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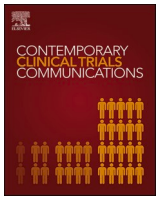

Constricting Gaps: Protocol development, implementation challenges and lessons learned for the reality map of unmet needs for Palliative Care Interventions in advanced cancer patients study in Romania and Switzerland

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ABSTRACT

Background: Patients with advanced cancer experience many symptoms and needs requiring a Palliative Care Intervention (PCI). Identifying gaps between needs for PCIs and experienced delivery may improve health care, furthermore the association of gaps with quality indicators (QI). The multicentre Romanian (RO)-Swiss (CH) reality map study implemented a novel protocol based on needs concepts and culturally adapted quality indicators (QI).

Methods: An interactive mapping guide measuring unmet needs for PCIs monthly over six months, patient characteristics (cognition, EAPC basic data set, Cofactors) and QI (Inappropriate Anticancer Treatment, High Symptom Burden [IPOS, EQ5D], Repeated ER Admissions, Aggressive End-of-Life Care, and Quality of Death-and-Dying) were developed, applying swiss standards for quality assurance. A composite endpoint (QI, cofactors) was planned. Finally, local solutions responding to gaps were piloted.

Results: From 308 patients (RO: 262, CH: 46, age 62j [mean], 74 % ECOG PS 1&2, 81 % current anticancer treatment) baseline and first follow-up data revealed main gaps (symptom management, spiritual needs, family support), country differences (e.g. illness understanding, spiritual needs) and a significant association of the number of gaps with depression. Later data become less, and data quality on QI variable, revealing gaps in research conduct competences, resources, and applicability of over-sophisticated quality assurance tools. Nevertheless, the unmet needs data promoted local initiatives, 81 patients participated in feasibility studies. Finally, the joint experience stimulated academic developments and national integration of palliative care into oncology.

Conclusions: Pairing motivation and enthusiasm with more modest aims, feasibility testing of all outcomes and investment in research competences may disperse gaps.

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Abbreviations

CPW-CL	Care Pathway Checklist
CRF	Case Report Form
EAPC	European Association of Palliative Care
ER	Emergency Room
HCP	Health Care Professionals
IAT	Inappropriate Anticancer Treatment
IPOS	Integrated Palliative care Outcome Scale
PC	Palliative Care
PCI	Palliative Care Intervention
QI	Quality Indicator
QoDD	Quality of Death-and-Dying
MMSE	Mini-Mental State Exam
SDV	Source Data Verification
SQID	Single Question in Delirium

1. Introduction

Patients with advanced cancer experience many symptoms and needs concerning physical, intellectual, emotional, social, existential, and spiritual issues until death [1], and family members beyond. The interventions applied to ease such suffering encompass the key elements of palliative care (PC), the PC Interventions (PCIs). They include *pharmacological* interventions for symptom management, *procedural* (e.g., pleural tapping), *nursing* (e.g., body care, spiritual aspects, family support [2], *communication* (e.g. addressing illness and prognosis understanding [3], information and care planning [4]), *counselling* (e.g. psychosocial approach for pain [5], or *coordination* interventions (e.g. network planning [6]).PCIs shall be integrated early together with anticancer treatment, as evidence shows and guidelines recommend [7]. Oncology professionals (physicians, nurses, other) ideally collaborating with General Practitioners [8], play a sentinel role responding to these needs [9], especially in health care settings with limited access to specialized PC. However, many oncologists struggle with manifold constraints including financial resources, education and role function [9], even pronounced in resource- and corruption challenged health care settings [10]. To improve patient care both public and political awareness of unmet needs and daily patient care improvements with pragmatic solutions of integration of oncology and PC [11] are required. The Joint Research Project "Integration of medical oncology and PC procedures in various institutional and economical settings" financed by the Swiss National Foundation as part of the Romanian-Swiss Research Program Partnership pursued these aims (Fig. 1). The key element was the "Reality Map of Integrated-Oncology-and-PC in Romanian and Swiss Cancer Centres", ClinicalTrials.gov Identifier: NCT03237884 (***Figure S-1***).

2. Methods

Ethics committees (EKSG 13/157; IOCN 7305/October 07, 2013) approved for all institutions the protocol (***Supplement B)***, all patients gave informed consent.

2.1. Needs assessment: concepts, unmet needs and of interventions to respond to unmet need

Tackling unmet needs of advanced cancer patients to foster awareness and clinical action requires understanding of needs [12,13] and implementation of needs assessments [14]. A need for healthcare can be defined as a person's ability to benefit from that care and can be assessed in a population using three main different approaches, which have also been specified for PC [15]. The epidemiological approach identifies gaps in provision in a population by contrasting three sources: *size of the need* (estimation from prevalence of diseases or symptoms, cause of death, or residency), *services available locally*, and *effectiveness of services* [16]. The comparative approach simply contrasts the provision of services received by one population with those elsewhere, raising substantial concerns how to compare different health care systems, resources, and cultures [17]. In contrast, the corporative approach engages with the receiving population (patients, family members, multi-professional health care professionals (HCPs)) to establish their needs [18]. In early integrated PC, patient needs are typically fluctuating and individual [19], suggesting this approach most suitable.

