Randomized clinical trial of the MyPal ePRO-based early palliative care system in adult patients with hematologic malignancies

Acronym: MyPal4Adults

Identifiers:	**TBD**
Sponsor:	Centre for Research and Technology Hellas (CERTH, partner 1, Greece)
Name of Chief Investigator:	Prof. Paolo Ghia; Prof. Heleni Papadaki; Dr. Michael Doubek; Prof. Richard Rosenquist; Dr. Niki Stavroyianni
Study design:	Unblinded 1:1 randomized controlled interventional non pharmacological trial
Protocol Version:	1.0 – 16.12.2019

RESPONSIBILITIES

Sponsor representative:

Kostas Stamatopoulos
Director of Institute of Applied Biosciences Institute of Applied Biosciences
Centre for Research & Technology Hellas
6th Km. Charilaou-Thermi Road, Thermi, Thessaloniki
GR 57001, GREECE
Tel.: +30 2311 257615
E-Mail: kostas.stamatopoulos@certh.gr

The Sponsor's medical expert for the study:

Prof. Paolo Ghia
Director of the Strategic Research Program on CLL
IRCCS Ospedale San Raffaele and Università Vita Salute San Raffaele
Via Olgettina 60, 20132 Milano, Italy
Phone: +39-0226434797
email: ghia.paolo@hsr.it

Chief investigators who are responsible for conducting the study in the respective nation states:

Prof. Paolo Ghia (UniSR/OSR); Prof. Heleni Papadaki (PAGNI); Dr. Michael Doubek (FN BRNO); Prof. Richard Rosenquist (KI); Dr. Niki Stavroyianni (CERTH/Papanicolau)

Responsible for all study-site related medical decisions:

Prof. Paolo Ghia (UniSR/OSR); Prof. Heleni Papadaki (PAGNI); Dr. Michael Doubek FN BRNO); Prof. Richard Rosenquist (KI); Dr. Niki Stavroyianni (CERTH/Papanicolau)

Technical departments involved in the study:

CENTRAL IT DEPARTMENT
Centre for Research & Technology Hellas (CERTH)
6th Km. Charilaou-Thermi Road, Thermi, Thessaloniki
GR 57001, GREECE

LOCAL IT DEPARTMENT
Università Vita Salute San Raffaele
Via Olgettina 60, 20132 Milano, Italy

Protocol Version 1.0 – 31.10.2019

SIGNATURE PAGE

MyPAL-ADULT *Trial Protocol v1.0 16 December 2019*

This protocol has been approved by:

Name:	Prof. Paolo Ghia	Trial Role:	Chief Investigator
Signature:	_____	Date:	__/____/ 2019
Name:	Prof. Heleni Papadaki	Trial Role:	Chief Investigator
Signature:	_____	Date:	__/____/ 2019
Name:	Dr. Michael Doubek	Trial Role:	Chief Investigator
Signature:	_____	Date:	__/____/ 2019
Name:	Prof. Richard Rosenquist	Trial Role:	Chief Investigator
Signature:	_____	Date:	__/____/ 2019
Name:	Dr. Niki Stavroyianni	Trial Role:	Chief Investigator
Signature:	_____	Date:	__/____/ 2019
Name:	Kostas Stamatopoulos, MD PhD	Trial Role:	Sponsor
Signature:	_____	Date:	__/____/ 2019

This protocol describes the MyPAL-ADULT clinical study and provides information about procedures for patients taking part in the it. **The protocol should not be used as a guide for treatment of patients not taking part in the MyPAL-ADULT RCT.**

Protocol Version 1.0 – 31.10.2019

TRIAL SYNOPSIS

Study Title	Randomized clinical trial of the MyPal ePRO-based early palliative care system in adult patients with hematologic malignancies
Study Code	**MyPAL4Adults**
Clinicaltrials.gov Number	Not applicable
Study Phase	2
Study Type	Interventional
Study Sites	1. Karolinska Institutet (Sweden) 2. Università Vita-Salute San Raffaele (Italy) 3. University Hospital of Crete (Greece) 4. University Hospital Brno (Czech Republic) 5. G. Papanicolaou Hospital of Thessaloniki (Greece; affiliated with CERTH)
Planned Sample Size	300 patients
Background and Rationale	MyPal will operate according to the "palliative care" definition provided by the World Health Organization which states: '*Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual*'[1] MyPal also supports the notion that palliative care can be offered to improve quality of life of patients and their families who are receiving active treatment either curative or aiming at disease control. Furthermore, it differentiates between *specialist palliative care*, which can be provided by specialized services for patients with complex problems not adequately covered by other treatment options and delivered by specially trained staff and *general palliative care* which can be offered by professionals who might have acquired training or education in general palliative care and recognises that these are complementary rather than mutually exclusive. As such, palliative care is an essential component of serious illness care, which can be initiated as early as the time of diagnosis. Therefore, it should be viewed as a necessary component of care for patients with cancer. Palliative care requirements may increase throughout the illness trajectory, focusing on quality of life across the continuum of care. Though palliative care plays a crucial role, tools helping normal health care providers to better identify palliative care needs are still lacking. MyPal introduces a digital health based, personalized intervention for palliative cancer care exploiting the value of electronic Patient Reporting Outcomes (ePROs), i.e. tools and apps for implicit/explicit self-reporting and tracking of health. A PRO is a measurement based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a physician or anyone else.

[1] Sepúlveda C, Marlin A, Yoshida T, Ullrich A. Palliative care: the World Health Organization's global perspective. Journal of pain and symptom management. 2002 Aug 1;24(2):91-6.

Protocol Version 1.0 – 31.10.2019

Study Objectives	To evaluate the effectiveness and cost-effectiveness of use of the MyPal ePRO system as a novel, patient-centred, palliative care intervention for patients with haematological malignancies (CLL/MDS). Primary Objective The primary objective is to determine whether - compared to standard care - the MyPal-ADULT intervention can lead to improved QoL as evidenced by statistically significant higher scores in EORTC QLQ-C30[2] General Questionnaire and EQ-5D[3]. Secondary Objectives To determine whether - compared to standard care - the MyPal system intervention can lead to the following outcomes in patients with hematological cancers (CLL/MDS): 1. Improvement in physical and emotional functioning as evidenced by higher scores in the Integrated Palliative Care Outcome Scale (IPOS)[4] at prespecified timepoints [Time Frame: baseline, and every month for the first six months and 12-month follow-up] 2. Increase in satisfaction with care score as evidenced by higher scores in the EORTC Patient Satisfaction with Cancer Care questionnaire (EORTC PATSAT C33)[5] at prespecified timepoints [Time Frame: baseline, and every month for the first six months and 12-month follow-up] 3. Increase in overall survival as evidenced by longer survival times [Time Frame: N/A] | To evaluate the cost effectiveness of the MyPal intervention compared to standard care taking into account the Euroqol EQ-5D data from both groups as well as other parameters such as hospital visits, doctor visits, hospitalizations, medications, treatments and investigations. And to determine whether the MyPal system intervention can lead to the following outcomes in patients with hematological cancers (CLL/MDS) over time: 1. Reduced symptom burden as evidenced by lower scores in the Edmonton Symptom Assessment System (ESAS)[6] at prespecified timepoints [Time Frame: every week until the end of the study] 2. Reduced pain score as evidenced by lower scores in the Brief Pain Inventory (BPI)[7] at prespecified timepoints [Time Frame: every week until the end of the study] 3. Reduced emotional distress as evidenced by lower scores in the Emotion Thermometers (ET)[8] at prespecified timepoints [Time Frame: every week until the end of the study]

