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FINAL CLINICAL STUDY ANALYSIS

eCAN

Strengthening eHealth for Cancer Prevention & Care

DELIVERABLE 5.3

Outline

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1. Introduction

1.1. Summary of the pilots

The eCAN JA explores the role of eHealth interventions in three clinical trials focusing on tele- rehabilitation and tele-psychological support in different populations of cancer patients in 10 European Union (EU) Member States. Patients' data, i.e. Patient Reported Outcomes Measures (PROMs) and Patient Reported Experience Measures (PREMs) will be monitored by a dedicated telemonitoring system. Pilot projects will assess the potential for wider implementation of the piloted telemedicine solutions including teleconsultation and telemonitoring program. The main aim of the pilots is to assess the effect of the eCAN telemedicine program on PROMs. Apart from the evaluation of clinical benefits (i.e. effectiveness) of the interventions the project aims to assess the PREMs with patients' satisfaction, i.e. the perceived usefulness of the piloted solutions and the usability of teleconsultation and telemonitoring solutions implemented in clinical settings. The outcomes of the project may give insights into an equitable roll-out of telemedicine services across Europe.

1.2 Design of the study

The pilot projects were multicentric, prospective, randomized, open label trials among patients affected by breast cancer (BC) (Pilot 1a), head and neck (H&N) cancer (Pilot 1b) and any type of advanced cancer (Pilot 2). These trials were designed to enroll about 350 patients across 18 European cancer centers. Patients were randomly assigned either to the intervention group or to the control group using a 1:1 ratio.

In the intervention group, PROMs have been monitored by a dedicated telemonitoring system. They received weekly teleconsultation for 8 consecutive weeks: tele-rehabilitation training in Pilot 1a/b and tele-psychological support in Pilot 2. Data on health-related quality of life (HRQoL), pain and distress levels have been collected longitudinally from patients manually via a dedicated App (eCAN App) operating on patients' smartphone. Patients in the control group did not perform teleconsultation sessions and received usual care performed by their clinical centers. They also did not have access to the eCAN App. PROMs data have been collected at the beginning and at the end of the study.

2. Methods

2.1. Aim of the pilots

The main objectives of the pilots were:

1. To assess the effect of teleconsultation and telemonitoring services focused on rehabilitation of patients with BC (Pilot 1a) and H&N (Pilot 1b) cancer, based on their PROs (HRQoL and pain) compared to usual care.
2. To assess the effect of teleconsultation and telemonitoring services focused on psychological support for patients with advanced cancer (Pilot 2), based on their PROs (HRQoL and distress) compared to usual care.

2.2 Primary and secondary outcomes

The primary end point is the HRQoL measured with the questionnaire EORTC QLQ-C30. The EORTC QLQ-C30 [1] is a HRQoL measure specifically designed for cancer patients. It consists of 30 items which form functional scales, a global health status/ HRQoL scale, and symptoms scales (including financial difficulty). Scores of all scales and single-item measures range from 0 to 100. For the functioning scales and global HRQoL scales, higher scores indicate better functioning; for the symptom scales, higher scores indicate higher symptom burden.

The secondary end points, in the pilot 1a/b, is the pain level measured with a Pain Visual Analogical Scale (VAS). Pain VAS is a unidimensional measure of pain intensity, used to record patients' pain progression. The simplest VAS is a straight horizontal line of fixed length, usually 100 mm. The ends are defined as the extreme limits of the parameter to be measured (orientated from the left (0 the worst) to the right (100 the best). In the area of cancer pain assessment, Pain VAS score is the most common measure for pain intensity.

The secondary end points, in pilot 2, is the distress level measured by the Distress Thermometer. This tool is a single-item tool using a 0 (no distress) to 10 (extreme distress) point Likert scale resembling a thermometer. The patient rates his/her level of distress over the past week. The established cutoff score is 4.

2.3 Hypotheses

The hypothesis of the pilot 1a and 1b is that patients in the tele-rehabilitation intervention group, receiving distant monitoring of PROMs, will report better HRQoL and less pain compared to the control group.

The hypothesis of the pilot 2 is that patients in the tele psycho-oncology support group, receiving distant monitoring of PROMs-measures, will perceive better HRQoL and less distress compared to the control group.

2.4 Sample size

PILOT 1A-1B

For the sample size calculation, we based our hypothesis on the mean score, and the relative standard deviation (SD), of quality of life in general population. According to Nolte et al (2019) [2] and to our clinical experience we hypothesized:

- A HRQoL mean score equal to 66.1 out of 100 in the control group;
- An increase on 12 points in terms of mean score (SD), that is 78.1, in the group that will receive the telemedicine program;
- A standard deviation of 21.7 in both groups

Considering an effect size equal to 0.55, with an expected increase of HRQoL score of 12 points, a percentage of lost to follow-up equal to 10%, the Student's T-test, at the significance level of 5% with a statistical power of 80%, will let to randomize a total sample of 236 patients, 118 patients (59 vs 59) in Pilot 1a, and 118 patients (59 vs 59) in Pilot 1 b as follow:

- Intervention arm group: 59 patients affected by newly diagnosed BC (Pilot 1-a) and 59 patients affected by newly diagnosed H&N cancer (Pilot 1-b) after surgical treatment will be enrolled in the program of rehabilitation teleconsultation.
- Control arm group: 59 patients affected by newly diagnosed BC (Pilot 1-a), and 59 patients affected by H&N cancer (Pilot 1-b) after surgical treatment will receive usual care (no teleconsultation intervention).

In each pilot we estimated that each center should randomized about 13 patients.

PILOT 2

For the sample size calculation, we based our hypothesis on the mean score, and the relative standard deviation (SD), of HRQoL. According to Nolte et al (2019) [2] and to our clinical experience, we hypothesized:

- A HRQoL mean score equal to 66.1 out of 100 in the control group;
- An increase on 12 points in terms of mean score (SD), that is 78.1, in the group that will receive the telemedicine program;
- A standard deviation of 21.7 in both groups.

Considering an effect size equal to 0.55, with an expected increase of HRQoL score of 12 points and a percentage of lost to follow-up equal to 10%, the Student's T-test, at the significance level of 5% with a statistical power of 80%, will let to randomize a total sample of 118 patients (59 vs 59) in Pilot 2 as follow:

- Intervention arm group: 59 patients affected by advanced/recurrent cancer (including lung, prostate, colorectal, breast cancer) will be enrolled in the program of psychological teleconsultation.
- Control arm group: 59 patients affected by advanced/recurrent cancer will receive usual care (no teleconsultation intervention).

We estimated that each center should randomized about 12 patients.

2.5 Randomisation

We centrally randomized patients based on minimization approach. Minimization is a randomization method that ensures balance of important prognosis factors between treatment groups without the weakness of stratification. Minimization, a form of restricted randomization, is considered to be a dynamic method, since the randomization list in not produced before the trial starts, but during participant recruitment. Participant allocation was automatically balanced according to the following factors: Geographic Area; Gender and Age. Potential patients were identified during medical consultations at participating pilot centers. After determining whether patients meet the inclusion criteria, randomization was centralized on a cloud platform, that is REDCap®. Due to the nature of the intervention, it is not possible to blind patients or clinicians involved in the trial. Outcome assessment was analyzed centrally, using data collected by each center.

Pilot 1a - randomisation scheme

- Geographic Area (North / Central / South Europe)
- Gender (Female)
- Age (45-55 years, 55-65 years)

Pilot 1b - randomization scheme

- Geographic Area (North / Central / South Europe)
- Gender (Male, Female)
- Age (≤51 years, >51 years)

Pilot 2 - randomization scheme

- Geographic Area (North / Central / South Europe)
- Gender (Male, Female)
- Age (≤51 years, >51 years).

2.6 Data collection

Patient characteristics (age, education, marital status, type of work, living arrangement, household size, residence place, travel time to hospital, experience with teleconsultation, experience with health or monitoring applications, experience with monitoring devices, country and centre of enrolment, sleep quality and physical activity) and clinical data (type of cancer, date of diagnosis, date of surgery, type of surgery, type of treatment, comorbidities, Charlson Comorbidity Index (CCI), ECOG PS, severity of symptoms, questionnaire EORTC QLQ-C30, VAS for pain, distress level and physical activity) were collected at study entry using a case report form (eCRF) by the health care provider. All the data were anonymized and saved in a secure, web-based application designed to support data capture for research studies Data about HRQoL and pain/distress were monitored during the pilot using the eCAN App.

