated that chemotherapy regimens were possible comparators for progressed disease. No changes have been made.

Section	Consultees	Comments [sic]	Action
	Ipsen	It is important to make clear that Somatuline Autogel is used earlier in the treatment paradigm for patients with GEP-NETs than the other interventions listed within scope. Everolimus, sunitinib or lutetium-177 DOTATATE are recommended usually only after the disease has taken a more aggressive course and after discussion about the specific patient at a multidisciplinary team meeting. Patients may remain on Somatuline Autogel whilst receiving additional treatment with everolimus, sunitinib or lutetium-177 DOTATATE therapy. In the pivotal trials for everolimus (Yao JC et al. NEJM 2011;364:514-23) and sunitinib (Raymond E et al. NEJM 2011;364:501-13), high proportions of patients had already received somatostatin analogue therapy, and in the NETTER-1 trial for lutetium-177, progression on octreotide LAR was an inclusion criterion for the trial. For the reasons documented above, it is challenging to suggest that any of these comparators can be described as 'best alternative care'. Chemotherapy is not an appropriate comparator to lanreotide in this patient population, as its use is usually limited to grade 2 and more usually grade 3, pancreatic NETs in which there is rapid clinical or radiological progression (Ramage JK et al 2012;61:6-32). It is however an appropriate compactor to everolimus, lutetium-177 DOTATATE and sunitinib. Best supportive care is not an appropriate comparator in patients who have disease progression. SSAs should be used as standard of care in the majority of patients diagnosed with a GEP-NET (approximately 90%) regardless of progressive status. Octreotide LAR should be included as a comparator for midgut NETs only, as it gained a licence for the treatment of midgut NETs in 2009.	Comments noted. Please note that the technologies will be appraised within their marketing authorisations. Consultees will have the opportunity to provide additional information on the use of the technologies at the Stakeholder information meeting and in their evidence submissions.

Section	Consultees	Comments [sic]	Action
	Novartis	The evidence base for the technologies in this appraisal should determine the appropriate comparisons. Pancreatic NETs The current scope proposes everolimus, sunitinib, lanreotide and lutetitum-177 DOTATATE as treatment options for progressive pancreatic NETs. As described in the "appropriateness" section we believe the somatostatin analogues should be excluded from this MTA since they are considered the standard of care as a first-line therapy in NETs[1] and are available in the UK with no access issues. However, should the institute choose to appraise the analogues, it should be noted that although the PROMID[2] trial for octreotide-LAR was conducted in patients with **progressive disease,** it did not include pancreatic NETs. The CLARINET[3] trial for lanreotide included patients with **non-progressive pancreatic NETs** and is outside the remit of this appraisal in **progressive disease**. Consequently, the patient populations in the two trials will not inform a meaningful indirect comparison. The NETTER-1 trial[7] for lutetitum-177 DOTATATE + octreotide 30mg did not include pancreatic patients, therefore lutetitum-177 DOTATATE should be excluded from the review of pancreatic NETs in progressive disease. We conclude that the only robust and comparable clinical evidence available to inform an appraisal in the **progressive pancreatic NET** population is RADIANT 3[5] (everolimus) and SUN111[6] (sunitinib)	Comments noted. Please note that the technologies will be appraised within their marketing authorisations. The appraisal committee will consider all available evidence presented to it when making decisions on the clinical and cost effectiveness of the technologies being appraised. Consultees will have the opportunity to discuss the evidence in more details at the Stakeholder information meeting and in their submissions. Given that there was no clear agreement among the consultees on whether to include octreotide as an intervention in the STA for non-progressive disease and in the absence of any comment on its inclusion for the progressed disease; a referral was not sought for octreotide as an intervention. However, octreotide has been included as a comparator in the final scope in line with the comments from consultees.