[2] Fayers P, Bottomley AE, EORTC Quality of Life Group. Quality of life research within the EORTC—the EORTC QLQ-C30. European Journal of Cancer. 2002 Mar 1;38:125-33.
[3] Rabin R, Gudex C, Selai C, Herdman M. From translation to version management: a history and review of methods for the cultural adaptation of the EuroQol five-dimensional questionnaire. Value in Health. 2014 Jan 1;17(1):70-6.
[4] Hearn J, Higginson IJ. Development and validation of a core outcome measure for palliative care: the palliative care outcome scale. Palliative Care Core Audit Project Advisory Group. BMJ Quality & Safety. 1999 Dec 1;8(4):219-27.
[5] Brédart A, Anota A, Young T, Tomaszewski KA, Arraras JI, Moura De Albuquerque Melo H, Schmidt H, Friend E, Bergenmar M, Costantini A, Vassiliou V. Phase III study of the European Organisation for Research and Treatment of Cancer satisfaction with cancer care core questionnaire (EORTC PATSAT-C33) and specific complementary outpatient module (EORTC OUT-PATSAT7). European journal of cancer care. 2018 Jan;27(1):e12786.
[6] Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. Journal of palliative care. 1991 Jun;7(2):6-9.
[7] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Annals, Academy of Medicine, Singapore. 1994 Mar.
[8] Mitchell AJ, Baker-Glenn EA, Granger L, Symonds P. Can the Distress Thermometer be improved by additional mood domains? Part I. Initial validation of the Emotion Thermometers tool. Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer. 2010 Feb;19(2):125-33.

<table>
<tr><td></td><td>4. Increase in patient engagement in care as evidenced by satisfactory adherence to reporting (e.g. 70% answered scheduled reports). [Time Frame: every week until the end of the study]</td></tr>
<tr><td>Study Endpoints</td><td>
<table>
<tr><th>Primary Endpoint</th><th>Measure/Scale</th></tr>
<tr><td>Improvement in quality of life</td><td>EORTC QLQ-C30 General Questionnaire and EQ-5D</td></tr>
</table>
<table>
<tr><th>Secondary Endpoint</th><th>Measure/Scale</th></tr>
<tr><td>Symptom reduction</td><td>Edmonton Symptom Assessment System (ESAS)</td></tr>
<tr><td>Pain reduction</td><td>Brief Pain Inventory (BPI) severity</td></tr>
<tr><td>Emotional distress reduction</td><td>Emotion Thermometers (ET)</td></tr>
<tr><td>Improvement in psychological and physical functioning</td><td>Integrated Palliative Care Outcome Scale (IPOS)</td></tr>
<tr><td>Increase in patient engagement in care</td><td>Adherence to reporting (e.g.70% answered of scheduled reports)</td></tr>
<tr><td>Increase in satisfaction with care</td><td>EORTC Satisfaction with Cancer Care questionnaire</td></tr>
<tr><td>Overall survival</td><td>Event of death</td></tr>
</table>
</td></tr>
<tr><td>Study Design</td><td>Randomized unblinded interventional clinical trial:
<table>
<tr><th>Arm</th><th>Intervention</th></tr>
<tr><td>Experimental arm (n=150): Intervention group
Administration of the MyPal ePRO system</td><td>The intervention group will use the ePRO tools provided in the project.</td></tr>
<tr><td>Standard care arm (n=150): no intervention besides general palliative care if required</td><td>General palliative care if required</td></tr>
</table>
</td></tr>
<tr><td>Key Inclusion Criteria</td><td>1. Adults (≥18 years)
2. Diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or myelodysplastic syndrome (MDS)
3. Scheduled to receive any line of treatment for CLL/SLL or MDS or who have been previously exposed to any treatment for CLL or MDS
4. Able to understand and communicate in the respective language
5. Users of an Internet connected device (smartphone/tablet)</td></tr>
<tr><td>Key Exclusion Criteria</td><td>1. Patients who are already participating in another experimental study
2. Patients needing immediate referral for specialized palliative care
3. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator’s opinion, could compromise the subject’s safety or put the study outcomes at undue risk
4. Patients unable to provide written informed consent
5. Life expectancy <3 months
6. For CLL cohort: patients who have experienced Richter transformation</td></tr>
<tr><td>Intervention</td><td>Patients will be randomly assigned in a 1:1 fashion to use the MyPal system and receive related-intervention versus general palliative care, stratified by cancer type (i.e. CLL vs MDS), using a computer-generated number sequence, which will be concealed until after group assignment.</td></tr>
</table>

Study Duration	Total study duration: 25 months Study duration for each participant is expected to be 12 months. Study analysis: 3 months after the end of the study Expected First patient in date: 01.05.2020 Expected Last patient in: 30.03.2021 End of study: 30.03.2022
Efficacy Assessments	Patients will be asked to complete self-report questionnaires at baseline, and every month for the first six months and at 12-month follow-up (please refer to study endpoints section). QoL, symptom burden as well as other psychological and physical functioning questionnaire results will be analysed by independent-samples t tests and analysis of variance (ANOVA) models. . Analysis of covariance (ANCOVA) that will control for baseline criterion scores and potential confounders such as age group and gender, which may be imbalanced between groups and associated with outcomes of interest will also be performed. Subgroup analysis of the outcome measures will also be performed in order to detect potential differences between specific groups of participants. The grouping variables that will be employed are (a) the clinical center (origin), (b) the country of residence, (c) the age group, (d) the disease stage, and (e) the diagnosis (CLL, MDS). In the case an interaction effect is observed, separate subgroup analyses in the CLL and MDS cohorts with repeated measures ANOVA will be performed to assess the effect of intervention on quality of life and other outcome measures.
Safety Assessments	The intervention proposed by MyPal relies on the adaptation of digital health tools that are available from previous projects (e.g. from the H2020 iManageCancer project). The tools that will be employed have been tested in pilots in the respective projects. Prior to conducting the MyPal-ADULT study, all the tools will be tested to see whether these are in line with the needs and preferences of the targeted end-users through end-user Workshops.
Statistical Methods and Planned Analyses	Descriptive analysis will be performed, based on standard measures. To evaluate the changes in outcome measures over time in the intervention group and/or in the control group, one-way and two-way repeated measures analysis of variance (ANOVA) will be applied (or a non-parametric equivalent). Post-hoc analysis will be applied as appropriate. The level of significance is set to a=0.05. Assuming relatively acceptable values for the attrition rate (i.e., 20%) and the missing data (i.e., 30%), the sample size analysis concluded that 300 recruited patients providing one measure at enrolment (baseline) and 7 repeated measures (at Months 1, 2, 3, 4, 5, 6 and 12) are sufficient for the power of the intended statistical testing to be over 90% in all cases, given (a) a 0.05 significance level, and (b) an effect size of 0.2, which was estimated based on a priori knowledge of the domain.

