EUonQoL

Quality of Life in Oncology: measuring what matters for cancer patients and survivors in Europe

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Introduction

The present Deliverable reports on the activities implemented within Work Package 7 up to month 12 (December 2023) of the project "Quality of Life in Oncology: measuring what matters for cancer patients and survivors in Europe (EUonQoL)," funded by the European Union.

The main objective of Work Package 7 is to carry out the first large-scale European application of the EUonQoL-Kit, a unified patient-driven tool for the assessment of quality of life, based on preferences and priorities of cancer patients and survivors.

This application consists in an European of an observational cross-sectional multicentre study (pilot survey), with the specific aim of validating the new tool.

Organizing and implementing a multi-centre observational study involves a series of strategic steps to ensure the study is well-designed, ethically conducted, and produces reliable results.

An overview of the preparatory activities we have implemented for the EUonQoL pilot survey up to December 2023 is detailed below.

1) **Fine tune the research objectives:**
- Revise the research questions and objectives of the study.
- Specify the outcomes and variables of interest.

2) **Feasibility assessment:**
- Evaluate and confirm the feasibility of conducting the study in **27 EU Member States and 6 Associated Countries** and UK.
- Consider regulatory requirements, data availability, cultural differences, and logistical challenges.

3) **Protocol final definition together with Appendices** (Annex 1)**:**
- Develop a detailed study protocol outlining the study rationale, design, methods, patient inclusion/exclusion criteria, data collection procedures, and data analyses.
- Develop Appendices, including Case Report Form draft, patient information leaflet and informed consent form.

4) **Clinical site selection:**
- Identify and engage clinical sites in each of the **27 Member States and 6 Associated Countries** based on their capacity, patient population, and willingness to participate.
- Standardize procedures to ensure uniform step-by-step actions for study implementation across countries.
- Organisation of two informative meetings to the clinical centres having accepted to participate.

5) **Preparation of legal documents to be signed by 35 clinical centres not included in the project Consortium:**

- Definition of Agreements between OECI and each clinical centre
- Negotiation meetings
- Signature

6) **Ethical Approval:**

- Fondazione IRCCS Istituto Nazionale dei Tumori, the study Coordinator and Sponsor, obtained on the 23rd of May 2023 the ethical approval from the Ethics Committee (Annex 2).
- Each of the clinical centre has received from the study coordinator the documents (Protocol, SOPs for obtaining ethical approval, INT ethical approval) needed to obtain ethical approval from institutional review boards (IRBs) or ethics committees (ECs)
- Ensure that the study adheres to international ethical standards.

7) Study registration on a WHO or JCMJE approved registry:

The study protocol was submitted and registered on **Clinicaltrial.gov,** a web-based registry and results database, in compliance with the International Committee of Medical Journal Editors (ICMJE), that requires registration as a condition of the publication of research results generated by a clinical study (see Annex 3 for study registration details).

8) Communication and Coordination:

Establish regular communication channels between study sites.

Implement a centralized coordination system to manage logistics and address issues promptly.

Annex 1 - Final version of study protocol

Validation of the European Oncology Quality of Life Toolkit.

A European pilot survey.

Protocol version: 1 Date: April 13th, 2023

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ABBREVIATIONS

QoL: Quality of life

EUonQoL-Kit: European Oncology Quality of Life Toolkit

EU: European Union

CAT: computer adaptive testing

EORTC: European Organisation for Research and Treatment of Cancer

EORTC-QLQ-C30: EORTC Quality of Life Questionnaire, CORE version

EFA: Exploratory Factor Analyses

CFA: Confirmatory Factor Analyses

SOPs: Standard Operating Procedures

PC: Palliative Care

OECI: Organisation of the European Cancer Institutes

PROMs: Patient-Reported Outcomes Measures

ISPOR: The International Society for Pharmacoeconomics and Outcomes Research

IRT: Item Response Theory

TERMINOLOGY

CAT: Computer Adaptive Testing is a form of computer-based test that automatically selects individualised sets of items to assess patient-reported health states.

SOPs: Standard Operating Procedures are detailed written instructions, aimed to achieve uniform step-by-step actions for study implementation

EXECUTIVE SUMMARY

Quality of life (QoL) has been defined by the World health Organization as “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns.” The improvement or preservation of quality of life is one of the three pillars of the European Union (EU) Mission on Cancer, which underpins the needs of patients from cancer diagnosis throughout treatment, survivorship, and advanced terminal stages of non-curable cases. Clinical studies and real- world data show that self-reported QoL assessment in routine oncology practice has positive effects on patient well-being and healthcare resource utilization. However, full implementation of QoL assessment, also called Patient Reported Outcome Measures (PROMs), is not yet part of standard of care and is not adequately considered in the development of cancer policies and programs.

While several questionnaires have been developed and validated to measure QoL in cancer patients, a comprehensive tool incorporating the perspective of patients at different stages of the disease trajectory and widely applicable across Europe is still lacking.

The EU funded EUonQoL project aims to develop, pilot test, and validate the European Oncology Quality of Life Toolkit (EUonQoL-Kit), a unified patient-centred tool for the assessment of QoL, developed from preferences and priorities of people with past or current cancer experience. The EUonQoL-Kit includes three electronic questionnaires, specifically designed for different disease phases (patients in active treatment, survivors, and patients in palliative care), available in both static and dynamic versions and in several European languages.

The aim of the present study is to perform the psychometric validation of the EUonQoL-kit through its first large-scale application in a wide European pilot survey of cancer patients and survivors. The survey will also provide preliminary estimates of QoL across different European countries, as well as data on socio-demographic and clinical factors potentially associated with QoL in European cancer patients and survivors.

1. INTRODUCTION

1.1 The EUonQoL project

In the last decades, several generic and either disease or treatment-specific patient-reported questionnaires have been developed and validated to measure quality of life (QoL) of patients with cancer (Schipper H, 1984; Haes JCJM, 1990; Schag CAC, 1991; Aaronson NK, 1993; Cella DF, 1993). They have often been translated and adapted into many languages, mainly being used in the context of clinical trials to assess effectiveness and tolerability of health care interventions (Rock EP, 2007). Most of these tools are "static" (the same set of questions is presented to all patients) and have often been designed by health professionals and researchers. A comprehensive tool, developed in close collaboration with people who have experienced cancer, widely applicable across Europe and tailored to the health status of the individual patient, is lacking. Such a tool will be important for incorporating the patient's perspective into the evaluation of policies and programs addressing cancer at the European level.

The EU funded EUonQoL project aims to develop, pilot test, and validate the European Oncology Quality of Life Toolkit (EUonQoL-Kit), a unified patient-centred tool for the assessment of QoL based on preferences of cancer patients and survivors. The EUonQoL-Kit is developed from a patient perspective, administered digitally, available in the languages of the EU27 and several associated countries, and applicable in future, periodic surveys to contribute to the EU's mission on cancer. The EUonQoL-Kit includes three static questionnaires specifically developed for different disease phases (patients in active treatment, survivors and patients in palliative care), and three dynamic versions of the same questionnaires based on Item Response Theory (IRT) and Computer Adaptive Testing (CAT). With dynamic questionnaires, patients are presented subsequent questions based on their answers to the previous ones, thus allowing an assessment tailored to the patient condition.

EUonQoL project covers EU27 member states and several associated countries. The partnership is composed by research institutions, cancer centres, as well as scientific, professional, and patient representative organizations involved in cancer research, all with extensive experience and robust scientific background in the development of self-reported QoL measures.

1.2 This study

This study is the final step of the development of the tool, with the general objective to perform the psychometric validation of all the components of the EUonQoL-Kit through its first large scale application in a pan European pilot survey of cancer patients and survivors.

2. OBJECTIVES

2.1 Primary aim.

The primary aim of the study is to assess validity and reliability of the EUonQoL-Kit among cancer patients and survivors in Europe.

2.2 Secondary aims

Secondary aims are:

1. To assess the acceptability of the EUonQoL-Kit and reasons for refusal, including patient burden in filling in the questionnaire.
2. To validate the CAT version of the EUonQoL-Kit.
3. To provide preliminary estimates of QoL across different European countries, and to analyse QoL inequalities across clusters of populations, countries, and healthcare systems.
4. To explore socio-demographic and clinical factors potentially associated with QoL in European cancer patients and survivors.

3. METHODS

3.1 Study design

This is an observational study focused on the validation of the newly developed EUonQoL-Kit. Patients enrolled in this survey will not receive any kind of intervention, either pharmacological or non-pharmacological as part of the survey. Patients will be asked to fill in one or more questionnaires, on a single occasion. In a subsample of patients (10%) a retest administration of the EUonQoL-Kit will be performed to estimate its test-retest reliability.

