UNIVERSITÀ DEGLI STUDI DI TRIESTE

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NEUROSCIENZE E SCIENZE COGNITIVE

Data science to support decision making in chronic pain

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1 INTRODUCTION

Pain is "an unpleasant sensory and emotional experience associated with, or described as such, present or potential tissue damage. Pain is always a subjective experience. Everyone learns the meaning of this word through experiences related to an injury during the first years of life. It is certainly accompanied by a somatic component, but it also has an unpleasant character and therefore an emotional charge". This is the definition associated by the International Association for the Study of Pain - IASP (1986; revised in 1994 - Task Force on Taxonomy) [1] with pain.

Defining the concept of pain in a univocal and concise way is difficult. It is not possible to reduce the description of pain to a sensory phenomenon, rather it must be seen as the combination of two components: a perceptual component, called nociception, which constitutes the neurobiological aspect of pain, and provides for the sensory modality that allows the reception and transport to the central nervous system of stimuli potentially harmful to the body; and an experiential component (therefore completely private, the actual experience of pain), which is the psychic state connected to the perception of an unpleasant sensation [2].

Pain is physiological, a vital/existential symptom, a defense system, when it represents an alarm signal for a tissue injury, essential to avoid damage. It becomes pathological when it maintains itself, losing its initial meaning and becoming a disease itself [3]. Pain that goes beyond the alarm function is often represented by chronic pain, which is highly disabling for the individual.

Chronic pain has been defined as "pain that lasts for more than three months" or "is pain that lasts beyond the normal healing time" [4]

Chronic pain has negative repercussions on many areas of the life of those affected, compromising quality of life, functioning and psychological well-being [5].

Chronic pain itself becomes a disease, or a consequence of a diagnosed illness (as, for example, in the case of oncological pathology), with a heavy impact on the person's relationship life and on the psychological and social aspects characteristic of the person.

Pain, especially chronic pain, is one of the main health problems in Europe, relevant both in quantitative terms, because it is widespread among the population, and in qualitative terms because, in addition to causing high costs for society, it causes a drastic reduction in the quality of life and a tearing of the social fabric for those affected. Chronic pain is a destabilizing experience that affects many aspects of the patient's life but also that of his or her family members, modifying pre-existing dynamics, the distribution of family roles, affecting the marital relationship, the performance of daily activities, goals and hopes for future life [6]. Scientific literature, in fact, describes chronic pain as a pathology that is not only individual since its interpersonal nature inevitably leads to negative consequences for both the patient and the people close to him.

The search for new treatments for pain, in this sense, assumes fundamental importance in several dimensions [7]:

- for basic research, in the understanding of the basic mechanisms of pain and related neurobiological phenomena.
- for clinical research, to formulate more accurate and effective therapeutic designs for patients.
- for public health, with a view to reducing the enormous costs of pain therapy.
- last, but most important of all, to improve the quality of life of the suffering individual, who is often unable to find an effective remedy for his or her suffering for a long time.

1.1 Health Integrated Ecosystems for Chronic Pain Management

In the field of information and communication technologies, much progress has been made to allow the adoption of a new and stimulating approach to the management of care and treatment of chronic pain, especially in the oncology field, through the development of integrated ecosystems [8, 9]. Recent studies highlight the great potential that new integrated health technologies must improve the management of chronic pain in affected patients [10][11]. Furthermore, studies have suggested that healthcare technology could optimally manage the physical and psychological morbidities associated with the painful experience by enabling and ensuring continuous monitoring [12] of clinical health status in real time and transmitting related data to their healthcare providers, incorporating them into patient electronic health records. [13] [14][15].

Among the existing support tools for chronic pain, mobile health apps have been increasingly applied and help patients monitor and reduce the pain experience by promoting self-management skills and improving quality of life. Furthermore, mobile apps, if interconnected with the health technology ecosystem and managed by healthcare professionals, increase patient involvement in their care journey [9].

This type of technological architecture would allow various clinical results to be achieved:

- monitor the physical and psychological well-being of patients through self-report questionnaires and momentary ecological assessments (for example, using the electronic diary), in particular, the regular administration of standardized self-report questionnaires effectively tracks the variation in physical and psychological well-being symptoms, allowing an assessment of affective instability in chronic pain [12].
- promote two-way and immediate communication between healthcare professionals and patients [15]. For example, patient-reported outcome measures can be managed by mobile health apps and stored in patient electronic health records, facilitating rapid and direct clinical response to alert conditions. [16]
- allows scheduled clinical follow-ups, reducing the risk of continuous failures in clinical monitoring.
- stimulates patients to be more involved in their therapeutic decisions, allowing them to reach a shared decision on their treatment path through the implementation of decision-making aids. Growing evidence [17, 18] has

highlighted the critical role of decision aids as an excellent strategy for increasing the likelihood of achieving a shared and involved decision.

Decision aids are tailor-made tools designed to provide evidence-based information about the disease, available treatments and associated risks; furthermore, they can help patients think about therapeutic alternatives from a personal perspective [17] [18]. Overall, health technologies are recognized as facilitators of shared decision making (SDM), reducing decisional conflicts and improving patient satisfaction.

Evidence has highlighted that, when implemented on mobile apps, decision aids can support patients by increasing awareness of treatment preferences, reducing decisional conflicts and improving adherence to medical treatments [19] [20].

2 OBJECTIVES

My research activity is developed within the PainRelife project aimed at creating a dynamic and integrated technological ecosystem based on big data management and analysis technologies for the continuity of care of pain patients.

The general purpose of this project is to design and implement a tool for PROs collection for chronic pain patients, to allow reliable efficacy assessment of therapies, as well as patient's support, and, finally, to support the identification of possible prognostic factors, also using data analytics techniques. Specific attention to transcranial direct current stimulation (tDCS) efficacy analysis will be given.

To this end, the project is developed according to the following research objectives:

- Objective 1 - to develop a digital platform for creation and implementation of digitized care pathways for patient with chronic pain, in particular treated with tDCS; and to implement a mobile tool based on an application that can support monitoring by collecting patient reported outcomes.
- Objective 2- to implement, in the same tool, features for supporting patients and caregivers in the management and administration of treatment. Among them, tools for progress visualization and self-evaluation, communication tools to put patients in contact with their doctors, to ask for assistance and to talk with the community.
- Objective 3- to identify prognostic factors based on the PROs collected through the application and the platform, in conjunction with patient's clinical history by performing an analytical study on the data collected to implement analytical dashboards.

The digitalization of treatment paths in digital platform (Objective 1) represents the preliminary and necessary activity, together with the creation of the app (described in the following paragraphs), to manage patient care and obtain the collection of fundamental data to achieve the objective: identifying prognostic factors based on the PROs collected through the application and the platform, in order to allow a reliable evaluation of the effectiveness of therapies, as well as patient support.

The correct execution of digitalization requires:

- a preliminary analysis of the clinical protocols provided by the clinical centers involved in the project.
- a configuration and implementation of care pathways in digital platform, NuPlatform

These steps are described in Section 3.2, where the PainRelife ecosystem implementation is described.

Within the PainRelife project, an ecosystem of apps has been developed, which allow patients to respond to questionnaires (PRO) to detect the progress of pain, the state of health, the effectiveness of treatments and support the decision-making process at critical moments of the therapeutic process (Objective 2).

Thanks to the integration with the Nuplatform, healthcare professionals receive monitoring data every time the patient responds to the questionnaires, so that they can personalize the therapy. Patients receive, through a notification system, the request to fill in according to a personalized calendar defined by the treatment plan. The app ecosystem and their integration in the platform are described in Section 3.3 and 3.4.

PainRelife data collection takes place within the NuPlatform. The data collected within the NuPlatform will be managed by the analytics engine.

The analytics engine performs analyzes of the data on the platform, generating graphs that can initially be thought of as analytical, i.e., based on historical data, but can later be used to make predictions. Then the platform is interrogated to extract data of interest, which will be processed by the analytics engine so that it can be visualized. Following the organization of several focus groups with the clinical centers participating in the project, the data and expectations from the analytics system were defined and translated into functional requirements and differentiated by clinical pathway analyzed. Analytics dashboards were implemented for post-stroke nerve pain and cancer pain use cases and are are described in Section 3.3 and 3.4.

The real application and usability of the platform in three case studies with a specific focus on early-stage breast cancer patients has been described in sections 4.1 and 4.2.

3 PAINRELIFE ECOSYSYEM IMPLEMENTATION

3.1 General Architecture

My research activity is developed within the PainRelife project. The PainRelife project, financed by the Lombardy Region (Italy), aimed to create a dynamic and integrated technological ecosystem based on big data management and analysis technologies aimed at continuity of care for patients with pain that involves the entire health chain, from diagnosis to therapy home care, telemonitoring, patient/caregiver support and which allows the choice process to be supported (decision aid).

The ecosystem, in addition to the technological component, also guarantees the presence of the human factor, as the therapeutic relationship with the patient cannot be conveyed only through technological solutions, however innovative, but also involves an interaction with a professional figure in order to connect with the person, generate trust and understand the personal needs that each person/patient has.

The PainRelife project involves a multidisciplinary team covering both technological skills and clinical expertise. From the technical side, Nuvyta Srl, a company providing advanced FHIR based solutions for modular and configurable electronic health record (EHR) systems, the University of Trieste, involved for the artificial intelligence and bioengineering expertise, and Zadig Srl, a company with long-term expertise in scientific communication and personalized digital health system development; from the clinical side, two clinical centers (the Casa di Cura del Policlinico Rehabilitation Center, and the Oncology Hospital Istituto Europeo di Oncologia), and Euleria Healt, a start-up company active in home-based telerehabilitation.

The dynamic and personalized nature of the PainRelife ecosystem has as key assets (Figure 1 - PainRE-Life architecture):

- A FHIR based cloud technological platform (big data HUB) for integrated, scalable data collection with dynamic and customizable contents capable of interoperating both with institutional systems and with personal and therapeutic devices, in compliance with current legislation for the security and confidentiality of data, and to generate and manage digitalized care paths.
- A big data analytics infrastructure, connected to the FHIR server, for the analysis of the data collected to develop new decision-making strategies for the treatment of patients, to validate guidelines and recommendations and to extract new knowledge to develop new ones, to obtain safety and effectiveness of therapies, collected in ecological contexts and to create new "decision aid" models aimed at encouraging "shared decision making".
- A clinical network of excellence for the diagnosis and treatment of pain integrated with a network of professionals dedicated to the home treatment of patients with pain, to guarantee the human relationship with the patient (HUB of expertise).
- A set of business models that make the care supply chain sustainable (HUB of integrated services).
- An ecosystem of profiled apps for different users (Paziente7caregiver/nurse/GP) to view personalized therapeutic paths, send feedback on the progress of treatment and support the decision-making process (Front end HUB)

- A remote training model for doctors on the responsible use of sensitive data and the management of chronic pain (real life knowledge HUB)

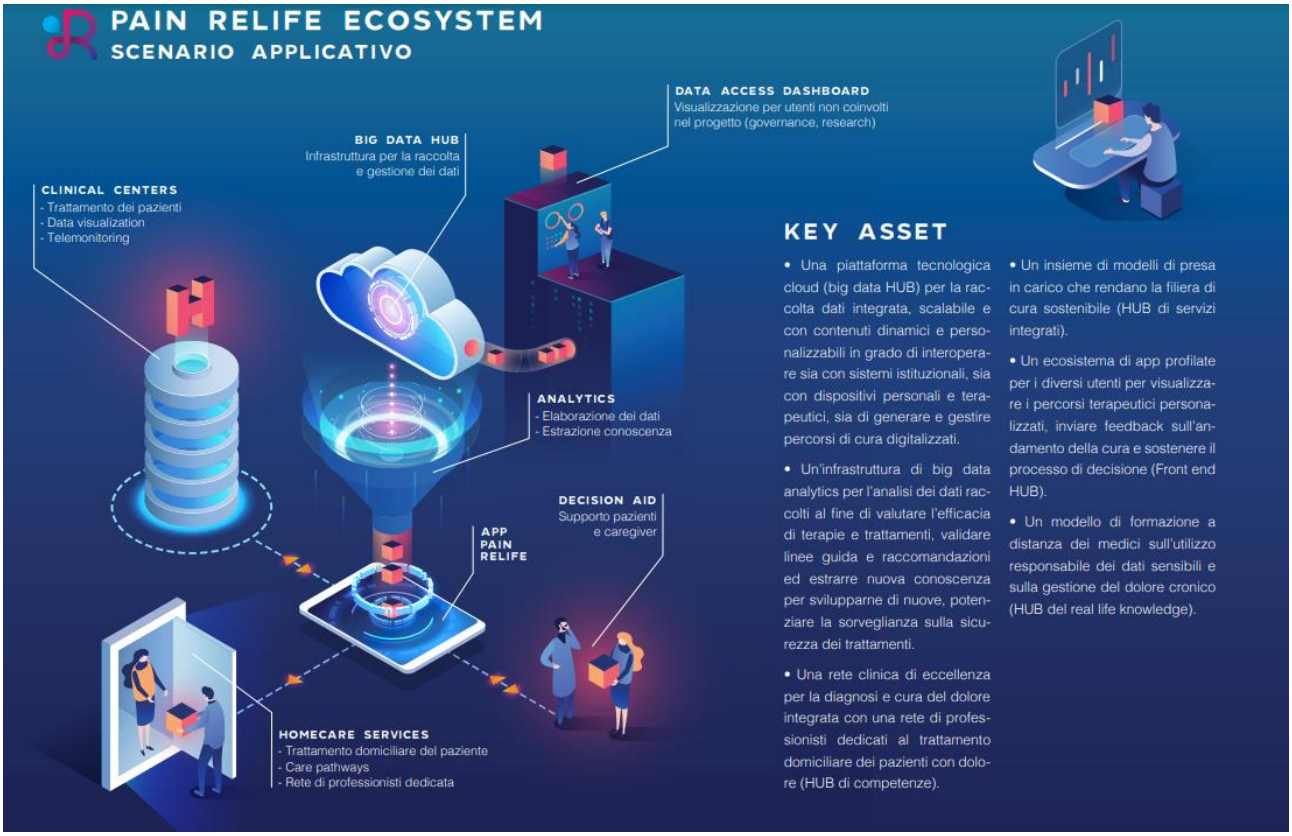

Figure 1 PainRelife ecosystem: main technological assets

Two clinical centers, and a home-based telerehabilitation service provider served as case studies for the PainRelife platform. The project also provided a e-learning platform for general practitioners (GPs). Finally, the system was also designed to be integrated, in the future, to routine healthcare, through electronic health records. In fact, the whole system conforms to the FHIR standard that allows connecting and exchanging medical information in a secure and structured way using REST APIs. PainRelife is based on a

configurable FHIR platform that allows the definition of care pathway, clinical evaluation scales, and questionnaires.

Figure 2 PainRelife ecosystem

3.2 Care pathways definition

The platform is essentially a backbone of an electronic health record (EHR) with dynamic capabilities (workflows).

The PainRelife ecosystem prototype has been developed together with clinical domain experts to collect heterogeneous information reflecting clinical management (e.g. therapy adherence, therapy response), patient reported outcomes (PROs from multiple digital sources, e.g. pain perception, psychological status, patient preferences) and home care monitoring.

The infrastructure was designed, considering clinical pathways for selected use cases that integrate international disease guidelines and clinical practices in the clinical centers, to help healthcare professionals develop personalized therapeutical plans and empower patients (more informed decisions).