Protocol Version 1.0 – 31.10.2019

Table of contents

1 BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Digital health

According to World Health Organization (WHO)[9], digital health (also known as eHealth) is defined as *the use of information and communications technology in support of health and health-related fields*. Digital health has become a salient field of practice for employing a wide range of digital technologies to address health needs. The technologies that are employed by digital health include both hardware devices (such as mobile phones, wearable devices, remote monitoring sensors) and software products and services (telemedicine services, text messages, email, web-based or smartphone applications). In 2018, the World Health Assembly Resolution on Digital Health, which was unanimously approved by WHO Member States, recognized the value of digital technologies towards advancing universal health coverage sustainable health care.

However, the enthusiasm for digital health has also led to a number of short-lived digital implementations characterized by overwhelming diversity, limited understanding of their impact on health systems and people's well-being. For this reason, both Food and Drug Administration (FDA) and WHO have published guidelines for the development of high-quality, evidence-based digital health interventions (i.e., discrete functionalities of digital technology that are applied to achieve health objectives), namely the Digital Health Innovation Action Plan[10] and recommendations on digital interventions for health system strengthening[9], respectively.

On top of that, WHO has produced a classification of digital health intervention to describe the various uses of digital health technology for health[11].

1.1.2 Patient reported outcome measures

Cancer patients' experience is multi-faceted and can include a physical dimension relating to symptoms or functional status, a psychological dimension relating to thoughts and feelings, a social dimension relating to relationships or finances and a spiritual dimension relating to existential questions[12] . Changes in the patients' experience across the illness trajectory can be captured and measured using Patient-Reported Outcome (PROs). PROs are standardized, validated self-report questionnaires, considered the gold standard as far as subjective experiences are concerned[13] .

PROs have a major role to play in improving the quality, efficiency and availability of palliative care. Their consideration along with biochemical and clinical data within the palliative care clinical setting can help provide patients the most appropriate support at every stage of their care[14] . Specifically, in palliative care PROs can: a) monitor changes in the patients' health status and b) facilitate the identification and screening of unmet needs which could have been overlooked (psychological, social, physical etc.) of patients and their families; c) provide information on the evolution of disease and the

[9] World Health Organization. WHO guideline: recommendations on digital interventions for health system strengthening web supplement 2: summary of findings and GRADE tables. World Health Organization; 2019.
[10] US Food and Drug Administration. Digital health innovation action plan. Available from https://www.fda.gov/media/106331/download
[11] World Health Organization. Classification of digital health interventions v1. 0: a shared language to describe the uses of digital technology for health. World Health Organization; 2018.
[12] Bausewein, C., Daveson, B., Benalia, H., Simon, S.T. and Higginson, I.J., 2011. Outcome measurement in palliative care: the essentials. PRISMA, pp.1-48
[13] Basch, E., Abernethy, A.P., Mullins, C.D., Reeve, B.B., Smith, M.L., Coons, S.J., Sloan, J., Wenzel, K., Chauhan, C., Eppard, W. and Frank, E.S., 2012. Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. J Clin Oncol, 30(34), pp.4249-4255.
[14] Antunes B, et al. Implementing patient-reported outcome measures in palliative care clinical practice: a systematic review of facilitators and barriers. Palliat Med. 2014;28(2):158-75.

impact of treatment interventions care or services; d) facilitate patient/family/caregiver/physician interaction and communication, and e) aid clinical decision making[12,13].

For the MyPal ADULT clinical trial, measurements appropriate for use in palliative care with adults have been selected. Multidimensional Patient Reported Outcomes Measures such as the Palliative care Outcome Scale aiming to identify patients' needs, Edmonton Symptom Assessment Scale for identification of common symptoms experienced by cancer patients. In terms of well-being, the EORTC QLQ-C30 can be used to assess patients' cancer related quality of life. Generic measures such as the EQ-5D assessing the overall physical, psychological and social quality of life will also be used. Please section 4 on objectives and outcome measures[12].

1.1.3 Palliative care

According to the WHO definition (2002)[1] palliative care is "an approach that improves the quality of life of patients and their families facing the problems associated with life threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychological and spiritual". Definitions of palliative care have changed from a focus on end-stage cancer to include the trajectory of all life-limiting conditions. They remain both contested and poorly understood by healthcare professionals, and more importantly, by patients and the public[15] Palliative care is interdisciplinary in its approach and encompasses the patient, the family and the community in its scope. Palliative care aims to assess and provide for the needs of the patient wherever he or she is cared for, either at home or in a hospital, or other place. Palliative care affirms life and regards dying as a normal process; it neither hastens nor postpones death. It sets out to preserve the best possible quality of life until death. Palliative care focuses not only on the patient but also his/her family. Furthermore, as the main purpose of palliative care is to improve quality of life by supporting the patient not only through physical problems but other additional problems of a social, psychological and spiritual nature. Palliative care can be offered to improve quality of life of patients and their families who are receiving active treatment either curative or aiming at disease control. Palliative care encompasses much more than just end-of-life or hospice care. Instead, palliative care is an essential component of serious illness care, much further upstream from the terminal phase. Therefore, palliative care should be viewed as a necessary component of care for patients with cancer from the time of diagnosis. Palliative care begins at diagnosis and increases in "dosage" or focus as needed throughout the continuum of illness. There is evidence from randomised control trials in the USA of the benefits of early integration of palliative care into clinical care[16] but this was not replicated in Europe[17].

[15] McIlfatrick S, Hasson F, McLaughlin D, Johnston G, Roulston A, Rutherford L, Noble H, Kelly S, Craig A, Kernohan WG. Public awareness and attitudes toward palliative care in Northern Ireland. BMC palliative care. 2013 Dec;12(1):34.
[16] Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA. Early palliative care for patients with metastatic non–small-cell lung cancer. New England Journal of Medicine. 2010 Aug 19;363(8):733-42.
[17] Groenvold M, Petersen MA, Damkier A, Neergaard MA, Nielsen JB, Pedersen L, Sjøgren P, Strömgren AS, Vejlgaard TB, Gluud C, Lindschou J. Randomised clinical trial of early specialist palliative care plus standard care versus standard care alone in patients with advanced cancer: The Danish Palliative Care Trial. Palliative medicine. 2017 Oct;31(9):814-24.

1.1.4 Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most prevalent type of leukemia in the Western world with an age-adjusted incidence of 4.2/100,000[18,19,20,21]. CLL typically occurs in elderly patients, median age at diagnosis lies between 67 and 72 years[18,19,21].