3.2 Study population

The EUonQoL-Kit will be tested in a sample of cancer patients and survivors from 46 oncological centres located in 33 European countries.

3.2.1 Operational definitions

Patients in one of the following three conditions will be screened for their eligibility:

A) In active treatment:

- Undergoing or recently completed curative treatment for early-stage cancers.

Example:

  - *Early stage 1-2 breast cancer during or up to 3 months following radio-therapy, surgery or systemic treatments*

OR

- Undergoing or recently completed non-curative treatment for advanced/metastatic cancers, including disease controlling/life prolonging tumour-directed treatment (e.g., patients with metastatic disease receiving chemotherapy, immunotherapy, or targeted agents).

Examples:

  - *Metastatic breast cancer on 1st line chemotherapy.*
  - *Lung cancer on immunotherapy.*

B) Survivors:

- Being disease-free without evidence of active cancer, and at least one year off ac-

tive treatment (with the exception of long-term adjuvant hormonotherapy).

Example:

- *ER/PR+ breast cancer treated with surgery, adjuvant radiotherapy and on 10 years of hormonal treatment.*

C) Palliative Care (PC): patients with advanced cancers who meet one of the following criteria:

- Patients with projected prognosis <12 months and ECOG ≥2.
  OR
- Patients referred to a specialist palliative care team for symptom control.
  OR
- Patients receiving non-curative systemic treatment or radiotherapy purely for symptom control.

Examples:

- *Patients with castrate-resistant prostate cancer, progressed through systemic treatment options referred for radiotherapy for bone pain.*
- *Metastatic breast cancer patient on 5th line systemic treatment.*

NOTE: these definitions are not exhaustive of the whole cancer patient population, but they are aimed to be used in to validate the tool and to be able to distinguish 3 different patient populations with relative precision.

3.2.2 Eligibility criteria

Inclusion criteria

- Age 18 years or more.
- Present or past histologically confirmed diagnosis of solid tumour or haematological malignancy.
- Being in one of the three conditions previously described: A) Patients in active treatment; B) Survivors; C) PC (see par. 3.2.1, “Operational definitions”).
- Native tongue or fluent in the language of the questionnaire
- Written informed consent to the study.

Exclusion criteria

- Cognitive impairment preventing the completion of the questionnaire.

3.3 Study procedures

3.3.1 Clinical sites

The EUonQoL-Kit will be tested in a European sample of cancer patients and survivors from cancer centres/institutes mostly selected among members of the Organisation of the European Cancer Institutes (OECI) and through the network of contacts of OECI Management. The centres participating in this study are 46, covering 26 EU Member States, 6 associated countries, and one third country.

The list of the centres is reported in *Appendix 1*.

3.3.2 Patient recruitment

Each centre will recruit a total sample of 100 patients and survivors. In order to allow the validation of the EUonQoL-Kit in the three separate patient populations (A, B and C, see par. 3.2.1, "Operational definitions"), in each centre patients will be recruited according to pre-defined sample sizes:

- A: In active treatment (40 patients)
- B: Survivors (30 patients)
- C: PC (30 patients)

In order to guarantee a minimum variability in terms of primary oncological diagnosis, each centre will be asked to approximately enrol a number of patients according to the stratification shown in *Table 1*. For the same variability purposes, each centre will be asked to enrol survivors with more than 5 years off treatment.

Table 1. Enrolment in each centre according to disease condition and primary diagnosis.

	A In active treatment	B Survivors	C PC	Total
Lung cancer	6	5	5	**16**
Breast cancer	6	5	5	**16**
Colorectal cancer	6	4	4	**14**
Haematological malignancies	6	4	4	**14**
Prostate cancer	6	4	4	**14**
Other cancer	10	8	8	**26**
Total	**40**	**30**	**30**	**100**

Note: Haematological malignancies include lymphomas.

3.3.3 Data collection

Each centre will be provided with specific Standard Operating Procedures (SOPs) for the different roles, namely:

- SOPs aimed at the local PI of the study.
- SOPs aimed at the professionals involved in the screening of the patients and in administering the questionnaires.

In each centre, data collection will be performed in pre-identified outpatient clinics and inpatient wards during specific days previously agreed upon with the centre and the coordinator. During these days, participation in the study will be offered to eligible patients in the outpatient clinics and inpatient wards of the centre, until the sample size indicated in the previous table is reached.

All patients in the sample will be asked to fill in the electronic version of the EUonQoL-Kit.

To assess the acceptability, validity, and reliability of the EUonQoL-Kit, as well as the acceptability and concurrent validity of the CAT version, three subgroups out of the total sample of patients will be proposed to fill in the following additional questionnaires:

a) EORTC QLQ-C30 (Aaronson NK,1993), to evaluate concurrent validity ("concurrent validity" sub-sample: 10% of the overall sample, stratified for the three disease conditions: A, B, and C).

b) Live CAT version of the EUonQoL-Kit, to test the feasibility of such implementation ("live CAT" sub-sample: 10% of the overall sample, stratified for

the three disease conditions).

c) EUonQoL-Kit, a second time, (2-7 days after the first administration), to assess test-retest reliability ("test-retest" sub-sample: 10% of the overall sample, stratified for the three disease conditions).

The number of patients enrolled in the three sub-samples is reported in *Table 2*.

Table 2. Enrolment in each centre according to disease condition, requiring additional assessment.

	A **In active treatment**	**B** **Survivors**	**C** **PC**	**Total**
EUonQoL-Kit + EORTC QLQ-C30	4	3	3	**10**
EUonQoL-Kit + CAT	4	3	3	**10**
EUonQoL-Kit test-retest	4	3	3	**10**
Only EUonQoL-Kit	28	21	21	**70**
Total	**40**	**30**	**30**	**100**

The following points describe the main steps of the study to be followed in all centres during the days identified for the assessment:

1. All patients attending outpatient clinics or admitted to the inpatient wards of the centre are screened for eligibility assessment.
2. Eligible patients are provided with information about the study, including Patient Information Sheet and Informed Consent Form.
3. Patient consent or refusal to study participation are elicited. Reasons for refusal and withdrawal of the study are collected.
4. Patients complete the EUonQoL-Kit via a webAPP.
5. Basic socio-demographic and clinical data are collected by health professionals in a dedicated eCRF (a draft of the CRF is reported in *Appendix 2*).
6. Patients are thanked for their contribution to the study (for the 70% patients not included in any of the sub-samples) and are provided with the website address where they will be able to find study results.

The following additional steps will concern only patients included in the three sub-samples described above:

- "Concurrent validity" sub-sample (10% of the overall sample of patients):

1. Patients complete the EORTC QLQ-C30 via a webAPP.
2. Patients are thanked for their contribution to the study.

- "Live CAT" sub-sample (10% of the overall sample of patients):

1. Patients complete the live CAT version via a webAPP.
2. Patients are thanked for their contribution to the study.

- "Test-retest" sub-sample (10% of the overall sample of patients):

1. Patients are provided with a QRcode for a web access to the questionnaire. The day of the planned retest a reminder call will be performed by a professional.

The timing for completing the re-test questionnaire will be the following:

- A) In active treatment: after 7 days (± 1)
- B) Survivors: after 7 days (± 1)
- C) PC: after 2 days (± 1).

NOTE: The different retest timing for patients in subgroup C is due to their more unstable health conditions, compared to patients in subgroups A and B.

3.3.4 Study timelines

For each enrolled patient, participation in the study will be considered concluded after completion of the expected questionnaires.

We estimate to begin enrolment of the planned study sample by April 2024 and complete the pilot survey by the end of October 2024.

4. THE QUESTIONNAIRES

4.1 The EUonQoL-Kit

The development of the EUonQoL-Kit has involved multiple stakeholder groups, also including patients, through different steps. The following are the main steps in synthesis:

a) Systematic search, collection, and analysis of existing self-assessment validated QoL tools, metrics, item banks and databases with the purpose to identify QoL dimensions not adequately covered by existing tools.

b) A mixed-method study including patient interviews, a Delphi survey with patients and

healthcare providers, aimed at collecting patient priorities and preferences on QoL dimensions to be included within the toolkit. A usability testing of a very preliminary version of the EUonQoL-Kit, based on a framework of previously validated items, literature search and results from the mixed-method study, will follow.

c) Development of the EUonQoL-Kit to be applied in different stages of the cancer disease trajectory: patients in active treatment, survivors and in palliative care. The EUonQoL-Kit includes three static questionnaires specifically developed for different disease phases, and three dynamic versions of the same questionnaires. A list of potential items to be included in the EUonQoL-Kit is reported in *Appendix 3*. The final version of the six EUonQoL questionnaires will be submitted as an amendment to the current protocol when available.

d) Translation and cultural adaptation of The EUonQoL-Kit across European countries, in accordance with the quality standards and principles of good practice for the translation and cultural adaptation process for PROMs, based on the ISPOR guidelines (Wild D, 2005).

4.2 The CAT version of the EUonQoL-Kit

Computer Adaptive Testing (CAT) is based on Item Response Theory (IRT). CAT is a sophisticated form of administering PROMs by tailoring the questions to the health status of the individual patient. CAT requires an item bank (set of items) containing a number of IRT-calibrated items (questions) and an algorithm for selecting the most relevant item to ask, based on the answers previously provided by that specific responder (Wainer H, 2000, Petersen NA, 2018). Such dynamic assessment can ensure that each patient is asked the most relevant and informative items within each domain (e.g., physical function, pain, depression).

CAT/IRT-based technology will be implemented in EUonQoL using the same underlying IRT-calibrated item banks in two ways:

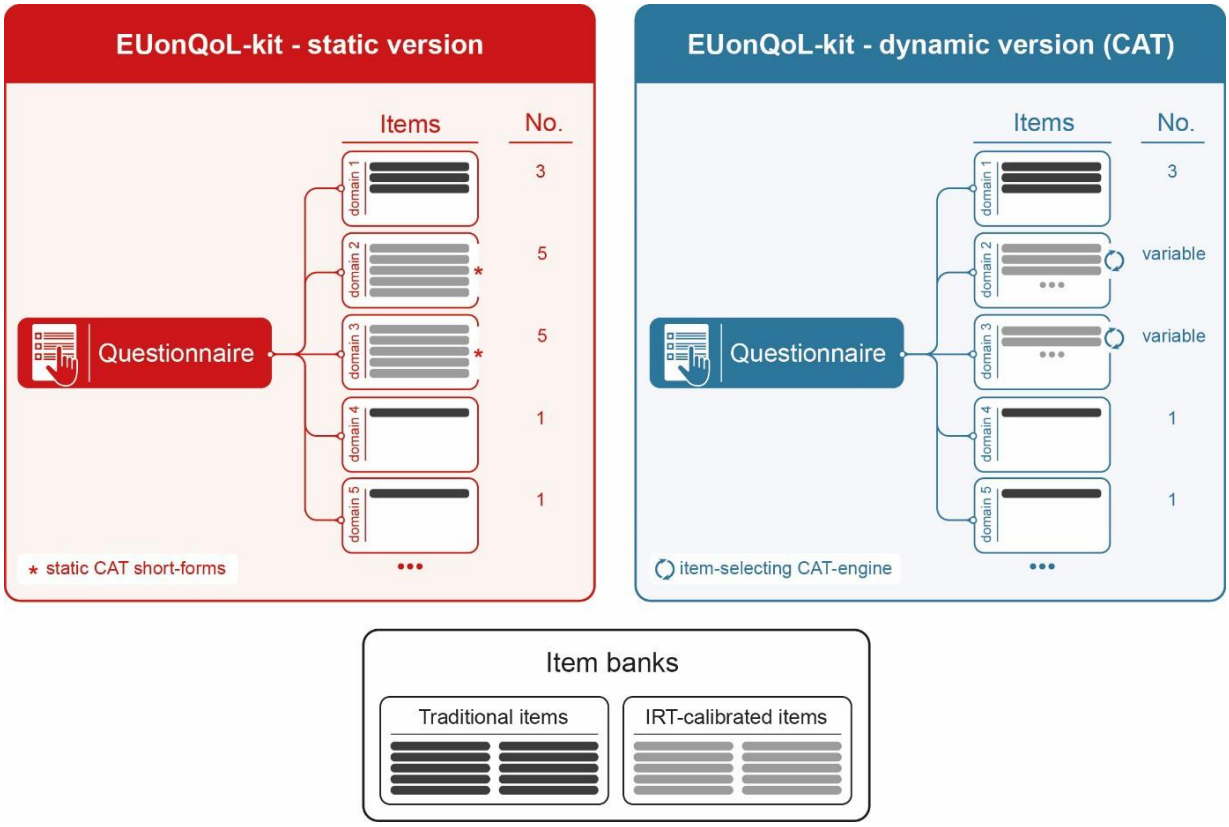
1. As short forms based on IRT within the EUonQoL static version, inserted in exactly the same way as traditional items. Importantly, different static versions will be designed for different groups of patients to secure the optimal fit between items and patient groups. As the items are from the same underlying item bank, they are scored on the same metrics using IRT. This allows for comparison of scores between patients who have completed different short forms,

e.g., the survivors and patients in palliative care.

2. As 'live, interactive CAT' based on the same IRT models and item banks, within the EUonQoL dynamic versions. In the dynamic version each item is selected based on the previous answers, while the patient completes the questionnaire. As an example, for physical function: if unable to walk a short distance, there is no reason to ask if the patient can walk for a long distance. This way the questionnaire is tailored to the patient's condition.

The final EUonQoL-kit will include both traditional and CAT/IRT-based items since not all QoL dimensions are suitable for CAT assessment and because IRT-calibrated items are not always available. An example structure for both the static and dynamic version of the EUonQoL questionnaire is shown in *Figure 1*.

Figure 1 Example structure of static and dynamic versions of each of the three EUonQoL questionnaires specific for each disease condition.



4.3 The EORTC QLQ-C30

The EORTC QLQ-C30 is a 30-item questionnaire specifically developed to assess the quality of life of cancer patients. The original version was published in 1993 (Aaronson NK, 1993) The current version (QLQ-C30 v.3.0) has been translated and validated in over 120 languages and is used in more than 5,000 studies worldwide (Velikova G, 2012).

The QLQ-C30 includes 5 functional scales assessing physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning, 9 scales assessing fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties, and a global health status/QoL scale.

5. STATISTICAL METHODS

5.1 Sample size

This study will be performed in 46 centres with a planned sample of 100 patients for each centre (40 patients in active treatment, 30 survivors and 30 in palliative care). Consequently, the overall sample size for the three populations (A, B, and C) is planned to be 1840, 1380 and 1380, for a total study sample of 4600 patients. Based on an expected lower recruitment rate of 10-15% in the different centres, we assume to enrol at least 4000 patients suitable for data analyses.

Scientifically sound recommendations on statistical power/sample size in validation studies are lacking (Anthoine E, 2014). The power of tests performed will depend not only on the number of items, the number of scales and the magnitude of the correlations, but also on the heterogeneity of the sample. Based on such consideration, many authors have provided minimum rule-of-thumb requirements for sample size in validation studies. Considering that the highest number of participants recommended by various authors for exploratory and confirmatory factor analyses is 1000, the sample size by subgroup mentioned above is appropriate to evaluate construct validity, in the hypothesis of potential missing answers up to 20%. The above size considerations were based on confirmatory and exploratory factor analyses criteria, as they usually require the highest number of participants, and therefore the size is considered to be adequate also for the other psychometric as well as secondary analyses.

5.2 Analysis of the primary aim

Internationally accepted methodological guidelines for the validation of patient reported outcome measures will be followed (Mokkink LB, 2010, Reeve BB, 2013).

The primary aim of the study includes the evaluation of validity and reliability of the EUonQoL static version under classical test theory, as recommended by the international guidelines mentioned above (Mokkink LB, 2010; Reeve BB, 2013). In particular, the following analyses will be conducted for the

whole sample, as well as stratifying by disease stage (patients in active treatment, survivors and in palliative care) and, if feasible, by country:

- Exploratory and confirmatory factor analyses (EFA & CFA) will be performed to assess EUonQoL-kit structural validity. The global sample will be divided into two random sub-samples, stratifying by disease stage and country. The first sub-sample will be used to perform EFA, and the model obtained will be confirmed by CFA in the second sub-sample. Goodness-of-fit will be measured by the Root Mean Square Error of Approximation (RMSEA, adequate if below 0.08), and the Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI), which are recommended to be over 0.95 (Muthén, 2004).
- Distribution of scale scores will be examined by calculating the observed range of scale scores, floor and ceiling effects (proportion of participants with the worst and best possible score, respectively), and statistics of central tendency and dispersion.
- Reliability will be evaluated in terms of internal consistency and reproducibility. Internal consistency will be assessed with Cronbach's alpha coefficient of multi-item scales (Cronbach LJ, 1951). To assess reproducibility, a sub-sample of patients will complete the EUonQoL-kit a second time a few days apart (test-retest), and agreement will be estimated with the Intra-class Correlation Coefficient (ICC).
- Concurrent validity of the EUonQoL-kit will be evaluated in selected sub-samples due to logistic issues. It will be assessed by the multi-trait multimethod matrix (Campbell DT, 1959) between the EUonQoL-Kit and the EORTC-QLQ-C30 questionnaire with Pearson or Spearman correlation coefficients according to the variables' distribution. Hypothesis, established a priori, on the strength of the logical relationships expected between them (0.61–0.90 strong, 0.31–0.60 moderate, and ≤ 0.30 weak) will be tested.

