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D6.2. Data collection and usability clinical study results

30/08/2022

WP6 PERSIST

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DOCUMENT

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Acronyms and abbreviations

ACRONYM	TITLE
API	Application Programming Interface
BMI	Body mass index
C 50	Breast cancer diagnosis
C18 / C19	Colorectal cancer diagnosis
CASE cancer	Communication and Attitudinal Self-Efficacy scale for cancer
CDSS	Clinical decision support system
CHU	Centre Hospitalier Universitaire De Liege
CTC	Circulating tumor cells
DAPI	4′,6-diamidino-2-phenylindole, is a fluorescent stain that binds strongly to adenine–thymine-rich regions in DNA
EC	Ethical Committee
EDTA	Ethylenediaminetetraacetic acid
EHR	Electronic health record
FHIR	Fast Health Interoperability Resources
GDPR	General Data protection Regulation
ICF	Informed consent form
mHealth	Mobile health system
mHealth app	Mobile health application
PAM	Patient Activation Measure
PAM	Patient Activation measure
PREM	Patient- reported experience
PRM	Physical and Rehabilitation Medicine
PROM	Patient Reported Outcome Measures
QoL	Quality of life
REUH	Riga East Clinical University Hospital in Latvia
SERGAS	Complejo Hospitalario Universitario de Ourense (SERGAS)
SOP	Standard operating procedure
SSES	Strengths Self-Efficacy Scale
UKCM	University Medical Centre Maribor
UL	University of Latvia
SUS	System Usability Scale
WP	Work package

Executive Summary

The PERSIST European Project: "Patients-centered SurvivorShIp care plan after Cancer treatments based on Big Data and Artificial Intelligence technologies" was developed to improve health outcomes, quality of life (QoL) and promote stress reduction for breast and colorectal cancer survivors after treatment. The long-term result will be to reduce the socio-economic burden related to cancer survivors' care.

The aim of this deliverable is to describe the outcomes and work done in WP6 task 6.2. "Patient recruitment" and Task 6.3. "Data collection and usability". In order to accomplish this task, the clinical trial was designed in the previous task 6.1 and already started in four countries: Belgium, Latvia, Slovenia and Spain. The present report gives an overview of the preparatory activities, the recruitment activities, the start of the clinical trial, the data collection and their usability evaluation. The report includes also the outcomes of task 6.3 that have been focused on the co-creation activities involving patients through data collections and achieving to develop and integrate the overall PERSIST data. The report includes the initial feedback gathering and usability testing, which might impact the course of further PERSIST system development and the full clinical study that starts on September 2022.

Patient inclusion in PERSIST clinical trial

1. Background

As part of the PERSIST project, a pilot clinical study is contemplated to assess the feasibility of patient interaction with the smart bracelet, the data reported by patients using the mHealth application (mHealthApp), and the usefulness of data collected and their correlation with clinical and demographic data.

This pilot study is carried out by four clinical centres - Centre Hospitalier Universitaire De Liege (CHU) in Belgium, University Medical Centre Maribor (UKCM) in Slovenia, Complejo Hospitalario Universitario de Ourense (SERGAS) in Spain and Riga East Clinical University Hospital (REUH) in Latvia in collaboration with University of Latvia (UL), as well as collaboration with other project partners. The study involves 160 patients (80 survivors of breast cancer and 80 survivors of colon cancer, split equally among four clinical pilots.

The objective is to determine whether a mobile health system (mHealth), supported by a data-driven Clinical Decision support system, to be developed under the project, will positively affect the behaviour/activation of survivors of Breast Cancer and Colon Cancer.

The individuals included in the pilot study have been using a mobile phone with the mHealth application and a smart bracelet. The application collects data, including sociodemographic, clinical, lifestyle and biomarkers (soft) data. Vital signs (i.e. heart rate, sleep patterns) and fitness data (step counter, activity) are measured by a smart bracelet connected to the smartphone. Both were provided to the individuals at the recruitment. After the pilots, the devices will be donated to the individuals. It is planned that the mHealth app will provide personalised follow-up and recommendations delivered by clinicians, based on new patient trajectories and cohorts learned from Big Data.

In two piloting countries (Slovenia, and Spain), 80 individuals. 40 per pilot (20 breast and 20 colon cancer survivors) donates blood samples for circulating tumour cell (CTC) counting, recognized as new prognostic biomarkers.

As stated in Clinical protocol:

PERSIST clinical trial is a single-case experimental prospective study within each individual that serves as its own control group with the first measurement done prior to intervention, during recruitment and subsequent measurements during follow-up. The intervention will be implemented via mHealthApp for collecting objective biomarkers (vital signs) and subjective biomarkers (PREMs/PROMs and symptoms of depression) with support of an (embodied) conversational agent (chatbot). Additionally, the CDSS (with cohorts and trajectories) will enable oncologists to personalise treatment and care plans/follow-up for efficient management of patients. Self-efficacy has been highlighted as a protective effect for survivors who have a higher perceived risk of recurrence.

Hypothesis: Performing a comparison at the beginning and the end of the intervention, participants will significantly increase their self-efficacy following **the personalised intervention supported by the mHealthApp**.

2. General description of the patient population

Altogether 167 patients were recruited in the PERSIST clinical trial in four hospitals (see Table No.1). This number slightly exceeds the initial goal mentioned in the clinical protocol – 160 patients. Among the recruited patients, 85 have had breast cancer and 81 colorectal cancer, which is in line with including an equal number of patients in each group. The average age of the patients at the time of inclusion was 55 years old. Therefore, most of them are expected to be able to learn how to use a mobile phone, a smart bracelet and an application. In total, there were 37 male and 129 female patients included in the study. The rarity of breast cancer in men and a slightly higher inclusion of women in the group of patients who presented with colorectal cancer explain the greater inclusion of women and therefore the gender imbalance in inclusion.

CLINICAL PARTNER	RECRUITED PATIENTS	MEAN AGE	BREAST CANCER	COLORECTAL CANCER	MALE	FEMALE
UL	47	54	24	22	7	39
UKCM	40	57	20	20	11	29
CHU	41	55	21	20	7	34
SERGAS	39	56	20	19	12	27
TOTAL	167	55	85	81	37	129

Table 1 General description of patients

3. Inclusion process

Before starting the recruitment, clinical and technical partners involved in the development of the PERSIST mobile app developed the training materials dedicated to patients. All the materials were translated into Spanish, French, Slovenian, Latvian and Russian.

→ Informative material for clinicians/personnel involved into clinical trial (See attachment PERSIST_Materials for clinical research staff training in PERSIST google drive folder D6.2. Deliverable attachments (https://drive.google.com/drive/folders/1oDpDXkDySGMb4A0D9aFvnDAskE8KVO1h).

Informative materials prepared for patients in all PERSIST partners languages:

→ Short informative brochure. See attachments in PERSIST google drive folder D6.2. Deliverable attachments: Persist Brochure EN-web; Persist Brochure_FR-web; Persist Brochure_LV_final; Persist Brochure_RU; Persist Brochure_Spain_final; Persist-Brochure_SLO-web (https://drive.google.com/drive/folders/1oDpDXkDySGMb4A0D9aFvnDAskE8KVO1h).

➔ User manual. See attachments in PERSIST google drive folder D6.2. Deliverable attachments: PERSİST USER MANUAL_CHU; PERSİST USER MANUAL_SERGAS_ES; PERSİST USER MANUAL_UL_LV; PERSIST_USER_MANUAL_UL_RUS (https://drive.google.com/drive/folders/1oDpDXkDySGMb4A0D9aFvnDAskE8KVO 1h).

➔ Smart bracelet usage video. See attachments in PERSIST google drive folder D6.2. Deliverable attachments: smarband-FR; smartband-EN; smartband-ES; smartband-LV; smartband-RU; smartband-SL (https://drive.google.com/drive/folders/1oDpDXkDySGMb4A0D9aFvnDAskE8KVO 1h).

➔ Patient infographic about informed consent. See attachments in PERSIST google drive folder D6.2. Deliverable attachments: PERSIST IC infographic CHU; PERSIST IC infographic ENG; PERSIST IC infographic SERGAS; PERSIST IC infographic UKCM; PERSIST IC infographicLV; PERSIST IC infographicsRUS (https://drive.google.com/drive/folders/1oDpDXkDySGMb4A0D9aFvnDAskE8KVO 1h).

During recruitment, several activities were carried out at first for all clinical partners and then in each hospital:

➔ Training of clinical partners: introduction of the app, phone, and smart-bracelet.

➔ Training of clinical research staff in each hospital (they received prepared training material / translated Information about PERSIST project in general; Inclusion/exclusion criteria of patients; Time-scale of clinical research; Prepared recruitment materials (brochure, user manual, videos); Clinical protocol; Explanations given).

➔ Patients who completed cancer treatment were invited personally to join the clinical study by clinicians.

➔ Patients with inclusion and without exclusion criteria were assessed in an outpatient setting informed about the study and offered to participate. Nurses or Data managers supporting the medical doctors/physiotherapists explained the study to the patients and invited them to sign the informed consent.

➔ As we have previously stated in the clinical protocol PERSIST inclusion and exclusion criteria were the following:

"Breast and colorectal cancer patients who have survived beyond curative cancer treatment. We will consider a survivor patient, all breast and colorectal cancer patients who survive without recurrence beyond 3-12 months after the end of treatment (surgery ± radiation therapy ± chemotherapy), whatever they have received.

Colorectal cancer survivors group: We will include two subgroups defined (chemotherapy and non-chemotherapy). None of the groups will be lower than 33% in ratio to the other.

➔ Breast cancer survivors. We will differentiate two subgroups. At least 33% of patients that have had chemotherapy.

Inclusion criteria ≥18 and ≤75 years at the moment of recruitment; Stable clinical situation, life expectancy of more than two years according to researcher opinion; Ability to understand study instructions, fulfil follow-up visits and sign informed consent; Enough technology literacy that enables the patient to manage with mobile terminals (smartphones, smartphone apps, tablets); Good cover to an internet connection in his/her place of residence.

Exclusion criteria: Life expectancy, under the physician's opinion, of less than one year; Diagnosis of dementia or cognitive decline that makes him/her unable to understand study information and/or sign informed consent; Unable to self-management due to dependence on another person for medication compliance, or measuring blood pressure and daily weigh; Lacking decision capacity in relation with diet or preparing meals; Current participation in other clinical studies; Patient has no further follow-up possibilities with enrolling investigation during the planned study period (such as anticipated relocation); Patients with major depression, a psychiatric medication that hinders their daily activity.

➔ Table of events (Table 2):

Study procedure	Screening	Baseline collection	Follow-up 2	Follow-up 3	Follow-up 4
Dates	Jan-Apr21	Apr-Aug21	Sep-Nov21	Apr-May-22	Sep-Oct22
Inclusion/ exclusion criteria	X				
Invitation to participate	X				
Candidate signs documents and receives devices		X			
User manual / infographic for patients		X			
Medical history (data collection)		X	X	X	X
Questionnaires		X	X	X	X
CTC test (UKCM; SERGAS)			X	X	X

Table 2 Proposed table of events

4. Patients leaving trial

4.1. Creating Standard operating procedure (SOP)

Shortly after the inclusion and during the study, some of the patients wished to step out of the clinical study after using the devices and newly developed system. Altogether, (up to 16.06.2022.) 34 patients left the clinical study. In order to tackle the leaving process, clinical partners created a specific Standard Operating Procedure (SOP). Specific documents contained pathways for patients, research personnel, and project administrators (see attachment See attachment in PERSIST google drive folder D6.2. Deliverable attachments: SOP_patient_leave_PERSIST
(https://drive.google.com/drive/folders/1oDpDXkDySGMb4A0D9aFvnDAskE8KVO1h)).

Consent for the continuation of personal data processing was updated and each patient signed it upon leaving. See attachments: PERSIST_data proc_v2; PERSIST_IZSTASHANAS_FORMA2022; PERSIST withdrawal vloga za umik_SLO in PERSIST google drive folder D6.2. Deliverable attachments (https://drive.google.com/drive/folders/1oDpDXkDySGMb4A0D9aFvnDAskE8KVO1h). According to patients' wishes, already taken data within the PERSIST system were deleted or left in the system. Patient reasons for leaving were listed (see attachment PATIENT_LEAVE_REASONS_PERSIST_2022 in PERSIST google drive folder D6.2. Deliverable attachments (https://drive.google.com/drive/folders/1oDpDXkDySGMb4A0D9aFvnDAskE8KVO1h)) and analysed on a case-by-case basis.

4.2. Reasons for leaving and analysis

Up to July 2022, 38 patients have left the clinical study (see Table 3). Among them 30 were females and eight were males. The mean age for this group was 56 years old, showing that age was not a significant factor for stepping out of the study due to the inability to use the PERSIST technology. In total 22 breast cancer and 16 colon cancer patients stepped out of the study.

CLINICAL PARTNER	WITHDRAW	MEAN AGE	BREAST CANCER	COLORECTAL CANCER	MALE	FEMALE
UL	14	54	8	6	3	11
UKCM	4	57	2	2	0	4
CHU	15	56	8	7	4	11
SERGAS	5	55	4	1	1	4
TOTAL	38	56	22	16	8	30

Table 3 General description of patients who have left the study

Leave reasons can be seen in the previously mentioned excel file. Analysis of patient explanations revealed that the most frequent reasons for leaving were a change of personal life situation, smart-bracelet malfunctions and other technical problems (see Table 4). In addition to these, we can highlight complaints about cumbersome participation taking too much time, problems with application and overall dislike of the system that was underdeveloped at the time patient started to participate in the study. This could in particular be the reason of the higher dropout rate at CHU and UL, which started recruiting earlier than the other 2 sites (SERGAS and UKCM) as soon as they obtained the green light from the technical partners.

Reasons for leaving	Times mentioned
Personal life situation	11
Device malfunction, technical problems	10
Participation takes too much time	9
Does not like the system in general	7
Complaints about app	6
Induces stress, anxiety	5
Not specified	4
Reminds of cancer	3
No need for follow-up	2
Light at night from bracelet	2
Recurrence	1

Table 4 Summary of reasons patients mention leaving

4.3. Mitigation strategies and actions

Considering the analysis, mitigations strategies for avoiding the remaining patients to leave the study were carried out. On a daily basis, research personnel involved in PERSIST communicated with patients (mostly by phone or by email), explained unclear processes (for example, how to charge the smart-bracelet), and resolved issues patients encountered during their daily participation following their request. Additional consultations or meetings with patients happened in case face-to-face support (for example reconnecting the smart-bracelet with the mobile phone) was needed.

In specific cases (hot weather, disturbing light from smart bracelet at night etc.), PERSIST consortium gave the patients the freedom not to use the smart-bracelet.

In order to gain experience from other related clinical trials/studies, the consortium joined the eHealth cluster and participated in their meetings.

Other mitigation strategies were planned and suggested to accomplish in the future, including, but not limited to:

→ Loyalty program for patients staying in the study (connected with a healthy lifestyle, possibly water bottles, yoga mat, massage etc.) but not approved later.

→ Additional workshops / lectures about themes that are interesting for patients / partly done in workshops with patients.

→ Video integration into the system, new features in the app / done for latest app versions.

➔ WhatsApp/Telegram group for patients (the idea was not approved in discussions).

