Applying Reflective Multicriteria Decision Analysis (MCDA) to Patient–Clinician Shared Decision-Making on the Management of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET) in the Spanish Context

Monika Wagner · Dima Samaha · Jesus Cuervo · Harshila Patel · Marta Martinez · William M. O’Neil · Paula Jimenez-Fonseca

Received: May 10, 2018 / Published online: July 9, 2018 © The Author(s) 2018

ABSTRACT

Introduction: Unresectable, well-differentiated nonfunctioning gastroenteropancreatic neuroendocrine tumors (GEP-NETs) can be monitored (watchful waiting, WW) or treated with systemic therapy such as somatostatin analogues (SSAs) to delay progression. We applied a reflective multicriteria decision analysis (MCDA) shared-decision framework (previously developed for the USA) to explore what matters to Spanish patients and clinicians considering GEP-NET treatment options.

Methods: The EVIDEM-derived framework was updated and adapted to the Spanish context. During a Chatham House session, five patients and six physicians assigned criteria weights using hierarchical point allocation and direct rating scale (alternative analysis). Informed by synthesized evidence embedded in the framework, participants scored how each criterion favored SSA treatment (reference case lanreotide) or WW and shared insights and knowledge. Weights and scores were combined into value contributions (norm. weight x score/5), which were added across criteria to derive the relative benefit–risk balance (RBRB, scale -1 to +1). Exploratory comparisons to US study findings were performed.

Results: Focusing on intervention outcomes (effectiveness, patient-reported, and safety), the mean RBRB favored treatment over WW (+0.32 ± 0.24), with the largest contributions from progression-free survival (+0.11 ± SD 0.07), fatal adverse events (+0.06 ± SD 0.08), and impact on HRQoL (+0.04 ± SD 0.04). Consideration of modulating criteria (type of benefit, need, costs, evidence, and feasibility) increased the RBRB to +0.50 ± 0.14, with type of therapeutic benefit (+0.10 ± SD 0.08) and quality of evidence (+0.08 ± SD 0.06) contributing most towards treatment. Alternative weighting yielded similar results. Results were broadly comparable to those derived from the US study.

Enhanced digital features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.6610124.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12325-018-0745-6) contains supplementary material, which is available to authorized users.

M. Wagner (✉) · H. Patel · W. M. O’Neil
Analytica Laser, Montreal, Canada
e-mail: m.wagner@analytica-laser.com

D. Samaha
Analytica Laser, London, UK

J. Cuervo · M. Martinez
Analytica Laser, Madrid, Spain

P. Jimenez-Fonseca
Department of Medical Oncology, Hospital Universitario Central de Asturias, Oviedo, Spain

△Adis
Conclusion: The multicriteria framework helped Spanish patients and clinicians identify and express what matters to them. The approach is transferable across decision-making contexts.

Funding: IPSEN Pharma.

Keywords: EVIDEM; Gastroenteropancreatic neuroendocrine tumors; MCDA; Shared decision-making

INTRODUCTION

Nonfunctioning gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are slow-growing tumors with non-specific symptoms, which may lead to erroneous or delayed diagnosis [1]. Up to 60% of these tumors have already metastasized at the time of diagnosis [2]. In Europe, the prevalence of well-differentiated, nonfunctioning, neuroendocrine tumors of the pancreas and digestive organs is estimated to be 13 per 100,000 [3]. In the Spanish National Cancer Registry for Gastroenteropancreatic Neuroendocrine Tumors, 887 patients were registered from June 2001 through December 2008 [4]. Median survival among these patients exceeded 12 years, and the estimated 5-year relative survival was 78.1% for GEP-NETs of pancreatic and 80.4% for GEP-NETs of gastrointestinal (GI) origin [4].

According to the Sociedad Española de Oncología Médica [5], for patients with unresectable, advanced or metastatic, well-differentiated NETs, management options depend on tumor grade:

- For grade 1 disease (proliferative index, Ki67 ≤ 2%) observation with computed tomography (CT) scans every 3–6 months is recommended and somatostatin analogue (SSA) therapy (lanreotide or octreotide) may be considered if the octreoscan is positive.
- For grade 2 disease (Ki67 = 3–20%) or in patients with significant tumor burden, or in case of disease progression, SSA therapy (lanreotide or octreotide) is recommended if the octreoscan is positive and the proliferative index (Ki67) is below 10%. Other options include interferon, if SSA therapy fails; targeted agents (everolimus or sunitinib); chemotherapy if Ki67 > 10%; clinical trials; and peptide receptor radionucleotide therapy, if available.

More generally, the European Neuroendocrine Tumor Society Consensus Guidelines [6] state that SSAs may be used in stable or progressive disease or in patients with unknown tumor behavior. SSAs are recommended as first-line therapy in midgut, intestinal, and pancreatic NETs to control tumor growth.

These recommendations are primarily based on two double-blind clinical trials. In the multicenter PROMID study, 85 patients with well-differentiated, metastatic, midgut NETs were randomized to 30 mg octreotide LAR (long-acting formulation) monthly via intramuscular injection or matching placebo. Octreotide LAR significantly improved time to progression when compared with placebo [median 14.3 vs 6 months; hazard ratio (HR) 0.34; 95% confidence interval (CI), 0.20–0.59; \( P = 0.000072 \)]. After 6 months of treatment, 66.7% of patients in the octreotide LAR group had stable disease compared to 37.2% in the placebo group [7]. In the multinational CLARINET study, 205 patients with advanced, well- or moderately differentiated, nonfunctioning GEP-NET were randomized to lanreotide 120 mg via deep subcutaneous injection every 28 days or placebo. Lanreotide significantly improved progression-free survival (PFS) when compared with placebo (median not reached vs 18.0 months; HR 0.47; 95% CI 0.30–0.73, \( P < 0.001 \)) [8].

The guidelines above leave it open as to whether SSA therapy should be started at initial diagnosis of unresectable disease or after observation of the spontaneous tumor growth and initiated when disease progression occurs [6]. In such circumstances, in addition to the intervention’s potential risks and benefits, factors such as the impact of the disease, personal costs, and constraints as well as individual values and preferences would play a role in treatment decisions and should be discussed between patients and physicians. The right to patient autonomy is recognized by Spanish law [9] and several initiatives have been launched in Spain to empower patients to actively participate in healthcare decisions [9, 10]. In a recent
survey, the majority of Spanish cancer patients preferred a shared approach to decision-making, but only about half of them reported that this is what they actually experienced in practice [11], indicating a need to further develop approaches to support patient involvement.

