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Development and validation of a patient-reported outcome tool to assess cancer-related financial toxicity in Italy

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Development and validation of a patient-reported outcome tool to assess cancer-related financial toxicity in Italy

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Abstract

Introduction. Financial toxicity (FT) is a well-recognized problem in oncology. US-based studies have shown that: (a) cancer patients have a 2.7 times risk of bankruptcy; (b) patients who declare bankruptcy have a 79% greater hazard of death; (c) financial shortcuts significantly impair quality of life (QoL), and (d) reduce compliance and adherence to treatment prescriptions. The aim of the project is to develop and validate a patient-reported-outcome (PRO) measure to assess FT of cancer patients in Italy, where, despite the universal health coverage given by the national health service, FT is an emerging issue.

Methods and analysis. Our hypothesis is that a specific FT measure, which considers the relevant socio-cultural context and health care system, would allow to understand the main determinants of cancer-related financial toxicity in Italy and to contrast them. According to the International Society for Pharmaco-economics and Outcomes Research (ISPOR) guidelines on PROs, the project will include the following steps: (1) concept elicitation (from focus groups with patients and caregivers; literature; oncologists; nurses) and analysis, creating a coding library; (2) item generation (using a format that includes a question and a response on a 4-point Likert scale) and analysis through patients' cognitive interviews of item importance within different coding categories to produce the draft instrument; (3) factor analysis and internal validation (with Cronbach's alpha and test-retest for reliability) to produce the final instrument; (4) external validation with QoL anchors and depression scales. The use of the FT measure in prospective trials is also planned.

Ethics and dissemination. The protocol is approved by the ethical committees of all the participating centres. The project will tentatively produce a validated tool by the spring 2021. The

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3 project might also represent a model and the basis for future cooperation with other European
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5 countries, with different health care systems and socio-economic conditions.
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11 **ARTICLE SUMMARY**

12 **Strengths and limitations of this study**

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19 • Previous research data support that financial problems do affect the outcome of cancer
20 patients in Italy, and despite the Italian health care system is grounded on universal
21 coverage, financial constraints may greatly impact in the future on cancer patient access to
22 health care goods and services in the future.
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28 • The way health care and welfare systems are shaped does impact on financial toxicity
29 suffered by cancer patients and instruments for its description need to be developed
30 locally.
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36 • This protocol applies a widely accepted methodology for the production of patient
37 reported outcome measures.
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43 • The rational of this protocol is that an instrument measuring cancer-related financial
44 toxicity may be conducive to corrective policies that might ultimately benefit patients
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49 • For the same reasons that make appropriate the development of a local instrument more
50 than the application of an already existing tool developed elsewhere, one intrinsic
51 limitation is that, being developed in Italy, our instrument will be applicable to Italian
52 patients only.
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INTRODUCTION

Financial problems are a matter of global attention in oncology, focusing on two levels of financial difficulties: third payer and individual patient. Payers are generally affected the rising cost of anticancer drugs.^{1 2} At the patient level, in the United States (US), co-payment is becoming unaffordable and, as a dramatic consequence, cancer patients have higher likelihood to file for bankruptcy than the general population.³ In addition, financial difficulties have been associated with lower patient satisfaction,⁴ worse compliance,⁵ worse quality of life (QoL),⁶⁻⁸ and worse survival.⁹ Particularly, Ramsey and collaborators have shown that US cancer patients who declared bankruptcy have a hazard ratio of death of 1.79 (95% CI 1.64-1.96) as compared with a population of cancer patients who did not file for bankruptcy and were matched in a propensity score analysis.⁹ The problem is being reported in other countries and with varied types of health care systems.¹⁰⁻¹³

The need for specific tools to address this problem has been acknowledged in the scientific community, and in the US a patient-reported-outcome (PRO) instrument, called "COST", has been recently proposed for measuring financial distress.¹⁴ COST is a questionnaire composed of 11 items addressing psychologic response to financial problems and coping behaviours. This questionnaire does not address material conditions that cause financial problems, and is highly specific for US context, where cancer diagnosis translates into an excess of out-of-pocket expenses.¹⁵ COST has been validated in some clinical settings, e.g. in a series of 100 multiple myeloma patients after at least 3 months of medical treatment and in a series of 233 patients undergoing chemotherapy for solid tumors.^{16 17} However, this questionnaire is not applicable in health systems where co-payment for anticancer drugs is not required.

In Italy, we have recently shown that financial difficulties exist and negatively affect the outcomes of cancer patients undergoing anticancer treatment, in terms of both QoL and life expectancy.¹⁸ We

1
2
3 used the EORTC QLQ-C30 questionnaire in several clinical trials of treatment of solid tumours,
4
5 promoted by the National Cancer Institute of Napoli during the last two decades. Therefore, taking
6
7 advantage of the existing databases, we performed a pooled analysis of 16 trials including 3670
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9 patients, with the aims of exploring the relevance of financial difficulties in the Italian public health
10
11 care system. We analysed question 28 of the EORTC QLQ-C30 asking: 'During the last week, has
12
13 your physical condition or medical treatment caused you financial difficulties?', where financial
14
15 difficulties related to disease or treatment are measured in four categories, from 'not at all' to 'very
16
17 much'.¹⁹ We defined financial burden (FB) as any financial difficulty reported at baseline
18
19 questionnaire, and financial toxicity (FT) as score worsening in a subsequent questionnaire. We
20
21 investigated (i) the prognostic role of FB on clinical outcomes (survival, global QoL response
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23 [items 29/30] and severe toxicity), and (ii) the effect of FT on survival. For the latter analysis, a
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25 landmark time of 4.5 months was applied, excluding all the patients dead or censored before the
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27 landmark, because they had no or fewer chances to suffer FT, and their inclusion in the analysis
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29 would have biased toward a worse prognosis the group of patients without FT. Analyses were
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31 performed using logistic regression models or the Cox model adjusting for trial, gender, age, region
32
33 and period of enrolment, baseline global QoL and, where appropriate, FB and global QoL response.
34
35 At baseline, 26% of the 3670 study patients reported FB. Such FB was not associated with
36
37 increased risks of death (HR 0.94, 95%CI: 0.85-1.04, p=0.23) or increased risk of severe toxicity
38
39 (OR 0.90, 95%CI: 0.76-1.06, p=0.19) but was predictive of a higher chance of worse global QoL
40
41 response (OR 1.35, 95%CI: 1.08-1.70, p=0.009). During treatment, 2735 patients filled in
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43 subsequent questionnaires; out of them, 616 (22.5%) developed FT. FT was associated with a
44
45 statistically significant higher risk of death (HR 1.20; 95% CI: 1.05-1.37, p=0.007), when the
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47 landmark time of 4.5 months was used. Results did not vary in sensitivity analyses when landmark
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49 threshold was increased and trials or disease or setting of treatment were removed one at a time.
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The hypothesis underlying this project is that a specific instrument might help to describe and understand determinants and effects of cancer-related FT in Italy and that some of these may be modified, ultimately improving prognosis of cancer patients.

Therefore, the aim is to develop and validate a PRO instrument to describe and measure FT of Italian patients on cancer treatment, hereby described as “patient reported outcome for Fighting Financial Toxicity of cancer” (proFFiT).