CLL is a chronic leukemia, characterized by the clonal proliferation and accumulation of mature B-cells within the blood, bone marrow, lymph nodes, and spleen. CLL cells co-express the B-cell surface antigens CD19, CD20, CD23 and immunoglobulin as well as the T-cell antigen CD5[2122]. However, the expression of surface immunoglobulin, CD20, and CD79b are characteristically low compared to normal B cells [23,24].

The disease has a highly variable clinical course and ranges from patients who do not require therapy for many years, if at all, to others who require treatment soon after diagnosis[25] .

In routine clinical practice, newly diagnosed low-risk patients with asymptomatic early-stage disease (Rai 0, Binet A [2627] ; Table 1), should be monitored without therapy unless they have disease progression or symptomatic/active disease as defined by the International Workshop on CLL (iwCLL) guidelines[22]. Patients with active or symptomatic disease or with advanced Binet or Rai stages require therapy (iwCLL guidelines)[22].

In CLL many host- and tumor-related features with prognostic and/or predictive value have been identified over the years, assisting in the stratification of patients into subgroups with distinct clinical course and response to treatment. Amongst tumor-related biomarkers, those recommended by the iwCLL for predictive assessment prior to treatment initiation in both general practice and clinical trials pertain to the genomic background of the malignant clone, more particularly the TP53 gene that should be investigated for both deletions by Fluorescence in situ hybridization (FISH) and mutations by Sanger or Next-generation sequencing; and, the somatic hypermutation status (SHM) of the rearranged immunoglobulin heavy variable (IGHV) gene expressed by the clonotypic B cell receptor

[18] Hallek M. Chronic lymphocytic leukemia: 2015 Update on diagnosis, risk stratification, and treatment. Am J Hematol. 2015;90(5):446-460.
[19] National Cancer Institute [Website]. Surveillance Epidemiology and End Results Cancer Statistics review. 2009. Available at: http://seer.cancer.gov/statfacts/html/clyl.html. Last accessed January 26 2016.
[20] Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v78-84.
[21] Panovska A, Doubek M, Brychtova Y, Mayer J. Chronic lymphocytic leukemia and focusing on epidemiology and management in everyday hematologic practice: recent data from the Czech Leukemia Study Group for Life (CELL). Clin Lymphoma Myeloma Leuk. 2010;10(4):297-300.
[22] Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-5456.
[23] Ginaldi L, De Martinis M, Matutes E, et al. Levels of expression of CD19 and CD20 in chronic B cell leukaemias. J Clin Pathol. 1998;51(5):364-369.
[24] Moreau EJ, Matutes E, A'Hern RP, et al. Improvement of the chronic lymphocytic leukemia scoring system with the monoclonal antibody SN8 (CD79b). Am J Clin Pathol. 1997;108(4):378-382.
[25] Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leukaemia. Nature reviews. Disease primers. 2017;3:16096.
[26] Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46(2):219-234.
[27] Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981;48(1):198-206.

immunoglobulin (BcR IG) [28,29,30,31,32]. Moreover, recent evidence suggests that complex karyotype (CK) may be relevant for prognosis and treatment decision-making in CLL[33].

The treatment of patients with CLL can include chemotherapy, targeted therapy (B cell signalling inhibitors or Bcl-2 inhibitors), immunotherapy and stem cell transplantation (SCT) or chimeric antigen receptor T cell (CAR-T) therapy.

Chemotherapy, the core treatment option for the past 50 years, includes purine analogues (fludarabine or cladribine) and alkylating agents (chlorambucil, cyclophosphamide or bendamustine).

Targeted therapy includes monoclonal antibodies: anti-CD20 (rituximab, obinutuzumab or ofatumumab), anti-CD52 (alemtuzumab); inhibitors of B cell signalling such as Bruton´s kinase (BTK) inhibitors (ibrutinib) and PI3K inhibitors (idelalisib); and Bcl-2 inhibitor (venetoclax).

For young fit patients with mutated IGHV genes devoid of TP53 aberrations, the combination of fludarabine, cyclophosphamide, and rituximab (FCR) remains the current gold standard. For unfit and elderly patients, treatment options include BTK inhibitors or a milder chemotherapy (chlorambucil, bendamustine) with an anti-CD20 antibody (rituximab, obinutuzumab, ofatumumab). Patients with a del(17p) or TP53 mutation should be treated with new agents (ibrutinib, combination of idelalisib and rituximab, venetoclax). Novel drugs are also the treatment of choice in relapsed and refractory patients with CLL [22]. An allogenic SCT may be considered in relapsing younger and fit patients that are refractory to chemoimmunotherapies and to novel drugs.

Table 1. Rai and Binet scoring systems for chronic lymphocytic leukemia.

Rai staging system	
0	Lymphocytosis
I	Lymphocytosis + lymphadenopathy
II	Lymphocytosis + spleno- or hepatomegaly
III	Lymphocytosis + anemia (hemoglobin <110 g/L)
IV	Lymphocytosis + thrombocytopenia (<100×10^9/L)
Binet staging system	
A	< 3 areas of lymphoid involvement
B	≥ 3 areas of lymphoid involvement
C	Cytopenia [anemia - hemoglobin (Hb) ≤100 g/L (≤10 g per dL) and/or thrombocytopenia ≤100×10^9/L]

[28] Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343(26):1910-1916.
[29] Eichhorst B, Hallek M. Prognostication of chronic lymphocytic leukemia in the era of new agents. Hematology Am Soc Hematol Educ Program. 2016;2016(1):149-155.
[30] Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood. 1999;94(6):1848-1854.
[31] International CLLIPIwg. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncol. 2016;17(6):779-790.
[32] Baliakas P, Hadzidimitriou A, Sutton LA, et al. Clinical effect of stereotyped B-cell receptor immunoglobulins in chronic lymphocytic leukaemia: a retrospective multicentre study. Lancet Haematology. 2014;1(2):74-84.
[33] Baliakas P, Iskas M, Gardiner A, et al. Chromosomal translocations and karyotype complexity in chronic lymphocytic leukemia: a systematic reappraisal of classic cytogenetic data. Am J Hematol. 2014;89(3):249-255.

1.1.5 Myelodysplastic syndrome

The myelodysplastic syndromes (MDS) consist of a heterogeneous group of malignant hematopoietic stem cell disorders characterized by ineffective hematopoiesis resulting in blood cytopenias and a variable risk of transformation to acute myeloid leukemia (AML)[34] . Myelodysplastic syndromes are generally diseases of older people, with a median age at diagnosis of 65–70 years[35]. The annual incidence is approximately 4 cases per 100,000 people (reaching 40-50 per 100,000 after age 70 years)[35], with male predominance[36] Notably, with an aging population and improved awareness of disease, it is likely that the number of new patients diagnosed with MDS each year will increase in the future.