In a previous study conducted in the USA, a framework to support shared decision-making for GEP-NET management had been designed on the basis of the open-source, multicriteria decision analysis (MCDA) EVIDEM framework [12]. The framework, in which the available evidence for GEP-NET management options was embedded, enabled patients and clinicians to identify what mattered to them in their individual decision-making context and share their diverse perspectives, thus supporting individual reflection and patient–clinician communication. In the current study, the framework was applied in the Spanish context with the objectives of validating the applicability of the approach across countries as well as exploring the preferences and underlying criteria that Spanish patients and clinicians use when considering and making their decisions on the treatment options for unresectable, well- or moderately differentiated, locally advanced or metastatic nonfunctioning GEP-NET.

METHODS

The study involved adaptation of the previously designed MCDA-based decision support framework for unresectable, well-differentiated, locally advanced or metastatic nonfunctioning GEP-NET to the Spanish context and its application to a group of Spanish patients and clinicians in a decision support workshop. The framework is designed in two modules: [12] the first allows one to derive a benefit–risk balance based solely on intervention outcomes ("core benefit–risk criteria", including comparative efficacy/effectiveness, comparative patient-perceived health/patient-reported outcomes, and comparative safety/tolerability), organized in the core benefit–risk tree. The second contains, in addition to the three core criteria, other decision-making factors that may modulate the benefit–risk balance (modulating criteria, organized in the modulated benefit–risk tree) (see Supp. Appendix A for full list of criteria and subcriteria and their definitions). The primary decision scenario, defined on the basis of Spanish and European clinical practice guidelines, explored whether to start SSA therapy (using lanreotide as reference case) or to monitor the disease (watchful waiting); a second scenario explored the choice between two SSA therapies, lanreotide and octreotide.

Evidence on GEP-NET and Management Options: MCDA Evidence Matrices

An evidence matrix was created following EVIDEM’s targeted systematic literature review methodology and data synthesis approach as reported previously [12, 13]. It was updated and adapted to the Spanish context, and translated into Spanish. Briefly, relevant evidence was retrieved from the biomedical literature databases (PubMed/Medline), Cochrane systematic reviews, clinical trial registries, conferences, bibliographies of pertinent publications, and patient and professional association websites (as well as other gray literature and proprietary data, as applicable). Clinical data were validated by a Spanish clinical GEP-NET expert. The evidence matrices included a total of 36 references.

Decision Support Workshop

Both patients and clinicians were invited to participate in the decision support workshop as experts in decision-making on the disease, following predefined recruitment criteria (Supp. Appendix B). Patients—adults with locally advanced or metastatic nonfunctioning (asymptomatic) GEP-NET receiving SSA treatment or under watchful waiting—were recruited through the local patient organization. Clinicians had to be active practitioners (oncologist or endocrinologist) specialized in treating patients with locally advanced or metastatic GEP-NET. In order to capture potential variations in practice and healthcare delivery, patients and clinicians were recruited from different regions of Spain.
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients. The study protocol was approved by the Ethics Committee of Clinical Investigation of the University Hospital Puerta de Hierro, Madrid. To create an environment for in-depth discussion, the decision support workshop aimed to include a maximum of 12 participants (patients and physicians) and was held under the Chatham House Rule [14]. The workshop was held in the Spanish language.

Study investigators first introduced the approach and decision criteria definitions (provided in Supp. Appendix 2). Then participants individually weighted the relative importance of the criteria on the basis of what mattered most and least to them when making a decision on the management options for unresectable, well-differentiated nonfunctioning GEP-NET. Participants applied two weighting methods: first, they distributed 100 weighting points across the domains, criteria, and subcriteria of the benefit–risk trees (hierarchical point allocation, HPA [15]); these weights were used for the primary analysis. Then, they rated the relative importance of each (sub)criterion on a scale from 1 to 5 (direct rating scale, DRS); the weights derived from this method were used in an alternative analysis [16].

Weighting was followed by a stepwise exploration of primary decision scenario on the basis of the evidence matrix: the evidence for a criterion was presented by study investigators, the group exchanged their views and comments, and then each participant expressed individually how consideration of the criterion would impact his/her decision by assigning a score on a constructed, cardinal scale ranging from +5 ("Much in favor of option 1") to −5 ("Much in favor of option 2"). Participants also recorded individual insights and needs for additional information in writing. For qualitative criteria, participants specified the type of impact on the decision (positive, no or negative impact). The same steps were followed to explore the second scenario. Participants provided their feedback on the process in a structured discussion at the completion of the workshop or in written form. Two weeks after the workshop, participants received the results of their own assessments and were asked to comment on whether these reflected their reasoning during the exercise (face validity).

**Data Analysis**

Data was analyzed as reported previously [12, 17]. Briefly, for both weighting methods, crude weights were normalized to sum up to 1.0 across all subcriteria and criteria of the core and modulated benefit–risk tree, respectively. Relative benefit–risk balances (RBRB) and modulated RBRBs were calculated following a linear additive model as the sums of the products of the normalized weights and standardized scores (= score/5). RBRBs can range in theory from −1 to +1.

To examine the impact of the weighting technique, the mean RBRBs, incorporating weights from the two weighting techniques, were compared. In addition, the proportions of participants for whom these RBRBs differed by more than 0.1 and by more than 0.05 points (corresponding to 5% and 2.5% of the total RBRB range) were determined.

Numerical outputs were calculated for individual participants and then combined into mean group values. Variability was quantified using standard deviations (SD). Written and verbal comments were organized and summarized by criteria. Exploratory analyses were performed to compare patient and clinician subgroups as well as to compare quantitative outcomes of the current and the US study, which followed a similar design and included the same number of patients and clinicians.