The impact of this project might be relevant for patients’ prognosis if we were able to understand how to intervene on FT, through adequate policies, because the size of the prognostic impact that we described in our preliminary study is similar to the magnitude of the benefit produced by several new drugs approved and reimbursed in Italy during the last few years.¹⁸ Therefore, the negative effect of FT, when occurring, may ultimately frustrate the positive impact of some anticancer drugs; but, on the contrary, effective strategies contrasting FT, might synergize with anticancer treatment and produce relevant benefit for cancer patients without increasing side-effects.

METHODS AND ANALYSIS

The project will be conducted according to the methodology delineated by the International Society for Pharmaco-economics and Outcome Research (ISPOR) Patient Reported Outcomes Content

Validity Good Research Practices Task Force.^{20 21}

The project includes 5 tasks, summarised in table 1.

Task 1: concept elicitation and coding

Specific aim

To elicit concepts and coding them into a thematic library.

Context of use

Our preliminary data were obtained in a context of Medical Oncology units in public general hospitals, University Oncology units and public Cancer Institutes in Italy, where patients with specific types of solid tumours (lung, breast or ovarian cancer), mostly at an advanced stage of disease, underwent medical treatment, prevalently first-line therapy. In this project, the context will be expanded in order to include patients with any type of solid cancer or haematological malignancy who are undergoing or have recently completed medical treatment, including chemotherapy, target agents, immunotherapy, hormonal treatment, radiotherapy and combinations of such therapies.

Inclusion and exclusion criteria

The following are the major inclusion/exclusion criteria of the patients who will be involved in the project, also representing the target population for the use of the instrument in future studies.

Inclusion Criteria

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- 2
- 3 - Adult patients (>18 years)
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- 5 - Histologically or cytologically confirmed diagnosis of any type of solid cancer or
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- 7 haematological malignancy
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- 10 - Written informed consent provided
- 11
- 12 - Medical treatment (chemotherapy, target agents, immunotherapy, hormonal treatment,
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- 14 radiotherapy or combinations of such therapies) ongoing or terminated within the previous 3
- 15
- 16 months.
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- 19 - Caregivers of patients who meet the above criteria
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24 *Exclusion Criteria*

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- 26 - Patients with major cognitive dysfunction or psychiatric disorders
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- 28 - Patients who have never received anticancer medical or radiation treatment
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33 **Sources for concept elicitation**

34 Four different sources of information will be used for concept elicitation.

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41 *Literature review*

42 A literature review will be conducted including international and Italian documents including

43 scientific documents found through PubMed, CINAHL and EMBASE by cross checking references,

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45 and publicly available documents not cited in PubMed but found through patients' advocacy

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47 websites, government agencies and common web research engines. Content will be divided in

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49 single items that will be subsequently categorized according to the conceptual framework.

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Focus groups

Focus groups will be carried out in three towns, distributed in North, Central and South Italy. In order to reach a point of saturation, two focus groups will be organized in each town: one with patients receiving or having recently received medical anticancer treatment, and one with caregivers of patients receiving or who have recently received anticancer treatment. A maximum of 10 individuals will be included, led by a skilled moderator with the help of an assistant moderator.²² All focus groups will be audio-recorded and transcribed verbatim. Content analysis will be conducted with a qualitative software (T-Lab). Qualitative analysis of focus group outcomes will be done using the constant comparison technique guided by the Grounded Theory approach.^{23 24}

Expert opinions

Expert opinions will be sought through the cooperation with Associazione Italiana di Oncologia Medica (AIOM), Collegio Italiano dei Primari di Oncologia Medica Ospedalieri (CIPOMO), Federation of Italian Cooperative Oncology Groups (FICOG), Associazione Italiana Infermieri di Area Oncologica (AIIAO), using web or email surveys.

Interviews

Two types of interviews will be conducted. Patients and caregivers presenting at the info-points of Italian Association of Cancer Patients (AIMAC) in Italian hospitals in Northern, Central and Southern Italy will be invited to respond to question 28 of the EORTC QLQ-C30 questionnaire after a brief identification of baseline socio-cultural characteristics. Those who reveal some degree of economic problem at question 28, will be invited to participate in a brief semi-structured interview to describe individual experiences of financial difficulties during cancer treatment. Sample size will be determined based on findings during ongoing qualitative analysis, in order to guarantee saturation.

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3 Qualitative interviews of consenting patients and caregivers will be conducted by nurses in 3
4 participating centres representing Southern (Naples), Central (Rome) and Northern (Turin) Italy,
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6 with the aim of exploring the lived experience of financial difficulties that occur during cancer
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8 treatment. The sample size will be defined by the principle of saturation (in order to guarantee the
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10 presence of patients and caregivers who have experienced the phenomenon, and to have
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12 demographic variability by region, sex, gender and age, when possible). It is estimated that 8-10
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14 patients and caregivers from each centre will be adequate. Subjects participating in the interviews
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16 will have signed informed consent, be at least 18 years of age, have had experience of financial
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18 difficulty as a patient who has received cancer treatment, or as caregiver who has experienced
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20 financial difficulty while caring for a family member receiving treatment for cancer. Subjects with
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22 cognitive impairments or any physical or medical reason (i.e. excessive fatigue) that would not
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24 permit participation in an interview will be excluded. Patients will be interviewed individually, and
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26 in private. Interviews will be audio recorded and later transcribed verbatim.
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35 **Coding and interpretation**

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37 Concepts collected through the analysis of the different sources will be coded in an iterative process
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39 with opportunities for data to be re-examined and reanalyzed until no new codes or code groupings
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41 are identified and all passages from the transcripts have been assigned one or more codes.
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44 Redundancy and overlapping content will be controlled. Content comparison analysis will be also
45
46 associated with the analysis of a qualitative software (e.g. T-Lab), and concepts will be divided into
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48 different themes.
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51 Data interpretation will flow upward from content comparison analysis, coding procedure results
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53 and data outputs from qualitative software. A quasi-statistics approach will be used to attain simple
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55 descriptive counts of categories, levels of consensus/dissent and about response patterns among the
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57 focus group members or the professionals responding to surveys and interviewees.²²
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Products and timelines of Task 1

A list of concepts organized in a thematic coding library will be the product of task 1 activities, within 6 months from the beginning of the project. The protocol will be published to encourage debate and prompt cooperation with other European countries.

Task 2: Item generation and analysis

Specific aim

To generate a draft version of the instrument.

Criteria for item generation

Major criteria informing item generation are based on the prevalent characteristics of PRO instruments already available in Italian language and widely used in oncology (e.g. EORTC questionnaires). Major criteria include:

- Item structure using a question/response model (rather than statement/agreement)
- Short questions
- Simple language (avoiding technical words)
- No jargon.

Recall period

No single recall period is definitely best for all measures or all phenomena.²⁵ In the context of PROs, the recall period must correspond to the characteristics of the phenomenon of interest and the purpose of the assessment. Similar to the COST instrument, a 7-day recall period will be initially used.

Wording of items and responses

The formulation of each new item will respect the wording and the language suggested during the concept elicitation phase in order to maintain a high level of fidelity and transparency.²⁶ The response scheme will follow a 4-point Likert scale (not at all/a little/quite a bit/very much).

