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Effectiveness of the HuCare Quality Improvement Strategy on health-related quality of life in patients with cancer: study protocol of a stepped-wedge cluster randomised controlled trial (HuCare2 study)

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ABSTRACT

Introduction Our group previously demonstrated the feasibility of the HuCare Quality Improvement Strategy (HQIS), aimed at integrating into practice six psychosocial interventions recommended by international guidelines. This trial will assess whether the introduction of the strategy in oncology wards improves patient's health-related quality of life (HRQoL).

Methods and analysis Multicentre, incomplete stepped-wedge cluster randomised controlled trial, conducted in three clusters of five centres each, in three equally spaced time epochs. The study also includes an initial epoch when none of the centres are exposed to the intervention, and a final epoch when all centres will have implemented the strategy. The intervention is applied at a cluster level, and assessed at an individual level with cross-sectional model. A total of 720 patients who received a cancer diagnosis in the previous 2 months and about to start medical treatment will be enrolled. The primary aim is to evaluate the effectiveness of the HQIS versus standard care in terms of improvement of at least one of two domains (emotional and social functions) of HRQoL using the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items) questionnaire, at baseline and at 3 months. This outcome was chosen because patients with cancer generally exhibit low HRQoL, particularly at certain stages of care, and because it allows to assess the strategy's impact as perceived by patients themselves. The HQIS comprises three phases: (1) clinician training—to improve communication-relational skills and instruct on the project; (2) centre support—four on-site visits by experts of the project team, aimed to boost motivation, help with context analysis and identification of solutions; (3) implementation of Evidence-Based Medicine (EBM) recommendations at the centre.

Ethics and dissemination Ethics committee review approval has been obtained from the Ethics Committee of Parma. Results will be disseminated at conferences, and in peer-reviewed and professional journals intended for policymakers and managers.

Trial registration number NCT03008993; Pre-results.

Strengths and limitations of this study

- This trial addresses the lack of evidence on patient outcomes of implementation strategies for the integration of psychosocial interventions in routine cancer care. To this end, a robust methodology will be used, with a cluster randomised stepped-wedge design, which enables all enrolled clusters to receive the evidence-based intervention and to assess effectiveness in time.
- The restriction of eligibility to a population at a high risk of reduced quality of life (diagnosis within the past 2 months) should help counter the potential measurement floor effect, highlighted in the literature, which arises when the effect of an intervention is measured in patients who would not need it.
- The inclusion of centres located all over the country will enable to determine the strategy's generalisability, but the participation of hospitals exhibiting cultural and organisational barriers may reduce feasibility.
- The hypothesis of effectiveness in this study is not based on preliminary data, but refers to the findings of a recent Cochrane systematic review, which however considers different types of psychosocial interventions.
- To reduce the time some centres must wait to receive the intervention, a limitation of the stepped-wedge design, implementation time for each cluster was set at 4 months. This may not be sufficient to introduce change, and may thus decrease the strategy's effect.

INTRODUCTION

Background and rationale

Cancer has a significant impact on the lives of patients and their families, which is not restricted to symptoms and treatment side effects. Research points to the existence of

a wide range of psychosocial needs, defined as psychological, emotional, social and spiritual aspects of health, which frequently are not detected or adequately dealt with.[1] Although prevalence of psychological distress among patients with cancer is difficult to estimate, because of the many different tools and diagnostic criteria used, research reports that up to 75% of patients with newly diagnosed cancer develop psychological distress.[2] Furthermore, the burden of the disease is increased by frequent practical demands (economic problems due to absence from work, transportation to reach the hospital, and so on) and information needs concerning the disease and available support services.[1 3] These aspects are so relevant that Bultz and Carlson suggest to consider cancer a biopsychosocial illness,[4] and to strongly advocate for the need to integrate the psychosocial domain into practice.[4 5]

Although there are now numerous guidelines providing best evidence psychosocial and supportive care for oncology patients,[6 7] evidence suggests that many patients with cancer who might benefit from these interventions do not receive them.[8–10] Barriers to implementation may be related to personal characteristics of healthcare professionals (such as knowledge and beliefs about appropriate psychosocial care, and existing skills), and to environmental/organisational factors (such as time restraints and lack of formal support).[11 12] Notably, several of these barriers are modifiable.[11]

These findings emphasise the need for implementation strategies to effectively transfer evidence into practice.[7 13 14] Such a strategy should be tailored to potential barriers and obstacles,[15] and should be feasible (it can be implemented and maintained) and effective (able to modify both individual behaviour and the local organisation).[16 17]

Choosing the strategy to improve psychosocial care

These considerations formed the basis for the HuCare (Humanisation in Cancer Care) implementation study, funded by the Italian Ministry of Health and by the Lombardy Regional Health Trust, conducted in 28 cancer centres nationwide. The project, completed in 2014, evaluated the feasibility of the 'Hucare Quality Improvement Strategy—HQIS', aimed at integrating into practice six psychosocial interventions recommended by international guidelines. The HQIS was developed and implemented following the model by Pronovost *et al* for the translation of evidence into practice.[18] A multidisciplinary task force first reviewed the relevant research and identified interventions with the greatest benefit and the lowest barriers to use. An improvement team (IT) then conducted four to six visits in each centre to assist clinic staff in identifying obstacles, finding solutions and strengthening motivation to carry out recommended changes. Following an implementation period, adherence to each of the six recommendations was assessed and the objective was considered to be met if the centre's adherence percentage was at least 75%. HuCare has demonstrated the strategy's feasibility in a real context,[19] since over 75% of patients had received the psychosocial interventions in 27 of the 28 participating centres. Although these results are promising, it must be pointed out that participating sites were primarily leading centres of excellence, mainly located in wealthier Northern Italy. Also, the evidence of improvement was limited to process indicators and not outcome indicators of quality (eg, patient's psychological well-being). Randomised trials are therefore necessary to demonstrate that implementation strategies aiming to integrate psychosocial care into practice may improve knowledge and skills,[20] as well as health outcomes, and that they are sustainable.[9 21]