**RESULTS**

Five patients and six clinicians from different regions of Spain participated in the decision support workshop.
Clarifying Values and Preferences: Criteria Weights

Using hierarchical point allocation, the majority of participants assigned a non-zero weight to all criteria and subcriteria of the benefit–risk and the modulated benefit–risk tree, with the exception of level of chromogranin A and size of the affected population, both of which received a 0 weight from 7 of the 11 participants.

Distributing weights across the core benefit–risk tree (intervention outcomes), participants assigned the highest weight to impact on health-related quality of life (HRQoL) (normalized mean ± SD 0.15 ± 0.06), followed by fatal adverse events (0.13 ± 0.06), overall survival (0.12 ± 0.07), progression-free survival (0.12 ± 0.07), and impact on autonomy (0.09 ± 0.05), and the lowest weight to level of chromogranin A (0.01 ± 0.02) (Fig. 1a). The largest variations in weights were recorded for progression-free survival and overall survival (both SD ± 0.07). Exploratory subgroup analysis indicated that patients assigned the most weight to impact on HRQoL (0.15 ± 0.06), impact on autonomy (0.12 ± 0.06), and fatal adverse events (0.11 ± 0.08), whereas clinicians assigned the most weight to overall survival (0.14 ± 0.07), impact on HRQoL (0.14 ± 0.06), and fatal adverse events (0.14 ± 0.05).

Weighting all criteria (including the modulating), participants allocated the most weight to system capacity and appropriate use and type of therapeutic benefit (normalized mean ± SD 0.14 ± 0.07 for both), followed by comparative effectiveness (0.11 ± 0.05), quality of evidence (0.10 ± 0.08), and disease severity (0.10 ± 0.05) and the least weight to size of affected population (0.01 ± 0.02) and non-medical costs and constraints (0.02 ± 0.01) (Fig. 1b). Weights varied most for the criteria quality of evidence (SD ± 0.08), type of therapeutic benefit and system capacity and appropriate use (SD ± 0.07 for both). Exploration of subgroups revealed that both patients and clinicians assigned the highest weight to type of therapeutic benefit (0.15 ± 0.06 and 0.13 ± 0.08, respectively) and system capacity and appropriate use (0.14 ± 0.05; 0.15 ± 0.08), followed by patient-perceived health/PROs (0.11 ± 0.04) among patients and quality of evidence (0.12 ± 0.09) among clinicians.

Which Option Does Consideration of Each Criterion Favor? Criteria Scores, Impacts, Comments, and Insights

Exploring how each intervention outcome criterion favors SSA treatment (with lanreotide as a reference case) or watchful waiting, progression-free survival was clearly considered in favor of treatment, with a mean score of +4.5 (scale −5 to +5) and little variation among participants (SD ± 0.7) (Table 1). All other outcomes were also scored on the group level in favor of treatment; however, mean scores remained within the range of 0 to +1, with the exception of fatal adverse events (+2.2 ± 2.7), level of chromogranin A (+1.9 ± 1.9), and impact on HRQoL (+1.4 ± 1.3). The largest individual variations in scores (SD > ±2.5) were observed for the comparative safety/tolerability subcriteria as well as for convenience/ease of use/mode and setting of administration and impact on autonomy. In exploratory subgroup analysis, the greatest difference in scores was seen for tumor regression rate (patients +2.4 ± 1.8 vs clinicians −0.1 ± 1.0) and for non-fatal non-serious adverse events (−1.2 ± 3.4 vs +1.3 ± 2.1).

Among modulating criteria, disease severity and quality of evidence were clearly considered to be in favor of treatment [mean (SD) scores +3.8 ± 0.6 and +3.8 ± 1.0, respectively], with minor variation among participants and between patient and physician subgroups. Conversely, the greatest variations in scores (SD ≥±2.3) were seen for criteria of the domain economic consequences and constraints of intervention. In exploratory subgroup analyses, patients’ and clinicians’ assessments differed the most for cost of intervention to the healthcare system (patients vs clinicians +2.5 ± 1.6 vs −2.1 ± 2.2) and other medical costs and constraints to patient (+2.4 ± 2.5 vs +0.5 ± 2.0).

With respect to the qualitative modulating criteria (data not shown), five of the 11
Participants considered that opportunity costs and affordability had an impact in favor of treatment, but one considered it to favor watchful waiting. Four participants considered common goal and specific interests to favor treatment, while three deemed it to favor watchful waiting. For the other qualitative criteria (mandate and scope of the healthcare system, environmental impact, political/historical/cultural context), the majority of participants indicated that these were either not considered or had no impact on their decision-making.

Participants commented on the validity and (un)certainty of the clinical, economic, and epidemiological data presented and the potential availability of data from other sources (Table 1). They also noted the importance of considering the impact of the treatment on HRQoL, expressed the assumption that slowing disease progression could have a positive impact on HRQoL, and exchanged their insights on the impact of non-serious adverse events, such as diarrhea. The potential challenges and benefits of patient self-administration of lanreotide (i.e.,

Fig. 1 Mean (SD) normalized weights assigned by 11 participants using hierarchical point allocation to each domain/criterion/subcriterion of the MCDA a core and b modulated benefit-risk trees
Table 1: Condensed evidence synthesis and participant scores ($N = 11$) and individual comments exploring the decision scenario of treatment (lanreotide as a reference case) versus watchful waiting