3.2.1 Clinical care pathway definition

The system implements three digital care pathways for the management of pain in post-stroke, early breast cancer, and fibromyalgia (treated with transcranial direct current stimulation, tDCS) patients. Each care pathway involves the execution of a workflow in the Nu platform, that allows collecting all the data (pain severity scales, pain location, psychologic assessment) to be completed by the patient/caregiver at home or by the healthcare professional in the hospital setting and the integration with devices providing patient's related information (tDCS devices and smartbands for activity monitoring).

Before proceeding with the configuration of the care pathways in the platform, it was essential to carry out a depth study and analysis of the protocols provided by the clinical centers involved in the project:

1. CCPP protocol: The protocol involves managing and monitoring the post-stroke pain patient in a hospital or home setting, using tools to monitor and quantify the three identified pain conditions (central pain, painful hemiplegic shoulder, painful spasticity) and additional multidimensional secondary clinical measures.
2. IEO Protocol: The protocol is to manage and monitor the course of pain and its response to pharmacological and non-pharmacological treatment for individuals with Early Breast Cancer.
3. GTS protocol: the protocol is designed to manage and monitor the progress of pain in the home care pathway of patients treated with tDCS on a predefined target of patients.

From the analysis of the protocols, it was possible to carry out a high-level modelling of the use cases of the care pathways.

These use cases concern little-known forms of chronic pain for which the clinicians involved believe the project can lead to a significant improvement in patient management:

- *a. Chronic pain occurring in **post-stroke** patients, particularly in relation to three specific diagnoses (central neuropathic pain, shoulder pain of the hemiplegic, pain related to spasticity and/or contractures)*
- *b. Chronic pain occurring in patients treated for **breast cancer** (cancer pain)*
- *c. Use of an innovative method, **transcranial Direct Current Stimulation** (tDCS) for the treatment of chronic pain.*

Chronic pain occurring in post-stroke patients.

The stroke event prevents blood from reaching the brain, causing damage to brain tissue. It is estimated that at least 10% of people who have suffered a stroke develop intense pain over time. The pain that occurs following a stroke is called post-stroke pain, central pain or thalamic pain (named after the part of the brain typically affected). [21]

The onset and character of this pain are very variable. It can occur days or years after the stroke, it can occur after a major or minor stroke.

Typical forms of post stroke pain are: central pain, pain secondary to spasticity/contractures, hemiplegic shoulder pain, headache, joint pain, complex regional syndrome, chondrocalcinosis and other mixed forms.[22]

The parts affected by this pain can be different, including the face, arm, leg, trunk or even an entire half of the body.

Common characteristics are that the pain is constant and is more likely to occur if the stroke occurred in the right side of the brain. The pain usually gets worse over time and can sometimes be aggravated by changes in temperature or movement.

Therefore, post-stroke pain is made up of a spectrum of clinical conditions depending on the location of the brain lesion and the clinical consequences of the cerebrovascular event. [22]. It has a significant impact on life (quality of life, limitation in participation in physical/rehabilitative activities, social isolation, accentuates secondary symptoms such as depression, fatigue or insomnia). The management of post-stroke pain may require multidisciplinary approaches that are not always available and due to its heterogeneity and possible cognitive and/or language problems, to date, there are few monitoring tools available (e.g. scales, questionnaires).

The analysis for the development of treatment paths for patients with neurological pain was addressed by examining the clinical protocols provided by the CCP clinical center (the Casa di Cura del Policlinico Rehabilitation Center).

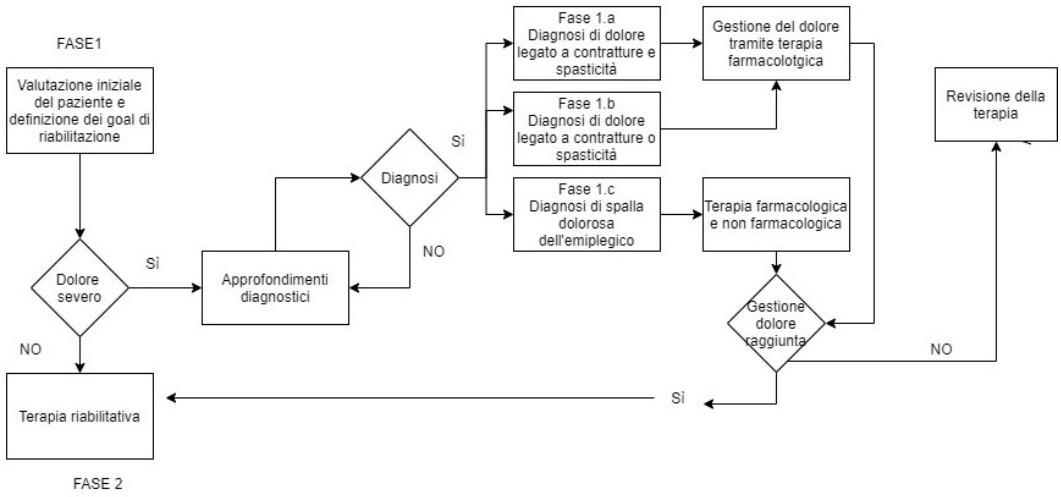

Figure 3 CCPP protocol

About chronic post-stroke pain, the following activities were implemented:

- Analysis of good practice according to literature evidence with respect to monitoring and quantification tools for the 3 identified post-stroke pain conditions (central pain, painful hemiplegic shoulder, painful spasticity) and additional multidimensional secondary clinical measures.
- Analysis of 'clinical practice' of pain management and monitoring in CCPs (CCP protocol) and mapping of therapeutic pain management services in CCPs.
- Drawing up home monitoring pathways in different cases (subject with post-stroke shoulder hemiplegic pain, central pain, pain and spasticity) and identification of specific protocols in patients with cognitive and/or language problems.

As described previously, typical forms of post stroke pain are central pain, pain secondary to spasticity/contractures, hemiplegic shoulder pain, headache, joint pain, complex regional syndrome, chondrocalcinosis and other mixed forms. In the PainRelife project, attention was paid to 3 specific forms of chronic pain: central pain, pain secondary to spasticity/contractures, hemiplegic shoulder pain.

The general protocol provides:

- Initial pain assessment. The patient with mild pain is ready to carry out rehabilitation therapy, patients with severe and severe pain continue the path.
- Definition of the patient's diagnosis (hemiplegic shoulder pain, pain related to contractures or spasticity, central neuropathic pain) with consequent treatment path and prescription of pharmacological therapy.
- Evaluation of the tolerability of the drug.
- Administration of specific questionnaires for the treatment path undertaken.

- Pain monitoring.

The CPP protocol differs based on the patient's cognitive abilities.

In particular, the following scales are administered for patients with post-stroke pain and preserved cognitive abilities:

- Central Pain Diagnosis: NIHSS, DN6, mBI, BPI, SIS 3.0, HADS, SF12, VAS, FPRS, FM AASS or AAII
- Diagnosis of Hemiplegic Shoulder Pain: NIHSS, mBI, BPI, SIS 3.0, HADS, SF12, VAS, FPRS, FM AASS or AAII
- Diagnosis of Spasticity Pain: NIHSS, DN6, MAS, mBI, BPI, SIS 3.0, HADS, SF12, VAS, FPRS, FM AASS or AAII

While the following scales are administered for patients with post-stroke pain and unpreserved cognitive abilities:

- Central Pain Diagnosis: NIHSS, mBI, BPI, PAINAD, FM AASS or AAII,
- Diagnosis of Hemiplegic Shoulder Pain: NIHSS, mBI, BPI, PAINAD, FM AASS or AAII
- Diagnosis of Spasticity Pain: NIHSS, MAS, mBI, PAINAD, FM AASS or AAII

Chronic pain occurring in patient with early breast cancer

Chronic pain management represents a critical issue in the care pathway of breast cancer patients.

It is estimated that at least 30% of breast cancer survivors experience chronic pain, which can last up to 10 years after the end of cancer-specific treatments [23] [24]. Furthermore,

due to surgical procedures and chemotherapy-induced toxicity, chronic pain very often tends to increase during treatment.

In the context of patients with breast cancer, different causes of pain incidence have been identified: 25-60% related to post-surgery; 47% related to adjuvant hormonal treatments, including aromatase inhibitors; and, finally, 58% related to long-term chemotherapy-induced toxicities [25]. As in the case of post-stroke pain, chronic pain following breast cancer interferes with psycho-emotional well-being by causing increased anxiety, depression and fatigue, psychological adaptation to the disease, personal relationships (e.g. partners, family members, colleagues) and therefore the return to work [24][25]. Furthermore, chronic pain is not always recognized promptly, leading to alterations in patients' health-related quality of life, influencing health status, disease and medication adherence [26] [27]. Compared to those without chronic pain, breast cancer patients with chronic pain have shown low adherence to cancer treatments (e.g., hormone therapy), with a demonstrated reduction in treatment efficacy and five-year survival rate [24].

Furthermore, compared to hospitalized patients, out-of-hospital cancer patients have less pain relief [28]. Patients living in regions with poor medical resources, an inadequate healthcare system, or low health literacy are at increased risk of experiencing high levels of pain and related disabilities [29]. This pain management difference is produced by the fragmented management of cancer survivors [30], which causes non-adherence to treatments and follow-ups, poor control of side effects, and long-term physical and psychological consequences. Therefore, the international scientific community has supported the urgency of introducing interventions that can promote timely identification of chronic cancer-related pain, which could ensure continuous and tailored management.

The analysis for the development of treatment paths for patients with oncological pain was addressed by examining the clinical protocols provided by the IEO clinical center (Istituto Europeo Oncologico).

About breast cancer pain, the following activities were implemented:

- Analysis of good practice according to literature evidence with respect to tools for monitoring and quantification of chronic pain related to breast cancer.
- Analysis of the treatment and management of patients with breast cancer and in particular "early breast cancer" at IEO.
- Analysis of "clinical practice" of chronic pain management and monitoring in the type of patients studied at the IEO.

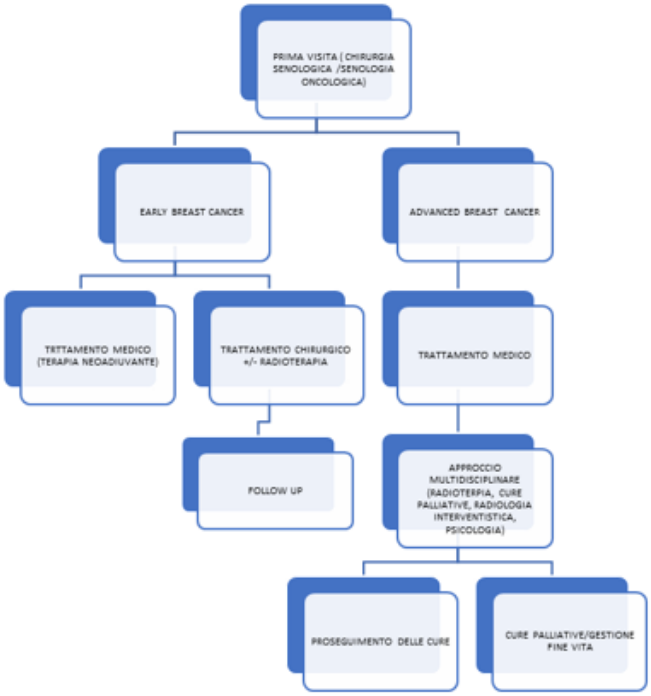

Figure 4 IEO protocol

The general protocol provides:

1. A specialist visit is carried out, with an associated psychological evaluation, to assess whether surgery is necessary.
2.
    2.1 Surgery may not be necessary: checks are carried out over time.
    2.2 Diagnostic investigations may be necessary to evaluate preoperative treatment before surgery.
    2.3 Surgery may be necessary with associated evaluation of neoadjuvant therapy.

3 In cases 2.2 and 2.3 the pre-hospitalization phase begins in which the necessary tests are carried out to assess suitability for the intervention.

4 We make sure that an anaesthetic examination is not necessary, otherwise we start one and evaluate the suitability for the operation.

5 The pre-intervention phase begins with associated pain monitoring (NRS scale is administered, if the patient is unable to provide appropriate responses, the VAS is administered).

6 If the pain is very severe, the patient is sent to the palliative care and pain therapy division, otherwise surgery is performed.

In particular, the following scales are administered in the pre-hospitalization phase: Brief Pain Inventory (BPI), Pain Catastrophizing Scale (PCS), Numeric Rate Scale (NRS)-Visual Analogue Scale (VAS); Hospital Anxiety and Depression Scale (HADS); ALGA brief. The following scales are administered in the pre-intervention phase: BPI, PCS, NRS-VAS, termometro del distress.

In the therapy phase the following scales are administered: BPI, PCS, HADS, NRS/VAS. Finally, in the follow-up phase the following scales are administered: BPI (every two weeks), PCS (every two weeks), HADS (every two weeks).

Chronic pain occurring in patient with fibromyalgia treated with tDCS:

Fibromyalgia or fibromyalgia syndrome is a chronic disease characterized by widespread muscle pain in the absence of signs of inflammation and often in association with other symptoms such as fatigue, sleep disturbances, memory and concentration deficits [31]

The exact causes that lead to the onset of fibromyalgia are not entirely known, the main hypothesis is that the multiplicity of genetic and environmental factors (for example infections or psycho-physical traumas) may contribute to the development of the disease [32]. The most accredited hypothesis is that the basis of chronic pain is an impairment of the way in which the brain processes painful stimuli. In particular, in those suffering from fibromyalgia the pain threshold would be lower than normal following brain sensitization to painful stimulation.

To date there is no specific medical therapy, some drugs can help manage symptoms and improve quality of life, especially if associated with targeted physical activity [33]. In this context, treatment with transcranial direct current stimulation (tsDCS) is also introduced. Some studies show that the application of transcranial stimulation with direct currents (tDCS) in patients with chronic neuropathic pain can reduce the intensity of pain by 30 to 50% on the VAS intensity scale (Visual Analog Scale for Pain).

The tDCS is a non-invasive brain stimulation technique that consists in the application on the scalp of electrodes that emit a low intensity direct current not perceivable by the

stimulated subject [34]. However, it is a type of treatment that requires close monitoring of the patient. This is because pain is a subjective symptom and therefore assessable only by the patient himself; a correct pain assessment system represents the first step to choose the most appropriate treatment and also allows you to evaluate its effectiveness, in fact the pain assessment provides crucial information for the management of care plans. The most reliable method of assessment is represented by the detection of the patient's subjective perception of pain by means of a self-assessment tool or self-report. Within the family of self-report methodologies, the Ecological Momentary Assessment (EMA) is uniquely positioned to evaluate the patient's pain experience with high precision. In this context, Patient Recorded Outcomes may be relevant, in fact the health data collected independently by users are currently considered widely useful for the well-being, prevention, management of diseases and clinical research, especially when longitudinal, chronic and home [35]. The tDCS, accompanied by monitoring / telemonitoring techniques, represents an interesting perspective for the treatment of chronic pain but the fact that the exact profiles of the patients are not known or in any case what are the prognostic factors that help predict the outcome of the patients regardless of treatment, it makes it difficult to assess the true efficacy of tDCS.

Regarding the use of tDCS in the treatment of chronic pain, analytical work was conducted with the partner GTS, in the first months of the project, before the partner left the consortium.

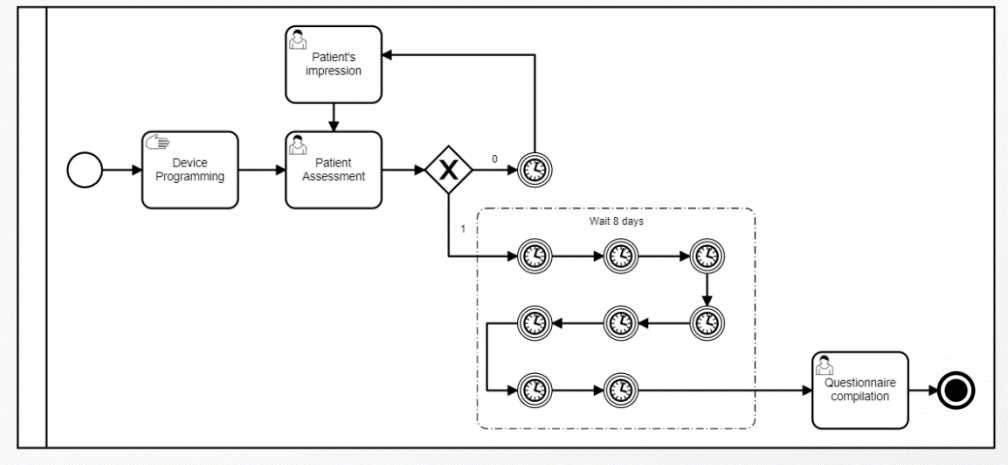

Figure 5 GTS protocol

The patient's treatment pathway, following the identification of the diagnosis, included:

- The prescription of the device with its configuration parameters.
- Scheduling of nurses' sessions at the patient's home to monitor data and fill in the relevant questionnaires.
- Completion of questionnaires for each appointment.
- The evaluation of the patient's clinical condition based on the applied therapy.

When the diagnosis is identified, the protocol is activated on the patient and a treatment episode is created. To define the prescription parameters, the doctor can proceed to fill in the form with the selection of the device and the definition of the specific configuration parameters.

Depending on the appointment, the questionnaire is proposed to be filled in:

- Beck Depression Inventory II (CRF_BDI_2).
- Hamilton Rating Scale for Depression (CRF_HAM-D).
- Pain Catastrophizing Scale (CRF_PCS).

- Patients' Global Impression of Change Scale (CRF_PGIC).
- Questionario sullo stato di salute (CRF_SF12).
- Brief Pain Inventory (CRF_BPI).

The analysis of this case study was fundamental for the subsequent analysis of the chronic pain management protocol in patients suffering from fibromyalgia, introduced thanks to the inclusion of the partner Euleria Srl. in the consortium.

In this context, patients with fibromyalgia are treated with tDCS combined with exercise therapy. The combination of these two techniques leads to an increase in the clinical effectiveness of the exercise on pain by acting directly at the cortical-motor level.

The analysed protocol includes:

- Administration of tDCS 3 times a week
- Exercise therapy, 3 times a week
- Exercise therapy, combined with tDCS, 3 times a week.

The clinical monitoring scales used in this context are:

- Visual Analogue Scale (VAS)
- 12-item Short Form Survey (SF12)
- Brief Pain Inventory (BPI)
- Hospital Anxiety and Depression Scale (HADS)
- System Usability Scale (SUS)

3.2.2 Configuration and implementation of care pathways in NuPlatform

The analysis of the identified use cases and the study of the protocols allowed the modelling of the paths and the following/subsequence configuration and implementation in the platform through:

Definition of workflows (in BPMN notation) relating to the care pathways identified and analyzed and consequent configuration of the workflows in BPMN notation on the NuPlatform with identification of the user profiles that perform the activities.

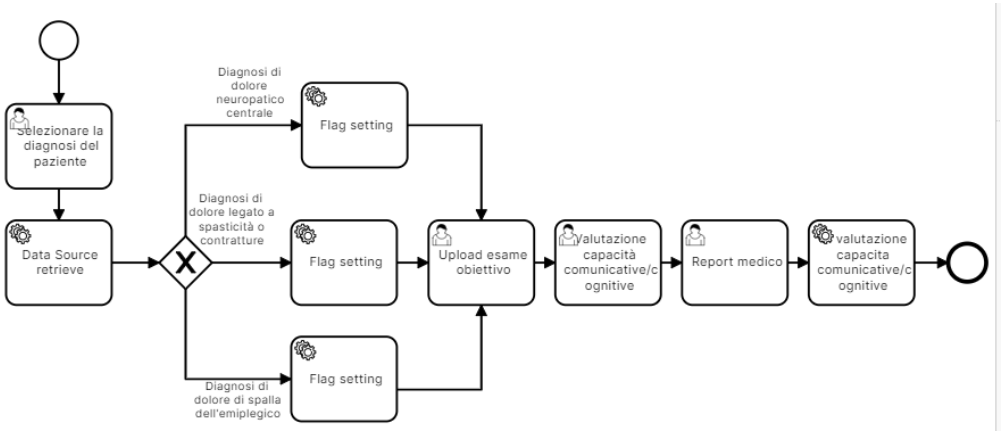

Figure 6 Example of Workflow

- Configuration of cards for tracking clinical information by doctor or patient.

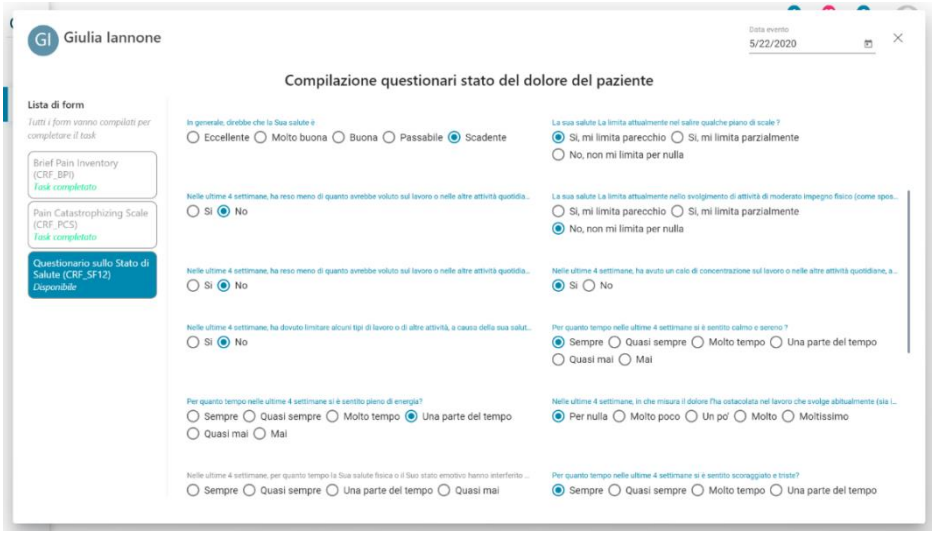

Figure 7: Example of form

- Monitoring dashboard configurations of patients enrolled in the protocol allowing the visualization of:
    - list of patients enrolled for each protocol with display of alerts or flags relating to the status of execution of activities, condition / diagnosis active on the patient, health status of the patient.

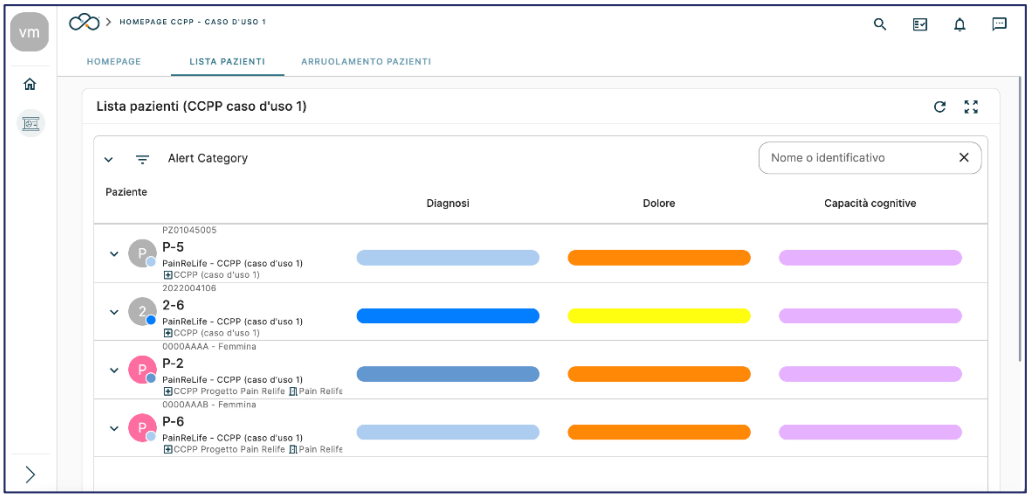

Figure 6 Example of patient list

- data for each specific patient enrolled to display the results of the questionnaires and the results of the scales administered.

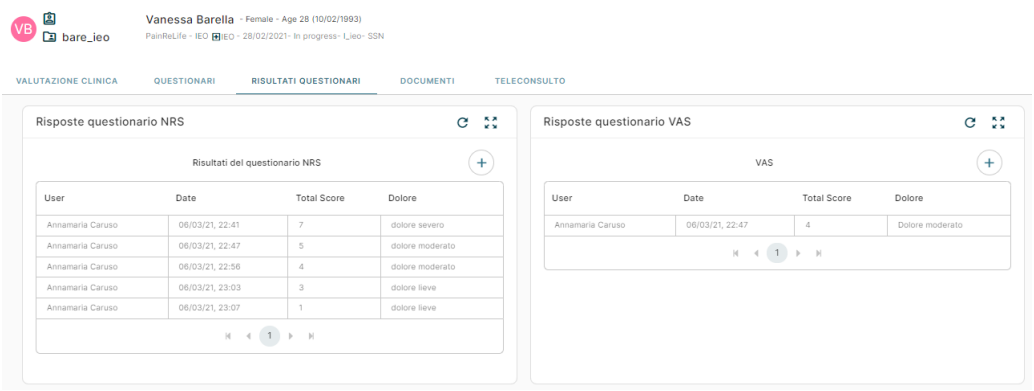

Figure 7 Result of questionnaire

Therefore, configuration components were created for each care pathway, such as:

- Form: questionnaires, clinical scales, pharmacological prescriptions, diagnostic evaluations, clinical reports, upload documentation, etc.

- Widgets: tables, lists, graphic components which aim to facilitate the use of the program by acting as an intermediary between the user and the System.

- Flag: indicator that signals a change in initial conditions, the presence of an error or the occurrence of a certain condition

- Dashboard: a set of graphical objects which, structured and displayed in a certain way, make a large amount of information, including information of a different nature and complexity, accessible immediately in real time.

3.3 PainRelife FHIR mapping to allow interoperability

In addition to the implementation of the Nuplatform, which is mainly used by doctors and healthcare professionals following the patient's care pathway, another key objective of the PainRelife project was the implementation of an APP to collect data directly from the patient. Collecting data while the patient is at home and monitoring this data remotely is easier and cheaper for patients than traditional methods that require constant examinations by a medical specialist. This APP has been designed for a multi-platform environment and developed according to international standards for eHealth interoperability, in particular using the FHIR infrastructure.

The FHIR infrastructure plays a crucial role in this project and deserves further investigation.

3.3.1 The Hl7 FHIR standard concept

FHIR (Fast Healthcare Interoperability Resource) is an interoperability standard developed by HL7 (the association that manages Health Level 7 standards) and designed to allow the exchange of health data in electronic format between different systems in the healthcare sector. HL7 has been producing healthcare data and modeling standards for 20 years; FHIR is the latest specification for data sharing and includes experience and knowledge of existing logical and theoretical models. As a result, it provides a simplified implementation for exchanging data between healthcare applications without sacrificing data integrity [36].

FHIR uses the application programming interfaces (APIs) to allow different applications to "plug in" to a core operating system, feeding all relevant information into the vendor's workflow. FHIR supports sharing information in multiple formats, including documents, messages, services and interface RESTful.

The main objective of the FHIR is to respond to the growing digitalization needs of the healthcare sector and to simplify data exchange without compromising the integrity of the information. FHIR aims to make electronic health records (EHRs) available, discoverable, and easily understandable to stakeholders as patients move through the healthcare ecosystem. This standard not only makes it easier for the patient to track their health but promotes automated clinical decision support and the use of other AI- or machine-based processes. From a clinical perspective, the most important components of the FHIR specification are Resources. FHIR resources reflect different types of clinical and administrative information. The FHIR specification defines a generic "form template" for each type of clinical information, so one for allergies, one for prescriptions, one for recommendations, etc.

FHIR data consists of repositories containing completed "modules" (resource instances). Resource instances describe patient information (such as demographics, health conditions, and procedures) as well as administrative information (such as professionals, organizations, and locations). Some resources are infrastructure components used to support the technical exchange of information by describing what systems can do, defining permitted code sets, etc.

FHIR repositories could be electronic health record (EHR) systems, pharmacy systems, hospital information systems (HIS), etc.

Each resource defines a small amount of data. A single resource doesn't say much, but a collection of resources taken together creates a useful medical record.

Each resource type is a rigid hierarchy of elements, each of which can be a primitive value, a complex value, or a set of child elements. In addition,

an element can be a foreign key, i.e. a reference to a different resource. The FHIR specification provides a logical definition, a UML definition, and representations through XML and JSON templates for each resource.

Any resource can be retrieved on the FHIR server of the platform through specific APIs provided.

FHIR APIs integrate seamlessly with resources. Since each resource has a unique identifier, each resource has a unique URL through which it can be retrieved from the FHIR server using the GET method. The search functionality is central as GET requests can be created by specifying parameters to compare against resource-specific item values. For example, you can query an FHIR server to find a patient with a specific ID, to find patients with birth dates in a specific range, and more.

All this allows us to understand the role of the standard FHIR in this project, fundamental for the collection, extraction and interrogation of data.

So far, we have talked about how it was possible to build the tool to allow data collection. We have a digital platform, used by medical users, for entering clinical data relating to patients and we have a mobile app, used by patients at home, to collect data relating to their health status and treatment path.

Data integration and connection is possible thanks to the FHIR standard.

In fact, within the PainRelife project, each clinical data is mapped to a specific FHIR resource.

A given FHIR resource can be connected, referenced, to another FHIR resource and this is how we obtain the connection between clinical data referring to one or more patients.

3.3.2 Terminology services: relevance in interoperability

Many elements in FHIR resources have an encoded value, represented by a sequence of characters assigned elsewhere and which identifies a known "concept". These encoded values can be represented by, for example, some external terminology or ontology (e.g. LOINC or SNOMED CT), or as a locally managed dictionary or lookup table.

In the context of healthcare processes, the existence of globally shared and semantically understandable terminologies is fundamental. The importance of terminologies is linked to the aim of minimizing errors related to the lack of understanding of information relating to the healthcare process and to the aim of optimizing the healthcare process itself. The technological tools most used for sharing terminology resources are terminology services. In this context, HL7 International, an international association for the development of standards in the healthcare IT sector, has developed the technical specifications for the development of a terminology service called "FHIR Terminology Service", which allows healthcare applications, through a unique RESTful interface, to easily use codes and sets of values.