As regards to clinical features, patients can be asymptomatic or, if anemia is more severe, can exhibit pallor, weakness, loss of a sense of well-being and dyspnea on exertion[37] Fatigue is by far the most common symptom endorsed by patients and is not necessarily related to degree of anemia[38]. A small proportion of patients have infections related to neutropenia or neutrophil dysfunction, or hemorrhage related to severe thrombocytopenia or platelet dysfunction at the time of diagnosis[37]. Many MDS patients also have immune disorders, including polyarthritis[37]

The diagnosis of MDS is generally suspected based on the presence of an abnormal complete blood cell count[34] and is confirmed by bone marrow analysis which usually reveals hypercellularity, dysplastic cell morphology with or without excess of immature cells (blasts)[39]. To complete the laboratory evaluation of a patient with MDS, the analysis of bone marrow cytogenetics is required. An abnormal karyotype is shown by conventional cytogenetic analysis in 40–50% of cases at diagnosis[34]. Cytogenetics have major impact in MDS, not only as regards to prognosis, but also in the choice of the most effective treatment, at least in subset of patients[3439] .

The disease course and natural history varies significantly between MDS patients, thereby necessitating the development of prognostication systems to estimate the probability of disease progression and survival and enable clinical decision making[40] The most prevalent prognostic model in clinical use is the IPSS[41] (Table 1,2), which includes percent of blasts, number of cytopenias and cytogenetics. Patients are thus assigned to one of 4 risk categories (Table 1,2) with significant differences in overall survival and risk of clonal evolution to AML. The system has several limitations that have become evident over the years. The IPSS-R includes different cut off points of cytopenias and incorporates the new cytogenetic MDS score. Based on the total risk score, patients are assigned to one of five risk groups.

Although MDS treatment has improved over the last years, it still remains challenging. The therapeutic strategy is largely based on the IPSS[3439]. More precisely, in patients classified as high or intermediate 2 on the IPSS (higher risk) with median survival if untreated of only about 12 months, treatment should aim at modifying the disease course, avoiding progression to acute myeloid leukemia, and extending survival[34,39]. In contrast, in those classified as low or intermediate 1 on the IPSS (lower risk), survival is longer and many patients die from causes other than myelodysplastic syndromes. Therefore, their

[34] Ades L, Itzykson R, Fenaux P. Myelodysplastic syndromes. Lancet. 2014;383(9936):2239-52.
[35] Neukirchen J, Schoonen WM, Strupp C, Gattermann N, Aul C, Haas R, et al. Incidence and prevalence of myelodysplastic syndromes: data from the Dusseldorf MDS-registry. Leukemia research. 2011;35(12):1591-6.
[36] Ma X. Epidemiology of myelodysplastic syndromes. The American journal of medicine. 2012;125(7 Suppl):S2-5.
37 Steensma DP, Bennett JM. The myelodysplastic syndromes: diagnosis and treatment. Mayo Clinic proceedings. 2006;81(1):104-30.
38 Steensma DP, Heptinstall KV, Johnson VM, Novotny PJ, Sloan JA, Camoriano JK, et al. Common troublesome symptoms and their impact on quality of life in patients with myelodysplastic syndromes (MDS): results of a large internet-based survey. Leukemia research. 2008;32(5):691-8.
39 Montalban-Bravo G, Garcia-Manero G. Myelodysplastic syndromes: 2018 update on diagnosis, risk-stratification and management. American journal of hematology. 2018;93(1):129-47.
[40] Lee EJ, Podoltsev N, Gore SD, Zeidan AM. The evolving field of prognostication and risk stratification in MDS: Recent developments and future directions. Blood reviews. 2016;30(1):1-10.
[41] Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2079-88.

treatment mainly aims to ameliorate the consequences of cytopenias and transfusions and improve quality of life[34,39]. Current available therapies include growth factor support, lenalidomide, hypomethylating agents, intensive chemotherapy and allogeneic stem cell transplantation, which is the only curative treatment of higher-risk MDS. Finally, additional supportive care measures may include the use of prophylactic antibiotics and iron chelation[3439].

Table 2. International Prognostic System (IPSS)[41]

	0 points	0·5 points	1·0 point	1·5 points	2·0 points
Bone-marrow blasts (%)	<5%	5–10%	..	11–20%	21–30%
Number of cytopenias*	0–1	2–3	..	..	..
Cytogenetics	Good: normal, Y, del(5q), del(20q)	Intermediate: other abnormalities	Poor: complex ≥3 abnormalities, chromosome 7 abnormalities	..	..

*Platelet count <100 × 10^9/L; haemoglobin <100 g/L; absolute neutrophil count <1·8 × 10^9/L.

Table 3. IPSS risk category clinical outcomes

	Low	Intermediate 1	Intermediate 2	High
Risk score	0	0·5–1·0	1·5–2·0	≥2·5
Proportion of patients (%)	33%	38%	22%	7%
Median survival (years)	5·7	3·5	1·2	0·4
Time to 25% AML evolution (years)	9·4	3·3	1·1	0·2

IPSS=international prognostic scoring system. AML=acute myeloid leukaemia.

Table 4. Revised IPSS (IPSS-R)[42]

	0 points	0·5 points	1·0 point	1·5 points	2·0 points	3·0 points	4·0 points
Cytogenetics*	Very good	..	Good	..	Intermediate	Poor	Very poor
Bone-marrow blasts (%)	≤2%	..	>2 to <5%	..	5–10%	>10%	..
Haemoglobin (g/L)	≥100	..	80 to <100	<80	..	..	..
Platelet count (×10^9/L)	≥100	50 to <100	<50	..	..	..	..
Absolute neutrophil count (×10^9/L)	≥0·8	<0·8	..	..	..	..	..

*As in table 2.

Table 5. IPSS-R risk category clinical outcomes

[42] Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454-65.

	Very low	Low	Intermediate	High	Very high
Risk score	≤1·5	>1·5–3·0	>3·0–4·5	>4·5–6·0	>6·0
Proportion of patients (%)	19%	38%	20%	13%	10%
Median survival (years)	8·8	5·3	3·0	1·6	0·8
Time to 25% evolution to AML (years)	NR	10·8	3·2	1·4	0·73

IPSS=international prognostic scoring system. AML=acute myeloid leukaemia. NR=not reached.

1.2 Trial Rationale

1.2.1 Chronic lymphocytic leukemia

In addition to its effects on life expectancy, CLL can have profound effects on quality of life (QOL) because of disease-related symptoms, the toxic effects of therapy, and the emotional, socio-economic, and functional effects of living with an incurable illness[43].

Despite considerable advances, current conventional therapy for CLL does not lead to a complete cure. All patients eventually relapse and require further treatment for their disease, with many of them following a pattern of relapse and re-treatments. In addition, CLL treatment is associated with several complications, such as higher risk of infections or higher incidence of secondary malignancies, and many patients are elderly and have comorbid conditions [44,45].

Not surprisingly, available evidences support that patients with treated and untreated CLL have poorer quality of life compared to the general population, as it might be expected [46,47,48]. Studies also found that patients with CLL are significantly bothered by relevant physical symptoms with 81% of them reporting fatigue and 56% sleep disturbances at treatment initiation[48]

Despite the changing landscape of treatment and in contrast to the large number of quality of life (QoL) studies in patients with solid tumours, relatively few studies have reported QoL in patients with CLL.