| CRITERION | CONDENSED EVIDENCE SYNTHESIS BY MEAN SCORE (SD) | COMMENTS |
|-----------|-----------------------------------------------|----------|
| **COMPARATIVE EFFECTIVENESS** | | |
| Progression-free survival | **CLARINET** [22]: Lanreotide: median not reached (IQR: 24.3 months; 95% CI 30–64.0); Placebo: median: 18 months (95% CI 13.2–24.0); HR: 0.47 (95% CI 0.30–0.73); P = 0.001 | • It would also depend initially on the risk of progression of the disease<br>• The data are very robust. Primary endpoint on a registration/pivotal trial<br>• Important to note that the lanreotide-placebo benefit ratio was 2:1<br>• The OLE study is biased since it only included patients who had not progressed with lanreotide for 2 years (excluding 48% of patients who progressed before being in the CLARINET study)<br>• There is other evidence from Spanish case studies; however, these have much lower validity<br>• Patients have few symptoms, so this parameter is of little importance in this context<br>• A lot of uncertainty with respect to this point. However, clinicians are used to dealing with lack of perfect information and need to take decisions in daily practice considering different levels of uncertainty<br>• Clinical experience of the physician is also important, independently of the study data<br>• In my clinical experience, there is no evidence indicating a negative effect of lanreotide on symptoms related to the disease<br>• Here we should also consider the placebo effect |
| Disease symptoms | No data on tumor-related symptoms for either option | |
| Tumor regression rate | No data for either option | |
| Overall survival | **CLARINET** [22]: No statistically significant difference between lanreotide and placebo 0.8 (1.9) | • Green long follow-up in NET; 2 years of follow-up is very little and not sufficient to determine survival<br>• It is very difficult to measure the magnitude of benefit achieved on this criterion since we are dealing with an indolent disease<br>• This parameter is affected not only by the [SSA] treatment but also by any kind of intervention/management after completing the treatment, so it is almost impossible to establish causation<br>|
| Level of chromogranin A | **CLARINET** [22] % of pts with >50% reduction: Lanreotide 42%; placebo: 5%; P < 0.001 | |
| **COMPARATIVE PATIENT-PERCEIVED HEALTH / PROS** | | |
| HRQoL | **CLARINET** [22]: No significant differences between lanreotide and placebo in EORTC QLQ-C30 and EORTC QLQ-GI.NET21 scores 0.5 (0.4) | • From a clinical perspective, it is important that the treatment has no negative impact on patients’ HRQoL<br>• If the treatment can slow disease progression, it could also have a positive feedback on HRQoL<br>• With lanreotide, a negative impact on patients HRQoL has not been described<br>• There is a lack of information about the HRQoL of patients at baseline and during follow-up<br>• From a clinical perspective, it is important that the treatment has no negative impact on patients’ HRQoL<br>• If we compare it with placebo, not getting treatment will always be more “convenient” in terms of posology than any drug<br>• In Spain, lanreotide self-administration is not indicated for this condition<br>• From the patient perspective, self-administration of lanreotide is a bit complicated. However, many patients living in small villages would benefit from this form of administration<br>• Dignity is not usually measured for cancer drugs<br>• From a clinical perspective, there is no difference between alternatives in this aspect |
| Impact on autonomy | *EORTC Gastrointestinal NET21 study* (27) patients preferring self-injection experienced more independence (reduced visits to clinic). "Partner can handle injections when travelling." 0.8 (2.1) | • The information provided in the manual is describing a preference-based comparison between self-injection of lanreotide versus attending a medical site (and not real differences in autonomy between lanreotide vs watchful waiting)<br>• From a clinical perspective, it is important that the treatment has no negative impact on patients’ HRQoL<br>• If we compare it with placebo, not getting treatment will always be more “convenient” in terms of posology than any drug<br>• In Spain, lanreotide self-administration is not indicated for this condition<br>• From the patient perspective, self-administration of lanreotide is a bit complicated. However, many patients living in small villages would benefit from this form of administration<br>• From a clinical perspective, it is important that the treatment has no negative impact on patients’ HRQoL<br>• If we compare it with placebo, not getting treatment will always be more “convenient” in terms of posology than any drug<br>• In Spain, lanreotide self-administration is not indicated for this condition<br>• From the patient perspective, self-administration of lanreotide is a bit complicated. However, many patients living in small villages would benefit from this form of administration<br>• Dignity is not usually measured for cancer drugs<br>• From a clinical perspective, there is no difference between alternatives in this aspect |
| Impact on dignity | No data for either option 0.2 (0.4) | • From a clinical perspective, it is important that the treatment has no negative impact on patients’ HRQoL<br>• If we compare it with placebo, not getting treatment will always be more “convenient” in terms of posology than any drug<br>• In Spain, lanreotide self-administration is not indicated for this condition<br>• From the patient perspective, self-administration of lanreotide is a bit complicated. However, many patients living in small villages would benefit from this form of administration<br>• Dignity is not usually measured for cancer drugs<br>• From a clinical perspective, there is no difference between alternatives in this aspect |
| Convenience / ease of use / mode & setting of administration | Lanreotide: prefilled syringe allows self-administration 0.7 (0.7) | • Dignity is not usually measured for cancer drugs<br>• From a clinical perspective, there is no difference between alternatives in this aspect |
| **COMPARATIVE SAFETY / TOLERABILITY** | | |
| Non-fatal non-serious adverse events | *CLARINET* [22]: treatment-related lanreotide vs placebo: diarrhea: 26 vs 9%; abdominal pain: 14 vs 3%; cholestasis: 10 vs 3%; nausea 7 vs 2%<br>• Vomiting: 7 vs 0%<br>• Hyperglycemia: 5 vs 0% | • Diarrhea is normally transient and mild<br>• These effects are of little relevance because they do not usually decrease quality of life or autonomy<br>• From a clinical perspective, it is important that the treatment has no negative impact on patients’ HRQoL<br>• If we compare it with placebo, not getting treatment will always be more “convenient” in terms of posology than any drug<br>• In Spain, lanreotide self-administration is not indicated for this condition<br>• From the patient perspective, self-administration of lanreotide is a bit complicated. However, many patients living in small villages would benefit from this form of administration<br>• Dignity is not usually measured for cancer drugs<br>• From a clinical perspective, there is no difference between alternatives in this aspect |
| Non-fatal serious adverse events | **CLARINET** [22]: treatment-related lanreotide: 3% (hyperglycemia, diabetes mellitus, nausea, vomiting, abdominal pain, bile duct stenosis); placebo: 1% ( bile duct stenosis) 0.7 (0.4) | • NA<br>• From a clinical perspective, it is important that the treatment has no negative impact on patients’ HRQoL<br>• If we compare it with placebo, not getting treatment will always be more “convenient” in terms of posology than any drug<br>• In Spain, lanreotide self-administration is not indicated for this condition<br>• From the patient perspective, self-administration of lanreotide is a bit complicated. However, many patients living in small villages would benefit from this form of administration<br>• Dignity is not usually measured for cancer drugs<br>• From a clinical perspective, there is no difference between alternatives in this aspect |
| Fatal adverse event | **CLARINET** [22]: No fatal AEs in either arm 0.5 (0.1) | • NA<br>• From a clinical perspective, it is important that the treatment has no negative impact on patients’ HRQoL<br>• If we compare it with placebo, not getting treatment will always be more “convenient” in terms of posology than any drug<br>• In Spain, lanreotide self-administration is not indicated for this condition<br>• From the patient perspective, self-administration of lanreotide is a bit complicated. However, many patients living in small villages would benefit from this form of administration<br>• Dignity is not usually measured for cancer drugs<br>• From a clinical perspective, there is no difference between alternatives in this aspect |
### Table 1 continued

| TYPE OF BENEFIT OF INTERVENTION | Type of Therapeutic Benefit | Type of Preventive Benefit | Need for Intervention |
|--------------------------------|-----------------------------|----------------------------|-----------------------|
| **S** | **S** | **S** | **S** |