The choice of health-related quality of life to assess the strategy's efficacy

Health-related quality of life (HRQoL) is a multidimensional concept referring to the effect of an illness and its therapy on a patient's physical, psychological and social well-being as perceived by the patient himself.[22] Numerous studies conducted in different countries show that HRQoL of patients affected with diverse cancer types is lower than that of the general population,[23–25] and that the risk of a reduced QoL is greater at certain stages of the care process, such as the first few months of treatment, a period characterised by high levels of anxiety and depression.[25 26]

Today, there is general agreement on the importance of HRQoL as an outcome in clinical trials.[27] As far back as 1996,[28] the American Society of Clinical Oncology recommended that it be considered a primary outcome in any phase III trial.[28] Similarly, the Food and Drug Administration supports the importance of incorporating patient-reported outcomes (PRO), such as QoL, both in cancer research, and in the decision process for the approval of medicinal products in oncology.[29] A review of phase III studies performed by the National Cancer Institute of Canada Clinical Trials Group shows how detection of HRQoL represents an added value in research, and in some cases can modify the clinical interpretation of trial results.[30]

HRQoL also plays a central role as a measure of the quality of care.[31 32] The policy statement of the European Partnership Action Against Cancer Consensus Group, an initiative of the European Commission launched in 2009, considers the QoL of a patient an essential element in the decision-making process, which must be discussed with the patient.[33]

Given the relevance of HRQoL for people with cancer, the literature is increasingly emphasising the importance of identifying ways of maintaining and improving their QoL. In this regard, a Cochrane systematic review[2] summarises findings from 30 randomised and quasiexperimental trials (5155 patients, of which 1249 were included in the meta-analysis), published between 1981 and 2009, aimed at assessing the effect in terms of HRQoL (as the primary outcome) of a psychosocial intervention comprising an interpersonal relationship between patients and specially

trained healthcare professionals. The authors conclude that no statistically significant results have been obtained on HRQoL at 6 months, probably also due to methodological limitations, heterogeneity of the detection tools used, high risk of contamination bias and of a dilution of the observed effect. Based on these considerations, the review provides indications for future research, emphasising the need for randomised controlled trials (RCT) on those patients who are more likely to benefit from psychosocial interventions, and using adequate tools and sensitive measures, that is, capable of capturing changes in the psychosocial domain.

Research question and hypotheses

Building on the findings of the HuCare implementation study, and following the indications of the literature, this randomised trial was therefore designed to assess whether the introduction of the HQIS in oncology wards, compared with standard care, improves the QoL of patients at 3 months (primary endpoint), and in the long term at 6 months and 1 year after the intervention (secondary endpoints).

The main hypotheses are the following:

- Improving communication and relational skills of clinical staff (medical oncologists and nurses) facilitates change of behaviour.
- Providing support for context analysis and for the solution of problems detected at a local level favours implementation of recommended psychosocial interventions.
- Carrying out such recommendations improves the QoL of patients with cancer who are at high risk of experiencing a decrease in their HRQoL.

The study follows the methodology outlined in the Medical Research Council guidelines on complex interventions,[34] in the CONSORT (Consolidated Standards of Reporting Trials) statement and its extensions (PRO extension, and extension to cluster randomised trials), and in the SQUIRE (Standards for Quality Improvement Reporting Excellence) guidelines for quality improvement reporting.[35] This protocol was written following the indications contained in the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement.[35]

METHODS AND ANALYSIS

Aims

The study's primary aim is to evaluate the effectiveness of the HQIS versus standard care in terms of improvement of at least one of the two functional domains of HRQoL, emotional or social, detected at baseline (before treatment initiation) and at clinical follow-up (approximately 3 months after study enrolment).

The secondary aims are:

1. To investigate whether the strategy has an effect:
   - on patient mood
   - in the long term (6 and 12 months)
   - on overall HRQoL or on specific domains
   - on specific patient types (case mix).
2. To measure adherence rate (process indicators) in terms of:
   - percentage of clinical staff who complete training and exhibit improvement in their communication skills
   - percentage of eligible patients who systematically receive the interventions.

Study setting and design

This is a multicentre, incomplete stepped-wedge cluster randomised controlled trial (SWD-CRT) (since data are not collected during implementation), where the intervention strategy is sequentially carried out in three groups of centres (clusters with five centres each) and in three equally spaced time periods (epochs) (every 4 months, from the second to fourth epochs), as depicted in figure 1. The study also includes an initial epoch, during which none of the centres are exposed to the intervention, and a final epoch when all centres will have implemented the strategy.[36 37] The implementation epoch for each centre is randomly assigned, and by the end of the study, all centres will have received the strategy. The intervention is applied at a cluster level, which constitutes the unit of randomisation, and assessed

Centres		Epoch 1 (Months 1-4)	Epoch 2 (Months 5-8)	Epoch 3 (Months 9-12)	Epoch 4 (Months13-16)	Epoch 5 (Months 17-20)
Cluster 1	1	Control	HQIS implementation	Post-Intervention	Post-Intervention	Post-Intervention
	2	Control	HQIS implementation	Post-Intervention	Post-Intervention	Post-Intervention
	3	Control	HQIS implementation	Post-Intervention	Post-Intervention	Post-Intervention
	4	Control	HQIS implementation	Post-Intervention	Post-Intervention	Post-Intervention
	5	Control	HQIS implementation	Post-Intervention	Post-Intervention	Post-Intervention
Cluster 2	6	Control	Control	HQIS implementation	Post-Intervention	Post-Intervention
	7	Control	Control	HQIS implementation	Post-Intervention	Post-Intervention
	8	Control	Control	HQIS implementation	Post-Intervention	Post-Intervention
	9	Control	Control	HQIS implementation	Post-Intervention	Post-Intervention
	10	Control	Control	HQIS implementation	Post-Intervention	Post-Intervention
Cluster 3	11	Control	Control	Control	HQIS implementation	Post-Intervention
	12	Control	Control	Control	HQIS implementation	Post-Intervention
	13	Control	Control	Control	HQIS implementation	Post-Intervention
	14	Control	Control	Control	HQIS implementation	Post-Intervention
	15	Control	Control	Control	HQIS implementation	Post-Intervention

Figure 1 Study design: stepped-wedge cluster randomised controlled trial (SWD-CRT). HQIS, HuCare Quality Improvement Strategy.

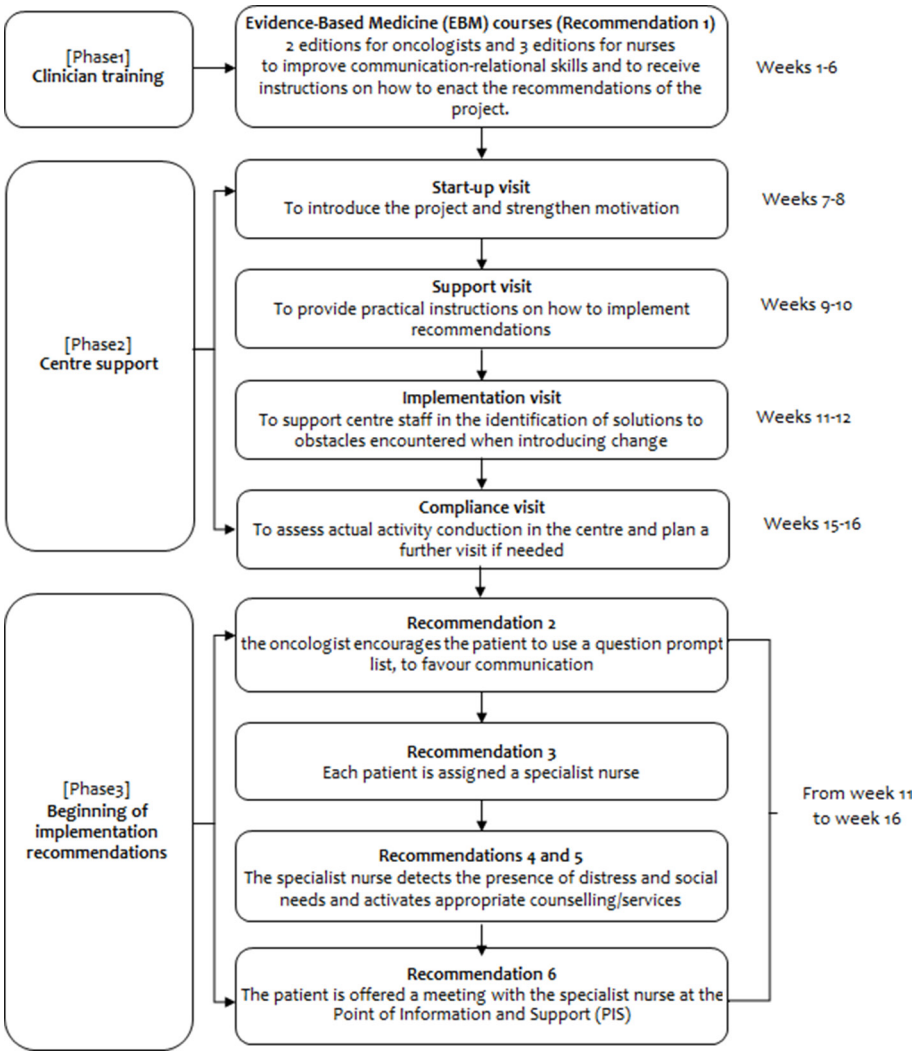

Figure 2 HuCare Quality Improvement Strategy (HQIS) flow chart.

at an individual level (on the patients of eachcluster) with cross-sectional model (for each epoch, patients are different).

The cluster randomised design was selected because the intervention is organisational and requires high involvement of all centre staff; therefore, randomising individual oncologists or patients would not be possible, as it would entail a high risk of contamination bias. Furthermore, the stepped-wedge design enables to overcome the logistic difficulty of simultaneously providing the intervention to all centres, and it is ethically acceptable since it ensures that all patients may receive an intervention considered to be beneficial. Finally, it offers the opportunity to measure the effect of the intervention in time (secondary objective), which is one of the gaps highlighted in the literature for psychosocial interventions.[19 21]

The project was presented in October 2015 at the national conference of the Italian Association of Medical Oncology, during a meeting open to interested members. Study recruitment was performed using the 'Facilities Questionnaire', a brief survey developed for the project to ascertain the presence of essential prerequisites for study conduction and to ensure centre representativeness according to size and geographical location. The number of centres to be included has been determined based on feasibility (costs and logistics restrictions) and clusters have been defined geographically (North, Centre-South and Islands).

The directors of the participating centres declared that all staff were informed on the aims and conduction of the project and accepted to take part in the study.

Study patients

Patients with cancer of any type and stage, who consecutively access the participating centres (outpatient care) during an index period and who fulfil the following inclusion criteria:

- age ≥18
- diagnosis (histological or cytological) of solid tumour communicated to the patient within the previous 2 months
- about to start a new medical cancer treatment: chemotherapy (intravenous or oral), molecular target drugs, hormonal therapy, immunotherapy
- expected survival >3 months
- good comprehension of the Italian language

- who have read, understood and signed the informed consent.

Exclusion criteria are:

- previous chemotherapy or other medical cancer treatment
- recruited in a previous epoch of the study (ie, patients can only participate during one epoch)
- currently participating in other trials which imply the completion of PROs in the same period
- hospitalised
- currently receiving psychiatric treatment
- affected by mental or psychiatric disorders, due to cancer or coexisting illness, which interfere with the state of consciousness or impede judgement
- inability to complete the questionnaire or ensure participation in the 3-month follow-up.