Types of data	Recorded by	Recorded @ (home/clinic)	Recording frequency	Collection method	Type
Intervention group					
eCRF	Clinician	Clinic	At baseline visit (Week 0)	eCAN web platform/ dashboard	Predefined set of data

HRQoL	Patient	Home	Every two weeks (Week 0,2,5,8)	eCAN app	Scored questionnaire
Pain/distress	Patient	Home	Weekly (Week 0,1,2,3,4,5,6,7,8)	eCAN app	Scale selection
Control group					
eCRF	Clinician	Clinic	At baseline visit (Week 0)	eCAN web platform/ dashboard	Predefined set of data
HRQoL	Patient	Home/clinic	At baseline and at the end of the study (Week 0, 8)	eCAN web platform/ dashboard	Scored questionnaire
Pain/distress	Patient	Home/clinic	At baseline and at the end of the study (Week 0, 8)	eCAN web platform/ dashboard	Scale selection

Table 1. Data collection scheme

2.7 Statistical analysis

Statistical analysis was carried out with SPSS v.29.1 on the v.11 of eCAN Database extracted on the 1st of August 2024. Descriptive statistics of all variables of interest of the included patients were presented. Categorical variables were reported with frequencies and percentage values while continuous variables were presented with median values and first and third quartile. The comparisons have been performed with the non-parametric Mann-Whitney test (comparisons between independent groups at the same time-point) or Friedman non parametric test (comparisons between dependent data) in the same group, intervention or control arm, across the eight weeks. Chi-square non parametric test, or Fisher exact test, when appropriate, was applied to compare the two arms in terms of missing data. A p-value < 0.05 has been considered statically significant. Data from EORTC QLQ-30 were standardized according to formulas presented in the scoring manual. [3]

2.8 Data management

2.8.1 Data cleaning

The analysis of the data in database version 11 was preceded by a data cleaning phase. Specifically, the initial number of 279 patients reported in the database underwent the following correction:

A total of 28 patients were excluded from the pilot phase due to the following reasons:

- 9 cases have been excluded because were entered in the randomization platform as testand were not corresponding to real patients.
- 3 patients have been excluded due to non-compliance with the protocol. These patients were in pilot 2 and they did not meet the inclusion criteria of this pilot (different cancerhistology respect to that required in the inclusion criteria).
- 16 patients have been excluded because they were not compliant with the randomization process reported in the pilot protocol (although they were still used for the PREM analysis). These patients were randomized on a platform different from the one designated for the project.

Additionally, the following adjustments were made:

- 1 patient has been incorrectly reported as part of pilot 1a has been moved to pilot 2.
- 2 patients incorrectly reported in the control group have been moved to the intervention group
- 4 patients incorrectly reported in the intervention group have been moved to the controlgroup.

The results of the data cleaning process were as follows:

A total of 251 patients have been enrolled:

- Pilot 1a: 107 patients (50 in the intervention group and 57 in the control group);
- Pilot 1b: 40 patients (18 in the intervention group and 22 in the control group);
- Pilot 2: 104 patients (54 in the intervention group and 50 in the control group).

2.8.2 Data preparation, manipulation and standardisation

After receiving the final version of the database (v.11) in an Excel format, we processed each field to enable proper import into SPSS v.29.0.1 software. Upon correctly importing the database into SPSS we began the process of raw data manipulation in order to create the final variables to analyse:

1. Convert strings into scales
2. Convert strings into ordinal variables
3. Add appropriate labels
4. Standardize EORTC-30 raw data following the technique showed into the EORTC QLQ-C30 Scoring Procedures Manual [3]. We finally obtained the Global Health status (QoL), five functional scales (Physical, role, emotional, cognitive and social) and

nine items related to symptoms scales (Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).

3. Final analysis report

3.1 Pilot conduction and data collection: issues and mitigation strategies implemented

The three clinical trials conducted during the eCAN project aimed to assess the effect of telemedicine in various oncology centres across Europe. The conduction of the study proved to be complex due to the involvement of 18 oncology centres across 10 European countries. This highlighted a heterogeneous level of experience in telemedicine and in the management of clinical trials among the various centres involved, which had implications for both the management of the pilots and the approach to telemedicine activities.

The final results were preceded by a detailed identification, analysis, and resolution of certain critical aspects that emerged during the conduction of the pilots. The issues addressed are following reported:

1. Administrative issues: the approval of the pilot protocol by the different ethic committees of each various centre was a crucial juncture for the start of the study. Unfortunately, the approval timelines were very uneven across centres. This caused delays in the full activation of all the centres involved in the project, leading to a subsequent delay in patients' recruitment. Furthermore, the significant variability in the interpretation of GDPR rules by the data protection office of each centre led to the non- activation of 2 centres. This negatively affected the patient enrolment capacity in the study.
2. Clinical cancer centres issues: the high degree of heterogeneity in telemedicine expertise across the different oncology centres involved in the study was another factor that negatively impacted the conduction of the pilots. A large percentage of the centres involved had never had experience with telemedicine activities, while only a small percentage had used telemedicine before. Additionally, almost all the centres did not have their own telemedicine platform. Therefore, to promote standardized use of telemedicine services, it was decided to adopt a single, open source, telemedicine platform (EDUMEET) for all centres. This mitigation strategy required unexpected

activity of platform hosting and vulnerability assessment. Moreover, the utilization of EDUMEET platform required a dedicated training activity for research teams.

3. Pilot protocol issues: The main issue is associated with the Pilot 1b protocol (head & neck cancer). The overly strict inclusion criteria resulted in the enrolment of very few patients, which negatively affected the final data analysis in this pilot.
4. Patient issues: in general, the patients enrolled in the pilots showed a fairly high level of compliance with the project. However, it is important to note that the duration of the treatment (8 weeks) and the excessive burden of questionnaires compilation led, in some cases, to lower patient engagement and a reduced rate of completed questionnaires.
5. In the annex 1 and 2 are reported the number and the reasons of the patient's refusal or dropping out of the study.
6. Research team issues: the level of experience of the research teams from each country involved in the project was a factor that inevitably influenced the starting and conduction of the pilots. The lack of experience in managing clinical trials among some of the teams involved certainly caused a delay in the patient enrolment plan initially envisioned. Moreover, the quality of monitoring and data collection was also affected, as in some cases there was not proper management of the enrolled patients in both the intervention and control groups.
7. In the annex 3 are reported all the clinical questions received by WP5 from each centre involved in the study.
8. Technical issues: during the conduction of the pilots, some technical issues also emerged that negatively affected the monitoring and data collection from patients. The main ones are related to the eCAN app: the app screen size did not fit with the smartphone screen size, the patients were not able to submit VAS pain scale or distress thermometer on the app, in some cases the app week calculation was not aligned with the real weeks. Some errors have also been found in the control group dashboard during the filling out of the questionnaires. Equally important were the technical issues related to the extraction of the final data from the central database. The firsts database extractions did not include all the data collected in the app and in the dashboard control group and this led in a delay of the final analysis.

To face all these issues a series of mitigation strategies have been implemented:

1. Administrative issues: to speed up and standardize the ethics committee approval process in the 18 oncology centers involved, we, as the IFO-IRE center and coordinator

of WP5, having obtained approval from our ethics committee right away, immediately shared the approval document with each center to facilitate the approval process by other ethics committees. In addition, we provided continuous support to the various centers to constantly monitor the approval status.