#### Disease severity
- Slow-growing tumors, no defining symptoms: 0% metastasized at diagnosis; 5-year survival: 78% pancreatic GEP-NETs, 80% GI GEP-NETs. Osimertinib: local, physical function and general health (SF-36) and PROMIS-29(SF) Utilities: 0.77 stable disease, 0.63 progressive disease, 0.64-0.74 with treatment

#### Continent needs
- Other anti-proliferative treatment options are generally recommended only after failure of SSA therapy. Chemotherapy is an early intervention option for pancreatic NET (advanced/metastatic G1-G2 NETs).

#### Size of population
- Prevalence in Europe (RARECARE data): 11,000/100,000 of differentiated, non-functioning, endocrine tumor of the pancreas and digestive organs.

#### Economic consequences and constraints of intervention
- Cost of intervention to patient
  - Lanreotide: €5,000 patient co-payment per year (3,34).
  - Watchful waiting: not applicable
  - Exact price is available

- Cost of intervention to the healthcare system
  - Lanreotide: €15,000-20,000 per patient (3,34).
  - Watchful waiting: no data

- Other medical costs & constraints to the patient
  - Lanreotide: potential constraints related to AE monitoring and, possibly, AE treatments. Both: Lanreotide and watchful waiting: potential constraints related to monitoring for disease progression

- Other medical costs & constraints to the healthcare system
  - Lanreotide: potential costs & constraints related to AE monitoring and treatments. Both: Lanreotide and watchful waiting: costs & constraints related to monitoring for disease progression

#### Knowledge about intervention
- Quality of evidence
  - Lanreotide: phase III placebo-controlled RCT (GARINNIT22) (i.e., hyperglycemia, diabetes, etc.)

#### Expert consensus/Clinical practice guidelines
- SEOM: Grade 3, disease with CT scan or consider SSAs; Grade 2 or significant tumor burden, or disease progression; SSA therapy (other options available). ENETS: may use SSA therapy in stable or progressive disease or in unknown tumor behavior

#### Feasibility
- System capacity and appropriate use of intervention
  - Lanreotide: nurses report short preparation and administration time (15-30 seconds).
  - Watchful waiting: usual standard of care (regular visits and scans).

### Notes
- AE: adverse event; CI: confidence interval; ENETS: European Neuroendocrine Tumor Society; HR: hazard ratio; HRQoL: health-related quality of life; NA: not available (no comments provided); OLE: open-label extension; QoL: quality of life; RCT: randomized clinical trial; SEOM: Sociedad Espanola de Oncologia Medica; SSA: somatostatin analogue.
difficult to self-administer but useful for remote populations) were also highlighted.

**Combining Weights and Scores to Derive the Overall Relative Benefit–Risk Balance**

At the group level, the mean RBRB (linear combination of weighted scores across all core benefit–risk subcriteria) favored treatment over watchful waiting ($0.32 \pm 0.24$, scale $-1$ to $+1$), but with wide individual variations across the 11 participants ($0.05$ to $+0.64$). In exploratory analysis, the RBRB favored treatment among both patients and physicians ($0.25 \pm 0.27$ vs $0.39 \pm 0.21$). Progression-free survival made the highest contribution to the mean RBRB ($0.11 \pm 0.07$), followed by fatal adverse events ($0.06 \pm 0.08$) and impact on HRQoL ($0.04 \pm 0.04$) (Fig. 2a).

Inclusion of the modulating criteria in the participants’ assessment increased the group’s overall RBRB to $0.50 \pm 0.14$ (Fig. 2b), with individual values ranging from $0.34$ to $+0.79$. Consideration of type of therapeutic benefit made the largest contribution ($0.10 \pm 0.08$) to the modulated RBRB, followed by quality of evidence ($0.08 \pm 0.06$), disease severity ($0.07 \pm 0.04$), system capacity and appropriate use ($0.07 \pm 0.08$), and comparative effectiveness ($0.05 \pm 0.03$). Similar modulated RBRBs were derived for the patient and the clinician subgroups ($0.52 \pm 0.13$ vs $0.47 \pm 0.18$).

Considering a potential choice between the SSA therapies (lanreotide and octreotide), the majority of criteria did not favor either option (data not shown), with a mean RBRB ($0.07 \pm 0.12$, range $-0.04$ to $+0.31$) and a modulated RBRB ($0.10 \pm 0.10$, range $-0.04$ to $+0.32$), slightly favoring lanreotide. Impact on autonomy contributed most to the RBRB ($0.06 \pm 0.06$) and quality of evidence to the modulated RBRB ($0.03 \pm 0.05$).

**Face Validity and Impact of the Weighting Method**

Seven patients and clinicians responded to the post-workshop face validity exercise; all confirmed that the visual representation of their weights and RBRBs reflected their thinking. Group-level RBRBs that incorporated weights elicited using the alternative weighting method (DRS) were similar to the RBRBs that incorporated weights elicited using the primary method (HPA) (Table 2). On an individual level, RBRBs elicited using the two methods differed by less than 0.10 points (on a scale of $-1$ to $+1$) for over 80% of participants and by less than 0.05 points for 45% to 63% of participants, depending on scenario and type of RBRB.