➔ Patients use their own devices (report data once a day; for example, smartphones have step counters, and manually measure blood pressure in other devices for insertion into mHealth app). The option used upon request.

➔ Individual patient consultations about problems with smart-bracelet, mHealth app and phone by:

 ✓ Email - answering questions regularly and providing information to technical partners; sending information about changes in app versions.

 ✓ Phone - answering phone calls; calling all the patients.

 ✓ Person - in case of older participants, meet with them face-to-face to fix the problems.

Data collected in the study

5. Data type description

5.1. Data from smart-bracelets

Each patient included in the clinical study received Naicoms smart-bracelet. The specific device model was chosen by the technical partners (WP4) considering data safety reasons (GDPR concerns in regard to patient`s wearable data) and price (which aligns with the budget of European citizens). The bracelets' requirements were: the ability to measure steps/activity, sleep, heartbeats and blood pressure. In addition, the system should be able to develop a kit to access the bracelet directly from a smartphone without using the manufacturers' cloud storage.

Each mobile phone (app) collects the following data from the patient' smart-bracelet and then to the PERSIST system:

➔ Heart rate - collected automatically.

➔ Blood pressure - collected by manual pressing the button. The patient has to sit down and do the measurement while not moving.

➔ Steps done during a day - collected automatically.

➔ Calories - collected automatically.

➔ Time spent sleeping - collected automatically.

The most relevant data for patient health condition and comorbidities evaluation will be blood pressure, physical activity and sleep[4].

5.2. Data from patients by manual input

mHealth application was designed to allow patients to collect additional data by manual data input. As these data is necessary for the evaluation of the emotional and physical health of the patients, they received notifications through the app to remind them to complete the questionnaires. In the case of PAM and CASE Cancer questionnaires – we collected them physically (or by phone) two times – at the recruitment and at the follow-up, and then gathered the answers in an excel file.

➔ Questionnaires - collected automatically

  ✓ CASE-cancer (Communication and Attitudinal Self-Efficacy scale for cancer).

  ✓ Patient Activation Measure (PAM-13).

  ✓ System Usability Scale (SUS).

  ✓ User Experience Questionnaire (UEQ).

  ✓ Directed Questions Scale – DQS.

  ✓ PERSIST Block A, B and C.

➔ Video diaries - patients record a short three-minute video of themselves talking about their day. Ideally three times a week.

➔ Emotions - patients were invited every day to choose their emotions from a pre-established list (Plutchik's Wheel of Emotions).

5.3. Data from mClinican

Additionally, the specific webpage mClinican for healthcare givers and researchers working with patients was established (more information about this could be found in PERSIST Deliverable D5.7). mClinician gathered data from the electronic health records and displayed data collected from each patient's mHealth. The most relevant data needed to be gathered from patients' electronic health records was decided together with the clinicians from each hospital.

The main pages of mClinician are:

➔ General and medical history.

➔ Diagnosis and symptoms.

➔ Tests.

➔ Cancer treatment.

➔ mHealth data.

5.4. Blood sample collections

In order to assess objective cancer biomarkers, peripheral blood was collected from UKCM and SERGAS patients to detect circulating tumour cells (CTCs). CTCs are rare cancer cells that can be found in blood. Their numbers have been associated with disease recurrence, progression and resistance to therapy. CTCs are a relevant tool to monitor cancer patient progression.

Under the scope of the evaluation of the presence of CTCs in blood samples from patients enrolled in PERSIST, a blood collection scheme was defined with the clinical partners. This included the collection of blood from patients (7.5 mL of whole blood in EDTA tubes) at three different time points: 1) Baseline collections: M20-M22, 2) 6-month Follow up: M26-M28 3), 12-month Follow-up: M32-M34. Only patients from UKCM and SERGAS were included in the study. The target was set at 20 cancer patients, per type, per hospital. In total, 70 patients participated in this assessment, 34 breast cancer and 36 colorectal cancer patients. The process is shown in Figure 1.

Briefly, samples were collected in the hospitals and sent to RUBY premises. RUBY, processed the samples in the RUBYchipTM immediately after receiving them. After processing, the samples were fixed and stored until the next step, which included staining of the cells, imaging and finally image analysis. The antibody panel to be applied was selected by clinicians as follows. The isolated CTCs were labelled with antibodies against cytokeratin, DAPI, Vimentin and CD45 (negative marker) for colorectal cancer samples and with antibodies against cytokeratin, DAPI, CD45 and HER2 in case of breast cancer.
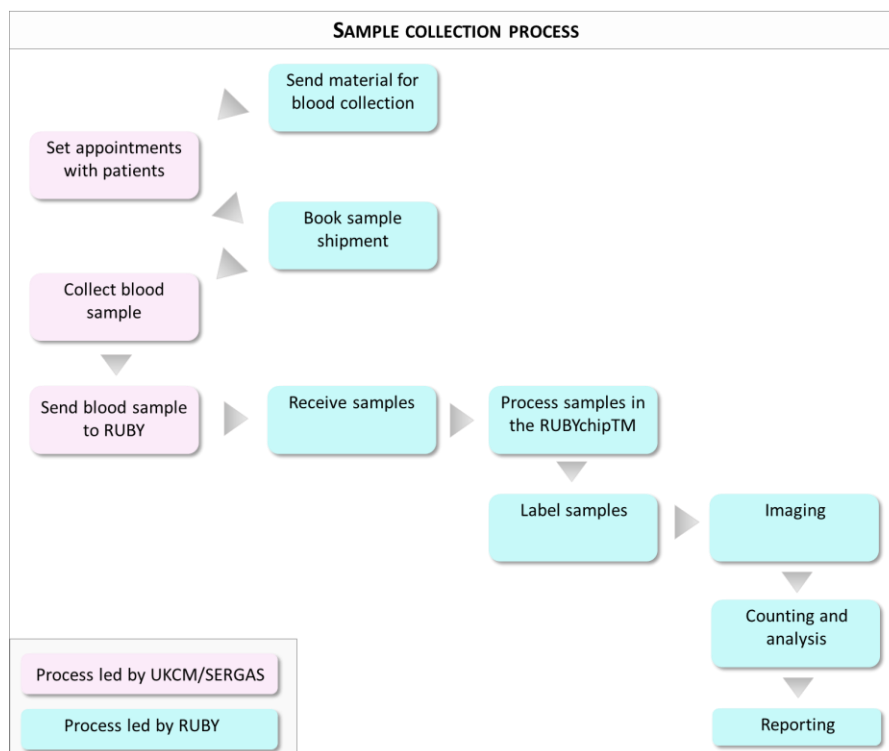

Figure 1 Sample collection process

The goal was to deliver and process the samples within 24 hours after collection. However, the distance between UKCM (Maribor, Slovenia) and RUBY (Braga, Portugal) converted this goal into a challenge, sample shipment was occasionally delayed, and it was not always possible to process the sample in the defined time window. Therefore, in the case of samples collected in UKCM some were processed 48 h after collection, as depicted in table 5. Note that, in one of the shipments, samples were delivered 72 h after collection, due to consecutive issues in the transport. These samples were discarded, but UKCM managed to attract the affected patients to repeat the collection and hence the substitution of these samples was achieved with two extra sample shipments.

	Sample type	Baseline (M20-M22)		6 month (M26-M28)	
		#samples	%processed in 24hrs	#samples	%processed in 24hrs
UKCM	CRC	18	50%	18	92%
	BRC	18		18	
SERGAS	CRC	18	50%	18	100%
	BRC	18		15	

Table 5 Sample types and processing time

At the time of the present deliverable, two blood collections were performed, corresponding to baseline and 6-month follow-up. Samples from the first collection have already been analysed and are reported in this deliverable. Samples from the second collection were collected and processed at RUBY, but the results have yet to be analysed. The next sample collection is planned for August until October 2022. This will be the last blood sampling.

6. Data evaluation and analysis

In initial versions of mHealth data transfer from bracelet to mHealth was automated resulting in a great amount of data. Unfortunately, besides the bad functionality of smart bracelet both devices (smart bracelet and mobile phone) discharged quickly.

Thus, the decision was made to transfer the data at least once a day only after the patient has measured his/her blood pressure measurement. Thus, patients received a notification every day reminding them to measure their blood pressure after which all other data was transferred. This approach managed to fix discharging issues but when the patient did not manage to transfer data from mHealth app (either by technical issues or by not measuring the blood pressure) to mClinican page, there were less data.

Review of gathered patient data that are clinically significant and could be analysed further.

6.1. Data from smart-bracelets

➔ Heart rate – it is possible to follow the pattern of measurement amplitude variations. In order for doctors to visually see the changes over a longer period visually it is considered to incorporate the corresponding graphs into mClinician.

→ Blood pressure - as smart-bracelet is not a medical device, these measurements could not be considered reliable medical results. We can only follow the pattern of measurement amplitude variations.

→ Steps - being measured by hand movement; steps represent general physical activity, not just steps. Similarly, as above, it is possible to follow the pattern of measurement amplitude variations. Preliminary results can be seen in attachment PERSIST_Number of steps_preliminary_results in PERSIST google drive folder D6.2. Deliverable attachments (https://drive.google.com/drive/folders/1oDpDXkDySGMb4A0D9aFvnDAskE8KVO 1h).

→ Calories - could not be considered useful for further analysis as patients do not update their weight measurements on a daily or monthly basis.

→ Sleep data - gathered data are unreliable, bracelets detect sleeping in the evening even if the patient just sits and doesn't move his/her hand. On the contrary, if the patient moves his/her hand at night while sleeping, the sleep counter stops. Therefore, the recorded sleep time varies from a few minutes to hours, therefore unable to be used for further analysis.

6.2. Data from patients by manual input

These data are the most reliable because the patients register themselves in the system. Still, some irregularities should be considered:

→ Questionnaires - in some cases patients from the breast cancer group receive questionnaires about colorectal cancer or vice versa. Some patients also report that sometimes the questionnaire starts in the patient language, but some other following questions are displayed in other languages. This could lead to partly filled questionnaires. Complaints were always sent to technical partners for evaluation and resolution as soon as possible.

→ Diaries - In general, patients do not like to record videos of themselves, as they are the older population. In some cases, a technical problem arises (for example, video stops) and they do not wish to redo the recording. In other cases, video is done, but not transferred.

→ Emotions - patients need to fill the emotion list in the mHealth every day. The first version of the emotion wheel was considered difficult to use by some patients. For example, they complained that they did not understand the meaning of some emotions; buttons were too small, etc. Adjustments were made to overcome these problems. Preliminary emotion analysis can be seen in attachment PERSIST_Patient_emotions _preliminary_results in PERSIST google drive folder D6.2. Deliverable attachments (https://drive.google.com/drive/folders/1oDpDXkDySGMb4A0D9aFvnDAskE8KVO 1h).

→ Other data by manual input - due to a malfunction and in case of wish to use their devices, some patients inserted also the number of steps and/or blood pressure measurement results. We do not know the quality of the devices from which this data was pulled from. Likewise, there could be a human error when writing numbers into the app.

6.3. Data from mClinican

Although mClinican has been designed to help clinicians for gathering patients data and enable them to have a data overview (long list of measurements), during the project the need for ingesting retrospective patient data has occurred so it's decided to develop a simple web interface for clinicians to enter and modify patients data. This user interface displays concepts from SYMPTOMA's API to create structured data for patients in FHIR format. The scale of the context has grown larger with the revealed information and feedback but from the user experience perspective, there is still room for progress and adjustments. For example, the page works slowly. Lots of information should be introduced manually, which takes a lot of time for clinicians/researchers. For example, manual radiotherapy dose introduction is quite long as one patient has several sessions with different dosages for long periods. For some clinical parameters, the values were different from what is used in some of the hospitals, so the specialists had to calculate the value and convert it before input.

As the Clinical Decision Support System (CDSS) is still under development, the clinicians do not receive feedback about specific patients' prognoses. According to the project, planning this will be introduced in September 2022. In order to engage clinicians, the plan for the mClinician mobile application had been reviewed and the following patient-related data will be available priorly; charts, questionnaire responses and CTC results.

All the data about patients from mHealth is not shown in a user-friendly way and no overview (latest trends) is seen. Accordingly, if a doctor needs to review the latest medical values, he/she has to scroll down all the measurements one by one.

6.4. Blood sample collections

Patient's blood samples were collected in SERGAS and UKCM in order to analyse the presence of CTCs. The presence of CTCs is considered a bad prognosis, being a hallmark of the occurrence of metastasis

Following the analysis of each sample, RUBY prepared a report for the clinicians that will be uploaded to the mClinician platform. Additionally, for each sample, the number of detected CTCs per classification was also independently introduced in the report. In the report, it is presented the CTC enumeration in the sample and the classification. For colorectal cancer (CRC) CTCs are classified as epithelial (CTCs expressing cytokeratin), mesenchymal (expressing vimentin) and EMT – epithelial to mesenchymal transition in

which cells are positive for both biomarkers. In breast cancer (BRC), CTCs are divided in HER2-positive and HER2-negative cells. Although the CTC enumeration is the parameter taken into consideration for the establishment of a good / bad prognosis, the classification of the cells into a specific phenotype is critical to assist clinician decisions in terms of treatment. The reports include representative images and specific comments that aim to support the clinician in the analysis of the presented results. An example of a report is presented in Figure 2 and 3.

Project	PERSIST
Report Date	05/08/2022

Patient ID	PRST_UKCM_CRC_P19_C1
Sample	1st collection
Sample Collection date	13/09/2021
Sample Processing date	15/09/2021
Responsible	Liliana Pires

BIOMARKERS

NUCLEUS	Blue (DAPI)
CYTOKERATIN	Green (FITC)
VIMENTIN	Orange (Or)
CD45	White (Cy5)

RESULTS

Epithelial CTC	DAPI+|CK+|Vim-|CD45-	FITC+|Or-|Cy5-	2
Epithelial-to-mesenchymal transition (EMT CTC)	DAPI+|CK+| Vim-|CD45-	FITC+|Or+|Cy5-	3
Mesenchymal CTC	DAPI+|CK-| Vim+|CD45-	FITC-|Or+|Cy5-	3
Comments	Eight different CTCs detected. All phenotypes observed (Epithelial, Mesenchymal and EMT).		