Improved QOL is a key goal in the treatment of patients with cancer in general[49], but it is particularly relevant for individuals with incurable conditions, such as CLL.

Significant psycho-oncologic improvements, clinically meaningful improvement in fatigue and overall QoL, and fewer early hospitalizations were observed with novel targeted agents in patients with CLL enrolled in pharmacological clinical trials, but the lack of data on what QOL issues CLL patients face limits the ability to design effective interventions to address their needs.

On one side, improving the quality of life of patients with CLL will reasonably lead to improved compliance in patients who are long-term taking new drugs and thus will improve treatment outcomes. On the other side, for patients who are receiving the best supportive care, improving the quality of life could lead to a reduction in the number of outpatient controls and hospitalizations.

---

[43] Molica, S. Quality of life in chronic lymphocytic leukemia: a neglected issue. Leuk Lymphoma. 2005;46(12):1709-14

[44] Shanafelt T. Treatment of older patients with chronic lymphocytic leukemia: key questions and current answers. Hematology Am Soc Hematol Educ Program 2013;2013:158-167.

[45] Tsimberidou AM, Wen S, McLaughlin P, et al. Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. J Clin Oncol 2009;27:904-910.

[46] Holzner B, Kemmler G, Kopp M, Nguyen-Van-Tam D, Sperner-Unterweger B, Greil R. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. Eur J Haematol. 2004;72(6):381-9.

[47] Eichhorst BF, Busch R, Obwandner T, Kuhn-Hallek I, Herschbach P, Hallek M; German CLL Study Group. Health-related quality of life in younger patients with chronic lymphocytic leukemia treated with fludarabine plus cyclophosphamide or fludarabine alone for first-line therapy: a study by the German CLL Study Group. J Clin Oncol. 2007;25(13):1722-31.

[48] Else M, Smith AG, Cocks K, Richards SM, Crofts S, Wade R, Catovsky D. Patients' experience of chronic lymphocytic leukaemia: baseline health-related quality of life results from the LRF CLL4 trial. Br J Haematol. 2008;143(5):690-7.

[49] Sloan JA, Frost MH, Berzon R, Dueck A, Guyatt G, Moinpour C, Sprangers M, Ferrans C, Cella D; Clinical Significance Consensus Meeting Group. The clinical significance of quality of life assessments in oncology: a summary for clinicians. Support Care Cancer. 2006;14(10):988-98.

CLL-specific characteristics, comorbid conditions, and degree of fatigue all appear to have important impact on the QOL of patients with CLL, with particular relevance on emotional QOL[50] Research identifying effective interventions for patients with CLL is necessary to address this need.

1.2.2 Myelodysplastic syndrome

Patient-reported outcomes (PROs) have attracted much attention as a tool to gain more insight in the burden of malignancy in patients' lives. By collecting data on quality of life, symptoms and the sense of well-being, everyday functioning, disease and therapy perception, toxicities and adverse events as well as patient evaluation of health care PROs can provide essential information to properly capture the patient's condition[42].

Cancer patients carry a substantial physical and psychosocial disease burden and are often obliged to cope with disease and/ or treatment consequences which occur outside the hospital[51]. Yet there is an increasing body of evidence suggesting that these consequences may go unnoticed by clinicians and therefore not properly treated[52]. Recent studies have shown that routine follow-up of patients via PRO monitoring can fill the gap in the patient-clinician communication, improve physician's awareness of symptoms and result in better symptom management[53]. Eventually this may exert a positive impact on the quality of life and overall survival of patients with cancer[54].

As regards to MDS patients, they may suffer from a wide variety of symptoms, including fatigue, anxiety, insomnia and dyspnea[55,56], which result in impaired quality of life[57]. Notably, a study in which patients with acute myeloid leukemia or advanced MDS were included has demonstrated that QOL is most important to patients than the length of survival per se[58]. Interestingly, hypomethylating agents, which are mostly used in advanced MDS have been shown to improve QOL[53,59]. Assessment of QOL as a

[50] Shanafelt TD, Bowen D, Venkat C, Slager SL, Zent CS, Kay NE, Reinalda M, Sloan JA, Call TG. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. Br J Haematol. 2007;139(2):255-64.

[51] Basch E, Geoghegan C, Coons SJ, Gnanasakthy A, Slagle AF, Papadopoulos EJ, et al. Patient-Reported Outcomes in Cancer Drug Development and US Regulatory Review: Perspectives From Industry, the Food and Drug Administration, and the Patient. JAMA oncology. 2015;1(3):375-9.

[52] Howell D, Molloy S, Wilkinson K, Green E, Orchard K, Wang K, et al. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. Annals of oncology : official journal of the European Society for Medical Oncology. 2015;26(9):1846-58.

[53] Laugsand EA, Sprangers MA, Bjordal K, Skorpen F, Kaasa S, Klepstad P. Health care providers underestimate symptom intensities of cancer patients: a multicenter European study. Health and quality of life outcomes. 2010;8:104. 5353

[54] Basch E, Barbera L, Kerrigan CL, Velikova G. Implementation of Patient-Reported Outcomes in Routine Medical Care. American Society of Clinical Oncology educational book American Society of Clinical Oncology Annual Meeting. 2018;38:122-34.

[55] Steensma DP, Heptinstall KV, Johnson VM, Novotny PJ, Sloan JA, Camoriano JK, et al. Common troublesome symptoms and their impact on quality of life in patients with myelodysplastic syndromes (MDS): results of a large internet-based survey. Leukemia research. 2008;32(5):691-8.

[56] Efficace F, Gaidano G, Breccia M, Criscuolo M, Cottone F, Caocci G, et al. Prevalence, severity and correlates of fatigue in newly diagnosed patients with myelodysplastic syndromes. British journal of haematology. 2015;168(3):361-70.

[57] Thomas ML. The impact of myelodysplastic syndromes on quality of life: lessons learned from 70 voices. The journal of supportive oncology. 2012;10(1):37-44.

[58] Sekeres MA, Stone RM, Zahrieh D, Neuberg D, Morrison V, De Angelo DJ, et al. Decision-making and quality of life in older adults with acute myeloid leukemia or advanced myelodysplastic syndrome. Leukemia. 2004;18(4):809-16.

[59] Kornblith AB, Herndon JE, 2nd, Silverman LR, Demakos EP, Odchimar-Reissig R, Holland JF, et al. Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002;20(10):2441-52.

relevant PRO[6061] has also showed that its impairment predicts an unfavorable clinical outcome[62,63,64] and that it constitutes a parameter of response evaluation[65]. Furthermore, apart from QOL, a recent report has also demonstrated that self-reported fatigue has prognostic value beyond standard MDS risk stratification systems[65].

The aforementioned data provide the rationale for systematic collection of PRO information in routine MDS practice as PROs can provide the theoretical background for patient-centered clinical decisions. By acting as early indicators of MDS progression, PROs can guide treatment adjustments or even changes to better suite patient's needs. Moreover, PROs and especially ePROs can help the clinician to quickly focus on symptoms that require attention and prompt action and thus schedule accordingly patient's next visit.

