Title:

NUTRITIONAL STATUS OF PATIENTS WITH GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOR IN SPAIN: NUTRIGETNE

Sponsor:

Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)

[redacted]

Abbreviated title:

Nutrition in gastroenteropancreatic neuroendocrine tumor

Research Coordinators:

María Isabel del Olmo García/ María Argente Pla
Grupo de investigación: Unidad Mixta de Endocrinología, Nutrición y Dietoterapia. Hospital Universitario La Fe

Protocol version and date:

GETNE-S2109 - 1.0 March 12th, 2021

SPONSOR'S SIGNATURE PAGE

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SPONSOR REPRESENTATIVE: _____ Full Name Tittle	 _____ Signature date
COORDINATING INVESTIGATORS _____ Full Name Site Coordinating Investigator	 _____ Signature date
  _____ Full Name Site Coordinating Investigator	 _____ Signature date

PRINCIPAL INVESTIGATOR Dr. _____ Principal Investigator Site: _____	 _____ Signature date (dd/mm/yyyy)

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ABBREVIATIONS

BIA	Bioelectric Impedance Analysis
BMI	Body Mass Index
CI	Confidence Interval
CRO	Contract Research Organization
DEXA	Dual-Energy X-ray Absorptiometry
DMP	Data Management Plan
DMR	Data Management Report
eCRF	Electronic Case Report Form
EN	Enteral Nutrition
EOM	Estudio Observacional con Medicamentos (siglas en castellano)
GEP	GastroEnteroPancreatic
HDL	High Density Lipoprotein
ICF	Informed Consent Form
LDL	Low Density Lipoprotein
NEN	NeuroEndocrine Neoplasm
NET	NeuroEndocrine Tumor
NRS	Nutritional Risk Screening
ONS	Oral Nutritional Supplement
PA	Phase Angle
QoL	Quality of Life
SDV	Source Data Verification
SGA	Subjective Global Assessment
SSA	Somatostatin Analogs
VEGF	Vascular Endothelial Growth Factor
WOCBP	Women Of Child Bearing Potential

1. STUDY INFORMATION

OBSERVATIONAL STUDY WITH MEDICINES

Study title: **NUTRITIONAL STATUS OF PATIENTS WITH GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOR IN SPAIN: NUTRIGETNE**
Short title: **Nutrition in gastroenteropancreatic neuroendocrine tumor**
Acronym: **NUTRIGETNE**
Protocol code: **GETNE-S2109**
Protocol version and date: **1.0 from March 12th, 2021**
Reason for developing the study: **Initiative of the sponsor**
Medical product of interest **Not applicable, epidemiological study**
Territorial scope: **Spain**
Type of study: **Observational / Epidemiologic / Non-Interventional Study**

2. STUDY SPONSOR

Sponsor: **Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)**
Sponsor's contact address: [redacted]
Sponsor's representative: **Dr. Jaume Capdevila Castillón** **GETNE chairman** **Vall d'Hebrón University Hospital** **Medical Oncology Department** [redacted]

3. RESPONSIBLE PARTIES

First Ethical Committee that evaluated the study: **CEIc Hospital Universitari i Politécnic la Fe** [redacted]
Coordinating Investigators: **Dr. Maria Isabel del Olmo García; M.D. Ph.D.** **Unidad Mixta de Endocrinología, Nutrición y Dietoterapia** **Phone:** **E-Mail:** **Dr. Maria Argente Pla; M.D. Ph.D.** **Unidad Mixta de Endocrinología, Nutrición y Dietoterapia** **Phone:** **E-Mail:**
Coordinating Investigator Centers: **Grupo de investigación: Unidad Mixta de Endocrinología, Nutrición y Dietoterapia.** **Hospital Universitario La Fe** [redacted]
Autonomous Community of the Coordinating Investigator **Comunitat Valenciana**
Clinical monitor: **MFAR Clinical Research S.L.**
Monitor contact address: [redacted]

4. SUMMARY

4.1. Administrative Information

Protocol code: **GETNE-S2109**
Study title: **NUTRITIONAL STATUS OF PATIENTS WITH GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOR IN SPAIN**
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Sponsor: **Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)**
Sponsor's contact address: [redacted]
Coordinating Investigators: **Dr. Maria Isabel del Olmo García; M.D. Ph.D.** **Unidad Mixta de Endocrinología, Nutrición y Dietoterapia** **Phone:** **E-Mail:** **Dr. Maria Argente Pla; M.D. Ph.D.** **Unidad Mixta de Endocrinología, Nutrición y Dietoterapia** **Phone:** **E-Mail:**
Coordinating Investigator Centers: **Grupo de investigación: Unidad Mixta de Endocrinología, Nutrición y Dietoterapia.** **Hospital Universitario La Fe** **Avinguda de Fernando Abril Martorell, 106** **46026 València**
Clinical monitor: **MFAR Clinical Research S.L.**
Monitor contact address: [redacted]
First Ethical Committee that evaluated the study: **CEIc Hospital Universitari i Politécnic la Fe** [redacted]

4.2. Methodological Aspects

Rationale and context	It is well known that the prevalence of malnutrition or risk of malnutrition in cancer patients is high, as well as its impact on different parameters such as hospitalization, survival or response to certain treatments. In patients with gastroenteropancreatic (GEP) neuroendocrine tumors (NET), due to their heterogeneity and longer survival, it is expected that the prevalence of malnutrition is probably underdiagnosed, as well as the existence of a negative impact on different parameters (quality of life, survival). So far, the studies carried out on nutrition and NET are very scarce and none has been carried out so far in Spain. Before being able to carry out nutritional intervention studies on these patients, it is necessary to know the reality of the nutritional status of patients with NETs in Spain. The main motivation for the NUTRIGETNE study is to evaluate the epidemiological status of nutrition in NETs in the spanish population. In addition to know the epidemiological picture, it is intended to study the nutritional status from different points of view: analytical, clinical, anthropometric, etc. Besides, the study of nutritional status will allow us to closely monitor the patients who have a higher risk of malnutrition and to propose early interventions for those, as well as the impact of their nutritional status on different parameters: survival, hospitalization, quality of life or responses to the treatments.
Hypothesis and Objectives	NUTRIGETNE aims to be the first stage to subsequently allow to carry out nutritional intervention studies in NET patients. The study will make an extensive description of the impact of the nutritional status in patients with NET. The results will allow us to advance in the knowledge about different nutritional problems that appear in patients with NET, in the use of screening tools in these patients and in relevant information for future clinical practice guidelines. There are 3 main hypothesis: 1. Malnutrition and the risk of malnutrition in patients with GEP NET is frequent, but its prevalence in our environment is unknown. 2. The nutritional status may influence the prognosis, survival, quality of life or response to treatments in GEP NET patients. 3. Therapeutic approaches in GEP NET patients could have a direct impact on the nutritional status of these patients and may be a possible benefit on early intervention in the event that this negative impact exists. <u>Objectives:</u> PRIMARY: - Describe the prevalence of malnutrition and risk of malnutrition in GEP NET patients in Spain. SECONDARY: - Describe the nutritional status of NET patients by using clinical malnutrition scores, anthropometry, bioimpedanciometry, and analytical parameters. - Describe the nutritional status of NET patients according to the type of NET. - Study the association between the nutritional status and the quality of

	life of the patients. - Study the association between the nutritional status and the stage of the disease and tumor grade. - Study the association between the nutritional status and the treatments received by the patient. - Study the association between the nutritional status and the hormonal functionality of the tumor. - Study the association between nutritional status and survival of NET patients. - Describe specific deficiencies or deficiencies of vitamins or trace elements in these patients and study if there is a correlation of these with the treatments or tumor types.
Study Design	NUTRIGETNE is a cross-sectional, open and multicenter study in which the nutritional status of patients with GEP NET in Spain will be evaluated. It is planned to include 400 GEP NET patients. Patients will be included consecutively when visiting the corresponding health centers for outpatient visits or hospitalization. The study comprises 3 stages with a total duration of 10 to 40 days for the participation of each subject in the study: - Screening visit, First day (day 0): The initial screening will take place on the first day the patient visits the hospital. The inclusion and exclusion criteria will be reviewed to assess the eligibility of the patient. The implications of the study will be explained to the patient and the informed consent will be signed. - Visit for assessment of nutritional status (days 0-10): taking a medical history, complete physical examination including anthropometry, bioelectrical impedance (BIA) and dynamometry, as well as laboratory analysis. The evaluation of the nutritional status will be carried out by a registered nutritionist, specialized nurse or specialist doctor (variable depending on the characteristics of the center). - Data collection (day 10-40): collection of analytical, anthropometric, BIA, dynamometry and clinical results and introduction into the eCRF. After the end of recruitment and database lock, all data will be subsequently analyzed and presented when applicable through study reports and scientific communications.
Number of investigators (estimated)	A total of 16 investigators from 16 hospitals are expected to be included in the study.
Population of Study	Inclusion criteria: - Patients diagnosed with a gastroenteropancreatic neuroendocrine tumor by histopathological study. - Legally capable patients ≥ 18 and ≤ 80 years of age. - Patients who have signed the informed consent for this study as specified in section 10.3. - Patients in active treatment: active treatment is considered to be those patients in an advanced stage and in any type of medical treatment (somatostatin analogues, molecular therapies, chemotherapy, radionuclides...), or locoregional therapies. *Note: Decision was taken to treat the patient with an specific treatment prior and independently of patient inclusion in this non interventional*

	study. Exclusion criteria: - Patients <18 or > 80 years of age. - Female patients that are currently pregnant. - Patients with a gastroenteropancreatic neuroendocrine tumor lacking an histopathological diagnosis. - Patients in palliative treatment or terminal stage. - Patients who have not signed the informed consent or any situation or condition that compromises the giving of patient voluntary informed consent.
Endpoints	● Demographic characteristics: Age and ECOG at inclusion, sex, complete physical examination (including blood pressure and heart rate), enolic and smoking habits, other cancer history. ● NET diagnosis: date of initial diagnose, age at diagnose. ● NET at baseline: location of primary tumor, histological grade, TNM grade, Ki-67, mitotic index, metastatic locations, functional status of the tumor. ● NET treatment: a. Prior treatments: systemic therapies for NET (type, start and end date, best response, progression date), locoregional therapies (type, start and end date, best response, progression date), surgery (dates, outcome) and radiotherapy (type, dose, start and end date). b. Current treatments (at baseline): systemic therapies for NET (type, start date, best response), locoregional therapies (type, start date, best response) and radiotherapy (type, dose, start date). c. Hospitalizations (at baseline): cause, start and end date. ● Target nutritional history: regular weight, loss of weight (start date, duration), weekly food intake (calculation of mean daily caloric intake, mean protein intake, (animal and vegetal), mean carbohydrates intake (simple or complex), mean fat intake (saturate, monounsaturated, polyunsaturated, n-3 and n-6), and mean fiber intake (soluble and insoluble). The PREDIMED score test will be used (appendix 2). Calculation of caloric-protein nutritional requirements, according to ESPEN guidelines. Need for supplementation, if necessary, type of oral nutritional supplement (ONS) used, volume administered (ml / day), type of administration regimen (continuous or discontinuous). Number of intakes per day and volume of intakes and existence of intolerance related to enteral nutrition (EN): Diarrhea, constipation, bloating, nausea, vomiting, regurgitation, fever, ...). ● Nutritional screening test: NRS test (nutritional risk assessment) (appendix 3) and SGA test (subjective global assessment) (appendix 4). The GLIM criteria for diagnosis and stratification of malnutrition will be applied. ● Quality of life (QoL) test: EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire)(appendix 5) and the NET specific questionnaire

	(GI.NET21)(appendix 6). • Anthropometry: height, weight at baseline, BMI, triceps fold, brachial circumference, abdominal circumference, calf circumference. • Bioelectrical impedance: resistance and reactance recording, phase angle calculation, total body water, fat compartment, muscle compartment. Obtaining the basal metabolic rate. • Dynamometry: measurement of muscle strength. • Blood biochemical analysis: glucose, A1c, peptide c, complete lipid profile (total cholesterol, HDL, LDL and triglycerides), renal function, blood count, hemostasis, total proteins, albumin, prealbumin, transferrin, iron metabolism, calcium-phosphorus metabolism, magnesium, vitamin B12 , folic acid, vitamin A, D and E, retinol binding protein. • Pregnancy test at screening (only when applicable, WOCBP).
Data sources	Study data must be verifiable with source data, which requires access to all original records, laboratory reports, and subject records. Therefore, the patients or their legal representatives must be informed and allow access to the patient's medical records, whose agreement will be expressed when providing informed consent (ICF). Prior to documentation of any patient data, the patient will be informed about this project using the Patient Information and Informed Consent Form (Stand-alone document). At any time during the study or thereafter, the patient is free to withdraw his/her consent regarding the participation in this project and the use of his/her data. In this case, the patient will be asked to fill in the Informed Consent Withdrawal Form (Stand-alone document). In case of such withdrawal, the documented patient data will not be deleted to comply with study quality and regulatory requirements, but no further data will be collected. After provision of Informed Consent, patient, disease and treatment data will then be collected. Nutritional status and QoL data will be measured/collected on the patient visit for assessments (days 0-10 after signing the informed consent). All data will be transferred by qualified site staff from the patient records into an electronic Case Report Form (eCRF)(stand-alone document) in a pseudonymous form, i.e. encoded by a unique patient pseudonymization number and without the documentation of any patient identifiers such as full name, initials, full date of birth, address, etc. A period of 30 days (days 10-40 after signing the informed consent) is pre-established for the collection of each patient data in the eCRF. Upon completion of the case, the responsible physician will sign the forms. The patient identification list allocating the pseudonymization number to the patient identification data will be confidentially held at the site. The CRO, MFAR Clinical Research, will check the eCRF with regard to completeness, correctness and plausibility – in exchange with the Sponsor – will request completion and correction from the sites as necessary and will then proceed with the statistical processing decided by the Sponsor and defined in the statistical plan.

Study Sample size	It is planned to include 400 GEP NET patients in Spain. Patients will be included consecutively when visiting the corresponding health centers for outpatient visits or hospitalization. Assuming an estimated prevalence of malnutrition of around 30% (according to previous studies) and establishing as a precision criterion for its determination a length of the confidence interval (CI) of +/- 5 percentage units, it has been estimated by Monte Carlo simulation that the sample size required to reach the 5% CI would be 300 patients. However, taking into account the uncertainty in the initial assumption, it has been decided to increase the precision to a confidence interval length of +/- 3 percentage units, resulting in a required sample size of 400 patients. This size of 400 patients will also allow the secondary endpoints to be addressed with sufficient statistical power to obtain conclusive results or generate new hypotheses of interest to be tested in future studies.
Data Analysis	The data will be summarized using the mean (standard deviation) and the median (1st and 3rd quartiles) in the case of continuous variables and using relative and absolute frequencies in the case of categorical variables. The prevalence together with its corresponding 95% confidence interval will be estimated by fitting a binomial model. The associations between the nutritional status and the quality of life of the patients, the stage of the disease and the tumor grade will be contrasted using ordinal regression models. Survival will be analyzed using cox regression models or parametric survival models according to the assumptions that meet the data. All analyzes will be performed using R software (version 4.03 or higher).
Timelines and Study Calendar	Study activation: 1Q 2021 1st patient in: 2Q 2021 Study close-out (end of recruitment): 2Q 2022 End of study (including statistical analysis): 4Q 2023

5. AMENDMENTS AND UPDATES

No amendments yet recorded

6. STUDY CALENDAR AND MILESTONES

Study activation: 1Q 2021
1st patient in (star data capture): 2Q 2021
Study close-out (end of recruitment): 2Q 2022
End of study (including statistical analysis, results interpretation/publication): 4Q 2023

Final study report: 4Q 2023

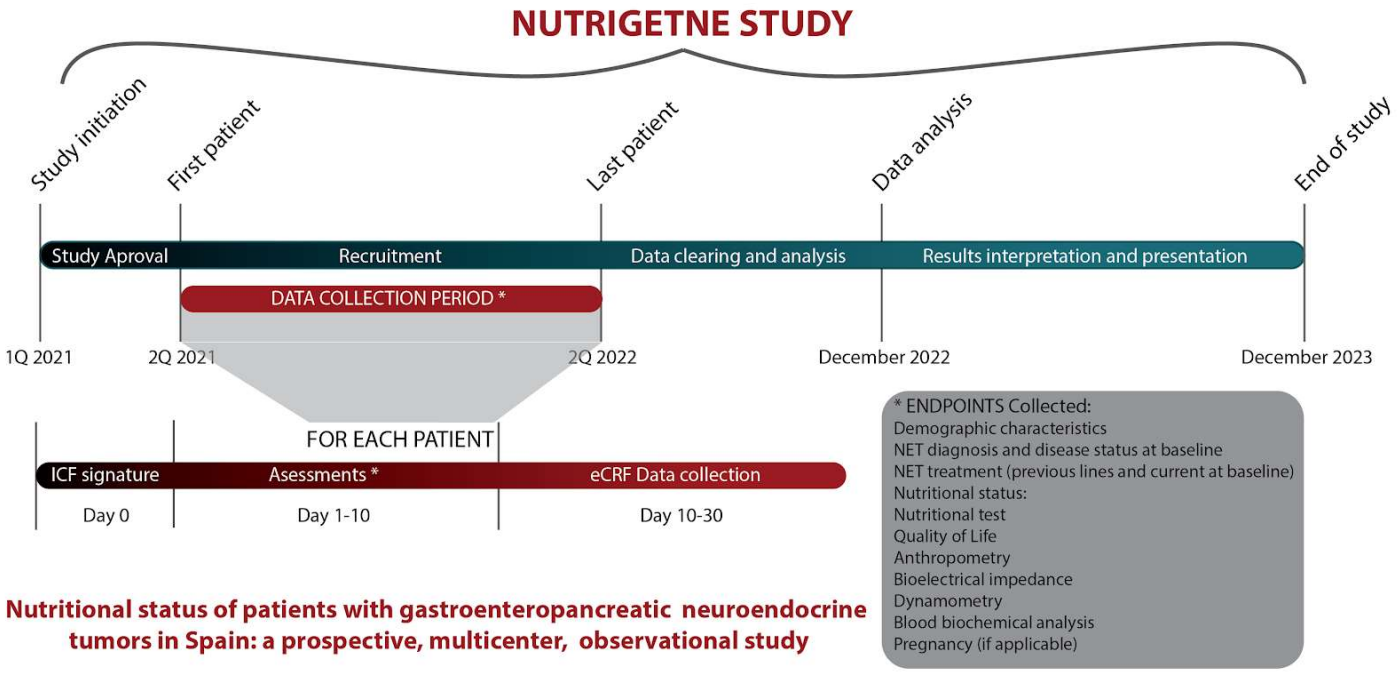

Figure 1. Study calendar scheme and milestones.

7. RATIONALE AND BACKGROUND

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms whose incidence has increased considerably in recent years, reaching approximately 7.4 cases per 100,000 inhabitants. NETs can appear in any organ or tissue, although they usually affect the gastroenteropancreatic (GEP) or pulmonary system and show a high prevalence and considerable survival. The age of onset varies considerably but the peak of incidence is in the 6th decade of life, except when it is related to hereditary syndromes such as Multiple Endocrine Neoplasia type 1 or Von Hippel Lindau disease in which disease onset is more precocious. The clinical manifestations include specific syndromes related to hormonal secretion and local symptoms in relation to the location of the primary tumor and its mass effect, but NETs can also be diagnosed incidentally. GEP NETs are characterized by hormonal secretion that can lead to significant metabolic imbalances. However, universal screening for hormone secretion is not recommended in the absence of specific signs or symptoms related to the syndromes in question, but early diagnosis is essential as it may positively impact in the course of the disease.

Although NETs have a relatively indolent disease course, they are frequently diagnosed in advanced stages with the presence of metastases, especially in the liver. Throughout the natural course of the disease, patients are treated with multiple lines of therapy. Apart from the corresponding surgeries, the first line of treatment is usually somatostatin analogues (SSA) that control hormonal hypersecretion and have an antiproliferative effect. Following progression to SSA, molecular targets such as sunitinib or everolimus, radionuclide therapy, and chemotherapy can be used in different treatment sequences.

Both the tumor itself (functionality or location) and the treatments used (surgeries and systemic treatments) can have a direct impact on the nutritional status of the patient. Nutritional status plays a very important role in those patients with functioning GEP NETs, since nutrition is very affected due to the excessive production of gastrointestinal hormones, peptides and amines that can lead to malabsorption, diarrhea, steatorrhea or alterations in intestinal motility. In the case of carcinoid syndrome, serious nutritional deficits can also occur because hormonal secretion leads to an increase in the production of serotonin and, as consequence, to a deficit of niacin. Besides, surgical management of NETs, that involves resection and / or alteration of the anatomy of the gastrointestinal tract, or the treatment with SSA, which suppresses the secretion of pancreatic enzymes as well as the secretion and functioning of gastrointestinal hormones, can condition secretory, motor or malabsorptive alterations with relevant consequences at the nutritional level such as fat malabsorption or fat-soluble vitamin deficiencies. Systemic drugs such as chemotherapy, interferon, mTOR inhibitors or vascular endothelial growth factor (VEGF) inhibitors also have deleterious effects on nutritional status as they cause anorexia, weight loss, diarrhea and alterations of the hepatic function.

Therefore, disease-related malnutrition (DRM) in patients with NETs is multifactorial [1]

and its importance relies in the clinical repercussions it has on the patient: it worsens quality of life, decreases response to treatment and increases the complications, the need for hospitalization, the hospital stay, the costs and mortality. Diverse studies have shown that poor nutritional status in patients with pancreatic NETs can negatively influence patient survival and can even predict tumor response in patients who receive chemoembolization as a treatment for liver metastases [2-5]. Another study published in 2018 demonstrated a novel association between nutritional status and GEP-NET aggressiveness in a selected cohort of adult patients, in part due to their adherence to the Mediterranean diet [6]. The study concluded that the dietary pattern of the Mediterranean diet could be beneficial for GEP-NET patients and could modulate the risk of tumor aggressiveness, offering a practical strategy for the treatment of these patients [6].

However, the nutritional intervention and approach of patients with NETs is often relegated to a second place or not performed. There are very few studies that have evaluated the direct impact in the case of patients with NET, their epidemiology or the consequences of direct nutritional interventions. Several authors also point out that malnutrition is probably underdiagnosed in this patient population [1,7]. Thus, several studies [1,7] show that nutritional assessment is not usually performed routinely in patients with NETs: in one study, only 28% of specialists reported that they performed nutritional assessments as part of their routine care; in another, less than 50% of patients with NETs had their weights measured, and body mass index (BMI) was available in only 14% of these patients. There is a single cross-sectional study [5] carried out in Germany on 203 patients in which the authors described that up to 25% of the patients were at risk of malnutrition defined by subjective global assessment (SGA) scores and nutritional risk screening (NRS), especially those patients with high grade or under treatment with chemotherapy. The authors concluded that malnutrition was an independent prognostic risk factor apart from the proliferative capacity of the tumor.

Therefore, early detection of DRM and appropriate treatment can help to improve the prognosis of these patients. Clinical guidelines [8-9] systematically advise the detection of nutritional risk in an early stage of cancer followed by a complete nutritional assessment when the risk is present, with the aim of establishing a nutritional intervention. Nutritional screening should be performed upon diagnosis of the disease and reassessed before and during each stage of treatment. There are multiple validated tests to perform nutritional screening, but there is no specific nutritional screening test for patients with NETs.

Currently, the complete assessment of nutritional status is based on several methods, which generally reflect the metabolic status of a patient in a composite way. These methods include assessment of oral intake, muscle mass, physical performance, and systemic inflammation.

Involuntary weight loss is the main clinical feature of cancer cachexia [8]. However, on many occasions it goes unnoticed given the degree of obesity or previous overweight

of the patients. For this reason, the prognostic importance of weight loss in relation to BMI has been described in cancer patients [10]. There is also evidence that excess body fat represents a cause of cancer development, specifically, there is a meta-analysis [11] that showed that an increase in BMI was the second risk factor after family history for developing a NET. In a series of non-functioning GEP NETs [2], the presence of metabolic syndrome was associated with greater severity in the tumor, in both terms size or Ki-67 proliferation index. On the contrary, the “obesity paradox” suggests that a higher BMI reduces the risk of mortality in cancer patients, despite a higher risk of developing cancer with higher BMIs. For this reason, it is of special interest to know the body composition of these patients: fat mass, muscle mass and total amount of body water. The reduction in muscle mass can be recognized by anthropometry, with special attention to the muscular perimeter of the arm, or by more precise techniques such as dual-energy X-ray absorptiometry (DEXA), lumbar computed tomography (L3) or bioelectrical impedance analysis (BIA). BIA provides the phase angle (PA), which has been proposed as a marker of nutritional status and also to assess disease progression. In general, lower PA values are indicative of a worse prognosis and higher morbidity and mortality.

Other methods to assess nutritional status consist of the measurement of various circulating serum proteins, such as albumin or transferrin, as indicators of protein turnover and, therefore, of systemic inflammation; or the combination of albumin with body weight as the nutritional risk index. Finally, it is essential to value functionality, which is the characteristic by which a person manages and develops independently for different activities, from the most elementary and in the most immediate environment, to the most complex in the community. Functional tests make it possible to determine the impact of the nutritional status on the functional capacity of the individual, the most used being dynamometry, functional tests such as gait speed and validated scales for this purpose (ECOG, Karnofsky...).

At the national level, the Spanish Neuroendocrine Tumors Group (GETNE) was created in 2005 with the intention of analyzing the reality of NETs in our country, improving the diagnosis and management of patients with NETs, facilitating continuous medical training, identify the needs of patients and promote the development of clinical and translational research both nationally and internationally. There is a NET registry in which there are currently about 3,000 patients with a diagnosis of NET from the different participating centers. So far in Spain no study has been carried out to evaluate the nutritional status of patients with NETs. Thus, the knowledge on this subject in our environment continues to be fragmented and incomplete, and this is where the motivation to carry out the current study arises, aiming to evaluate the nutritional status of patients with NET in our country.

8. HYPOTHESIS AND OBJECTIVES

Malnutrition in GEP NET patients entails greater morbidity and mortality and has been described as frequent. However, the prevalence of malnutrition or risk of malnutrition in patients with GEP NET in our country is unknown and its diagnosis is probably underestimated. Knowledge on this subject is still scarce and this is where the motivation for this observational study has arisen from.

NUTRIGETNE aims to be the first stage to subsequently allow to carry out nutritional intervention studies in NET patients. The study will make an extensive description of the impact of the nutritional status in patients with NET. The results will allow us to advance in the knowledge about different nutritional problems that appear in patients with NET, in the use of screening tools in these patients and in relevant information for future clinical practice guidelines.

There are 3 main hypothesis:

1. Malnutrition and the risk of malnutrition in patients with GEP NET is frequent, but its prevalence in our environment is unknown.
2. The nutritional status may influence the prognosis, survival, quality of life or response to treatments in GEP NET patients.
3. Therapeutic approaches in GEP NET patients could have a direct impact on the nutritional status of these patients and may be a possible benefit on early intervention in the event that this negative impact exists.

8.1. Main Objective

- Describe the prevalence of malnutrition and risk of malnutrition in GEP NET patients in Spain.

8.2. Secondary Objectives

- Describe the nutritional status of NET patients by using clinical malnutrition scores, anthropometry, bioimpedanciometry, and analytical parameters.
- Describe the nutritional status of NET patients according to the type of NET.
- Study the association between the nutritional status and the quality of life of the patients.
- Study the association between the nutritional status and the stage of the disease and tumor grade.
- Study the association between the nutritional status and the treatments received by the patient.

- Study the association between the nutritional status and the hormonal functionality of the tumor.
- Study the association between nutritional status and survival of NET patients.
- Describe specific deficiencies or deficiencies of vitamins or trace elements in these patients and study if there is a correlation of these with the treatments or tumor types.

9. RESEARCH METHODS

9.1. Study design

NUTRIGETNE is an observational *cross-sectional, epidemiologic, non-interventional, multicenter* study in which the nutritional status of patients with GEP NET in Spain will be evaluated. It is planned to include 400 GEP NET patients. Patients will be included consecutively when visiting the corresponding health centers for outpatient visits or hospitalization.

The study will use secondary data retrieved from medical records from each patient. The medical records include all the clinical variables defined in order to perform the analysis and it is not necessary to access additional sources. Patients will be asked to provide a signed informed consent as detailed in section 10.3 and fulfill a set of tests and questionnaires in one visit during their participation in the study to assess their nutritional status. Detailed information about the tests and determinations to be performed to the patients during their participation in the study is listed on section 9.3.

The assignment of a patient to a specific therapeutic strategy has been already decided in advance by the usual clinical practice of medicine; the decision to prescribe a specific treatment was clearly dissociated from the decision to include a patient in the study. There will be no specific target treatment or medicine for this study, only epidemiological methods will be used to analyse the data collected.

The study comprises 3 stages with a total duration of 10 to 40 days for the participation of each subject in the study:

- Screening visit. First day (day 0): The initial screening will take place on the first day the patient visits the hospital. The inclusion and exclusion criteria will be reviewed to assess the eligibility of the patient. The implications of the study will be explained to the patient and the informed consent will be signed.

- Visit for assessment of nutritional status (days 0-10): taking a medical history, complete physical examination including anthropometry, bioelectrical impedance (BIA) and dynamometry, as well as laboratory analysis. The evaluation of the nutritional status will be carried out by a registered nutritionist, specialized nurse or specialist doctor (variable depending on the characteristics of the center).

- Data collection (day 10-40): collection of analytical, anthropometric, BIA, dynamometry and clinical results and introduction into the eCRF.

After the end of recruitment and database lock, all data will be subsequently analyzed and presented when applicable through study reports and scientific communications.

9.2. Setting and study population

Approximately 400 adult patients diagnosed with gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) will be selected at 16 hospitals in Spain.

The beginning of patients' documentation with first patient enrolment is planned for 2Q 2021; the planned total duration of inclusion is 12 months (2Q 2022). The last patient observation is planned in 2Q 2022. Subsequently, it is considered a period of data analysis and clearing of 6 months and 12 months more for results interpretation, presentation and / or publication. End of study, including data publication, is planned for December 2023.

9.2.1. Inclusion Criteria

1. Patients diagnosed with a gastroenteropancreatic neuroendocrine tumor by histopathological study.
2. Legally capable patients ≥ 18 and ≤ 80 years of age.
3. Patients who have signed the informed consent for this study as specified in section 10.3.
4. Patients in active treatment: active treatment is considered to be those patients in an advanced stage and in any type of medical treatment (somatostatin analogues, molecular therapies, chemotherapy, radionuclides...), or locoregional therapies.

Note: Decision was taken to treat the patient with an specific treatment prior and independently of patient inclusion in this non interventional study.

9.2.2. Exclusion Criteria

1. Patients <18 or > 80 years of age.
2. Female patients that are currently pregnant.
3. Patients with a gastroenteropancreatic neuroendocrine tumor lacking an histopathological diagnosis.
4. Patients in palliative treatment or terminal stage.
5. Patients who have not signed the informed consent or any situation or condition that compromises the giving of patient voluntary informed consent.

9.3. Study Size

The sample size calculation is based on the expected prevalence of malnutrition

among NET patients in Spain, which was inferred from previous studies [1-7]. We expect to include a total number of 400 patients with GEP NETs.

Assuming an estimated prevalence of malnutrition of around 30% (according to previous studies) and establishing as a precision criterion for its determination a length of the confidence interval (CI) of +/- 5 percentage units, it has been estimated by Monte Carlo simulation that the sample size required to reach the 5% CI would be 300 patients. However, taking into account the uncertainty in the initial assumption, it has been decided to increase the precision to a confidence interval length of +/- 3 percentage units, resulting in a required sample size of 400 patients. This size of 400 patients will also allow the secondary endpoints to be addressed with sufficient statistical power to obtain conclusive results or generate new hypotheses of interest to be tested in future studies.

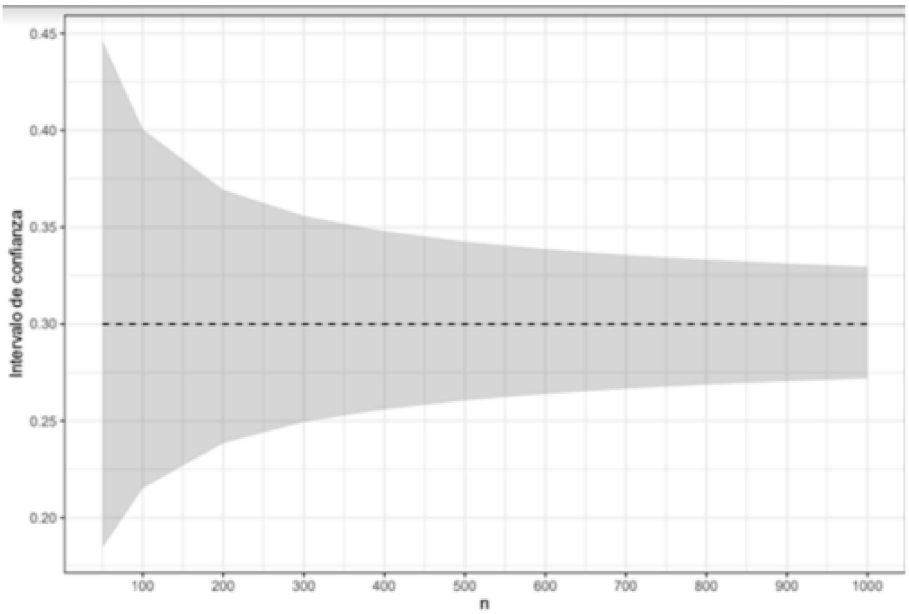

Figure 2. Calculation of sample size for a 5% CI on malnutrition prevalence.

9.4. Sampling and recruitment method

Patients will be consecutively included, in compliance with the previously established inclusion criteria. Recruitment at that centre will stop until further notice (e.g. if there is a need for recruitment).

According to the definition of study population and disease established in this scientific report, patients will be selected from cases histologically diagnosed with GEP NETs.

To prevent two or more reporting physicians from logging the same case, a coordinator, who controls the cases included in his or her centre, is appointed in health centres with several reporting physicians, and preventive measures are implemented in the tool controlling duplications in variables (such as age, gender, centre or diagnosis date).

9.4.1. Case Definition

A ‘case’ is defined as any patient, diagnosed, treated, or followed in the different health centres where reporting physicians authorised by the sponsor, who meets the inclusion criteria.

Healthcare will be provided following the applicable clinical criteria, in the context of usual clinical practice, regardless of patient inclusion in the study and following the best criteria of the specialists responsible for the patients.

9.5. Endpoints

- Demographic characteristics: Age and ECOG at inclusion, sex, complete physical examination (including blood pressure and heart rate), enolic and smoking habits, other cancer history.

- NET diagnosis: date of initial diagnose, age at diagnose.

- NET at baseline: location of primary tumor, histological grade, TNM grade, Ki-67, mitotic index, metastatic locations, functional status of the tumor.

- NET treatment:
  a. Prior treatments: systemic therapies for NET (type, start and end date, best response, progression date), locoregional therapies (type, start and end date, best response, progression date), surgery (dates, outcome) and radiotherapy (type, dose, start and end date).
  b. Current treatments (at baseline): systemic therapies for NET (type, start date, best response), locoregional therapies (type, start date, best response) and radiotherapy (type, dose, start date).
  c. Hospitalizations (at baseline): cause, start and end date.

- Target nutritional history: regular weight, loss of weight (start date, duration), weekly food intake (calculation of mean daily caloric intake, mean protein intake, (animal and vegetal), mean carbohydrates intake (simple or complex), mean fat intake (saturate, monounsaturated, polyunsaturated, n-3 and n-6), and mean fiber intake (soluble and insoluble). The PREDIMED score test will be used (appendix 2). Calculation of caloric-protein nutritional requirements, according to ESPEN guidelines. Need for supplementation, if necessary, type of oral nutritional supplement (ONS) used, volume administered (ml / day), type of administration regimen (continuous or discontinuous). Number of intakes per day and volume of intakes and existence of intolerance related to enteral nutrition (EN): Diarrhea, constipation, bloating, nausea, vomiting, regurgitation, fever, ...).

- Nutritional screening test: NRS test (nutritional risk screening) (appendix 3) and SGA test (subjective global assessment) (appendix 4). The GLIM criteria for diagnosis and stratification of malnutrition will be applied.

- Quality of life (QoL) test: EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire)(appendix 5) and the NET specific questionnaire (GI.NET21)(appendix 6).

- Anthropometry: height, weight at baseline, BMI, triceps fold, brachial circumference, abdominal circumference, calf circumference.

- Bioelectrical impedance: resistance and reactance recording, phase angle calculation, total body water, fat compartment, muscle compartment. Obtaining the basal metabolic rate.

- Dynamometry: measurement of muscle strength.

- Blood biochemical analysis: glucose, A1c, peptide c, complete lipid profile (total cholesterol, HDL, LDL and triglycerides), renal function, blood count, hemostasis, total proteins, albumin, prealbumin, transferrin, iron metabolism, calcium-phosphorus metabolism, magnesium, vitamin B12 , folic acid, vitamin A, D and E, retinol binding protein.

  Note: If there is a previous blood biochemistry analysis performed within 15 days prior to patient inclusion and containing all the items required and listed above, this test may be used for the patient in order to avoid further interventions.

- Pregnancy test at screening (only when applicable, WOCBP).

9.5.1. Timing for documenting endpoints

Once the patient accepts to participate in the study by signing the informed consent, information on the clinical history will be reviewed to gather the necessary data and to complete the electronic forms of the study designed for this purpose. The patient will have a visit with a nutritionist, specialized nurse or specialist doctor (variable depending on the characteristics of the center) within the next 10 days after ICF signature to perform the test and fulfill the questionnaires specified below:

- Complete physical examination
- PREDIMED and nutritional history
- Nutritional screening test (NRS, SGA)
- Quality of life test (EORTC QLQ-C30, GI.NET-21)
- Anthropometry
- Bioelectrical impedance
- Dynamometry
- Blood biochemical analysis and pregnancy test (if applicable, see section 9.5)

After the gathering of all the information specified in the eCRF, data from clinical history, test and questionnaires performed, the qualified site staff will fill all the information on the eCRF during a stipulated period of 30 days after the patients visit.

9.6. Data sources

Study data must be verifiable with source data, which requires access to all original records, laboratory reports, and subject records. Therefore, the patients or their legal representatives must be informed and allow access to the patient's medical records, whose agreement will be expressed when providing informed consent (ICF).

Prior to documentation of any patient data, the patient will be informed about this project using the Patient Information and Informed Consent Form (Stand-alone document). At any time during the study or thereafter, the patient is free to withdraw his/her consent regarding the participation in this project and the use of his/her data. In this case, the patient will be asked to fill in the Informed Consent Withdrawal Form (Stand-alone document). In case of such withdrawal, the documented patient data will not be deleted to comply with study quality and regulatory requirements, but no further data will be collected.

After provision of Informed Consent, patient, disease and treatment data will then be collected. Nutritional status and QoL data will be measured/collected on the patient visit for assessments (days 0-10 after signing the informed consent).

All data will be transferred by qualified site staff from the patient records into an electronic Case Report Form (eCRF)(stand-alone document) in a pseudonymous form, i.e. encoded by a unique patient pseudonymization number and without the documentation of any patient identifiers such as full name, initials, full date of birth, address, etc. The eCRF will have a selection section where information from all patients screened will be captured. Those patients that do not fulfill eligibility criteria and are defined as screening failure will be recorded in the eCRF selection section, but no further information will be captured. A period of 30 days (days 10-40 after signing the informed consent) is pre-established for the collection of each patient data in the eCRF. Upon completion of the case, the responsible physician will sign the forms. The patient identification list allocating the pseudonymization number to the patient identification data will be confidentially held at the site.

The CRO, MFAR Clinical Research, will check the eCRF with regard to completeness, correctness and plausibility – in exchange with the Sponsor – will request completion and correction from the sites as necessary and will then proceed with the statistical processing decided by the Sponsor and defined in the statistical plan.

9.7. Data management

The Contract Research Organization (CRO) MFAR Clinical Research (Barcelona, Spain) was assigned for elaboration of the eCRF. The eCRF allows documentation of the relevant study variables by all participating sites in a standardized way.

By documenting baseline patient data at initiation visit into the Site patient identification chart, patients will be registered with an automatically derived study patient number to ensure pseudonymized data collection. Additionally, patient name, address and study

patient number will be listed in a confidential manner on patient identification sheets at the respective sites to enable source data verification (SDV) at quality assurance visits.

All data will be transferred by qualified trained and identifiable site staff from the patient records into these forms in a pseudonymous form, i.e. encoded by a unique patient pseudonymization number and without the documentation of any patient identifiers such as full name, initials, full date of birth, address, etc. Upon completion of the case (between 10 and 40 days after patient ICF signature), the responsible physician will sign the eCRF and MFAR team will perform the data entry in the study database.

The patient identification list allocating the pseudonymization number to the patient identification data will be confidentially held at the site.

Regarding the handling of Solicited Adverse Event Collection Forms see section 11 “Safety reporting”.

The CRO will check the CRF with regard to completeness, correctness and plausibility – in exchange with the Sponsor – will request completion and correction from the sites as necessary and will then proceed with the statistical processing decided by the Sponsor and defined in the statistical plan. If in any case is written as a case report, a case presentation, a full paper, etc., within these finally generated documents, the patient data will be completely anonymous, i.e. not any identifier will be present.

9.7.1. Collection, monitoring, processing of data and archiving

The following chapters describe the software employed and measures applied for data security.

Data is recorded, processed and stored using the restricted access cloud system of MFAR in Google Drive, the server of this external vendor is located within the European Union and complies with the highest standards for data protection, and data security (see section 9.7.1.2).

Wherever applicable, GPV Module VI (collection, management and submission of reports of suspected adverse reactions to medicinal products), actual technical standards and guidelines are regarded.

9.7.1.1. Database software

The Study Database contains all study data in pseudonymous fashion collected by sites in the eCRF. The Database will be filed in the restricted access cloud system of MFAR in Google Drive, the server of this external vendor is located within the European Union.

9.7.1.2. Database security

For client / server communication via the Internet only encrypted transmissions are applied. State of the art encryption technology is used exclusively. For data

transmission in this observational study an encryption algorithm (sha256 RSA) is employed by means of the Transport Layer Security (TLS) version 1.2.

In addition, the server identifies itself to the client workstation by means of a digital server certificate issued by an authorized certification authority. By this, it is ensured that data is sent to the server of MFAR only.

Data is protected from potential virtual attacks and physical damage. Views on data or reports as well as edit or read only rights are controlled with individual passwords. Assurance of data will be made by RAID-Systems (Redundant Array of Independent Disks), thereby ensuring data security even if one hard disc fails.

9.8. Data analysis

The study will be analyzed descriptively, using descriptive epidemiological methods as detailed below. All results, including p-values and confidence intervals, are to be interpreted descriptively only.

- The analyses will be performed to the total population included fulfilling all selection criteria.

Additional subgroup analyses may be performed to fulfill secondary objectives (depending on the finally observed number of patients in such subgroups), including but not limited to: Tumor type, stage, grade and functionality, treatment type or survival.

The data will be summarized using the mean (standard deviation) and the median (1st and 3rd quartiles) in the case of continuous variables and using relative and absolute frequencies in the case of categorical variables. The prevalence together with its corresponding 95% confidence interval will be estimated by fitting a binomial model. The associations between the nutritional status and the quality of life of the patients, the stage of the disease and the tumor grade will be contrasted using ordinal regression models. Survival will be analyzed using cox regression models or parametric survival models according to the assumptions that meet the data. All analyzes will be performed using R software (version 4.03 or higher).

The final analysis will be performed within 6 months after the inclusion of the last patient. The final data interpretation and presentation in reports, scientific publications and/or congresses will be done within 12 months after the final analysis. The final report will be presented to the competent authorities 12 months after the end of study.

9.9. Quality assurance

9.9.1. Control of data consistency

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data.

- The study will use eCRFs. A designated CRO staff will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the findings and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.
- Concomitant treatments and all information on medications will be entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.
- Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.
- The site staff designated by the investigator will enter the information required by the protocol onto the eCRFs as well as onto the designated CRO's requisition form.

9.9.2. On site quality control

- Before study initiation, the protocol and CRFs will be reviewed with the investigators and their staff through a telephonic site initiation visit.
- During the study, the monitor will contact the selected sites through remote monitoring visits to check the completeness of patient records, the accuracy of entries on the CRFs. Key study personnel must be available to assist the field monitor during these visits.
- The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments.
- All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).
- The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries.

9.9.3. Audits

- To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the "Sponsor" may conduct site visits to institutions participating in this study

- The investigator, by accepting to participate to this protocol, agrees to cooperate fully with any quality assurance visit undertaken by third parties, including representatives from the “Sponsor”, national and/or foreign regulatory authorities or companies involved in the study, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorized individuals.
- The investigator must inform the “Sponsor” immediately in case a regulatory authority inspection would be scheduled.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Applicable Legislation

This is an observational, descriptive, non-interventional study with the main objective of collecting information on nutritional status of GEP NET patients, under clinical attention and follow-up in oncology departments of centres distributed across national level (Spain).

The study design includes prospective data collection. Information will be gathered from medical records and one visit to assess several variables related to nutritional status. Therefore, in accordance with the Royal Decree 957/2020 which regulates the observational studies with medicines for human use and in compliance with the same legislation, the participation of any centre will be conditional upon approval of a Clinical Research Ethics Committee and/or authorisation through the institution conformity.

Participating in this study does not pose any additional risk to patients because this is a study developed from information retrieved from the clinical histories and clinical assessment of patients, all in the context of the usual clinical practice and without the involvement of patients in any type of intervention that modifies the treatment that they would had receive if they not participated in the study.

The present protocol will be conducted in accordance with the principles adopted by the 18th World Medical Assembly (Helsinki, 1964) and their subsequent amendments (Fortaleza, 2013), following the rules of good clinical practice and deontological code.

10.2. Oversight Clinical Research Ethics

The study will be initially submitted for evaluation by the Clinical Research Ethics Committee of the Hospital Universitari i Politécnic La Fe (Valencia). As detailed in section 10.1, the study will also have the corresponding and applicable authorisations according to the local regulations of each centre and the guidelines of the Royal Decree 957/2020 which regulates the observational studies with medicines for human use.

10.3. Informed Consent

All the information will be extracted from the medical records of the participating patients who have authorized its use by signing the informed consent.

Given the need to interview the subjects to obtain certain data on their nutritional status, this protocol does not consider the exemption of signing informed consent. For this reason, written authorization is required by signing the informed consent (as

established by local Spanish regulations: the Royal Decree 957/2020 which regulates the observational studies with medicines for human use).

For all patients, the data are included in the study in an anonymized and dissociated way, guaranteeing that they cannot be associated with any identified or identifiable person. The use of patient data will be subject to a confidentiality commitment by all personnel participating in the study, including the researcher and her collaborators, data managers, data analysts, and monitors; this must be correctly recorded in the patient's medical record, with specific reference to the GETNE-S2109 - NUTRIGETNE study.

10.4. Confidentiality

Pursuant to the Statutory Law on Personal Data Protection (*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos de Carácter Personal y garantía de los derechos digitales* – LOPD), the sponsor guarantees the adoption of necessary measures to ensure the confidential treatment of personal data.

Before their inclusion in the study, patients will receive all information on this study and will sign the ICF (Stand alone document).

Only reporting physicians will know the full name of their patients. No sensitive information unnecessary for the intended purposes of the study is collected.

An electronic platform will be used to log data in the electronic Case Report Form (eCRF). To access the application, users must identify themselves with a username and a password strictly for personal use. Each reporting physician will only access the data he or she introduced that is strictly necessary for the job. Any document containing identifying data of the principal investigator, hospital, contact person, and telephone number will remain in the centre at all times, without being included in the database.

Data will be collected in a research file under the responsibility of the Sponsor and will be treated in the framework of the study, guaranteeing that the Sponsor will adopt pertinent measures to ensure compliance with the current legislation on data protection in all cases. The coded data can be transmitted to third parties and to other countries but in no case they will contain information that can directly identify any patient, such as name and surnames, initials, address, or social security number, among others. If this transfer occurs, it will be for the same study purposes as those described above or for scientific publications only, but always maintaining patient confidentiality according to current legislation.

The database will be examined exclusively by the scientific and medical staff of the Sponsor. No personal data or any information that may be related to patients will be included in this database. The database administrator, treatment manager, and monitor

(if applicable) will have access to all data that are not linked to any identifiable person.

In data explorations by researchers authorised by the Scientific Committee and in international data transfers to International Registries, if applicable, patients will be identified by a numerical code automatically and randomly assigned by the computer application at the start of logging of each case to maintain the confidentiality of personal patient data, as established in the European Union (EU) Parliament and Council General Data Protection Regulation 2016/679 on April 27, 2016 and the local Organic Law: 3/2018, de 5 de diciembre, de Protección de Datos de Carácter Personal y garantía de los derechos digitales – LOPD. This type of coding is used because it guarantees patient confidentiality while respecting the exercise of their access, revocation, consultation, and opposition rights.