Alternative formats will be explored, if needed.

Items will be reviewed separately by the members of the Steering Committee and a consensus will be sought for each of them, also checking for redundancy, overlapping content and ambiguous language.

Item importance analysis

Item importance will be ranked by a sample of 45 patients (15 for each centre). Patients will be asked to score importance of items within each theme by using a 4-point Likert scale (not important at all / a little important / quite a bit important / extremely important). Within each theme, at least three items with the highest rank will be retained for subsequent steps.

Cognitive interviews

The list of items remaining after importance analysis, will be administered to a separate sample of 45 patients (15 for each centre) followed by cognitive interviews conducted by trained psychologists.²⁷ The number of patients is based on a convenience sampling inspired by a grounded theory framework.²⁴ According to this framework, frequencies are rarely important, as one occurrence of the data is potentially as useful as many in understanding the process behind a topic. Therefore, sample size should generally follow the concept of saturation, a point when the collection of new data does not shed any further light on the issue under investigation.

Within such semi-structured interviews, items will be evaluated for comprehensibility, recall, judgment and response, mapping a standardized feedback evaluation. Also, the structure and format of the instrument will be evaluated for readability, clarity of presentation, ease of administration.

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3 Consideration will be given to potential changes in mode of administration, as this study will
4 evaluate the administration via tablet or smart phone. In this phase, criteria to retain, modify or
5 reject items will be also based on missing values, item difficulty, discriminatory ability,
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7 comprehensibility and relevance.
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14 **Products and timelines of Task 2**

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17 A draft instrument will be the product of task 2 and should be available by month 15. A paper
18 focusing on the qualitative research outcomes of the first phases of the project is planned.
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23 **Task 3: Instrument refinement and internal validation**

24 **Specific aim**

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27 To generate the final version of the proFFiT instrument.
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33 **Definition of scoring procedures**

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37 A global score deriving from the rough sum of the response scores at each item might be calculated,
38 representing a continuous numeric measure of FT. This will be discussed within the Steering
39 Committee, in order to take into account the information contained in retained items. It is expected
40 that single-item questions will be produced to check for possible determinants of FT.
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48 **Factor analysis**

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51 To refine the instrument from the draft to the final version, a principal components analysis
52 (explorative factor analysis) will be undertaken with data from the first field test (eigenvalue limit
53 will be set at 1). Structural equation models could also be used to take into account causal variables.
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Reliability

Internal reliability of multi-item scales will be assessed by analysing inter-item correlations and Cronbach's α coefficient adjusted by the number of items. Estimates of $\alpha > 0.70$ will be considered acceptable, confidence intervals will be provided by bootstrap methods.

To assess the test-retest reliability, the intraclass correlation coefficient (ICC) will be estimated repeating the questionnaire administration within a week from the first use. With one-sided alpha 0.05, 80% power, a minimally acceptable level of reliability equal to 0.70 and an expected ICC of 0.80, 118 patients are needed.²⁸

Products and timelines of Task 3

The final instrument will be the product of task 3 and should be available by month 24. A paper presenting the final instrument is planned.

Task 4: External validation

Specific aim

To generate data on external validity of the final proFFiT instrument.

External validation

Criterion validity will be performed using different anchors. First, the correlation of proFFiT with response to question 28 of the EORTC QLQ-C30 questionnaire will be assessed. Second, based on the assumption that a high degree of financial problems correlates with worse quality of life, the correlation with the global health-related quality of life EORTC score (questions 29-30) will be assessed. A similar analysis done with the COST score showed a Pearson correlation coefficient of 0.26.¹⁶ We plan to test correlations with bilateral alpha 0.05, 80% power and expected Pearson correlation coefficient of 0.20. For this analysis, 194 patients are required and around 220 patients

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3 will be enrolled to allow for some missing data. Descriptively, correlation of proFFiT with the
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5 Hospital Anxiety and Depression Scale (HADS) will be studied as well. For this analysis, patients
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7 beginning a therapeutic cycle, already experienced with medical or radiation treatment of cancer,
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9 will be enrolled.
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14 **Responsiveness**

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17 To test responsiveness (to which extent the instrument is sensitive in capturing the changes of the
18
19 variable of interest within-patients) repeated measures (at each cycle or every 3-4 weeks) of
20
21 proFFiT will be collected together with the EORTC QLQ-C30. Changes over time will be
22
23 estimated. Further correlation of proFFiT with response to question 28 will be evaluated.
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26 Responsiveness will be longitudinally tested with the same sample of patients planned for criterion
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28 validity.
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33 **Products and timelines of Task 4**

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35 Description of correlation of the final instrument with external anchors will be the product of task 4
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37 and should be available by month 36. A paper will be submitted reporting the external validation
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39 data.
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45 ***Task 5: Application in clinical studies***

46 **Specific aim**

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49 Use of proFFiT in subsequent prospective patient series is the aim of task 5. This task is reported
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51 here for completeness. Specific protocols will be developed and will undergo proper approval once
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55 Tasks 1 to 4 have been completed.
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Endpoint models

proFFiT may be used in at least three different endpoint models, depicted in the **figure 1**.

Clinical study within the endpoint model 1

A large scale multi-centre cross-sectional observational study will be performed, where proFFiT will be used to describe financial toxicity across a patient population defined according to type or stage of disease, or any other selection criteria.

The study will include patients with any type of solid tumours or hematologic malignancy.

Specific aims will be:

- to describe prevalence of financial toxicity in general and according to different subcategories (geographical, personal, socio-economical, cancer-related, treatment-related);
- to describe the behaviour of proFFiT within repeated measures over the time in patients undergoing medical treatment for cancer;
- to describe variability of psychometric properties of proFFiT over the time;
- to describe the correlation between proFFiT and typical endpoint of cancer treatments (e.g. compliance, QoL, survival).

The study will include at least 1000 patients and efforts will be done to include relevant categories in terms of gender, age, geographic location, type of cancer, performance status and type of treatment (classes of drugs, radiotherapy). During this phase, the cooperation of major cooperative Italian groups will be of primary importance.

Clinical study within the endpoint model 2

In the end-point model 2, studies might be proposed based on the content of proFFiT instrument.

According to the content of the items that will be retained in the final instrument, we might face with different material conditions that may be cause of financial distress. All the efforts will be

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3 done to understand how such conditions can be experimentally modified and prospective pilot
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5 studies will be planned to produce preliminary evidence on the possible efficacy of corrective
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7 actions. The number and the type of these trials will depend on the type of material conditions listed
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9 in the proFFiT.

14 15 *Clinical study within the endpoint model 3*

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17 In the endpoint model 3, the planned use of the instrument is more traditional, being one of the
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19 elements that should be analysed as secondary endpoint in trials testing the efficacy of new drugs or
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21 treatment strategies. In principle, in this model, consideration should always be given to the context
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23 of development of the instrument and therefore this model would apply to the Italian context only.
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25 Such studies might be implemented within this project, either based on the findings of the previous
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27 phases or planned by other independent investigators, once proFFiT has been made available to the
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29 Italian scientific community.
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36 **Data collection procedures**

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38 The Unità Sperimentazioni Cliniche at Istituto Nazionale per lo Studio e la Cura dei Tumori
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40 Fondazione G. Pascale IRCCS manages a website (www.usc-intnapoli.net) hub platform for the
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42 conduction of multicentre clinical trials, including facilities for patients registration, randomization,
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44 data collection through electronic case report forms, data management through an e-query system,
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46 and collection of radiological examination for independent review. Recently, the collection of
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48 patient-reported-outcome questionnaires from mobile devices has been implemented and will be
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50 used in this project. All web-site activities are fully tracked and verifiable and the whole system is
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52 under a quality assurance program. The site is accessible by username and password, and is
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54 protected through encrypted data certified by SSL and HTTPS protocols. From 2007 to 2015,
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3 180.000 web accesses have produced 216.000 electronic case report forms. Data are managed by an
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5 in-house server, with regular backup, redundant features and onsite maintenance.
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7 Therefore, patient registration and data collection will be centralized and web-based. Interviews,
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9 audio-visual data management will be analysed and transferred for storage by a dedicated software.
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14 ***Patient and Public Involvement***

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17 The Steering committee of the protocol includes four representatives (FDL, LDC, EI, FT) of Italian
18
19 and European patients' associations (FAVO, AIMAC, ECPC) who meet regularly with all the other
20
21 members and share all the decisions assumed by the committee. Therefore, they partnered for the
22
23 design of the study, some of the activities performed in the concept elicitation phase, and in all the
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25 steps where the Steering Committee will assume decisions regarding the project. They will also be
26
27 involved in dissemination and proposition of future studies using the proFFiT instrument.
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36 ***Project status***

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38 March 2018: Start of tasks including patients (focus groups)

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40 October 2019: planned time for submission of a paper reporting on qualitative tasks

41
42 March 2020: planned time for final instrument availability

43
44 March 2021: planned time for submission of a paper reporting on the final validated instrument
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46 (end of task 4).
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52 ***Ethics and dissemination***

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55 The present research is a non-profit investigator study. The promoter (National Cancer Institute of
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57 Naples) will stipulate an agreement with participating centres. Study protocol, patient information
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3 and informed consent have been approved by the coordinating Ethical Committee on November
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5 2017.
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8 At each centre, the study will only be started after being approved by the institutional Ethical
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10 Committee. Furthermore, Ethical committees will be informed of any planned changes of study
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12 protocol.
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15 The study has been registered on clinicaltrials.gov with the code NCT03473379.
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18 Publications arising from study data will be determined by the Study Steering Committee.
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21 All the Authors reported in the front page will be actively involved in manuscript preparation. All
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23 study publications will report the statement "... on behalf of the proFFiT Investigators".
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Table 1. Summary table of planned tasks

	Task 1	Task 2	Task 3	Task 4	Task 5
Title	Concept elicitation and coding	Item generation and analysis	Instrument refinement and internal validation	External validation	Application in clinical studies
Aim	To elicit concepts and coding them into a thematic library.	To generate a draft version of the instrument.	To generate the final version of the instrument.	To generate data on external validity of the final instrument.	Use in prospective clinical studies.
Actions	Literature review. Focus groups with patients and caregivers. Opinion of oncologists and nurses, through scientific societies. Info points AIMAC (patients and caregivers).	Wording of items. Importance analysis with patients (15 patients per geographic region). Item analysis with cognitive interviews of patients (15 patients per geographic region).	Factor analysis. Reliability analysis (Cronbach alpha, test-retest with 118 patients). Communication of results.	Correlation with anchors (EORTC QLQ-C30 – namely Q28 and Q29&30; HADS) and responsiveness; with patients. Communication of results.	Promote and perform a large scale multicentre cross-sectional clinical trial. Communication of results.
Psychologists involved	Yes, for focus group and coding activities.	Yes, for cognitive interviews and analysis.	No	No	No
Patients involved	30 divided in 3 focus groups and approximately 25 for qualitative interviews.	90 (45 for importance analysis and 45 for cognitive interviews).	118 based on sample size estimation.	220 based on sample size estimation.	1000 based on gross estimation.
Products	Thematic library of concepts. Paper reporting the protocol.	Pre-final instrument. Paper reporting on qualitative research outcomes of the project.	Final instrument. Paper presenting the final instrument.	Correlation with external anchors. Paper reporting on validation.	Knowledge on prevalence and risk factors for FT in Italy. At least one paper describing results of the cross-sectional study.
Duration	6 months	9 months	9 months	12 months	24 months

Legend of figure

Figure 1. Endpoint models for future use of proFFIT

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Contributors

FP obtained funding. SR, JB, CG and FP planned qualitative and statistical analysis and drafted the protocol. All Authors participated in writing the study protocol and the manuscript and approved the final version.

Data

There are no data yet to be accessed. The original protocol is available for registered users on the website of the coordinating centre at [https:// www.usc-intnapoli.net](https://www.usc-intnapoli.net).

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Competing interests

SR has received personal fees from CSL-Behring and GlaxoSmithKline Foundation. JB has received personal fees from Novartis, AstraZeneca, Merck Sharp & Dohme. MDM has received personal fees from Bristol Myers Squibb, Merck Sharp & Dohme, Roche, AstraZeneca, Janssen. FE has received personal fees from Bristol Myers Squibb, Incyte, Orsenyx and Amgen. LG has received personal fees from Bristol Myers Squibb. CJ has received personal fees from Amgen, Astra Zeneca, Biogen, Boehringer Ingelheim, Celgene, Gilead, GSK, Ipsen, Janssen-Cilag, Takeda and Sanofi. VM has received personal fees from Bristol Myers Squibb and Italfarmaco; a member of his family is employee in Bayer. CV has received personal fees from from Baxter, MSD, Novartis, Sanofi, Sanofi Genzyme FP has received personal fees from Bayer, Ipsen, Astra Zeneca, Bristol Myers Squibb, Sandoz, Incyte, Celgene, Pierre Fabre, Janssen-Cilag. The other Authors have no conflict to disclose.

Ethics approval

By 6 May 2019, the protocol has been approved by Ethical Committees at all centres participating in the first two tasks of the protocol.