2 AIM & OBJECTIVES

2.1 Aim

The main aim of the MyPal ADULT is to evaluate the effectiveness and cost-effectiveness of use of the MyPal ePRO system as a novel, patient-centred, palliative care intervention for patients with haematological malignancies (CLL/MDS).

2.2 Objectives

Primary Objective

The primary objective is to determine whether - compared to standard care - the MyPal-ADULT intervention can lead to improved QoL as evidenced by statistically significant higher scores in EORTC QLQ-C30[2] General Questionnaire and EQ-5D[3].

Secondary Objectives

To determine whether - compared to standard care - the MyPal system intervention can lead to the following outcomes in patients with hematological cancers (CLL/MDS):

1. Improvement in physical and emotional functioning as evidenced by higher scores in the Integrated Palliative Care Outcome Scale (IPOS)[4] at prespecified timepoints [Time Frame: baseline, and every month for the first six months and 12-month follow-up]
2. Increase in satisfaction with care score as evidenced by higher scores in the EORTC Patient Satisfaction with Cancer Care questionnaire (EORTC PATSAT C33)[5] at prespecified timepoints [Time Frame: baseline, and every month for the first six months and 12-month follow-up]

[60] Abel GA, Buckstein R. Integrating Frailty, Comorbidity, and Quality of Life in the Management of Myelodysplastic Syndromes. American Society of Clinical Oncology educational book American Society of Clinical Oncology Annual Meeting. 2016;35:e337-44.
[61] Patel SS, Gerds AT. Patient-Reported Outcomes in Myelodysplastic Syndromes and MDS/MPN Overlap Syndromes: Stepping Onto the Stage with Changing Times. Current hematologic malignancy reports. 2017;12(5):455-60.
[62] Deschler B, Ihorst G, Platzbecker U, Germing U, Marz E, de Figuerido M, et al. Parameters detected by geriatric and quality of life assessment in 195 older patients with myelodysplastic syndromes and acute myeloid leukemia are highly predictive for outcome. Haematologica. 2013;98(2):208-16.
[63] Efficace F, Gaidano G, Breccia M, Voso MT, Cottone F, Angelucci E, et al. Prognostic value of self-reported fatigue on overall survival in patients with myelodysplastic syndromes: a multicentre, prospective, observational, cohort study. The Lancet Oncology. 2015;16(15):1506-14.
[64] Buckstein R, Wells RA, Zhu N, Leitch HA, Nevill TJ, Yee KW, et al. Patient-related factors independently impact overall survival in patients with myelodysplastic syndromes: an MDS-CAN prospective study. British journal of haematology. 2016;174(1):88-101.
[65] Cannella L, Caocci G, Jacobs M, Vignetti M, Mandelli F, Efficace F. Health-related quality of life and symptom assessment in randomized controlled trials of patients with leukemia and myelodysplastic syndromes: What have we learned? Critical reviews in oncology/hematology. 2015;96(3):542-54.

3. Increase in overall survival as evidenced by longer survival times [Time Frame: N/A]

To evaluate the cost effectiveness of the MyPal intervention compared to standard care taking into account the Euroqol EQ-5D data from both groups as well as other parameters such as hospital visits, doctor visits, hospitalizations, medications, treatments and investigations.

And to determine whether the MyPal system intervention can lead to the following outcomes in patients with hematological cancers (CLL/MDS) over time:

1. Reduced symptom burden as evidenced by lower scores in the Edmonton Symptom Assessment System (ESAS)[6] at prespecified timepoints [Time Frame: every week until the end of the study]
2. Reduced pain score as evidenced by lower scores in the Brief Pain Inventory (BPI)[7] at prespecified timepoints [Time Frame: every week until the end of the study]
3. Reduced emotional distress as evidenced by lower scores in the Emotion Thermometers (ET)[8] at prespecified timepoints [Time Frame: every week until the end of the study]
4. Increase in patient engagement in care as evidenced by satisfactory adherence to reporting (e.g. 70% answered scheduled reports). [Time Frame: every week until the end of the study]

3 TRIAL DESIGN

MyPal ADULT study is a randomized clinical trial conducted in multiple European sites (i.e. Italy, Greece, Sweden and the Czech Republic). Patients (n=300) will be recruited from all four countries. Patients will be randomly assigned in a 1:1 fashion to receive early palliative oncology care using the MyPal system versus standard care (including general palliative care if needed), stratified by cancer type (i.e. CLL vs MDS), using a computer-generated number sequence, which will be concealed until after group assignment. The present study is unblinded, hence no method for blinding will be utilized. (For a summary of details please see Tables below).

The herein introduced digital health intervention is linked with the following categories of the aforementioned WHO classification: 1.4 – Personal health tracking, 2.2 – Client health records, and 4.1 – Data Collection, Management and Use.

Table 6. MyPal ADULT clinical study details

Study design	Interventional (clinical trial)
Estimated enrolment:	300 participants
Allocation:	Randomized (stratified according to disease)
Intervention model:	Parallel assignment
Masking: none	Unblinded
Primary purpose:	Supportive care
Official title:	Randomized clinical trial of the MyPal ePRO-based early palliative care system in adult patients with hematologic malignancies
Accrual study start date:	01.05.2020
Estimated study completion date:	30.03.2022

Arms and interventions

Table 7. Arms and interventions

Arm	**Intervention**

Experimental arm (n=150): Intervention group Administration of the MyPal ePRO system	The intervention group will use the ePRO tools provided in the project.
Standard care arm (n=150): control group General palliative care can be provided if desired.	None

The design of the study in schematic form is depicted in Figure 1 below.

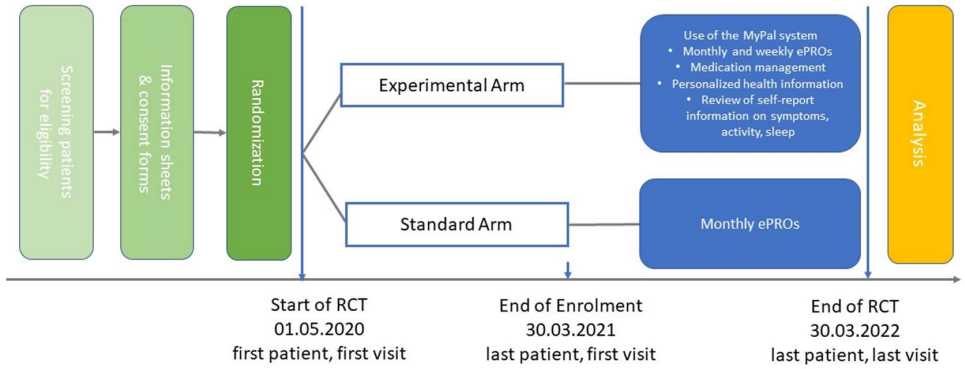


Figure 1. Schematic representation of the study design

Table 8 below outlines the main phases of the RCT and the events or actions due to take place during each phase.