Section	Consultees	Comments [sic]	Action
		GI NETs The current scope proposes everolimus, lanreotide and lutetitum-177 DOTATATE as interventions for progressive GI NETs. As described in the “appropriateness” section we believe the somatostatin analogues should be excluded from this MTA since they are considered the standard of care as a first-line therapy in NETs1 and are available in the UK with no access issues. However, should the institute choose to appraise the analogues, it should be noted that: • PROMID2 provides the only robust RCT evidence for the effect of a somatostatin analogue in the progressive GI NET population. Should NICE wish to appraise the somatostatin analogues, octreotide LAR should be assessed as an intervention. • CLARINET3 included patients with non-progressive GI NETs and is outside the remit of this appraisal in progressive disease. Therefore should NICE wish to appraise the somatostatin analogues, it should be noted that patient populations in the PROMID2 and CLARINET3 trials will not inform a meaningful indirect comparison. • NETTER-17 data for lutetitum-177 DOTATATE + octreotide 30mg describes midgut patients who had progressed following octreotide LAR therapy. Should NICE wish to include the analogues in this MTA, it would be inappropriate to compare lutetitum-177 DOTATATE to a somatostatin analogue within GI NET.	Please note that this topic was referred for appraisal before April 2016, when the new process for cancer topics came into place. However, NICE is still committed (as we were previously) to publishing guidance as quickly as possible following marketing authorisation, whilst also balancing the needs and efficiency of the TA work programme and what the NHS requires from NICE in this area. Removing everolimus from the MTA at this point, will not necessarily result in earlier publication of final guidance for everolimus, as it would need to be allocated a slot in the work programme which is under increasing demand. Also please note that an MTA will still allow the committee to consider whether a drug could be recommended in the context of the Cancer Drugs Fund.

Section	Consultees	Comments [sic]	Action
		Given the unmet need for Non- functioning GI-NET patients who have progressive disease, we request that the institute considers reviewing the new indication of everolimus for [redacted] (anticipated date of CHMP positive opinion [redacted] through the STA process. Lung NETs Everolimus is the only targeted therapy with robust clinical evidence (RADIANT 4) to demonstrate efficacy in lung NET patients. While the institute has decided an MTA in NETs is necessary, the inclusion of everolimus risks an avoidable delay for patients to the availability of an effective and innovative targeted cancer therapy. Everolimus is the only targeted therapy to show efficacy in the lung NET patient population. We therefore request that the lung NET and GI NET indication is included in a separate STA for RADIANT 4, given the high unmet medical need, and are appraised by NICE in the new reimbursement process due to commence 1st July 2016. We believe an appropriate comparator in this setting would be chemotherapy/radiotherapy. We would advise expert opinion is sought from lung NET Specialists.	

Section	Consultees	Comments [sic]	Action
	Pfizer	On the basis of available evidence, marketing authorisations and international guidelines Pfizer believe that the only appropriate comparator for sunitinib in unresectable or metastatic pancreatic NETs with disease progression is everolimus. The latest ENETs guidelines position lanreotide prior to sunitinib and everolimus in the patient pathway for pancreatic NETs (4). This reflects the evidence for long-acting lanreotide (Somatuline Autogel) at an earlier stage in the disease in a different subgroup of patients, with non-progressive locally advanced disease (5). 96% of patients in the pivotal CLARINET trial had unresectable or metastatic NETs with stable disease and patients with Ki67 >10% were excluded. Furthermore, 87% of patients had a Ki67 <2%, which represents a non-progressed population. Sunitinib and everolimus are licensed for progressed pancreatic NETs with a Ki67 <20% (2, 3). Consequently, comparison of lanreotide with either sunitinib or everolimus is inappropriate. Lutetium-177 DOTATATE should not be considered a comparator as it does not have a marketing authorisation for the treatment of NETs. Furthermore, on the basis of a lack of prospective randomised data the latest ENETs guidelines only recommend it as an option in pancreatic NETs after the interventions included in the draft scope (4). Pfizer consider the chemotherapy comparators listed as established treatment options for some patients with NETs. However, they are unlicensed and there is only limited low quality trial evidence available (4). ENETs guidelines recommend chemotherapy for progressive or bulky pancreatic NETs and in grade 3 neuroendocrine neoplasms. Neither, sunitinib or everolimus are licensed for the treatment of grade 3 (poorly-differentiated) pancreatic NETs (2, 3). Consequently, comparison between sunitinib and chemotherapy is infeasible and inappropriate.	Comment noted. Please note that the technologies will be appraised within their existing and anticipated marketing authorisations. The appraisal committee will consider all available evidence presented to it when making decisions on the clinical and cost effectiveness of the technologies being appraised. The Guide to the Methods of Technology Appraisal states that the appraisal committee can consider as comparators technologies that do not have a marketing authorisation for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS.