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End-point model 1. Interventional, to reduce financial toxicity (FT)

<u>Concept</u>	<u>Endpoints</u>
Intervention Modifying conditions that may cause FT	Primary <i><u>FT score (proFFiT)</u></i>
Supportive concept Management efficacy outcomes	Secondary Survival QoL Toxicity

End-point model 2. Interventional, to test efficacy of new treatments

<u>Concept</u>	<u>Endpoints</u>
Intervention Comparison of new vs standard treatment	Primary Survival Other time outcomes
Supportive concept Effect on other efficacy/activity measure	Secondary QoL Toxicity Response rate <i><u>FT score (proFFiT)</u></i>

End-point model 3. Observational, cross sectional, describing FT

<u>Concept</u>	<u>Endpoints</u>
Intervention Describing FT	Primary <i><u>FT score (proFFiT)</u></i>
Supportive concept Anchors	Secondary Socioeconomical condition QoL Survival

BMJ Open

A protocol for the development and validation of a patient-reported outcome tool to assess cancer-related financial toxicity in Italy

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-031485.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Aug-2019
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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Health economics, Public health
Keywords:	Patient Reported Outcome Measures, Financial toxicity, Italy, Cancer, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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SCHOLARONE™
Manuscripts

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3 **A protocol for the development and validation of a patient-reported outcome tool to assess cancer-**
4 **related financial toxicity in Italy**
5

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58 **Keywords** Patient Reported Outcome Measures, Italy, Financial toxicity, Cancer, Health
59 economics
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Abstract

Introduction. Financial toxicity (FT) is a well-recognized problem in oncology. US-based studies have shown that: (a) cancer patients have a 2.7 times risk of bankruptcy; (b) patients who declare bankruptcy have a 79% greater hazard of death; (c) financial burden significantly impairs quality of life (QoL), and (d) reduces compliance and adherence to treatment prescriptions. The aim of the project is to develop and validate a patient-reported-outcome (PRO) measure to assess FT of cancer patients in Italy, where, despite the universal health coverage provided by the National Health Service, FT is an emerging issue.

Methods and analysis. Our hypothesis is that a specific FT measure, which considers the relevant socio-cultural context and health care system, would allow us to understand the main determinants of cancer-related financial toxicity in Italy, in order to address and reduce these factors. According to the International Society for Pharmaco-economics and Outcomes Research (ISPOR) guidelines on PROs, the project will include the following steps: (1) concept elicitation (from focus groups with patients and caregivers; literature; oncologists; nurses) and analysis, creating a coding library; (2) item generation (using a format that includes a question and a response on a 4-point Likert scale) and analysis through patients' cognitive interviews of item importance within different coding categories to produce the draft instrument; (3) factor analysis and internal validation (with Cronbach's alpha and test-retest for reliability) to produce the final instrument; (4) external validation with QoL anchors and depression scales. The use of the FT measure in prospective trials is also planned.

Ethics and dissemination. The protocol is approved by the ethical committees of all the participating centres. The project will tentatively produce a validated tool by the spring 2021. The

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3 project might also represent a model and the basis for future cooperation with other European
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5 countries, with different health care systems and socio-economic conditions.
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11 **ARTICLE SUMMARY**

14 **Strengths and limitations of this study**

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19 • Previous research data support that financial problems affect the outcome of cancer
20 patients in Italy, and despite an Italian health care system grounded on universal coverage,
21 financial constraints may possibly affect cancer patient access to health care goods and
22 services in the future.
23
- 24 • The way health care and welfare systems are structured impacts financial toxicity suffered
25 by cancer patients, and instruments for describing and measuring FT need to be developed
26 taking health care and welfare context into account.
27
- 28 • This protocol applies a widely accepted methodology for the development of patient
29 reported outcome measures.
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- 31 • The rationale of this protocol is that an instrument measuring cancer-related financial
32 toxicity may be conducive to corrective policies that might ultimately benefit patients
33
- 34 • For the same reasons that favour the development of a local instrument rather than the
35 application of an existing tool developed elsewhere, one intrinsic limitation is that the
36 instrument being developed will be properly applicable to Italian patients only.
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INTRODUCTION

Financial problems are a matter of global attention in oncology, focusing on two levels of financial difficulties: third payer and individual patient. Payers are generally affected by the rising cost of anticancer drugs.^{1 2} At the patient level, in the United States (US), co-payment is becoming unaffordable and, as a consequence, cancer patients have higher likelihood to file for bankruptcy than the general population.³ In addition, financial difficulties have been associated with lower patient satisfaction,⁴ worse compliance,⁵ worse quality of life (QoL),⁶⁻⁸ and worse survival.⁹ Particularly, Ramsey and collaborators have shown that US cancer patients who declared bankruptcy have a hazard ratio of death of 1.79 (95% CI 1.64-1.96) as compared with a population of cancer patients who did not file for bankruptcy and were matched in a propensity score analysis.⁹ The problem is being reported in other countries and with varied types of health care systems.¹⁰⁻¹³

The need for specific tools to address this problem has been acknowledged in the scientific community, and in the US a patient-reported-outcome (PRO) instrument, called "COST", has been recently proposed for measuring financial distress.¹⁴ COST is a questionnaire composed of 11 items addressing psychologic response to financial problems and coping behaviours. This questionnaire does not address material conditions that cause financial problems, and is highly specific for US context, where cancer diagnosis translates into an excess of out-of-pocket expenses.¹⁵ COST has been validated in some clinical settings, e.g. in a series of 100 multiple myeloma patients after at least 3 months of medical treatment, in a series of 233 patients undergoing chemotherapy for solid tumors, and in a series of 191 Japanese patients receiving chemotherapy for a solid tumor for at least 2 months.¹⁶⁻¹⁸ However, this questionnaire might not be sensitive to relevant issues in health systems where co-payment for anticancer drugs and other health care costs is not required.

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3 On this ground, and cognizant of the challenges of cross-cultural applicability to the Italian cancer
4 patient population, we initiated the development of a country specific tool to ensure highest possible
5 content validity. In Italy, we have recently published that financial difficulties exist and negatively
6 affect the outcomes of cancer patients undergoing anticancer treatment, in terms of both QoL and
7 life expectancy. ¹⁹ We used the EORTC QLQ-C30 questionnaire in several clinical trials of
8 treatment of solid tumours, promoted by the National Cancer Institute of Napoli during the last two
9 decades. Therefore, taking advantage of the existing databases, we performed a pooled analysis of
10 16 trials including 3670 patients, with the aims of exploring the relevance of financial difficulties in
11 the Italian public health care system. We analysed question 28 of the EORTC QLQ-C30 asking:
12 'During the last week, has your physical condition or medical treatment caused you financial
13 difficulties?', with four possible response categories, from 1='not at all' to 4='very much'. At
14 baseline, 26% of the 3670 study patients reported a financial burden (response ≥ 2) that was
15 associated with a higher chance of worsening global QoL response (OR 1.35, 95%CI: 1.08-1.70,
16 $p=0.009$). During treatment, out of 2735 patients who completed subsequent questionnaires, 616
17 (22.5%) developed financial toxicity (worsening response as compared to the baseline) that was
18 associated with a statistically significant higher risk of death (HR 1.20; 95% CI: 1.05-1.37,
19 $p=0.007$). ¹⁹

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45 The hypothesis underlying this project is that a specific instrument might help to describe and
46 understand determinants and effects of cancer-related FT in Italy and that some of these
47 determinants may be modified, ultimately improving prognosis of cancer patients.

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51 Therefore, the aim is to develop and validate a PRO instrument to describe and measure FT of
52 Italian patients on cancer treatment, hereby described as "Patient Reported Outcome for Fighting
53 Financial Toxicity of cancer" (PROFFIT).