Published corporative needs assessments in PC focussed mainly on bio-medical criteria such as performance status, disease or comorbidities or overall access to PC services [18] and were based on HCP- or proxy-information [16]. To assess needs for PCI, however, direct patient data might be needed. Current patient-reported needs assessment tools for individual patients with advanced cancer assess symptoms (e.g. pain, weakness, cough), general problems (e.g. worried about illness, losing independence), and few selected individual interventions [20], but not all domains of PCI [21] are covered. In these tools different assessment approaches are used: a) presence of a symptom or problem (e.g., loss of appetite, life not worth living [22]), b) patient perceived (unmet) need for an intervention (e.g., insufficient information [20], religious or spiritual needs not being met [22], needing more help than family could give [22]), or c), whether a specific intervention took place, mostly only partially based on the need for it (e.g., information giving, addressing practical matters [29], support from a spiritual care provider [23]). These three approaches are most often mixed in existing tools [20,22,24,25].

To decide from an unmet need the appropriate PCI, professional competences, time resources and typically multi-professional team members are required. Therefore, to systematically assess patient unmet need for PCI in health care settings with limited such capacities, a two-steps approach seems needed, assessing first the presence of a specific need, and then whether the specific PCI was delivered [21]. In order to balance inclusivity of domains, time needed, and quality requirements,

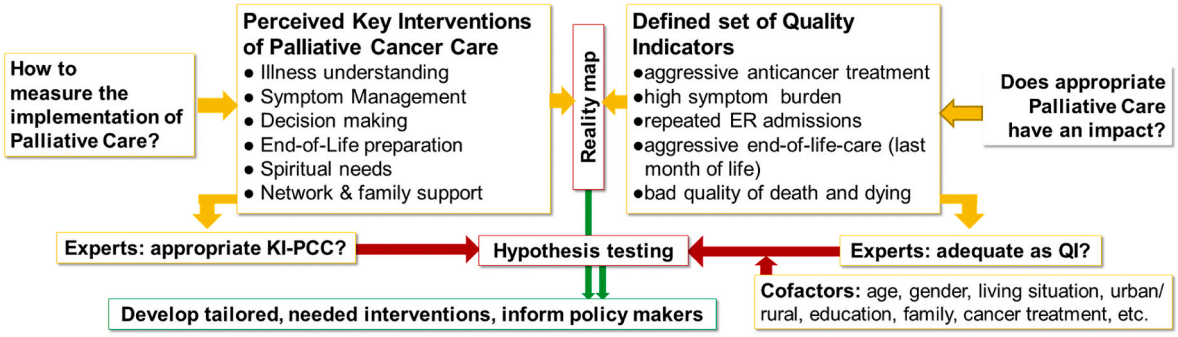

Fig. 1. Project overview.

an approach utilizing HCP interaction with the patient [2,19] might be preferable to a solitary patient-reported tool [26]. Studies reported patients' ability to voice preferences for interventions, however, lacking connection to an unmet need [27]. Patients are able recall delivered PCIs, such as End-of-Life conversations [28] or spiritual care [29].

2.2. Interactive assessment of unmet needs for PCIs and recalled delivery of PCIs

To define the key-PCI for patients with advanced cancer [30,31], we identified randomised controlled trials on early multi-professional PC, extracted isolated PCI, identified for each PCI literature supporting its applicability as isolated intervention and adapted the PCIs to the clinical realities in Romania and Switzerland (Fig. 2, Table S1). The methodology is published elsewhere [32].

For each retrieved Key-PCI the Romanian-Swiss study team decided by in-depth discussions and finally consensual agreements whether the need for the intervention could by assessed directly by a study nurse from the patient after a request (*felt need*) or inferred from patient-reported events, triggers or contexts (*comparative* or *normative need*), according to Bradshaw's taxonomy of needs [33]. The (spontaneously) *expressed need of any kind* [32] was not considered. A question to assess interactively the patients need for a Key-PCI and the recalled delivery of it (to assess whether the need was met, ***Figure S-2***) was then formulated for each Key-PCI (Fig. 3). The reality-map-assessment-tool was formally translated following the POS-guidance [34], followed by cognitive debriefing and pilot testing [32]. To "anchor" the patient cognitively to the time the PCIs are asked about, a question emphasizes the time since diagnosis of stage IV cancer disease (if at baseline) or since the last interview (if at follow-up's). In case the patient is no longer able to answer the PCI questions (e.g. cognitive impairment, emotional burden, frail), and after patients' death, a proxy is answering the adapted questions as surrogate. If no proxy is available, an involved staff member will answer the question. To educate the study nurses and other researchers, senior team members experienced in PC education [35] developed a training manual, applied in a one-day team meeting.