Section	Consultees	Comments [sic]	Action
	The NET Patient Foundation	No comments	Response noted.
	British Nuclear Medicine Society	An alternative treatment, although not commercially available, is Y-90 DOTATATE (used in 6 UK centres in 2012). I-131 mIBG has been widely used in the past. Some centres are also using Y90 microsphere therapies for liver predominant disease.	Comment noted. Treatments that are not commercially available would not normally be included as comparators. Please see the Guide to the Methods of Technology Appraisal for details on how appropriate comparators are selected.
	Royal College of Pathologists	Yes, to the best of my knowledge	Comment noted.
	UK and Ireland NET Society	Comparators have been included such as interferon alpha which is infrequently used in the UK but embolisation, SIRT and RFA are well utilised in highly selected cases.	Comments noted. Given the mixed responses from consultation regarding the use of interferon alpha, it was decided that interferon alpha should be included as a comparator. However, most consultees did not consider the other interventions to be appropriate comparators.

Section	Consultees	Comments [sic]	Action
	Healthcare Improvement Scotland	Comparators have been included such as interferon alpha which is infrequently used in the UK but embolisation, SIRT and RFA are well utilised in highly selected cases.	Comments noted. Given the mixed responses from consultation regarding the use of interferon alpha, it was decided that interferon alpha should be included as a comparator. However, most consultees did not consider the other interventions to be appropriate comparators.
	Peninsular Technology Assessment Group	We believe that Octreotide (Sandostatin LAR) should be definitely considered as a comparator. Possibly also Interferon alfa should be considered as a comparator (although much less used).	Comments noted. These have now been included as comparators in the scope. Please note that there were mixed responses from consultees regarding the appropriateness of interferon alpha as a comparator.
Outcomes	Imaging Equipment	Yes	Comment noted.
	Ipsen	The outcome measures stated are appropriate, except for symptom control. Except for lanreotide, all other interventions in this scope are not used for symptom control of functioning NETs. In addition this MTA is investigating the anti-proliferative benefit of these agents on patients with NETs with disease progression, it is not assessing symptom control.	Comment noted. The outcomes were considered to be appropriate, therefore no change has been made.
	Novartis	The outcome measures to be considered are appropriate.	Comment noted.
	Pfizer	No comments	Response noted.

Section	Consultees	Comments [sic]	Action
	The NET Patient Foundation	No comments	Response noted.
	Royal College of Pathologists	Yes	Comment noted.
	UK and Ireland NET Society	Progression free survival is usually accepted as the preferred method of assessing response in these tumours. Due to their longevity of survival and cross over to other treatments since they are given sequentially, overall survival is often of limited value.	Comment noted.
	Healthcare Improvement Scotland	Progression free survival is usually accepted as the preferred method of assessing response in these tumours. Due to their longevity of survival and cross over to other treatments since they are given sequentially, overall survival is often of limited value.	Comment noted.
	Peninsular Technology Assessment Group	No comments	Response noted.
Economic analysis	Imaging Equipment	We are in early stages of planning our economic case so cannot comment yet. Somatostatin receptor diagnostic testing is standard of care for NET patients in England as per guidelines (Ramage et al., 2012).	Comment noted.
	Ipsen	As confirmed in the background information section, confirmation of somatostatin receptor positivity via current methods such as use of an Octreoscan or 68Gallium DOTATATE PET/CT is not required within the Somatuline Autogel licence.	Comment noted. The scope has been amended accordingly.

Section	Consultees	Comments [sic]	Action
	Novartis	The economic analysis is appropriate and consistent with the NICE reference case.	Comment noted.
	Pfizer	No comments	Response noted.
	The NET Patient Foundation	No comments	Response noted.
	British Nuclear Medicine Society	Economic analysis must take full account of the patient journey including nuclear medicine costs, including radiopharmacy, imaging, dosimetry and nursing as well nuclear medicine physician resources. The BNMS can provide full costings.	Comment noted. Consultees are encouraged to provide all relevant evidence in their written submissions or at the Stakeholder information meeting.
	Royal College of Pathologists	No comments	Response noted.
	UK and Ireland NET Society	No comments	Response noted.
	Healthcare Improvement Scotland	No comments	Response noted.
	Peninsular Technology Assessment Group	No comments	Response noted.
Equality and Diversity	Imaging Equipment	There are no equity issues to raise.	Comments noted.
	Ipsen	No comments	Response noted.

Section	Consultees	Comments [sic]	Action
	Novartis	No comments	Response noted.
	Pfizer	No comments	Response noted.
	The NET Patient Foundation	No comments	Response noted.
	British Nuclear Medicine Society	No comments	Response noted.
	Royal College of Pathologists	If the pathology of these lesions does require more specialist pathological workup this will create issues for cancer centres requiring additional investment in necessary laboratory facilities and MDT arrangements to support these new therapies; the UKINETS accreditation is one example of this where the standards required for pathology in the accreditation process are actually higher and more exacting for UKINETS accredited centres than for those required by other existing professional guidance e.g. by the Royal College of Pathologists	Comment noted. Issues about additional investments for treatment centres are not considered equality issues under the equalities legislation. In addition these are not issues that can be addressed by a technology appraisal. However, consultees are encouraged to present evidence of additional resource associated with these technologies.

Section	Consultees	Comments [sic]	Action
	UK and Ireland NET Society	NETs are relatively rare cancers that are difficult, even for parts of the NHS concerned with managing complex conditions, to understand meaning the whole NET population is disadvantaged compared to more common cancers. The relatively long and increasing survival means this is a reasonably sized group of disadvantaged patients that is having difficulty gaining access to efficacious therapies. Concerns remain around equality of access to advanced therapies as not all patients will be referred to a specialist centre at the time of diagnosis. UKINETS and NET Patient Foundation are working with Public Health England to identify what happens to patients once a diagnosis of neuroendocrine tumour is made, whether they are then referred to a specialist centre. This will allow us to identify outlier hospitals and target them for education.	Comments noted. Issues about access and rarity of disease are not considered equality issues under the equalities legislation. The appraisal committee will consider whether its recommendations could have a different impact on people protected by the equality legislation.
	Healthcare Improvement Scotland	NETs are relatively rare cancers that are difficult, even for parts of the NHS concerned with managing complex conditions, to understand meaning the whole NET population is disadvantaged compared to more common cancers. The relatively long and increasing survival means this is a reasonably sized group of disadvantaged patients that is having difficulty gaining access to efficacious therapies. Concerns remain around equality of access to advanced therapies as not all patients will be referred to a specialist centre at the time of diagnosis. UKINETS and NET Patient Foundation are working with Public Health England to identify what happens to patients once a diagnosis of neuroendocrine tumour is made, whether they are then referred to a specialist centre. This will allow us to identify outlier hospitals and target them for education.	Comments noted. Issues about access and rarity of disease are not considered equality issues under the equalities legislation. The appraisal committee will consider whether its recommendations could have a different impact on people protected by the equality legislation.
	Peninsular Technology Assessment Group	No comments	Response noted.

Section	Consultees	Comments [sic]	Action
Other considerations	Imaging Equipment	None	Response noted.
	Ipsen	No comments	Response noted.
	Novartis	No comments	Response noted.
	Pfizer	No comments	Response noted.
	The NET Patient Foundation	No comments	Response noted.
	British Nuclear Medicine Society	A key question to consider is the administration schedule, as the effectiveness of Lu-177 DOTATATE is dependent on how it is used and the radiation doses delivered to tumours and to normal organs. The concept of recording administered radiation dose in the patient record needs to be reiterated.	Comment noted. Further information regarding the administration of the technologies should be presented in the consultee submissions for consideration by the appraisal committee.
	Royal College of Pathologists	None	Response noted.

Section	Consultees	Comments [sic]	Action
	UK and Ireland NET Society	Given the rarity and complexity of the condition we do hope that, as part of the scoping exercise, recognised experts in the management of NETs will be involved in the evaluation process.	Comments noted. Consultees will have the opportunity to nominate experts to attend the committee meetings. Consideration would be given to the knowledge/ experience of the nominated experts. Please see the Guide to the process of Technology Appraisals for further details.
	Healthcare Improvement Scotland	Given the rarity and complexity of the condition we do hope that, as part of the scoping exercise, recognised experts in the management of NETs will be involved in the evaluation process.	Comments noted. Consultees will have the opportunity to nominate experts to attend the committee meetings. Consideration would be given to the knowledge/ experience of the nominated experts. Please see the Guide to the process of Technology Appraisals for further details.
	Peninsular Technology Assessment Group	No comments	Response noted.

Section	Consultees	Comments [sic]	Action
Innovation	Imaging Equipment	Lu-177 DOTATATE is an innovative therapy in a disease area of high unmet need. This treatment offers a step change in the treatment of NETs; reflected by its usage across Europe prior to licence: • Lu-177 DOTATATE has Orphan Drug designation in both Europe and the United States. • Based on current scientific evidence of efficacy and safety, Lu-177 DOTATATE is currently available in 10 European countries (Austria, Estonia, France, Finland, Greece, Portugal, Spain, Switzerland, Denmark and the UK) under compassionate use or named patient programs for the treatment of NETs. • Lu-177 DOTATATE has been used as a treatment in more than 2,900 NET patients (results are published in more than 80 international publications). • PRRT has already been adopted in European Oncology Guidelines (ESMO and ENETS) for the treatment of GEP-NETs. • The French National Agency for Medicines and Health Products Safety (ANSM) has granted an "Autorisation Temporaire d'Utilisation de Cohorte" (ATU de Cohorte) or Cohort Temporary Authorization for Use, for Lu-177 DOTATATE ® for the treatment of midgut Neuro Endocrine Tumors (NETs). An ATU is the regulatory mechanism used by the ANSM to make non-approved drugs available to patients in France when a genuine public health need exists. In the UK, via CDF funding, there has been a high level of national support for Lu-177 DOTATATE for patients that have progressed on all other treatments. This is demonstrated by the number of patients treated in England: 212 patients in 2013, 163 patients in 2014, and 234 patients in 2015). Now this has been removed, patients have no access to the treatment, until a NICE has an opportunity to complete an MTA. Removal from the CDF is a retrograde step in the management of progressive GEPNETs according to UKINETs.	Comment noted. If there are additional health effects associated with this treatment that are not captured in the QALY calculation, evidence may be provided in the submissions and will be considered by the committee accordingly.

Section	Consultees	Comments [sic]	Action
	Ipsen	No comment.	Response noted.
	Novartis	Everolimus is an innovative oral anti-cancer therapy that controls the progression of NET by inhibiting the mTOR pathway, effectively reducing cell metabolism, tumour angiogenesis and tumour cell growth and proliferation There are currently no oral anti-cancer therapies available for patients with progressive non-functioning GI or lung NETs	Comment noted. If there are additional health effects associated with this treatment that are not captured in the QALY calculation, evidence may be provided in the submissions and will be considered by the committee accordingly.
	Pfizer	NICE has not made recommendations for any treatments in this indication and Pfizer believe that there is clear unmet need. Pfizer consider that sunitinib has demonstrated significant and substantial health-related benefits in the management of patients with pancreatic neuroendocrine tumours, with advanced metastatic progressive disease (2).	Comment noted. If there are additional health effects associated with this treatment that are not captured in the QALY calculation, evidence may be provided in the submissions and will be considered by the committee accordingly.
	The NET Patient Foundation	No comment	Response noted.

Section	Consultees	Comments [sic]	Action
	British Nuclear Medicine Society	The technology is innovative and as with many radiopharmaceutical therapy procedures under used. It offers the potential for a substantial cost-effective impact on health benefit.	Comment noted. If there are additional health effects associated with this treatment that are not captured in the QALY calculation, evidence may be provided in the submissions and will be considered by the committee accordingly.
	Royal College of Pathologists	Yes, the technology is innovative	Comment noted. If there are additional health effects associated with this treatment that are not captured in the QALY calculation, evidence may be provided in the submissions and will be considered by the committee accordingly.

Section	Consultees	Comments [sic]	Action
Questions for consultation	Imaging Equipment	Have all the relevant comparators been included in the scope? In particular should the following be included as comparators? • Interferon alpha? No, as it is not in line with established clinical practice in the NHS in England or current guidelines (Pavel et al. 2016, Ramage et al. 2012). • Ablation therapy? No, only a treatment option for hepatic metastasis and not in line with established clinical practice in the NHS in England. • Radiotherapy? No, as it is not in line with established clinical practice in the NHS in England or current guidelines (Pavel et al. 2016, Ramage et al. 2012). • Octreotide long acting release formulation? Yes	Comments noted. Octreotide LAR and interferon alpha have now been included as comparators in the scope. Please note that there were mixed responses from consultees regarding the appropriateness of interferon alpha as a comparator.
		Which treatments are considered to be established clinical practice in the NHS for treating neuroendocrine tumours of lung origin? • Lu-177 DOTATATE has been used in neuroendocrine tumours of the lung, but will not form part of its marketing authorisation and therefore will not be assessed in this process.	Comment noted.
		The use of lutetium-177 DOTATATE is conditional on the presence of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours. Is the diagnostic testing for somatostatin receptor-positive neuroendocrine tumours considered to be established clinical practice in the NHS? • Yes, it is established clinical practice in the NHS. There are over 40 hospitals in England conducting diagnostic testing for somatostatin receptors with Tc-99m Tektrotyd, In-111 Octreotide or Ga-68 DOTATATE or DOTATOC	Comment noted.
		How should best supportive care be defined? Definition of BSC in GEP-NET: BSC is defined as treatment with long acting somatostatin analogues e.g. octreotide for GEP-NETs which offers only symptomatic and palliative relief.	Comment noted.
		Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom the technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately? No subgroup analysis has been decided at this point in time.	
		NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular	

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		Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom the technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately? • No subgroup analysis has been decided at this point in time. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the scope may need changing in order to meet these aims. In particular, please tell us if the scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the technologies are or will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technologies, • could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. • None.	Comment noted. Comment noted.