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58 The impact of this project might be relevant for patients' prognosis if we were able to understand
59 how to intervene on FT, through adequate policies, because the size of the prognostic impact that
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3 we described in our preliminary study is similar to the magnitude of the benefit produced by several
4
5 new drugs approved and reimbursed in Italy during the last few years.¹⁹ Therefore, the negative
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7 effect of FT, when occurring, may ultimately lessen the positive impact of some anticancer drugs;
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9 on the contrary, effective strategies contrasting FT, might synergize with anticancer treatment and
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11 produce relevant benefit for cancer patients.
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For peer review only

METHODS AND ANALYSIS

The project will be conducted according to the methodology delineated by the International Society for Pharmaco-economics and Outcome Research (ISPOR) Patient Reported Outcomes Content Validity Good Research Practices Task Force.^{20 21}

The project includes 5 tasks, summarised in table 1.

Task 1: concept elicitation and coding

Specific aim

To elicit concepts and coding them into a thematic library.

Context of use

Our preliminary data were obtained in a context of Medical Oncology units in public general hospitals, University Oncology units and public Cancer Institutes in Italy, where patients with specific types of solid tumours (lung, breast or ovarian cancer), mostly at an advanced stage of disease, underwent medical treatment, prevalently first-line therapy. In this project, the context will be expanded in order to include patients with any type of solid cancer or haematological malignancy who are undergoing or have recently completed medical treatment, including chemotherapy, target agents, immunotherapy, hormonal treatment, radiotherapy and combinations of such therapies.

Inclusion and exclusion criteria

The following are the major inclusion/exclusion criteria of the patients who will be involved in the project, also representing the target population for the use of the instrument in future studies.

Inclusion Criteria

- Adult patients (>18 years)
- Histologically or cytologically confirmed diagnosis of any type of solid cancer or haematological malignancy
- Written informed consent provided
- Medical treatment (chemotherapy, target agents, immunotherapy, hormonal treatment, radiotherapy or combinations of such therapies) ongoing or terminated within the previous 3 months.
- Caregivers of patients who meet the above criteria

Exclusion Criteria

- Patients with major cognitive dysfunction or psychiatric disorders
- Patients who have never received anticancer medical or radiation treatment

Sources for concept elicitation

Four different sources of information will be used for concept elicitation.

Literature review

A literature review will be conducted including international and Italian documents including scientific documents found through PubMed, CINAHL and EMBASE by cross checking references, and publicly available documents not cited in PubMed but found through patients' advocacy websites, government agencies and common web research engines. Content will be divided in single items that will be subsequently categorized according to the conceptual framework.

Focus groups

Focus groups will be carried out in three towns, distributed in North, Central and South Italy. Two focus groups will be organized in each town: one with patients receiving or having recently received medical anticancer treatment, and one with caregivers of patients receiving or who have recently received anticancer treatment. A maximum of 10 individuals will be included, led by a skilled moderator with the help of an assistant moderator.²²

All focus groups will be audio-recorded and transcribed verbatim. Content analysis will be conducted with a qualitative software (T-Lab). Qualitative analysis of focus group outcomes will be done using the constant comparison technique guided by the Grounded Theory approach.^{23 24}

Expert opinions

Expert opinions will be sought through the cooperation with Associazione Italiana di Oncologia Medica (AIOM), Collegio Italiano dei Primari di Oncologia Medica Ospedalieri (CIPOMO), Federation of Italian Cooperative Oncology Groups (FICOG), Associazione Italiana Infermieri di Area Oncologica (AIIAO), using web or email surveys.

Interviews

Two types of interviews will be conducted. Patients and caregivers presenting at the info-points of Italian Association of Cancer Patients (AIMAC) in Italian hospitals in Northern, Central and Southern Italy will be invited to respond to question 28 of the EORTC QLQ-C30 questionnaire after a brief identification of baseline socio-cultural characteristics. Those who reveal some degree of economic problem at question 28 (score ≥ 2), will be invited to participate in a brief semi-structured interview to describe individual experiences of financial difficulties during cancer treatment. Sample size will be determined based on findings during ongoing qualitative analysis, in order to guarantee saturation, a point when the collection of new data does not shed any further light on the issue under investigation.

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3 Qualitative interviews of consenting patients and caregivers will be conducted by nurses in 3
4 participating centres representing Southern (Naples), Central (Rome) and Northern (Turin) Italy,
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6 with the aim of exploring the lived experience of financial difficulties that occur during cancer
7
8 treatment. The sample size will be defined by the principle of saturation (in order to guarantee the
9
10 presence of patients and caregivers who have experienced the phenomenon), and to have
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12 demographic variability by region, sex, gender and age, when possible. It is estimated that 8-10
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14 patients and caregivers from each centre will be adequate. Subjects participating in the interviews
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16 will have signed informed consent, be at least 18 years of age, have had experience of financial
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18 difficulty as a patient who has received cancer treatment, or as caregiver who has experienced
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20 financial difficulty while caring for a family member receiving treatment for cancer. Subjects with
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22 cognitive impairments or any physical or medical reason (i.e. excessive fatigue) that would not
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24 permit participation in an interview will be excluded. Patients will be interviewed individually, and
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26 in private. Interviews will be audio recorded and later transcribed verbatim.
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35 **Coding and interpretation**

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37 Concepts collected through the analysis of the different sources will be coded in an iterative process
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39 with opportunities for data to be re-examined and reanalyzed until no new codes or code groupings
40
41 are identified and all passages from the transcripts have been assigned one or more codes.
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44 Redundancy and overlapping content will be controlled. Content comparison analysis will be also
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46 associated with the analysis of a qualitative software (e.g. T-Lab), and concepts will be divided into
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48 different themes.
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51 Data interpretation will flow upward from content comparison analysis, coding procedure results
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53 and data outputs from qualitative software. A quasi-statistics approach will be used to attain simple
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55 descriptive counts of categories, levels of consensus/dissent and about response patterns among the
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57 focus group members or the professionals responding to surveys and interviewees.²²
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Products and timelines of Task 1

A list of concepts organized in a thematic coding library will be the product of task 1 activities, within 6 months from the beginning of the project. The protocol will be published to encourage debate and prompt cooperation with other European countries.

Task 2: Item generation and analysis

Specific aim

To generate a draft version of the instrument.

Criteria for item generation

Major criteria informing item generation are based on the prevalent characteristics of PRO instruments already available in Italian language and widely used in oncology (e.g. EORTC questionnaires). Major criteria include:

- Item structure using a question/response model (rather than statement/agreement)
- Short questions
- Simple language (avoiding technical words)
- No jargon.

Recall period

No single recall period is best for all measures or all phenomena.²⁵ In the context of PROs, the recall period must correspond to the characteristics of the phenomenon of interest and the purpose of the assessment. Similar to the COST instrument, a 7-day recall period will be initially used.

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Wording of items and responses

The formulation of each new item will respect the wording and the language suggested during the concept elicitation phase in order to maintain a high level of fidelity and transparency.²⁶ The response scheme will follow a 4-point Likert scale (not at all/a little/quite a bit/very much).

Alternative formats will be explored, if needed.

Items will be reviewed separately by the members of the Steering Committee and a consensus will be sought for each item, also checking for redundancy, overlapping content and ambiguous language.

Item importance analysis

Item importance will be ranked by a sample of 45 patients (15 for each centre, Naples, Rome and Turin, selected with the same inclusion/exclusion criteria reported above). Patients will be asked to score importance of items within each theme by using a 4-point Likert scale (not important at all / a little important / quite a bit important / extremely important). Within each theme, at least three items with the highest rank will be retained for subsequent steps.