2. Clinical cancer centers issues: the standardization of knowledge on telemedicine was achieved through continuous and fruitful training activities offered from the joint action of different WPs (2-3-5-6-7-8) to all the centers involved. Additionally, choosing a single platform to provide telemedicine services (EDUMEET) allowed for uniform training and cybersecurity activities. This ensured a widespread correct use of the platform and secure data transmission.
3. Pilot protocol issues: unfortunately, it was not possible to mitigate this issue, but, as WP5 coordinator team, we decided to enroll as many patients as possible in pilot 1b and to focus our patient recruitment efforts on the remaining two pilots (1a and 2).
4. Patient issues: as WP5 coordinator team, we organized 1 to 1 meeting with each center involved in the project trying to find the best solution to increase patients' enrollment and compliance. These latter need to be constantly and gently pushed to fill out the questionnaires.
5. Research team issues: To standardize the level of experience in the clinical approach of the research teams involved 3 training sessions were conducted before the starting of the pilots and 2 meetings were held during the conduction of the pilots. This allowed for uniform preparation of the staff in the centers involved and for monitor and potentially resolve any issues during the conduction of the pilots.
6. Technical issues: the technological issues have been fixed thanks to the continuous anddirect contact with WP7 and to the data collection on paper in place of the digital data. The database extraction issue has been fixed thanks to the continuous coordination withWP7 in order to evaluate the best database extraction possible (the final analysis has been conducted on the database extraction V.11). However, in general, there was a continuously active helpdesk (coordinated by WP7) which answered to any kind of technical request.

3.2 Results

3.2.1 Analysis of missing data

Missing data may be classified as either missing items (one or more missing answers to questions within the questionnaire), or missing forms (the whole questionnaire is missing for a

patient). The strategy proposed by the EORTC QLQ-C30 Scoring Procedures Manual to retrieve as much information as possible is the following:

If at least half of the items from scale have been answered assume that the missing items have values equal to the average of those items which are present for that respondent. The missing items are simply ignored when making the calculations Using this method, none of the single- item measures can be imputed, such as the majority of the symptom items. After ending the process, we recovered data for a total of 35 patients out of 251 for specific PROMs items. In particular: 14 in Pilot 1 a, 6 in Pilot 1 b and 15 in Pilot 2.

	Week0	Week 2	Week5	Week 8
	N° case recovered	N° case recovered	N° case recovered	N° case recovered
Functional Scale				
Qol-Global	3	3	1	1
Physical	0	0	0	0
Role	0	1	0	0
Emotional	6	1	0	3
Cognitive	2	0	0	4
Social	2	0	0	2
Symptoms scales				
Fatigue	6	1	0	3
Nausea	3	1	0	0
Pain QoL	7	1	1	2
Dyspnoea	Not applicable**	Not applicable**	Not applicable**	Not applicable**
Insomnia	Not applicable**	Not applicable**	Not applicable**	Not applicable**
Appetite loss	Not applicable**	Not applicable**	Not applicable**	Not applicable**
Constipation	Not applicable**	Not applicable**	Not applicable**	Not applicable**
Diarrhoea	Not applicable**	Not applicable**	Not applicable**	Not applicable**
Financial Difficulties	Not applicable**	Not applicable**	Not applicable**	Not applicable**

Table 2. Patients with refillable missing values

* The sum is greater than 35 because one patient may present more than one field missing and was counted more than once

** These items are single-term measure

In Figure 1, 2 and 3 we reported the number of missing questionnaires during the study period for the principal outcome of interest at baseline (week 0) and at the end of the study

(week 8) by Pilot. Patients in the control group seemed to be less compliant than patients who received the intervention of telemedicine. We can interpret these results by hypothesizing that we gave a very big commitment in terms of questionnaires to be filled out by patients who already have a high disease burden. In general, less compliant patients had a median age of 52 years and a secondary level of education.

	QoL Week 0		
Panel A	Data present	Missing	Total
Intervention	47	3	50
Control	49	9	58
Total	96	12	108

	QoL Week 8		
Panel B	Data present	Missing	Total
Intervention	40	10	50
Control	36	22	58
Total	76	32	108

	Pain level Week 0		
Panel C	Data present	Missing	Total
Intervention	47	3	50
Control	48	10	58
Total	95	13	108

	Pain level Week 8		
Panel D	Data present	Missing	Total
Intervention	19	31	50
Control	33	25	58
Total	52	56	108

***Figure 1. Analysis of missing data in Pilot 1a**: We observed a statistically significant difference between the two arms only at week 8, both for QoL questionnaires (Panel B, p=0.042) and pains levels (Panel D, p=0.05). Patients in the control group seemed to be less compliant than patients who received the intervention of telemedicine. No differences were observed at baseline (week 0) (Panel A and Panel C).*

	QoL Week 0		
Panel A	Data present	Missing	Total
Intervention	17	1	18
Control	18	4	22
Total	35	5	40

	QoL Week 8		
Panel B	Data present	Missing	Total
Intervention	11	7	18
Control	9	13	22
Total	20	20	40

	Pain level Week 0		
Panel C	Data present	Missing	Total
Intervention	14	4	18
Control	17	5	22
Total	31	9	40

	Pain level Week 8		
Panel D	Data present	Missing	Total
Intervention	4	14	18
Control	8	14	22
Total	12	28	40

***Figure 2. Analysis of missing data in Pilot 1b:** We did not observe any statistically significant difference in terms of compliance between controls and patients who received the telemedicine intervention in any panel, probably due to the small sample size).*

Panel A	QoL Week 0		
	Data present	Missing	Total
Intervention	48	6	54
Control	45	4	49
Total	93	10	103

Panel B	QoL Week 8		
	Data present	Missing	Total
Intervention	36	18	54
Control	24	25	49
Total	60	43	103

Panel C	Distress thermometer Week 0		
	Data present	Missing	Total
Intervention	48	6	54
Control	42	7	49
Total	90	13	103

Panel D	Distress thermometer Week 8		
	Data present	Missing	Total
Intervention	34	20	54
Control	20	29	49
Total	54	49	103

Figure 3. Analysis of missing data in Pilot 2: *We observed a statistically significant difference between the two arms only at week 8 for Distress thermometer (Panel D, p=0.025). Patients in the control group seemed to be less compliant than patients who received the intervention of telemedicine. No differences were observed at baseline (week 0) in Panel A, Panel C and for QoL at week 8.*

3.2.2 Descriptive analysis of pilot studies

In table 3 we reported the descriptive statistics by each pilot. We finally enrolled a total of 251 patients, 107 in Pilot 1 a (descriptive figure 4), 40 in Pilot 1 b (descriptive figure 5) and 104 (descriptive figure 5) in Pilot 2. 27 patients dropped-out the study: 13 in Pilot 1 a, 7 in Pilot 1 b and 7 in Pilot 2. In each pilot, the two arms do not differ statistically for any parameter.

Variables	Pilot 1aN (%)	Pilot 1bN (%)	Pilot 2N (%)
Total patients enrolled	107	40	104
Arm			
Intervention	50 (47)	18 (45)	54 (52)
Control	57 (53)	22 (55)	50 (48)
Sex			
M/F	0/107 (0/100)	12/28 (30/70)	70/34 (67/33)
Missing values	-	-	-
Age			
Median	53	58	50
1st Quartile	49	44	42
3rd Quartile	59	66	61

Missing values	*3*	*3*	*3*
Country			
Cyprus	16 (15)	6 (15)	2 (2)
Greece	0	0	11 (10)
Hungary	12 (11)	4 (10)	7 (7)
Ireland	8 (7)	4 (10)	2 (2)
Italy	18 (17)	6 (15)	13 (13)
Lithuania	11 (10)	12 (30)	22 (21)
Portugal	19 (18)	4 (10)	14 (14)
Slovenia	9 (9)	1 (3)	18 (17)
Spain	14 (13)	3 (8)	15 (15)
Missing values	-	-	-
Types of cancer			
Breast	107 (100)	-	39 (36)
Head&Neck	-	40 (100)	-
Lung	-	-	21 (20)
Colon	-	-	13 (13)
Gynaecological	-	-	10 (10)
Prostate	-	-	7 (7)
Gastric	-	-	2 (2)
Urological	-	-	6 (6)
Testicular	-	-	1 (1)
Cutis	-	-	1 (1)
Sarcoma	-	-	1 (1)
Melanoma	-	-	1 (1)
Other (not specified)	-	-	2 (2)
Missing values	-	-	-
Charlson Comorbidity Index (CCI)			
0	85 (80)	33 (83)	77 (74)
>0	22 (20)	7 (17)	27 (26)
Missing values	-	-	-
Eastern Cooperative Oncology			

Group Performance status (ECOG)			
0	29 (36)	15 (54)	26 (37)
1	49 (62)	13 (46)	31 (44)
2-3	2 (2)	0	14 (19)
Missing values	*27*	*12*	*33*
Comorbidities			
Yes	24 (25)	7 (18)	28 (31)
No	69 (73)	26 (69)	45 (50)
UK	2 (2)	5 (13)	17 (19)
Missing values	*12*	*2*	*14*
Marital status			
Married/Non marital partnership	72 (68)	29 (76)	63 (63)
Divorced	12 (11)	4 (11)	14 (14)
Single	16 (15)	3 (8)	14 (14)
Unknown	1 (1)	0	0
Widow/Widower	5 (5)	2 (5)	9 (9)
Missing values	*1*	*2*	*3*
Education			
ISCED 1-primary	8 (8)	5 (13)	6 (6)
ISCED 2-lower secondary	8 (8)	6 (16)	9 (9)
ISCED 3-upper secondary	29 (27)	6 (16)	19 (20)
ISCED 4-post secondary	7 (8)	2 (5)	10 (9)
ISCED 5-short cycle tertiary	7 (7)	8 (21)	13 (13)
ISCED 6-Bachelor's or equivalent	31 (29)	3 (8)	18 (19)
ISCED 7-Master's or equivalent	13 (12)	6 (16)	20 (21)
ISCED 8-Doctors' or equivalent	0	2 (5)	3 (3)
Missing values	*3*	*2*	*6*
Living arrangement			
Alone	17 (18)	3 (8)	18 (17)
Not alone	88 (82)	36 (92)	85 (83)
Missing values	*2*	*1*	*1*
Residence place			

City < 100.000	41 (38)	8 (20)	28 (28)
City => 100.000	40 (37)	20 (50)	39 (38)
Rural area distant from city	4 (4)	2 (5)	3 (3)
Rural area close to city	22 (21)	10 (25)	32 (31)
Missing values	*0*	*0*	*2*
Travel Time			
<30 minutes	42 (39)	19 (48)	35 (35)
30-90 minutes	47 (44)	13 (32)	41 (40)
90-180 minutes	15 (14)	5 (12)	20 (20)
>180 minutes	3 (3)	3 (8)	5 (5)
Missing values	*0*	*0*	*3*
Prior experience with tele-consultation			
None	86 (81)	33 (83)	66 (64)
Occasional videos	5 (5)	0	9 (9)
Only via phone	14 (13)	7 (17)	22 (22)
Regular videos	1 (1)	0	5 (5)
Missing values	*1*	*0*	*2*
Prior experience with monitoring devices			
None	76 (72)	33 (83)	67 (65)
Use for oneself	27 (25)	6 (14)	33 (33)
Use for medical healthcare	2 (2)	1 (3)	1 (1)
Participation in a clinical trial	0	0	1 (1)
Other use (job)	1 (1)	0	0
Missing values	*1*	*0*	*2*
Hours of sleep			
Median (min-max)	6 (1-10)	7 (3-9)	7 (3-14)
Missing values	*1*	*2*	*3*
Work			
Employed	62 (57)	17 (42)	45 (45)
Employed but sick-leave	17 (16)	4 (10)	15 (15)
Unemployed	13 (13)	5 (13)	9 (8)

Retired	14 (13)	13 (33)	32 (32)
Student	0	1 (2)	0
Missing values	*1*	*0*	*3*
Moderate/intense sport			
Yes	62 (60)	20 (53)	54 (54)
No	43 (40)	18 (47)	47 (46)
Missing values	*2*	*2*	*3*

Table 3. Sociodemographic and clinical data of pilot 1a, pilot 1b and pilot 2

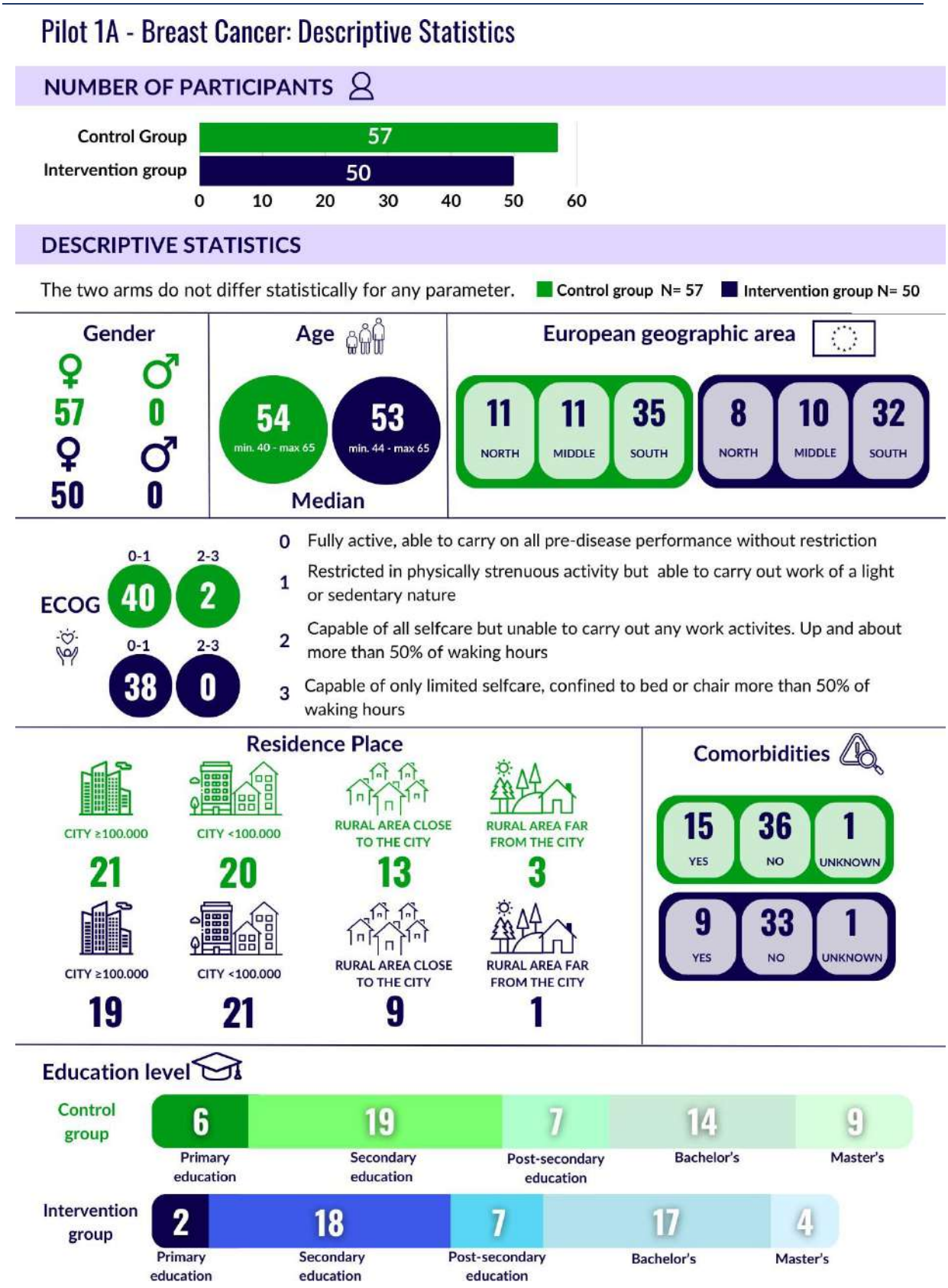

Figure 4. Graphical representation of pilot 1a descriptive analysis

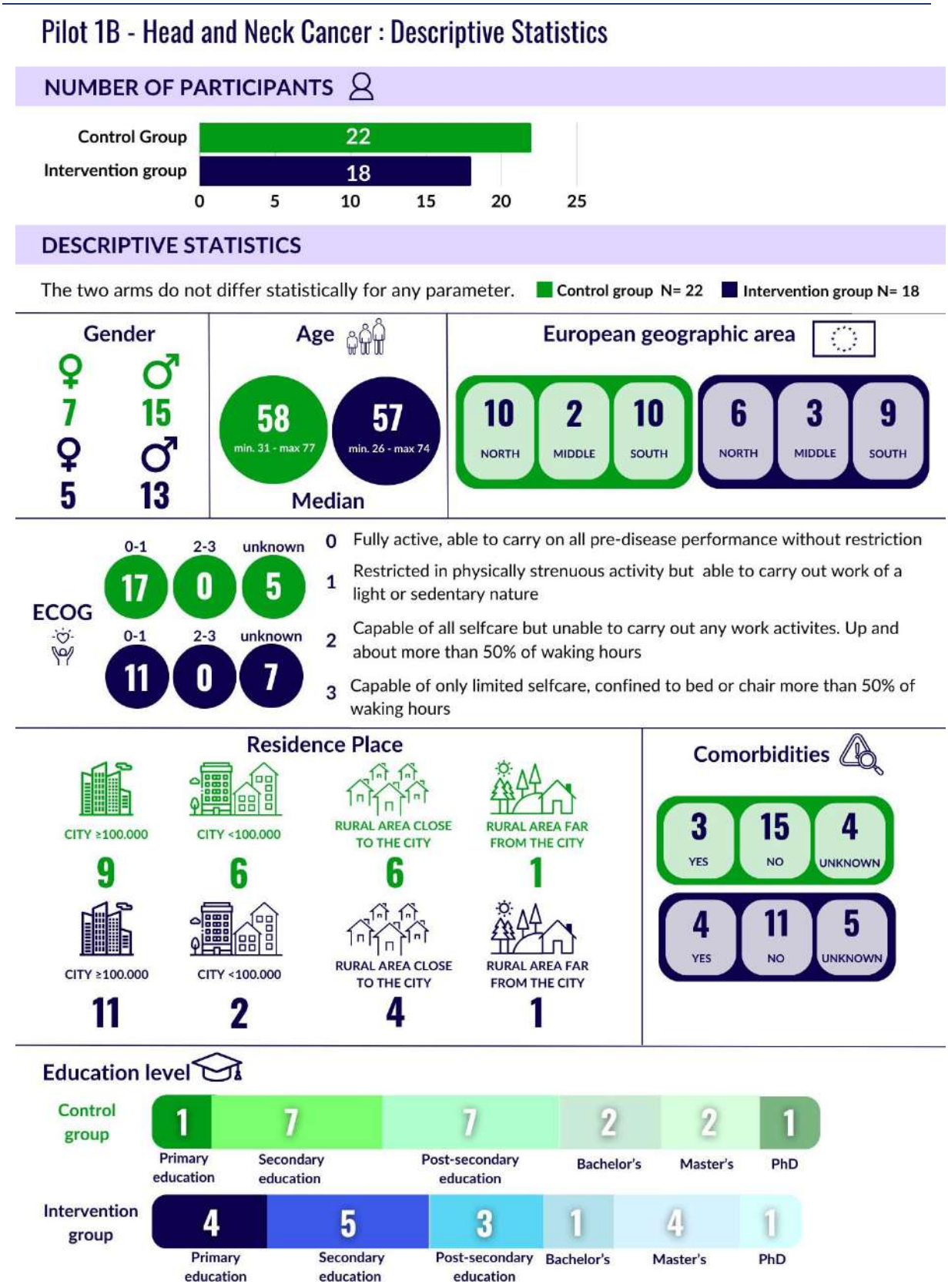

Figure 5. Graphical representation of pilot 1b descriptive analysis

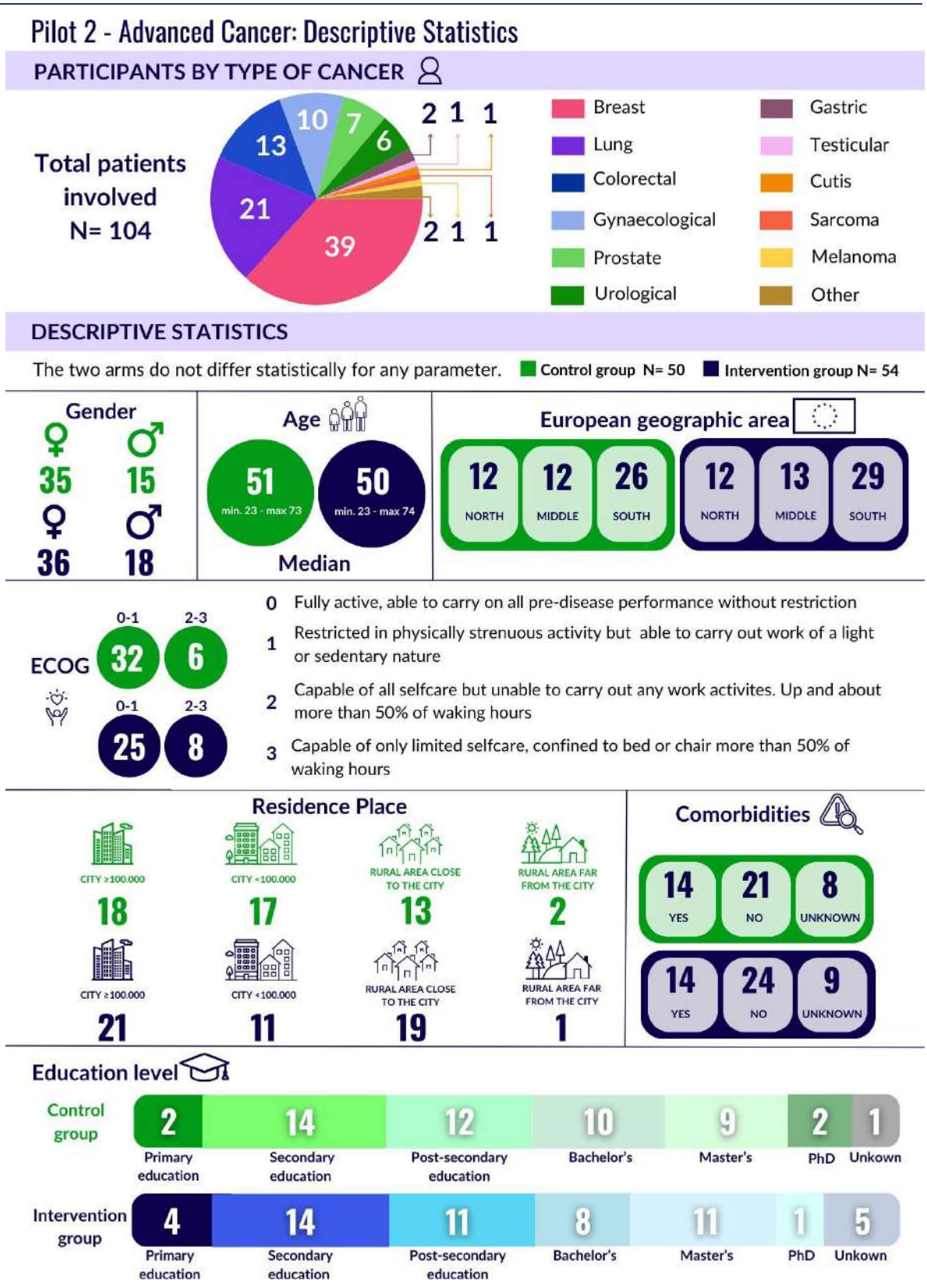

Figure 6. Graphical representation of pilot 2 descriptive analysis

3.2.3 Inferential statistics

a) Pilot 1a

In table 4 we reported the main results for Pilot 1a. We observed a statistically significant difference in terms of QoL-Global health at week 8 respect to baseline value (week 0). Patients who received telemedicine intervention reported a better HRQoL than those in the control group. No statistically significant differences were found between the two groups at week 8 for the other items.

	Week 0			Week 8		
Item-Functional Scale	Intervention Group (N=47)	Control group (N=49)	p-value*	Intervention Group (N=40)	Control group (N=36)	p- value*
Physical	73.3	66.7	0.241	83.3	80.0	0.337
Role	66.7	50.0	0.402	83.3	66.7	0.065
Emotional	66.7	66.7	0.223	75.0	66.7	0.109
Cognitive	83.3	83.3	0.631	83.3	75.0	0.113
Social	66.7	66.7	0.579	83.3	66.7	0.189
QoL-Global Health	62.5	58.3	0.690	75.0	62.5	0.047
	Week 0			Week 8		
Item-Symptoms Scale	Intervention Group (N=47)	Control group (N=49)	p-value*	Intervention Group (N=40)	Control group (N=36)	p- value*
Fatigue	44.4	44.4	0.244	33.3	33.3	0.079
Nausea and vomiting	0	0	0.158	0	0	0.083
Pain-QoL	33.3	50.0	0.003	25.0	33.3	0.058
Dyspnoea	0	0	0.942	0	0	0.438
Insomnia	33.3	33.3	0.322	33.3	33.3	0.419
Appetite Loss	0	0	0.147	0	0	0.065

Constipation	0	0	0.475	0	0	0.385
Diarrhoea	0	0	0.728	0	0	0.557
Financial Difficulties	0	0	0.456	0	33.3	0.400

*Table 4. Pilot 1a. QoL results. * Mann-Whitney non parametric test*

In table 5 and 6 we reported the trend over time for intervention group and the control group, respectively. We observed a statistically significant improvement for two functional items: Physical function and Role function, and QoL global Health. (descriptive figure 7). Specifically, the Physical function is referred to daily common activities such as carrying a heavy shopping bag, taking a long or a short walk outside of the house, need to stay in bed or seated, need help with eating, dressing, washing, using the toilet; while Role function is referred to pursuing hobbies or other leisure time activities. The score of these items progressively improved over time in patients receiving telemedicine intervention, in parallel with QoL global Health perception.

Item	Week 0	Week 2	Week 5	Week 8	p-value* (calculated on all data)
	N=28	N=28	N=28	N=28	
Physical	73.3	80.0	86.7	86.7	<0.001
Role	66.7	66.7	83.3	83.3	<0.001
Emotional	66.7	66.7	75.0	75.0	0.169
Cognitive	83.3	83.3	83.3	83.3	0.459
Social	66.7	83.3	66.7	83.3	0.159
QoL-Global Health	66.7	58.3	66.7	75.0	<0.001
Fatigue	44.4	33.3	33.3	33.3	0.117
Nausea and vomiting	0	0	0	0	0.471
Pain-QoL	33.3	33.3	16.7	33.3	0.007
Dyspnoea	0	0	0	0	0.777
Insomnia	33.3	33.3	33.3	33.3	0.831
Appetite Loss	0	0	0	0	0.545
Constipation	0	0	0	0	0.978
Diarrhoea	0	0	0	0	0.881

Financial Difficulties	0	0	0	0	0.075

*Table 5. Pilot 1a. Trend over time. Intervention group. * Friedman test for paired data.*

Item	Week 0	Week 8	p-value* (calculated on all data)
	N=29	N=29	
Physical	66.7	80,0	0.006
Role	33.3	66.7	<0.001
Emotional	58.3	75.0	0.185
Cognitive	83.3	83.3	0.344
Social	66.7	66.7	0.064
QoL-GlobalHealth	58.3	66.7	0.225
Fatigue	44.4	33.3	0.228
Nausea and vomiting	0	0	0.258
Pain-QoL	50.0	33.3	<0.001
Dyspnoea	0	0	0.77
Insomnia	66.7	33.3	0.089
Appetite Loss	0	33.3	0.683
Constipation	33.3	0	0.818
Diarrhoea	0	0	0.118
Financial Difficulties	0	0	0.072

*Table 6. Pilot 1a. Trend over time. Control group. * Wilcoxon non parametric test*

In table 7 (and in the descriptive figure 7) we reported the results of pain level, both at baseline and at the end of the study. We can observe a statistically significant difference between the two arms both at week 0 and at week 8 measurements. Although this data showed statistical significance in both the baseline and final collection, and it may therefore seem less impactful clinically, it actually allowed us to confirm that the improvement trend in the intervention group is confirmed. Thus, patients in the intervention group had less pain than those in the control group.

	Week 0			Week 8		
PROM	InterventionGroup (N=47)	Control group (N=48)	p-value*	Intervention Group (N=19)	Control group (N=33)	p-value*
Pain level	3.0	4.0	0.031	2.0	3.0	0.032

*Table 7. Pilot 1a, pain level results. * Mann-Whitney non parametric test*

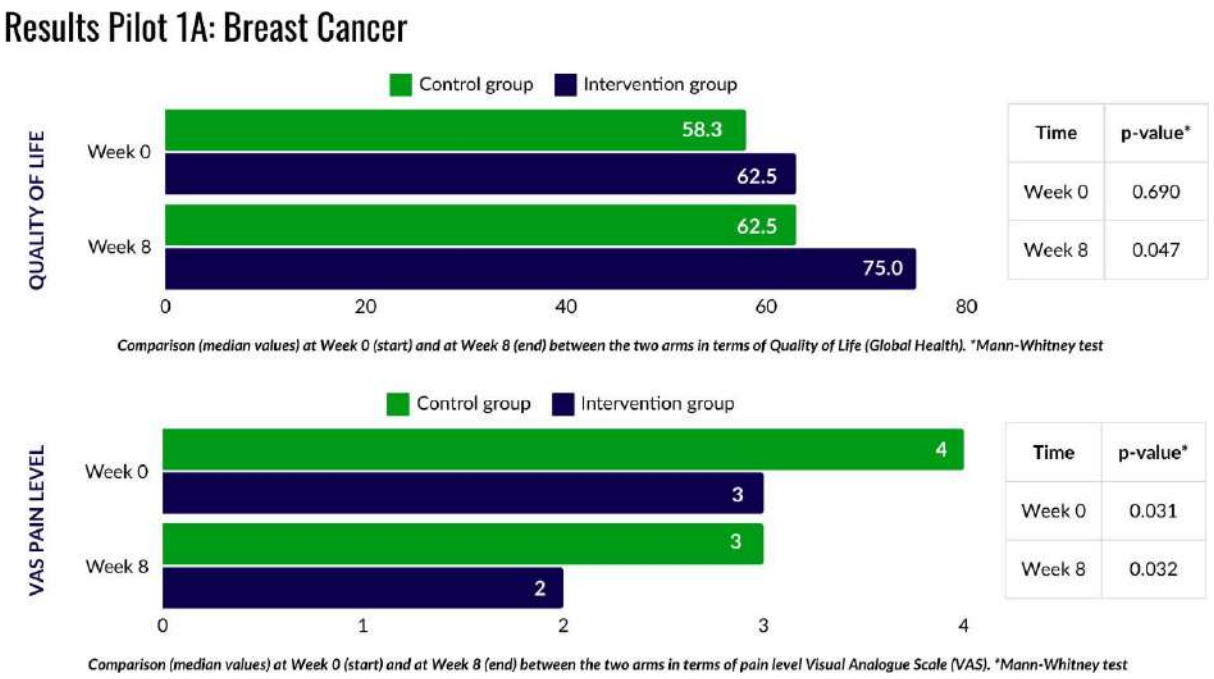

Figure 7. Graphical representation of QoL and VAS pain results in pilot 1a

b) Pilot 1b

In table 8 we reported the main results for Pilot 1b. Due to the small sample size (40 patients) we were not able to observe any statistically differences.