Section	Consultees	Comments [sic]	Action
	Ipsen	1. Have all the relevant comparators been included in the scope? In particular should the following be included as comparators? • Interferon alpha? Intereron α is not commonly used, due to the side effect profile. Its use would be limited to situations where other approved drugs are unavailable or use in combination with SSAs. As such it would not be an appropriate comparator (Pavel M et al. Neuroendocrinology2016;103:172-185). • Ablation therapy? A decision to use ablation therapy would be very patient specific, as there are no clear guidelines on patient selection for this intervention. Where used, it would normally be alongside lanreotide and would therefore not be an appropriate comparator. • Radiotherapy? Standard radiotherapy is not a recommended treatment option. Its use would be limited to palliative treatment of bony metastases only. As such it would not be an appropriate comparator. • Octreotide long acting release formulation? Octreotide LAR gained a licence for the treatment of midgut NETs in 2009, and as such is an appropriate comparator for midgut NETs only.	Comment noted. Octreotide LAR and interferon alpha have now been included as comparators in the scope. Please note that there were mixed responses from consultees regarding the appropriateness of interferon alpha as a comparator.

Section	Consultees	Comments [sic]	Action
	Ipsen	*2. Which treatments are considered to be established clinical practice in the NHS for treating NET of lung origin?* Somatostatin analogues may form part of first-line therapy in lung NETs which are associated with the carcinoid syndrome. Somatostatin analogues may be considered as first-line systemic antiproliferative therapy in unresectable lung NETs, particularly low-grade typical carcinoid and atypical carcinoid lung NETs (Caplin ME et al. Annals of Oncology 2015;26:1604-20). However there are no RCTs investigating the use of lanreotide in this setting. *3. How should BSC be defined?* It is not possible to define BSC in this patient population as a whole, as the care needed will differ from patient to patient (based on tumour location, burden of disease, other comorbidities etc). *4. Is the diagnostic testing for somatostatin analogue receptor-positive NETs considered to be established practice in the NHS?* Diagnostic testing for somatostatin receptor positivity is established practice in the UK. However please note the comment above that confirmation of somatostatin receptor positivity is <u>not</u> required within the Somatuline Autogel licence, nor is it routine clinical practice to obtain this confirmation before initiating therapy with Somatuline Autogel. *5. Are the subgroups suggested in 'other considerations' appropriate?* Yes, these are appropriate.	Comment noted. Comment noted. Comment noted. The scope has been amended accordingly. Comment noted.

Section	Consultees	Comments [sic]	Action
	Novartis	Have all the relevant comparators been included in the scope? In particular, should the following be included as comparators? • Interferon alpha? • Ablation therapy? • Radiotherapy? • Octreotide long acting release formulation? Interferon alpha could be considered as comparator for GI NETs, in accordance with the consensus guidelines1. The guidelines recommend octreotide-LAR (and lanreotide) as first-line therapy in G1 and G2 non-functional GI (mid-gut NETs) and recommend interferon alpha as on option in the event of disease progression following a somatostatin analogue or a watch and wait protocol. However, interferon alpha is seldomly used in routine clinical practice.	Comment noted. Octreotide LAR and interferon alpha have now been included as comparators in the scope. Please note that there were mixed responses from consultees regarding the appropriateness of interferon alpha as a comparator.
		Which treatments are considered to be established clinical practice in the NHS for treating neuroendocrine tumours of lung origin? A recent advisory board meeting with 4 UK physicians8 that actively treat patients with lung NETs described the standard of care for patients with lung NETs to be chemotherapy, radiotherapy, or PRRT.	Comment noted.
		• How should best supportive care be defined? A recent advisory board meeting with 5 UK physicians that actively treat patients with NETs suggested that BSC included analgesia and anti-diarrhoeals.	Comment noted.

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	Novartis	The use of lutetium-177 DOTATATE is conditional on the presence of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours. Is the diagnostic testing for somatostatin receptor-positive neuroendocrine tumours considered to be established clinical practice in the NHS? We believe this to be standard clinical practice for evaluating whether a NET patient should commence any type of PRRT including Lutetitum-177 DOTATATE.	Comment noted.
	Pfizer	Have all the relevant comparators been included in the scope? In particular should the following be included as comparators? • Interferon alpha? • Ablation therapy? • Radiotherapy? • Octreotide long acting release formulation? Pfizer believe that all the relevant comparators have been identified. However, as outlined above, due to differences in marketing authorisation and evidence base the appropriateness of comparisons will need to be considered for each sub-population of interest, for example by tumour grade or location. Regarding the additional potential comparators included in the consultation we have the following comments: • Interferon alpha: Interferon-alpha 2b (IntronA) is the only interferon with a marketing authorisation in the treatment of NETs. It is licensed for treatment of carcinoid tumours with lymph node or liver metastases and with 'carcinoid syndrome' and should therefore be considered as a comparator for this subgroup of patients (6).	Comment noted. Octreotide LAR and interferon alpha have now been included as comparators in the scope. Please note that there were mixed responses from consultees regarding the appropriateness of interferon alpha as a comparator.

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	Pfizer	• Ablation therapy and radiotherapy: Pfizer are not aware of sufficient data to support inclusion of these treatment options as comparators • Octreotide LAR: Octreotide (Sandostatin LAR) is a potentially relevant treatment for a subgroup of patients included in the appraisal, but should not be compared to sunitinib. It is licensed for "treatment of patients with advanced neuroendocrine tumours of the midgut or of unknown primary origin where non-midgut sites of origin have been excluded" (7). Patients were excluded from the pivotal PROMID trial if their primary tumour was within the pancreas, chest, or elsewhere. Therefore, octreotide (Sandostatin LAR) is not an appropriate comparator for sunitinib in patients with tumours of pancreatic origin. Which treatments are considered to be established clinical practice in the NHS for treating neuroendocrine tumours of lung origin? No comments How should best supportive care be defined? There is no clear accepted definition of best supportive care. Given the wide range of treatments included in scope we propose that this is removed. The use of lutetium-177 DOTATATE is conditional on the presence of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours. Is the diagnostic testing for somatostatin receptor-positive neuroendocrine tumours considered to be established clinical practice in the NHS? No comments	Response noted. Comment noted. Response noted.

Section	Consultees	Comments [sic]	Action
	The NET Patient Foundation	No comments	Response noted.
	British Nuclear Medicine Society	In answer to questions for consultation: Diagnostic testing with radiopharmaceuticals is standard practice. In particular, Ga-68 Peptide PET is increasingly used and could potentially inform personalised treatment. Evidence should include multi-centre trials to establish radiation doses.	Comment noted.
	Royal College of Pathologists	No comments	Response noted.
	UK and Ireland NET Society	PRRT with lutetium dotatate represents a significant therapeutic advance for NETs patients. The future directions may also include combining lutetium with other radionuclides therapeutically. The mTOR pathway inhibitors and tyrosine kinase inhibitors such as Sunitinib are still relatively new but with randomised trial evidence of efficacy. The treatments available have the potential to greatly increase life expectancy in NET patients whilst maintaining a good quality of life.	Comment noted.
	Healthcare Improvement Scotland	PRRT with lutetium dotatate represents a significant therapeutic advance for NETs patients. The future directions may also include combining lutetium with other radionuclides therapeutically. The mTOR pathway inhibitors and tyrosine kinase inhibitors such as Sunitinib are still relatively new but with randomised trial evidence of efficacy. The treatments available have the potential to greatly increase life expectancy in NET patients whilst maintaining a good quality of life.	Comment noted.

Section	Consultees	Comments [sic]	Action
	Peninsular Technology Assessment Group	No comments	Response noted.
Additional comments on the draft scope.	Imaging Equipment	Any additional comments on the draft scope [redacted] The first controlled comparative study with a radiolabelled versus somatostatin analogue has reached its primary end point. The phase III Netter-1 trial compares the effect of Lu-177 DOTATATE on progression free survival (PFS), QoL and overall survival (OS) against treatment with double the prescribed dose of somatostatin analogue (octreotide). Since November 2015, Lu-177 DOTATATE has been removed from the CDF list of drugs to be reimbursed. Although not currently licensed, Lu-177 DOTATATE is endorsed as a therapeutic option for patients with GEP-NETs by the European Neuroendocrine Tumour Society (ENETS), the British Society of Gastroenterology and the European Society for Medical Oncology (ESMO) in their treatment guidelines for GEP-NETs. The implications of the CDF delisting has resulted in the removal of reimbursement and access to Lu-177 DOTATATE for patients with GEP-NETs as well as the dismantling of referral infrastructures across England which have grown as a direct result of Lu-177 DOTATATE reimbursement by the CDF. [redacted]	Comment noted.