- Construct validity based on hypotheses-testing will be assessed by examining the patterns of EUonQoL-Kit scores across known groups defined by variables such as disease stage, treatment, and Eastern Cooperative Oncology Group (ECOG) performance status. The hypothesis is that we will observe better QoL scores for survivors (subgroup B) as compared to patients in active treatment (subgroup A) and palliative care (subgroup C), for patients in early stage, and for patients with a good performance status. Mean differences among groups will be tested with ANOVA, and the magnitude of the difference between

  them will be estimated by Effect Size coefficient (difference in mean scores between groups/pooled standard deviation): > 0.8 high, 0.5 moderate, and 0.2 low (Kazis LE, 1989).

- Test of differential item functioning (DIF) will be used to assess item equivalence; that is, to evaluate if patients from different countries show differing probabilities of success on any item, after matching on the scale score (Petersen MA, 2003). An ordinal logistic regression approach will be used to assess DIF (uniform and non-uniform) with item response as the dependent variable in the models, and scale and country as the independent variables, together with the scale-country interaction.

5.3 Analysis of the secondary aims

Regarding secondary outcomes analyses, we will follow the STROBE guidelines for reporting observational studies (Von Elm E, 2007).

5.3.1 Acceptability and patient burden

Acceptability will be assessed based on the response rate of the EUonQoL-Kit and on the percentage of missing items, and respondent burden will be evaluated based on time needed to complete the EUonQoL-Kit (statistics of central tendency and dispersion).

5.3.2 Validation of the dynamic-CAT version of the EUonQoL-Kit

There are two primary aims of this validation: 1) to compare scores obtained with the static and dynamic versions to test if they produce similar, interchangeable results; and 2) to assess whether the items selected for the static version and the related CAT-settings should be adjusted to obtain optimal assessment.

1) As static and dynamic versions are based on the same item banks, they are expected to produce interchangeable scores. This is verified by comparing scores from the two versions in the sub-sample which has completed both tools. Mean score differences (and standard deviations) will be calculated and tested. Only trivial differences are expected. Furthermore, Bland-Altman plots, Pearson correlations and Intra-class Correlation Coefficients (ICCs) between the two types of assessment will be calculated. Strong associations are expected.
2) Items selected for the static version and the settings for the dynamic CAT version have been selected prior to the pilot survey based on expected score distributions of the patient populations in the survey. However, the efficiency and precision of the tools depend on these choices. Therefore, based on the observed ('true') distributions in the survey samples, it will be assessed whether the pre-selected items and the CAT settings chosen are optimal or whether adjustments are required to improve efficiency and precision. This will be done by estimating how informative each item is on average for each patient sample, and accordingly, assessing which are the most informative items and what are the optimal CAT-settings.

5.3.3 Estimates of QoL across different European countries

To analyse QoL inequalities across clusters of populations, countries, and healthcare systems, multi-level regression models will be applied across three levels: individual, cancer centre and country (Leylan AH, 2020). QoL will be the dependent variable and individual-level variables as well as country/health system level variables will be included as independent variables to explore the extent to which these variables explain variance in QoL. In these analyses it will also be explored whether the magnitude of subgroup differences (for example, for age or education) varies across countries. Ideally, these analyses are based on data from multiple centres per country, as that will allow separating country effects from centre effects. As the pilot data collection in the present project is limited to a few centres per country for reasons of feasibility (often one centre per country), analyses will be more exploratory to produce first preliminary results, explore the explanatory power of the independent variables included, and inform stakeholders regarding recommendations for the sampling design of future surveys.

5.3.4 Analysis of the socio-demographic and clinical factors potentially associated to QoL

Analysis of QoL disparities across different patient groups will include gender, ethnicity, religion, area (rural vs. urban and across different countries), psychological and socio-economic factors, and education level. The initial analyses will involve extensive exploratory visual plots to compare crude estimates of QoL outcomes grouped by different combinations of conditions and, if applicable, procedures. The classification of procedures and conditions will be based on the OMOP-CDM (Liyanage H, 2018) classification to ensure reproducibility across other studies. Adjusted analyses will be conducted using a combination of regular statistical regression (generalized linear models) adjusted for potential confounders. The latter will include socio-demographic and comorbidity information. In the second step, we will use decomposition methods, where the contribution of each measured variable will be linked to the percentage explained in the model regarding the disparity.

6. PATIENT AND PUBLIC INVOLVEMENT

The EUonQoL project is based on a co-design approach where patients will be included as co- researchers in the different phases of the project, including the pilot study. Researchers and health care professionals will draft the clinical study protocol. Based on this draft protocol, a patient journey through the clinical study process will be visualized. In an interactive session with patient co-researchers, this patient journey will be assessed step-by-step to understand how patients may experience the full trajectory of the clinical study and to identify any opportunities for making the clinical study protocol more patient friendly. The authors of the clinical study protocol will be present during this interactive session to receive the input from patient co- researchers directly and, where possible, explore potential improvements to the protocol.

7. ETHICAL, LEGAL AND REGULATORY ASPECTS

7.1 Privacy and data management

Data collected include personal information belonging to special categories like health-related data, origins, lifestyles etc. Legal basis to collect and process information is the data subject consent, which is necessary to participate to this study.

In order to protect the availability, confidentiality, and integrity of data a series of organisational and technical measures have been envisaged in the project. A data protection expert has been appointed and a continuous data protection impact assessment will be kept updated for the duration of the study.

Patient registration and CRF data collection will be centralized through the CRF.net platform, developed and owned by Istituto Nazionale Tumori, IRCCS - Fondazione G. Pascale, Napoli (INT-NA) and released with the GPL v3 license. Therefore, data will be stored by INT-NA on cloud services provided by Telecom Italia S.p.A. and located in Acilia (Italy).

Patient reported data associated to QR codes will be collected by an ad hoc mobile app developed by Clinical Research Technology (CRT), Salerno (Italy), Tax ID code 07501100635. Such a separation of data processing activities constitutes a safeguard that contributes to the anonymization of the flows of data by avoiding any possible association between patient identities and provided answers.

EUonQoL dynamic version will be administered through the integration of a CAT engine provided by the European Organization for Research and Treatment of Cancer (EORTC), site in Bruxelles (Belgium).

Data processing is managed by:

- Istituto Nazionale Tumori, IRCCS – Milan (INT); as principal investigator INT serves as the data controller as it decides means and purposes of data processing activities.
- Istituto Nazionale Tumori, IRCCS - Fondazione G. Pascale, Napoli (INT-NA). Through CRF.net, INT-NA is to be responsible for patient enrolment, questionnaire assignment in agreement with table 2 through the generation of a QR code, clinician reported data collection through an eCRF, management of the interface with the mobile app for the administration of EUonQoL-kit items, management of the interface with the CAT

engine to allow the administration of the dynamic version of EUonQoL. INT-NA will be appointed as data processor under article 28 GDPR.

- CRT: based on a QR code provided by CRF.net platform, the mobile app administers specific QoL questionnaires for specific subgroup of patients as defined in table 2. For each item administered, the app will directly transfer the answer to the platform, without recording/storing any content. Such a procedure avoids any possibility to link contents to patients' IDs.
- EORTC in case of EUonQoL dynamic version administration, EORTC CAT gets access to each pseudonymized patient reported answer as provided by CRF.net platform (no patient identification is shared with EORTC CAT); answers are stored up to the submission of the entire questionnaire in order to address the proper question according to the provided answer. The EORTC CAT will delete any content once the questionnaire has been submitted including scores sent to thee CRF.net platform. EORTC will be appointed as data processor under article 28 GDPR as it stores the combination of provided answers even if for a very short delay.

The CRF.net platform is accessible online by investigators and data managers through username and password and is protected through encrypted data certified by SSL certificates and HTTPS protocols. For each registered patient, the CRF.net platform generates a QR code that will be scanned with the tablet to allow the patient to complete the related questionnaires.

The interface of the platforms allows data review and cleaning in the central archive directly (with a limited and controlled access of data-managers and investigators). Each operation done in the archive database is registered through track-change. The CRF.net platform is designed to produce automatic routine report (planned according to study specific characteristics) and to be interrogated to produce ad hoc report if needed. The platform allows data extraction for statistical analysis that will be performed with external software.

Each participating centre will receive tablet devices from the sponsor in order to get access to the CRF.net platform and collect study data directly from patients. A paper version of the questionnaire for the patients will be also downloadable through the platform in case of impossibility to use the tablets. In this case data collected will be entered into the platform by instructed and authorized staff, committed to specific confidential obligations – researchers and

data managers - keeping track of the data collection mode (electronic vs paper & pencil). Results will be shared as open data in a completely anonymous and aggregated form under the conditions established by the Grant Agreement of the EUonQoL project. In any case, after 5 years from the data collection, all personal information related to the study, including the informed consents, will be completely anonymized/destroyed according to the delay stated by the Ethics Code on data processing for statistics or scientific research purposes issued by the Italian Data Protection Authority under article 20, para 4, LD 101/2018.

Patients could exercise their rights by submitting requests to the staff identified in the private information. In any case, all the centres have appointed a data protection officer under the GDPR and an internal data breach policy.

7.2 Ethical considerations

This study was designed and shall be implemented and reported in accordance with national and European legal and ethical requirements. Moreover, the survey will follow the ethical principles laid down in the Declaration of Helsinki (World Medical Association, 2013) and the ethical principles of observational research on potentially fragile patients.

7.3 Ethics Committee Approval

To be sure the study will be performed according to Ethical principles, the protocol, Informative Sheet, and Informed Consent Form (see *Appendix 4*) must be reviewed and approved by ethics committees of each centre involved. Written EC approval must be obtained prior to subject enrolment.

7.4 Informative sheets and Informed consent

Eligible subjects may only be included in the study after providing written EC-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e., all the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents. No study procedure can be performed before the written informed consent has been provided.

7.5 Participant burden and risks

The subjective experience of discomfort and benefit in cancer patients when they fill in a QoL

questionnaire has never been explored in depth. A few studies have reported emotional distress in healthy people with pre-existing emotional vulnerabilities when they are asked to participate in a survey.

For this kind of study, we do not expect any negative issue from the patients, but we are going to implement some safety procedures, namely:

- A detailed informative sheet will be provided to the patients before asking them to give their consent to the study. The general dimensions explored by the questionnaire will be reported in the sheet.
- Professionals involved in the survey will be trained to explain the patients the general topics explored by the QoL questionnaire and to appropriately assist them during the compilation, when needed.
- A final question will explore the distress they experienced in filling-in the questionnaire.
- It will be possible for the patient to withdraw from the study at any time and without requiring any justification.

8. GOVERNANCE OF THE STUDY

8.1 Actions implemented by the sponsor

The study procedures must guarantee a high level of scientific and ethical conduct in all the centres. To deal with this issue the subsequent action will be implemented by the sponsor:

- **Support for Ethical Committee application**. Each centre will receive specific support for all the procedures requested for the application of the study protocol to the local Ethical Committee.
- **Training**. Professionals involved in the conduction of the study will be specifically trained about the procedures of the study through ad hoc organized webinars in order to reach all the personnel which will be involved in data collection in all centres.
- **Manual**. Besides the final protocol, each centre will receive an Operational Manual for an appropriate conduct of the survey.
- **Site Initiation Visit (SIV).** A formal remote SIV will be organised in all participating centres. During the meeting the protocol will be discussed, especially the inclusion criteria and the study procedures.

- **Central data monitoring** will be applied during the study to verify data completeness, consistency, accuracy, and data entry timing, and analyse trends per study and per centre, to identify possible casual or systematic deviations.

On-site data monitoring visits will be performed to verify informed consent, eligibility criteria and data accuracy. A risk analysis will be performed to produce a monitoring plan once the list of the centres is completed. However, it can be anticipated that the risk will be defined as low (non-interventional study performed in centres with research experience, no collection of biological samples, primary outcome constituted by a self- report of QoL assessment). Moreover, additional targeted visits can be organized in case of centres that are defined at high-risk.

8.2 Governing boards

Study Steering Committee (SSC). The SSC has agreed the final protocol submitted to the Ethical Committee. The SSC is composed of one representative of each working group of the EUonQoL

consortium involved in the survey. The SSC has the responsibility to take all decisions related to budget, to scientific issues, ethical aspects and any other survey related issue.

Study Management Board. It includes one member per centre involved in the study. The Board provides a continuous monitoring of survey progress, with a specific attention to adherence to the protocol procedures.

The meetings can take place either in person or via teleconference according to the specific needs.

9. REFERENCES

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10. APPENDICES

10.1 Appendix 1: List of the centres

Centre # 1

Fondazione IRCCS Istituto Nazionale dei Tumori

Via Venezian 1, 20133 Milan

Country: Italy

Local PI: Dott.ssa Cinzia Brunelli, email cinzia.brunelli@istitutotumori.mi

Centre # 2

Comprehensive Cancer Center Vienna

Spitalgasse 23, 1090 Vienna

Country: Austria

Local PI: Prof. Widder Joachim, email joachim.widder@meduniwien.ac.at

Centre # 3

Mother Teresa University Hospital of Tirana

Rruga e Dibrës 372 Tirana AL, 1000

Country: Albania

Local PI: Prof. Helidon Nina, email ninahelios@yahoo.com

Centre # 4

Kortrijk Kankercentrum AZ Groeninge

Campus Kennedylaan | Pres. Kennedylaan 4 | B-8500 Kortrijk

Country: Belgium

Local PI: Dr. Philip Debruyne, email philip.debruyne@azgroeninge.be

Centre # 5

Bulgarian Joint Cancer Network

15 Andrey Saharov Blvd., Bild. 1, Entr. A, Atelie 19, 9000 Varna

Country: Bulgaria

Local PI: Mr. Ivaylo Petrov, email ivaylo.petrov@shemhahealth.com

Centre # 6

Klinika za tumore Klinički bolnički centar Sestre milosrdnice

Sestre milosrdnice University Hospital Center, Vinogradska 29, 10000 Zagreb

Country: Croatia

Local PI: Dr. Vesna Ramljak, email vesna.ramljak@kbcsm.hr

Centre # 7

Cyprus Association of Cancer Patients and Friends (PASYKAF)

2 Chalkanoros str., 2000 Strovolos, Nicosia

Country: Cyprus

Local PI: Ms Maria Krini, email mariakr@pasykaf.org

Centre # 8

Masarykův onkologický ústav

Žlutý kopec 7, 602 00 Brno

Country: Czech Republic

Local PI: Dr. Tomas Kazda, email: tomas.kazda@mou.cz

Centre # 9

Region Hovedstaden (Rigshospitalet)

Kongens Vaenge 2, Hillerod 3400

Country: Denmark

Local PI: Prof. Helle Pappot, email Helle.Pappot@regionh.dk

Centre # 10

Sihtasutus Tartu Ülikooli Kliinikum

L. Puusepa 1a, 50406 Tartu

Country: Estonia

Local PI: Mrs Liina Pääbo, email Liina.Paabo@kliinikum.ee

Centre # 11

North Estonia Medical Centre

J.Sütiste tee 19, 13419 Tallinn

Country: Estonia

Local PI: Dr. Vahur Valvere, email Vahur.Valvere@regionaalhaigla.ee

Centre # 12

HUS Syöpäkeskus Helsingin Yliopistollinen Sairaala

Haartmanninkatu 4, 00290 Helsinki

Country: Finland

Local PI: Prof. Mattson Johanna, email Johanna.Mattson@hus.fi

Centre # 13

lnstitut de Cancérologie de l'Ouest (ICO)

15 Rue André Boquel-49 055 Angers Cedex 02

Country: France

Local PI: Dr. Robert Marie, email Marie.Robert@ico.unicancer.fr

Centre # 14

Institut Curie

Rue d'Ulm 26, 75005 Paris

Country: France

Local PI: Dr. Anne Brédart, email anne.bredart@curie.fr

Centre # 15

Gustave Roussy

114 rue Edouard Vaillant. 94 805 Villejuif

Country: France

Local PI: Dr. Maria A. Franzoi, email Mariaalice.BORINELLI-FRANZOI@gustaveroussy.fr

Centre # 16

Petre Shotadze Tbilisi Medical Academy

Ketevan Tsamebuli avenue 51/2, 0144 Tbilisi

Country: Georgia

Local PI: Prof. Ekaterina Kldiashvili, email: e.kldiashvili@tma.edu.ge

Centre # 17

Universitäres Centrum für Tumorerkrankungen (UCT) Frankfurt

Theodor-Stern-Kai 7, 60590 Frankfurt

Country: Germany

Local PI: Dr. Christian Brandts, email christian.brandts@kgu.de

Centre # 18

CCC Munich - Comprehensive Cancer Center Munich

Campus Großhadern | Marchioninistr. 15 | 81377 München

Country: Germany

Local PI: Dr. Theres Fey, email Theres.Fey@med.uni-muenchen.de

Local co-PI: Dr. Nicole Erickson, email Nicole.Erickson@med.uni-muenchen.de

Centre # 19

Deutsches Krebsforschungszentrum (DKFZ)

Im Neuenheimer Feld 280, Heidelberg 69120

Country: Germany

Local PI: Dr. Volker Arndt, email v.arndt@Dkfz-Heidelberg.de

Centre # 20

General Oncology Hospital of Athens - Saint Savvas

171 Alexandras Avenue, 11522 Athens

Country: Greece

Local PI: Mr Olga Balaoura, email olga.balaoura@gmail.com

Centre # 21

Országos Onkológiai Intézet

Ráth György street 7-9., 1122 Budapest

Country: Hungary

Local PI: Dr Orsolya Horvath, email horvath.orsolya@oncol.hu

Centre # 22

Trinity St. James's Cancer Institute

James Street Dublin 8, D08 NHY1

Country: Ireland

Local PI: Prof. Claire Donohoe, email donohoe.claire@gmail.com

Centre # 23

Istituto Tumori Giovanni Paolo II, IRCCS

Viale Orazio Flacco, 65, Bari, Italy

Country: Italy

Local PI: Dr. Alessandro Rizzo, email rizzo.alessandro179@gmail.com

Centre # 24

Istituto Nazionale Tumori Regina Elena

Via Chianesi 53, Roma 00144

Country: Italy

Local PI: Dr. Andrea Pace, email andrea.pace@ifo.it

Centre # 25

Istituto Europeo di Oncologia

Via Filodrammatici 10, Milano 20121

Country: Italy

Local PI: Prof. Gabriella Pravettoni, email: gabriella.pravettoni@ieo.it

Centre # 26

Riga East University Hospital

Hipokrata street 2, Riga, LV-1038

Country: Latvia

Local PI: Prof. Sandra Lejniece, email Sandra.lejniece@aslimnica.lv

Centre # 27

National Cancer Institute

Santariskiu 1 - 08406 Vilnius

Country: Lithuania

Local PI: Dr. Audrius Dulskas, email Audrius.dulskas@nvi.lt

Centre # 28

Health-Sir Anthony Mamo Oncology Centre

WF2F+PQH, Msida

Country: Malta

Local PI: Dr. Marmara Danika, email danika.marmara@gov.mt

Local co-PI: Mr. Aquilina Reginald, email reginald.aquilina@gov.mt

Centre # 29

Oncologic Institute of Moldova

str. Testemitanu 30, Chisinau MD-2025

Country: Moldova

Local PI: Dr. Vadim Pogonet, email vadimpg@gmail.com

Centre # 30

Netherlands Cancer Institute

Plesmanlaan 121, Amsterdam 1066 CX

Country: Netherlands

Local PI: Prof. Lonneke van de Poll, email l.vd.poll@nki.nl

Centre # 31

Oslo University Hospital (OUS)

166 Tarnbygget, Oslo 0450

Country: Norway

Local PI: Prof. Marianne Grønlie Guren, email m.g.guren@medisin.uio.no

Centre # 32

Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie Państwowy Instytut Badawczy

02-781 Warszawa, ul. W. K. Roentgena 5 POLSKA

Country: Poland

Local PI: Prof. Iwona Ługowska, email Iwona.Lugowska@pib-nio.pl

Co-PI: Prof. Katarzyna Pogoda, email Katarzyna.Pogoda@pib-nio.pl

Centre # 33

Greater Poland Cancer Centre

im. Marii Skłodowskiej-Curie, Garbary 15 street, 61- 866 Pozna

Country: Poland

Local PI: Prof. Maria Litwiniuk, email maria.litwiniuk@wco.pl

Centre # 34

Instituto Português de Oncologia do Porto Francisco Gentil, E.P.E. (IPO-Porto)

Rua Dr. António Bernardino de Almeida, 4200-072 Porto

Country: Portugal

Local PI: Prof. Maria José Bento, email mjbento@ipoporto.min-saude.pt

Centre # 35

The "Prof. Dr. Ion Chiricuta"Institute of Oncology (IOCN)

Republicii Street, 34-36, Cluj-Napoca 400015

Country: Romania

Local PI: Prof. Tudor Ciuleanu, email tudor_ciuleanu@hotmail.com

Centre # 36

Institutul Oncologic "Al. Trestioreanu" (IOB)

Șoseaua Fundeni nr. 252, Sector 2, Bucharest, postal code 022328

Country: Romania

Local PI: Prof. Laurenția Galeș, email laurentia.gales@yahoo.com

Centre # 37

Oncology Institute of Vojvodina

Put dr Goldmana 4, 21204 Sremska Kamenica

Country: Serbia

Local PI: Dr. Milana Mitric Askovic, email mitric.milana@onk.ns.ac.rs

Centre # 38

Onkološki Inštitut Ljubljana

Zaloška cesta 2, 1000 Ljubljana

Country: Slovenia

Local PI: Dr. Ratoša Ivica, email iratosa@onko-i.si

Centre # 39

National Cancer Institute (Národný onkologický ústav)

Klenová 1, 83310 Bratislava

Country: Slovakia

Local PI: Prof. Michal Chovanec, email: michal.chovanec1@gmail.com

Centre # 40

Vall Hebron Institute of Oncology (VHIO)

Carrer Natzaret 115-117, 08035 Barcelona

Country: Spain

Local PI: Dr. Maria Vieito, email mvieito@vhio.net

Centre # 41

Fundación Instituto Valenciano de Oncología (IVO)

C/Profesor Beltrán Báguena 8. 46009 Valencia

Country: Spain

Local PI: Dr. Héctor Aguilar, email haguilar@fivo.org

Centre # 42

Fundacion Jimenez Diaz University Hospital

Reyes Catolicos 2, 28040-Madrid

Country: Spain

Local PI: Ms Eva Ruiz, email eva.ruizh@quironsalud.es

Centre # 43

Sahlgrenska comprehensive cancer centre

Bruna stråket 10, 413 45 Gothenburg

Country: Sweden

Local PI: Prof. Karin Ahlberg, email karin.ahlberg@fhs.gu.se

Centre # 44

Anadolu Medical Center

Cumhuriyet Mah, 2255. Sk. No: 3, 41400 Gebze/Kocaeli

Country: Turkey

Local PI: Ass. Prof. Dr Eda Tanrıkulu Simsek, email eda.simsek@anadolusaglik.org

Centre # 45

Turkey Cancer Institute

TÜSEB İstanbul Yerleşkesi, Koşuyolu Mahallesi, Koşuyolu Caddesi No: 71 Kadıköy / İSTANBUL 34718

Country: Turkey

Local PI: Prof. Dr. Mahmut Gumus, email Mahmut.Gumus@tuseb.gov.tr

Centre # 46

Leeds Teaching Hospitals NHS Trust

Great George St, Leeds LS1 3EX

Country: United Kingdom

Local PI: Alexandra Gilbert, email A.Gilbert@leeds.ac.uk

10.2 Appendix 2: Draft list of socio-demographic and clinical variables to be included in the CRF for the pilot survey.

Socio-demographic variables

- Gender
- Age group
- Civil status
- Living alone (number of co-habitants)
- Education level
- Present employment (occupational) status
- Employment (occupational) status prior to the diagnosis
- Living area (urban, semi-urban, rural)
- Income
- Nation of birth

Target population assessment (filtering to different CRFs):

- A) Patients in treatment
- B) Survivors
- C) PC

Clinical variables

- Cancer type
- Year of primary cancer diagnosis
- Relapsed (Y/N)
- Presence of metastases (Y/N)
- ECOG
- Comorbidities (Charlson index)
- Current anti-cancer treatment (Y/N)
- Type of ongoing treatment (present line)
    - Chemotherapy (Y/N)
    - Radiotherapy (Y/N)
    - Hormonal therapy (Y/N)
    - Other
- Date of last tumor-directed treatment administration
- Presence of psychiatric syndromes (Y/N)
- Undergoing psycho-pharmacological treatment (Y/N)

- Followed by a specialized palliative care team (Y/N)
- Undergoing treatment for physical symptoms (Y/N)

10.3 Appendix 3: List of example items from EORTC Item Library, including EORTC-QLQ C30

11. Health domains	Examples of questions
Physical health	
Pain/pain interference	Have you had pain?
Fatigue/Energy	Have you lacked energy?
Insomnia	Have you had trouble sleeping? *Not at all, A little, Quite a bit, Very much*
Appetite loss	Have you lacked appetite? *Not at all, A little, Quite a bit, Very much*
Nausea	Have you felt nauseated? *Not at all, A little, Quite a bit, Very much*
Constipation	Have you been constipated? *Not at all, A little, Quite a bit, Very much*
Diarrhoea	Have you had diarrhoea? *Not at all, A little, Quite a bit, Very much*
Dyspnoea	Were you short of breath? *Not at all, A little, Quite a bit, Very much*
Sensory Neuropathy	Have you had tingling or numbness in your hands or feet? *Not at all, A little, Quite a bit, Very much*
Symptom awareness	How much has your disease been a burden to you? Have you been watching yourself closely for any new symptoms? *Not at all, A little, Quite a bit, Very much*
Impact of treatment side-effects	To what extent have you been troubled with side-effects from your treatment? *Not at all, A little, Quite a bit, Very much*
Physical function	

Mobility	Do you need to stay in bed or a chair during the day?

	Not at all, A little, Quite a bit, Very much
Physical exercise	Do you have any trouble taking a short walk outside of the house? Do you have any trouble taking a long walk? *Not at all, A little, Quite a bit, Very much*
Activities Daily Living	Do you need help with eating, dressing, washing yourself or using the toilet? *Not at all, A little, Quite a bit, Very much*
Instrumental ADL	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? *Not at all, A little, Quite a bit, Very much*
Sexual health	
Sexual problems (physical)	Has the treatment affected your sexual activity? Have you worried about your ability to have sexual intercourse? *Not at all, A little, Quite a bit, Very much*
Sexual pleasure	Was sexual activity enjoyable for you? Have you had problems becoming sexually aroused? *Not at all, A little, Quite a bit, Very much*
Body Image	
	Have you been dissatisfied with your physical appearance? *Not at all, A little, Quite a bit, Very much*
Mental Health	
Anxiety	Did you worry? *Not at all, A little, Quite a bit, Very much*
Depression	Did you feel depressed? *Not at all, A little, Quite a bit, Very much*

Distress	Have you felt stressed? *Not at all, A little, Quite a bit, Very much*
Fear of recurrence	
	Have you worried about recurrence of your disease? *Not at all, A little, Quite a bit, Very much*

Health outlook	
Uncertain prognosis	Have you been worried about your health in the future? *Not at all, A little, Quite a bit, Very much*
Future Life plans	Have you had to limit your life plans or goals? Have you worried about not being able to continue working or your education? *Not at all, A little, Quite a bit, Very much*
Cognitive function	
Cognitive problems	Have you had difficulty remembering things? Have you had difficulty in concentrating on things, like reading a newspaper or watching television? *Not at all, A little, Quite a bit, Very much*
Positive affect	
	Has the experience of cancer helped you to distinguish between important and unimportant things in life? *Not at all, A little, Quite a bit, Very much*
Life satisfaction	
Positive life outlook	Have you had a positive outlook on life in the last week? *Not at all, A little, Quite a bit, Very much*
Spirituality	
	I have felt at peace with myself *Not at all, A little, Quite a bit, Very much*

	I feel connected to God or to someone or something greater than myself *Not at all, A little, Quite a bit, Very much*
	Do you feel that your life has more purpose? *Not at all, A little, Quite a bit, Very much*
Social Health	
Ability to Work	Were you limited in doing either your work or other daily activities? *Not at all, A little, Quite a bit, Very much*
Leisure activities - Hobbies	Were you limited in pursuing your hobbies or other leisure time activities?
	Not at all, A little, Quite a bit, Very much
Leisure travel	Have you been limited in your ability to travel? *Not at all, A little, Quite a bit, Very much*
Social activity limitations	Has your physical condition or medical treatment interfered with your social activities? *Not at all, A little, Quite a bit, Very much*
Impact on children/family	Has your physical condition or medical treatment interfered with your family life? *Not at all, A little, Quite a bit, Very much*
Fertility: Ability to have children	Have you been concerned about your ability to have children? *Not at all, A little, Quite a bit, Very much*
Partner relations	Is your relationship with your partner stronger? *Not at all, A little, Quite a bit, Very much, N/A*
Social isolation	
	Have you felt isolated from those close to you (e.g. family, friends)? *Not at all, A little, Quite a bit, Very much*
Social support	
	I have felt able to share thoughts about life with people who are close to me. *Not at all, A little, Quite a bit, Very much*

Self-efficacy	
	Have you lacked self-confidence? Have you taken better care of yourself? During your current disease or treatment, how much information have you received on: Things that you can do to help yourself get well (rest, contact with others..)? *Not at all, A little, Quite a bit, Very much*
	Have you worried that you are a burden to other people? *Not at all, A little, Quite a bit, Very much*
Financial aspects	
	Not at all, A little, Quite a bit, Very much
Insurance	Have you had problems with obtaining insurance, loans, and/or a mortgage? *Not at all, A little, Quite a bit, Very much*
Global QOL	
Overall QOL	How would you rate your overall quality of life during the past week? Very poor (1) – Excellent (7)
Health	
Health behaviour change	How would you rate your overall health during the past week? Very poor (1) – Excellent (7)

10.4 Appendix 4: Patient Information Sheet and Informed Consent Form

Patient Information sheet and Informed Consent Form
Adult Patient

This form, which will be delivered to you well in advance of your final decision, contains essential information about the clinical study in which you are being asked to participate. It is important that you read this information and discuss it with your doctor before signing the consent form to participate in the study.

Only patients who will give their informed consent, can participate in the study. You can withdraw your consent at any time.

Study Identification Code:

Patient Identification Code:

Title of the Study: "**Validation of the European Oncology Quality of Life Toolkit. A European pilot survey"**

Version No.

Date: _ / _ / _____

Sponsor:

Introduction

Dear Ms/Mrs,

Before you decide whether to take part in this study, it is important that you are informed about the aims of the study and what taking part will mean for you. Please, take your time to read this information carefully and, if you wish, discuss it with friends, relatives, and your clinical team.

Please, ask questions if something (e.g., some medical terms or expressions) is unclear to you or if you would like more information. The study we are proposing to you has been reviewed and approved by the Ethics Committee currently in charge.

What is an observational clinical research study?

During an observational study, a patient is treated for his/her disease according to routine medical practice.
Regardless of your participation in the observational study, you will continue with the currently available diagnostic pathways and therapies that are best suited to the treatment of your disease. Information and data resulting from the procedures and tests performed during the observational study are collected and analysed to answer the question of the research.

What is the aim of this study? How many patients and centres will take part?

This study is part of a larger project, funded by the European Union, aimed at developing a set of questionnaires (EUonQoL-kit) intended to assess the quality of life of European oncological patients who are at different stages of the care continuum.

It is important to have scientifically sound questionnaires for measuring quality of life. On the one hand, this helps cancer researchers to ensure that healthcare practices provide good QoL for patients; on the other, it can help clinicians to understand what is going on with their patients, in terms of physical and psychological symptoms, functional and relational skills, that contribute to determining their quality of life.

This study represents the last phase of development of the questionnaires included in the EUonQoL-kit and consists in their *validation*. *To validate* a questionnaire means to test that it measures what it intends to measure, and that this measurement is reliable, i.e., stable in the case of repeated measurements under stable conditions.

To this end, the present study will ask a sample of European patients, who are at different stages of their disease trajectory, to fill in a questionnaire in electronic format. For validation purposes, 3 small sub-groups of patients will be asked to complete a second questionnaire:

- Sub-group 1: A widely used validated questionnaire for the assessment of quality of life in oncology (EORTC QLQ-30)
- Sub-group 2: A dynamic version of the first questionnaire, in which the proposed ques- tions will be automatically selected based on the answers provided to previous questions (Computer Adaptive Testing version)

- Sub-group 3: The same questionnaire as for the first compilation, after a short time in- terval (a few days).

The study will involve 46 different European clinical centres, each recruiting 100 patients (for a total of 4.600 patients). To ensure consistency in the selection of participating patients, in the methodology, in the collection and analysis of the acquired data, the centres will refer to a shared study protocol.

What will happen if I take part?

You are being invited to take part in this project because the clinical team looking after you has identified you as someone who has been diagnosed or treated for an oncological disease. Therefore, your experiences and views are important to our research study.

Since this is a non-pharmacological observational study, if you decide to take part in the study, your participation will only consist in completing one questionnaire (or two questionnaires, only in the case that you will be selected to complete a second questionnaire, as described above) and you will be asked for permission to use your data for research purposes. With your consent, we will also collect some personal information (e.g., employment status) and clinical data from your hospital records about your disease diagnosis and medical history.

You will be asked to complete the questionnaire in electronic format, via tablet. There is no need to have any experience using computers to be able to take part. There are no right or wrong answers to the questionnaire, we are simply collecting your opinions.

Completing the questionnaire will take about 15-20 minutes and will take place in the hospital. In the event that you are selected to complete a second questionnaire, this will take place immediately after completion of the first questionnaire and will require approximately 10 additional minutes.

Only if you will be assigned to sub-group 3 described above, you will be asked to fill in the second questionnaire a few days after completing the first one, possibly in the hospital during your next visit, or at home. In the latter case, you will fill out the questionnaire directly from your electronic device by scanning a QR code that will be given to you when completing the first questionnaire.

What are the possible risks of taking part?

Given the observational nature of the study, there are no medical risks associated with the participation. While some people find it helpful to think about the issues addressed in the questionnaire, a few people may find this upsetting. You can stop the compilation or take a break at any time, and you do not need to give a reason.

Can I withdraw my participation from the study?

It is up to you to decide whether or not you want to take part. If you do decide to take part, you will

be given this information sheet, then you will be asked to sign a consent form to take part in the study. However, you can withdraw at any time without giving any explanation, and your decision will not affect the medical care you are receiving.

How will my data and samples be handled?

This study does NOT imply the collection of biological samples. Your clinical data and your answers to the questionnaires, collected to the extent that they are indispensable in relation to the objective of the study, will be processed in compliance with EU Regulation 2016/679 known as GDPR (General Data Protection Regulation). This means that the data will be kept securely and will not contain your name, but an identification code that will be only known to your doctor and clinical staff. Details on the processing of your data are present in the information sheet on the processing of personal data which you can read carefully to decide whether to give your consent. Without consent to the processing of your personal data, you will not be able to participate in the proposed study.

Will I receive compensation for participating in this study?

You will not receive any compensation for your participation in this study.

Will I have access to the study results?

Once the study is concluded, the data and information collected will be analysed to draw conclusions. The sponsor and the researchers of the study will make them available to the scientific community; therefore, you can ask your medical staff or the study coordinator how to access the results.

Patient Consent Form

This form must be signed only if you decide to participate in the study. It is important that you have discussed in depth with your GP before signing this consent, and that you have read the "Information Sheet" above. Only patients who sign the consent form, will participate in the study.

Please sign to show that you have read and agree to each statement:

1. **I confirm that I have read and understand the information sheet for the above study.**
2. **I declare that I have received a copy to keep.**
3. **I agree to inform my General Practitioner, Dr .....about my participation in this study.**

☐ **Yes**

☐ **No**

Name of Patient …… …… …../…../…….
Signature Date:

Name of Researcher …… …… …../…../…….
Signature Date:

Annex 2 - Ethical approval of the first clinical site

Sistema Socio Sanitario

Fondazione IRCCS Istituto Nazionale dei Tumori — Regione Lombardia

COMITATO ETICO E-mail: comitato.etico@istitutotumori.mi.it – Tel.: +39 02 2390 2546, 2744, 3452 – Fax: +39 02 2390 3453

Milano, 23 Maggio 2023

Oggetto: Studio dal titolo "EUonQoL- Validazione dell'EUonQoL-toolkit, un insieme di strumenti per la valutazione della qualità della vita in oncologia. Uno studio pilota europeo"

Promotore: Fondazione IRCCS Istituto Nazionale dei Tumori (MI)

Tipologia: Osservazionale prospettico non su farmaco

In riferimento allo studio osservazionale in oggetto, si comunica che durante la seduta del 27 Aprile 2023, il Comitato Etico della Fondazione IRCCS "Istituto Nazionale dei Tumori" ha preso visione della documentazione completa allegata e informa che, per quanto di sua competenza, nulla osta alla effettuazione dello studio.

A questo studio l'ufficio di segreteria ha assegnato il **N. INT 106/23**. A questo numero ufficiale va fatto riferimento per ogni corrispondenza.
Si ricorda che l'avvio dello studio da parte del Promotore è subordinato a:

- stipula della convenzione economica (se applicabile);
- rilascio della delibera autorizzativa del Direttore Generale della Fondazione.

E' fatto obbligo al Promotore di notificare al Comitato Etico:

- data di arruolamento primo paziente;
- stato di avanzamento dello studio;
- fine periodo di arruolamento;
- data di conclusione dello studio a livello locale ed a livello globale;
- risultati dello studio, entro un anno dalla conclusione dello stesso.

Dott. Giovanni Apolone
Su delega del Presidente

Firmato da:
GIOVANNI APOLONE
Codice fiscale: PLNGNN56E10B664E
Organizzazione: NON PRESENTE
Valido da: 02-09-2020 09:24:10 a: 02-09-2023 02:00:00
Certificato emesso da: InfoCert Qualified Electronic Signature CA 3, InfoCert S.p.A., IT
Riferimento temporale 'SigningTime': 23-05-2023 09:29:03
Motivo: Approvo il documento

Allegati: 1) Elenco documentazione pertinente allo studio
2) Pagina presenze componenti CE

Allegato 1: Elenco documentazione pertinente allo studio (INT 106/23)

Documento	Nome file	Ver	Data Ver
Lettera di trasmissione	A1_Lettera trasmissione_V1.pdf		13/04/2023
Elenco centri partecipanti	A3_Lista centri_V1.docx	1	07/04/2023
Informativa e Consenso main	B1_Informativa studio_V1.docx	01	07/04/2023
Informativa e consenso privacy	B2_Informativa trattamento dati_V1.docx	01	07/04/2023
Materiale informativo paziente	B6_Materiale pz_V1.docx	01	07/04/2023
Protocollo	C1_Study protocol_V1.docx	1	13/04/2023
Sinossi in italiano	C2_Sinossi_V1.doc	1	11/04/2023
CRFs	C3_CRF_V1.docx	1	07/04/2023

Sistema Socio Sanitario

Fondazione IRCCS Istituto Nazionale dei Tumori

Regione Lombardia

Il Comitato Etico della Fondazione IRCCS "Istituto Nazionale dei Tumori" la cui composizione risponde ai requisiti minimi individuati dai D.M. 08/02/13 e D.M. 12/05/06, è stato deliberato, per il triennio 01.01.2017-31.12.2019 dal CdA della Fondazione il 22.12.2016 , aggiornato il 02.04.2019 e prorogato da RL (13/04/2022) fino alla fine del periodo transitorio (AIFA).

Allegato 2: pagina presenze componenti CE

Riunione in teleconferenza del Comitato Etico del 27 Aprile 2023

	ASSENTE PRESENTE (A/P)
Dott. LABIANCA ROBERTO (Clinico) **Presidente**	**P**
Dott. APOLONE GIOVANNI (Direttore Scientifico)	**A**
Dott. BOMBARDIERI EMILIO (Clinico)	**P**
Dott. CELENTANO CARLO (Medicina Generale Territoriale)	**P**
Dott. CEREDA EMANUELE (Esperto in Nutrizione) in relazione allo studio di prodotti alimentari sull'uomo	**P**
Dott.ssa CRIPPA FLORIANI FRANCESCA (Esperto in assistenza sanitaria)	**P**
Dott. D'INCALCI MAURIZIO (Farmacologo) **Vice Presidente**	**P**
Prof. FOA PAOLO (Clinico)	**P**
Dott. JANKOVIC MOMCILO (Pediatra)	**P**
Dott. LADISA VITO (Farmacista del SSR)	**A**
Avv. MANTOVANI RENATO (Esperto in materia giuridica)	**P**
Dott. MIADONNA ANTONIO (Clinico)	**P**
Avv. MIGONE de AMICIS AGOSTINO (Esperto in materia giuridica)	**P**
Prof.ssa MIOZZO MONICA ROSA (Esperto in genetica)	**A**
Ing. PAVESI ROBERTA ELENA (Esperto in dispositivi medici) in relazione all'area medico-chirurgica oggetto dell'indagine con il dispositivo medico in studio	**A**
Don TULLIO PROSERPIO (Esperto di bioetica)	**P**
Dott. RAMPOLDI ANTONIO GAETANO (Esperto nuove procedure) in relazione a nuove procedure tecniche, diagnostiche e terapeutiche, invasive e mini-invasive	**A**
Prof. SCAGLIONE FRANCESCO (Farmacologo)	**A**
Prof.ssa SCORSETTI MARTA (Clinico)	**A**
Dott.ssa TOGNI SERENA (Rappresentante Professioni Sanitarie)	**P**
Dott. TORRI VALTER (Biostatistico)	**A**
Dott. TRIARICO ANTONIO (Direttore Sanitario)	**A**
Dott.ssa VETERE RITA (Volontariato/Associazionismo)	**P**
Dott. PEROTTI GABRIELE MARIO (Sostituto permanente che ha partecipato alla seduta in vece del Direttore Sanitario)	**A**

Annex 3 - Registration number of the clinical study

The clinical study "Validation of the European Oncology Quality of Life Toolkit. A European Pilot Survey." was submitted on ClinicalTrials.gov on the 28th of June 2023, and was given the following ID: NCT05947903.

https://clinicaltrials.gov/study/NCT05947903

Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the granting authority can be held responsible for them.