	Week 0			Week 8		
Item-Functional Scale	Intervention Group (N=17)	Control group (N=18)	p- value*	Intervention Group (N=11)	Control group (N=9)	p- value*
Physical	86.7	80.0	0.920	86.7	86.7	0.549
Role	66.7	75.0	0.139	66.7	66.7	0.907
Emotional	66.7	75.0	0.828	75.0	83.3	0.878
Cognitive	83.3	83.3	0.512	83.3	100	0.178

Social	83.3	83.3	0.126	66.7	66.7	1.000
QoL-Global Health	58.3	58.3	0.534	58.3	75.0	0.297
	Week 0			Week 8		
Item-Symptoms Scale	Intervention Group (N=17)	Control group (N=18)	p- value*	Intervention Group (N=11)	Control group (N=9)	p- value*
Fatigue	33.3	33.3	0.287	33.3	22.2	0.603
Nausea and vomiting	0	0	0.782	0	0	0.941
Pain-QoL	33.3	41.7	0.832	33.3	33.3	0.941
Dyspnoea	0	0	0.782	0	33.3	0.131
Insomnia	33.3	33.3	0.590	33.3	33.3	0.603
Appetite Loss	0	0	0.590	0	0	0.603
Constipation	0	0	0.909	33.3	33.3	0.603
Diarrhoea	0	0	0.443	0	0	0.824
Financial Difficulties	0	0	0.961	33.3	33.3	0.882

*Table 8. Pilot 1b. QoL results. * Mann-Whitney non parametric test*

In table 9 and 10 we reported the trend over time for intervention group and the control group, respectively. Due to the small sample size we were not able to observe any statistical significant result.

Item	Week 0	Week 2	Week 5	Week 8	p-value* (calculated on all data)
	N=4	N=4	N=4	N=4	
Physical	80.0	73.3	86.7	86.7	0.673
Role	25.0	50.0	75.0	75.0	0.087
Emotional	62.5	58.3	70.8	70.8	0.820
Cognitive	58.3	66.7	83.3	66.7	0.048
Social	16.7	58.3	50.0	66.7	0.077
QoL-Global Health	58.3	58.3	70.8	62.5	0.241

Fatigue	61.1	44.4	33.3	33.3	0.121
Nausea and vomiting	8.3	0	0	0	0.494
Pain-QoL	41.7	50.0	50.0	33.3	0.468
Dyspnoea	0	16.7	0	0	0.261
Insomnia	16.7	33.3	0	0	0.532
Appetite Loss	0	0	0	0	0.392
Constipation	33.3	50.0	33.3	50.0	0.392
Diarrhoea	0	0	0	16.7	0.392
Financial Difficulties	33.3	50.0	50.0	50.0	0.733

*Table 9. Pilot 1b. Trend over time. Intervention group. * Friedman test for paired data.*

Item	Week 0	Week 8	p-value* (calculated on all data)
	N=9	N=9	
Physical	93.3	86.7	0.058
Role	83.3	66.7	0.234
Emotional	83.3	83.3	0.056
Cognitive	100	100	0.414
Social	100	66.7	0.131
QoL-GlobalHealth	66.7	75.0	1.000
Fatigue	22.2	22.2	0.285
Nausea and vomiting	0	0	0.655
Pain-QoL	16.7	33.3	0.725
Dyspnoea	0	33.3	0.334
Insomnia	33.3	33.3	0.129
Appetite Loss	0	0	1.000
Constipation	0	33.3	0.705
Diarrhoea	0	0	0.317
Financial Difficulties	0	33.3	0.257

*Table 10. Pilot 1b. Trend over time. Control group. * Wilcoxon non parametric test*

In table 11 we reported the results of Pain level, both at baseline and at the end of the study. Also, for this PROM we did not observe any significant result.

	Week 0			Week 8		
PROM	Intervention Group (N=14)	Control group (N=17)	*p-value	Intervention Group (N=4)	Control group (N=8)	*p-value
Pain level	3.0	5.0	0.186	2.5	3.5	0.214

*Table 11. Pilot 1b, pain level results. * Mann-Whitney non parametric test*

b) Pilot 2

In table 12 we reported the main results for Pilot 2. We were not able to observe any statistically differences between the two arms at the two time-points.

	Week 0			Week 8		
Item-Functional Scale	Intervention Group (N=48)	Control group (N=45)	p- value*	Intervention Group (N=36)	Control group (N=25)	p- value*
Physical	**80.0**	**80.0**	**0.585**	**73.3**	**76.7**	**0.574**
Role	50.0	66.7	0.211	66.7	66.7	0.241
Emotional	66.7	66.7	0.613	66.7	58.3	0.268
Cognitive	83.3	83.3	0.923	83.3	83.3	0.446
Social	66.7	66.7	0.139	66.7	66.7	0.857
QoL-Global Health	66.7	66.7	0.910	66.7	66.7	0.886
	Week 0			Week 8		
Item-Symptoms Scale	Intervention Group (N=48)	Control group (N=45)	p- value*	Intervention Group (N=36)	Control group (N=25)	p- value*
Fatigue	44.4	33.3	0.397	44.4	55.5	0.894
Nausea and vomiting	0	0	0.626	0	0	0.853
Pain-QoL	33.3	33.3	0.616	25.0	16.7	0.628
Dyspnoea	0	0	0.681	0	0	0.959
Insomnia	33.3	33.3	0.941	33.3	33.3	0.809

Appetite Loss	0	0	0.797	0	0	0.722
Constipation	0	0	0.676	0	0	0.933
Diarrhoea	0	0	0.034	0	0	0.315
Financial Difficulties	33.3	0	0.392	33.3	0	0.545

*Table 12. Pilot 2. QoL results. * Mann-Whitney non parametric test*

In table 13 and 14 we reported the trend over time for intervention group and the control group, respectively. We were not able to observe any statistically significant result in the intervention group while we observed a significant decrease of value of social functioning in the control group. In fact, patients in the control group reported that their own physical condition interfered negatively in family life and social activities.

Item	Week 0	Week 2	Week 5	Week 8	p-value* (calculated on all data)
	N=26	N=26	N=26	N=26	
Physical	80.0	80.0	76.7	73.3	0.230
Role	50.0	50.0	66.7	66.7	0.762
Emotional	75.0	66.7	66.7	66.7	0.641
Cognitive	83.3	83.3	83.3	83.3	0.367
Social	66.7	66.7	75.0	66.7	0.662
QoL-Global Health	66.7	66.7	66.7	66.7	0.408
Fatigue	38.9	33.3	33.3	38.9	0.957
Nausea and vomiting	16.7	0	0	0	0.271
Pain-QoL	33.3	16.7	33.3	33.3	0.840
Dyspnoea	0	0	0	0	0.906
Insomnia	33.3	33.3	33.3	33.3	0.905
Appetite Loss	c	0	0	0	0.425
Constipation	0	0	0	0	0.754
Diarrhoea	0	0	0	0	0.156
Financial Difficulties	0	0	0	16.7	0.196

*Table 13. Pilot 2. Trend over time. Intervention group. * Friedman test for paired data.*

Item	Week 0	Week 8	p-value* (calculated on all data)
	N=25	N=25	
Physical	86.7	73.3	0.112
Role	83.2	83.3	0.321
Emotional	66.7	66.7	0.902
Cognitive	83.3	83.3	0.916
Social	83.3	66.7	0.010
QoL-GlobalHealth	66.7	66.7	0.958
Fatigue	33.3	33.3	0.140
Nausea and vomiting	0	0	0.541
Pain-QoL	16.7	16.7	0.954
Dyspnoea	0	0	0.782
Insomnia	33.3	33.3	0.285
Appetite Loss	0	0	0.589
Constipation	0	0	0.739
Diarrhoea	0	0	0.783
Financial Difficulties	0	33.3	0.755

*Table 14. Pilot 2. Trend over time. Control group. * Wilcoxon non parametric test*

Finally, in table 15 we reported the results of distress thermometer. We can observe a significant decrease of distress in the intervention group. These patients showed improvements in managing emotional, social, spiritual, or physical distress. Additionally, they demonstrated a better ability to cope with both the changes caused by the illness and its stages, such as diagnosis, physical symptoms, or treatment.