2.3. Quality indicators (QI)

To approach the hypothesis that patients with more unmet needs for PCI (gaps) will experience poorer care, the study assesses systematically QIs from medical charts, doctor's letters and patient dairy. Each QI gets predefined points (based on literature and assigned by the study team) at each month (***Table S-2***).

The QI "*inappropriate anticancer treatment*" (QI-IAT) was defined as futile chemotherapy [36] or aggressive anticancer treatment [37]. Since inappropriateness carries also subjective interpretations, the protocol detailed oncologists' (two clinically experienced medical oncologists not involved in the study) data review to evaluate the appropriateness of the QI-IAT.

To investigate the quality of "*management of symptoms*", overall symptom scores seem not appropriate in our setting because of the heterogeneity of our patients, therefore we use individual symptom threshold on the Integrated PC Outcome Scale (IPOS; 0 = no, 4 = maximal), analogue to the thresholds chosen in the "E-MOSAIC"-trial [38].

The variable "*Emergency Room (ER)-admission in the last month of life*" [39] was adapted for repeated ER admissions. Since ER visits can signify a poor support network, the study team decided not to only measure the ER admissions in the last month of life, but repeated admissions in the whole study period.

The published "*aggressive End-of-Life-Care variables*" (ER-visits, hospitalisations, ICU-admission, cardiopulmonary resuscitation, mechanical ventilation) have been subject of debate but accepted widely [39].

The 17-item "*Quality-of-Dying-and-Death-Questionnaire*" [40]was translated into Romanian and German language and validated (guide for cross-cultural validation [32]), finally cognitive debriefing was performed with the target population resulting in minor adaptions (e.g. new example question, answering option "not applicable", options to terminate life). The practice of contacting the family after death is widely accepted [41], also in eastern European countries [42], but contacting proxies by phone less performed [43]. A small feasibility study confirmed that completing the QODD by phone to be feasible and acceptable. Since there is no official threshold for a "good" or "bad"

7 Key PCI	Need	Recalled Delivery
Addressing Illness and Prognosis Understanding	Do you have all the information you need to understand your illness?	Since the last interview, did one of your hcp actively asked you about your under-standing, and took time to explain you?
Symptom Management	Since the last interview, did you experience one or more distressing symptoms such as pain, tiredness, nausea, lack of appetite, shortness of breath, depression, anxiety, or others?	…, did one of hcp actively engage in their management aiming to improve it?
Support in Decision Making	a) …, were there any changes or new decisions regarding your anticancer treatment? b) …, did you experience severe unpleasant side effects which would have or did require a reconsideration of the treatment?	…, did you have the opportunity to get involved in the decisions concerning your anticancer treatment as you wanted to?
Network Planning	…, was care at home so burdensome and difficult that you would have needed or you got medical or nursing care at home or did you need to go to the ER to get help?	…, did at least one of your hcp provide a care plan including coordination with other hcp?
Family Support	Does your family play an important role in your care?	…, did at least one of your hcp offer support to your family?
End of Life Preparation	…, did you (also) worry that (illness spreading; un-relievable suffering; limited life time; family not prepared to cope; not cared at preferred place; unresolved business; legacy; others)? If yes, would you like to talk about one of these worries?	…, was this need addressed by any of your hcp?
Addressing Spiritual Needs	…, did you have the need to address religious/spiritual aspects / values & meaning in life, inner peace, peace with others/ God?	…, was this satisfactorily addressed by one of your hcp or other professionals?

Fig. 2. Main questions of the interactive Reality Map assessment tool.

Patient perceived Key Interventions Palliative Cancer Care (KI-PCI)

Introduce the questions as follows: *The following questions are posed to all patients for the purpose of this study, regardless of their current illness situation.*

1. Illness understanding
a) Do you have all the information you need to understand your illness?
□**yes** □**no**

b) Tell me in your own words what you understand about your illness and its stage (ask this question regardless how the patient has answered the previous question!):
Don't ask the patient the following question, judge for yourself the patient's understanding of his/her disease:
□***Full understanding***
□***Partial understanding***
□***No understanding***

c) Since the last interview did at least one of your doctors, nurses, or other professionals, actively asked you about it, and took time to explain you?
□**yes** □**no** **I don't know/remember**

d) If yes, what professional(s) and how often?

What professional (physician, nurse..)….. how often?

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2. Symptoms
a) Did you experience one or more distressing symptoms **since the last interview** such as pain, tiredness, nausea, lack of appetite, shortness of breath, depression, anxiety, or others?
□**yes** □**no** **I don't know/remember**

If yes, what was/ were the main symptom(s)?
Symptom 1: .....
Symptom 2: .....
Symptom 3: .....
Symptom 4: .....

b) Since the last interview did at least one of your doctors, nurses, or other professionals, actively engage in their management aiming to improve it (for each of the symptoms)?
Symptom 1: yes/no----if yes, what professional?
Symptom 2: yes/no----if yes, what professional?
…

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3. Decision making
a) Since the last interview were there any changes in the treatment or new decisions regarding the treatment for this illness?

□**yes** □**no** □**I don't know/remember**

b) Since the last interview did you experience severe unpleasant side effects such as fatigue, weakness, nausea, anorexia, stomatitis, diarrhea, neuropathy, skin problems, and infections (febrile neutropenia) which would have required or did require a reconsideration of the treatment?

□**yes** □**no** □**I don't know**

If yes, specify: ..... (quantify according to form "summary of most relevant adverse events adapted from CTC-AE")

c) If yes to **3a)** or **3b)**: did you have the opportunity to get involved in this decision concerning your treatment as you wanted to?
□**yes** □**no** □**I don't know/remember**

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4. Spirituality
a) Since the last interview did you have the need to address religious/spiritual aspects /values and meaning in life, inner peace, peace with others/ God)?
□**yes** □**no** □**I don't know/remember**

b) If yes, was this sufficiently/satisfactorily addressed by at least one of your doctors, nurses, hospital chaplains or other professionals?
□**yes** □**no** □**I don't know/remember**
If yes, who? (doctor, nurse, other professional(s)?)
.....

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5. End-of-life

Fig. 3. Reality map assessment tool

Introduce these questions like this to the patient:
As mentioned at the introduction, we are posing these questions regardless of your current illness situation. Patients with severe illness often worry about certain topics, such as progression of illness and the finiteness of life and so on. First, we will ask you whether you also had some of these worries, later we will ask whether you would like to talk about them with a professional.

a) Since the last interview did you also worry...
- that the illness is spreading?
□**yes** □**no** □**I don't know/remember**

- that you might have suffering that cannot relieved by the health care professionals?
□**yes** □**no** □**I don't know/remember**

- that the life time left is limited?
□**yes** □**no** □**I don't know/remember**

- that the family is not prepared to cope with the situation?
□**yes** □**no** □**I don't know/remember**

- that you won't be cared for in the place you would like to be (eg., at home)?
□**yes** □**no** □**I don't know/remember**

- that there are unresolved business concerning material aspects, legacy?
□**yes** □**no** □**I don't know/ remember**

- others, please mention:

.....

b) if yes to one above: are you a person who would like to talk about at least one of these worries?
□**yes** □**no** □**I don't know/ remember**

c) if yes to b): was this need addressed by any of your doctors, nurses or other professionals since the last interview **?**
□**yes** □**no** □**I don't know/ remember**

If yes, by whom? (doctor, nurse, other professional(s)?)

.....

---

6. Professional and family support
a) Since the last interview was care at home was so burdensome and difficult that you would have needed or you got medical or nursing care at home?
□**yes** □**no** □**I don't know/ remember**

b) Since the last interview did you need to go to the emergency room to get help?
□**yes** □**no** □**I don't know/ remember**

c) If yes to **6a)** or **b), since the last interview** did at least one of your doctors, nurses or other professionals provide a care plan including coordination with other health care service providers or other professionals?
□**yes** □**no** □**I don't know/remember**

If yes, who (doctor, nurse, or other professionals)?
.....

d) Does your family play an important role in your care?
□**yes** □**no** □**not applicable**

e) If yes to **d)** did at least one of your doctors, nurses or other professionals offer support to your family **since the last interview**?
□**yes** □**no** □**I don't know/remember**

If yes, who? (doctor, nurse, other professional(s)?)

.....

Fig. 3. (*continued*).

death, the protocol foresaw an expert judgment (Case Report Form [CRF] review through 3 independently reviewing professionals, ≥1 from Romania and Switzerland).

2.4. Study population and cofactors

From institution-specific defined population (e.g. all outpatients of one day) all patients were screened for main inclusion criteria (Stage IV cancer disease, ≥18 years old, ECOG-performance status 1–3, prognosis ≥1 month [treating physician estimation], no cognitive impairment), eligible patients with minimal symptom burden (≥3 items of IPOS ≥2) were informed about the study. In case of high patient load, a random selection was applied. A screening log was mandatory to detect selection bias.

Known cofactors potentially influencing the interventions or the outcomes (e.g. age, gender, living situation, education, income, treatment strategy, comorbidities, ECOG, Cachexia, place-of-care, type-of-care, place-of-residence, institution, country, survival status) were

extracted from the literature and institutional focus groups were planned to discover additional cofactors. After thematic content analysis the whole study group decided about CRF-inclusion. (***Table S-3***).

2.5. Trial design and study flow

The reality-map was a prospective, multicenter data collection. Included patients were assessed monthly for 6 months or until death, what comes first, including a post-death follow-up (six to twelve weeks after death) with the bereaved proxies (***Figure S-1***).