Section	Consultees	Comments [sic]	Action
	Ipsen	Since the original MTA scoping meeting we have been concerned that due to the lack of understanding of the disease area and present clinical practice within NICE that lanreotide would not be positioned correctly versus the other drugs in the MTA. I would like to suggest that NICE involve a clinical expert to help them understand the disease area and present clinical practice prior to the scoping meeting.	Comments noted. Consultees will have the opportunity to nominate experts to attend the committee meetings. Consideration would be given to the knowledge/ experience of the nominated experts. Please see the Guide to the process of Technology Appraisals for further details.

Section	Consultees	Comments [sic]	Action
	Novartis	Any additional comments on the draft scope In addition to the current appraisal proposal for Everolimus, lanreotide, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression (ID858), Novartis Pharmaceuticals are aware of several other proposals by NICE to appraise technologies in the neuroendocrine tumour disease area: • Lanreotide for treating unresectable metastatic gastroentero-pancreatic tumours without disease progression (ID961) • Lutetium-177 DOTATATE for treating inoperable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours without disease progression'. NICE technology appraisal guidance (ID857) In order for everolimus be fairly assessed in accordance with its planned market authorisation in GI and lung NETs, and for the institute to provide guidance in a timely fashion, we request that NICE consider conducting an STA for everolimus in this indication given the high unmet clinical need and lack of effective treatment options for patients with non-functioning GI & Lung NETs. As per the principles for the new reimbursement process, NICE should appraise everolimus in GI and lung NETS as a new indication, within the timelines and principles outlined in the CDF operating model presented to NHS England board on the 25th February 2016. It should also be noted that patients with pancreatic NETs in England have been disadvantaged and have had no routine access to everolimus since May 2015. In contrast patients in Scotland and Wales have continued to access everolimus since 2012. The inclusion of everolimus for GI and lung NETs in an MTA risks an avoidable delay in progressive GI NET and lung NET patients gaining access to an effective treatment where there are no other treatments available. There is a risk that the current disadvantage for Pancreatic NET patients may also apply for the GI and Lung NET patients in future.	Please note that this topic was referred for appraisal before April 2016, when the new process for cancer topics came into place. However, NICE is still committed (as we were previously) to publishing guidance as quickly as possible following marketing authorisation, whilst also balancing the needs and efficiency of the TA work programme and what the NHS requires from NICE in this area. Removing everolimus from the MTA at this point, will not necessarily result in earlier publication of final guidance for everolimus, as it would need to be allocated a slot in the work programme which is under increasing demand. Also please note that an MTA will still allow the committee to consider whether a drug could be recommended in the context of the Cancer Drugs Fund.

Section	Consultees	Comments [sic]	Action
	Pfizer	Any additional comments on the draft scope References 1) Kulke et al. 2011. Future directions in the treatment of neuroendocrine tumors: Consensus report of the National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting. J Clin Oncol 29:934-943. 2) SPC Sutent, 2015. http://www.medicines.org.uk/emc/medicine/18531 Accessed March 2016. 3) SPC Afinitor, 2015. http://www.medicines.org.uk/emc/medicine/22281. Accessed March 2016. 4) Pavel et al, 2016. Consensus Guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology (ePub January 2016) 5) SPC Somatuline Autogel, 2015. http://www.medicines.org.uk/emc/medicine/25104. Accessed March 2016. 6) SPC IntronA, 2015. http://www.medicines.org.uk/emc/medicine/12194. Accessed March 2016. 7) SPC Sandostatin LAR, 2015. http://www.medicines.org.uk/emc/medicine/1321. Accessed March 2016.	Comment noted.
	The NET Patient Foundation	No comments	Response noted.
	Royal College of Pathologists	No comments	Response noted.
	UK and Ireland NET Society	No comments	Response noted.

Section	Consultees	Comments [sic]	Action
	Healthcare Improvement Scotland	No comments	Response noted.
	Peninsular Technology Assessment Group	No comments	Response noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

The Royal College of Nursing
Department of Health