	Week 0			Week 8		
PROM	Intervention Group (N=48)	Control group (N=42)	*p-value	Intervention Group (N=34)	Control group (N=20)	*p-value
Pain level	5.0	5.0	0.710	3.0	5.5	0.039

*Table 15. Pilot 2. Distress thermometer results. * Mann-Whitney non parametric test*

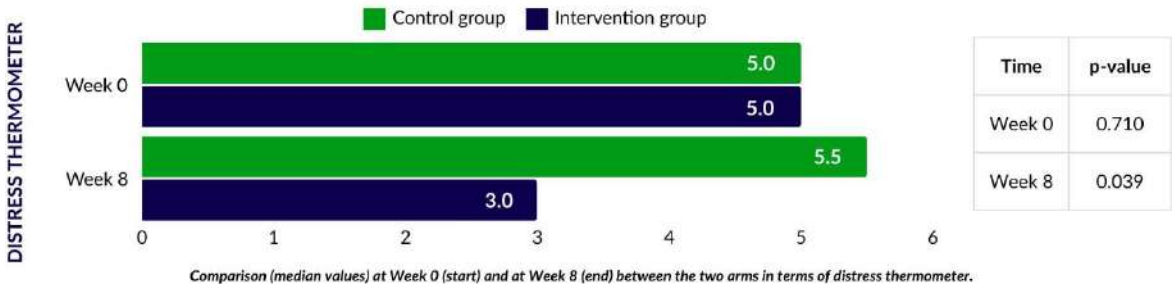

Figure 8. *Graphical representation of distress thermometer results in pilot 2*

3.2.4 Discussion

The eCAN project aimed to evaluate the effect of telemedicine (including teleconsultation and telemonitoring) on cancer care.

To assess sustainable telemedicine programs in cancer care and to facilitate the development of interoperable solutions we designed 3 pilots projects exploring telemedicine intervention in rehabilitative and in psychological support setting of care.

Overall, the results of the pilots showed that tele-rehabilitation and tele-psychological support significantly improved Patients Reported Outcome measures like HRQoL, pain and distress.

In addition, the pilots achieved high rates of patients' enrollment in a relatively short time, particularly for pilot 1 a (breast cancer) and Pilot 2 (advanced cancer), while the enrollment of pilot 1 b (Head and Neck cancer) was less satisfactory. Also, the low rates of missing data, as well as high retention among participants randomly assigned to the intervention group, demonstrate the feasibility and acceptability of telemedicine programs in cancer care.

The telemedicine tools utilized in this project (EDUMEET platform and dedicated APP for PROMs telemonitoring) demonstrated a good usability and interoperability, promoting stakeholder engagement and training to telemedicine programs implementation.

The promising results of this study have important clinical implications and highlights the importance of the accurate selection of more suitable setting of care for telemedicine program application.

The results of eCAN pilots study seem to demonstrate that population of patients with less burden of disease or in early stage of disease like breast cancer patients enrolled in Pilot 1a are more compliant to telecare and to longitudinal monitoring of PROMs, respect to Pilot 1b patients affected by Head and Neck cancer, with higher clinical burden of disease, showing less adherence to tele-rehabilitation visit and PROMs repeated collection.

However, pilot 2 results demonstrated the feasibility and acceptability of telemedicine care delivery, even among patients with advanced cancer.

Furthermore, it is evident that the presence of a dedicated APP (intervention group) ensures greater patients' compliance in completing questionnaires and, therefore, greater engagement compared to patients in the control group.

In conclusion, the results of this large clinical trial demonstrate that telemedicine interventions in rehabilitation and psychological support setting of care led to significantly quality of life, pain and distress improvement, measured with PROMs, after intervention compared with usual care.

Future studies are needed to better explore the role of telemedicine intervention in different setting of care and cancer population; to better define telemedicine tools and their usability; to implement stakeholder telemedicine literacy and facilitate accessibility to telecare for more frail population of patients.

3.3 Lessons learned

The eCAN clinical study provided positive evidence accompanied by a series of lessons learned that will implement telemedicine services in the future applications. The main lessons learned are outlined below:

- The duration of the clinical trial was very short, however the number of enrolled patients (251) was high, even if not sufficient for sample size. It is worth noting that the trial started at the end of September 2023 with only 4 centres active until December 2023. From December onwards, 16 centres were gradually activated, leading to the final enrolment of 251 patients by mid-April 2024. This observation highlights the importance of coordinating the activation of the various centres involved, with the goal of ensuring a consistent and homogeneous patient enrolment rate.
- In two centres, the intervention of the ethics committee and the DPO led to their non- activation. This highlights the opportunity to better standardize the ethical and

legal approach of clinical trials in the future, to avoid similar situations. These topics, along with cybersecurity issues, were addressed in deliverable 6.2.

- Pilot 1b unfortunately negatively affected the level of patients' enrolment due to the overly strict inclusion criteria included in the pilot protocol. This suggests that telemedicine may be better applied in certain care settings compared to others and emphasizes the importance of clarity and inclusivity within a clinical pilot protocol.
- The patients collaborated fairly consistently with all the questionnaires proposed in the project. However, in some cases, patients were not completely compliant, skipping many questionnaires. This suggests that in the design of the pilot protocol, it is important not to overburden patients with too many tasks (in this case, weekly questionnaires) and to keep patients regularly updated, making them aware of their responsibilities.
- The research teams involved generally responded well, even though for some research groups telemedicine activities were entirely new. Nevertheless, it was crucial to provide continuous training activities and educational materials.
- The technical aspects of the clinical trial revealing several challenges; however, the overall outcome remains positive, especially considering the workload required, particularly in the setting of EDUMEET and in the development of the eCAN app and dashboard. The issues that emerged provide an important starting point for the development and application of future telemedicine services.

4. References

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5. Annexes

5.1 Patients refusal

During the screening process for patient enrolment in the clinical study, 75 patients declined to participate. Below are all the reasons (if any) taken directly from the screening log of each centre involved:

- Not want participate in the study: 32 patients
- Not reported any specific reason: 18 patients
- Not want psychological support: 6 patients
- Digital illiteracy: 6 patients
- Not want to be randomized in the intervention group: 3 patients
- Not want physiotherapy: 2 patients
- Informed consent not signed: 2 patients
- Recurrence of disease: 1 patient
- Already had physiotherapy sessions:1 patient
- Want to do physiotherapy somewhere else: 1 patient
- Want to do physiotherapy in person: 1 patient
- Language issues: 1 patient
- Wife not compliant: 1 patient

5.2 Patients dropping out

During the conduction of the pilots, 27 patients decided (voluntarily and not) to drop out the study. Below are all the reasons taken directly from the screening log of each centre involved:

- Not reported any specific reason: 9 patients
- Deceased; 7 patients
- Clinical reasons: 5 patients
- Personal reason: 1 patient
- Not complete questionnaires requested: 1 patient
- Treatment in another centre: 1 patient
- Want the intervention group (randomized in the control group): 1 patient
- Digital illiteracy: 1 patient
- Terminally ill patient: 1 patient

5.3 Research Teams' Clinical Questions

During the conduction of the study, as coordinators of WP5, we received a series of questions related to clinical aspects from the various involved centers. Below are the questions:

1. Only patients who have undergone mastectomy can be included in the study? Or can also patients who have undergone conservative surgery be included?
2. Only female patients can be included in this pilot, isn't it?
3. We would like to confirm that the term "axillary dissection" includes sentinel lymph node extraction. Is this correct? In accordance, would you please let us know if the option axillary dissection would be the best description of the surgery (the options are axillary dissection/lymphadenectomy/prothesis)?
4. Do you consider that the diagnosis of "anxiety depressive syndrome" would be considered as major depression, excluding the patient from the study?
5. Our main concerns are regarding the exclusion criteria "having breast reconstruction", which we would really appreciate if you could define it to us (so as not to ask you every time we have a candidate patient).
6. We have 2 potential candidates:
    a. One patient who has undergone a targeted lumpectomy + sentinel node. In her Clinical records it is indicated that she has undergone breast remodelling (no prothesis), as part of a conservative surgery.
    b. The second patient has also undergone a targeted lumpectomy + sentinel node. In her Clinical records it is indicated that she has undergone a local breast remodelling (no prothesis), as part of a conservative surgery.

    Would these 2 patients fulfil the eligibility criteria and could they be included in the study?
7. A patient has undergone the surgery on the 04/01/2024, so if we recruit her for the baseline visit this week, and if she is assigned to the intervention group, she would be starting the teleconsultations 1 month and at least 27 days since her surgery. Would that be ok for you?
8. Is sentinel lymph node biopsy accepted in the inclusion criteria?
9. We have just identified a patient who has undergone lymph node dissection with a previous thyroidectomy. Can we offer him to participate in the study?
10. Do you plan protocol amendment regarding group 1b-maybe including patients after thyroidectomy?

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