Table 8. RCT Phases and events due to take place in each phase

Time point	Event	Details
Preparation Phase	Finalising the MyPal platform	Evaluation of the MyPal platform regarding usability and guaranteeing the safe and secure handling of data
	Ethical Approval	Application for ethical approval at all clinical sites
Before enrolment of patients	Recruitment of patients	Screening inclusion and exclusion criteria for all new patients with cancer in each clinical site
	Information and Informed consent	Inform patients about the study, provide information sheets for participants and seek informed consent after 24 hours. Those who give informed consent will be enrolled in the study Randomization to experimental and standard arms
	Training on the MyPal platform and the use of different tools	Explain the MyPal platform and the tools and the questionnaires to the healthcare professionals

Start of the study	Training of the MyPal platform and the different tools	HCPs will explain the MyPal platform and the tools and the questionnaires to the participants randomized to the experimental arm
Conduct of the study	Usage of the MyPal platform and the different tools	The patients randomized to the intervention arm will use the MyPal platform and the corresponding tools.
	Supervision of the study	HCPs will use the MyPal platform and will supervise the engagement of patients with the MyPal tools
	Data collection	All data generated by the tools will be collected for analysis
End of the study	Information	All participants will be informed about the end of the study and what will happen with their data
After the end of the Study	Analysis	The collected data will be analysed
	Dissemination of results	Results of the study will be presented in scientific papers, scientific meetings, congresses, to patient groups and news.
	Exploitation	Continuation of the MyPal platform and tools

The study design is based on the comparison of a standard arm with an experimental arm. Only patients randomized to the experimental arm will use the MyPal eHealth system. Patients enrolled in the standard and experimental arms will complete PROs at pre-specified timepoints.

The completion of ePROS in both experimental and standard arms is depicted in Table 9 below.

Table 9. ePROs in Experimental and Standard Arms

ePROS	Frequency	Standard Arm	Experimental Arm
EORTC QLQ-C30 Quality of Life	Monthly from Baseline and for the first 6 months and at 12 months follow-up	×	×
Euroqol EQ-5D-3L Quality of Life	Monthly from Baseline and for the first 6 months and at 12 months follow-up	×	×
Integrated Palliative Outcome Scale	Monthly from Baseline and for the first 6 months and at 12 months follow-up	×	×
EORTC Patient Satisfaction with Cancer Care	Monthly from Baseline and for the first 6 months and at 12 months follow-up	×	×
Edmonton Symptom Assessment Scale	Weekly from Baseline and until the end of the trial		×
Brief Pain Inventory	Weekly from Baseline and until the end of the trial		×
Emotional Thermometers	Weekly from Baseline and until the end of the trial		×

Specifically, patients in both arms (experimental and standard) will be asked to complete the following self-report questionnaires at baseline, and every month for the first six months of the study as well as at 12-month follow-up. Patients will come to the site for a visit on a monthly basis for the first 6 months and then at 12 months after baseline assessment. The completion of the assessment questionnaires (EORTC QLQ-C30,Euroqol EQ-5D-3L, EORTC PAATSAT and IPOS) will occur at the time of the visit and will be done via the web:

1) the EORTC QLQ-C30 which is a 30-item Quality of Life questionnaire. It is specific to cancer and evaluates areas common to different tumour sites and treatments and contains five functional scales, three symptom scales and one global QL scale, as well as single items that evaluate additional symptoms and the perceived financial impact of the disease and treatment.
2) The Euroqol, EQ-5D – 3L, a 25-item general QoL measure evaluating domains such as mobility, self-care, usual activities etc.
3) The Integrated Palliative Outcome Scale (IPOS) is a 10-item questionnaire, specific to palliative care, which measures patients' physical symptoms, psychological, emotional and spiritual, as well as information and support needs.
4) The Satisfaction with Cancer Care developed by The European Organization for Research and Treatment of Cancer (EORTC) group which has 33 items divided into 4 domains, namely satisfaction with doctors, nurses, services and care organization for patients to assess their most recent inpatient or outpatient experience with care.

In the context of the MyPal intervention, patients in the experimental arm will additionally be reporting symptoms through the MyPal app on a weekly basis (scheduled reporting) throughout the study:

1) The Edmonton Symptom Assessment System (ESAS), is a questionnaire assessing symptoms experienced by patients with cancer, which has 10 questions plus a visual analogue scale.
2) The Brief Pain Inventory (BPI), is a questionnaire designed to assess cancer pain. It is available in a short (nine items) form. There is a first, optional, item is a screening question about the

respondent's pain on the day. The questionnaire is then composed of pain drawing diagrams, four items about pain intensity (worst pain, least pain, average pain, pain right now), two items on pain relief treatment or medication, and one item on pain interference, with seven sub-items (general activity, mood, walking ability, normal walk, relations with other people, sleep, and enjoyment of life).

3) The Emotional Thermometers, a tool for simple rapid detection of emotional issues though visual analogue scales for four domains (distress, anxiety, depression, anger) as well as a need for help domain. The tool constitutes a multidomain extension and adaptation of the American Distress Thermometer adopted by the National Comprehensive Cancer Network and has been developed for the assessment of psychological complications of cancer.

Patients in the experimental arm will also be able to report symptoms spontaneously through the MyPal system. Apart from symptom reporting, which is an essential component of the MyPal intervention, patients will be able to use the MyPal system to better manage their medication intake by registering medication reminders. They will also be able to perform personalized searches in a repository developed by medical experts and thus have access to valid medical information specific to their condition. Furthermore, patients can review their own information such as physical or emotional symptoms overtime, should they choose to do. Finally, at the start of the trial patients will be equipped with a fit-bit watch which will allow monitoring of their physical activity and sleep quality. Information collected about the patients through the MyPal system such as physical and psycho-emotional symptoms, physical activity, sleep quality etc. will be monitored and periodically reviewed (every 72 hours maximum) by the health-care professionals (HCPs). Appropriate actions will be taken according to the HCP's judgement and medical expertise. These actions will be recorded by the HCPs via the MyPal system i.e. referral for diagnostics, prescription of medication etc.

As the MyPal eHealth system constitutes a complex intervention comprising of a number of individual elements, the fidelity of the intervention implementation will be evaluated by collecting the following information on the web interface (to be completed by the HCPs accessing the system):

- Symptom/questionnaire review by HCPs (audit trail)
- Action taken (yes vs no)

And competing and integrating them with the information reported in the clinical records.

4 ELIGIBILITY

4.1 Inclusion Criteria

1. Adults (≥18 years)
2. Diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or myelodysplastic syndrome (MDS)
3. Scheduled to receive any line of treatment for CLL/SLL or MDS or who have been previously exposed to any treatment for CLL or MDS
4. Able to understand and communicate in the respective language
5. Users of an Internet connected device (smartphone/tablet)

4.2 Exclusion Criteria

1. Patients who are already participating in another interventional study
2. Patients needing immediate referral for specialized palliative care

3. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk
4. