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Validation of the European Oncology toolkit for the self-assessment of Quality of Life (EUonQoL-Kit) in cancer patients and survivors: study protocol of a pan European survey

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Abstract

Background European cancer programmes and policies lack a unified health-related quality of life (HRQoL) assessment tool. The European oncology quality of life toolkit (EUonQoL-Kit) is a novel set of HRQoL questionnaires, co-designed with cancer patients and survivors, translated and culturally adapted into 31 European languages, and with both static and dynamic electronic administration modes. The main aim of this study is the psychometric assessment of the static version. Secondary aims include evaluating the EUonQoL-Kit acceptability, cross-validating the administration modes, exploring individual factors potentially affecting HRQoL and HRQoL inequalities between countries.

Methods A sample of 4,500 participants, including three groups (active treatment, survivors, and palliative care) from 45 centres in 25 EU Member States and 7 associated countries, will be enrolled in a multicentre observational cross-sectional study. All participants will complete the static EUonQoL-Kit; three subsamples (each 10% of the total sample) will also respectively complete the following: a) dynamic EUonQoL-Kit, based on Item Response Theory (IRT)/Computer Adaptive Testing (CAT), b) FACT-G and EQ-5L-5D, and c) static EUonQoL-Kit (re-test). Psychometric analyses will encompass exploratory and confirmatory factor analyses (measurement model and structural validity), Cronbach's alpha (internal consistency), intraclass correlation coefficient (test–retest reliability), Pearson/Spearman correlation (concurrent validity), comparison of group scores (construct validity), and Differential Item Functioning (cross-country item equivalence). Secondary analyses will evaluate participant response time and rate, and static/dynamic score differences. Regression models will estimate associations between individual factors and HRQoL.

Discussion The EUonQoL-Kit will serve to systematically incorporate patient perspectives into European cancer policies and to address HRQoL inequalities across Europe.

Trial registration ClinicalTrials.gov Identifier: NCT05947903, 2023–06-28.

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Keywords Neoplasms, Health-Related Quality of Life, Patient Reported Outcome Measure, Treatment Related Cancer, Palliative Care, Cancer Survivor

Background

Health-Related Quality of Life (HRQoL) is a multidimensional construct used to operatively estimate how disease and treatment impact a patient's perception of overall functioning and wellbeing. Key dimensions of HRQoL include an individual's physical health, emotional/psychological state, self-care, role functioning, and social relationships, reflecting a dynamic interplay of preferences, life priorities, past experiences, current circumstances, and future expectations [1–5]. HRQoL is commonly evaluated using Patient-Reported Outcome Measures (PROMs), assessment tools, often questionnaires, designed to collect "any report of the status of a patient's health condition that comes directly from the patient without interpretation by a clinician or anyone else" [6]. PROMs serve as the gold standard for understanding "what matters to patients", as they provide self-reported insights into HRQoL, invaluable for optimising benefits for both individuals and society.

HRQoL is acknowledged as a central health outcome in cancer care and represents one of the pillars of the European Union (EU) Mission on Cancer [7], which aims to support the needs of cancer patients throughout the entire disease pathway. Within this context, aggregated PROM data may inform the development of targeted interventions, research priorities, and evidence-based policymaking, to address unmet needs and improve cancer patients' quality of life outcomes across the EU. Indeed, PROMs are increasingly acknowledged as being of value at the overarching levels of health systems, as they help assess how the system is performing from a patient's perspective. On the meso/institutional level, they can be used for healthcare quality improvement purposes, i.e., to benchmark the performance of providers, assess the effectiveness of services and publicly report on issues that are relevant to informed and shared decision-making. On the macro/systemic level, their purpose is mainly to complement population-based information from surveillance data for supporting health policymakers in resource planning and allocation [8]. However, despite significant advances in the application of PROMs in real world settings and effective examples of large-scale PROM implementation in many international initiatives [9–11], the use of PROM data at the meso and macro level is limited.

PROMs are well established at the micro/individual patient level and in clinical research, where cancer-specific PROMs have been developed, validated and translated into many languages with the primary aim to assess effectiveness and tolerability of healthcare interventions in the context of clinical trials [12–17]. Traditionally, these questionnaires are based on Classical Test Theory (CTT) [18] and they are "static", that is, the same set of questions is presented to every respondent. However, Computer Adaptive Testing (CAT) technology, which applies Item Response Theory (IRT) to adapt the choice of questions to the specific health status of each respondent based on their answers during questionnaire completion, has recently paved the way for dynamic PROMs to potentially improve HRQoL assessment in oncology [19, 20]. Most of the existing instruments have been designed some decades ago and need to be updated. In addition, it is well established that collaborative forms of patient and public involvement are useful in achieving appropriate and valid PROMs in oncology [21]. Involving patients not only by collecting their input on PROMs (usually through interviews and focus groups), but also by actively engaging them as co-researchers in the development process of the tools is of paramount importance to increase the relevance and acceptability of PROMs [21, 22].

At present, European cancer policies and programs lack a comprehensive HRQoL assessment tool with these innovative features, which can be widely used with a multi-level approach in different healthcare systems and countries. The EU-funded project "Quality of Life in Oncology: measuring what matters to cancer patients and survivors in Europe (EUonQoL)" aims to develop, validate and disseminate the EUonQoL-Kit, a unified patient-centred toolkit for HRQoL assessment, based on preferences and priorities of cancer patients and survivors, to be used to support the development and evaluation of European cancer programs and policies [23, 24].

The EUonQoL-Kit, developed from a patient perspective, is an electronic PROM available in the languages of the EU27 member states and several associated countries. It is designed to be applicable for future, periodic surveys contributing to the EU's Mission on Cancer. The EUonQoL-Kit includes three questionnaires, each designed for a specific cancer condition: patients in active treatment, survivors, and patients in palliative care. Each questionnaire allows for two modes of administration: static and dynamic.

The main aim of this study is to assess the metric properties (measurement model, validity, and

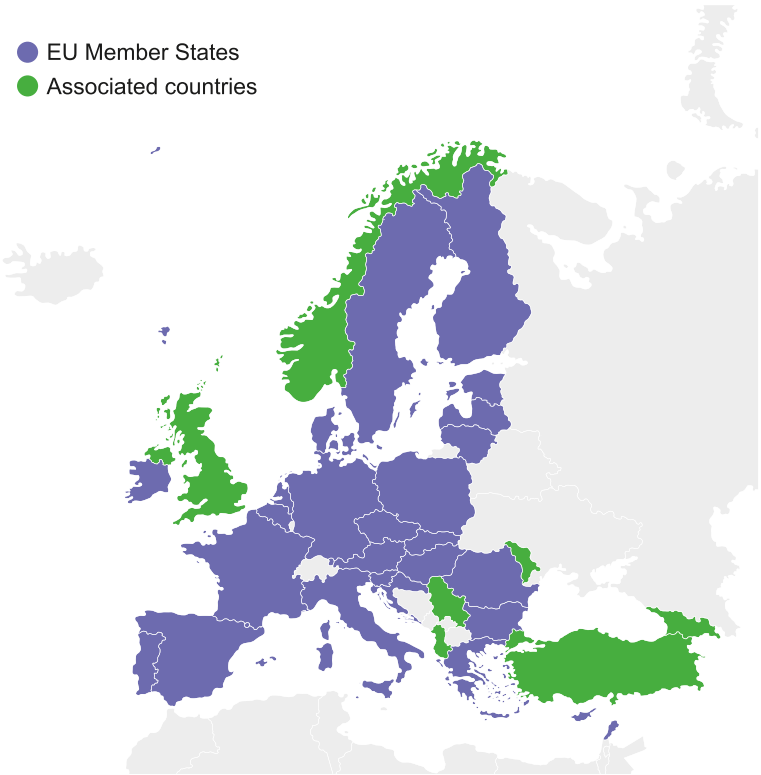

Fig. 1 Countries (25 EU Member States and 7 associated countries) participating in the EUonQoL validation study

reliability) of the EUonQoL-Kit static version through its first large-scale application in a pan-European survey of cancer patients and survivors. Secondary aims comprise: 1) Assessing the acceptability of the EUonQoL-Kit and reasons for refusal, including patient burden; 2) Validating the static and dynamic modes of administration of the EUonQoL-Kit against each other; 3) Exploring sociodemographic and clinical factors potentially associated with HRQoL; 4) Providing preliminary estimates of HRQoL across different European countries.

Methods/design

Patient and public involvement

The EUonQoL project is based on a co-design approach, involving patients as co-researchers in the different phases of the project, including the development of the EUonQoL-Kit and the validation study. The term "co-researchers" is used for people diagnosed with any kind of cancer, and their caregivers, who collaborate with the researchers. Three co-researchers have participated in the preparatory activities for the implementation of the survey by offering their views on the patient's journey during the study, as perceived through the description given in the present protocol. They collaborated with the researchers through regular online meetings and email contact. With the aim of exploring any potential for improvement in the patient experience, they have provided feedback on the patient documentation (study information sheet, informed consent form, data processing information sheet) and helped to draft the Standard Operating Procedures (SOPs), i.e. detailed written instructions aimed to achieve uniform step-by-step actions for study implementation across the clinical centres involved in conducting the survey. An important outcome of this collaborative involvement of patient co-researchers is a list of dos and don'ts guiding researchers and healthcare professionals in their interaction with patients during the critical stages of the survey. This list is reported in Supplementary Information 1, Additional File 1. After data collection and analyses are completed, patient co-researchers will be involved in results interpretation as well.

Study design and target population

This is a multicentre observational cross-sectional study, involving 45 clinical sites from 25 EU Member States and 7 associated countries, mostly selected among members of the Organisation of the European Cancer Institutes (OECI). The study has been registered on ClinicalTrials.gov (Identifier: NCT05947903, 2023–06-28). Figure 1 shows geographical coverage of the data collection.

Table 1 Operational definitions of the disease conditions for the three target groups

Target group	Disease condition definition	Examples
A) **Patients in active treatment**	Patients undergoing or having recently completed: • Curative treatment for early-stage cancers • 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)	• Stage 1–2 breast cancer during or up to 3 months following radiotherapy, surgery, or systemic treatments • Stage 4 breast cancer on 1st line chemotherapy • Lung cancer on immunotherapy
B) **Survivors**	Patients who are disease-free without evidence of active cancer, and at least one year off active treatment (except for long-term adjuvant hormonotherapy)	• Breast cancer treated with surgery and adjuvant radiotherapy three years ago and on 10 years of hormonal treatment
C) **Patients in palliative care**	Patients with advanced cancers who meet at least one of the following criteria: • Projected prognosis < 12 months and ECOG* ≥ 2 • Referred to a specialist palliative care team for symptom control • Receiving non-curative systemic treatment or radiotherapy purely for symptom control	• 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

* ECOG (Eastern Cooperative Oncology Group) performance status [25]

Eligibility criteria

Individuals will be considered eligible for the study if they meet the following inclusion criteria: i) Age 18 years or more; ii) Present or past histologically confirmed diagnosis of solid tumour or haematological malignancy; iii) Being in one of three disease conditions, i.e., active treatment, survivors, palliative care (definitions are detailed in the following paragraph, " Disease condition operational definitions"); iv) Native tongue or fluent in the language of the questionnaire; v) Written informed consent to the study. Individuals will be ineligible to study participation in the presence of cognitive impairment preventing them from completing the questionnaire.

Disease condition operational definitions

For the validation purposes of the study, three operational disease condition definitions are adopted with the pragmatic objective of distinguishing among participants in the three different target groups: Group A) Patients in active treatment; Group B) Survivors; Group C) Patients in palliative care. The full definitions complemented by examples are provided in Table 1.

The EUonQoL-Kit

The development of the EUonQoL-Kit involved multiple stakeholders, also including patients, through an iterative process of several steps: (i) two systematic literature reviews on existing QoL questionnaires and on qualitative studies exploring QoL dimensions relevant to the three different target groups; (ii) a mixed-method study, including interviews with patients and a Delphi survey with both patients and healthcare providers, aimed at collecting priorities and preferences on HRQoL dimensions for cancer patients and survivors; (iii) triangulation of the above results through a consensus methodology to create a first static version of the EUonQoL-Kit that (iv) was tested in a usability study; (v) revision of the questionnaire based on the results of the usability study and on a consensus development panel methodology to develop a second version of the EUonQoL-Kit that will be used in the present validation survey; (vi) translation and cultural adaptation of this second version of the EUonQoL-Kit across European languages, in accordance with the ISPOR guidelines [26]. More details on the EUonQoL-Kit development process will be reported in a separate paper.

The EUonQoL-Kit consists of 6 questionnaires (Fig. 2): for each of the three target groups (i.e., active treatment, survivors, palliative care, according to the operational definitions described above), a specific questionnaire has been developed that is available in both a static version (i.e., a traditional questionnaire composed by a fixed set of pre-selected items) and a dynamic version applying Computer Adaptive Testing (CAT, i.e., a questionnaire where items are selected based on the responses provided by the participants while filling in the questionnaire). CAT is based on Item Response Theory (IRT), a set of mathematical models that describe the relationship between an individual's 'ability' or 'trait' and how they respond to items on a scale [27]. The static and dynamic versions of the EUonQoL-Kit include both traditionally scored items and IRT-scored items (i.e., items calibrated based on an IRT model).

Table 2 shows the item number and composition of the EUonQoL-Kit in both the static and dynamic versions. Each questionnaire covers several HRQoL dimensions, as well as patient experiences, two items on overall health

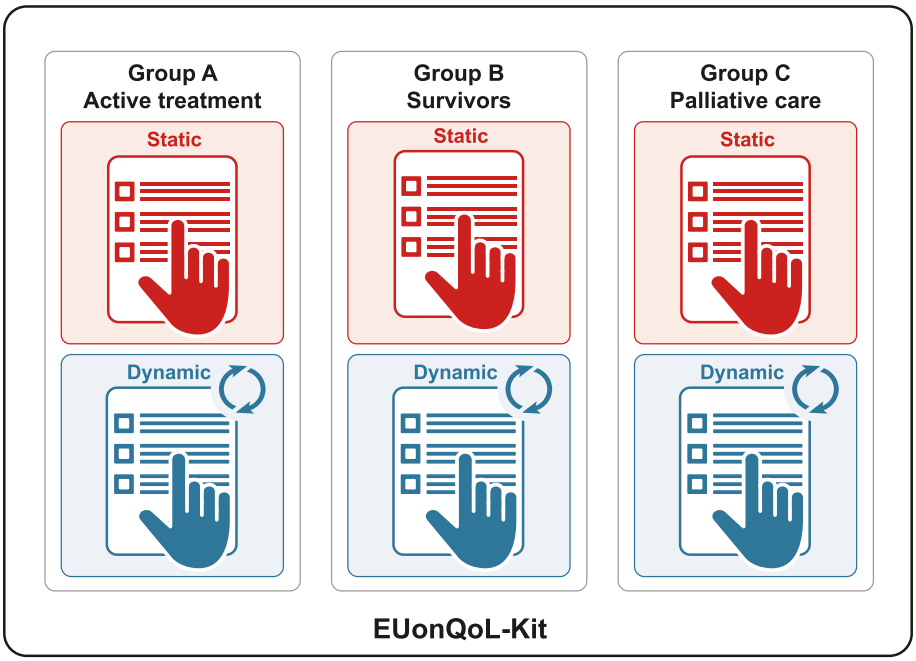

Fig. 2 Structure of the EUonQoL-Kit

Table 2 Item number and composition of the static and dynamic versions of the EUonQoL-Kit

	EUonQoL-Kit	
Dimensions	**Static version**	**Dynamic version**
IRT-scored items		
Mobility & Activity/Physical Functioning (PF)	2-3[c]	7
Social Role & Activities/Role Functioning (RF)	2	6
Pain (PA)	2	6
Energy/Fatigue (FA)	2	6
Sleeping problems (SL)	1	6
Anxiety & Worry/Emotional Functioning (EF)	3	7
Family & Relationships/Social Functioning (SF)	3–4	6
Financial aspects/difficulties (FI)	2-4[c]	6
Total number of IRT-scored items	**16-18**[c]	**50**
Traditionally scored items		
Other physical symptoms - single items[a]	6	6
Other mixed items[b]	10-13[c]	11-16[c]
Patient experiences	6-7[c]	6-7[c]
Overall health and QoL + WISP (Write In 3 Symptoms/Problems)	3	3
General QoL open-ended question	1	1
Total number of traditionally scored items	**28-32**[c]	**28-32**[c]
Total number of items	**44-50**[c]	**78-82**[c]

[a] Cover appetite, nausea, constipation, diarrhoea, breathing problems and symptom side effects

[b] Cover fear of recurrence, future outlook, spirituality, concentration, body image, sex life/intimacy, maintenance of independence, health behavioural change, isolation and symptom worries + traditionally scored "Financial aspects" and "Family & Relationships"

[c] Min. and max. number of items included in the three questionnaires for the three target groups

Table 3 Enrolment in each centre according to target groups and primary cancer diagnosis

Primary cancer diagnosis	Group A Active treatment	Group B Survivors	Group C Palliative care	Total
Lung cancer	6 ± 1	5 ± 1	5 ± 1	16 ± 2
Breast cancer	6 ± 1	5 ± 1	5 ± 1	16 ± 2
Colorectal cancer	6 ± 1	4 ± 1	4 ± 1	14 ± 2
Haematological malignancies*	6 ± 1	4 ± 1	4 ± 1	14 ± 2
Prostate cancer	6 ± 1	4 ± 1	4 ± 1	14 ± 2
Other cancer	10 ± 2	8 ± 2	8 ± 2	26 ± 2
Total	**40**	**30**	**30**	**100**

* Haematological malignancies include lymphomas

and QoL perception, one open-ended question to report up to three additional symptoms or problems not covered by the questionnaire ("Write In three Symptoms/Problems"—WISP item [28]), and a general open-ended question regarding what mostly impacts the respondents' HRQoL.

It should be noted that items on a dimension may be common or unique to the three groups. In addition, traditionally scored items are the same in the static and dynamic versions. Finally, the total number of items tested in this validation study ranges from 44 to 50 in the static version and from 78 to 82 in the dynamic version (shorter questionnaires are for patients in palliative care, group C). The items to be included in the final version of the questionnaire will be chosen based on the psychometric properties of the items and scales emerging from the present study. It is worth noting that the final dynamic version is expected to be shorter than the present one.

Study procedures

Sample size

One hundred patients will be enrolled in each of the clinical centres involved in the survey, stratified according to the three target groups as follows: A) Active treatment, 40 patients; B) Survivors, 30 patients; C) Palliative care, 30 patients. Scientifically sound recommendations on statistical power/sample size in validation studies are lacking and minimum rule-of-thumb requirements are provided [29]; in particular, the sample size recommended for structural validity is 1,000, considering that exploratory and confirmatory factor analyses (EFA & CFA) will be performed sequentially in two random subsamples of 500 participants each. We initially aimed at involving 40 cancer centres in 32 countries (at least 1 centre and 100 patients per country), resulting in a total of 4,000 participants with 1,600, 1,200 and 1,200 responders in each group, appropriate to both psychometric and secondary analyses stratified by country. As a potential risk mitigation measure, we enrolled 5 additional centres (45 instead of 40, overall sample of 4,500 participants, with 1,800, 1,350 and 1,350 in groups A, B, and C, respectively) to account for potential dropout of centres during both the preparatory and conduction phase of the study.

Patient recruitment

To guarantee a minimum variability in terms of primary cancer diagnosis, each centre will be recommended to enrol patients in agreement with the stratification scheme shown in Table 3.

Data collection

Enrolment is planned to begin at the end of August 2024 and the survey is expected to be completed by the end of March 2025.

In each centre, data collection will be performed in pre-identified outpatient clinics and inpatient wards during specific days previously agreed upon with the study coordinator. Participation in the study will be offered to consecutive eligible patients until the pre-defined sample size for each target group and primary diagnosis (Table 3) is reached. All participants in the sample will fill out one of the three versions of the EUonQoL-Kit (determined by their assignment to one of the three target groups) as a static administration. In addition, three subsamples of patients will be randomly selected to complete the following additional questionnaires on the same occasion (Table 4):

1) FACT-G (Functional Assessment of Cancer Therapy – General) [16] and EQ-5D-5L (5-level European Quality of Life Five Dimension) [30] with the aim to evaluate concurrent validity ("concurrent validity" subsample: 10% of the overall sample, stratified for the three disease conditions, A, B, and C).
2) The HRQoL domains covered by the IRT-scored items in the dynamic version of the EUonQoL-Kit; the aim is to identify the optimum number of items

Table 4 Random allocation of participants to specific subsamples, with EUonQoL-Kit version determined by the patient group

Questionnaire	Group A Active treatment	Group B Survivors	Group C Palliative care	Total
EUonQoL-Kit static + FACT-G/EQ-5D-5L	4	3	3	10
EUonQoL-Kit static + dynamic administration of the IRT-scored items[a]	4	3	3	10
EUonQoL-Kit static test–retest	4	3	3	10
EUonQoL-Kit static only	28	21	21	70
Total	**40**	**30**	**30**	**100**

[a] The traditionally scored items of the dynamic version will not be administered in the present study, as they are the same of the static version, which will be administered to all patients in the sample

for each domain to be used in the dynamic version as well as to test the real-world feasibility of such implementation ("dynamic" subsample: 10% of the overall sample, stratified for the three patient groups).

3) The same version of the EUonQoL-Kit (determined by the participant assignment to one of the three target groups) as a static administration, a second time at least one hour after the first completion, to assess test–retest reliability ("test–retest" subsample: 10% of the overall sample, stratified for the three disease conditions).

Box 1 reports the list of sociodemographic and clinical variables collected for this study.

The sociodemographic information will be self-reported by the participants through an electronic form after the completion of the questionnaires. Individual clinical characteristics will be entered into a dedicated electronic Case Report Form (eCRF) by healthcare professionals, who will also provide feedback on the participants' ability to self-complete the EUonQoL-Kit and collect information on their familiarity with the use of digital devices and the Internet.

E-tools and procedures for participant registration and data collection are described in Supplementary Information 2, Additional File 1.

Data analysis and statistics

Psychometric validation

Internationally accepted methodological guidelines for the validation of PROMs will be followed [31, 32].

The primary aim of the study includes the evaluation of conceptual and measurement model, validity and reliability of the EUonQoL-Kit static version under CTT, as recommended by the international guidelines mentioned above. In particular, the following analyses will be conducted for the whole sample, as well as stratifying by disease condition (patients in active treatment, survivors, and patients in palliative care) and, in some of them stratifying by country:

- EFA and CFA will be performed to assess EUonQoL-Kit conceptual and measurement model and structural validity. The global sample will be divided into two random sub-samples, stratifying by target group and country. The first sub-sample will be used to perform EFA, and the second sub-sample for CFA. The conceptual measurement model obtained during the development of the EUonQoL Kit, together with the results of EFA will be considered to construct the model to be confirmed by CFA. 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 [33].
- Distribution of answers to items will be examined by calculating the absolute and relative frequencies of the different response options.
- 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 [34]. To assess reproducibility, a sub-sample of patients (10 patients per centre, corresponding to 10% of the total sample, see Table 4) will complete the EUonQoL-Kit a second time at least 1 hour after the first completion (test–retest), and agreement will be estimated with the Intra-class Correlation Coefficient (ICC).
- Concurrent validity of the EUonQoL-Kit will be evaluated in the selected sub-sample by the multi-trait multimethod matrix [35] between the EUonQoL-

Box 1 List of sociodemographic and clinical variables collected for the three target groups

Variables
Sociodemographic
Age
Country of birth
Sex and gender identity
Place of residence
Living situation
Members in household
Education level
Main activity status (prior to cancer diagnosis and current)
Financial situation (total expenses in relation to household income, ability to keep up with household and medical bills)
Presence of disabilities
Lifestyle behaviour (smoking, drinking, diet, physical activity)
Importance of religious belief/spirituality
Clinical
Primary cancer diagnosis (ICD-10 code and date)[a]
Stage of cancer disease[a]
Presence of local relapse (date)[b]
Presence of metastases (site and date)[b]
ECOG performance status
Charlson Comorbidity Index
Tumour-directed treatment (date of last treatment, type, line)[a]
Pharmacological treatment for psychiatric disorders, pain, and other physical symptoms
Weight/Height, and duration and amount of involuntary weight loss (if any)
Follow-up frequency[c]
Followed by a specialized palliative care team[b]
Followed by a psycho-oncologist
Setting of care[b]

[a] Current, for Groups A and C, previous for Group B

[b] Groups A and C only

[c] Group B only

Kit and the FACT-G/EQ-5D-5L questionnaires with Pearson or Spearman correlation coefficients according to the variables' distribution. Hypotheses, established a priori, will be tested on the strength of the logical relationships expected between them (0.61–0.90 strong, 0.31–0.60 moderate, and ≤ 0.30 weak).

- 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 tumour stage, treatment, and ECOG performance status. The hypothesis is that we will observe better QoL scores for patients in early stage, less invasive treatment modalities, 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, 0.5–0.8 moderate, and 0.2–0.5 low [36].
- Test of Differential Item fFunctioning (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 [37]. 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 score and country as the independent variables, together with the scale-country interaction.

Analysis of secondary outcomes

Acceptability and patient burden

Acceptability will be assessed through EUonQoL-Kit response rate (number of patients successfully

completing the questionnaire among those offered to fill in it), and average percentage of missing items per questionnaire; respondent burden will be assessed through the time needed to complete the EUonQoL-Kit (statistics of central tendency and dispersion).

Validation of IRT-scored items

There are two primary aims of this validation: 1) to compare scores obtained with the static and dynamic administration 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 administrations, respectively, 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 administration and the settings for the dynamic CAT administration have been selected prior to the validation study based on the 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.

Analysis of factors potentially associated with HRQoL in cancer patients and survivors

Analysis of the association between HRQoL outcomes and individual characteristics will involve extensive exploratory visual plots to compare crude average estimates of the different HRQoL dimensions assessed by the EUonQoL-Kit (Table 2) grouped by different participant characteristics (Box1). Then, multivariable regression models will be fitted for each HRQoL dimension; for scores that can be assumed to be a continuous measurement with normal distribution (i.e. those coming from multi-item scales), linear generalized models with normal link will be applied, while for QoL scores in which normal distribution assumption does not hold (i.e. those from single items scales), quantile regression models [39] or multinomial regression models, where appropriate, will be used. The most relevant variables to be included in the regression models will be chosen by applying appropriate variable selection methods. All the analyses will be performed separately in each target group (patients in active treatment, survivors, and patients in palliative care).

As the data collection in the present study is limited to a few centres per country for reasons of feasibility (often one centre per country), analyses of HRQoL inequalities across EU countries will be exploratory and based on descriptive comparison of crude estimates by country. Heterogeneity among countries will be firstly explored in the statistical models allowing for inclusion of a country random effect; the latter will be tested using the likelihood ratio test. Moreover, the different countries will be grouped according to EU geographic areas (North, East, Center, Sud, West) and the corresponding terms will be included in the statistical models fitted for each HRQoL dimension to test for possible differences among macro areas.

Before the analyses described above, a preliminary analysis of missing data pattern will be performed by assessing the proportion of missing data for each participant characteristic variable (Table 5) and for the HRQoL dimension used as dependent variable in the model. Little's MCAR test [39] will be used to test the MCAR null hypothesis. If the latter will not be rejected at the 5% level and/or if missingness will be below 5%, missing data will be ignored, and an available case analysis will be performed; this analysis will have a reduced statistical power due to the reduced sample size but it will not be biased [39]. In case of MCAR assumption refusal, the possibility to perform multiple imputation will be evaluated by selecting, among those collected, the variables that could contribute to the missing data imputation models. Ninety-five percent confidence intervals (95%CIs) will be calculated for all estimates provided.

Discussion

The EUonQoL project is an important step in the progress towards high value patient-centred care, as it takes up the challenge of providing an innovative HRQoL assessment instrument (the EUonQoL-Kit), aimed at ensuring that patients' perspectives will be systematically incorporated into future European cancer programs and policies. Co-designed with patients to address their priorities and needs, translated and culturally adapted into several European languages, integrating both static and dynamic questionnaires, the EUonQoL-Kit is intended to serve as a unified tool to assess variation in HRQoL among different European countries and specific subgroups within the cancer patient population.

Access to reliable outcome measurement systems will allow policymakers to make more informed decisions on which interventions to fund, prioritize, or modify. Underlying the development and validation of the EUonQoL-Kit is in fact the assumption that having a standardised instrument for the collection and analysis of HRQoL data will facilitate its use as a performance measure in healthcare systems. The latter will then be able to prioritise interventions that align with patients' goals and values, eventually leading to better health outcomes and enhanced quality of life.

This paper provides a comprehensive description of the validation study aimed to establish the psychometric properties of the EUonQoL-Kit in a very large European sample of cancer patients and survivors. Based on this validation study results, the toolkit will be further refined and finalised. In particular, the settings of the dynamic version will be adjusted defining the number of items to be proposed to the three population groups to obtain optimal efficiency and precision of the tool.

After the validation phase of the EUonQoL-Kit, a number of implementation strategies will be put in place to guide and disseminate the use of the tool in (i) future European HRQoL surveys, to enable healthcare providers to monitor longitudinal outcomes or identify emerging issues in order to adjust plans and resource allocation as needed to optimize cancer programs; (ii) in the framework of the EU Mission on Cancer, to provide support to one of the core principles of EU initiatives on cancer, namely improving or preserving QoL at all stages of the disease; (iii) in coordination with other EU-funded projects and other research activities, to complement and integrate existing health outcome measures. For example, the European Cancer Inequalities Register (ECIR) is a database designed to identify and analyse systemic disparities in cancer care across different demographic, socioeconomic, and geographic population groups within and between member states and regions of Europe. This initiative provides policymakers and healthcare stakeholders with valuable data to develop targeted interventions and policies aimed at reducing inequalities and improving outcomes for cancer patients across Europe. Integrating future EUonQoL-Kit data into the ECIR could enhance the register's ability to capture patients' experiences and outcomes, thereby strengthening its role as an effective guiding tool for evidence-based policies addressing cancer inequalities.

We are aware that despite the large overall sample size, which ensures an adequate psychometric evaluation of the EUonQoL-Kit, this study may not have a sufficiently large and representative sample per country to ensure the generalisability of estimates of HRQoL of cancer patients and survivors in different European countries. However, the preliminary exploratory results that will be obtained will serve to inform sampling design in future more comprehensive studies.

Conclusion

The EUonQoL-Kit will be a keystone for advancing patient-centred care in several significant ways. Aligned with patient priorities and needs, it will provide reliable and actionable HRQoL data serving as a performance measure in healthcare systems and a guiding tool for prioritising interventions. This will ultimately lead to more effective cancer care strategies.

Abbreviations

EUonQoL-Kit	European oncology quality of life toolkit
HRQoL	Health-related quality of life
CTT	Classical Test Theory
IRT	Item Response Theory
CAT	Computer Adaptive Testing
PROMs	Patient-Reported Outcome Measures
EU	European Union
SOPs	Standard Operating Procedures
OECI	Organisation of the European Cancer Institutes
ECOG	Eastern Cooperative Oncology Group
WISP	Write In three Symptoms/Problems
FACT-G	Functional Assessment of Cancer Therapy – General
EQ-5D-5L	5-Level European Quality of Life Five Dimension
eCRF	eElectronic Case Report Form
ECIR	European Cancer Inequalities Register
EC	Ethics Committee
RMSEA	Root Mean Square Error of Approximation
CFI	Comparative Fit Index
TLI	Tucker-Lewis Index
ICC	Intra-class Correlation Coefficient
DIF	Differential Item Functioning

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by CB, MC and LC, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The survey will be performed in line with the principles of the Declaration of Helsinki and the ethical principles of observational research on potentially fragile patients [39]. The study was approved by the Ethics Committee (EC) of the coordinating centre (Fondazione IRCCS Istituto Nazionale Tumori di Milano): Comitato Etico Territoriale Lombardia 4, approval number INT 106/23. All 45 clinical centres have received ethical approval from their local EC, with the list of approving ECs and associated approval numbers provided in Additional file 2. A detailed list of the clinical centres participating in the study is published on Clinicaltrials.gov (study ID: NCT05947903) and each centre's approval package is published on the project website as deliverable D7.2 [24]). Written informed consent will be obtained from all individuals participating in the study. Study-specific ethics approval and informed consent statements are available in Supplementary Information 3, Additional File 1. Data will be managed and curated in accordance with the EU regulation 2016/679. Study-specific statements concerning data management and confidentiality are reported in Supplementary Information 4, Additional File 1.

Consent for publication
Not applicable.

Competing interests
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References

1. Ferrans CE, Zerwic JJ, Wilbur JE, Larson JL. Conceptual Model of Health-Related Quality of Life. J Nurs Scholarsh. 2005;37:336–42.
2. Sajid MS, Tonsi A, Baig MK. Health-related quality of life measurement. Int J Health Care Qual Assur. 2008;21:365–73.
3. Bakas T, McLennon SM, Carpenter JS, Buelow JM, Otte JL, Hanna KM, et al. Systematic review of health-related quality of life models. Health Qual Life Outcomes. 2012;10:134.
4. Sitlinger A, Zafar SY. Health-Related Quality of Life. Surg Oncol Clin N Am. 2018;27:675–84.
5. Olsen JA, Misajon R. A conceptual map of health-related quality of life dimensions: key lessons for a new instrument. Qual Life Res. 2020;29:733–43.
6. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes. 2006 Oct 11;4:79. doi: 10.1186/1477-7525-4-79. PMID: 17034633; PMCID: PMC1629006.
7. EU Mission: Cancer - European Commission. 2023. https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/eu-missions-horizon-europe/eu-mission-cancer_en. Accessed 21 Mar 2024.
8. Al Sayah F, Lahtinen M, Bonsel GJ, Ohinmaa A, Johnson JA. A multi-level approach for the use of routinely collected patient-reported outcome measures (PROMs) data in healthcare systems. J Patient-Rep Outcomes. 2021;5:98.
9. Patient Reported Outcome Measures (PROMs). NHS England Digital. https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/patient-reported-outcome-measures-proms. Accessed 21 Mar 2024.
10. International Consortium for Health Outcomes Measurement's Mission: Putting Patients at the Heart of Healthcare. ICHOM. https://www.ichom.org/aboutus/. Accessed 21 Mar 2024.
11. Patient-Reported Indicator Surveys (PaRIS) - OECD. https://www.oecd.org/health/paris/. Accessed 21 Mar 2024.
12. Schipper H, Clinch J, McMurray A, Levitt M. Measuring the quality of life of cancer patients: the Functional Living Index-Cancer: development and validation. J Clin Oncol Off J Am Soc Clin Oncol. 1984;2:472–83.

13. de Haes JC, van Knippenberg FC, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. Br J Cancer. 1990;62:1034–8.
14. Schag CA, Ganz PA, Heinrich RL. CAncer Rehabilitation Evaluation System--short form (CARES-SF). A cancer specific rehabilitation and quality of life instrument. Cancer. 1991;68:1406–13.
15. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI J Natl Cancer Inst. 1993;85:365–76.
16. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11:570–9.
17. Rock EP, Kennedy DL, Furness MH, Pierce WF, Pazdur R, Burke LB. Patient-reported outcomes supporting anticancer product approvals. J Clin Oncol. 2007;25:5094–9.
18. Spearman C. The proof and measurement of association between two things. Am J Psychol. 1904;15:72–101.
19. Computerized adaptive testing. A primer. 2nd ed. Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers; 2000.
20. Petersen MAa, Aaronson NK, Arraras JI, Chie W-C, Conroy T, Costantini A, et al. The EORTC CAT Core—The computer adaptive version of the EORTC QLQ-C30 questionnaire. Eur J Cancer. 2018;100:8–16.
21. Staniszewska S, Haywood KL, Brett J, Tutton L. Patient and Public Involvement in Patient-Reported Outcome Measures: Evolution Not Revolution. Patient Patient-Centered Outcomes Res. 2012;5:79–87.
22. Wilson R. Patient led PROMs must take centre stage in cancer research. Res Involv Engagem. 2018;4:7.
23. Apolone G, Brunelli C. Quality of Life in Oncology: Measuring What Matters for Cancer Patients and Survivors in Europe: The EUonQol Project. J Ambulatory Care Manage. 2023;46:139–42.
24. EUonQoL. https://euonqol.eu/. Accessed 17 Nov 2024.
25. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649–55.
26. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: Report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005;8:94–104.
27. Nguyen TH, Han H-R, Kim MT, Chan KS. An introduction to item response theory for patient-reported outcome measurement. The patient. 2014;7:23–35.
28. Rojas-Concha L, Hansen MB, Petersen MA, Groenvold M. Which symptoms and problems do advanced cancer patients admitted to specialized palliative care report in addition to those included in the EORTC QLQ-C15-PAL? A register-based national study. Support Care Cancer. 2020;28:1725–35.
29. Anthoine E, Moret L, Regnault A, Sébille V, Hardouin J-B. Sample size used to validate a scale: a review of publications on newly-developed patient reported outcomes measures. Health Qual Life Outcomes. 2014;12:2.
30. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:1727–36.
31. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. J Clin Epidemiol. 2010;63:737–45.
32. Reeve BB, Wyrwich KW, Wu AW, Velikova G, Terwee CB, Snyder CF, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res. 2013;22:1889–905.
33. Muthén B. Latent Variable Analysis: Growth Mixture Modeling and Related Techniques for Longitudinal Data. In: Handbook of Quantitative Methodology for the Social Sciences. Newbury Park. CA: age: D. Kaplan (Ed.). p. 345–68.
34. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika. 1951;16:297–334.
35. Campbell DT, Fiske DW. Convergent and discriminant validation by the multitrait-multimethod matrix. Psychol Bull. 1959;56:81–105.
36. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care. 1989;27(3 Suppl):S178-189.
37. Petersen MA, Groenvold M, Bjorner JB, Aaronson N, Conroy T, Cull A, et al. Use of differential item functioning analysis to assess the equivalence of translations of a questionnaire. Qual Life Res. 2003;12:373–85.
38. Koenker R. Quantile Regression. Cambridge: Cambridge University Press; 2005. (Econometric Society Monographs).
39. Little RJA. A Test of Missing Completely at Random for Multivariate Data with Missing Values. J Am Stat Assoc. 1988;83:1198–202.
40. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Med Res Methodol. 2017;17:162.
41. World Medical Association Declaration of Helsinki. ethical principles for medical research involving human subjects. JAMA. 2013;310:2191–4.

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