Patients can refuse consent and can revoke once granted. In this case (revoking consent), no new data will be added to the database and/or logged for this study, although those data collected will be maintained in the database to guarantee the validity of the research and to comply with applicable legal and regulatory requirements.

Access to personal information of the study subjects will be restricted to the study physician/collaborators, health authorities (Spanish Medicines Agency), Clinical Research Ethics Committee, and staff authorised by the Sponsor, when they need to assess study data and procedures, but always maintaining patient confidentiality in compliance with the current legislation.

This assessment will be performed in the presence of the principal investigator or collaborators, responsible for guaranteeing the data confidentiality on the clinical histories of the study subjects. Only data collected for the study will be transmitted to third parties, which in no case will contain information that can directly identify the study subjects, such as name and surnames, initials, address, or social security number, among others. If this transfer occurs, it will be for the same study purposes as those described here and maintain patient confidentiality, at least with the level of protection of the current legislation, including data transfer outside the area of application of the reference legislation.

10.5. Funding Source

The study sponsor funds the study according to the guidelines of the present protocol. This funding covers all research materials; the cost of registration and control processes in Ethics Committees and health authorities; the design, maintenance, and management of the database; eventual statistical consultations, if necessary; and publishing and reporting costs. The funding will be, in any case, independent of the results of the study.

The sponsor guarantees non-interference in the processes of case selection, data

analysis, or in any other process that may affect the study results involving data exploration and presentation.

The participating physicians receive compensation for the expenditure of time related to the following activities:

- Familiarization with the study and the eCRF prior to the recruitment period;
- Patient information and obtaining written informed consent;
- Source data review and eCRF documentation during the recruitment period;
- Handling the patient visit to assess patient nutritional status through the determinations listed in section 9.

Detailed information of the planned compensations to the physicians, amount and distribution, will be enclosed in the economic dossier.

10.6. Potential advantage and limitations of research methods

The observational and epidemiological approach of this study offers the advantage of generating scientific data directly reflecting the current clinical routine with regard to the characteristics of the treated patients as well as with regard to the applied treatment regimens.

Inherent limitations of non-interventional, observational studies in general are the risk of selection/ascertainment bias, the inclusion of non-standardized assessments and evaluations, the non-standardization of time-points, and the lack of a parallel control group, which complicate the interpretation of the causality between treatments, nutritional status and outcomes. Furthermore, as with any "as observed" analysis, there is a potential risk of bias due to missing outcome data; this specific risk increases with the number of missing outcome data.

Sites are informed to enter all their patients fulfilling inclusion and exclusion criteria consecutively and in a period of 10 to 40 days after ICF signature to avoid selection bias and missing information.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

As stipulated in the Royal Decree 957/2020 which regulates the observational studies with medicines for human use, for those studies in which detection of suspected serious adverse reactions during the study is not possible or where the individual evaluation or causality of a clinical event within an specific drug is not appropriate, expedite notification of suspected adverse reactions will not be mandatory.

Accumulated data on safety aspects (serious adverse events and adverse drug reactions) related to medical products subject of study will be recorded by sites in the eCRF and included in the clinical study report by the sponsor, as this study is based on secondary use of data, no expedite reporting to the Sponsor is required.

In addition to the details specified in the previous paragraph, any relevant safety finding detected during the study will be brought to the attention of the AEMPS and competent bodies of Autonomous Communities involved, regardless of the study design or type.

12. WORK PLAN (TASKS, MILESTONES AND STUDY CHRONOLOGY)

2021 (Month)	1	2	3	4	5	6	7	8	9	10	11	12
Study activation												
Recruitment period												
Data and endpoint capture												
2022 (Month)	1	2	3	4	5	6	7	8	9	10	11	12
Recruitment period												
Data and endpoint capture												
Analysis of results												
2023 (Month)	1	2	3	4	5	6	7	8	9	10	11	12
Management and presentation of data for publication												

Figure 3. Working plan and calendar, GANTT chart

Please refer to section 6 for further detail on the study calendar.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study Sponsor holds the rights of exploring the data collected, stores and safeguards them, and acts as a Scientific Committee for the approval of proposals for data exploration and publication of results made by researchers.

The objective of the study, openly epidemiological, is to collect information on the management of the study disease and the nutritional status assessment of GEP NET patients in different participating hospitals to establish a framework for action (usual practice) and, therefore, study options for disease management beneficial for the patients.

13.1. Commitment and Publication Rules

The Coordinating Investigators and the Sponsor are responsible for the preparation of monographs or manuscripts summarising the logged data for publication.

Finally, it should be noted that the results of this study will serve as the basis for sending communications and presenting the results of both national and international congresses as well as the publication of different articles of interest, mentioning the study and the Sponsor.

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APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	2.0	10/02/2021	Patient Information Sheet and Consent Form
2	1.0		eCRF
3	1.0	12/03/2021	Contact details and list of all participating sites and physicians
4	1.0	12/03/2021	Economic dossier

APPENDIX 2. PREDIMED NUTRITIONAL STATUS SCORE TEST

ESTUDIO PREDIMED Cumplimiento de la dieta

Identificador del participante:

Nodo _____ C.Salud _____ Médico _____ Paciente _____ Visita _____

Nodo: anotar el número de nodo correspondiente.
01. Andalucía - Málaga / 02. Andalucía - Sevilla - S.Pablo / 03. Andalucía - Sevilla - V.Rocío / 04. Baleares / 05. Cataluña - Barcelona norte / 06. Cataluña - Barcelona Sur / 07. Cataluña - Reus - Tarragona / 08. Madrid Norte / 09. Madrid Sur / 10. Navarra / 11. País Vasco / 12. Valencia

C.Salud: anotar el número del centro de salud correspondiente.

Médico: anotar el número del médico correspondiente.

Paciente: anotar el número del paciente correspondiente.

Visita: anotar el número de visita correspondiente.
00. Inclusión - exclusión / 01. Visita Inicial / 02. Visita 3 meses / 03. Visita 1 año / 04. Visita 2 años / 05. Visita 3años

Fecha del examen

____ / ____ /200__
Día Mes Año

1. ¿Usa usted el aceite de oliva como principal grasa para cocinar?	Sí = 1 punto	☐
2. ¿Cuanto aceite de oliva consume en total al día (incluyendo el usado para freir, comidas fuera de casa, ensaladas, etc.)?	4 o más cucharadas = 1 punto	☐
3. ¿Cuantas raciones de verdura u hortalizas consume al día? (las guarniciones o acompañamientos = 1/2 ración) 1 ración = 200g.	2 o más (al menos una de ellas en ensalada o crudas) = 1 punto	☐
4. ¿Cuantas piezas de fruta (incluyendo zumo natural) consume al día?	3 o más al dia = 1 punto	☐
5. ¿Cuantas raciones de carnes rojas, hamburguesas, salchichas o embutidos consume al día? (ración: 100 - 150 g)	menos de 1 al dia = 1 punto	☐
6. ¿Cuantas raciones de mantequilla, margarina o nata consume al día? (porción individual: 12 g)	menos de 1 al dia = 1 punto	☐
7. ¿Cuantas bebidas carbonatadas y/o azucaradas (refrescos, colas, tónicas, bitter) consume al día?	menos de 1 al dia = 1 punto	☐
8. ¿Bebe usted vino? ¿Cuánto consume a la semana?	7 o más vasos a la semana = 1 punto	☐
9. ¿Cuantas raciones de legumbres consume a la semana? (1 plato o ración de 150 g)	3 o más a la semana = 1 punto	☐
10. ¿Cuantas raciones de pescado-mariscos consume a la semana? (1 plato pieza o ración: 100 - 150 de pescado o 4-5 piezas o 200 g de marisco)	3 o más a la semana = 1 punto	☐
11. ¿Cuantas veces consume reposteria comercial (no casera) como galletas, flanes, dulce o pasteles a la semana?	menos de 2 a la semana = 1 punto	☐
12. ¿Cuantas veces consume frutos secos a la semana? (ración 30 g)	3 o más a la semana = 1 punto	☐
13. ¿Consume usted preferentemente carne de pollo, pavo o conejo en vez de ternera, cerdo, hamburguesas o salchichas? (carne de pollo: 1 pieza o ración de 100 - 150 g)	Sí = 1 punto	☐
14. ¿Cuantas veces a la semana consume los vegetales cocinados, la pasta, arroz u otros platos aderezados con salsa de tomate, ajo, cebolla o puerro elaborada a fuego lento con aceite de oliva (sofrito)?	2 o más a la semana = 1 punto	☐

APPENDIX 3. NUTRITIONAL RISK STATUS (NRS) TEST

ESPEN Guidelines for Nutrition Screening 2002

J. KONDRUP,* S. P. ALLISON,† M. ELIA,‡ B. VELLAS,¶ M. PLAUTH§

*Rigshospitalet University Hospital Copenhagen, Denmark, †Queen's Medical Centre, Nottingham, UK, ‡University of Southampton, Southampton, UK, ¶University Hospital Centre, Toulouse, France, §Community Hospital Dessau, Germany (Correspondence to: JK, Nutrition Unit–5711, Rigshospitalet University, 9 Blegdamsvej, 2100 Copenhagen, Denmark)

Abstract—Aim: To provide guidelines for nutrition risk screening applicable to different settings (community, hospital, elderly) based on published and validated evidence available until June 2002.

Note: These guidelines deliberately make reference to the year 2002 in their title to indicate that this version is based on the evidence available until 2002 and that they need to be updated and adapted to current state of knowledge in the future.

In order to reach this goal the Education and Clinical Practice Committee invites and welcomes all criticism and suggestions (button for mail to ECPC chairman).

Key words: Nutritional Assessment; malnutrition; hospital; community

Background

About 30% of all patients in hospital are undernourished. A large part of these patients are undernourished when admitted to hospital and in the majority of these, undernutrition develops further while in hospital (1). This can be prevented if special attention is paid to their nutritional care. Other features of the patient's primary disease are screened routinely and treated (e.g. dehydration, blood pressure, fever), and it is unacceptable that nutritional problems causing significant clinical risk are not identified. Neglect is also beginning to have medico-legal consequences, since an increasing number of cases of nutritional neglect are being brought to the courts. There is every reason, therefore, for hospitals and healthcare organizations to adopt a minimum set of standards in this area.

However, the lack of a widely accepted screening system which will detect patients who might benefit clinically from nutritional support is commonly seen as a major limiting factor to improvement.

It is the purpose of this document to give simple guidelines as to how undernutrition, or risk for development of undernutrition, can be detected, by proposing a set of standards which are practicable for general use in patients and clients within present healthcare resources.

Purpose of screening

The purpose of nutritional screening is to predict the probability of a better or worse outcome due to nutritional factors, and whether nutritional treatment is likely to influence this. Outcome from treatment may be assessed in a number of ways:

1. Improvement or at least prevention of deterioration in mental and physical function
2. Reduced number or severity of complications of disease or its treatment.
3. Accelerated recovery from disease and shortened convalescence.
4. Reduced consumption of resources, e.g. length of hospital stay and other prescriptions.

The nutritional impairment identified by screening should therefore be relevant to these aims and outcomes and may vary according to circumstances, e.g. age or type of illness. In the community, undernutrition, with or without chronic disease, may be the primary factor determining the mental or physical function of an individual, whereas in hospital or in a nursing home, disease factors assume a greater importance with disease-associated undernutrition assuming an important albeit secondary role. Screening in the community can therefore be focused primarily on nutritional variables based on the results of semi-starvation studies such as those of Ancel Keys and his colleagues in 1950 (2). In hospitals, other aspects of disease need to be considered in combination with purely nutritional measurements in order to determine whether nutritional support is likely to be beneficial. Randomized controlled trials of nutritional support in particular disease groups may therefore provide important evidence on which to base our criteria of nutritional risk.

Methodological considerations

The usefulness of screening tools can be evaluated by a number of methods. The predictive validity is of major importance, i.e. that the individual identified to be at

risk by the method is likely to obtain a health benefit from the intervention arising from the results of the screening. This can be obtained in various ways, as described for the individual screening tools below. The screening tool must also have a high degree of content validity, i.e. considered to include all relevant components of the problem it is meant to solve. This is usually achieved by involving representatives of those who are going to use it in the process of designing the tool. It must additionally have a high reliability, i.e little inter-observer variation. It must also be practical, i.e. those who are going to use the tool must find it rapid, simple and intuitively purposeful. It should not contain redundant information, e.g. information about vomiting or dysphagia is unnecessary when dietary intake is part of the screening. The etiology of reduced dietary intake belongs to asssessment (see below) or is incorporated into the nutrition care plan. Several other aspects of evaluating screening tools are described in an analysis of 44 nutritional screening tools (3). Finally, a screening tool should be linked to specified protocols for action, e.g. referral of those screened at risk to an expert for more detailed assessment and care plans.

Screening leads to nutritional care

Hospital and healthcare organizations should have a policy and a specific set of protocols for identifying patients at nutritional risk, leading to appropriate nutritional care plans: an estimate of energy and protein requirements including posssible allowance for weight gain, followed by prescription of food, oral supplements, tube feeding or parenteral nutrition, or a combination of these. It is suggested that the following course of action be adopted.

1. *Screening* This is a rapid and simple process conducted by admitting staff or community healthcare teams. All patients should be screened on admission to hospital or other institutions. The outcome of screening must be linked to defined courses of action:
   a. The patient is not at risk, but may need to be re-screened at specified intervals, e.g. weekly during hospital stay.
   b. The patient is at risk and a nutrition plan is worked out by the staff.
   c. The patient is at risk, but metabolic or functional problems prevent a standard plan being carried out.
   d. There is doubt as whether the patient is at risk.

   In the two latter cases, referral should be made to an expert for more detailed assessment.
2. *Assessment.* This is a detailed examination of metabolic, nutritional or functional variables by an expert clinician, dietitian or nutrition nurse. It is a longer process than screening which leads to an appropriate care plan considering indications, possible side-effects, and, in some cases, special feeding techniques. It is based, like all diagnosis, upon a full history, examination and, where appropriate, laboratory investigations. It will include the evaluation or measurement of the functional consequences of undernutrition, such as muscle weakness, fatigue and depression. It involves consideration of drugs that the patient is taking and which may be contributing to the symptoms, and of personal habits such as eating patterns and alcohol intake. It includes gastrointestinal assessment, including dentition, swallowing, bowel function, etc. It necessitates an understanding of the interpretation of laboratory tests, e.g. plasma albumin which is more likely to be a measure of disease severity than of malnutrition per se. Calcium, magnesium and zinc levels may be important, and in some cases laboratory measurement of micronutrient levels may be appropriate.
3. *Monitoring and outcome.* A process of monitoring and defining outcome should be in place. The effectiveness of the care plan should be monitored by defined measurements and observations, such as recording of dietary intake, body weight and function, and a schedule for detecting possible side-effects. This may lead to alterations in treatment during the natural history of the patient's condition.
4. *Communication.* Results of screening, assessment and nutrition care plans should be communicated to other healthcare professionals when the patient is transferred, either back into the community or to another institution. When patients are transferred from the community to hospital or vice versa, it is important that the nutritional data and future care plans be communicated.
5. *Audit.* If this process is carried out in a systematic way, it will allow audit of outcomes which may inform future policy decisions.

Although this document will focus mainly on the process of screening, this cannot be considered in isolation and must be linked to the pathway of care described above.

Components of nutritional screening

Screening tools are designed to detect protein and energy undernutrition, and/or to predict whether undernutrition is likely to develop/worsen under the present and future conditions of the patient/client. Therefore, screening tools embody the following four main principles:

1. *What is the condition now?* Height and weight allow calculation of body mass index (BMI). Normal range 20–25, obesity >30, borderline underweight 18.5–20, undernutrition <18.5. In cases where it is not possible

to obtain height and weight, e.g. in severely ill patients, a useful surrogate may be mid-arm circumference, measured with a tape around the upper arm midway between the acromion and the olecranon. This can be related to centiles of tables for that particular population, age and sex.[1] BMI may be less useful in growing children and adolescents, and in the very elderly. Nevertheless, the BMI provides the best generally accepted measure of weight for height.

2. *Is the condition stable?* Recent weight loss is obtained from the patient's history, or, even better, from previous measurements in medical records. More than 5% involuntary weight loss over 3 months, is usually regarded as significant. This may reveal undernutrition which was not discovered by 1., e.g. weight loss in obesity, and may also predict further nutritional deterioration depending on 3 and 4.
3. *Will the condition get worse?* This question may be answered by asking whether food intake has been decreased up to the time of screening, and if so by approximately how much and for how long. Confirmatory measurements can be made of the patient's food intake in hospital or by food diary. If these are found to be less than the patient's requirements with normal intake, then further weight loss is likely.
4. *Will the disease process accelerate nutritional deterioration?* In addition to decreasing appetite, the disease process may increase nutritional requirements due to the stress metabolism associated with severe disease (e.g. major surgery, sepsis, multitrauma), causing nutritional status to worsen more rapidly, or to develop rapidly from fairly normal states of (1–3) above.

Variables 1–3 should be included in all screening tools, while 4 is relevant mainly to hospitals. In screening tools, each variable should be given a score, thereby quantifying the degree of risk and allowing a direct link to a defined course of action.

Screening tools recommended by ESPEN

The community: MUST for adults (see appendix)

The purpose of the MUST system is to detect undernutrition on the basis of knowledge about the association between impaired nutritional status and impaired function (5). It was primarily developed for use in the community, where serious confounders of the effect of undernutrition are relatively rare.

Evaluation. The predictive validity of MUST in the community is based on previous and new studies of the effect of semi-starvation/starvation on mental and physical function in healthy volunteers concurrent validity with other tools, and utilisation of health care resources. The new series of studies describe the impairment of function as a results of various extents of weight loss, with various rates of weight loss, from various initial nutritional statures (low or high BMI) (6).

It has been documented to have a high degree of reliability (low inter-observer variation) with a $\kappa = 0.88-1.00$. Its content validity has been assured by involving a multidisciplinary working group in its preparation. Its practicability has been documented in a number of studies in different community regions in the UK (5) (Table 1). The tool has recently been extended to other health care settings, including hospitals, where again it has been found to have excellent inter-rater reliability, concurrent validity with other tools, and predictive validity (length of hospital stay, mortality in elderly wards, and discharge destination in orthopaedic patients).

The hospital: NRS-2002 (see appendix)

The purpose of the NRS-2002 system is to detect the presence of undernutrition and the risk of developing undernutrition in the hospital setting (4). It contains the nutritional components of MUST, and in addition, a grading of severity of disease as a reflection of increased nutritional requirements. It includes four questions as a pre-screening for departments with few at risk patients. With the prototypes for severity of disease given, it is meant to cover all possible patient categories in a hospital. A patient with a particular diagnosis does not always belong to the same category. A patient with cirrhosis, for example, who is admitted to intensive care because of a severe infection, should be given a score of 3, rather than 1. It also includes old age as a risk factor, based on RCTs in elderly patients (4) (Table 2).

Evaluation. Its predictive validity has been documented by applying it to a retrospective analysis of 128 RCTs of nutritional support which showed that RCTs with patients fullfilling the risk criteria had a higher likelihood of a positive clinical outcome from nutritional support than RCTs of patients who did not fulfill these criteria (4). In addition, it has been applied prospectively in a controlled trial with 212 hospitalized patients selected according to this screening method, which showed a reduced length of stay among patients with complications in the intervention group (when adjusted for occurrence of operation and death).[2] Its content validity was maximized by involving an ESPEN ad hoc working group under the auspices of the ESPEN Educational and Clinical Practice Committee in the literature based validation. It has also been used by nurses and dietitians in a 2 years' implementation study in three hospitals (local, regional and university hospital) in Denmark (7),

[1] Data on simultaneous measurements of BMI and mid-arm circumference have not been published in a form that allows comparison of cut-off points for these measurements. An analysis of RCTs, in which mean values BMI were given together with mean values of mid-arm circumference, suggested that a mid-arm circumference <25 cm corresponds to a BMI <20.5 (4). The data did not allow for distinguishing between lower cut-off points for BMI.

[2] The trial was completed in April 2002 and a manuscript is in preparation by N. Johansen et al. A copy is available upon request (kondrup@rh.dk)

which indicated that staff and investigators seldomly disagreed about a patient's risk status. Its reliability was validated by inter-observer variation between a nurse, a dietitian and a physician with a $\kappa = 0.67$. Its practicability was shown by the finding that 99% of 750 newly admitted patients could be screened. The incidence of at-risk patients was about 20% (7).

The elderly: MNA

The purpose of MNA is to detect the presence of undernutrition and the risk of developing undernutrition among the elderly in home-care programmes, nursing homes and hospitals. The prevalence of undernutrition among the elderly may reach significant levels (15–60%) under these circumstances (8). The screening methods mentioned above will detect undernutrition among many elderly patients, but for the frail elderly the MNA screening is more likely to identify risk of developing undernutrition, and undernutrition at an early stage, since it also includes physical and mental aspects that frequently affect the nutritional status of the elderly, as well as a dietary questionnaire. It is in fact a combination of a screening and an assessment tool, since the last part of the form (not reproduced here) is a more detailed exploration of the items in the first part of the form.

Evalution. The predictive validity of MNA has been evaluated by demonstrating its association with adverse health outcome (9), social functioning (10), mortality (11, 12) and a higher rate of visits to the general practitioner (13). In a randomized trial of elderly at risk according to MNA, those given oral supplements increased body weight, but not grip strength (14), and in another similar (but small) randomized trial of elderly in a nursing home, the intervention group increased dietary intake but no functional or clinical outcome data were reported (15). The content validity has not been reported. The reliability (inter-observer variation) was estimated, with a $\kappa = 0.51$ (8). The MNA takes < 10 min to complete and its practicability has been shown by its use in a large number of studies, see (8).

Children

A universally accepted screening tool for children is not yet available (although guidelines are in preparation under the Chairmanship of Professor Bert Koletzko, Munich). It is already standard practice among paediatricians to maintain height and weight charts, allowing calculation of growth velocity which is high- sensitive to nutritional status. Pubertal development is also impaired during undernutrition.

Other screening systems

In their recent guidelines, the ASPEN board of directors stated that no screening system has been validated with respect to clinical outcome (16). They also suggested that, in the absence of an outcomes validated approach, a combination of clinical and biochemical parameters should be used to assess the presence of malnutrition. They suggest using the subjective global assessment, SGA (17), which classifies patients subjectively on the basis of data obtained from history and physical examination, since this system has been validated in several ways other than with respect to clinical outcome, e.g. inter-observer variation. However, the lack of a direct connection between the observations and the classification of patients leaves the tool more complex and less focused than desired for rapid screening purposes.

An analysis of a total of 44 screening tools for use in hospital and the community (3) indicated that tools were published with insufficient details regarding their intended use and method of derivation, and with an inadequate assessment of their effectiveness. No one tool satisfied a set of criteria regarding scientific merit. The present recommendations by ESPEN may share some of these short-comings, but in view of the massive neglect of nutritional problems in health institutions, and the explicit lack of generally accepted screening tools, the predictive validity given above is considered sufficient to provide a practical and reasonable approach in the light of present knowledge. These recommendations may need to be modified in the light of future experience.

Predictive validity vs meta-analyses of treatment

The predictive validity reported here needs to be commented upon in relation to recent meta-analyses, or systematic reviews. Such analyses suggest that nutritional support by the enteral or oral route improves functional capacity and clinical outcome, and reduces length of stay and mortality, e.g. (18, 19). In a recent meta-analysis of studies employing parenteral nutrition (20), it was pointed out that there are inadequate data to assess the efficacy of parenteral nutrition in patients who are severely undernourished, who have highly catabolic disease processes, or who cannot be provided with enteral nutrition for several weeks. These are in fact the patients who most commonly receive supportive parenteral nutrition now-a-days, and for ethical reasons, there will probably not be randomized trials available in the future either. The majority of studies available deal with the grey area of patients who are less undernourished/not undernourished and/or are mildly–moderately catabolic. With these studies at hand, it was difficult to identify clinical conditions where parenteral nutrition would be clinically effective (20). However, the literature analysis mentioned above (4) suggests that parenteral nutrition is clinically effective in studies of patients who rather more than just fulfill the criteria for being nutritionally at risk.

Furthermore, nutrients known to be essential for healthy humans are also essential for patients, and therefore the required documentation is not to confirm

the essentiality of nutrients among patients, but rather to define when a certain form of nutritional support is more beneficial than leaving the patient to develop nutritional deficiences. Therefore, meta-analyses and systematic reviews of nutritional support are too simplistic, if performed by analogy with treatment using a new drug. Finally, a nutritional care plan in most cases will involve food, oral supplements, tube feeding and parenteral nutrition, often used interchangeably in the same patient, whereas the majority of randomized trials, and meta-analyses, have dealt with studies of single modality treatments. The predictive validity of a screening tool therefore cannot be directly based on meta-analyses available at present.

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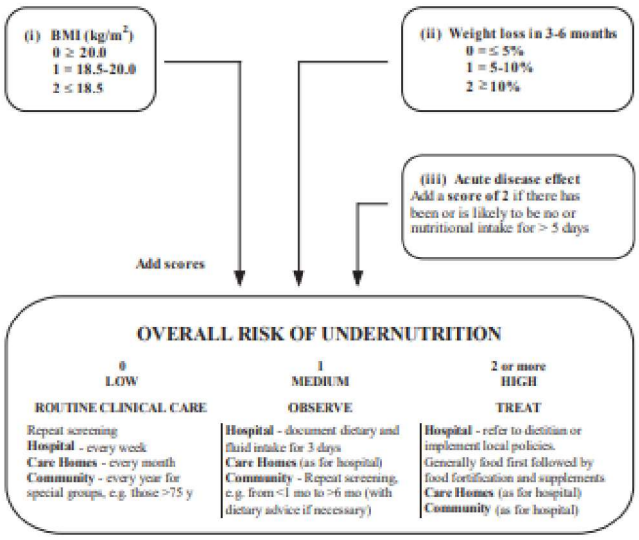
Appendix

Malnutrition Universal Screening Tool (MUST) for adults



Can be adapted for special circumstances (e.g. when weight and height cannot be measured or when there are fluid disturbances) using specified alternative measurements including subjective criteria. It also identifies obesity (BMI > 30 kg/m^2).

Nutritional Risk Screening (NRS 2002)

Table 1 Initial screening

		Yes	No
1	Is BMI <20.5?		
2	Has the patient lost weight within the last 3 months?		
3	Has the patient had a reduced dietary intake in the last week?		
4	Is the patient severely ill ? (e.g. in intensive therapy)		

Yes: If the answer is 'Yes' to any question, the screening in Table 2 is performed.
No: If the answer is 'No' to all questions, the patient is re-screened at weekly intervals. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.

Table 2 Final screening

Impaired nutritional status		**Severity of disease (≈ increase in requirements)**	
Absent **Score 0**	Normal nutritional status	Absent **Score 0**	Normal nutritional requirements
Mild **Score 1**	Wt loss >5% in 3 mths or Food intake below 50–75% of normal requirement in preceding week	Mild **Score 1**	Hip fracture* Chronic patients, in particular with acute complications: cirrhosis*, COPD*. *Chronic hemodialysis, diabetes, oncology*
Moderate **Score 2**	Wt loss >5% in 2 mths or BMI 18.5 – 20.5 + impaired general condition or Food intake 25–60% of normal requirement in preceding week	Moderate **Score 2**	Major abdominal surgery* Stroke* *Severe pneumonia, hematologic malignancy*
Severe **Score 3**	Wt loss >5% in 1 mth (>15% in 3 mths) or BMI <18.5 + impaired general condition or Food intake 0-25% of normal requirement in preceding week in preceding week.	Severe **Score 3**	Head injury* Bone marrow transplantation* *Intensive care patients (APACHE> 10).*
Score:	+	**Score:**	**=Total score**
Age	if ≥70 years: add 1 to total score above	**=age-adjusted total score**	

Score ≥3: the patient is nutritionally at-risk and a nutritional care plan is initiated
Score <3: weekly rescreening of the patient. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.

NRS-2002 is based on an interpre-tation of available randomized clinical trials.
*indicates that a trial directly supports the categorization of patients with that diagnosis. Diagnoses shown in *italics* are based on the prototypes given below.
Nutritional risk is defined by the present **nutritional status** and risk of impairment of present status, due to **increased requirements** caused by stress metabolism of the clinical condition.

A nutritional care plan is indicated in all patients who are

(1) severely undernourished (score = 3), or (2) severely ill (score = 3), or (3) moderately undernourished + mildly ill (score 2 + 1), or (4) mildly undernourished + moderately ill (score 1 + 2).

Prototypes for severity of disease
Score = 1: a patient with chronic disease, admitted to hospital due to complications. The patient is weak but out of bed regularly. Protein requirement is increased, but can be covered by oral diet or supplements in most cases.
Score = 2: a patient confined to bed due to illness, e.g. following major abdominal surgery. Protein requirement is substantially increased, but can be covered, although artificial feeding is required in many cases.
Score = 3: a patient in intensive care with assisted ventilation etc. Protein requirement is increased and cannot be covered even by artificial feeding. Protein breakdown and nitrogen loss can be significantly attenuated.

Initial Screening in Mini Nutritional Assessment (MNA®) for the elderly

A	**Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?** 0 = severe loss of appetite 1 = moderate loss of appetite 2 = no loss of appetite	
B	**Weight loss during last months?** 0 = weight loss greater than 3 kg 1 = does not know 2 = weight loss between 1 and 3 kg 3 = no weight loss	
C	**Mobility?** 0 = bed or chair bound 1 = able to get out of bed/chair but does not go out 2 = goes out	
D	**Has suffered physical stress or acute disease in the past 3 months?** 0 = yes 2 = no	
E	**Neuropsychological problems?** 0 = severe dementia or depression 1 = mild dementia 2 = no psychological problems	
F	**Body Mass Index (BMI) [weight in kg]/[height in m]2** 0 = BMI less than 19 1 = BMI 19 to less than 21 2 = BMI 21 to less than 23 3 = BMI 23 or greater	
Screening score (total max. 14 points)		
12 11	points or greater points or below	Normal—not at risk → no need to complement assessment Possible malnutrition → continue assessment

APPENDIX 4. SUBJECTIVE GLOBAL ASSESSMENT (SGA) TEST

VALORACIÓN GLOBAL SUBJETIVA GENERADA POR EL PACIENTE

Por favor, conteste al siguiente formulario escribiendo los datos que se le piden o señalando la opción correcta, cuando se le ofrecen varias

Nombre y Apellidos _____

Edad ____ años

Fecha / /

PESO actual _____kg
Peso hace 3 meses _____kg

ALIMENTACIÓN respecto hace 1 mes:
- como más
- como igual
- como menos

Tipo de alimentos:
- dieta normal
- pocos sólidos
- sólo líquidos
- sólo preparados nutricionales
- muy poco

ACTIVIDAD COTIDIANA en el último mes:
- normal
- menor de lo habitual
- sin ganas de nada
- paso más de la mitad del día
- en cama o sentado

DIFICULTADES PARA ALIMENTARSE:
- SÍ
- NO

Si la respuesta era SÍ, señale cuál / cuáles de los siguientes problemas presenta:
- falta de apetito
- ganas de vomitar
- vómitos
- estreñimiento
- diarrea
- olores desagradables
- los alimentos no tienen sabor
- sabores desagradables
- me siento lleno enseguida
- dificultad para tragar
- problemas dentales
- dolor. ¿Dónde? _____
  _____
- depresión
- problemas económicos

Muchas gracias. A partir de aquí, lo completará su Médico

ENFERMEDADES: _____
_____
_____

TRATAMIENTO ONCOLÓGICO: _____
_____

OTROS TRATAMIENTOS: _____
_____

ALBÚMINA antes de tratamiento oncológico:
_____ g/dl

PREALBÚMINA tras el tratamiento oncológico:
_____ mg/dl

EXPLORACIÓN FÍSICA:

Pérdida de tejido adiposo:
- SÍ. Grado _____
- NO

Pérdida de masa muscular:
- SÍ. Grado _____
- NO

Edemas y/o ascitis:
- SÍ. Grado _____
- NO

Úlceras por presión: SÍ NO

Fiebre: SÍ NO

VALORACIÓN GLOBAL, teniendo en cuenta el formulario, señale lo que corresponda a cada dato clínico para realizar la evaluación final:

DATO CLÍNICO	A	B	C
Pérdida de peso	<5%	5-10%	**>10%**
Alimentación	Normal	deterioro leve-moderado	deterioro grave
Impedimentos para ingesta	NO	leves-moderados	graves
Deterioro de actividad	NO	leve-moderado	grave
Edad	65	>65	>65
Úlceras por presión	NO	NO	SÍ
Fiebre / corticoides	NO	leve / moderada	elevada
Tto. antineoplásico	bajo riesgo	medio riesgo	alto riesgo
Pérdida adiposa	NO	leve / moderada	elevada
Pérdida muscular	NO	leve / moderada	elevada
Edemas / ascitis	NO	leve / moderados	importantes
Albúmina (previa al tto)	>3,5	3'0-3,5	**<3,0**
Prealbúmina (tras tto)	>18	15-18	**<15**

VALORACIÓN GLOBAL,

A: buen estado nutricional

B: malnutrición moderada o riesgo de malnutrición

C: malnutrición grave

VALORACIÓN GLOBAL SUBJETIVA GENERADA POR EL PACIENTE (VGS-GP)

Identificación del paciente:

HISTORIAL

A RELLENAR EXCLUSIVAMENTE POR EL PACIENTE

1. Peso:

Consideraciones sobre mi peso actual y sobre la evolución de mi peso en las últimas semanas:

En la actualidad peso alrededor de _____ kilos

Mido aproximadamente _____ cm

Hace un mes pesaba alrededor de _____ kilos

Hace seis meses pesaba alrededor de _____ kilos

Durante las dos últimas semanas mi peso:

- ha disminuido (1)
- no ha cambiado (0)
- ha aumentado (0)

*(ver **Tabla 1** en la hoja de instrucciones)*

1 ☐

2. Ingesta: en comparación con mi estado habitual, calificaría a mi alimentación durante el último mes de:

- sin cambios (0)
- mayor de lo habitual (0)
- menor de lo habitual (1)

Ahora como:

- alimentos normales pero en menor cantidad de lo habitual (1)
- pocos alimentos sólidos (2)
- solamente líquidos (3)
- solamente suplementos nutricionales (3)
- muy poco (4)
- solamente alimentación por sonda o intravenosa (0)

(consignar como marcador final la condición de más alta puntuación)

2 ☐

3. Síntomas: he tenido los siguientes problemas que me han impedido comer lo suficiente durante las últimas dos semanas (marcar según corresponda):

- no tengo problemas con la alimentación (0)
- falta de apetito; no tenía ganas de comer (3)
- náusea (1) vómitos (3)
- estreñimiento (3) diarrea (3)
- llagas en la boca (2) sequedad de boca (1)
- los alimentos me saben raros o no me saben a nada (1)
- problemas al tragar (2) los olores me desagradan (1)
- me siento lleno/a enseguida (3)
- dolor; ¿dónde? (3) _____
- otros factores** (1) _____

*** como: depresión, problemas dentales, económicos*

(sumar las puntuaciones correspondientes a cada uno de los síntomas indicados por el paciente)

3 ☐

Capacidad Funcional: en el curso del último mes calificaría mi actividad, en general, como:

- normal y sin limitaciones (0)
- no totalmente normal, pero capaz de mantenerme activo y llevar a cabo actividades bastante normales (1)
- sin ganas de hacer la mayoría de las cosas, pero paso menos de la mitad del día en la cama o sentado/a (2)
- capaz de realizar pequeñas actividades y paso la mayor parte del día en la cama ó sentado/a (3)
- encamado/a, raramente estoy fuera de la cama (3)

(consignar como marcador final la condición de más alta puntuación)

4 ☐

Suma de las Puntuaciones: 1+2+3+4 = A

EL RESTO DE ESTE FORMULARIO SERÁ COMPLETADO POR SU MÉDICO. GRACIAS.

5. Enfermedad y su relación con los requerimientos nutricionales *(ver **Tabla 2** en la hoja de instrucciones)*

Diagnóstico principal (especificar)_____

Estadio de la enfermedad (indicar el estadio si se conoce o el más próximo a él): I II III IV Otro:_____

Edad_____ B

B

6. Demanda Metabólica

C

*(ver **Tabla 3** en las instrucciones)*

sin estrés metabólico

estrés metabólico leve

estrés metabólico moderado

estrés metabólico elevado

7. Evaluación física

D

*(ver **Tabla 4** en las instrucciones)*

Puntuación Numérica Tabla 2 = B

Puntuación Numérica Tabla 3 = C

Puntuación Numérica Tabla 4 = D

8. Evaluación Global (VGS A, B o C)

Bien nutrido

Moderadamente ó sospechosamente mal nutrido

Severamente mal nutrido

*(ver **Tabla 5** en la hoja de instrucciones)*

Puntuación Numérica Total: A+B+C+D *(ver recomendaciones abajo)*

Firma: _____ Fecha: _____

Recomendaciones Nutricionales

La valoración cuantitativa del estado nutricional del paciente sirve para definir en que casos se recomienda intervención nutricional incluyendo: educación nutricional del paciente y familiares, manejo de síntomas, intervención farmacológica, e intervención nutricional apropiada. Una apropiada intervención nutricional requiere un apropiado manejo de los síntomas del paciente.

No requiere intervención nutricional en este momento. Volver a valorar durante el tratamiento.

2-3 Paciente y familiares requieren educación nutricional por parte de especialista en nutrición ú otro clínico, con intervención farmacológica según los síntomas (recuadro 3) y la analítica del paciente.

Requiere intervención de un especialista en nutrición junto con su médico/oncólogo según los síntomas indicados en el recuadro 3

9 Indica una necesidad crítica de mejorar el manejo de los síntomas del paciente y/o intervención nutricional / farmacológica".

FD Otery, 2000.

INSTRUCCIONES: HOJA DE RECOGIDA DE DATOS Y TABLAS PARA LA CUANTIFICACIÓN DE LA ENCUESTA DE VALORACIÓN GLOBAL SUBJETIVA GENERADA POR EL PACIENTE (VGS-GP)

La valoración numérica final de la VGS-GP proviene de las puntuaciones totales obtenidas en los apartados A, B, C y D al dorso. Los recuadros 1-4 deben ser completados por el paciente. Las puntuaciones correspondientes a esos recuadros vienen indicadas entre paréntesis. La siguiente hoja sirve como ayuda para valorar cuantitativamente las diversas secciones de que consta la encuesta.

TABLA 1.—Cuantificación de la Pérdida de Peso

Sumando puntos se determinan la pérdida aguda y subaguda de peso. **Subaguda**: si se dispone de los datos de pérdida de peso durante el último mes, añadir los puntos obtenidos a los puntos correspondientes a la pérdida de peso aguda. Sólo incluir la pérdida de peso de 6 meses si no se dispone de la del último mes. **Aguda**: se refiere a los cambios de peso en las últimas dos semanas: añadir 1 punto al marcador de subaguda si el paciente ha perdido peso, no añadir puntos si el paciente ha ganado o mantenido su peso durante las 2 últimas semanas

Pérdida Peso en 1 mes	Puntos	Pérdida de Peso en 6 meses
10% o superior	4	20% o superior
5 – 9,9%	3	10 – 1 9,9%
3 – 4,9%	2	6 – 9,9%
2 –2,9%1	2– 5,9%	
0 – 1,9%	0	0 – 1,9%

Puntuación Total Recuadro 1 = Subaguda + Aguda = 1

[ ] 1

TABLA 2.—Criterios de cuantificación de Enfermedad y/o Condiciones

La puntuación se obtiene adjudicando 1 punto a cada una de las condiciones indicadas abajo, que se correspondan con el diagnóstico del paciente:

Categoría	Puntuación
• Cáncer	1
• SIDA	1
• Caquexia Cardiaca o Pulmonar	1
• Úlcera por decúbito, herida abierta o fístula	1
• Existencia de Trauma	1
• Edad superior a 65 años	1

Puntuación Total Tabla 2 = [ ] B

TABLA 3.—Cuantificación del Estrés Metabólico

La valoración del estrés metabólico se determina mediante una serie de variables conocidas cuya presencia produce un incremento de las necesidades calóricas y proteicas del individuo. Esta puntuación **es aditiva**, de forma que un pacientes con fiebre superior a 39 ºC (suma 3 puntos) y si está siendo tratado con 10 mg de prednisona de forma crónica (suma 2 puntos más), lo que hace un total de 5 puntos para el paciente en esta sección.

Estrés	Ninguno (0)	Leve (1)	Moderado (2)	Elevado (3)
Fiebre	sin fiebre	37 y< 38 ºC	38 y< 39 ºC	39 ºC
Duración de la Fiebre	sin fiebre	<72 horas	72 horas	>72 horas
Esteroides	sin esteroides	dosis bajas (<10 mg prednisona o equivalente/día)	dosis moderadas (>10 y <30 mg prednisona o equivalente/día)	altas dosis de esteroides (30 mg prednisona o equivalente/día)

Puntuación Total Tabla 3 = [ ] B

TABLA 4.—Reconocimiento Físico

El reconocimiento físico del paciente incluye una evaluación subjetiva de tres aspectos de la composición corporal: tejido graso, masa muscular y estatus hídrico.
Ya que se trata de una valoración subjetiva, cada aspecto del examen es cuantificado por grado de deficiencia. Déficit musculares impactan más en la puntuación final que déficits de tejido graso. Definición de categorías:**0=sin déficit, 1+=déficit leve, 2+=déficit moderado, 3+=déficit severo**. Las puntuaciones en estas categorías ***no son aditivas***, pero son utilizadas para establecer clínicamente el grado de la deficiencia (ej.: presencia o ausencia de fluidos)

Tejido Graso:				
Grasa en orbitales parpebrales	0	1+	2+	3+
Pliegue tricipital	0	1+	2+	3+
Acúmulos grasos en la cintura	0	1+	2+	3+
Déficit Graso Global	**0**	**1+**	**2+**	**3+**

Estatus Hídrico:				
Edema de tobillo	0	1+	2+	3+
Edema de sacro	0	1+	2+	3+
Ascitis	0	1+	2+	3+
Estatus Hídrico Global	**0**	**1+**	**2+**	**3+**

Estatus Muscular:				
Músculos temporales	0	1+	2+	3+
Clavículas (pectorales y deltoides)	0	1+	2+	3+
Hombros (deltoides)	0	1+	2+	3+
Músculos interóseos	0	1+	2+	3+
Escápula (latisimus dorsi, trapecio, deltoides)	0	1+	2+	3+
Cuadriceps	0	1+	2+	3+
Gastronemios	0	1+	2+	3+
Estatus Muscular Global	**0**	**1+**	**2+**	**3+**

La evaluación cuantitativa global del estado físico del paciente se determina mediante una valoración global subjetiva de todos los déficits corporales que presente el paciente teniendo en cuenta que **las deficiencias musculares pesan más que los déficit del tejido graso y éstos más que el exceso de fluidos**.

Sin déficit	= 0 puntos
Déficit leve	= 1 punto
Déficit moderado	= 2 puntos
Déficit severo	= 3 puntos

Puntuación Total Tabla 4 = ____ D

TABLA 3.—Valoración Global Subjetiva del Estado Nutricional del Paciente. Categorías

Categoría	Estado A **Bien nutrido**	Estado B **Moderadamente malnutrido o sospechosamente malnutrido**	Estado C **Severamente malnutrido**
Peso	Sin pérdida de peso o sin retención hídrica reciente	a. 5% pérdida de peso en el último mes (o 10% en 6 meses) Peso no estabilizado	a. >5% pérdida de peso en 1 mes (o >10% en 6 meses) peso sin estabilizar
Ingesta	Sin deficit o Mejora significativa reciente	Disminución significativa en la ingesta	Déficit severo en la ingesta
Impacto de la Nutrición en los Síntomas	Ninguno o Mejora significativa reciente permitiendo una ingesta adecuada	Existe Impacto de la Nutrición en los Síntomas *(Sección 3 de la VGS-GP)*	Existe Impacto de la Nutrición en los Síntomas *(Sección 3 de la VGS-GP)*
Funcionalidad	Sin afectación o Mejora reciente significativa	Deterioro Moderado o Deterioro reciente de la misma	Deterioro severo o Deterioro reciente significativo
Examen Físico	Sin déficit o Deficiencia crónica pero con reciente mejoría clínica	Evidencia de pérdida de leve a moderada de masa grasa y/o masa muscular y/o tono muscular a la palpación	Signos evidentes de malnutrición (ej.: pérdida severa de tejidos graso, muscular, posible edema)

" *FD Ottery, 2000* **Evaluación Global (A, B, o C) =**

APPENDIX 5. EORTC QLQ C30 TEST

SPANISH (SPAIN)

EORTC QLQ-C30 (versión 3)

Estamos interesados en conocer algunas cosas sobre usted y su salud. Por favor, responda a todas las preguntas personalmente, rodeando con un círculo el número que mejor se aplique a su caso. No hay contestaciones "acertadas" o "desacertadas". La información que nos proporcione será estrictamente confidencial.

Por favor ponga sus iniciales:
Su fecha de nacimiento (día, mes, año):
Fecha de hoy (día, mes, año): 31

		En absoluto	Un poco	Bastante	Mucho
1.	¿Tiene alguna dificultad para hacer actividades que requieran un esfuerzo importante, como llevar una bolsa de compra pesada o una maleta?	1	2	3	4
2.	¿Tiene alguna dificultad para dar un paseo largo?	1	2	3	4
3.	¿Tiene alguna dificultad para dar un paseo corto fuera de casa?	1	2	3	4
4.	¿Tiene que permanecer en la cama o sentado/a en una silla durante el día?	1	2	3	4
5.	¿Necesita ayuda para comer, vestirse, asearse o ir al servicio?	1	2	3	4

Durante la semana pasada:		En absoluto	Un poco	Bastante	Mucho
6.	¿Ha tenido algún impedimento para hacer su trabajo u otras actividades cotidianas?	1	2	3	4
7.	¿Ha tenido algún impedimento para realizar sus aficiones u otras actividades de ocio?	1	2	3	4
8.	¿Tuvo sensación de "falta de aire" o dificultad para respirar?	1	2	3	4
9.	¿Ha tenido dolor?	1	2	3	4
10.	¿Necesitó parar para descansar?	1	2	3	4
11.	¿Ha tenido dificultades para dormir?	1	2	3	4
12.	¿Se ha sentido débil?	1	2	3	4
13.	¿Le ha faltado el apetito?	1	2	3	4
14.	¿Ha tenido náuseas?	1	2	3	4
15.	¿Ha vomitado?	1	2	3	4
16.	¿Ha estado estreñido/a?	1	2	3	4

Por favor, continúe en la página siguiente

Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
17. ¿Ha tenido diarrea?	1	2	3	4
18. ¿Estuvo cansado/a?	1	2	3	4
19. ¿Interfirió algún dolor en sus actividades diarias?	1	2	3	4
20. ¿Ha tenido dificultad en concentrarse en cosas como leer el periódico o ver la televisión?	1	2	3	4
21. ¿Se sintió nervioso/a?	1	2	3	4
22. ¿Se sintió preocupado/a?	1	2	3	4
23. ¿Se sintió irritable?	1	2	3	4
24. ¿Se sintió deprimido/a?	1	2	3	4
25. ¿Ha tenido dificultades para recordar cosas?	1	2	3	4
26. ¿Ha interferido su estado físico o el tratamiento médico en su vida familiar?	1	2	3	4
27. ¿Ha interferido su estado físico o el tratamiento médico en sus actividades sociales?	1	2	3	4
28. ¿Le han causado problemas económicos su estado físico o el tratamiento médico?	1	2	3	4

Por favor en las siguientes preguntas, ponga un círculo en el número del 1 al 7 que mejor se aplique a usted

29. ¿Cómo valoraría su salud general durante la semana pasada?

1	2	3	4	5	6	7
Pésima						Excelente

30. ¿Cómo valoraría su calidad de vida en general durante la semana pasada?

1	2	3	4	5	6	7
Pésima						Excelente

APPENDIX 6. GI.NET21 QLQ TEST

ENGLISH

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:			Not at all	A little	Quite a bit	Very much
31.	Did you have hot flushes?		1	2	3	4
32.	Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33.	Did you have night sweats?		1	2	3	4
34.	Did you have abdominal discomfort?		1	2	3	4
35.	Did you have a bloated feeling in your abdomen?		1	2	3	4
36.	Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37.	Have you had acid indigestion or heartburn?		1	2	3	4
38.	Have you had difficulties with eating?		1	2	3	4
39.	Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40.	Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41	Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42.	Were you concerned about disruption of home life?		1	2	3	4
43.	Have you worried about your health in the future?		1	2	3	4
44.	How distressing has your illness or treatment been to those close to you?		1	2	3	4
45.	Has weight loss been a problem for you?		1	2	3	4
46.	Has weight gain been a problem for you?		1	2	3	4
47.	Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48.	Have you had aches or pains in your muscles or bones?		1	2	3	4
49.	Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:						
50.	Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51.	Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4