1

Figure 2 Report example page one

REPRESENTATIVE IMAGES (SORTED BY CLASSIFICATION)

All the images were acquired with 10x objective and are presented applying same software magnification.
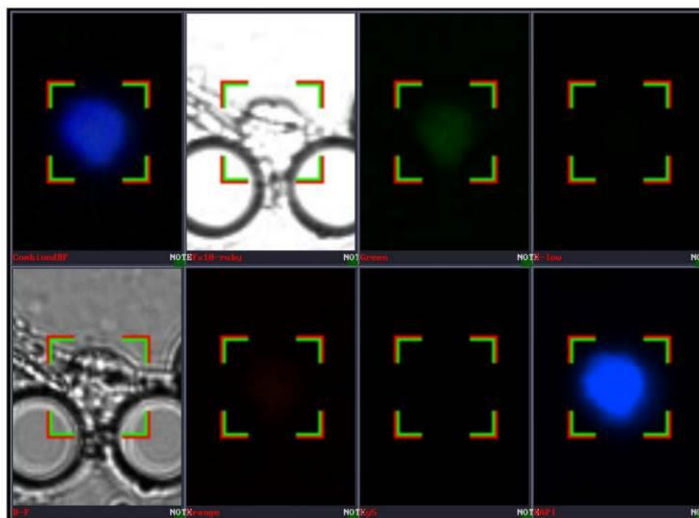
Epithelial CTC (FITC+|Or-|Cy5-)

2

Figure 3 Report example page two

From the results of the baseline sample collection, CTCs were detected in 21 out of 36 CRC patients and 14 out of 34 BRC patients. In most of the samples, the number of CTCs is low (<3) and the number of CTCs found in CRC patients was found to be higher in

comparison to BRC samples. The results are represented in Figure 4 along with the distribution according to the classification performed for the CTC type.
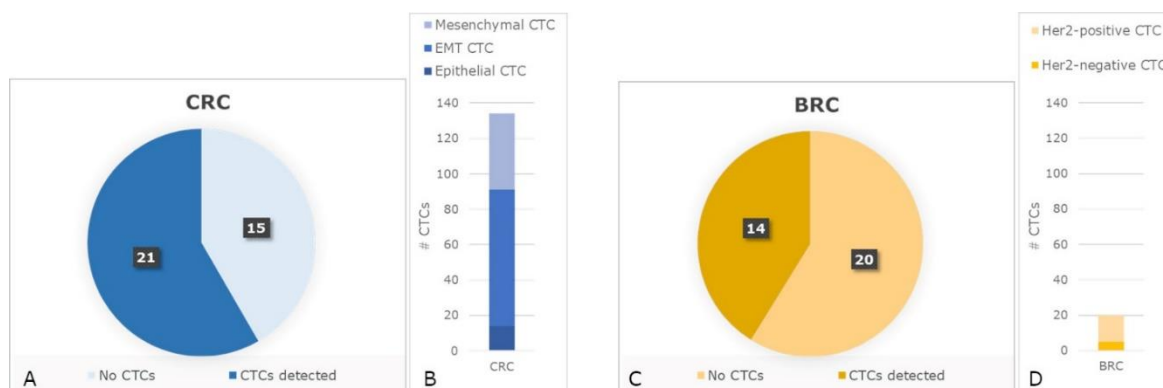

Figure 4 Detected CTCs in samples

In the majority of cases, the number of CTCs was very low with one or two cells per sample.

In order to give meaning to the results literature review by RUBYnanomed was done to find similar technologies and their used methods. The only technology currently approved and cleared for assessing CTCs is CellSearch. This technology uses magnetic beads that specifically bind the EpCam in the cell membrane of epithelial CTCs to isolate CTCs. This method fails to find mesenchymal CTCs as they lack epithelial markers and therefore are not recognized by the magnetic beads.

CellSearch has established the cut-off of ≥3 CTCs for CRC samples and ≥ 5 in BRC as a bad prognosis marker (https://www.cellsearchctc.com/clinical-applications/mcrc-clinical-trials-case-studies). Worth mentioning that the clinical validation trials were performed in metastatic patients.

RUBYnanomed is using the RUBYchipTM to isolate CTCs. The microfluidic device isolates CTCs based on their physical properties, namely size and deformability. In this context, the technology allows not only the isolation of epithelial CTCs, but also cells lacking endothelial markers, showing a mesenchymal phenotype. In this context, after CTCs isolation in the RUBYchipTM, the fluorescent labelling of the isolated cells using specific biomarkers allows the classification of the CTCs into different phenotypes.

RUBYnanomed has previously shown that a cut-off of ≥7 provides better discrimination of patients with bad and good prognosis, comparing to a cut-off of ≥ 3 (Ribeiro-Samy et al, (2019) Scientific Reports, https://doi.org/10.1038/s41598-019-44401-1). This difference is caused by the different method for the CTC isolation. Taking this into consideration the ≥7 cut-off in CRC and ≥ 5 in BRC the results are as follows (Figure 5).

These data will be completed with the analysis of the samples at the 6-month and 12-month follow up and contrasted with clinical data.
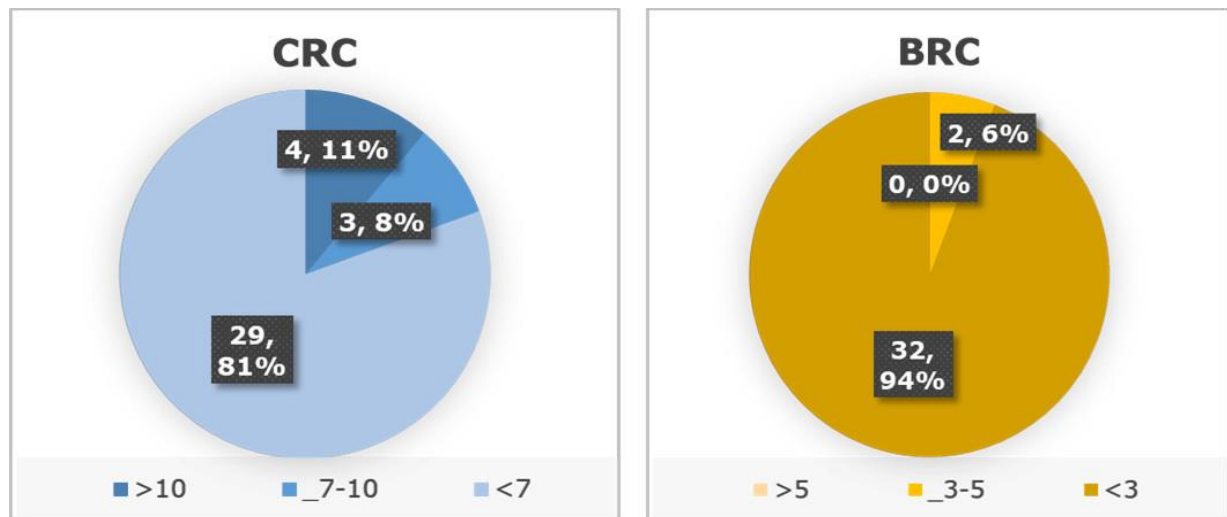
Figure 5 CTC amount in samples

Questionnaires filled by patients

7. General description

The scale communication and attitudinal self-efficacy for cancer (CASE-cancer) questionnaire was used to assess the primary endpoint of the clinical protocol, namely patients' perception of increased self-efficacy through the intervention of mHealthApp.

In addition, specific questionnaires related to satisfaction and usefulness were proposed to patients. For example, activation levels measured with the Patient Activation Measure (PAM) questionnaire and mHealthApp user acceptance assessed with the System Usability Scale (SUS) questionnaire were relevant tools to achieve one of the secondary endpoints.

At first, proposed questionnaires were explored (Table 6).

Questionnaires	N of items	Translations					Licence needed
		ES	FR	SL	LV	RU	
CASE-cancer (Communication and Attitudinal Self-Efficacy scale for cancer)	12	Not available. Translation needed.	Not available. Translation needed.	Not available. Translation needed.	Not available. Translation needed.	Not available. Translation needed.	
Patient Activation Measure (PAM-13)	13	Available.	Available	Not available. Translation needed.	Not available. Translation needed.	Available	YES (https://www.insigniahealth.com)
System Usability Scale (SUS)	10	Available	Available	Available	Not available. Translation needed.	Not available. Translation needed.	
User Experience Questionnaire (UEQ)	26	Available	Available	Available	Not available. Translation needed.	Available	
Directed Questions Scale - DQS	7	Not available. Translation needed.	Not available. Translation needed.	Not available. Translation needed.	Not available. Translation needed.	Not available. Translation needed.	

Table 6 Questionaire translation exploration

For questionnaires in English that do not have a validated translation in the five PERSIST languages, a translation-back translation methodology allowed to obtain them [1;3]. This

method is very often used for translating questionnaires to other languages. It consists of four steps:

➔ Step 1

✓ Independent translations of questionnaire items by several translators (at least three) from English into the target language (e.g. SL).

✓ It is recommended that translators have different professional backgrounds (e.g., health-care professional, psychologist, translator, native language speaker, this depends on the questionnaire itself).

➔ Step 2

✓ Independent translations are combined into one version in the target language.

✓ This should be done by a person who was not been involved in the first step.

➔ Step 3

✓ A combined version of the translation in the target language is translated back to English.

✓ This should also be done by a person who was not been involved in steps 1 or 2.

➔ Step 4

✓ Original version of the questionnaire and back-translated version in English are compared for possible discrepancies.

✓ These discrepancies are debated, and possible corrections for the translation to the target language are agreed.

✓ Ideally, this is done with two or more persons (who can be involved in previous steps).

8. System usability survey (SUS)

8.1. Analysis of System Usability Survey

The System Usability Survey consists of 10 statements about the user's perception of the system: the convenience of use, necessary skills etc. It was proposed in the five PERSIST languages: Latvian, Russian, Slovenian, Spanish and French. The survey and its translations can be seen in PERSIST google drive folder D6.2. Deliverable attachments: EN - SUS questionnaire; ES - SUS questionnaire; FR - SUS questionnaire; LV_SUS_questionnaire; RUS_SUS_questionnaire; SI - SUS questionnaire (https://drive.google.com/drive/folders/1oDpDXkDySGMb4A0D9aFvnDAskE8KVO1h).

The participants were asked to fill in the survey in three rounds. The first one was closed when the virtual agents were presented in the App (07.06.2022.). As all questionnaires were available at all times in the mHealth app all the time, some participants chose to complete these questionnaires more than once.

For each patient, the SUS score was calculated (77 questionnaires, filled 1st time). The sum score of the points of 10 questions can be seen in Figure 6. According to the definition of system usability level (table 7) most of the patients (39%) who replied think that system is acceptable to good. One quarter of patients replying (26%) considers that the system has some usability issues and 16% consider that it is not easy to use. Altogether, these results show that 46% of participants would like the system to be improved.
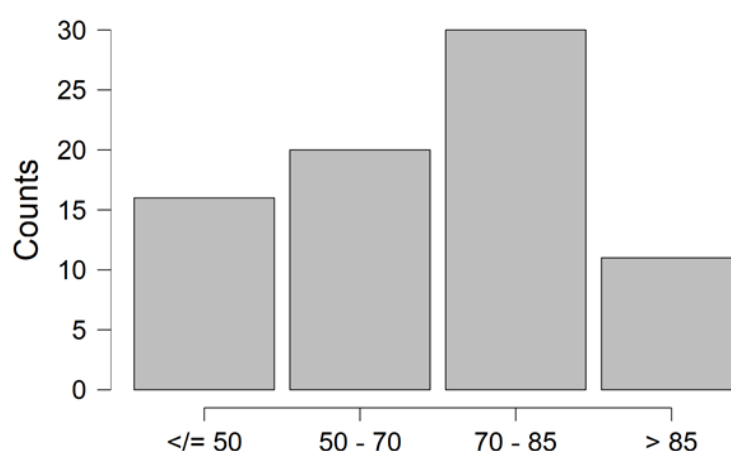
Figure 6 The sum score of the points acquired in all 10 questions

Level	Definition	Counts	Total	Proportion
<=50	Not easy to use	16	77	0.208
50-70	Experiencing usability issues	20	77	0.26
70-85	Acceptable to good	30	77	0.39
>85	Excellent usability	11	77	0.143

Table 7 The definition of system usability level

Figure 7 The score histogram

There is no significant difference in scores by the hospital; Kruskal-Wallis test p-value=0.075 (Figure 8).

Figure 8 The scores by centre

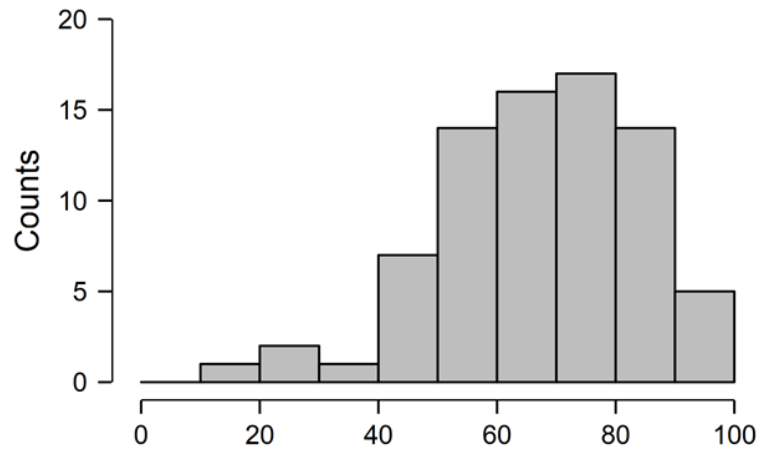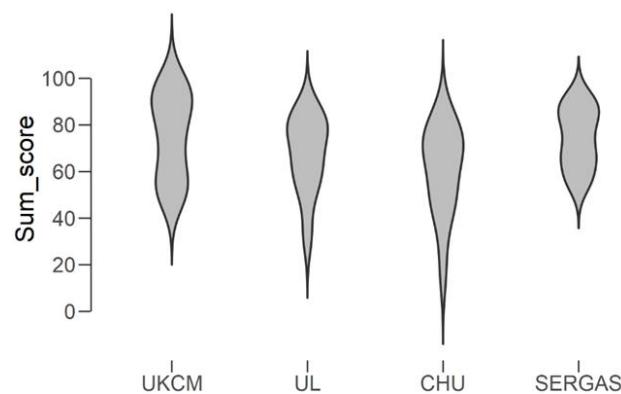In the initial analysis, we looked at the first feedback we received from each patient. Between January 19 and June 7 (year 2022), 77 participants filled in the survey at least once: 18 from CHU, 19 from SERGAS, 19 from UKCM and 21 from UL. The maximum number of times one patient had completed this survey was 56 (UKCM-47). The analysis is also carried out by grouping the responses by the centre to assess the potential differences that can be caused by differences in training, technical skills of the patients or different mentalities, and can be later analysed in more detail and acted upon if necessary.

➔ The first statement is: '**I think that I would like to use this system frequently**.' Here and for all the other statements in the survey the participant can choose an answer on a Likert scale from 1 (strongly disagree) to 5 (strongly agree). The descriptive statistics of the results are given in Table 8, and they show that the majority of the participants neither agree nor disagree with this statement.

	CHU	SERGAS	UKCM	UL	ALL
Median	3	4	4	3	3
Mode	3	3	5	3	3
25th percentile	2	3	3	3	3
75th percentile	3.75	4.5	5	4	5

Table 8 Descriptive statistics of SUS 1st statement

There are slight differences among centres (see Fig. 9): the participants from UKCM tend to agree with the statement 'I think that I would like to use this system frequently.' more often than participants from other hospitals, while participants from CHU tend to disagree more often than from other centres. However, this difference is small and statistically insignificant (Kruskal-Wallis test: p=0.069).
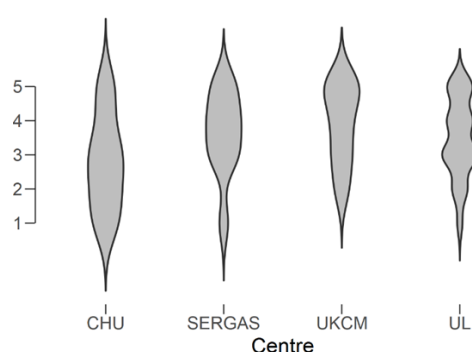
Figure 9 SUS 1st statement replies by the centres

➔ The second statement is: '**I found the system unnecessarily complex**.' The descriptive statistics are given in Table 9. Here the majority of the participants disagree, meaning that the majority of the participants believe the system is not unnecessarily complex.

	CHU	SERGAS	UKCM	UL	ALL
Median	3	2	2	2	2
Mode	3	1	1	2	1
25th percentile	2	1	1	2	1
75th percentile	3	3	3	3	3

Table 9 Descriptive statistics of SUS 2nd statement

The responses to this statement are similar across all centres (Fig. 10) and there is no statistically significant difference (Kruskal-Wallis test: p=0.097).
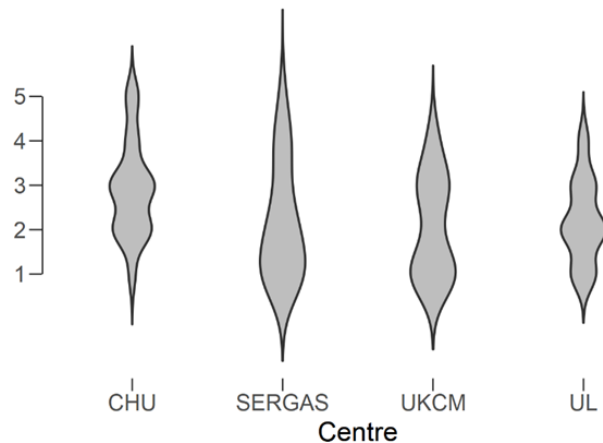
Figure 10 SUS 2ⁿᵈ statement replies by the centres

→ The third statement in the survey is: '**I thought the system was easy to use**.' The descriptive statistics are given in Table 10.

	CHU	SERGAS	UKCM	UL	ALL
Median	4	4	4	4	4
Mode	4	5	5	5	5
25th percentile	3	3	4	3	3
75th percentile	4	5	5	5	5

Table 10 Descriptive statistics of SUS 3ʳᵈ statement

Although there are minor differences among centres (e.g., there were higher variations in answers from SERGAS, see Figure 11), all participants were more likely to agree or strongly agree with the statement and the differences were not statistically significant (Kruskal-Wallis test: $p=0.296$).
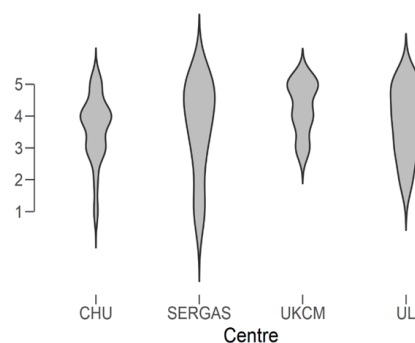

Figure 11 SUS 3ʳᵈ statement replies by the centres

→ The fourth statement in the survey is: '**I think that I would need the support of a technical person to be able to use this system**.' The descriptive statistics are given in Table 11. The majority of the participants disagree that they would need support from a technical person.

	CHU	SERGAS	UKCM	UL	ALL
Median	2	1	1	2	2
Mode	2	1	1	2	1
25th percentile	1.25	1	1	2	1
75th percentile	3	2	2.5	3	3

Table 11 Descriptive statistics of SUS 4th statement

There are some minor differences among centres: participants from SERGAS and UKCM centres strongly disagree with the statement while participants from CHU and UL disagree, and the variability of the answers is higher in CHU and UL. These differences (see Figure 12) are statistically significant (Kruskal-Wallis test: p=0.046), but they do not change the main conclusion.

Figure 12 SUS 4th statement replies by the centres

➔ The fifth statement in the survey is: '**I found the various functions in this system were well integrated**.' The descriptive statistics are given in Table 12. The majority of the participants are undecided or agree with the statement.

	CHU	SERGAS	UKCM	UL	ALL
Median	3	4	4	4	4
Mode	3	4	5	4	3
25th percentile	3	3	3	3	3
75th percentile	3	5	5	5	5

Table 12 Descriptive statistics of SUS 5th statement

There are some minor differences among centres: participants from CHU mostly neither agree nor disagree, while participants from other centres mostly agree. These differences (see Figure 13) are statistically significant (Kruskal-Wallis test: p=0.005), but they do not change the main conclusion.
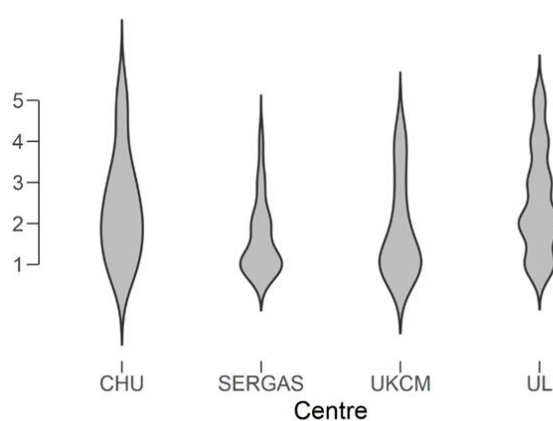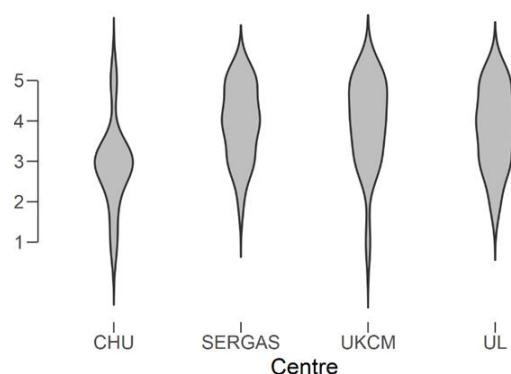
Figure 13 SUS 5th statement replies by the centres

➔ The sixth statement in the survey is: **'I thought there was too much inconsistency in this system.**' The descriptive statistics are given in Table 13. The majority of the participants are undecided or disagree with the statement.

	CHU	SERGAS	UKCM	UL	ALL
Median	3	3	2	2	3
Mode	3	3	2	1	3
25th percentile	2	2	1.5	1	2
75th percentile	3	3	3	4	3

Table 13 Descriptive statistics of SUS 6^{tht} statement

There are some minor differences among centres (see Figure 14) but they are not statistically significant (Kruskal-Wallis test: p=0.351).
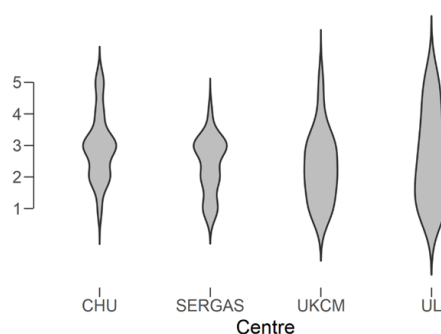
Figure 14 SUS 6th statement replies by the centres

➔ The seventh statement in the survey is: '**I would imagine that most people would learn to use this system very quickly**.' The descriptive statistics are given in Table 14. The majority of the participants agree with the statement.

	CHU	SERGAS	UKCM	UL	ALL
Median	4	4	4	4	4
Mode	3	5	5	5	5
25th percentile	3	4	4	3	3
75th percentile	4.75	5	5	5	5

Table 14 Descriptive statistics of SUS 7tht statement

There are some minor differences among centres (see Figure 15) but they are not statistically significant (Kruskal-Wallis test: p=0.411).

Figure 15 SUS 7th statement replies by the centres

➔ The eighth statement in the survey is: **'I found the system very cumbersome/awkward to use.'** The descriptive statistics are given in Table 15. The majority of the participants disagree with the statement.

	CHU	SERGAS	UKCM	UL	ALL
Median	2	2	2	2	2
Mode	1	1	1	2	1
25th percentile	1	1	1	1	1
75th percentile	3	2	3	3	3

Table 15 Descriptive statistics of SUS 8th statement

There are some minor differences among centres (see Figure 16) but they are not statistically significant (Kruskal-Wallis test: p=0.774).

Figure 16 SUS 8th statement replies by the centres

➔ The ninth statement in the survey is: **'I felt very confident using the system.**' The descriptive statistics are given in Table 16. The majority of the participants agree with the statement.

	CHU	SERGAS	UKCM	UL	ALL
Median	3.5	4	4	4	4
Mode	3	4	3	4	5
25th percentile	3	4	3	3	3
75th percentile	5	5	5	4	5

Table 16 Descriptive statistics of SUS 9th statement

There are some minor differences among centres (see Figure 17) but they are not statistically significant (Kruskal-Wallis test: p=0.553).

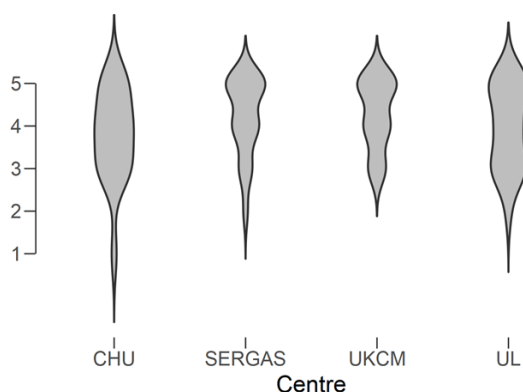

Figure 17 SUS 9th statement replies by the centres

➔ The tenth statement in the survey is: '**I needed to learn a lot of things before I could get going with this system**.' The descriptive statistics are given in Table 17. The majority of the participants disagree with the statement.

	CHU	SERGAS	UKCM	UL	ALL
Median	2	1	1	2	2
Mode	1	1	1	1	1
25th percentile	1	1	1	1	1
75th percentile	3	2.5	3	3	3

Table 17 Descriptive statistics of SUS 10th statement

There are some minor differences among centres (see Figure 18) but they are not statistically significant (Kruskal-Wallis test: p=0.503).
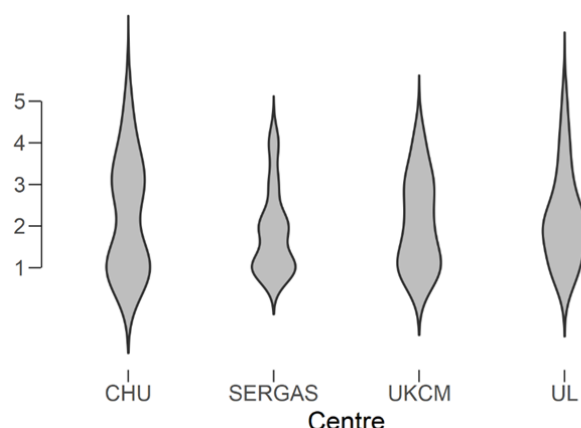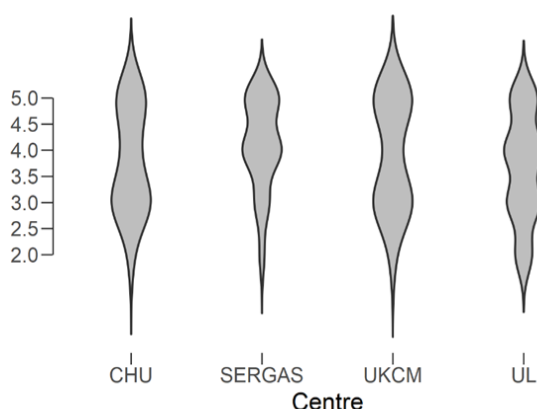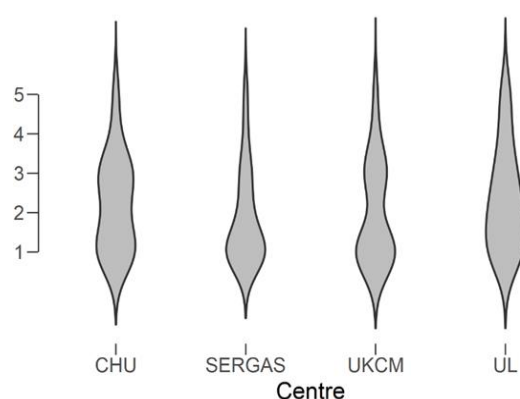

Figure 18 SUS 10th statement replies by the centres

➔ Although there have been some shortcomings during the introduction of the system, overall, the participants were comfortable using the system and the majority of them:

✓ 1. Were undecided if they would like to use this system frequently.

✓ 2. Did not find the system unnecessarily complex.

✓ 3. Thought that the system was easy to use.

✓ 4. Didn't think that they would need the support of a technical person to be able to use this system.

✓ 5. Were undecided or found the various functions in this system were well integrated.

✓ 6. Were undecided or thought there was not too much inconsistency in this system.

✓ 7. Would imagine that most people would learn to use this system very quickly.

✓ 8. Did not find the system very cumbersome/awkward to use.

✓ 9. Felt confident using the system.

✓ 10. Did not need to learn many things before they could get going with this system.

To address the points that show some inconvenience while using the system (1, 5, 6 points), the system managers will introduce the necessary changes at the end of the pilot to cause less confusion for future users, who will be able to use a well-tested and stable system. It is possible that this inconvenience was because of many of the updates of mHealth.

In order to evaluate if the feedback from the participants changed, we analysed the changes in participants' responses between their first survey and the last survey they had filled in if the time between completion of both surveys was more than one month: this time was assumed to be enough for the participant to get accustomed to the system. Overall, surveys from 31 participant matched these criteria.

The significance of these changes was analysed using the Wilcoxon Signed Ranks test. The test results for each question are given in Table 18. The p-values show that there were no significant changes in participants' responses after using the system for more than a month.

Statement	p-value
I think that I would like to use this system frequently.	0.674
I found the system unnecessarily complex.	0.961
I thought the system was easy to use.	0.679
I think that I would need the support of a technical person to be able to use this system.	0.103
I found the various functions in this system were well integrated.	0.134
I thought there was too much inconsistency in this system.	0.080
I would imagine that most people would learn to use this system very quickly.	0.346
I found the system very cumbersome/awkward to use.	0.718
I felt very confident using the system.	0.173
I needed to learn a lot of things before I could get going with this system.	0.677

Table 18 Wilcoxon Signed Ranks test results comparing SUS after more than one month

The summary of changes is given in the table 19 below: the numbers represent the count of participants with the particular change of response; the darker green corresponds to higher counts.

Statement	4 points towards disagreeing	3 points towards disagreeing	2 points towards disagreeing	1 point towards disagreeing	No change	1 point towards agreeing	2 points towards agreeing	3 points towards agreeing	4 points towards agreeing
I think that I would like to use this system frequently.		1	1	7	17	2	2		1
I found the system unnecessarily complex.	1	1	2	3	14	7	3		
I thought the system was easy to use.	1		3	5	14	5	3		
I think that I would need the support of a technical person to be able to use this system.	1		1	9	16	3	1		
I found the various functions in this system were well integrated.				4	18	8	1		
I thought there was too much inconsistency in this system.			8	5	10	7		1	
I would imagine that most people would learn to use this system very quickly.			1	8	16	6			
I found the system very cumbersome/awkward to use.			2	6	17	4	2		

I felt very confident using the system.			1	4	17	5	3	1	
I needed to learn a lot of things before I could get going with this system.	1		2	3	21	1	3		

Table 19 SUS responses changes summary

Mann-Whitney U test was run to evaluate differences between participants younger than 55 and those who are at least 55 years old. There were some statistically significant differences.

Older participants (55 years old and older) tend to agree more with:

→ I found the system unnecessarily complex (p=0.049)

→ I think that I would need the support of a technical person to be able to use this system. (p=0.002)

→ I found the system very cumbersome/awkward to use. (p=0.016)

→ I needed to learn a lot of things before I could get going with this system. (p=0.047)

And disagree with:

→ I would imagine that most people would learn to use this system very quickly. (p=0.002)

→ However, these differences were not enough for the total score to differ significantly (p=0.063).

9. Patient Activation Measure Scale (PAM) questionnaires

PAM Score is an interval-level scale from 0-100 that correlates to one of four levels of patient activation. PAM Levels 1 and 2 indicate lower patient activation, while PAM Levels 3 and 4 indicate higher patient activation.

→ Level 1: Disengaged and overwhelmed, individuals are passive and lack confidence. Healthcare knowledge is low, goal orientation is weak, and adherence is poor.

→ Level 2: Becoming aware but still struggling, Individuals have some health-care knowledge, but large gaps remain. They believe health is largely out of their control but can set simple goals.

→ Level 3: Taking action and gaining control, individuals have the key facts and are building self-management skills. They strive for best practice behaviours and are goal-oriented.

→ Level 4: Maintaining behaviours and pushing further, individuals have adopted new behaviours but may struggle at times of stress or change. Maintaining a healthy lifestyle is a key focus. In the first analysis, we used Wilcoxon test to compare median scores at the recruitment vs at the last follow-up. We didn't find any statistical differences (p=0.838).

		PAM Score pre	PAM Score post
N	Valid	128	128
	Lost	0	0
Median		68.3789	68.5781
Mean		65.5000	66.6500
Std. Dev.		16.31656	17.78457
Percentiles	25	55.6000	55.6000
	50	65.5000	66.6500
	75	77.7000	80.9000

Table 20 Descriptive statistics on PAM score results on recruitment and follow-up

Wilcoxon test p= 0.838

Next, we compared, with McNemar's test, the percentage of patients in each level at the recruitment vs at the last follow-up. We did not find any statistical differences.

Level	Recruitment (pre)	Last follow-up (post)	p
Level 1 n (%)	8 (6.3)	14 (10.9)	0.146
Level 2 n (%)	18 (14.1)	16 (12.5)	0.845
Level 3 n (%)	52 (40.6)	44 (34.4)	0.341
Level 4 n (%)	50 (39.1)	54 (42.2)	0.636

Table 21 The percentage comparison of patients in each level at the recruitment vs at the last follow-up

Conclusion: There were no statistical differences in the median PAM score at recruitment vs at the last follow-up. Regarding the percentage of patients in each level, although we didn't find statistical differences when comparing pre vs post, we observed that the percentage of patients in levels 1 and 4 increased in the last follow-up. On the contrary, the percentage of patients in levels 2 and 3 decreased in the last follow-up.

10. Communication and Attitudinal Self-Efficacy scale for cancer (CASE cancer) questionnaires

Wolf., et al (2005) developed the Communication and Attitudinal Self-Efficacy scale for cancer (CASE-cancer) [1]. They suggest three 4-item CASE-cancer factors in order to analyse patients' responses. These factors are 1) understanding & participate in care, 2) maintaining a positive attitude and 3) seeking & obtain information. We calculate a score for each factor, the higher the score, the better the result (more positive).

For each factor, we compare the scores obtained at recruitment and the last follow-up. We only included patients who have pre and post data. We did not find any statistical differences in the scores at recruitment vs the scores at the last follow-up.

10.1. Factor 1 understand & participate in care

No differences, in the understanding and participation in care at the recruitment vs at the last follow-up, were found (p=0.790).

		F1_UnderstandParticipateCare_pre	F1_UnderstandParticipateCare_post
N	Valid	126	126
	Lost	0	0
Median		14,00	13,92
Mean		14,00	14,00
Std. Dev.		1,939	2,010
Min		8	5
Max		16	16
Percentiles	25	12,75	13,00
	50	14,00	14,00
	75	16,00	16,00

Table 22 Descriptive statistics of differences in the understanding and participation in care

Wilcoxon test p= 0.790

10.2. Factor 2 maintain positive attitude

No differences, in maintaining a positive attitude at the recruitment vs at the last follow-up, were found (p=0.624).

		F2_PositiveAttitude_pre	F2_PositiveAttitude_post
N	Valid	126	126
	Lost	0	0
Median		13,67	13,47
Mean		14,00	14,00
Std. Dev.		2,150	2,442
Min		6	6
Max		16	16
Percentiles	25	13,00	12,00
	50	14,00	14,00
	75	15,25	16,00

Table 23 Descriptive statistics of differences in maintaining a positive attitude

Wilcoxon test p= 0.624

10.3. Factor 3 seek & obtain information

No differences, in seeking and obtaining information about their health condition at the recruitment vs at the last follow-up, were found (p=0.880).

		F3_SeekObtainInformation_pre	F3_SeekObtainInformation_post
N	Valid	126	126
	Lost	0	0
Median		14,01	13,84
Mean		15,00	15,00
Std. Dev.		2,163	2,364
Min		8	5
Max		16	16
Percentiles	25	12,00	12,00
	50	15,00	15,00
	75	16,00	16,00

Table 24 Descriptive statistics of differences in seeking and obtaining information about their health condition

Wilcoxon test p= 0.88

11. PERSIST A, B, C block questionnaires and analysis

In order to partly compensate for lesser follow-up visits due to Covid-19 situation restrictions and to gain direct feedback from patients whenever they are ready to give one, the PERSIST A, B, and C block questionnaires were created. A part mainly concentrates on feedback about Project, B part about mHealth, but C part – about devices given to patients (mobile phone and Smart-bracelet).

11.1. Part A: feedback about the project

78 complete surveys of part A were filled in: 16 from CHU, 21 from SERGAS, 25 from UKCM, 16 from UL.

➔ How do you rate your experience with participation in the PERSIST project (in general)?

There is a statistically significant difference among centres (Kruskal-Wallis test p-value=0.012): UL has significantly lower values (Table 25, Figure 19)

	CHU	SERGAS	UKCM	UL	ALL
Median	7	8	8	5	7
Mode	7	8	8	5	8
25th percentile	5.75	7	6	5	5
75th percentile	7.25	10	8	7.25	8

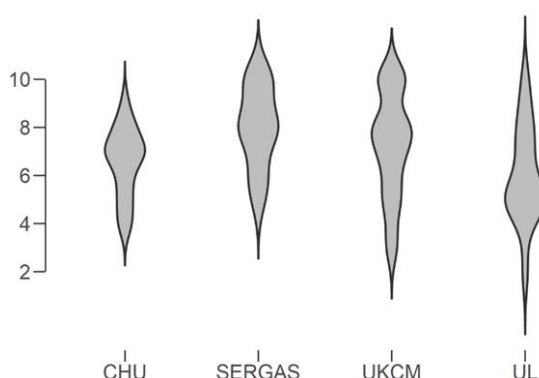*Table 25 Descriptive statistics of PERSIST Part A 1st statement*

Figure 19 PERSIST Part A 1st statement replies by the centres

➔ Are the instructions and explanations about the project from personnel understandable to you?

There is no statistically significant difference among centres (Kruskal-Wallis test p-value=0.148) (Table 26, Figure 20).

	CHU	SERGAS	UKCM	UL	ALL
Median	9	9	9	8	9
Mode	9	9	10	9	9
25th percentile	7	8	8	6.75	8
75th percentile	9	10	10	9	10

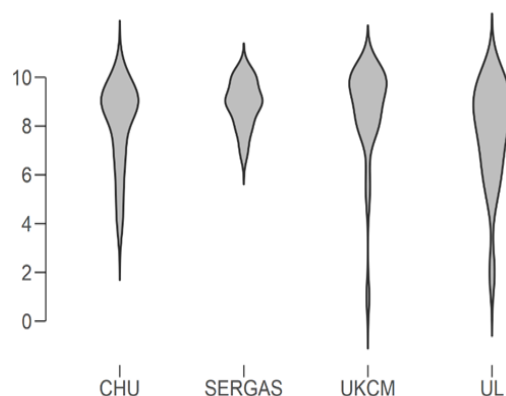*Table 26 Descriptive statistics of PERSIST Part A 2nd statement*

Figure 20 PERSIST Part A 2nd statement replies by the centres

➔ How does the participation in the PERSIST project make you feel?

There is a statistically significant difference among centres (Kruskal-Wallis test p-value=0.018): UL has significantly more lower values (Table 27, Figure 21).

	CHU	SERGAS	UKCM	UL	ALL
Median	8	9	8	6.5	8
Mode	9	10	10	5	10
25th percentile	6.75	8	7	5	7
75th percentile	9	10	10	8.25	10

Table 27 Descriptive statistics of PERSIT Part A 3rdt statement
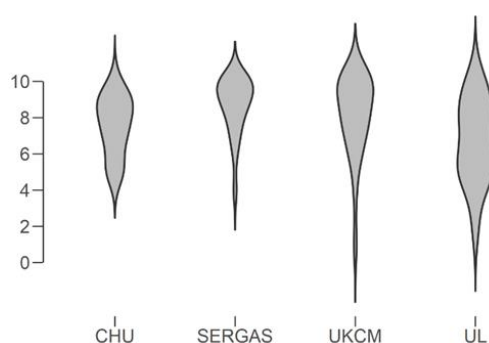

Figure 21 PERSIST Part A 3rd statement replies by the centres

To evaluate the dynamics of participants' feedback, the first and the last survey that they had filled in were compared (if the time between the two surveys was more than 1 month). Overall, 39 participants fit the criteria and the differences in their answers were compared. The Wilcoxon sign test results are given in Table 28.

Question	p-value
How do you rate your experience with participation in the PERSIST project (in general)?	0.220
Are the instructions and explanations about the project from personnel understandable to you?	0.606
How does the participation in the PERSIST project make you feel?	0.807

Table 28 Wilcoxon sign test results for PERSIST Part A response comparison

The results show that there are no statistically significant differences in the participants' answers. The differences in scores (1-10) for each question are given in Table 29.

Question	Difference in score for each question and their corresponding frequency (count)										
	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6
How do you rate your experience with participation in the PERSIST project (in general)?		2	1	4	21	5	4	2	1		
Are the instructions and explanations about the project from personnel understandable to you?		1	4	4	22	7	1		1		
How does the participation in the PERSIST project make you feel?	1		3	7	22	2	4				1

Table 29 Differences in the participants' answers of PERSIST Part A

➔ If you could change one or several things in PERSIST project that would be (for example, more follow-up visits or daily calls)

Only the first questionnaire filled in by each patient free text answers was analysed. Altogether there were 78 questionnaires (the first ones only; see Fig 22.).

The top four answers from patients asked whether something should be changed were – they would like to have more meetings and appointments with doctors (24,4%); they would like more calls from personnel (14,1%); everything is good (12,8%) and nothing should be changed (11,5%).
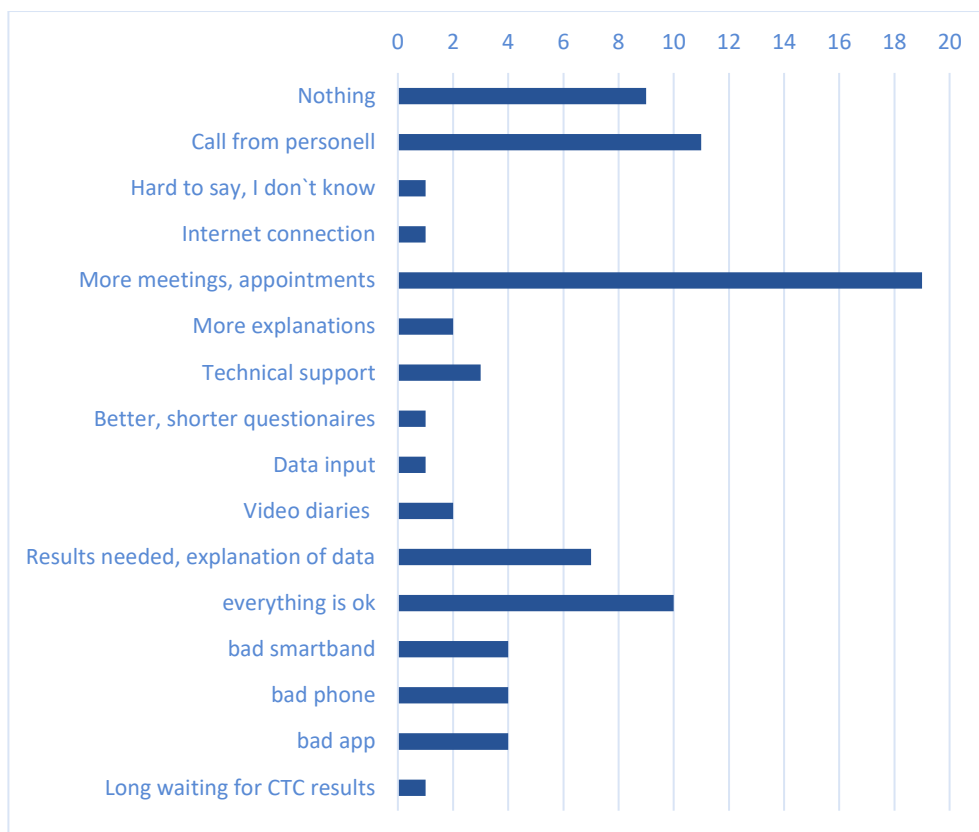

Figure 22 Patients answers whether something should be changed in the PERSIST system. (Numbers represent times mentioned)

Mann-Whitney U test was run to compare the responses between age groups (younger than 55 vs at least 55 years old). There were no significant differences in the responses to questions in Block A.

	W	p
How does the participation in the PERSIST project make you feel?	726.500	0.966
How do you rate your experience with participation in the PERSIST project (in general)?	804.500	0.386
Are the instructions and explanations about the project from personnel understandable to you?	807.500	0.360
Note. Mann-Whitney U test.		

Table 30 Mann-Whitney U test results comparing responses between age groups

11.2. Part B: feedback about mHealth

64 B surveys were filled in: 15 from CHU, 18 from SERGAS, 17 from UKCM, 14 from UL.

➔ How do you rate your experience with the mHealth app? From 1 (really bad) to 10 (excellent)

There is no statistically significant difference among centres (Kruskal-Wallis test p-value=0.216) (Table 31, Figure 23).

	CHU	SERGAS	UKCM	UL	ALL
Median	7	8	7	6	7
Mode	6	8	6	5	8
25th percentile	5.5	7	6	5	5
75th percentile	8	9	8	8	8.25

Table 31 Descriptive statistics of PERSIST Part B 1st statement
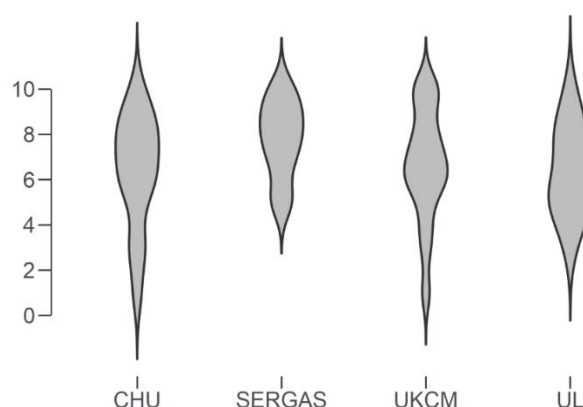

Figure 23 PERSIST Part B 1st statement replies by the centres

➔ Are the instructions and explanations about mHealth app usage understandable? **From 1 (completely confusing) to 10 (completely clear):**

There is no statistically significant difference among centres (Kruskal-Wallis test p-value=0.459). Data shows that most of the patients approve – instructions are understandable (Table 32, Figure 24).

	CHU	SERGAS	UKCM	UL	ALL
Median	8	9	8	7.5	8
Mode	8	9	7	10	10
25th percentile	5.5	7.25	7	5.25	6.75
75th percentile	9	9.75	9	9.75	9

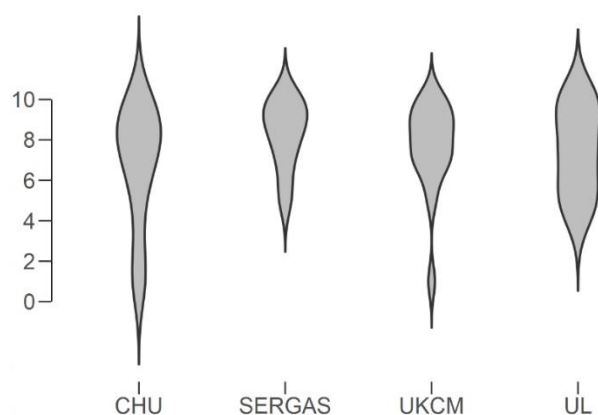*Table 32 Descriptive statistics of PERSIST Part B 2nd statement*

Figure 24 PERSIST Part B 2nd statement replies by the centres

➔ Do you follow up your gathered data in the mHealth app? **From 1 (no at all) to 10 (all the time):**

There is no statistically significant difference among centres (Kruskal-Wallis test p-value=0.065) (Table 33, Figure 25).

	CHU	SERGAS	UKCM	UL	ALL
Median	7	7.5	9	7.5	8
Mode	7	10	10	9	10
25th percentile	3.5	6	8	5.25	5
75th percentile	8	9	10	9	9

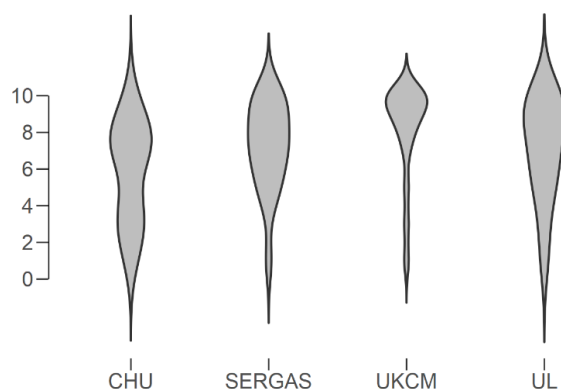*Table 33 Descriptive statistics of PERSIST Part B 3rd statement*

Figure 25 PERSIST Part B 3rd statement replies by the centres

➔ Does the mHealth app affect your behaviour? From 1 (no at all) to 10 (I modify my behaviour after looking at the data):

There is a statistically significant difference among centres (Kruskal-Wallis test p-value=0.049). The participants from UKCM have the higher scores (Table 34, Figure 26).

	CHU	SERGAS	UKCM	UL	ALL
Median	5	2.5	7	5	5
Mode	1	1	5	1	1
25th percentile	1.5	1	5	4	2
75th percentile	6.5	5	8	8	7

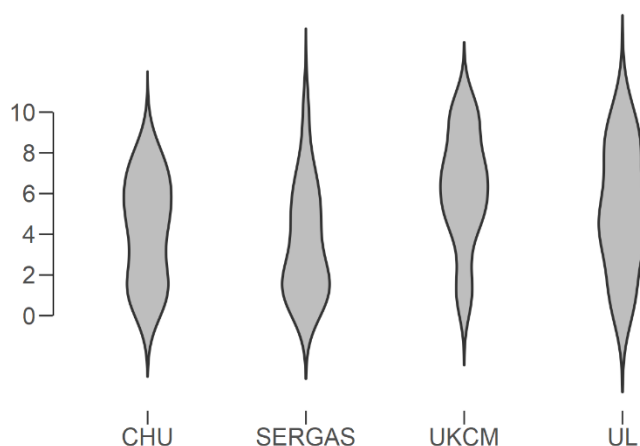*Table 34 Descriptive statistics of PERSIST Part B 4th statement*

Figure 26 PERSIST Part B 4th statement replies by the centres

→ How do you rate the emotion wheel/detection in the app? From 1 (bad, confusing) to 10 (super, interesting):

There is no statistically significant difference among centres (Kruskal-Wallis test p-value=0.829) (Table 35, Figure 27).

	CHU	SERGAS	UKCM	UL	ALL
Median	6	5	6	5	5
Mode	8	5	8	2	8
25th percentile	4	4.25	4	3	3
75th percentile	8	5.75	8	8	8

Table 35 Descriptive statistics of PERSIST Part B 5th statement
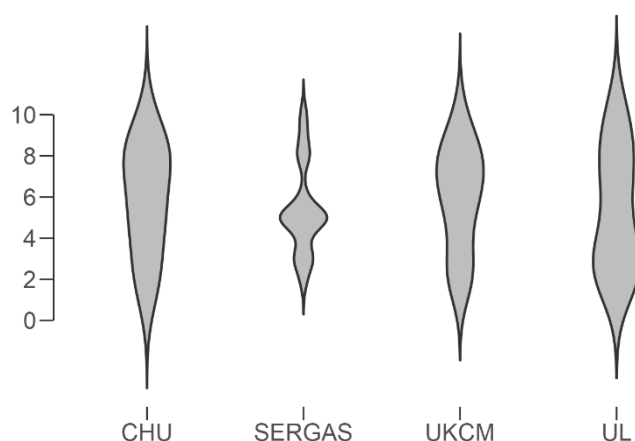

Figure 27 PERSIST Part B 5th statement replies by the centres

➔ How do you rate your experience with diary recording? **From 1 (bad, confusing) to 10 (super, interesting):**

There is a statistically significant difference among centres (Kruskal-Wallis test p-value=0.005). Participants from UL gave the lowest scores to their experience recording video diaries (only 2.5). 75% of the participants from UL assigned this functionality a score of 5 or less. Participants from CHU and SERGAS rate video diaries experience as average, but UKCM have the highest rate (Table 36, Figure 28).

	CHU	SERGAS	UKCM	UL	ALL
Median	5	5	7	2.5	5
Mode	5	5	7	1	5
25th percentile	3	3.25	6	1.25	3
75th percentile	6.5	7.75	8	5	7

Table 36 Descriptive statistics of PERSIST Part B 6th statement
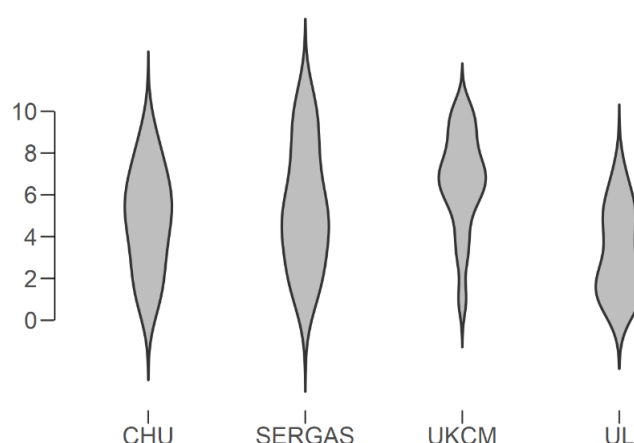
Figure 28 PERSIST Part B 6th statement replies by the centres

➔ How do you rate your experience with questionnaires in the app? **From 1 (bad) to 10 (excellent):**

There is no statistically significant difference among centres (Kruskal-Wallis test p-value=0.076) (Table 37, Figure 29).

	CHU	SERGAS	UKCM	UL	ALL
Median	6	7	8	7	7
Mode	6	6	8	7	8
25th percentile	5	6	7	5.25	6
75th percentile	6.5	8.75	9	8	8

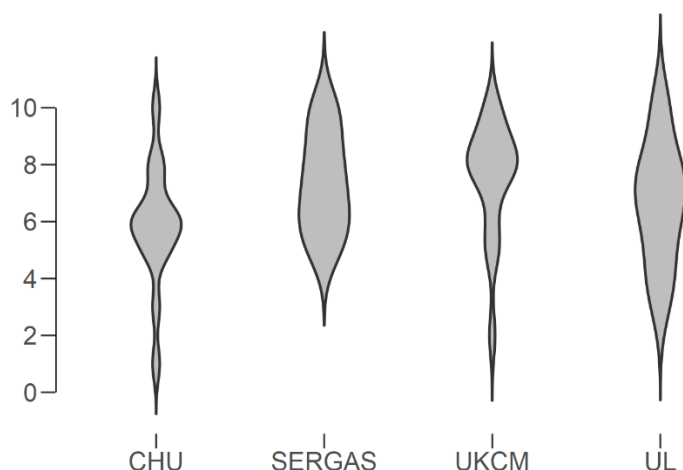*Table 37 Descriptive statistics of PERSIST Part B 7th statement*

Figure 29 PERSIST Part B 7th statement replies by the centres

To evaluate the dynamics of participants' feedback, the first and the last survey that they had filled in were compared (if the time between the two surveys was more than 1 month). In total, 28 surveys (part B) fit the criteria and the differences in their answers were compared. The Wilcoxon sign test results are given in Table 38.

Question	p-value
How do you rate the emotion wheel/detection in the app?	0.519
How do you rate your experience with questionnaires in the app?	0.291
How do you rate your experience with diary recording?	0.743
How do you rate your experience with the mHealth app?	0.476
Are the instructions and explanations about mHealth app usage understandable?	0.138
Do you follow up your gathered data in the mHealth app?	0.618
Does the mHealth app affect your behaviour?	0.190

Table 38 The Wilcoxon sign test results of PERSIST Part B

The results show that there are no statistically significant differences in the participants' answers over time. The differences in scores (1-10) for each question are given in Table 39.

Question	Change in the score (score in the last survey - score in the first survey)																
	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7
How do you rate the emotion wheel/detection in the app?				1	1	1	1	2	4	11	2	3		1	1		1
How do you rate your experience with questionnaires in the app?							2	4	2	14	3	3					
How do you rate your experience with diary recording?						1	1	3	4	9	3	6					
How do you rate your experience with the mHealth app?					1	1	2	1	1	16	4	1			1		
Are the instructions and explanations about mHealth app usage understandable?							1		5	12	4	5				1	
Do you follow up your gathered data in the mHealth app?	1			1	1		1	1	3	12	5		1	1	1		
Does the mHealth app affect your behaviour?					1		1	4	3	6	3	2	6	1	1		

Table 39 Statistical differences in the participants' answers over time in PERSIST Part B

→ If you could change one or several things in mHealth app that would be (name it/write):

Only the first questionnaire filled in by each patient was analysed. Altogether there were 64 questionnaires (the first ones only). The most controversial thing in mHealth app for patients (23% of all answers) still seems emotion wheel, followed by – no changes are necessary (17%) and diaries (9%) (Figure 30.).
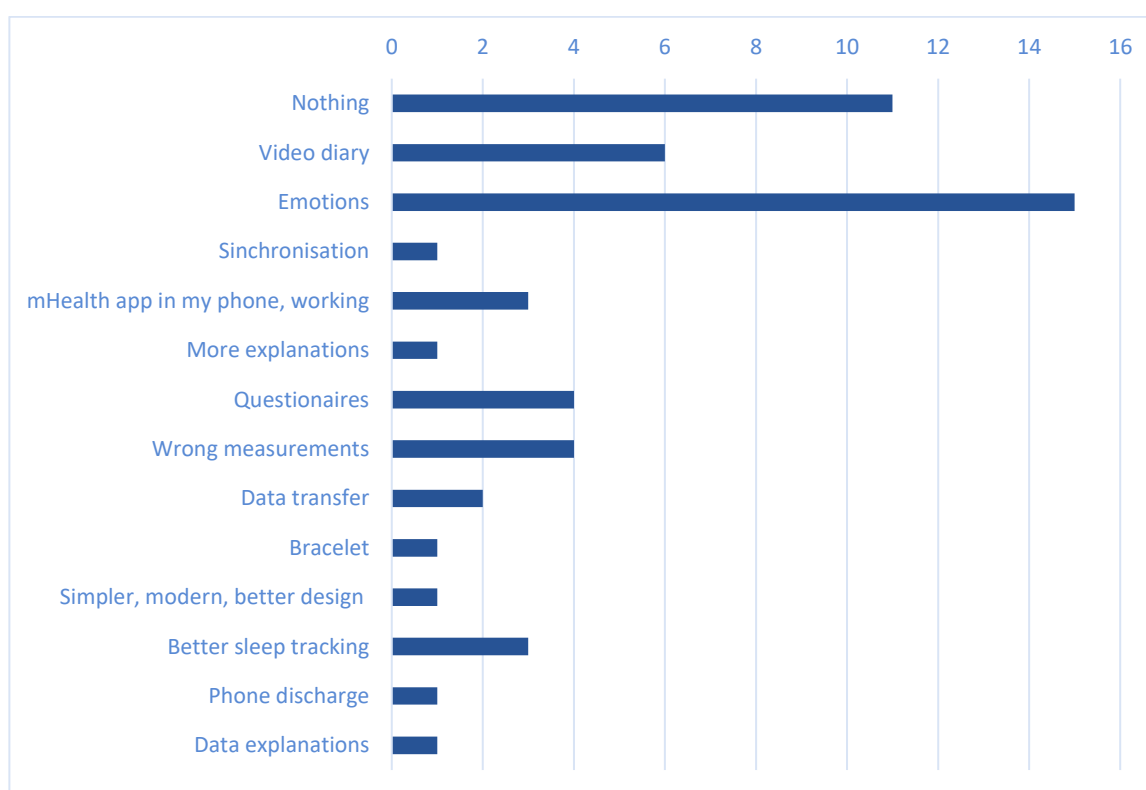

Figure 30 Patient replies about changes in mHealth

The differences between age groups were also analysed in Block B answers (Mann-Whitney U test). There were no significant differences between groups in any question (Table 40.).

	W	p
How do you rate the emotion wheel/detection in the app?	563.500	0.237
How do you rate your experience with questionnaires in the app?	519.000	0.582
How do you rate your experience with diary recording?	430.500	0.487
How do you rate your experience with the mHealth app?	457.000	0.749
Are the instructions and explanations about mHealth app usage understandable?	580.000	0.155
Do you follow up your gathered data in the mHealth app?	547.500	0.340
Does the mHealth app affect your behaviour?	502.500	0.754
Note. Mann-Whitney U test.		

Table 40 Mann-Whitney U test results for PERSIST Part B

11.3. Block C feedback about devices

59 C surveys were filled in 15 from CHU, 14 from SERGAS, 19 from UKCM, 11 from UL. The following surveys were dismissed from the analysis due to missing answers to at least one question: UKCM-31, UL-30.

➔ How do you rate your experience with smart-bracelets?

There is no statistically significant difference among centres (Kruskal-Wallis test p-value=0.914) (Table 41, Figure 31).

	CHU	SERGAS	UKCM	UL	ALL
Median	7	7.5	7	8	7
Mode	5	5	8	5	8
25th percentile	5	5	5.5	5	5
75th percentile	8	8.75	8	8.5	8

Table 41 Descriptive statistics of PERSIST Part C 1st statement

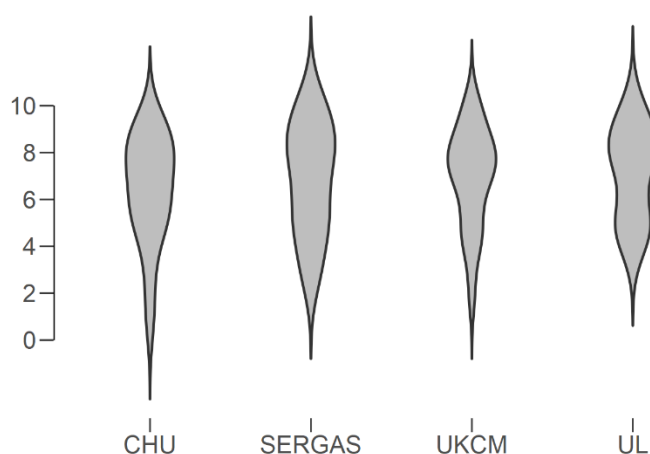*Figure 31 PERSIST Part C 1st statement replies by the centres*

➔ How do you rate your experience with mobile phones?

There is no statistically significant difference among centres (Kruskal-Wallis test p-value=0.058). The participants rate their experience as good (Table 42, Figure 32).

	CHU	SERGAS	UKCM	UL	ALL
Median	6	7	8	6	7
Mode	6	6	8	6	8
25th percentile	5.5	6	7	5.5	6
75th percentile	7	8.75	9	8	8

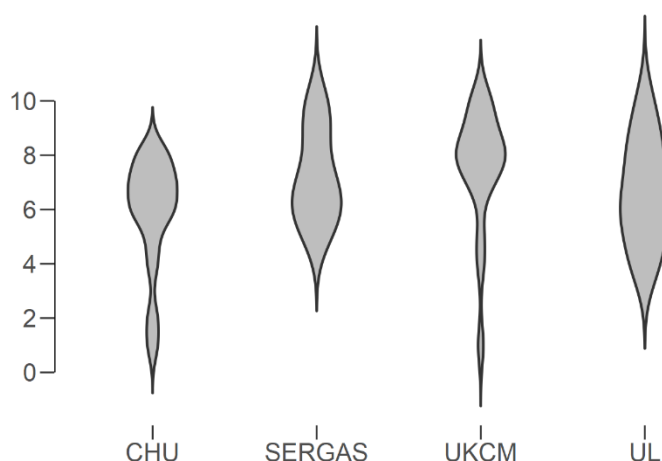*Table 42 Descriptive statistics of PERSIST Part C 2nd statement*

Figure 32 PERSIST Part C 2ⁿᵈ statement replies by the centres

To evaluate the dynamics of participants' feedback, the first and the last survey that they had filled in were compared (if the time period between the two surveys was more than 1 month). In total, 28 surveys (part C) fit the criteria and the differences in their answers were compared. The Wilcoxon sign test results are given in Table 43.

	p value
How do you rate your experience with smart-bracelets?	0.506
How do you rate your experience with mobile phone?	0.093

Table 43 Comparison of PERSIST Part C replies over time

The results show that there are no statistically significant differences in the participants' answers. The differences in scores (1-10) for each question are given in Table 44.

Question	Change in the score (score in the last survey - score in the first survey)										
	-7	-6	-5	-4	-3	-2	-1	0	1	2	3
How do you rate your experience with smart-bracelets?	1				1	4	5	10	2	4	1
How do you rate your experience with mobile phone?						2	3	11	6	6	

Table 44 Differences in participants` answers of PERSIST Part C over time

In rating experience with Smart-bracelets, more people have lowered it, but the difference is not statistically significant. In rating experience with mobile phone, people have raised their points for 1 or 2, but the difference is not statistically significant.

➔ What do you like most of smart-bracelets?

➔ What do you dislike most about the smart-bracelets?

As in those both questions there were some things that patients liked and the same others disliked we have combined the results (Figure 33).
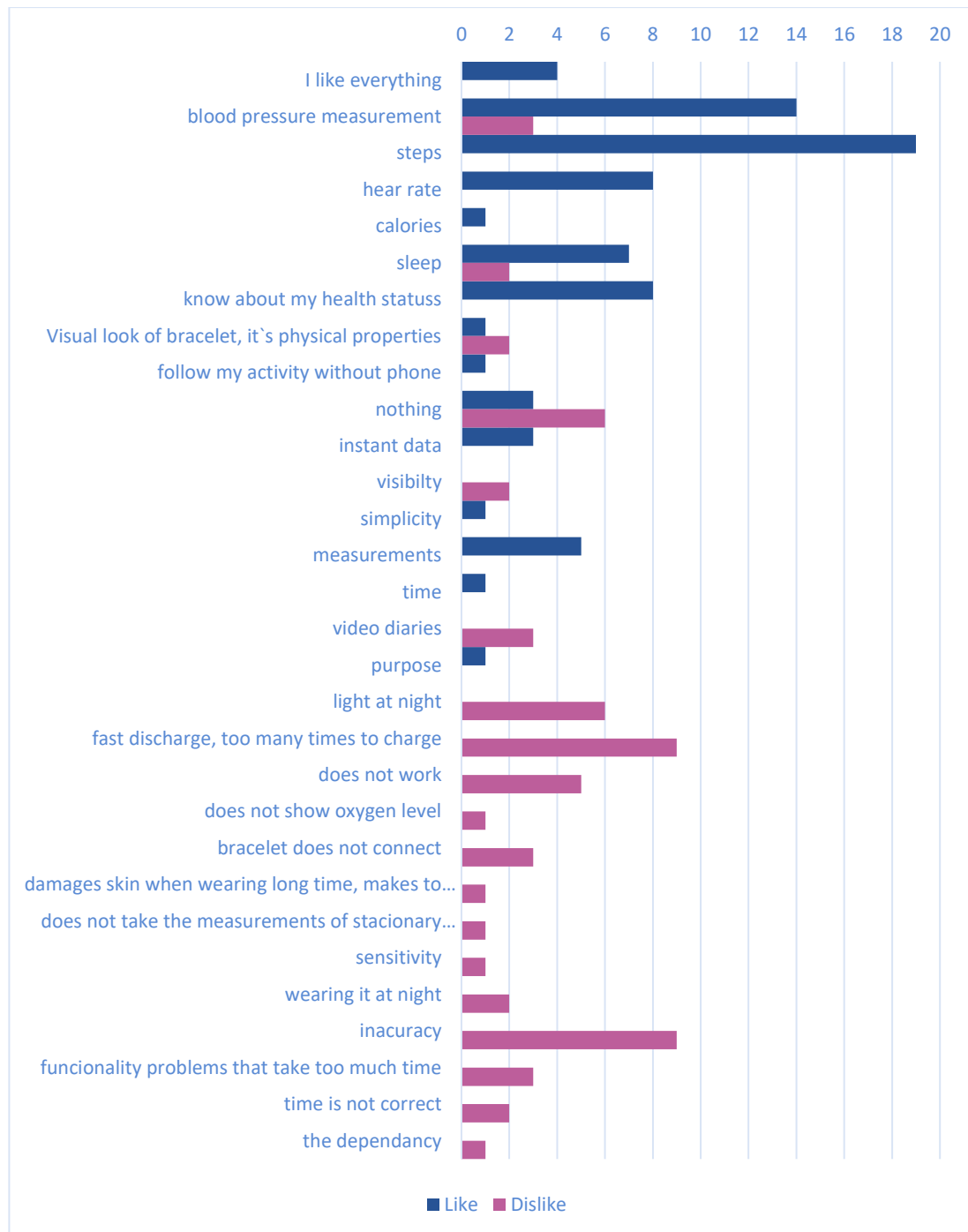
Figure 33 Patients opinion of smart-bracelets used in PERSIST

According to the results, most patients like to see their step count and blood pressure measurements. Most complaints are about fast discharge of devices, inaccuracy of data and light at night from Smart-bracelet.

→ What is (are) the major criticism(s) you could make regarding the use of the devices?
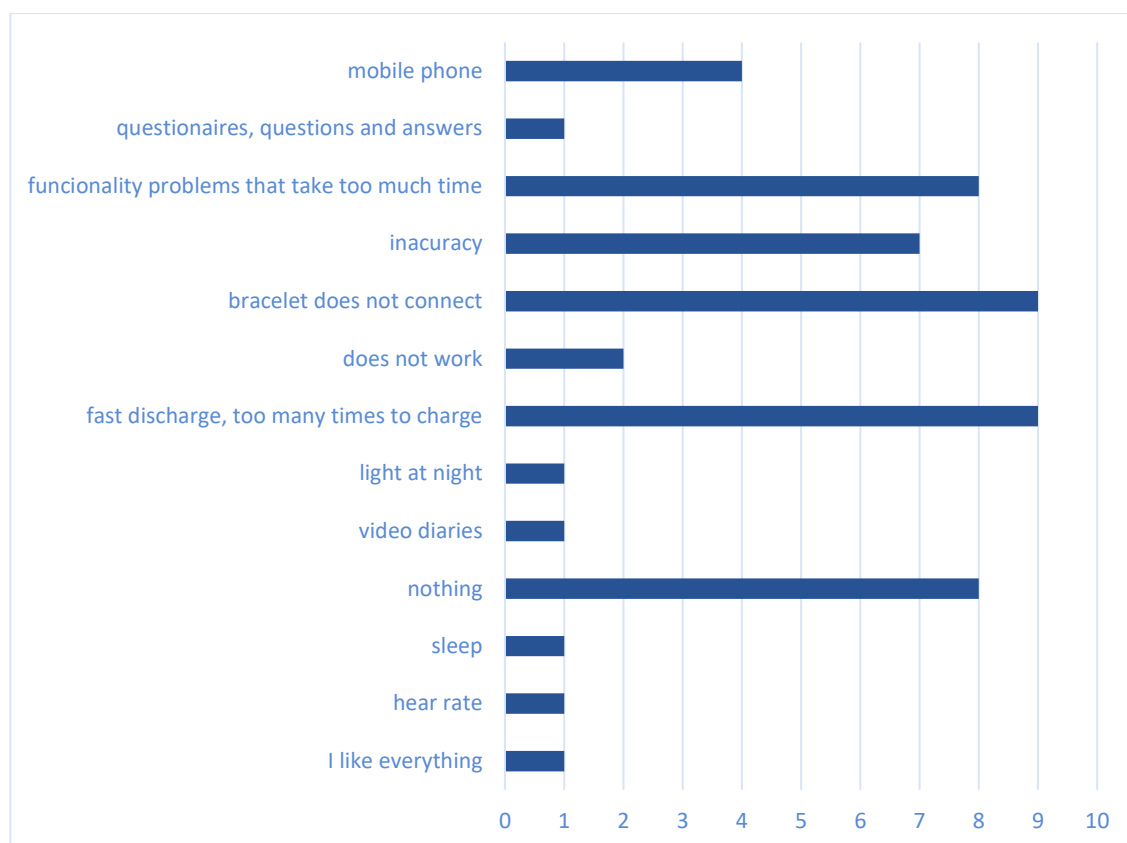

Figure 34 Patients' major criticism of the use of devices

Evaluating both devices, the patients have marked the most – fast discharge, bracelet connection problems, time consuming and inaccuracy (Figure 34.).

Mann-Whitney U test was run to compare the responses between age groups in Block C. There were no significant differences in the responses to questions in Block C (Table 45).

	W	p
How do you rate your experience with smart-bracelets?	335.500	0.223
How do you rate your experience with mobile phone?	423.500	0.867
Note. Mann-Whitney U test.		

Table 45 Mann-Whitney U test results of PERSIST Part C.

Workshops

12. General description of the workshops

Usability testing and feedback gathering happen constantly. One of the major co-creation activities were patient workshops in each hospital where patients, researchers and technical partners met. In on-site or online meetings, any unclear issues could be discussed. The purpose of the workshops was to further familiarize patients and researchers with the progress of the project and allow them to express their opinions.

→ Workshops for patients

→ Workshops for researchers

Considering feedback gathered in workshops, several changes were made. For example, suggestions about the emotion wheel were taken into account to modify it. The newest version to assess emotions had bigger buttons (so patients would not miss pressing them) and presented fewer of them with deeper explanations of their meaning.

Concerning the discomfort video recording problems, it was suggested to switch to voice recordings only, but evaluation of this led to the conclusion that important facial markers that could explain patients' emotional status could be lost. It was decided to make separate explanation for patients about the benefit of video diaries. Also motivating patients to keep using the system was acknowledged as important. In the case of each new version of the app additional information about changes were composed in text and screenshots from the app were added. Translations were sent to patients and clinicians by email. This task will also consider the feedback collected in T6.2 about patients' recruitment and their reasons to withdraw the trial for the usability analysis to be reported in D6.2 Data collection and usability clinical study results

13. The first round of workshops with patients

The first round of workshops in hospitals happened from October to November of 2021. This was the first opportunity patients had to discuss with technical partners of the project.

13.1.   University of Latvia (UL) 14.10.2021

An informative lecture for PERSIST patients about healthy eating in the frame of cancer and a co-creation workshop with technical partners were delivered online due the covid-19 restrictions. Although all the patients had the chance to participate just 10 of them showed interest and finally, three patients managed to connect only. Some of

them couldn`t be available on the day of the workshop for professional reasons and others had technical issues connecting to the meeting.

The first part of the workshop included the lecture "Healthy diet for cancer patients" performed by Dr. med. Daiga Šantare. In the second part, technical partners together with the participants evaluated the operation of the newly developed mHealth health application. Feedback and suggestions from participants will help technical partners to improve the PERSIST system.

Patient complaints: Bracelets not working properly, difficulties loading them, phones frequent discharge. Not possible to see the data overview (in a month). The emotion wheel is hard to use. Wishing to download mHealth app on other phones than the Huawei given by PERSIST. Missing notifications about diary recording and trouble of recording longer videos.

13.2.   Centre Hospitalier Universitaire De Liege (CHU) 08.10.2021

Patients attending the workshop were generally quite satisfied with the system. Even knowing that the smart bracelet gives inaccurate data, the patients mainly use it to track the number of steps per day. All patients were disappointed by the unreliable number of sleep hours. Similarly, although patients take their blood pressure with the smart bracelet they rely more on drugstore-bought devices.

Additionally, some patients complain that the bracelet turns on a light at night, waking them and their partners up. In addition, the smart bracelet causes skin itching in some patients, especially in hot weather. Patients ask to change the presentation of Plutchik`s wheel for helping them to answer easier "How are you feeling today". The slider to set the intensity of emotions was difficult to use.

Some patients don't like doing the video because it gives them a facial image that doesn't match what they perceive of themselves

Some technical issues like mobile freezing and others have been tackled to be fixed by the engineers.

13.3.   University Medical Centre Maribor (UKCM) 20.10.2022.

→ Two face-to-face Workshops (20th October 2021; 10.00 and 16.00) dedicated to patients were carried out together with technical partners (Emoda and UM). These workshops allowed explaining the difficulties encountered by patients when using the devices and mHealth app. Due to Covid-19 restrictions, these workshops were organized with a limited number of patients following the instructions of the Hospital Infection Control Unit. Sixteen patients who showed great interest and had

problems with the application and smart bracelets attended these workshops. Present the new app version and new characteristics

→ Co-creation with patients and training: help patients in managing the devices, explanation of devices, problem-solving, mHealthapp usage, feedback gathering

13.4.   Complejo Hospitalario Universitario de Ourense (SERGAS) 16.11.2022.

The workshop took place on the 16/11/2021. Only two patients were able to attend. Broadly, both of them didn´t have many problems with the app. They made some recommendations about the mood wheel, which they believe it presents extreme emotions. They explained how the app and the video recording made them feel, as some patients felt embarrassed. Finally, they also commented that some values recorded by the bracelets were not accurate.

14. Second round of workshop with patients

14.1.   Centre Hospitalier Universitaire De Liege (CHU) 02.06.2022.

Participation of six patients.

Information/Comments. In addition to the six patients, several CHU de Liège staff attended the workshop. Patients and staff saw the progress made by the PERSIST consortium since the last workshop

Suggestions: Patients suggested improving the refinement of feelings of the emotion wheel. In addition, some questions in questionnaires are not specific enough and the answer could lead to misinterpretation of the results.

Complaints: Still some problems with the smart bracelet. The data seems to be frozen in the smart bracelet and the straps are broken in some of the smart bracelets. In addition, the smart bracelets must be charged often because their batteries discharge very often

Situations solved: New smart bracelets from patients who left the study were given to those who are confronted with the smart bracelet issues.

14.2.   University of Latvia (UL) 08.06.2022.

In total ten patients participated.

Information received about mHealth apps new version, videos, virtual agent etc. + lecture about the importance of physical activity for cancer survivor patients (greatly appreciated by patients).

Complaints from patients:

→ Mobile phone battery discharges too fast. (Should be better with v18)

→ Questionnaires - notifications lead to all questionnaires (solved with v18.), patients would like to answer other questions that are not offered by the PERSIST questionnaires. They think the questions are not adequate. A clear example is that of pain – a patient may have back pain that is not the consequence of his past cancer. However, the questionnaires link pain to cancer only.

→ Sometimes breast and colorectal questionnaires are mixed up.

→ Too many notifications, too long list. Patients have hard time to remove them.

→ Patients want to see the results of their efforts. (the consortium has committed to dedicate of final workshop where patients will be informed about PERSIST results)

→ Data transfer sometimes is not done.

→ One patient had noticed that data transfer could speed when the connection of the mobile phone with smart-bracelet is reset in settings.

→ Two patients were not able to install the new versions of mHealth app what was done during the workshop.

14.3.   University Medical Centre Maribor (UKCM) 16.06.2022.

Attendance of seven patients.

When patients complete the questionnaires, they are redirected again to the list of questionnaires, whereas they should be redirected to the main screen.

A message of low battery for bracelet cannot be dismissed. In fact, all notifications should be dismissible in the app itself. In some questionnaires appears still a button "Answer" written in English although it should appear the Slovenia word Vredu). The appeared question was if the app still collect data from the smart bracelet and sync the data in the cloud, when the app and the smart bracelet are not Wi-Fi connected (for how many days the data transition can postponed). There are some visualization issues especially of text (check images) also in the video list.

Current positive outcomes of the Project:

→ Patients are more aware of their health condition thanks to the project.
→ Many of the involved patients improved their daily physical activity due to the use of smart bracelet and mobile application mHealth.
→ Patients are satisfied because they have more contacts and more one-on one encounters with their oncologists.
→ Many of the patients think that their quality of life improves because they can monitor daily their heart rate, blood pressure, and quality of sleep.

→ With the participation in the research, patients have a sense of security and safety because they are still under medical supervision even after their cancer treatments.

→ Patients can also express their feelings of anger, fear, sadness, and happiness when they record their video diaries in the mobile application mHealth.

14.4.   Complejo Hospitalario Universitario de Ourense (SERGAS) 21.06.2022.

Participation around ten patients were invited. Although four accepted the invitation, only two were able to attend the workshop. One female patient told her suggestions through the phone.

The new features of mHealth app + virtual agent were presented to the patients

Comments: the two participants have a very positive impression of the app, both were happy with the project and consider that this app could be of great support for future cancer survivor patients

Complaints & suggestions: Patients feel uncomfortable talking to the camera while recording the video diaries. They lack an interlocutor to talk to and intercommunication through the app in general.

One patient said that the app is not very user-friendly which is not a common complaint.

The app shows too many notifications which never disappear. This problem is already solved or almost solved.

The app usually requests to fill out the same questionnaires.

14.5.   Research group meeting on the second CTC collection + mHealth (UKCM) 10.03.2022.

Joint meeting of clinicians, Healthcare professionals and other researchers. Fifteen persons discussed about logistic coordination for the second CTC collection, PERSIST presentation on conference and data entry in the mHealth clinician application.

→ Following blood collection dates for CTC: Tuesday, 22/3, Monday, 28/3, Monday, 4/4, Monday, 11/4, Tuesday, 19/4. Appointments will be arranged internally within the research group. Up to eight patients can be booked for one appointment. As far as possible, participants who had the same type of cancer were grouped on the same day. Clinicians would enter all the necessary information regarding their patients in the mClinician application by the end of June 2022.

→ Participation in the conference: Dr. Horvat will present the activities of the project PERSIST at the conference organized by the University of Maribor on March 25, 2022.

→ Press conference - presentation of project PERSIST: As part of the Cancer Awareness Month on March 28 2022, in cooperation with Faculty of Electrical Engineering and Computer Science, University of Maribor.

Observation from clinicians, Healthcare professionals and researchers:

→ Healthcare professionals need deeper insights into patients' everyday life.

→ Several symptoms go under the radar of PERSIST solution.

→ The patients do not report many symptoms.

→ Modern technologies enable professionals to collect data in a new way and to process the enormous amount of data collected.

→ Daily clinical tasks allow professionals to spend a very limited amount of time with patients were only basic points can be discussed without, being able to delve into other medical aspects

→ PERSIST has enabled professionals to increase the number of medical contacts with patients with more follow-ups.

→ PERSIST has also enabled professionals to think differently about patient care in general. By implementing new medical monitoring technologies, PERSIST goes beyond traditional follow-up procedures.

→ According to professionals, PERSIST can help them develop a platform for easier and more efficient follow-up in the long run, by helping them discover their unmet needs.

→ However, in the long run, professionals should be careful and try to develop a user-friendly platform or even different platforms for a broad spectrum of patients. One size does not fit all.

CTC collection

15. 1st blood sampling

➔ UKCM

Period: August-September 2022

Gathering samples for CTC analysis between 20th August and 11th October 2021 (8 samplings) by the healthcare professionals- nurses;

Medical follow-up by the doctor

Individual meeting with coordination staff to discuss problems with smart-bracelet, mHealth app and phone.

- ✓ Coordination with patients and clinicians for scheduling
- ✓ Coordination (shipment organized by RUBY) of shipment of clinical samples and mitigation of problems connected to shipment.
- ✓ Usability testing, direct feedback gathering from patients; collection of objective data.
- ✓ Questionnaires PAM and CASE CANCER.

➔ SERGAS

Period: September- October 2021

Blood sampling for CTC analysis of patients between 7 September and 26 October 2021. Moreover, an individual meeting between patients and the coordination staff was held to solve possible problems with the smart-bracelet, mHealth app and phone.

- ✓ Coordination with patients for scheduling
- ✓ Coordination with RUBY for material and sample shipments
- ✓ Obtaining feedback from patients.
- ✓ Questionnaires PAM and CASE CANCER.

16. 2nd blood sampling

➔ UKCM

Period: March- April 2022

Blood sampling for CTC analysis between March 22th and April 19th (5 samplings) by the healthcare professionals- nurses;

Medical follow-up by the doctor

Individual meeting with coordination staff to discuss problems with smart-bracelet, mHealth app and phone.

- ✓ Coordination with patients and clinicians for scheduling
- ✓ Coordination (shipment organized by RUBY) of shipment of blood samples and mitigation of problems regarding shipments.
- ✓ Usability testing, direct feedback gathering from patients; collection of objective data.
- ✓ Due to the late CTC samples delivery by DHL from Slovenia to Portugal we had to call back eight patients. At the end, UKCM staff had to meet up with patients 7 times (dates: April 29th and May 3rd).

➔ SERGAS

Period: April- May 2022

The second blood sampling for CTC analysis took place between April 26 and May 10, 2022. During this individual visit UKCM staff took the advantage to clarify possible doubts and solve problems with smart-bracelet, mHealth app and phone.

- ✓ Coordination with patients for scheduling
- ✓ Coordination with RUBY for material and sample shipments
- ✓ Obtaining feedback from patients.
- ✓ Questionnaires PAM and CASE CANCER

Conclusions

➜ Gender imbalance in the participation of patients. The rarity of breast cancer in men and a slightly higher inclusion of women in the group of patients who presented with colorectal cancer explain the greater inclusion of women and therefore the gender imbalance at inclusion and participation in this research.

➜ Workshops. The workshops have been important for the motivation of patients, to inform them about the ongoing pilot and research and also to gather necessary feedback about system usability from them.

➜ Data from smart bracelets. Usable data collected by the smart-bracelets turned out to be only the steps, the heart rate and the blood pressure. Their analysis could reveal that PERSIST solution induces behavioural changes in patients with positive effects on their health.

➜ Circulating Tumour Cell (CTC) assessment tests. In most blood samples, the number of CTCs found was very low (one or two cells per sample). It might not be considered medically relevant. PERSIST participants who had a CRC show a higher CTC number than participants who presented breast cancer. Further blood sample analysis and clinical outcome are still necessary to evaluate CTC assessment usability in cancer survivor follow-up.

The results of PERSIST show that the CTCs of its participants are heterogeneous. In the remaining 6 months of the study, we hope to be able to make the link between the clinical outcome and the CTCs count as well as their type. Thus, we wish to be able to reinforce the idea that CTCs can be a robust tool to monitor local and/or remote progression and to support personalized treatments.

➜ System Usability Scale (SUS). According to the definition of system usability level most of the patients (39%) who replied to this questionnaire think that PERSIST solution is acceptable to good. One quarter of patients (26%), considers that the system has some usability issues and 16% consider that it is not easy to use. However, a combined 46% of patients would like the system to be improved.

Although there were some shortcomings when the system was introduced, overall, the participants filling the SUS survey indicated that they were comfortable using the system. Most of the participants found that the system was not unnecessarily complex but rather easy to use without even needing technical assistance. This translated into the confidence that most participants had in a system that would be learned and adopted very quickly by individuals given that it does not involve very cumbersome/awkward tasks. Patients did not answer negatively but rather responded positively or were undecided when evaluating the inconsistency of the system or the integration of the various functions into it.

To solve the points that present some inconveniences during the use of the system, the technical partners will introduce the necessary modifications before the full-scale clinical trial (for testing) and until the end of the study so that future users can

use a well-tested and stable system. It is possible that these inconveniences were and are still due to many mHealth updates.

In order to evaluate if the SUS feedback from the participants changed, we analysed the changes in participants' responses between their first survey and the last survey they had filled in, and if the time between completions of both surveys was more than one month: this time was assumed enough for the participant to get accustomed to the system. The p-values show that there were no significant changes in 31 analysed participants' responses after using the system for more than a month.

→ Communication and Attitudinal Self-Efficacy scale for cancer (CASE-cancer). Calculating score for three CASE-cancer survey factors: 1) understand & participate in care, 2) maintain positive attitude and 3) seek and obtain information The results of these 3 factors show no statistical difference between the responses obtained during recruitment (baseline) and those of follow-up (approximately 3-6 months after recruitment). This means that the clinical trial's primary endpoint "increased perceived self-efficacy in participants" has not been met to date. However, this could be achieved if patients received more comments and feedback from the consortium on their results.

→ Patient activation measure (PAM). There were no statistical differences in the median PAM score at recruitment vs at the last follow-up. Nevertheless, the percentage of patients in levels 1 (passive) and 4 (adopted new behaviours, but struggle in stress) increased in the last follow-up. On the contrary, the percentage of patients in levels 2 (some health-care knowledge) and 3 (taking action and gaining control) decreased in the last follow-up.

→ PERSIST block ABC. Patients enrolled in the PERSIST clinical study generally rate positively their participation in the project, the experience of using the mHealth application, the smart bracelet and the mobile phone (mean score 7 on a scale of 1 to 10). In addition, the instructions and explanations given by the staff, in general, are considered understandable (mean score 9). Explanations about mHealth were very good (mean score 8). Patients feel good participating in the project (mean score 8) and tend to track data from mHealth apps (mean score 8). As for the influence of the mHealth application on patient behaviour, it varies strongly between hospitals (mean score 7 for UKCM patients, but only 2.5 for SERGAS ones). We believe that this is due to the face-to-face participation of technical partners and doctors during workshops with UKCM patients. The difficulties encountered by many patients when using the Wheel of Emotions are reflected in an average score evaluation of 5. On the other hand, experience with questionnaires is noted above (mean score 7).

Regarding rating the experiences with participation in the PERSIST in general there was a statistically significant difference among centres – UL has significantly lower values and the same can be seen with answers to the question how does participation makes you feel. Analysis of in PERSIST block ABC answers (about Project, devices and mHealth app) show that UL participants have given the lowest

scores (statistically significant) to their experience recording video diaries (only 2,5, compared to 5 which is the mean score of CHU, SERGAS and 7 to UKCM).

According to the 24,4% of patients (from 78 filled questionnaires in A part), the PERSIST projects should hold more meetings and offer more appointments with doctors. 14,1% of them suggest more contact with the staff. 12,8% consider that everything is good and 11,5% think that nothing should be changed. The most controversial aspect of mHealth app still (68 questionnaires B part) seems the Wheel of Emotion (23% wanted to change this); the other 17% do not want to change anything, but 9% would like to change diaries.

According to the results, most patients like to see measurement data, but complain that it is inaccurate. Most complaints are also about the fast discharge of devices and light at night from Smart bracelets. In addition, the main criticisms regarding the use of the device were the connection of the smart bracelet with the mobile phone, the time consumption and the inaccuracy of data. This leads to the conclusion that for a positive experience it is extremely important to use well-functioning devices (e.g. Smart-bracelet). In addition, the first application tests must first be carried out within the company, followed by project partners and then in then in focus groups before presenting any solution to patients during the pilot study.

➔ Necessary updates – feedback for patients, overview for clinicians. It is important to develop fully clinical decision support system (CDSS) that is planned to be introduced in September 2022. This will help the clinicians to follow patients easier and to get feedback from the patients' participation.

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