**Exploratory Comparison with US Study Findings**

Overall, mean weights and scores were similar between patients and clinicians participating in the Spanish and the US studies (Figs. 3, 4); nevertheless, specific differences were noted: Spanish participants tended to assign higher weights to the comparative patient-perceived health/PROs (and its subcriteria), type of therapeutic benefit, and system capacity and appropriate use at the expense of comparative efficacy/effectiveness and comparative safety/tolerability. Furthermore, compared to the US study, Spanish participants tended to score several criteria (and subcriteria) more in favor of treatment (positive scores), including convenience/ease of use/mode and setting of administration, comparative safety/tolerability, and the economic (sub)criterion, especially the cost to patient (Spain $2.5 \pm 2.7$ vs USA $2.8 \pm 1.8$) and the cost and constraints to patient ($1.4 \pm 2.3$ vs $1.2 \pm 1.3$).

Numerically, both the RBRB and the modulated RBRB were larger in the Spanish than in the US study (RBRB $0.32 \pm 0.24$ vs $0.18 \pm 0.20$; modulated RBRB $0.50 \pm 0.14$ vs $0.29 \pm 0.28$), but all favored treatment over watchful waiting. The single largest contributor to the RBRB was progression-free survival in both studies ($0.11$ and $0.12$). Two of the top three largest contributors to the modulated RBRB were the same in both studies (type of therapeutic benefit and disease severity); the remaining (quality of evidence) ranked
fourth in the US study and (comparative efficacy/effectiveness) fifth in the Spanish study.

DISCUSSION

In this study, Spanish patients and clinicians explored what matters to them and how it matters when considering and deciding on the treatment options for unresectable, well-differentiated nonfunctioning GEP-NET, on the basis of a previously developed reflective MCDA decision support framework, which has been adapted to the Spanish context.

The weighting exercise indicated that most criteria of the framework had at least some importance for GEP-NET decision-making for a majority of Spanish patients and clinicians, thus confirming their relevance for patients and clinicians facing the same clinical situation across different countries. The relative weights assigned across the core benefit–risk criteria revealed the critical role of patient-perceived health/PRO outcomes for the Spanish participants, particularly the patient subgroup, who allocated more weight to impact on health-related HRQoL (0.15 ± 0.06) and impact on autonomy (0.12 ± 0.06) than to any other outcome. In contrast, clinicians tended to assign lesser importance to impact on autonomy (0.07 ± 0.03) and more to overall survival (0.14 ± 0.07 vs 0.10 ± 0.06). Although these differences should be interpreted with caution as the study was not designed to derive valid comparisons between patients and clinicians, they do highlight the need for effective patient–physician communication to incorporate patients’ individual priorities in decision-making [18]. Non-fatal non-serious adverse events and non-fatal serious adverse events received comparatively small weights, indicating willingness to trade non-life-threatening risks and moderate side effects for improved quality of life and survival, as was also observed in previous studies [19–21]. Type of therapeutic benefit, quality of evidence, and disease severity figured among the highest weighted modulating criteria, confirming the importance of these considerations for decision-making. Disease severity and type of therapeutic benefit were also among the top three modulating criteria in the US study [12]. Nevertheless, large variability in weights was observed, reflecting differences in individual value systems.

System capacity and appropriate use also figured among the most important criteria based on HPA weighting. However, this criterion ranked only 8th in weight (among 14 criteria) when using the alternative weighting method, DRS, which largely confirmed the HPA-derived ranking of the other criteria. Using the hierarchical weighting method (HPA), participants had to assign a weight to the feasibility domain relative to other domains of the modulated benefit–risk tree; however, system capacity and appropriate use was the only criterion under the domain feasibility. In contrast, domains were not weighted using the non-hierarchical DRS method, which assigns weights at the criteria level only. These differences may explain the discrepancies in the weights for system capacity and appropriate use derived from the two methods. Each weight elicitation method stimulates a slightly different thinking pathway [16] (e.g., in this case, the HPA method prompted reflection on the importance of feasibility as a concept), and therefore weights are expected to vary across methods. The effect of the weight elicitation method on value assessment was previously explored and demonstrated minor impact at the group level [16]. This was confirmed in this study, which showed good agreements of RBRBs derived using the two weighting techniques on the group level and good agreements at the individual level. Previous research has also demonstrated reproducibility of DRS weights at the individual level [15].
A

Progression-free survival
Disease symptoms
Tumor regression rate
Overall survival
Level of Chromogranin A
HRQoL
Impact on autonomy
Impact on dignity
Convenience / mode & setting of administration
Non-fatal non-serious adverse events
Non-fatal serious adverse events
Fatal adverse events

Relative Benefit-Risk Balance (RBRB)†

B

Comparative effectiveness
Comparative patient-perceived health/PRO
Comparative safety/tolerability
Type of therapeutic benefit
Type of preventive benefit
Disease severity
Unmet needs
Size of affected population
Cost of intervention
Other medical costs & constraints
Non-medical costs & constraints
Quality of evidence
Expert consensus клиническое практики guidelines
System capacity and appropriate use of intervention

Modulated Relative Benefit-Risk Balance (MRBRB)†
Using the scoring exercise, patients and clinicians expressed their views on how each criterion favored one or other management option, on the basis of the available evidence and their own knowledge, and shared their insights with others. Similar to their US counterparts, Spanish patients and clinicians viewed impact on progression-free survival, disease severity, quality of evidence, and type of therapeutic benefit consistently in favor of SSA treatment. Large variations in scores indicated areas where individual perspectives diverged and/or where evidence was limited or inconclusive. For example, for comparative safety/tolerability outcomes, safety data from a double-blind study was available [22], but its interpretation with respect to decision-making differed significantly among individuals. Some qualitatively considered criteria also impacted the decision-making. The relative consistency between the findings of the current and the US study in terms of criteria weights, scores, and RBRBs validates the applicability of the approach across different settings. Nevertheless, the approach was also able to capture specific differences that are possibly related to cultural and healthcare system aspects. These include the importance of the concept of autonomy to Spanish patients as well as differences in the costs to patients between the Spanish and the US context. In the Spanish universal healthcare system, SSAs are classified under “Medicamentos y productos sanitarios de ‘Aportación Reducida’” [23, 24], for which patients pay a maximum monthly of €4.24 per prescription. In contrast, in the US healthcare system, depending on type of insurance, patients may have to contribute a co-payment of 20% [25], which could amount to over $14,000 annually for SSA therapy [12].