2.6. Data collection

Characteristics of each participating institution included number, type and education of staff involved in the care of advanced cancer patients, advanced cancer patient population (e.g. main disease types), available infrastructure (ICU, ER), typical admission and discharge procedures. Every clinic provided the individually determined screening procedure (e.g. in what clinics patients were screened, how they were approached, etc.). The screening log includes reasons for not handing out the IPOS to otherwise eligible patients, patients not completing the IPOS, not informing eligible patients about the study and patients not consenting.

The data collection from patients was entered in paper versions of Case Report Forms (***Supplement B)*** and included a slightly adapted EAPC Basic dataset [44] (demographics: age, gender, marital status, residence, etc.; medical data: type and stage of cancer, comorbidities, current medications, etc.), ECOG, the novel IPOS [24] (translation for the study applying the POS-Guidance [32], without formal validation studies), EQ (5D) (health-related-QoL: mobility, self-care, everyday activity, pain, anxiety, depression; http://www.euroqol.org/), the novel "Interactive assessment of unmet needs for PCIs and recalled delivery of PCIs" *("Reality map assessment tool", see 1.3. and* Fig. 3*),* Quality Indicators *(see 1.4., and* ***Table S-2****),* and specific medical data ("epicrisis" for external review of patient eligibility and QIs).

2.7. Study procedures

The study personnel were required to separate their role as clinicians from acting as researcher. First, the patient was screened for cognitive impairment by the Single Question in Delirium (SQID) [45] or short-mini-mental state exam (MMSE) [46]. In case of cognitive impairment, emotional burden or other reasons, proxies or staff completed the assessments (using adapted tools). The assessments were performed stepwise, first demographic data and assessments (EAPC data set, IPOS, EQ (5D)), second the interactive unmet need for PCI assessment and third specific treatment history.

To minimize drop-outs in a heterogeneous environment with infrastructural challenges (e.g., no phone), a defined tracking procedure was applied.

Paper questionnaire data were entered in the e-CRF (*secuTrial*®) within 1 month after the interview. Medical documents relevant for QI were uploaded in the eCRF.

2.8. Study quality assurance and monitoring

Study procedure training occurred in a whole team meeting in Romania. Local principal investigators were primarily responsible for correct study procedures. The scientifically leading swiss team performed at study start randomly eligibility criteria and QI monitoring involving a Romanian speaking researcher. With weekly phone calls involving the whole study team, observing *secuTrial*® data and screening logs, monitoring of data entry and surveillance of study procedures was assured. Source date verification was randomly performed (visit of swiss PI in Romania).

Consortium payments were linked to defined deliverables and payed quarterly.

2.9. Objectives, data analysis and statistical plan

The study pursued two objectives: a) to test the hypothesis that need-based PCIs predict quality of care defined by QIs, b) to map unmet needs for PCIs in a well characterized patient population.

For hypothesis testing the dependent variable was the composite score of all QIs (0-23), either per time point or as median score of all collected composite scores. The independent variable was the median of appropriate, needs-based PCIs. The cofactor analysis was amended by survival status (QIs aggressive EOL Care, QODD.

Since the definitions of PCIs and QIs may considerably depend on the setting, likewise the interpretation of retrieved results (variable definitions of terms [e.g. ICU], setting-specific cofactors) international experts' data review was planned to propose whether a) the data were reliable to use them as a reality map for Romania, b) there are undefined or skewed cofactors and c) the hypothesis could be tested as planned.

The primary statistical analysis foresaw multiple linear regression to compare the number of appropriate PCIs to the composite endpoint score (mean of all follow-ups), adjusted for cofactors, amended by stepwise regression and linear mixed models. All collected information was summarized in tables and comparisons tested (McNemar's test).

Patients were evaluable if they complete baseline and $\geq$ one follow-up. For missing data and drop-outs sensitivity analysis elucidates their impacts on outcomes, possibly mandating a missing data strategy (mean horizontal imputation, last-value-carried-forward).

For sample size we estimated that with 24 variables included in regression models ($\geq$10 observations/variable needed [47]), 240 evaluable patients are needed, corrected for 20 % drop-outs, 300 patients. An interim analysis was foreseen after 100 patients.

3. Results

The kick-off meeting March 2013 (Cluj) served to present institutions, the project background and the planned prospective, multicentre data collection.

3.1. Protocol development for the reality map

While judged by the study team as a clear project, open issues included a) paper versus e-CRF, b) duration of follow-up, c) inclusion of patients experience of PCIs, d) inclusion of family members in the data collection, e) investigation of barriers to deliver appropriate PCIs, f) feasibility of post-death interviews in Romanian culture, g) measurement of economic burden of family members, h) invasive diagnostic/therapeutic interventions as QI, and i) regulatory and financial issues in Romania. Four group phone conferences were then performed for discussion of work packages according to personal interests of investigators [e.g. FACIT-TS-PS, education, lung cancer, pain, communication, care plan]). The study investigator meeting May 2013 (Brasov) served to detail PCIs, discuss several proposals (ESMO handbook for patients, definition of ER admission, assessment tools [ECS-CP, HADS, FACIT]), and resulted finally in a mutual consensus on the study protocol, perceived as feasible to conduct both in Romania and Switzerland and meaningful to reach the goals.

3.2. Study material, CRF, instruction of study procedures to study personnel

In 11 phone conferences the final Study materials were developed and instructed (Study Procedures Manual: ***Supplement B)*** in the next study team two-day meeting October 2013 (Sibiu). The team members expressed both confidence in the procedures and enthusiasm to perform the data collection. No formal research knowledge and skills examination were performed and no prior research experience and education

was requested to become a team member, this quality assurance was the responsibility of the local principal investigators.

3.3. Accrual and monitoring

Study start (first patient in) was first in Cluj (November 11, 2013) followed in January 2014 for Alba, Brasov, Bucarest and Iasi and April 1, 2014 in St. Gallen. To discuss accrual, study procedures and challenges (group phone calls) and to perform remote study monitoring (individual institution) 14 Phone conferences took place until the Study team meeting including international experts 6.2014 (EAPC congress).

The screening procedure revealed variability among institutions regarding percentages of screened patients being eligible (min 56 %, max 98 %; 23 %), IPOS given (83 %/100 %; 32 %), IPOS criteria ok (63 %/100 %; 56 %), refused (0 %/54 %; 52 %) or consented (53 %/98 %; 38 %) in Romanian Institutions (n = 5) and Switzerland (n = 1), respectively.

In two institutions with very high "IPOS critera ok" (98 %, 100 %) and low "refusal" (0 %, 8 %) the clinicians recruited their own patients, in contrast to two larger institutions with high "IPOS critera ok" (85 %, 88 %) but moderate consent rates (53 %, 69 %). Switzerland had far lower eligibility and "IPOS criteria ok" rates, screened more patients (n = 1516) compared to Romania (mean n = 133) and had only 38 % consent rates (main reasons: autonomic decision, not reachable, too symptomatic).

The study protocol foresaw monthly follow-ups of the 304 patients for 6 months, for patients still alive, at follow-up 1–6, respectively, 100 %, 83 %, 72 %, 64 %, 58 %, and 50 % were seen. 108 patients (36 %) had post-death interviews.

After the individual monitoring and group phone calls action points were agreed upon (***Supplement Table S-4:*** *Protocol vs Actual Reality-Summary Action points*) to improve adherence to the protocol.

Then an independent senior expert in PC research reviewed the data file in July 2014 and provided a written report, describing missing data and inconsistencies. Key points included misunderstanding (PCI decision making referring only to toxicity of anticancer treatments) or poor formulated (PCI family support: asked importance of family, not need for family support) of questions, leading to high missing data or cealing effects. Poor documentation of anticancer treatment was noted (documentation of response or ECOG missing, high G3 non-hematological toxicity). The QI ER and CPR last months showed very low numbers. In contrast, IPOS data showed no missing values. In the QoDD (17 items) a lot of "don't know" (mean 4.9 times) or "no response" (1.6 times) answers occurred, a common problem (http://www.dyingwell.org/downloads/JPSM02.pdf).

In 6 further group phone calls these issues were communicated but other issues arised; some study team members reacted to monitoring request on data clarification with entering the questioned not the real (source) data in the e-CRF, which required individual mentoring of data entry and controlling of source data of each institution by the PI.

3.4. Modification of the study protocol

To proceed from the grant application to the reality-map protocol the experience, opinions and preferences of the Romanian study team were consensual implemented (***Supplement Table S-5:*** Grant *vs Protocol)*. A conscious step requiring time, patience and understanding, but enabling personal involvement, enthusiasm and personal skills and knowledge development, and also assuring the protocol was adapted to the local and national needs.

The study group decided (11.2014, Iasi) not to invest substantial resources in correcting these issues (see 2.3), but to proceed to an implementation project building on the clinical relevant protocol procedures.

3.5. Identified gaps at baseline and first follow-up

From Romania 262 patients (5 institutions) were included, from Switzerland 46 patients (one institution): Age 62 years [mean, 27–88], female 46 %, residence rural 36 % (urban 64 %), living alone 18 %, education university 44 %, ECOG PS 1&2 74 %, inpatients 56 %, current anticancer treatment 81 %, various cancer types (GI 24 %, lung 22 %, urogenital/breast 16 %, other 37 %). Main gaps were in symptom management, spiritual needs, and family support (Fig. 4), their clinical meaningfulness was confirmed in institutional focus groups. Binary logistic regression revealed an association of the number of gaps (0–6) with depression ($p = 0.008$), not with other symptoms (Fig. 5). The gap number was non significantly ($p = 0.22$) higher in Romanian vs Swiss patients (OR 1.87 [CI 0.80–4.37]). Grade 3/4 non-hematological toxicity of anticancer treatment (27 %) was not significantly ($p = 0.135$) associated with high gap burden. Other Quality Indicators (***Table S-2***) were not analysed for missing data/low incidence (CPR: 1, ICU admission: 3, QoDD 101).

3.6. Institutional care pathway checklist (CPW-CL) feasibility study

Each institution performed multidisciplinary focus-groups discussing the local results, and how to address the unmet needs with a local CPW-CL. Content analysis of written protocols served as data extraction. The group agreed on six screening questions for each key-PCI. Due to the institutional, cultural and personal diversity of the consortium institutions, local solutions were pursued for the weekly CPW-CL intervention. One institution used specific algorithms (sheet), two institution an own document (booklet) and two institutions mixed forms. The five Romanian centres enrolled 81 patients in the prospective 2-week multicenter feasibility. Preliminary outcomes revealed significant improvements (ESAS). Twenty individual and group phone conference supported the process until 11.2015 (Bucharest).

3.7. Dissemination of results and closure of the project

The national symposium *"Integration of PC Interventions into Routine Oncology Care"*, Institute of Oncology Bucharest, November 20, 2015 discussed key findings of the project with oncology leaders.

At EAPC ten and at ESMO two presentation were held (**Supplement Table S-6).**

Until final closure 5.2016, five phone conferences emphasized administrative issues, institutional implementation of results, and academic publications. One workshop with academic leaders (Bucharest) pursued academic development, but without resulting publications, unfortunately.

The final meeting of the Romanian-Swiss Research Programme 5.2016 emphasized future challenges for scientific research in Romania and international collaboration.

Six years later (2022), a ministerial order regulates PC in the country, the key-PCI are mandatory for doctors in the national rural care model, and QoDD is used. The National Cancer Plan includes PC (Chapter 7), PC is compulsory for doctors and nurses in university education, and academic PC is growing (local project leaders proceeded to academic positions [Brasov, Iasi]). In (only) one cancer center specific chceklists for PC (referral to institutional mobile team PC, pain assessment, terminal care protocol) are applied and PC is included in institutional care pathways.

4. Discussion

This project aimed to foster integration of PC in routine cancer care [48] in a country, Romania, with minimal available PC services in oncology institutions, by first reveal the unmet needs focusing on patient-perceived unmet needs for key-PCIs, then apply tailored interventions. This approach was customized to the heterogeneity of the

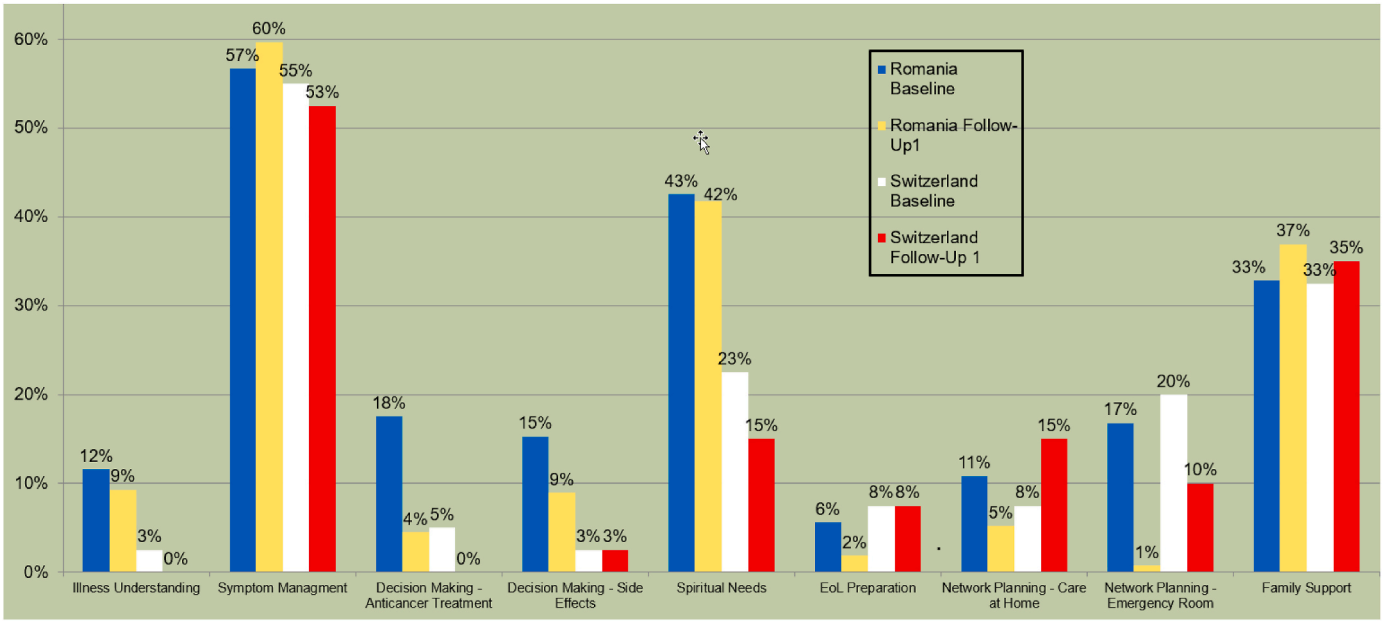
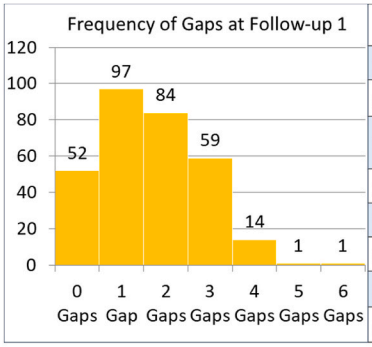


Fig. 4. Romanian and Swiss patients' gaps in patient-perceived needs for and delivery by HCPs of key interventions palliative cancer care at baseline and one month later.



Symptom	high burden	X^2 df	n	Test statistic	Significance
pain	IPOS ≥3 (n=66)	1	305	3.472	p=.062
shortness of breath	IPOS ≥3 (n=29)	1	304	1.661	p=.198
weakness/lack of energy	IPOS ≥4 (n=31)	1	305	2.208	p=.137
nausea	IPOS ≥3 (n=21)	1	306	0.949	p=.330
poor appetite	IPOS ≥4 (n=20)	-	306	*	p=.592
drowsiness	IPOS ≥4 (n= 5)	-	306	*	p=1.000
anxiety	IPOS ≥3 (n=94)	1	307	3.026	p=.082
depression	IPOS ≥3 (n=48)	1	307	7.077	p=.008

***2-sided Fisher's exact test due to small cell count**

Fig. 5. Associations of high gap burden and high symptom burden
*2-sided Fisher's exact test due to small cell count.

Romanian care setting, a paradigmatic example of non-north-american or UK settings where most research on integration of oncology and PC has been conducted [49]. The reality-map could not assess unmet access to PC programs (structure) [50], but succesfully identify gaps (at baseline and first follow-up) on patient reception of components of PC, the key-PCI,[51] which can be delivered by PC professionals or also by oncology clinicians [30,52,53].

From a pragmatic, clinical, awareness, personal development and political viewpoint the project achieved at least partly its aims. From an academic and sustainability viewpoint, however, the project failed to deliver reliable scientific data and achieve an evidenced-based sustainable implementation of PC in all Romanian oncological institutions.

A key lesson to learn is to *balance* PC-enthusiasm, over-ambitious aims, flexible adaptation of research procedures to optimise cultural acceptability, keep flow and motivation *with* enforcement of academic quality standards, focus on essential, deliverable, and modest goals and stringent stakeholder involvement (oncology leaders). To balance means to strengthen both scale pans, and for this project, to ask "what would we do different next time?"

- Keep enthusiasm ("Nothing great was ever achieved without enthusiasm" [Ralph W Emerson]) and cultural acceptability but ennoble it through focusing on few selected deliverables: cross-sectional (no follow-ups) reality-map of unmet needs for key-PCI and sustainable (not only feasibility GPW-CL) interventions.
- Ensure in a bi-national project, that both main leaders provide project-specific key competences: double boarded oncology-PC [54].
- Test newly developed interactive clinician-patient instruments more formally (without sophisticated psychometric testing) to reduce ceiling effects or missing data.
- Assess research competences of all team members [55] and provide tailored education (e.g. mandatory research competence training for local PIs) or competence-based study procedure assignments (e.g. required compepencies for data entry in *secuTrial*®.

5. Conclusion

The structured assessment of patients needs for a PCI, including illness understanding, symptom management, decision making, family support and end-of-life care, and patients perceived reception of the specific PCI, can successfully applied in clinical care and foster

institutional awareness of delivery gaps of PCIs, leading to local intitatives and foster national standards. However, systematic collection of medical chart-based quality indicators would require overwhelming ressources.

Despite all limitations, the Swiss-Romanian-Partnership fostered competences in PC, stimulated academic PC and leveraged the implementation of PC in national health policy.

CRediT authorship contribution statement

Kalbermatten Natalie: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Curca Razvan:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Grigorescu Alexandru:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Mosoiu Daniela:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Pop Florina:** Writing – review & editing, Methodology, Investigation. **Poroch Vladimir:** Writing – review & editing, Methodology, Investigation. **Rosiu Ariana:** Writing – review & editing, Methodology, Investigation. **Achimas-Cadariu Patriciu:** Writing – review & editing, Project administration, Investigation, Funding acquisition. **Strasser Florian:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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