So, terminological standards are considered an indispensable requirement for semantic interoperability. They provide universal and uniquely assignable identifiers that enable the exchange of clinical data between heterogeneous computing systems. The relationship

between data structure and semantics in FHIR is embedded within resources and therefore needs to be addressed when modelling profile information. Consequently, an important part of FHIR resource profiling is linking its elements to the most appropriate terminology systems and value sets. Some of the systems of greatest interest are:

- LOINC (Logical Observation Identifiers Names and Codes): it is a clinical terminology to identify measurements, observations and health records;
- SNOMED CT (Systematized Nomenclature of Medicine - Clinical Terms): is a systematically organized collection of medical terms that provides codes, terms, synonyms and definitions used in clinical documentation. It is considered the most complete and complex terminology standard in the medical field.
- ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification): it is a clinical terminology for the classification of diseases and related problems.

3.3.3 FHIR resources involved in the clinical environment

The data entered in the questionnaires and form within the platform were then mapped to FHIR standards. In particular, the following were carried out:

- Mapping of data on FHIR resources:
- Definition of the ER diagrams of the FHIR resources involved in the clinical environment (Patient, Encounter, DeviceRequest, Careplan, Observation, QuestionnaireResponse) and the user profiles that have access to them.

- Definition of FHIR resources for the definition of protocols (PlanDefinition), questionnaires (Questionnaire) and clinical observations (ObservationDefinition) for the implementation on the mobile APP of the protocols and scales.

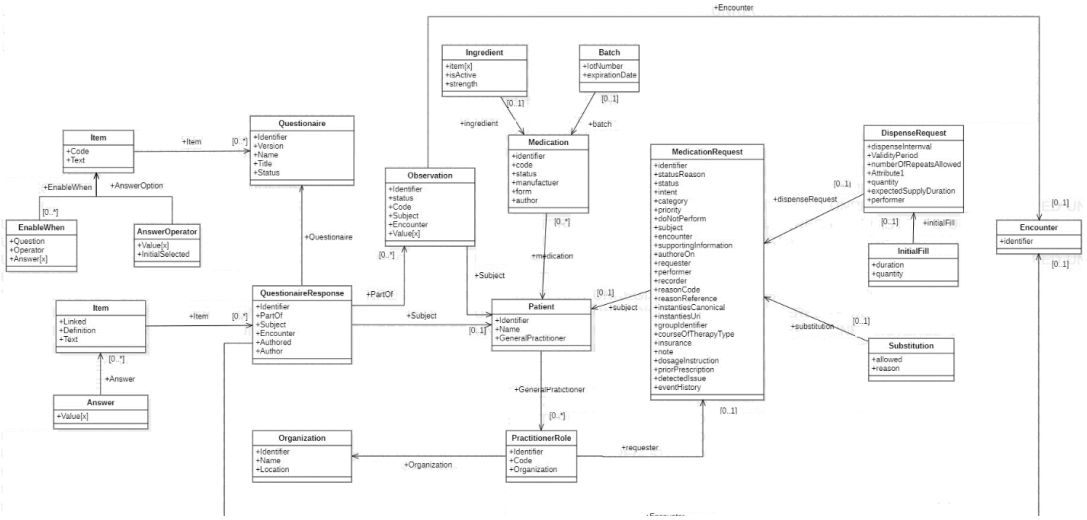

Figure 8 Definition of the ER diagrams of the FHIR resources involved in the clinical environment

The main resource is definitely the Patient resource.

The Patient resource collects general, demographic, and administrative information about the patient. The following figure shows the UML definition of the resource.

Some of the main properties are name, surname, gender etc.

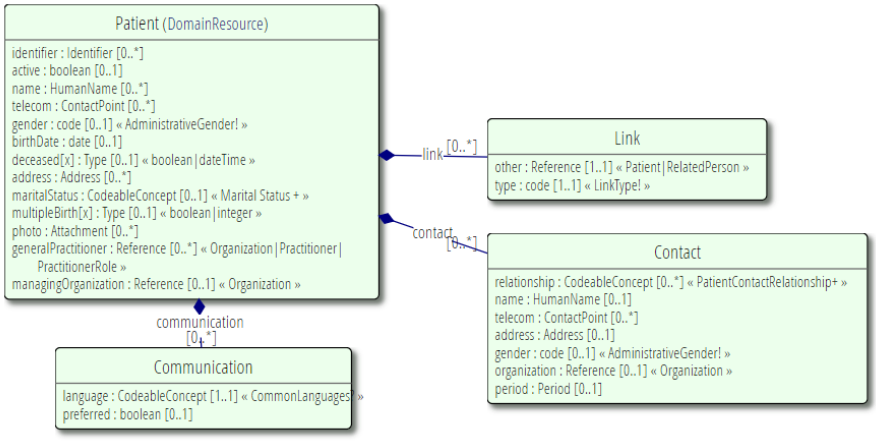

Figure 9 UML diagram of the patient resource

A form has therefore been built within the digital platform for the collection of patient data. This tab, represented by a form, has been mapped to the FHIR resource. Each piece of data has been mapped to a specific property, based on the meaning of the piece of data itself.

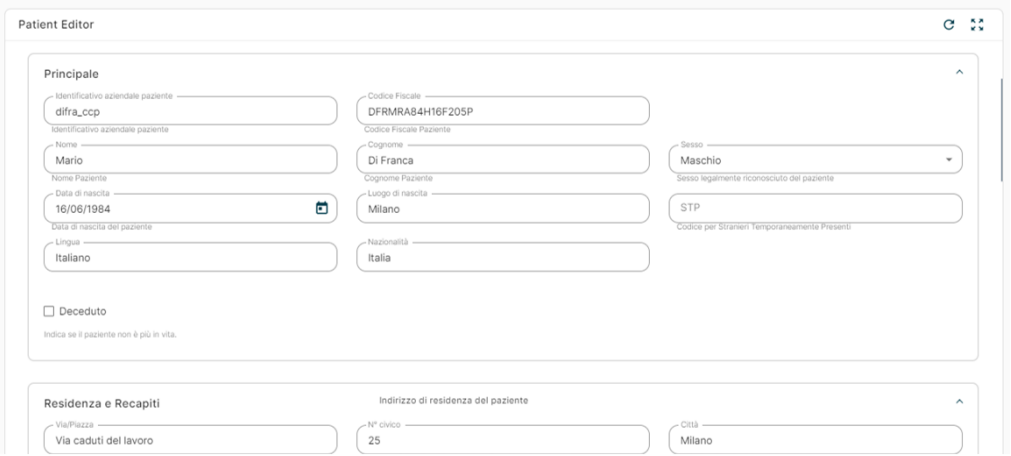

Figure 10 Example of a form for filling in patient data

The entire FHIR resource can be queried via FHIR, resulting in a JSON that encompasses all the information.


```
{
  "resourceType": "Patient",
  "id": "f001-cd56-7sdkmsmc-ddkdkd-pphd76",
  "identifier": [
    {
      "use": "usual",
      "system": "urn:oid:2.16.840.1.113883.2.4.6.3",
      "value": "738472983"
    }
  ],
  "active": true,
  "name": [
    {
      "family": "Di Franca",
      "given": [
        "Mario"
      ]
    }
  ],
  "telecom": [
    {
      "system": "phone",
      "value": "0648352638",
      "use": "mobile"
```

```
    },
    {
      "system": "email",
      "value": "m.difranca@gmail.com",
      "use": "home"
    }
  ],
  "gender": "male",
  "birthDate": "1994-06-16",
  "deceasedBoolean": false,
  "address": [
    {
      "use": "home",
      "line": [
        "Via Caduti del Lavoro 25"
      ],
      "city": "Milano"
    }
  ],
  "managingOrganization": {
    "reference": "Organization/f001",
    "display": "CCPP"
  }
}
```


In addition to the Patient resource, we need to discuss three other main resources: Observation QuestionnaireResponse and CarePlan.

These two resources are fundamental because through the QuestionnaireResponse resource it was possible to map all the clinical scales and evaluation questionnaires, through the Observation resource it was possible to map all the clinical observations and results of the administered scales.

As defined by the FHIR standard, the QuestionnaireResponse resource is a structured set of questions and their answers. The questions are sorted and grouped into coherent subsets, corresponding to the grouping structure of the questionnaire being answered. Questionnaire responses cover the need to communicate data from forms used in medical history examinations, research questionnaires, and sometimes complete medical records by specialty. The following figure shows the UML definition of the resource.

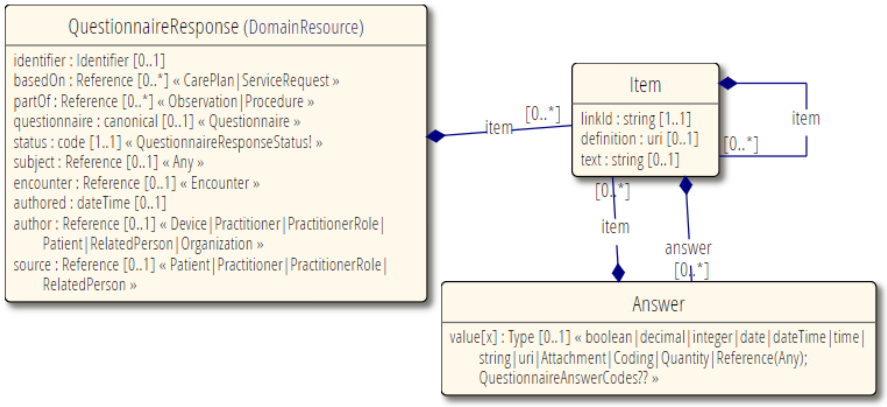

Figure 11 UML diagram of the QuestionnaireResponse resource

Within the QuestionnaireResponse resource it is possible to record, thanks to the "item" property, the responses to the clinical scales.

To allow data collection within the QuestionnaireResponse resource, a form mapped to the aforementioned resource was created for each form.

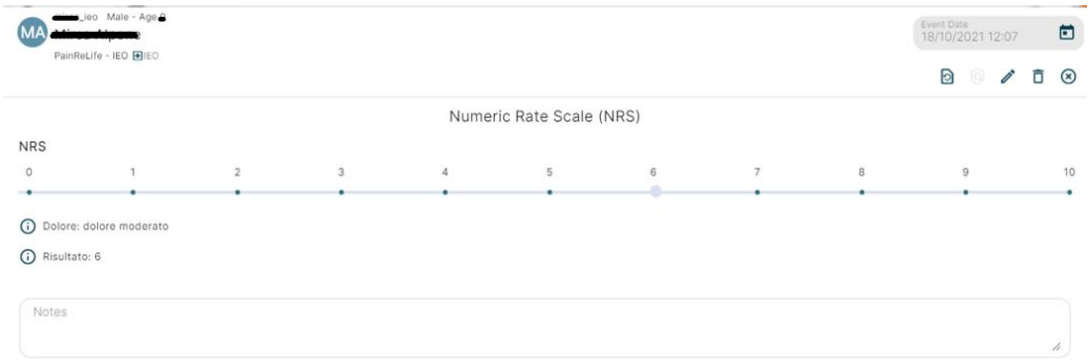

Figure 12 Example of a form to evaluate pain intensity

Correct execution of the form mapping and subsequent compilation by the operator guarantees the management of important data for the patient's clinical path. The mapping

of the scale shown in the figure provides a reference to the Patient resource. Fundamental reference to allow discrimination of information relating to a specific patient.

The Patient resource, contained in the “subject” property, will be used to indicate the patient to which the QuestionnaireResponse refers.

The form shown in the figure is characterized by a single item, the response to the pain assessment. Within the resource it was also possible to reference the author of the compilation, therefore the doctor who administered the scale and reported the value; in fact, the Practitioner resource, contained in the “author” property, will be used to indicate the professional responsible for compiling the QuestionnaireResponse resource.

In the example of the NRS scale there is only one item, but the result of this item represents a clinical result from which it is possible to determine clinical decisions. FHIR specifies that clinical data used to determine clinical decisions must be represented by the Observation resource. In our case therefore, in the QuestionnaireResponse resource we will have a second item, within which the Observation resource which represents the clinical result of the scale is referenced.

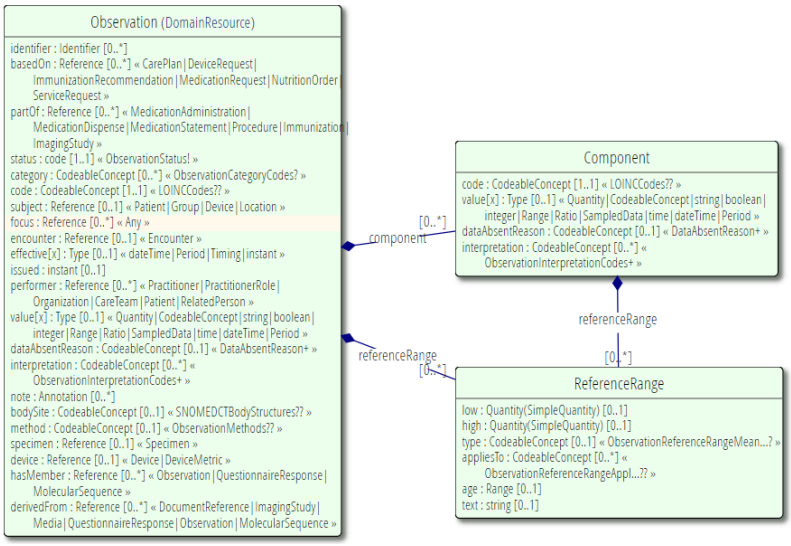

Figure 13 UML diagram of the Observation resource

We talked about the resources that allow you to define patient data and clinical observations. Within the Nuplatform platform, specific treatment plans have also been defined for each identified use case. Care Plans can be described in FHIR using the CarePlan resource, which reports how a professional intends to treat a particular patient. The resource captures details regarding the person involved and the actions to be taken. The field of use is very broad, ranging from planning an oncological treatment to planning a nutritional prescription. The resource can be used to represent both active and plans.

The resource has the following elements:

- Identifier: external identifier of the resource.
- Subject: reference to the patient.
- Status: status of the report.
- Context: reference to the meeting in which the plan was decided.
- Period: period to which the treatment plan dates back.
- Author: who wrote the treatment plan.

- Modified: date of the last update.
- Category: floor category.
- Description: summary description of the treatment plan.
- Addresses: health problems to which the treatment plan is addressed.
- Support: useful resources to associate with the treatment plan.
- RelatedPlan: treatment plans linked to the current one.
- RelatedPlan.code: code that identifies the type of care plan related to the current one.
- RelatedPlan.plan: reference to a CarePlan resource.
- Participant: identifies people/organizations involved in drafting the plan.
- Participant.role: specifies the role of the people involved.
- Participant.member: reference to the entity involved.
- Goal: link to the description of the objective of the treatment plan.
- Activity: describes the actions to be taken.
- Activity.actionResulting: link to a resource representative of the action to be taken.
- Activity.progress: notes on the status of the plan's activities.
- Activity.reference: details of the proposed activity represented in a resource.
- Activity.detail: details of the activities to be undertaken, without references to a specific resource.
- Activity.detail.category: code that identifies the care plan category.
- Activity.detail.code: code that identifies the type of treatment plan.
- Activity.detail.reasonCode: indicates the reasons for the treatment plan.
- Activity.detail.reasonReference: reference to a health condition.
- Activity.detail.goal: link to the purpose of the activity.
- Activity.detail.status: status of the activity.
- Activity.detail.statusReason: code identifying the reasons for the actions to be taken.

- Activity.detail.prohibited: establishes whether the activity in question should be carried out or not.
- Activity.detail.scheduled: period of occurrence of the activity.
- Activity.detail.location: place where the activity is carried out.
- Activity.detail.performer: person responsible for the activity carried out.
- Activity.detail.product: any drug administered.
- Activity.detail.dailyAmount: possible daily dose.
- Activity.detail.quantity: quantity administered.
- Activity.detail.description: textual description of the activity to be carried out.
- Notes: any comments

This resource is essential in the PainRelife project, as thanks to its drafting it was possible to define the scales that the doctor must submit to the patient via the platform and communicate to the mobile app which forms must instead be filled in by the patient, at home. The scales and observations entered by the patient within the app can be viewed within the digital platform thanks to the fact that the data is mapped into specific resources that are recognized and allow data management.

3.4 PainRelife Mobile App ecosystem and decision aids

In conjunction with the configuration an implementation of the platform, the mobile app was created in collaboration by one of project partners. My work, in this context was focused, mainly, on the analysis of case studies and connection and integration of resources through the FHIR standard. After having identified all the information to be digitized, for each of these a specific resource was identified that could represent it. The

work related to FHIR resource mapping was the crux of these activities and represents one of the actions I performed. So in relation to the creation of the app I dealt with the FHIR specifications to be maintained to guarantee communications between the app and the platform and vice versa.

The apps were designed by involving patients through interviews on usage preferences, submitting a storyboard of the user experience, defining the PROs and the timing of notifications in close collaboration with clinical partners. The apps were created by Zadig, a benefit company that encourages co-design and the active involvement of stakeholders to develop sustainable projects that respond to real needs, to promote people-centred medicine, also with the support of digital technologies. Decision support tools and features have been implemented in this tool to help patients and healthcare professionals in managing treatment and. Tools have been included to monitor the patient from home by completing clinical scales, notifications for the doctor, tools for viewing progress and self-assessment, tools for requesting an appointment or interview with the doctor.

The creation of the app was planned for the use cases of neurological pain and cancer pain. Thanks to the analysis of the protocols managed by the treatment centers, CCPP and IEO and the data management using FHIR standards, the integration between the digital platform and the mobile app has allowed complete management of the patient's clinical data.

The app designed for post-stroke pain management has three main sections:

- A section for compiling clinical scales.
- An educational section, born from the need to create content that could lead to knowledge and awareness of pain.

- A section that allows the patient to view notifications relating to the activities to be performed on the app to guide him in the operations.

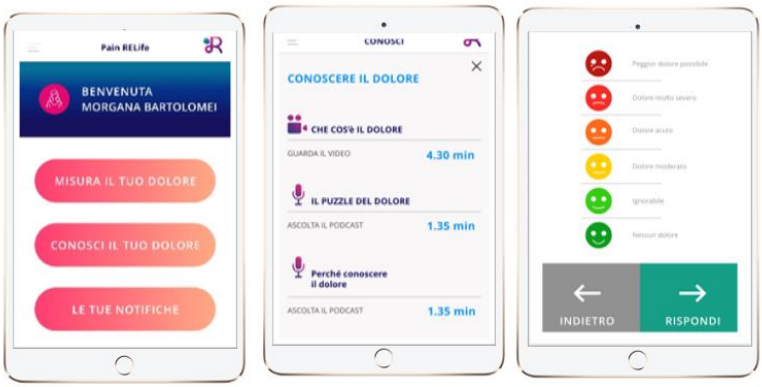

Figure 14 App developed for CCPP clinical center

The app designed for oncological pain management has five main sections:

- A section for compiling clinical scales.
- An educational section, born from the need to create content that could lead to knowledge and awareness of pain.
- A section that allows the patient to view notifications relating to the activities to be performed on the app to guide him in the operations.
- a section that allows you to collect a diary that allows the patient to describe his mood and observations.

- a section dedicated to decision aid.

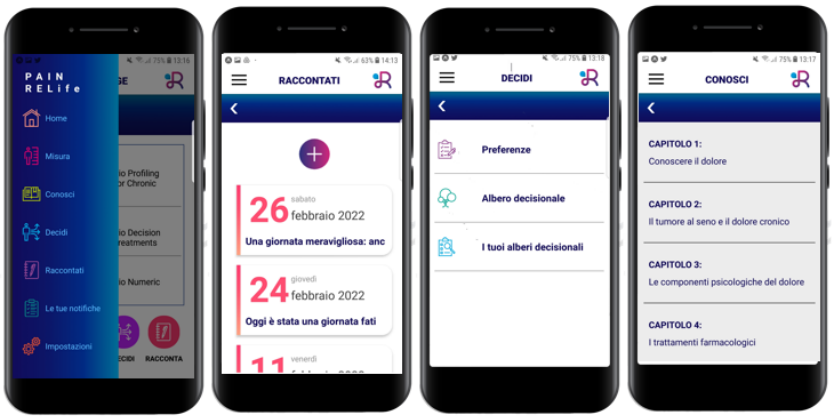

Figure 15 App developed for IEO clinical center

3.4.1 Decision AID

The theoretical concept of decision aid is to help, on the one hand, the doctor to understand the patient's preferences with respect to treatments (pharmacological and non-pharmacological) and their specific characteristics; on the other, to help the patient become aware of her own choice preferences, through a dynamic analysis of the utility associated with each treatment alternative. In accordance with scientific evidence [37], it has been hypothesized that this type of decision support can promote shared choice processes between doctor and patient on the one hand (shared decision-making models on chronic pain in oncology), on the other hand can increase adherence to the chosen treatments.

The PainRelife Decision aid, present in the App and connected to the platform, is made up of two distinct areas. In the first area, “Profiling Patients' Preferences for Chronic Pain Treatments”, patients' preferences are profiled with respect to the general characteristics of pharmacological and non-pharmacological treatments. The questions were constructed according to a series of dimensions identified in the reference literature as relevant in influencing the treatment decision in patients with chronic pain [38].

Figure 16 App developed for IEO clinical center - Decision AID

Specifically, as regards the dimensions identified for pharmacological treatments there are:

1 the evaluation of the perception of effectiveness, motivation and beliefs associated with the use of pharmacological therapies.
2 evaluation of how periodic dosing can influence the tolerability of the chosen treatment [39].
3 evaluation of the importance of the speed of the action effect and pain reduction [40].
4 evaluation of the importance that the treatment can induce addiction [40].

5 evaluation of the acceptability of the administration method.

6 evaluation of the tolerability of specific side effects (nausea or vomiting) [40].

7 evaluation of the importance of possible influences on cognitive functioning, for example, concentration and/or memory deficits.

While, for non-pharmacological treatments, the main dimensions include:

1. evaluation of the perception of effectiveness, motivation and beliefs associated with the use of alternative therapies to pharmacological ones.
2. predisposition towards interventions that act on thought patterns and emotions as pain mechanisms.
3. predisposition towards interventions that consider the mind-body relationship.
4. predisposition towards interventions that have immediate effects on the body area.
5. predisposition towards short-term interventions.
6. predisposition towards interventions to be carried out independently at home, outdoors or elsewhere.
7. treatments that require 'active' practice (e.g. physical exercise), rather than treatments that you receive from an operator while having a 'passive' role (e.g. massage, acupuncture);
8. group or individual dimension.

For each dimension the patient expresses her preference using a VAS scale from 0 (e.g. verbal label "not at all important") to 10 ("very important"). This allows us to have a quantifiable indication of the patients' preferences with respect to the macro-characteristics of the treatments (pharmacological and non-pharmacological) of chronic

pain, which will inform the doctor about the specificities of the treatment that the patient considers most important, for the treatment and management of pain related to your pathology. This information will be made available both to the patient, who at the end of the compilation will see a summary screen of the values associated with each characteristic, and to the doctor who will receive this information directly on the PainRelife Platform.

After having explored preferences with respect to pharmacological and non-pharmacological treatments following a structured approach, the PainRelife Decision aid allows the patient to access the second area "Decision Tree for Chronic Pain Treatment" and to build her own decision tree. The patient identifies advantages and disadvantages for each choice alternative (pharmacological treatments versus non-pharmacological treatments), to which she attributes a value (gain from 1 to 10 and loss from -1 to -10). The overall value obtained, given by the sum of the advantages and disadvantages for each choice alternative, identifies the utility associated with each treatment.

The decision tree can be filled in by the patient, at different times during the treatment process, for example, at key moments such as: the post-operative phase (1 month after surgery), during therapies (beginning and end) and the follow-up phase. This would allow us to analyze whether and how patients' preferences regarding the treatments proposed during the entire treatment process promote greater participation of the patient herself in the decision-making process regarding the treatments.

3.4.2 Further app integrations

The ecosystem of personalized applications available in PainRelife also integrates the "t-kura" tele-exercise solution proposed by Euleria (https://t-kura.it), a company that is part of the PainRelife consortium. The system is already CE-marked as Class 1/m medical device. It is composed by an inertial sensor and an app that allows the definition of a personalized motor rehabilitation protocol and the patient's monitoring through a continuous data collection. The system already includes report generations and visualization for both the patient and the clinician. It also implements a notification and alert system to improve patient's motivation. This solution is already integrated in the PainRelife platform and allows the collection of patient's results within the pre-defined clinical pathways. The system is also ready for the connection to a teleconsultation platform, and it is developed as a cloud-based solution in which other apps (e.g., for cognitive tele-rehabilitation, or mindfulness) can be integrated.

3.5 PainRelife Dashboards for aggregate data analytics

Data analysis refers to the practice of taking masses of aggregated data and analyzing it to derive important insights and information from it. Systems for visualizing aggregated data are called dashboards.

A dashboard is a set of graphical objects (such as histograms, pie charts, etc.) which, structured and displayed in a certain way, allow a lot of information, even of different nature and complexity, to be accessible immediately in real time.

A dashboard must:

- Show the information needed for a specific objective.

- Show information on a single computer screen.
- Provide information immediately.
- Have mechanisms that provide little information: concise, clear and intuitive.

Dashboards can be static or dynamic. Static dashboards are inflexible visualization systems, the parameters to be observed are established and cannot be changed. The dynamic ones are characterized by flexibility, in this type of system it is possible to vary some parameters and observe changes in the reference metrics in real-time. Therefore, in the latter case the user can choose what to display, for example he can decide to obscure some data and choose to display others (the system queries our analyses). There are also dashboards with intermediate features.

Clearly, static dashboards are simpler to create but dynamic ones allow you to filter through more information. It is central that the data remains in aggregate form, it must not be possible to trace it back to the patient and the type of analysis must not be used to profile the subjects inside. Profiling and extreme reduction of the sample that can trace it back to a single person are prohibited.

PainRelife data collection takes place within the NuPlatform. The data collected within the NuPlatform will be managed by the analytics engine.

The analytics engine performs analyses of the data on the platform, generating graphs that can initially be thought of as analytical, i.e., based on historical data, but can later be used to make predictions.

Figure 17 Dashboard and actor

Then the platform is interrogated to extract data of interest, which will be processed by the analytics engine so that it can be visualized.

Following the organization of several focus groups with the clinical centers participating in the project, the data and expectations from the analytics system were defined and translated into functional requirements and differentiated by clinical pathway analysed.

Analytics dashboards were implemented for post-stroke nerve pain and cancer pain use cases.

3.5.1 Functional and non-functional requirements

All data defined as useful based on the results of the focus groups can be extracted from the technology platform, according to the FHIR mapping also presented in the requirements tables below.

The identification of the functional requirements was possible thanks to the collaboration with the two clinical centres (CCPP and IEO). Questionnaires were submitted to the actors of the two centres which were then analysed for the precise definition of the requirements necessary for the generation of the dashboards.

The functional requirements identified for the generation of the analytical dashboard for the IEO clinical center were followed:

Requirement Code	Functional Requirement	Source	Resource
RF1	Extract patients' pain severity trends	NRS/VAS scale	Observation
RF2	Extract age distribution of patients	Patient card	Patient
RF3	Extract distress trend	Termometro distress psicologico scale	Observation
RF4	Extract trends related to anxiety and depression	HADS scale	Observation
RF5	Averaging anxiety and depression values by stage		
RF6	Extract trends related to: risk perception, self-efficacy, anxiety, cognitive closure, mental rumination, physical and mental health, memory, body image, and sexuality	ALGA scale	Observation
RF7	Extract Stage of Patient Care Pathway	Stage of the Care Pathway	Condition
RF8	Extract patients' preferences with respect to their role in medical decisions	PCS	Observation

RF9	Extract distribution of preferences with respect to pharmacological and non-pharmacological treatments in the care pathway	PROFILING PREFERENCES PATIENT…(APP)	Questionnaire Response
RF10	Extract Distribution of Prescribed Medications		
RF11	Extract Seat of Pain	Body Mapping (APP)	Observation
RF12	Average the frequency of visits to the app		
RF13	Average the time you use the app		
RF14	Sum up the number of requests for activation of pain therapies and palliative care		
RF15	Averaging pain values by stage		
RF16	Averaging distress values per phase		

Figure 18 Functional requirements for CCPP analytical dashbaord

The functional requirements identified for the generation of the analytical dashboard for the CCPP clinical center were followed:

Requirement Code	Functional Requirement	Source	Resource
RF1	Extract Stroke Severity Trend	NIHSS scale	Observation
RF2	Extract Patients' Gender Distribution	Patient card	Patient
RF3	Extract age distribution of patients	Patient card	Patient
RF4	Extract patients' pain severity trend	NRS/VAS scale	Observation
RF5	Extract information about the type of pain	CCP Diagnosis	Condition
RF6	Extract Distribution of Prescribed Medications	CCPP Drug Prescription	MedicationRequest
RF7	Extract SF12 Score Trend	SF12 scale	Observation
RF8	Extract PCS Score Trend	PCS scale	Observation
RF9	Extract HADS score trend (anxiety and depression)	HADS scale	Observation
RF10	Extract NIHSS Score Trend	NIHSS scale	Observation
RF11	Extract BI Score Trend	BI scale	Observation
RF12	Extract SIS score trend	SIS 3.0 scale	Observation
RF13	Extract FM Score Trend	FM scale	Observation
RF14	Extract PAINAD score trend	PAINAD scale	Observation
RF15	Extract DN4 Score Trend	DN4 scale	Observation

RF16	Estrarre tempo score MAS	MAS scale	Observation
RF17	Add up the number of logins by the user		
RF18	Sum up the number of accesses by the researcher		

Figure 19 Functional requirements for IEO analytical dashbaord

Furthermore, the following non-functional requirements were identified:

- RNF1: The dashboard must have access policies.
- RNF2: The dashboard must not store data internally.
- RNF3: The dashboard must allow mobile viewing.
- RNF4: The dashboard must handle FHIR calls.
- RNF5: The dashboard must not save raw data.
- RNF6: The dashboard must not display aggregate data with a number of subjects less than three.

Through domain analysis it was also possible to identify the actors who can consult the dashboards and who can benefit from the data displayed.

In particular:

- Clinical (display separated by center/pathology treated)
- General practitioners (GPs)
- IEO specialists (Doctors/Nurses/Psychologists/Other specialists);
- CCPP specialists (Doctors/Nurses/Psychologists/Other specialists);

Access rules based on different access levels have been defined; therefore, to protect patient privacy and avoid profiling or extreme reduction of the sample, it was decided to create different levels of access based on the roles of the subjects/entities who consult the platform.

To ensure the fulfilment of these requirements, an ad hoc system was created. As regards the development of the analytical models, we opted for an initial 'on the spot' implementation phase to study the different types of applicable models, which would then be exported to the cloud infrastructure.

3.5.2 Implementation of dashboards

The dashboard start screen is different based on the permissions of the user who accesses it. For users affiliated with a specific organization\clinical center, they will be allowed to view their organization's dashboard. For users with global permissions, researchers, institutions, etc., the initial screen will allow you to switch from one dashboard to another.

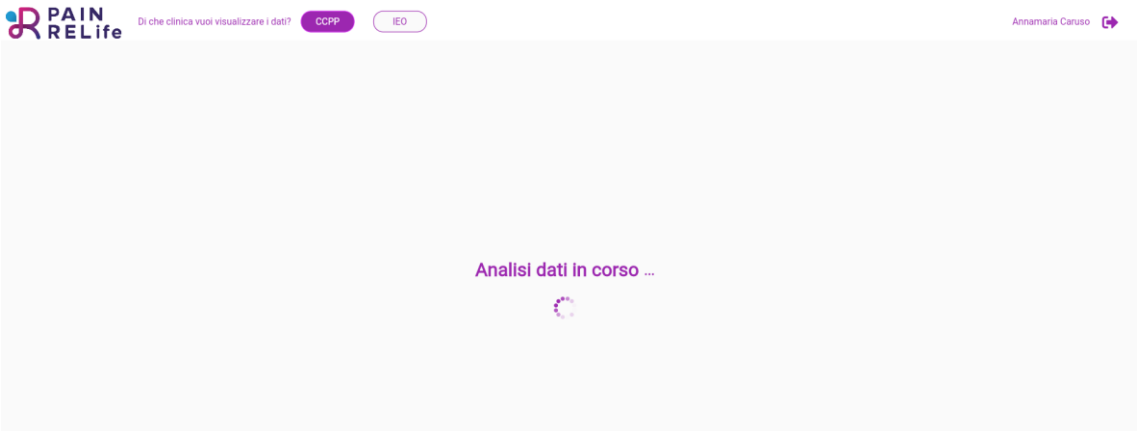

Figure 20 Dashboard login screen

a. CCPP analytical dashboard

Below is the dashboard created for the CCPP clinical center. The dashboard consists of:

- a section containing three pie charts that provide general information on the patients enrolled on the platform at a specific clinical center.

Figure 21 First section of analytical dashboard for CCPP

- The first diagram serves as a counter of enrolled patients. The graph allows the visualization of the number of patients enrolled at the reference clinical center and the remaining number of patients enrolled on the platform at other structures.
- The second diagram filters the patients enrolled by gender. Allows viewing of the number of male and female patients
- The third diagram divides the patients by age groups (<27, 28-45, 46-79, >80 years)

- a section containing graphics that provide clinical information on patients. Each of these graphs is characterized by specific filters through which the desired output information can be managed.

- The first graph allows you to view the average intensity value of the pain experienced by the patients. Using the filters at the bottom of the graph, it is possible to divide the list of patients by diagnosis, aphasia condition or stroke severity. It is also possible to further divide the patient list by gender and age group.

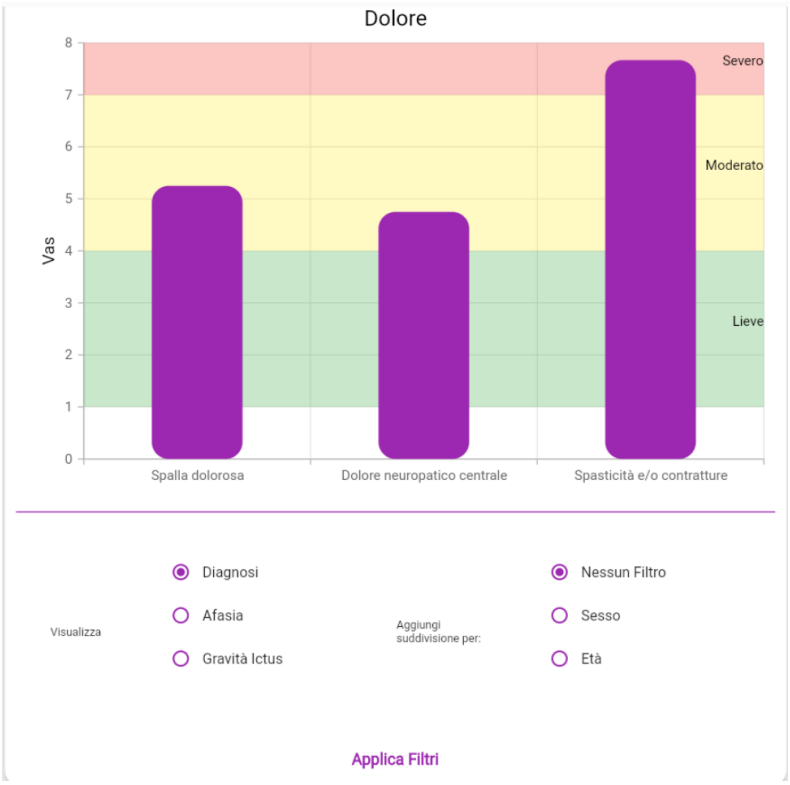

Figure 22 First graph - CCPP dashboard: average intensity value of the pain experienced by the patients.

This graph allows you to evaluate the variation in intensity of pain experienced by patients based on their clinical and general conditions, also allowing you to make clinical predictions based on the results obtained.

- The second graph allows the visualization of the average of the results detected via clinical scales submitted to the patients at time T0 (start of enrolment) and T1 (end of enrolment), allowing direct comparison. Each column of the graph indicates the average value of the scores obtained by patients with the same clinical diagnosis with respect to a specific rating scale. It is possible to further filter the list of patients from which to extract information based on the presence

or absence of communication and/or cognitive deficits (aphasia filters). The clinical scale is selected via the drop-down menu located next to the filters.

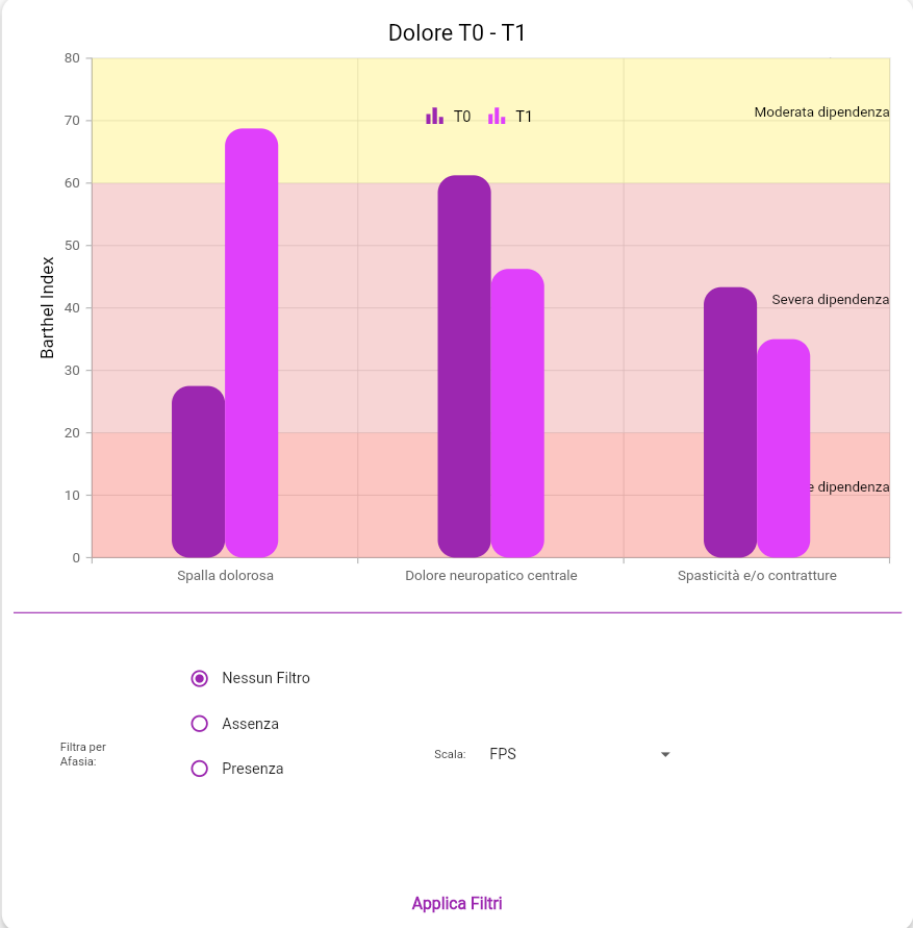

Figure 23 Second graph - CCPP dashboard: average of the results detected via clinical scales submitted to the patients at time T0 (start enrolment)

This graph allows you to evaluate the progress of the clinical conditions of patients with a certain diagnosis by comparing the results detected by the clinical scales at the beginning and end of enrolment.

- The third graph allows the visualization of the results of certain clinical scales submitted to patients during the clinical path. Each column of the graph indicates the average value of the scores obtained by patients with the same

stroke severity with respect to a specific rating scale. Through the filters at the bottom of the graph it is possible to select the rating scale for which you want to view the result. For scales that provide this, it is possible to select a maximum of

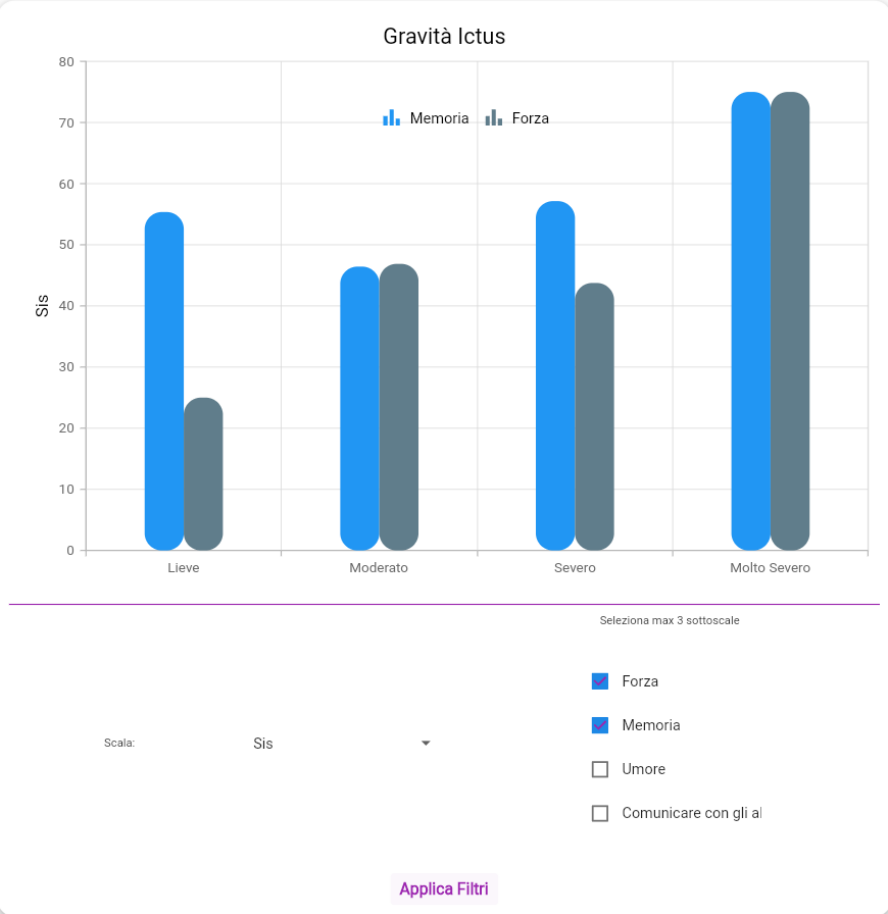

Figure 24 Third graph - CCPP dashboard: visualization of the results of certain clinical scales

three subscales to show the results at the same time.

- The fourth graph shows the intensity of pain experienced by patients in reference to a specific treatment. The list of patients is divided based on the type of drug used.

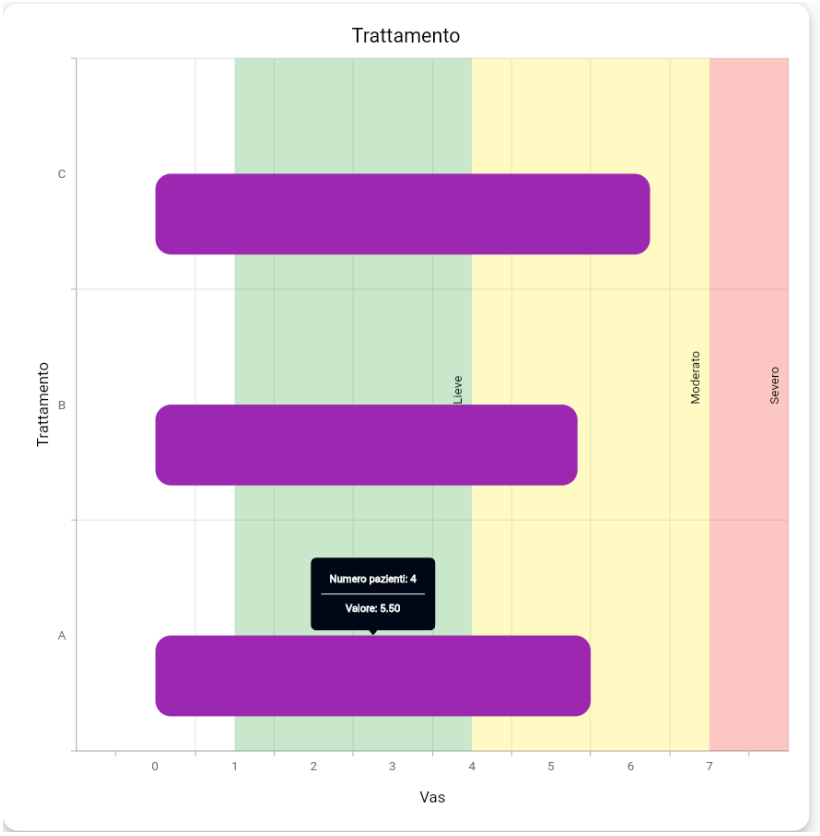

Figure 25 Fourth graph - CCPP dashboard: intensity of pain experienced by patients in reference to a specific treatment.

The purpose of this graph is to evaluate and predict the variation in pain based on the pharmacological treatment subjected to patients.

b. IEO analytical dashboard

Below is the dashboard created for the IEO clinical center. The dashboard consists of:

- a section containing three pie charts that provide general information on the patients enrolled on the platform at a specific clinical center.

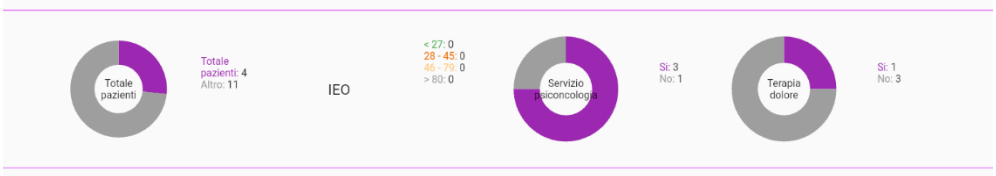

Figure 26 First section of analytical dashboard for IEO

The first diagram serves as a counter of enrolled patients.

The graph allows the visualization of the number of patients enrolled at the reference clinical center and the remaining number of patients enrolled on the platform at other structures.

The second diagram divides the patients by age groups (<27, 28-45, 46-79, >80 years).

The third diagram allows you to view the number of patients who have requested or for whom a psycho-oncology service is active.

The fourth diagram allows you to view the number of patients for whom pain therapy is active.

- a section containing graphics that provide clinical information on patients. Each of these graphs is characterized by specific filters through which the desired output information can be managed.

- The first graph allows you to view the scores of the evaluation scales submitted to patients in the various phases of the treatment process. Thanks to the filters at the bottom of the graph it is possible to select the rating scale for which you want to show the results. Is possible select up to four scales at once.

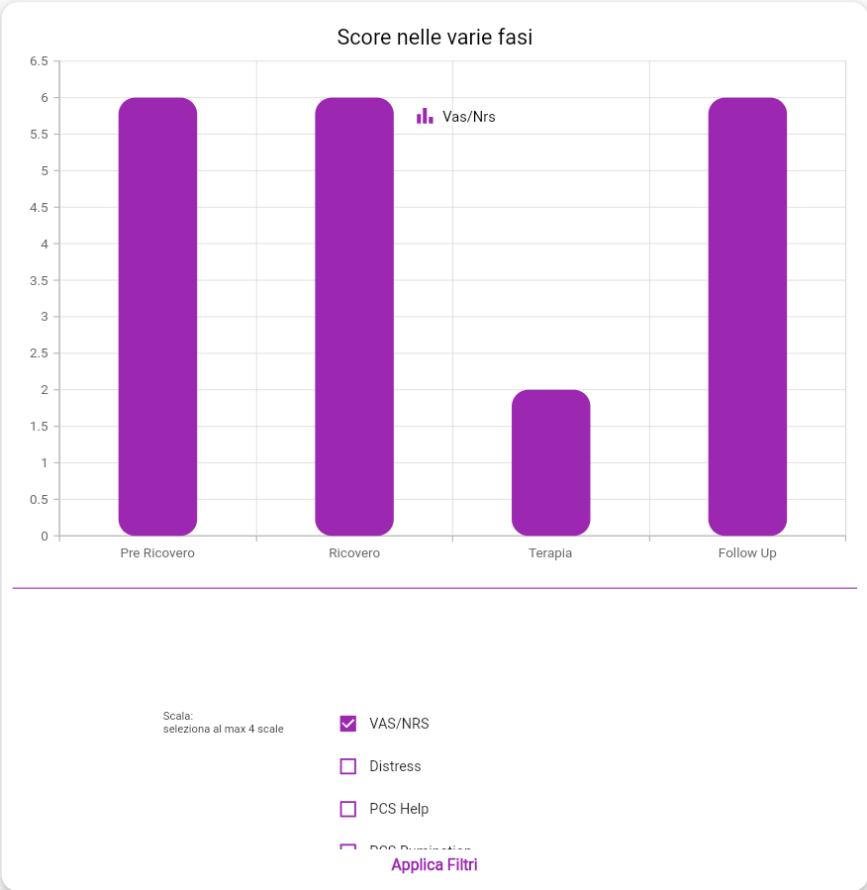

Figure 27 First graph - IEO dashboard: scores of the evaluation scales submitted to patients in the various phases of the treatment process.

- the second graph is a pie chart that shows the percentage of results compared to a specific scale. In particular, it indicates the average percentage of the degree of patient participation in the clinical decision.

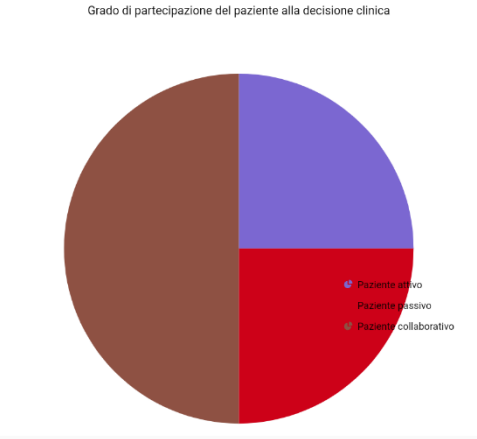

Figure 28 Second graph - IEO dashboard: average percentage of the degree of patient participation in the clinical decision

- The third graph allows you to show, via the visualization of a body map, the site of greatest pain intensity for patients.

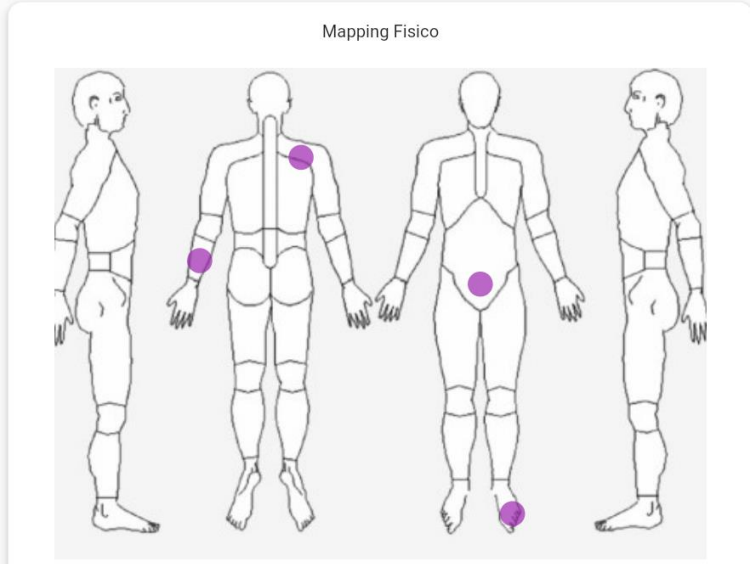

Figure 29 Third graph - IEO dashboard: site of greatest pain intensity for patients.

- The fourth graph shows the intensity of pain/anxiety/depression experienced by patients in reference to a specific treatment. The list of patients is divided based on the type of drug used.

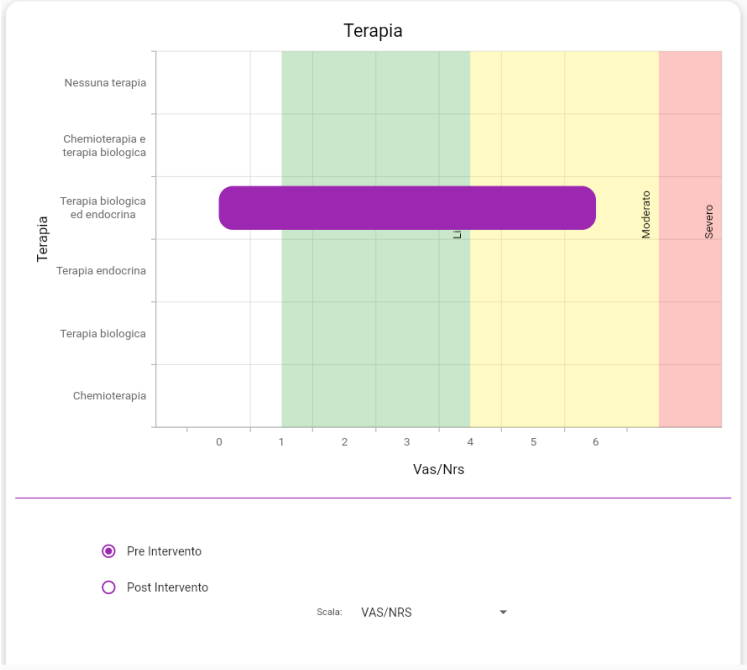

Figure 30 Fourth graph - IEO dashboard: intensity of pain/anxiety/depression experienced by patients in reference to a specific treatment.

By using the filters at the bottom, it is possible to decide whether to show the pre-intervention or post-intervention treatments. Furthermore, thanks to the possibility of being able to filter the information based on the intensity of the pain or the level of anxiety and depression, it is possible to preliminarily evaluate the effectiveness of the treatments.

4 PainRelife ecosystem use

The three use cases implemented in the ecosystem were applied to real patient populations through clinical studies.

The study on early breast cancer patients focuses on the management and monitoring of pain trends and the response to pharma/not pharma treatment. The study on post-stroke patients focuses on subjects' management in hospital and at home, with the aid of quantification tools and other secondary multidimensional clinical measures. The trial on fibromyalgia investigates the combined effects of tDCS and tele-rehabilitation. All protocols were implemented to promote a better/standardized evaluation of pain and the use of combined approaches, including periodic questionnaires and pain assessment scales such as 12-item Short Form Survey, Brief Pain Inventory, Hospital Anxiety and Depression Scale and Visual Analogue Scale.

All studies were approved by ethical committees and started, but only the early breast cancer study was concluded so far.

4.1 Early breast cancer study methods and protocol

Healthcare providers have used the NuPlatform platform to collect and store patient clinical data and enable continuous monitoring of patient health status (e.g., pain, psychological well-being, and treatment decision-making preferences. [44] A big data infrastructure connected to the FHIR server enabled a series of dynamic dashboards aimed at providing a systematic and intuitive profile of the characteristics of the patient population and which were used by researchers, doctors and healthcare stakeholders. The platform, as previously mentioned, is associated to a mobile app for patients called

PainRelife, which collects health data. This technological solution enabled dual communication between patients and healthcare professionals. The information collected by the mobile app was saved in the digital platform and supervised by healthcare professionals.

4.1.1 Primary End Point

The primary end point of this pilot study is the evaluation of patients' usability experience after 3 months of using a new digital and integrated technological ecosystem (engagement, judgment on usability, aesthetics, quality of given information, personal perception, and perceived impact on behaviors; *Nu*Platform connected with the PainRelife app) for patients with early breast cancer experiencing in chronic pain.

4.1.2 Secondary End Points

Secondary end points concern the following aspects:

- (1) assessing the usability of the mobile app in terms of the number of access and usage time.
- (2) assessing changes in self-efficacy related to chronic pain.
- (3) assessing SDM processes between patients and health care professionals.

4.1.3 Selection Criteria e Partecipant

Inclusion criteria included:

- patients >18 years.

- having an early breast cancer diagnosis.
- having undergone surgical intervention for breast carcinoma (quadrantectomy, mastectomy ± lymph node dissection)
- the presence of postsurgical pain with a score ≥3 in the Numerical Rating Scale (NRS) or VAS.
- patients with internet access and a personal smartphone; and (6) patients who have read and signed the informed consent.

Exclusion criteria included:

- the presence of primary psychiatric or neurological conditions preventing the ability to use the mobile app and the capacity to express free consent to join the study.
- the presence of other medical conditions which imply an active antalgic treatment.
- patients who refused to sign the informed consent.

The inclusion and exclusion criteria were established considering that chronic pain is a common side effect related in breast cancer patient (about 60%) and persistent acute pain after surgery is considered a risk factor for the development of chronic pain during survival.

Twenty-five breast cancer patients with a mean age of 47 years (age M=47.12, SD=8.41) were admitted to the Division of Medical Senology and the Division of Pain Therapy and Palliative Care of the European Institute of Oncology (IEO) with a diagnosis of breast cancer and pain participated in the pilot usability study described here. Participants were introduced to the mobile application after their clinic visit and instructed to use it for three consecutive months.

Marital Status	%	Education	%
Cohabiting	4 (1)	PhD	8 (2)
Widowed	12 (3)	Master's Degree	32 (8)
Single	20 (5)	High School	48 (12)
Married	64 (16)	Primary School	12 (3)

Table 1 The socio-demographical information of the BCPs enrolled is reported in the table.

Diagnosis	%	Cancer Type	%	Familiarity	%	Mutation	%
Lobular Carcinoma	12 (3)	Triple Negative	8 (2)	I° Breast	32 (8)	BRCA1	8 (2)
Ductal Carcinoma	68 (17)	HER2+	20 (5)	II° Breast	24 (6)	BRCA1	8 (2)
Ductal Carcinoma in Situ	12 (3)	Luminal	72 (18)	No Familiarity	44 (11)	Negative	24 (6)
Moucinosous Carcinoma	4 (1)	-	-	-	-	No testing	52 (13)
Occult Carcinoma	4 (1)	-	-	-	-	-	-

Table 2 The diagnosis, cancer type, familiarity, and genetic mutation of patients enrolled.

4.1.4 Measures

4.1.4.1 *Patient Demographic and Medical Variables*

Age, gender, education, marital status, cancer diagnosis, type of surgery, oncological treatments, and comorbid medical disorders were collected through electronic medical records and self-reports.

4.1.4.2 *Pain Self-Efficacy Questionnaire*

<< The PSE is a self-administered questionnaire composed of 10 items rated on a 7-point Likert scale from "*not at all confident*" to "*completely confident.*" [45] The Pain Self-Efficacy Questionnaire (PSEQ) [46] measures self-efficacy while performing activities

of daily living, despite experiencing pain. The total score of the PSEQ ranges from 0 to 60. >>

4.1.4.3 *Nine-Item Shared Decision-Making Questionnaire*

<< The 9-item Shared Decision-Making Questionnaire (SDM-Q-9) [47] is a self-administered questionnaire composed of 9 items on a 6-point Likert scale from "*completely disagree*" to "*completely agree.*" The SDM-Q-9 evaluates patients' perception of SDM and their level of involvement during the consultation, as well as the information received on possible treatments and potential risks and benefits of being involved in the decision-making process. The SDM-Q-9 showed high internal consistency in the original validation (Cronbach α=.94). >>

4.1.4.4 *Mobile Application Rating Scale*

<< The Mobile Application Rating Scale (MARS) [48] is a self-administered questionnaire specifically created to rate the quality of eHealth apps, and it is composed of 6 different sections (A, B, C, D, E, and F) for a total of 29 items with 5 possible answers. It assesses the quality of the app according to 4 specific dimensions: engagement experienced while using the app (A); functionality (B), aesthetics (C), quality of the information received (D), as well as the subjective perception of app quality (E) and the perceived impact on the app toward knowledge, attitudes, and probability to change user behaviors (F). >>

4.1.4.5 *VAS and NRS*

<< The VAS and NRS [49] are unidimensional assessment scales for evaluating pain intensity. The first one graphically represents the amplitude of perceived pain through a 10-cm predesigned line. The left extremity corresponds to the "*absence of pain*," whereas the right represents the "worst *pain possible.*" Next, the patient will be asked to draw a sign on the line representing the level of experienced pain. In the NRS scale, similarly, patients will be asked to verbally specify the number corresponding to their experienced pain, according to the following numerical graduation: (0: "*no pain*," 1-3: "*mild pain*," 4-6: "*moderate pain*," 7-10: "*severe pain*"). The use of the VAS or NRS is determined by the patient's degree of cognitive functioning. >>

4.1.5 Statistical Considerations

A series of descriptive analyses were performed to depict the characteristics of the sample. In order to evaluate the primary endpoint, the mean score and standard deviation were achieved in each subscale of the MARS (*a.* engagement experienced while using the application; *b.* functionality; *c.* aesthetics; *d.* quality of the information received; *e.* subjective perception of the application quality; and *f.* expected impact on knowledge, attitudes, and probability to change user behaviors) were calculated at three months, as well as the total number of accesses of each participant to the *PainRelife Mobile Application.*

Further, a new variable named total app quality was created using the mean values of the engagement, functionality, esthetics, and information quality subscale. The final

measurement of the *app quality* was obtained, which is the average value of the four means [50]. A Pearson Correlational Analysis was performed among all self-reports used (NRS - PSEQ - SDM - MARS) and the total number of accesses during the three months of the study. A repeated measures ANOVA was performed to detect variation in pain intensity (NRS) from T0 (baseline) to T2 (at three months). Further, a new dichotomous variable named *frequency of use* was created considering the whole number of accesses and the lowest number of accesses to the *PainRelife Mobile Application* required to address by participants to finalize the study's tasks. The *frequency of use* variable has permitted splitting participants between higher and lower frequencies. Further, the Student's t-test was run to evaluate the difference between *the frequency of use* and PSEQ, SDM, and MARS. Data were analyzed using SPSS version 26.0.

4.1.6 Ethics Approval

This protocol was assessed and certified by the ethical board of the European Institute of Oncology (approval number R1597/21-IEO 1701). All participants. Informed consent has provided informed consent. Participation in the study was voluntary and did not include any compensation. It is necessary to specify that the study data are de-identified.

4.2 Early Breast cancer study results

Thanks to the study carried out [51], which eliminates the critical issues present in previous studies due to sample size or inadequate follow-up, it was possible to evaluate the usability experience. The usability results made it possible to identify the quality of the features of the mobile app for chronic pain management used by patients to manage

their treatment path. The results on the patient's home monitoring, obtained thanks to the direct communication between the Nuplatform, from the point of view of healthcare professionals and the PainRelife mobile app, from the patients' point of view, made it possible to demonstrate the advantages of continuous monitoring of the patient's state of physical and psychological health of outpatients, allowing doctors to recognize warning signs. promptly. Furthermore, the implementation of decision aid to improve patients' ability to participate in their clinical decision has allowed us to define a better representation of the patient's processes in pain management.

The Mobile Application Rating Scale (MARS) [40] was used to evaluate usability. Furthermore, pain self-efficacy and participation in treatment decisions were evaluated. To evaluate the primary endpoint, the mean score and standard deviation were calculated for each MARS. The MARS total score (raging 1-5) provided overall medium-high mean values in each subscale (min. 3.31 - max. 4.18) and total app quality of 3.90 (SD = 0.506), suggesting generally good usability evaluation by the participants. Confirmed also by the participants' accesses during the whole study (M=22.92, SD= 15.60, min. 2 - max. 73).

MARS Subscales	M	SD.
a. Engagement	3.31	.617
b. Functionality	4.14	.629
c. Aesthetics	3.98	.849
d. Information	4.18	.607
e. Subjective Quality	3.50	.494
f. Behavioral Change	4.05	.665
Total App Quality	3.90	.506

Table 3 The mean and standard deviation of the MARS subscales

The descriptive analysis of the answers' distribution of the *functionality's subscale* (figure 33) reported that 56.5% of participants determined that the mobile app is easy to use. Additionally, 87% of participants affirms that interactions are consistent and intuitive (*easy to use:* agree 34.8% and strongly agree 52.2%) offering a positive valuation of the design (*gestural design:* agree 34.8% and strongly agree 52.2%), as well as, of the navigation properties (*navigation:* agree 52.2% and strongly agree 34.8%). However, some slight uncertainties were observed about the general performance of the mobile app in the shifting between pages and sections (*performance:* undecided 34.8%)

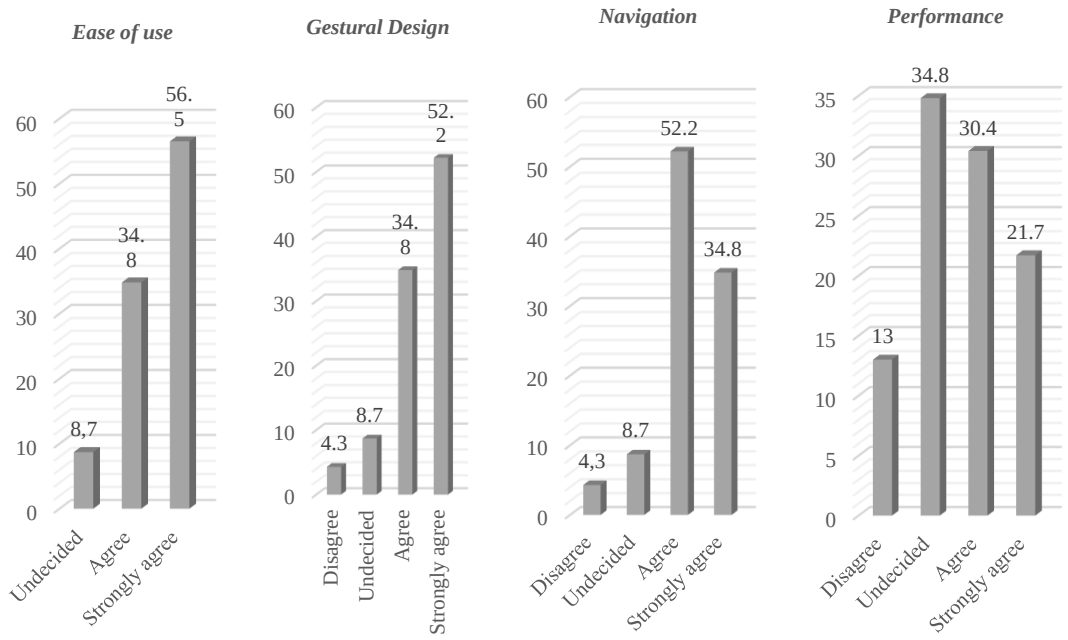

Figure 31 Functionalyty assesmentofthe PainRelife Mobile application using MARS scale

Moreover, 78.2% of participants consider that the information contained in the mobile app is evidence-based (information: agree 39.1% - strongly agree 39.1%), relevant, focused on chronic pain in breast cancer and its management during the clinical course of the disease (quality of information: agree 39.1% - strongly agree 47.8%) and reliable

(credibility: 95.7%). Furthermore, the amount (amount of information: agree 30.4% (n=7) - strongly agree 39.1%) and how the information is reported using different settings (information visual: agree 47.8% - strongly agree 39.1%) were considered positive by participants. Finally, many participants declared that the objectives of the mobile app are achievable reported some concern.

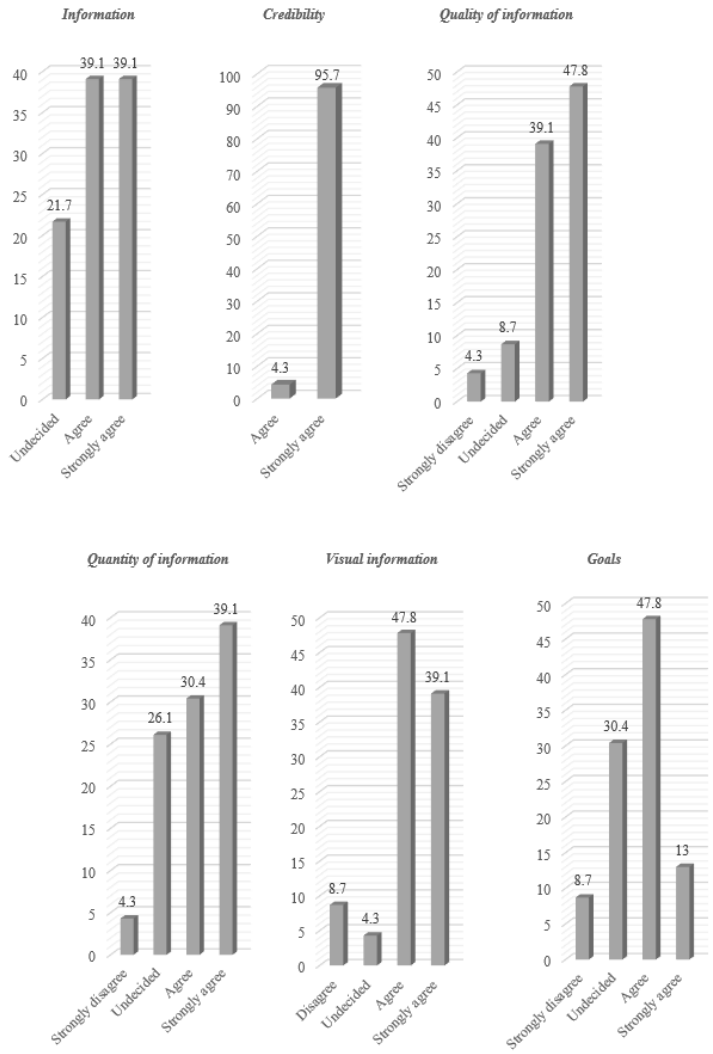

Figure 32 Information Assessment of the PainRELife Mobile Application Using the MARS Scale

Lastly, the examination of the answers' distribution of the *behavioral change's subscale* revealed that 82.6% of participants described that the mobile app had improved *awareness* about the issues of chronic pain in the cancer disease pathway, and 69.6% retains that has increased chronic pain related *knowledge*.

Likewise, 69.5% of participants affirms that the mobile app might support attitudes about chronic pain (*attitude:* agree 39.1% - strongly agree 30.4%)

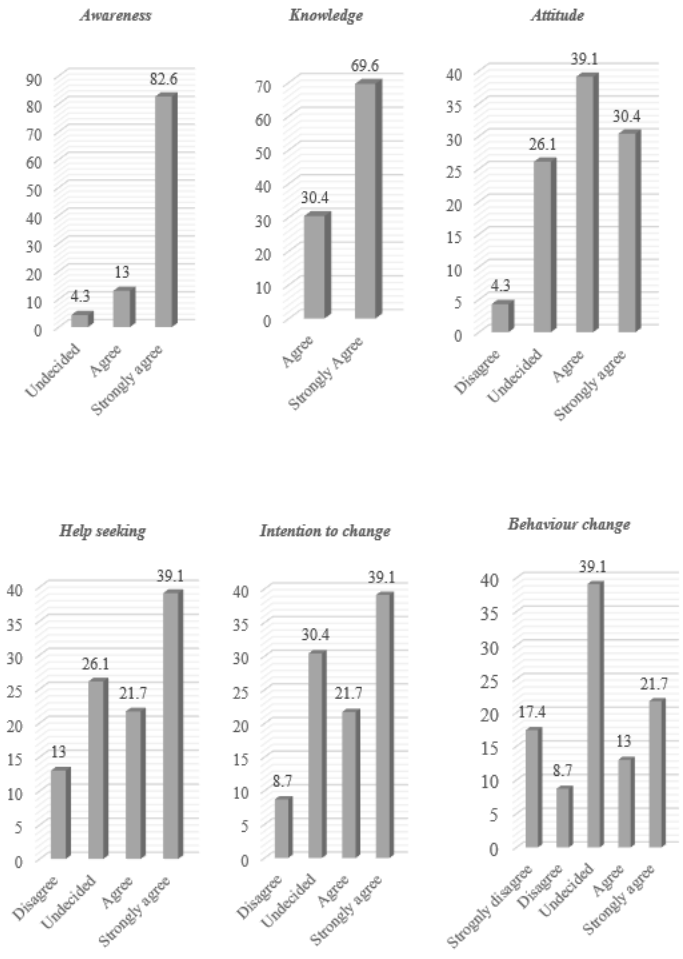

Figure 33 Behavior Change Assessment of the PainRELife Mobile Application Using the MARS Scale

Related to frequency of use and pain self-efficacy, according to the Student *t* test, younger participants used the mobile app less (mean = 44.15, SD = 7.11) than older participants. A difference in pain self-efficacy was observed between participants with higher versus lower frequency use (t_{23}=1.644, *P*=0.057; *d*=0.65). The latter data indicate that, at T2, participants with a lower pain self-efficacy (mean = 40.83, SD =14.58) used the mobile app more than participants with a higher pain self-efficacy (mean = 48.46, SD = 7.90).

Related pain intensity and shared decision-making, the repeated measures ANOVA revealed that participants reported a reduction in pain intensity from T0 (mean = 5, SD = 1.68) to T2 (mean = 3.72, SD = 2.59; $F_{2,x}$ = 3.407, *P* =.04). A positive correlation was found between the total number of times the mobile app was accessed and pain intensity at T2 (r = 0.458, *P* = .03).

No correlations were detected between the MARS subscales and PSEQ or NRS. A negative correlation was observed between the subjective quality subscale and the number of times the mobile app was accessed (r=–0.498, *P*=.02). Further, the engagement (*r*=0.445, *P*=.03), information (*r*=0.427, *P*=.04), and subjective quality (*r*=0.548, *P*≤.007) subscales were positively correlated with shared decision-making.

5 DISCUSSION

The general purpose of this doctoral project is to design and implement a tool for PROs collection for chronic pain patients, in order to allow reliable efficacy assessment of therapies, as well as patient's support, and, finally, to support the identification of possible prognostic factors, also using data analytics techniques. Specific attention to tDCS efficacy analysis will be given.

To this end, the project is developed according to the following research objectives:

Objective 1 - to develop a digital platform for creation and implementation of digitized care pathways for patient with chronic pain, in particular treated with tDCS, by collecting patient reported outcomes.

Objective 2- to implement a mobile tool based on an application that can support monitoring by collecting patient reported outcomes and integrated within a digital platform. In the same tool, are implemented features for supporting patients and caregivers in the management and administration of treatment. Among them, tools for progress visualization and self-evaluation, communication tools to put patients in contact with their doctors, to ask for assistance and to talk with the community.

Objective 3- identify the prognostic factors based on the PROs collected through the application and the platform, together with the patient's clinical history by performing an analytical study on the data collected for the creation of analytical dashboards.

Collectively, the results obtained so far showed that the PainRelife ecosystem allows full data collection and availability, through the integration of a clinical platform with mHealth apps for PROMs collection, thus supporting the chronic pain patient in the

definition and execution of her/his care pathway even when pain is connected to different pathologies. The use of PainRelife can increase patient's awareness and involvement in care pathway, thanks to the continuous monitoring of their physical, mental, cognitive, and behavioral states, as well as to the administration of controlled tele-rehabilitation therapies.

Data retrieved from the pilot study described in section 4 evaluating patient's experiences using a new and integrated healthcare ecosystem for chronic pain management, in particular for breast cancer survivors, in line with other studies highlighting digital health technologies, when developed using a patient-oriented approach, they represent valuable tools for increasing participation of breast cancer patients in clinical care. In Furthermore, these tools enable the achievement of critical clinical objectives results and improvement of and continuity of care. Furthermore, from the results obtained, it is possible to observe how integrated healthcare ecosystems enable secondary key outcomes how to reduce the burden on healthcare workers and optimize the resources of the healthcare system. Finally, what emerges is that integrated healthcare ecosystems could be important devices for improve continuous monitoring of physical status, psychological burden and socioeconomic problems during the chronic pain path.

In this research project a fundamental point was the use of the FHIR standard for process optimization. We know that one of the most difficult problems in the world of healthcare is related to data sharing and the possibility of finding all a patient's information. Furthermore, to date, despite the various and different digitalisation processes launched, health data is distributed across different sites with different formats. Looking at the current state of the clinical world and on behalf of what has been exposed so far, it is

important to underline how the FHIR standard and the concept of an integrated system have also taken hold in one of the most discussed areas: the electronic health record (FSE). In fact, although there are still many issues to be explored, the new generation of the FSE will be based on HL7 FHIR for the management of structured data.

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