Intervention

The HQIS has been thoroughly described elsewhere.[19] It takes 16 weeks to complete (4 months) and comprises three phases, outlined in figure 2. It consists of the introduction of six EBM psychosocial recommendations—one targeting clinicians and five targeting patients—and in support activities to the centres aimed to favour recommendation uptake. A description of each recommendation, its rationale and mode of implementation in our project are provided in table 1.

In short, in phase 1 (lasting approximately 6 weeks) medical and nursing staff of participating centres will attend communication skills training designed according to literature indications (recommendation 1). In phase 2, the project team will enact activities to support centres in the implementation. These will include provision of reference material and four on-site visits by the IT, composed of personnel not employed at the centre (sociologist, psychologist and research nurse). Phase 2 will take approximately 10 weeks. In phase 3, centres will implement the five psychosocial interventions targeting patients (recommendations 2–6): provision of a question prompt list, assignment of a specialist nurse, screening for psychological distress, screening for social needs and access to the Point of Information and Support (table 1). This final phase will last approximately 6 weeks, and will partly coincide with phase 2.

Outcomes

The study's primary endpoint is the difference between the means of changes of individual scores (at least one of the two domains, emotional or social, of the HRQoL) detected at baseline and at 3-month follow-up (within each group), during the postintervention epoch compared with control periods (between groups). Effect measure at 3 months was chosen because QoL trend has been observed to reach its negative peak 3 months after treatment initiation, and then to gradually improve over the first 12 months.[25] This trend may be explained by the fact that the emotional distress that results from a cancer diagnosis is typically followed by a phase of taking control, which involves seeking information and sourcing appropriate help.[2] Cocks *et al*[38] also indicate 3 months as the ideal timing for studies measuring intervention impact on HRQoL, since it increases study efficiency (smaller sample size) given the wider difference between baseline and 3-month follow-up scores.

The following secondary outcomes will also be assessed, again comparing baseline values with measurements at follow-up, during the postintervention epochs versus control epochs, in order to test HQIS impact:

- in the long term, that is, whether different effects on patients initiating a new treatment are detected over 6 months and 1 year
- on global HRQoL, on specific scales and on individual symptoms, detected by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30)
- on mood disorders, measured with the HADS-D (Hospital Anxiety and Depression Scale)
- according to patient subtypes defined by: baseline values of anxiety and depression,[39] metastatic disease (yes/no), cancer type, ECOG (Eastern Cooperative Oncology Group) performance status, treatment type (chemotherapy, hormonal therapy, immunotherapy).

To assess the actual degree of implementation at individual centres, the following secondary outcomes will be measured:

- percentage of clinical staff (oncologists and nurses) who complete training and exhibit improvement in their communication skills
- percentage of patients with unmet social needs, detected with the Needs Evaluation Questionnaire (NEQ), at baseline versus at 3-month follow-up
- percentage of eligible patients who receive HuCare recommendations, recorded during the implementation visit (figure 2) on a sample of five consecutive cases for each centre. This will be assessed by reviewing patients' clinical records, in which performed psychosocial interventions have to be noted.

Instruments for outcome measurement

Quality of life questionnaire

QoL, the primary endpoint of the study, will be assessed with the validated Italian version of the EORTC QLQ-C30 questionnaire,[40] specific for patients with cancer. The tool is self-administered, and comprises 30 questions, 24 of which form 9 multi-item scales representing the different aspects, or domains, of QoL: a global health status/QoL scale, five functional scales (physical, role, emotional, cognitive and social), and three symptom scales (fatigue, pain, nausea and vomiting), as well as six single items assessing additional symptoms (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea) and perceived financial impact of the disease. Various tools validated in many languages exist in the literature for the measurement of HRQoL, but two of them are most commonly used: the EORTC QLQ-C30[41] and the Functional Assessment of Cancer Therapy-General.[42] Luckett *et al*[43] report an interesting comparison between the two instruments, concerning content, scale, structure, psychometric properties, and

Table 1 The six recommendations of the HQIS. The table is designed following the SQUIRE guidelines

Recommendation	Description	Main factors that contributed to choice	How, when and by whom the intervention is implemented
Recommendation 1: Clinician communication skills training	All clinical staff (oncologists and nurses) should attend training designed according to available scientific evidence, to improve their communication-relational skills and to receive instructions on how to enact the five recommendations of the project targeting patients.	Communication skills can be taught, and the impact of training is enduring.[68 69] A Cochrane review shows some positive effects of communication skills training (CST) on health professional communication skills.[70]	3-day courses for physicians and nurses (maximum 20 participants for physicians and 30 for nurses) will be conducted.[71 72] Role-playing in small groups and interactive material will be used.[71 73] Each centre must ensure that at least 75% of medical staff and of nursing staff operating in the ward complete the training.
Recommendation 2: Question prompt list	A question prompt list (QPL), list of possible questions that patients may ask their oncologist, must be provided to patients during the initial consultations, and its use encouraged by the oncologist.	QPLs are inexpensive tools which have been shown to increase patient participation in the consultation, improve communication, patient satisfaction and recall, and possibly decrease anxiety.[74 75]	The oncologist will provide and introduce the QPL to the patient during the first consultation.[74] The oncologist shall encourage the patient to refer to the QPL at his/her own discretion.[74 75] A QPL cross-culturally validated into Italian will be used in this study.[76] Encouragement of QPL use, or reasons for not providing the QPL, must be noted in the patient's clinical record.
Recommendation 3: Specialist nurse	A specialist nurse (SN) should be assigned to each patient from the first cycle of therapy.	SNs accompany patients through their care, and act as a link with hospital services. Systematic reviews suggest positive effects on patient QoL, satisfaction with care and psychological outcomes.[77 78]	Patients will be assigned a specialist nurse at their first access to the centre. The oncologist will describe the role of the SN and if possible introduce the SN to the patient. Centres will define the ways in which patients may contact their SN throughout the care pathway.
Recommendation 4: Screening for psychological distress	All patients must undergo screening for psychological distress with a validated instrument starting at the initial visits, and those with distress exceeding the threshold value must be referred to psycho-oncological services.	Data suggest that screening for and addressing distress enhances quality of life and may be associated with improved cancer outcomes, however distress often goes unrecognised in oncology care.[79] Several organisations, including the NCCN, the Institute of Medicine, and the American Society of Clinical Oncology, have identified the assessment and treatment of psychosocial distress in routine cancer care as a quality care standard.[79 80]	The distress thermometer (DT)[81] will be provided and introduced to patients by the SN after the first visit with the oncologist and before the first cycle of therapy. Screening at regular intervals should be ensured to all patients, in particular when they are at greatest risk for distress. DT results will be assessed by specifically trained, qualified personnel of the centre. For patients exhibiting distress, psycho-oncological referral will be ensured, according to a written procedure defined at each centre. The DT must be included in the medical record, and any psycho-oncological referral noted. The psychologist of the ward is responsible for the supervision of questionnaire administration and retrieval, and will ensure assessment.
Recommendation 5: Screening for social needs	All patients should undergo screening for social needs with a validated instrument starting at the initial visits, and whenever a need is detected, solutions must be identified.	Evidence suggests several benefits of early recognition and management of needs, such as enhanced quality of care, trust and satisfaction, and improvement in patient–provider communication. Conversely, failure to address psychosocial problems results in needless patient and family suffering, obstructs quality healthcare and can potentially affect the course of the disease and patient's experience of cancer.[1]	The Needs Evaluation Questionnaire (NEQ)[52] will be provided and presented to patients by the SN after the first visit with the oncologist and before the first cycle of therapy. Screening at regular intervals should be ensured to all patients, in particular when they are at greatest risk of experiencing social needs. NEQ results will be assessed by the SN or other qualified trained personnel, as defined by each centre. For patients exhibiting needs, the appropriate services will be activated by the SN, according to a written procedure defined at each centre. The NEQ must be included in the medical record and any activation of services noted.
Recommendation 6: Point of Information and Support	All patients must be offered the opportunity to attend a Point of Information and Support (PIS) within the ward.	A PIS is a library for patients and their families, managed by nursing staff trained to inform on issues related to cancer. An RCT conducted by our group showed that when implemented according to the protocol PIS attendance can reduce psychological distress and increase patient satisfaction.[82]	The PIS must be adjacent to the oncology outpatient area, in a space where privacy is ensured. It must be equipped with internet access and selected information material. All patients must be offered the opportunity to meet their SN at the PIS before treatment initiation and whenever needed.

HQIS, HuCare Quality Improvement Strategy; NCCN, National Comprehensive Cancer Network; QoL, quality of life; RCT, randomised controlled trial; SQUIRE, Standards for Quality Improvement Reporting Excellence.

other aspects, and constructed an algorithm which helps researchers in choosing the more adequate questionnaire according to the items of interest. Another recent work[44] compares the two instruments' 'responsiveness' and statistical efficiency. Responsiveness, or sensitivity to change, is the most important property of a questionnaire used within a trial aiming to demonstrate the impact of an intervention, defined as the ability of an instrument to detect the minimal change considered to be clinically relevant by patients.[45] Statistical efficiency refers to the sample size needed to detect such effects. Considering the nature of psychosocial interventions implemented in this study, which we hypothesise to mainly impact the social and emotional domains, and following the indications of the aforementioned papers, the QLQ-C30 was selected.

The choice of the two domains and corresponding timing, that is, time of effect measurement, was based on the analysis of the work by Cocks *et al*,[38] with the aim to restrict assessment to the emotional and social functions, which are mostly affected by psychosocial interventions, and to the population at greatest risk of QoL deterioration (patients in the first 3 months of treatment).

The questionnaire is self-administered using a touch screen tablet device, at baseline and 3 months after enrolment during the follow-up visit. The electronic version was chosen as it reduces completion times[46 47] and the risk of missing data and entry errors,[48] making QoL detection more efficient and accurate.[49] Furthermore, the electronic device for PRO detection has been shown to be easily used also by people over 70 years old, who only take a few more minutes than the younger population.[46 47]

To ensure the correct use of the questionnaire during data collection, as well as appropriate data analysis and interpretation, the indications of the EORTC manual will be followed.[50]

Hospital anxiety and depression scale

The HADS is a self-report questionnaire, validated into Italian,[51] comprising 14 items, 7 assessing the level of anxiety (HADS-A) and 7 assessing the level of depression (HADS-D), with scores for each item ranging from 0 to 3 and an overall score ranging from 0 to 42. For each statement, patients are asked to select among four options the one which best describes their emotional state referred to the previous week.

Needs evaluation questionnaire

Social needs are detected using the NEQ, a tool developed in Italy, composed of 25 items, intended to record the main, potentially manageable social needs of people with cancer connected to their state of health.[52] Identified areas concern information, communication and relationship with healthcare professionals; symptoms or functional problems; involvement of other professionals (social worker, psychologist, spiritual advisor); financial issues and help with lodging; psychological needs at an individual, family and social level.

Participant timeline

Patients will be screened and enrolled over two consecutive index weeks, to ensure the necessary sample size and representativeness of different cancer types and treatments administered at the centres (see figure 3). Data collection will take place in two time points:

- enrolment stage, collection of patient's baseline data

Timing	**Epoch 1** From months 1 to 4	**Epoch 2** From month 5 to 8	**Epoch 3** From month 9 to 12	**Epoch 4** From month 13 to 16	**Epoch 5** From month 17 to 20
Enrolment					
Screening, Informed Consent and Baseline questionnaires Cluster 1	X		X	X	X
Screening, Informed Consent and Baseline questionnaires Cluster 2	X	X		X	X
Screening, Informed Consent and Baseline questionnaires Cluster 3	X	X	X		X
Interventions					
HQIS Implementation Cluster 1	Control	Implementation	Post-intervention	Post-intervention	Post-intervention
HQIS Implementation Cluster 2	Control	Control	Implementation	Post-intervention	Post-intervention
HQIS Implementation Cluster 3	Control	Control	Control	Implementation	Post-intervention
Assessments					
Questionnaires at month 3 Follow-Up Cluster 1	X		X	X	X
Questionnaires at month 3 Follow-Up Cluster 2	X	X		X	X
Questionnaires at month 3 Follow-Up Cluster 3	X	X	X		X

Figure 3 Schedule of enrolment, interventions and assessments. HQIS, HuCare Quality Improvement Strategy.

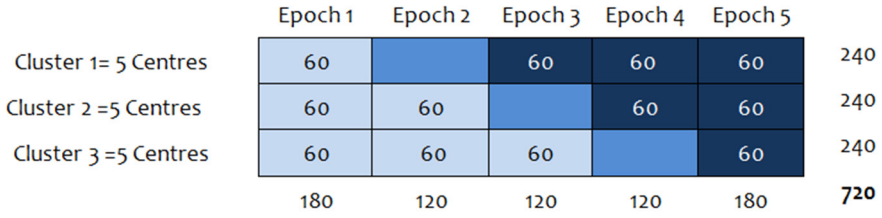

Figure 4 Sample size per epoch and cluster.

- assessment stage, collection of 3-month follow-up data for the same patients.

Sample size

The number of subjects to be enrolled was defined following the methodology for incomplete, cross-sectional stepped-wedge cluster randomised trials,[53–56] considering:

a. three clusters, each comprising five centres with equal size (capacity of enrolment per week);
b. a mean expected difference deemed clinically acceptable lying between 3 and 8 points of at least one domain (social or emotional), values indicated in the paper by Cocks *et al*[57] as minimal clinically relevant differences for the domains of this study;
c. an intraclass correlation coefficient equal to 0.80, as reported in two papers[45 58];
d. the Wald Test, with time as fixed effect and the cluster as the random effect[53];
e. a power of 80% and two-tailed alpha of 5%;
f. dropout of 20% at follow-up.[59]

By applying the STATA/MP V.11.2 *stepped-wedge* procedure,[55] we calculated an overall sample size of 720 patients, which means 60 patients in each cluster for every detection epoch (see figure 4).

Allocation and blinding

The unit of randomisation is the cluster, a group of five centres randomly assigned to one of the HQIS implementation epochs; given 15 participating centres, 3 clusters will be formed, each including 5 centres located in the same geographical area (North, Centre-South, Islands) to facilitate the work of the IT. The sequence of implementation is defined through SAS software (V.8.2) by the statistician, who will inform centres of their assigned implementation period with a 4-week notice. The unit of statistical analysis, on which the primary and secondary endpoints are measured (save for the percentage of clinical staff completing training), will be patients enrolled by clusters during two index weeks, randomly selected by the statistician.

Blinding will be ensured both for patients, who will not be aware of the study epoch in which they are providing information on their HRQoL (control period or postintervention period), and for the statistician, who will use anonymised data and encrypted identification codes for the study epochs. This should prevent ascertainment, performance and attrition biases, as reported in the SPIRIT guideline.[35] The nature of the intervention precludes blinding for clinical staff.

Data collection

Patient's eligibility assessment

After the first consultation with the oncologist and before initiation of the first cycle of therapy, patients consecutively accessing the centre (outpatient care) will be screened by the oncologist over a period of two index weeks indicated by the statistician. To this end, the oncologist verifies eligibility, introduces the study to eligible patients, provides the information sheet and obtains informed consent before initiation of the first cycle of therapy.

Baseline assessment

Prior to initiation of the first cycle of therapy, and before implementing the recommended interventions addressed to patients, a specially trained research nurse of the centre will enter demographic and clinical variables (taken from medical records) into the electronic data collection form (electronic-Case Report Form eCRF), and will instruct the patients on how to complete the questionnaires using a tablet. The time needed for completion is estimated not to exceed 20 min for each patient (12 min for the EORTC and 8 min for the other questionnaires). The research nurse will check completeness of entered information, and in the case of missing data will invite the patient to fill in the empty fields, noting any problems arisen in the process.

Three-month assessment

Before the medical follow-up appointment, the research nurse will invite the patient to complete the questionnaires using the tablet. At the end of the visit, the nurse will enter the following information taken from the clinical record into the eCRF: ECOG at 3 months, any disease progression (according to RECIST (Response Evaluation Criteria in Solid Tumours) criteria), and any reasons for incomplete questionnaires and for the premature interruption of the study.

Collection of outcome

The following patient demographic and clinical characteristics are collected at baseline to describe the study population and determine the factors associated with QoL:

- date of birth

- gender
- civil status
- education (primary, high school and above)
- date of diagnosis
- presence of metastases (yes/no)
- cancer site
- ECOG performance status
- type of treatment.

At 3-month follow-up, presence of disease progression will also be recorded (yes/no).

As for coding of QLQ-C30 questionnaire variables, responses are formulated on Likert scales and the sum of assigned values yields the score for each of the 15 domains. Highest values in the symptom domain (eg, diarrhoea, weakness, vomiting, and so on) will indicate severe symptomatology. Highest values in the other domains will indicate better QoL. Scores of each domain are linearly transformed into a 0–100 scale, where 0 and 100 are assigned to the lowest and highest possible values, respectively.

For the HADS-D,[60] a cut-off of >7will be used, a score considered clinically significant (ie, patients scoring above this value may benefit from psychological support therapy) and with high sensitivity (0.86) and specificity (0.81).[61] Missing values will be replaced with the mean of the other available values for anxiety or depression, if not more than four values are absent.

The NEQ detects the presence of different types of needs using dichotomous choices (yes/no). It will enable to assess the frequency of needs and to compare it across the two detection periods (baseline and follow-up). Specifically, this information will allow to determine whether the HQIS is effective in reducing needs and whether this also corresponds to a positive effect on QoL.

Data management

Data will be gathered anonymously by means of an eCRF which uses a remote single-entry system with electronic check of data congruence. Together with the usual data entry functions and online checks, this system, employing mobile devices (tablet, smartphone), also includes a control check of operator identification (investigator), check of patient's eligibility criteria and of data entry required by the three questionnaires used in the study. To reduce missing data, a banner will appear warning the patient to complete all fields or to indicate unwillingness to answer, when some fields are left empty. If >50% of responses are missing, the research nurse will indicate the reasons in the eCRF.

Statistical methods

Data will be processed with SAS software V.8.2 (Statistical Analysis System) and STATA/SE V.11.0.

Before database lock and cleaning, the statistical analysis plan will be defined, comprising the following essential elements:

- measure calculation and interpretation
- statistical methods for the analysis
- management of missing data
- tables, lists and figures for data collection monitoring and for the final analysis.

Statistical analysis

For the principal analysis of effectiveness, we considered an intention-to-treat (ITT) population composed of all clusters according to randomisation and all eligible patients with HRQoL assessments at baseline and at 3-month follow-up. Patients are considered to be exposed to the intervention according to randomisation, regardless of any delay or failure to conduct the intervention. A 'Per-protocol population' will also be assessed, composed of centres which will complete the trial without any breaches to the protocol and which exhibit a degree of compliance (per cent of trained clinicians and per cent of eligible patients who have received the intervention) greater than 75%. Sensitivity analyses will be conducted to assess the robustness of the missing data assumption made in the primary analysis.

Sample descriptive characteristics will be presented as means and SD when normally distributed, or as medians and IQRs. Although the majority of responses to an individual item/symptom/functional scale of the EORTC QLQ-C30 questionnaire exhibit asymmetric distribution, findings will nevertheless be described with both mean and median values.

The main unit of analysis is the individual. Differences of HRQoL values between the two groups, postintervention and control, relative to each of the two functional domains (emotional or social) of interest for the primary aim, will be analysed using a binomial beta (BB) regression model, as suggested by different authors,[62 63] due to the asymmetric value distribution. This model also enables to estimate the strategy's effect in terms of OR, the preferred measure by oncologists for its more immediate interpretation and greater usefulness in clinical practice, compared with absolute values.[62] For the BB model analysis, responses will be transformed into a scale (0, 1) by using the formula Y–a/ba, where a and b are the lowest and highest possible scores, respectively, and Y is the observed response. For instance, a score of 80 will be expressed as 80–0/(100–0)=80/100=0.8.

The demographic and clinical variables which influence the outcome with a p value <0.20 in the univariate analysis will be included in the regression model.

Since the study is an incomplete, cross-sectional SWD-CRT (with an implementation period), the following covariates will be included in the model: the implementation epoch (first, second or third) and time of exposure to the strategy; the cluster the patient belongs to (1, 2 or 3) and intracluster correlation.[37]

Concerning the secondary outcomes, the following ITT analyses will be performed:

- long-term variables (at 6 and 12 months) will be entered into the BB model as covariates, where the dependent variable indicates the differences of HRQoL values between the two groups, postintervention and control, relative to each of the two functional domains (emotional or social);

- the EORTC QLQ-C30's global scales and the other domain scales will be represented as observed response Y in the BB model, and the covariates will be those used in the primary analysis;
- to examine whether the HQIS has any effect on mood disorders, general linear modelling ($p<0.05$) will be used.

To investigate the actual degree of implementation at the centres, descriptive analyses will be performed and displayed in tables and figures.

Missing data

Data will be classified in two ways, according to the degree of completion: missing responses (questionnaires with one or more missing responses) or missing questionnaire (questionnaires with more than half missing responses). These two cases will be managed differently in the analysis process, as described below:

Missing responses

The expected proportion is 2%, as reported in the EORTC QLQ-C30 Scoring Manual,[50] with missing values casually distributed in the two groups. To reduce the proportion of missing data, patients who have not filled in all fields at the end of completion will see a banner reminding them to do so, or to state unwillingness to respond. If a response is given for at least half of the items, the missing values are assumed to correspond to the mean of the given responses and the imputation method deemed most appropriate will be applied. If the number of missing data is greater than the half of the items, the questionnaire will not be considered valid.[50]

Missing questionnaire

If no response is given, or if the number of missing responses exceeds half of the items, the research nurse will report the reasons in the eCRF, that is, patient participation withdrawal, refusal to complete the questionnaire without providing any reason, deterioration of health conditions precluding completion and lost to follow-up. As suggested by Fayers and Machin,[64] reasons for failure to complete the questionnaire will be used as covariates in a logistic regression model, to investigate the association between compliance and indicated reasons.

Feasibility study

Before the randomised trial begins, a pilot study will be performed at the cancer centre of Cremona, on a consecutive sample of eligible patients who access the facility over 2 weeks (approximately 20 patients). This investigation aims to measure feasibility and acceptability of questionnaire administration using a tablet. For this purpose, the following aspects will be recorded: the frequency of subjects declining participation in the survey and the corresponding reason (eg, the use of a tablet), time taken by patients to complete the three instruments (HRQoL-C30, HADS and NEQ) and perceived difficulty and appreciation for the use of the tablet (expressed on a 5-point Likert scale).[65 66]

Ethics and dissemination

Monitoring and confidentiality

Centralised trial monitoring will be carried out by a data monitoring committee. During data collection, entered data will be systematically checked and a report will be prepared for each centre, indicating expected questionnaires, questionnaires that were included and those deemed not valid. All errors, incongruences and omissions will be summarised in data query forms, which will be sent to the investigators to elicit the necessary corrections. All data collected, processed and stored for the purposes of the project will remain confidential at all times and comply with Good Clinical Practice guidelines and current privacy regulations. Data will be gathered anonymously and sent to the study group in charge of analysis and management, using a data communication system based on the HTTPS protocol (https://www.w3.org/2001/tag/doc/web-https) to ensure secure connections. Patients can only be identified by the clinical staff operating at the centre where they were recruited. Each patient will receive personal credentials which he/she will use to complete the questionnaires. The research nurse will be in charge of sending the information to the central database. Back-up will be performed daily on the central database.

Study integrity

The study will be conducted in compliance with the principles of the revision of the Helsinki Statement and the legislation on scientific research. Ethical approval for the study has been obtained from the Ethics Committee of the Hospital of Cremona and from the ethics committees of all participating centres. The current version of the protocol (2.0 as of 18 August 2016) was amended based on the findings of the pilot study in order to clarify patient's eligibility criteria. Before trial initiation at each site, authorisation from the legal representative of the institution will be obtained.

This trial does not involve the use of any experimental medicinal product, or changes to the diagnostic-therapeutic practice. Since the HQIS strategy is implemented at participating centres, regardless of patients' informed consent, eligible subjects will be required to give written consent to the management of their personal data, which must be dated and signed both by the patient and the medical investigator, and authorised in accordance with regulations of the centre's local ethics committee.

All amendments to the protocol shall be submitted to the ethics committees of participating centres. Should a violation to the protocol be necessary, the local study coordinator shall contact the principal investigator, possibly before the violation is implemented.

DISCUSSION

The literature emphasises the lack of evidence of the effectiveness of psychosocial interventions on patient outcomes. This project intends to address this gap, by

examining the impact of a quality improvement strategy aimed at integrating evidence-based psychosocial care interventions into oncological practice, on patient's HRQoL.

The strategy was developed and tested within our previous study,[19] which demonstrated its feasibility in 28 Italian cancer centres. Preliminary context analysis (identification of obstacles and barriers and of actions to overcome them) and support provided by an IT were the peculiar elements of the strategy which made implementation possible. It must be pointed out that no preliminary study has been conducted to determine the HQIS's effect on QoL, but we refer to the findings of a Cochrane review of 30 RCTs,[2] assessing the effects of psychosocial interventions to improve QoL in the first 12 months after diagnosis. Considered interventions had to involve a 'trained helper' providing therapeutic dialogue. The review combines research data from 1249 people who took part in clinical trials to test psychosocial interventions, and found no improvement in general QoL, although small improvements in 'illness related' QoL were observed. Among the reasons stated by the authors for the lack of effect, along with the heterogeneity of examined interventions, is a potential floor effect. The strength of our study in this regard is the restriction of inclusion to patients with cancer who have received a diagnosis within the past 2 months, a population at high risk of reduced QoL. This should help reduce the potential for measurement 'floor effects', in those who are not experiencing distress, to dilute the observe effects of the strategy. Furthermore, we opted to evaluate the effectiveness of the HQIS versus standard care in terms of improvement of the emotional and social domains of HRQoL, rather than considering overall QoL, because the emotional and social functions are mostly affected by psychosocial interventions.[38]

In this study, we use a robust methodology, with a cluster randomised stepped-wedge design, most appropriate for evaluating interventions that have been shown to be effective in more controlled research settings, or where there is lack of evidence of effectiveness but there is a strong belief that they will do more good than harm during routine implementation. In fact, this design offers a number of opportunities. In particular, it allows all centres to ultimately receive evidence-based interventions, to manage practical and logistical constraints of concurrent implementation in all clusters and to determine the modelling of the effect of time on effectiveness, a key aspect of implementation science which is often overlooked.[21 67] A downside of this design, however, is that some centres will wait a long time to receive the intervention, and this could result in reduced staff motivation, or make participation impossible because of changes in hospital management or ward staff. To counter these potential problems, it was decided to keep implementation time for each cluster to a minimum (4 months). This may not give centres enough time to introduce change, and thus decrease the strategy's effect on patient outcomes. In fact, in our previous study, implementation times in each centre were tailored according to the difficulties encountered, ranging from 3 to 6 months. Furthermore, this trial also suffers from financial and feasibility constraints, which only allowed to enrol 15 centres and form 3 clusters based on location.[53]

Our feasibility study[19] mainly included centres of excellence situated in wealthy areas of Northern Italy. The extension of HuCare2 to centres located nationwide will enable to determine the strategy's generalisability to diverse settings, information which may be useful for the introduction of this approach to other contexts. On the other hand, however, the participation of centres exhibiting various cultural and organisational barriers may have a negative impact on the project's feasibility.

A possible weakness of this protocol is the use of a general tool to measure QoL, which may be unable to detect an effect. In fact, in the aforementioned Cochrane review,[2] when the analysis was divided into general health-related and illness-specific QoL measures, a small but significant positive result was observed in the data utilising illness-specific measures. However, we ruled out the use of illness-specific QoL scales, because our protocol includes patients with any cancer type consecutively enrolled over a 2-week period, and employing different questionnaires would have greatly complicated the enrolment.

In conclusion, given the complexity of this trial, and based on our previous experience, we believe efficient project management, appropriate support to boost clinical staff motivation and an experienced project team will be key ingredients for success. In any case, regardless of the outcome, the findings of this trial will contribute to advance knowledge on implementation strategies aiming to integrate psychosocial interventions in cancer care.

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Contributors CC conceived and designed the study. EI was in charge of the statistical analysis plan and sample size calculation. RP provided guidance on clinical and organisational aspects pertaining to the project. CC and EI drafted the manuscript. All authors have read and approved the final version of the manuscript.

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Competing interests None declared.

Patient consent Obtained.

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