### Table 2 Comparison of RBRBs and modulated RBRBs incorporating weights elicited using the primary (HPA) and alternative (DRS) weighting methods

|                         | RBRB incorporates | Proportion of participants for whom HPA- and DRS-derived RBRBs differed by ≥ 0.1 points | ≥ 0.05 points |
|-------------------------|------------------|------------------------------------------------------------------------------------------|---------------|
|                         | HPA weights (primary analysis) | DRS weights (alternative analysis)         |                |
| Treatment vs watchful waiting |                  |                                                                                           |               |
| Mean (SD) RBRB          | 0.32 (0.24)      | 0.29 (0.22)                                                                               | 9% (1/11)     | 36% (4/11) |
| Mean (SD) modulated RBRB| 0.50 ± 0.14      | 0.45 ± 0.13                                                                               | 18% (2/11)    | 55% (6/11) |
| Treatment 1 vs treatment 2 |                  |                                                                                           |               |
| Mean (SD) RBRB          | 0.07 ± 0.12      | 0.06 ± 0.10                                                                               | 0% (0/11)     | 27% (3/11) |
| Mean (SD) modulated RBRB| 0.10 ± 0.10      | 0.08 ± 0.06                                                                               | 18% (2/11)    | 27% (3/11) |

RBRBs and modulated RBRBs can range from −1 to +1. N = 11 participants

**DRS** direct weighting scale, **HPA** hierarchical point allocation, **RBRB** relative benefit–risk balance, **SD** standard deviation

---

△ Adis
The overall feedback on the process was that the exercise was helpful to understand (“empathize with”) the point of view of those with different perspectives and thus the approach could have a role in supporting patient–clinician communication. Participants also noted

![Comparison of normalized weights from US and Spanish study participants](image)

Fig. 3 Comparison of normalized weights from US and Spanish study participants* for the (sub)criteria of the a core and b the modulated benefit–risk tree. *5 patients and 6 clinicians participated in each study. Error bars represent the standard error of the mean.
Fig. 4 Comparison of scores from US and Spanish study participants for the a benefit–risk intervention outcomes criteria and b the modulating criteria. *5 patients and 6 clinicians participated in each study. Error bars represent the standard error of the mean.
that the experience helped them realize the role of uncertainty in decision-making as well as the breadth of different aspects that can weigh on the decision and the challenge of balancing these considerations.

This study has a number of limitations, some of which have been highlighted by the participants and could be addressed in future research. Non-functioning GEP-NETs are heterogeneous in symptoms and prognosis [5]. Specifically, tumors of pancreatic and of intestinal origin may have distinct management implications and could have been explored separately [5]. Furthermore, although the language in the evidence matrix has been adapted, some patients commented that technical terms relating to clinical evidence were not always easy to understand, thus suggesting a need for additional efforts to convey technical information in more accessible language. An additional limitation was that the scoring scale, ranging from -5 to +5, may have subconsciously created a negative perception of the option that was associated with the negative score, which could be addressed by a different scale design. In this study, a reference case approach was used to explore the primary decision scenario, i.e., whether to start SSA therapy or to monitor the disease (watchful waiting), with lanreotide used as the reference SSA. Alternatively, the primary decision scenario could have been explored in a more comprehensive approach based on the data available for all SSAs; however, for certain clinical decision criteria, this would have doubled the amount of data to be considered by the participants during the workshop, while likely resulting in similar assessments as the reference case approach.

CONCLUSION

By providing a common platform to consider the wide range of factors that may impact a decision, the approach helped Spanish patients and clinicians identify and express what matters to them. Comparison with US study findings confirmed the transferability of the approach. This decision framework thus can be translated into a decision tool for supporting patient–clinician communication on individual values, preferences, and judgements, which extends beyond clinical factors and can be adapted to different decision-making contexts. Similar reflective multicriteria approaches could also be useful to collect stakeholder inputs for other applications, such as to inform clinical trial design or reimbursement decision-making.

ACKNOWLEDGEMENTS

The authors would like to thank all NET España patient experts and physicians who participated in the decision support workshop, including Drs. Javier Aller, Alberto Carmona-Bayonas, Rocio García-Carbonero, Paula Jimenez-Fonseca, and Alexandre Teule Vega. We thank NET España for their support in recruiting patients and Danielle Badgley for helping in data input and quality control.

Funding. This study was funded by IPSEN Pharma. The sponsor also provided funding for the journal’s article processing charges and the Open Access fee. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Disclosures. Monika Wagner is an employee of Analytica Laser, which has received consulting fees from Ipsen Pharma for the conduct of the study and writing of the manuscript. Dima Samaha is an employee of Analytica Laser, which has received consulting fees from Ipsen Pharma for the conduct of the study and writing of the manuscript. Jesus Cuervo was at the time of the study an employee of Analytica Laser, which has received consulting fees from Ipsen Pharma for the conduct of the study and writing of the manuscript. Harshila Patel is an employee.
of Analytica Laser, which has received consulting fees from Ipsen Pharma for the conduct of the study and writing of the manuscript. Marta Martinez is an employee of Analytica Laser, which has received consulting fees from Ipsen Pharma for the conduct of the study and writing of the manuscript. William O’Neil is an employee of Analytica Laser, which has received consulting fees from Ipsen Pharma for the conduct of the study and writing of the manuscript. Paula Jimenez-Fonseca is a medical oncologist who has received consulting fees from Ipsen Pharma for participating in the study.

Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients. The study protocol was approved by the Ethics Committee of Clinical investigation of the University Hospital Puerta de Hierro, Madrid.

Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Open Access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits any non-commercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. Gastroenterology. 2005;128(6):1717–51.

2. O’Connor JM, Marmissolle F, Bestani C, et al. Observational study of patients with gastroenteropancreatic and bronchial neuroendocrine tumors in Argentina: results from the large database of a multidisciplinary group clinical multicenter study. Mol Clin Oncol. 2014;2(5):673–84.

3. van der Zwan JM, Trama A, Otter R, et al. Rare neuroendocrine tumours: results of the surveillance of rare cancers in Europe project. Eur J Cancer. 2013;49(11):2565–78.

4. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). Ann Oncol. 2010;21(9):1794–803.

5. Garcia-Carbonero R, Jimenez-Fonseca P, Teule A, Barriuso J, Sevilla I. SEOM clinical guidelines for the diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) 2014. Clin Transl Oncol. 2014;16(12):1025–34.

6. Pavel M, O’Toole D, Costa F, et al. Consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NE) and NEN of unknown primary site. Neuroendocrinology. 2016;103(2):172–85.

7. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27(28):4656–63.

8. Caplin ME, Pavel M, Ruszniewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(16):1556–7.

9. Perestelo-Perez L, Rivero-Santana A, Alvarez-Perez Y, Alonso-Coello P, Orrego C, Serrano-Aguilar P. Shared decision making in Spain: supportive policies and research initiatives, trends and directions for future. Z Evid Fortbild Qual Gesundhwes. 2017;123–124:85–90.

10. Izquierdo F, Gracia J, Guerra M, Blasco JA, Andrades E. Health technology assessment-based development of a Spanish breast cancer patient decision aid. Int J Technol Assess Health Care. 2011;27(4):363–8.

11. Padilla Garrido N, Aguado CF, Ortega MM, Bayo CJ, Bayo LE. Shared decision making from the perspective of the cancer patient: participatory roles and evaluation of the process. An Sist Sanit Navar. 2017;40(1):25–33.
12. Wagner M, Samaha D, Khoury H, et al. Development of a framework based on reflective MCDA to support patient-clinician shared decision-making: the case of the management of gastroenteropancreatic neuroendocrine tumors (GEP-NET) in the United States. Adv Ther. 2018;35(1):81–99.

13. EVIDEM Collaboration. Evidence and value: impact on decision making. 2015. https://www.evidem.org/. Accessed 17 Sept 2015.

14. Royal Institute of International Affairs. Chatham House Rule. 2002. https://www.chathamhouse.org/about/chatham-house-rule. Accessed 15 Sept 2015.

15. Tony M, Wagner M, Khoury H, et al. Bridging health technology assessment (HTA) with multi-criteria decision analyses (MCDA): field testing of the EVIDEM framework for coverage decisions by a public payer in Canada. BMC Health Serv Res. 2011;11:329.

16. van Til J, Groothuis-Oudshoorn C, Lieferink M, Dolan J, Goetgebeur M. Does technique matter; a pilot study exploring weighting techniques for a multi-criteria decision support framework. Cost Eff Resour Alloc. 2014;12:22.

17. Goetgebeur MM, Wagner M, Nikodem M, Zyla A, Micaleff A, Anzal B. Pragmatic multicriteria decision analysis (MCDA) combined with advanced pharmacoepidemiology for benefit-risk assessments of medicines adapted to the real-life constraints of regulators: development and case study. Ther Innov Regul Sci. 2016;50(5):620–31.

18. Ubel PA, Scherr KA, Fagerlin A. Empowerment failure: how shortcomings in physician communication unwittingly undermine patient autonomy. Am J Bioeth. 2017;17(11):31–9.

19. Eichler HG, Bloechl-Daum B, Brasseur D, et al. The risks of risk aversion in drug regulation. Nat Rev Drug Discov. 2013;12(12):907–16.

20. Morel T, Ayme S, Cassiman D, Simoens S, Morgan M, Vandebroek M. Quantifying benefit-risk preferences for new medicines in rare disease patients and caregivers. Orphanet J Rare Dis. 2016;11(1):70.

21. Ashley D, Thomas D, Gore L, et al. Accepting risk in the acceleration of drug development for rare cancers. Lancet Oncol. 2015;16(4):e190–4.

22. Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(3):224–33.

23. Ministerio de Sanidad Servicios Sociales e Igualdad. Cartera de servicios comunes de prestación farmacéutica. 2017. https://www.msssi.gob.es/profesionales/CarteraDeServicios/ContenidoCS/5PrestacionFarmaceutica/FP-PrestacionFarmaceutica.htm. Accessed 19 Jan 2017.

24. Ministerio de Sanidad Servicios Sociales e Igualdad. Cartera de servicios comunes de atención especializada. 2017. https://www.msssi.gob.es/profesionales/CarteraDeServicios/ContenidoCS/3AtencionEspecializada/home.htm. Accessed 19 Jan 2017.

25. Casciano R, Chulikavit M, Perrin A, Liu Z, Wang X, Garrison LP. Cost-effectiveness of everolimus vs sunitinib in treating patients with advanced, progressive pancreatic neuroendocrine tumors in the United States. J Med Econ. 2012;15(Suppl 1):55–64.

26. Caplin ME, Pavel M, Cwikla JB, et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. Endocr Relat Cancer. 2016;23(3):191–9.

27. Johanson V, Wilson B, Abrahamsson A, et al. Randomized crossover study in patients with neuroendocrine tumors to assess patient preference for lanreotide Autogel® given by either self/partner or a health care professional. Patient Prefer Adherence. 2012;6:703–10.

28. Ipsen Pharma Biotech. Prescribing information. Somatuline depot. 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022074s011lbl.pdf. Accessed 29 June 2018.

29. Adelman DT, Burgess A, Davies PR. Evaluation of long-acting somatostatin analog injection devices by nurses: a quantitative study. Med Devices (Auckl). 2012;5:103–9.

30. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Neuroendocrine tumors. Version 1.2015. 2014. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 12 Nov 2015.

31. Beaumont JL, Cella D, Phan AT, Choi S, Liu Z, Yao JC. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. Pancreas. 2012;41(3):461–6.

32. Swinburn P, Wang J, Chandiwana D, Mansoor W, Lloyd A. Elicitation of health state utilities in neuroendocrine tumours. J Med Econ. 2012;15(4):681–7.

33. Ministerio de Sanidad Servicios Sociales e Igualdad. BOLETÍN OFICIAL DEL ESTADO. No. 185. I. Disposiciones generales. 2016.

34. Ministerio de Sanidad Servicios Sociales e Igualdad. BOLETÍN OFICIAL DEL ESTADO. No. 226. I. Disposiciones generales. Octreotide. 2016.