Cognitive interviews

The list of items remaining after importance analysis, will be administered to a separate sample of 45 patients (15 for each centre, Naples, Rome and Turin, selected with the same inclusion/exclusion criteria reported above) followed by cognitive interviews conducted by trained psychologists.²⁷ The number of patients is based on a convenience sampling inspired by a grounded theory framework.²⁴ According to this framework, frequencies are rarely important, as one occurrence of the data is potentially as useful as many in understanding the process behind a topic, therefore, sample size should generally follow the concept of saturation..

Within such semi-structured interviews, items will be evaluated for comprehensibility, recall, judgment and response, mapping a standardized feedback evaluation. Also, the structure and format

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3 of the instrument will be evaluated for readability, clarity of presentation, ease of administration.
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5 Consideration will be given to potential changes in mode of administration, as this study will
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7 evaluate the administration via tablet or smart phone. In this phase, criteria to retain, modify or
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9 reject items will be also based on missing values, item difficulty, discriminatory ability,
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11 comprehensibility and relevance.
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17 **Products and timelines of Task 2**

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19 A draft instrument will be the product of task 2 and should be available by month 15. A paper
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21 focusing on the qualitative research outcomes of the first phases of the project is planned.
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26 ***Task 3: Instrument refinement and internal validation***

27 **Specific aim**

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29 To generate the final version of the PROFFIT instrument.
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37 **Definition of scoring procedures**

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39 A global score deriving from the rough sum of the response scores at each item might be calculated,
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41 representing a continuous numeric measure of FT. However, in the definitive decision regarding
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43 scoring procedures, the Steering Committee will consider, in addition to a single composite
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45 measure, the production of subscores referring to different aspects of FT identified..
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51 **Factor analysis**

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53 To refine the instrument from the draft to the final version, a principal components analysis
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55 (explorative factor analysis) will be undertaken with data from the first field test (eigenvalue limit
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57 will be set at 1). Structural equation models could also be used to take into account causal variables.
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Reliability

Internal reliability of multi-item scales will be assessed by analysing inter-item correlations and Cronbach's α coefficient adjusted by the number of items. Estimates of $\alpha > 0.70$ will be considered acceptable, confidence intervals will be provided by bootstrap methods.

To assess the test-retest reliability, the intraclass correlation coefficient (ICC) will be estimated repeating the questionnaire administration within a week from the first use. With one-sided alpha 0.05, 80% power, a minimally acceptable level of reliability equal to 0.70 and an expected ICC of 0.80, 118 patients are needed (10-12 for each centre, in 10-12 oncologic centres distributed in North, Central and South Italy, selected with the same inclusion/exclusion criteria reported above).²⁸

Products and timelines of Task 3

The final instrument will be the product of task 3 and should be available by month 24. A paper presenting the final instrument is planned.

Task 4: External validation

Specific aim

To generate data on external validity of the final PROFFIT instrument.

External validation

Criterion validity will be performed using different anchors. First, the correlation of PROFFIT with response to question 28 of the EORTC QLQ-C30 questionnaire will be assessed. Second, based on the assumption that a high degree of financial problems correlates with worse quality of life, the correlation with the global health-related quality of life EORTC score (questions 29-30) will be assessed. A similar analysis done with the COST score showed a Pearson correlation coefficient of

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3 0.26.¹⁶ We plan to test correlations with bilateral alpha 0.05, 80% power and expected Pearson
4 correlation coefficient of 0.20. For this analysis, 194 patients are required and around 220 patients
5 will be enrolled to allow for some missing data. Descriptively, correlation of PROFFIT with the
6 Hospital Anxiety and Depression Scale (HADS) will be studied as well. For this analysis, 20
7 patients will be enrolled for each centre, in 10-12 oncologic centres distributed in North, Central
8 and South Italy; selection will be based on the same inclusion/exclusion criteria reported above.
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19 **Responsiveness**

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21 To test responsiveness (to which extent the instrument is sensitive in capturing the changes of the
22 variable of interest within-patients) repeated measures (at each cycle or every 3-4 weeks) of
23 PROFFIT will be collected together with the EORTC QLQ-C30.²⁹ Changes over time will be
24 estimated. Further correlation of PROFFIT with response to question 28 will be evaluated.
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30 Responsiveness will be longitudinally tested with the same sample of patients planned for criterion
31 validity.
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38 **Products and timelines of Task 4**

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40 Description of correlation of the final instrument with external anchors will be the product of task 4
41 and should be available by month 36. A paper will be submitted reporting the external validation
42 data.
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50 ***Task 5: Application in clinical studies***

51 **Specific aim**

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53 Use of PROFFIT in subsequent prospective patient series is the aim of task 5. This task is reported
54 here for completeness. Specific protocols will be developed and will undergo proper approval once
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60 Tasks 1 to 4 have been completed.

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Endpoint models

PROFFIT may be used in at least three different endpoint models, depicted in the **figure 1**.

Clinical study within the endpoint model 1

A large scale multi-centre cross-sectional observational study will be performed, where PROFFIT will be used to describe financial toxicity across a patient population defined according to type or stage of disease, or any other selection criteria.

The study will include patients with any type of solid tumours or hematologic malignancy.

Specific aims will be:

- to describe prevalence of financial toxicity overall, and according to different subcategories (geographical, personal, socio-economical, cancer-related, treatment-related);
- to describe the behaviour of PROFFIT within repeated measures over the time in patients undergoing medical treatment for cancer;
- to describe variability of psychometric properties of PROFFIT over the time;
- to describe the correlation between PROFFIT and typical endpoint of cancer treatments (e.g. compliance, QoL, survival).

The study will include at least 1000 patients and strategies will be undertaken to include relevant categories in terms of gender, age, geographic location, type of cancer, performance status and type of treatment (classes of drugs, radiotherapy). During this phase, the cooperation of major cooperative Italian groups (represented by the Federation of Italian Cooperative Oncology Groups - FICOG) will be of primary importance because it will guarantee feasibility with many participating centres.

Clinical study within the endpoint model 2

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3 End-point model 2, studies might be proposed based on the content of PROFFIT instrument.
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5 According to the items that will be retained in the final instrument, we might be faced with different
6
7 material conditions that may be cause of financial distress. All the efforts will be done to understand
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9 how such conditions can be experimentally modified and prospective pilot studies will be planned
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11 to produce preliminary evidence on the possible efficacy of corrective actions. The number and the
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13 types of these trials will depend on the type of material conditions listed in the PROFFIT.
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19 *Clinical study within the endpoint model 3*

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21 The planned use of the instrument in the endpoint model 3 studies is more traditional. The
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23 instrument may be used as one of the elements analysed as secondary endpoint in trials testing the
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25 efficacy of new drugs or treatment strategies. In principle, consideration should always be given to
26
27 the context of development of the instrument and therefore this model would apply to the Italian
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29 context only. Such studies might be implemented within this project, either based on the findings
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31 from previous phases or planned by other independent investigators, once PROFFIT has been made
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33 available to the Italian scientific community.
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41 **Data collection procedures**

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43 The Unità Sperimentazioni Cliniche at Istituto Nazionale per lo Studio e la Cura dei Tumori
44
45 Fondazione G. Pascale IRCCS manages a website (www.usc-intnapoli.net) hub platform for the
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47 conduction of multicentre clinical trials, including facilities for patients registration, randomization,
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49 data collection through electronic case report forms, data management through an e-query system,
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51 and collection of radiological examination for independent review. Recently, the collection of
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53 patient-reported-outcome questionnaires from mobile devices has been implemented and will be
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55 used in this project. All web-site activities are fully tracked and verifiable and the whole system is
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57 under a quality assurance program. The site is accessible by username and password, and is
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3 protected through encrypted data certified by SSL and HTTPS protocols. From 2007 to 2015,
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5 180.000 web accesses have produced 216.000 electronic case report forms. Data are managed by an
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7 in-house server, with regular backup, redundant features and onsite maintenance.
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10 Therefore, patient registration and data collection will be centralized and web-based. Interviews,
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12 audio-visual data management will be analysed and transferred for storage by a dedicated software.
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15 16 17 ***Patient and Public Involvement***

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19 The Steering committee of the protocol includes four representatives (FDL, LDC, EI, FT) of Italian
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21 and European patients' associations (FAVO, AIMAC, ECPC) who meet regularly with all the other
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23 members and share all the decisions assumed by the committee. Therefore, they partnered for the
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25 design of the study, some of the activities performed in the concept elicitation phase, and in all the
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27 steps where the Steering Committee will assume decisions regarding the project. They will also be
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29 involved in dissemination and proposition of future studies using the PROFFIT instrument.
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38 ***Project status***

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40 March 2018: Start of tasks including patients (focus groups)

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42 October 2019: planned time for submission of a paper reporting on qualitative tasks

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44 March 2020: planned time for final instrument availability

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46 March 2021: planned time for submission of a paper reporting on the final validated instrument

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48 (end of task 4).
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55 ***Ethics and dissemination***

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57 The present research is a non-profit investigator study. The promoter (National Cancer Institute of
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59 Naples) will stipulate an agreement with participating centres. Study protocol, patient information
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3 and informed consent have been approved by the coordinating Ethical Committee on November
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5 2017.
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8 At each centre, the study will only be started after being approved by the institutional Ethical
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10 Committee. Furthermore, Ethical committees will be informed of any planned changes of study
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12 protocol.
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15 The study has been registered on clinicaltrials.gov with the code NCT03473379.
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18 Publications arising from study data will be determined by the Study Steering Committee.
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21 All the Authors reported in the front page will be actively involved in manuscript preparation. All
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23 study publications will report the statement "... on behalf of the PROFFIT Investigators".
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Table 1. Summary table of planned tasks

	Task 1	Task 2	Task 3	Task 4	Task 5
Title	Concept elicitation and coding	Item generation and analysis	Instrument refinement and internal validation	External validation	Application in clinical studies
Aim	To elicit concepts and coding them into a thematic library.	To generate a draft version of the instrument.	To generate the final version of the instrument.	To generate data on external validity of the final instrument.	Use in prospective clinical studies.
Actions	Literature review. Focus groups with patients and caregivers. Opinion of oncologists and nurses, through scientific societies. Info points AIMAC (patients and caregivers).	Wording of items. Importance analysis with patients (15 patients per geographic region). Item analysis with cognitive interviews of patients (15 patients per geographic region).	Factor analysis. Reliability analysis (Cronbach alpha, test-retest with 118 patients). Communication of results.	Correlation with anchors (EORTC QLQ-C30 – namely Q28 and Q29&30; HADS) and responsiveness; with patients. Communication of results.	Promote and perform a large scale multicentre cross-sectional clinical trial. Communication of results.
Psychologists involved	Yes, for focus group and coding activities.	Yes, for cognitive interviews and analysis.	No	No	No
Patients involved	30 divided in 3 focus groups and approximately 25 for qualitative interviews.	90 (45 for importance analysis and 45 for cognitive interviews).	118 based on sample size estimation.	220 based on sample size estimation.	1000 based on gross estimation.
Products	Thematic library of concepts. Paper reporting the protocol.	Pre-final instrument. Paper reporting on qualitative research outcomes of the project.	Final instrument. Paper presenting the final instrument.	Correlation with external anchors. Paper reporting on validation.	Knowledge on prevalence and risk factors for FT in Italy. At least one paper describing results of the cross-sectional study.
Duration	6 months	9 months	9 months	12 months	24 months

Legend of figure

Figure 1. Endpoint models for future use of PROFFIT

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Contributors

FP obtained funding. SR, JB, CG and FP planned qualitative and statistical analysis and drafted the protocol. All Authors (SR, JB, FDL, LDC, MDM, FE, LF, DG, LG, EI, CJ, VM, FT, CMV, CG, FP) participated in writing the study protocol and the manuscript and approved the final version.

Data

There are no data yet to be accessed. The original protocol is available for registered users on the website of the coordinating centre at [https:// www.usc-intnapoli.net](https://www.usc-intnapoli.net).

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Competing interests

SR has received personal fees from CSL-Behring and GlaxoSmithKline Foundation. JB has received personal fees from Novartis, AstraZeneca, Merck Sharp & Dohme. MDM has received personal fees from Bristol Myers Squibb, Merck Sharp & Dohme, Roche, AstraZeneca, Janssen. FE has received personal fees from Bristol Myers Squibb, Incyte, Orsenyx and Amgen. LG has received personal fees from Bristol Myers Squibb. CJ has received personal fees from Amgen, Astra Zeneca, Biogen, Boehringer Ingelheim, Celgene, Gilead, GSK, Ipsen, Janssen-Cilag, Takeda and Sanofi. VM has received personal fees from Bristol Myers Squibb and Italfarmaco; a member of his family is employee in Bayer. CV has received personal fees from from Baxter, MSD, Novartis, Sanofi, Sanofi Genzyme. FP has received personal fees from Bayer, Ipsen, Astra Zeneca, Bristol Myers Squibb, Sandoz, Incyte, Celgene, Pierre Fabre, Janssen-Cilag. The other Authors have no conflict to disclose.

Ethics approval

By 6 May 2019, the protocol has been approved by Ethical Committees at all centres participating in the first two tasks of the protocol.

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End-point model 1. Interventional, to reduce financial toxicity (FT)

<u>Concept</u>	<u>Endpoints</u>
Intervention Modifying conditions that may cause FT	Primary <i><u>FT score (proFFiT)</u></i>
Supportive concept Management efficacy outcomes	Secondary Survival QoL Toxicity

End-point model 2. Interventional, to test efficacy of new treatments

<u>Concept</u>	<u>Endpoints</u>
Intervention Comparison of new vs standard treatment	Primary Survival Other time outcomes
Supportive concept Effect on other efficacy/activity measure	Secondary QoL Toxicity Response rate <i><u>FT score (proFFiT)</u></i>

End-point model 3. Observational, cross sectional, describing FT

<u>Concept</u>	<u>Endpoints</u>
Intervention Describing FT	Primary <i><u>FT score (proFFiT)</u></i>
Supportive concept Anchors	Secondary Socioeconomical condition QoL Survival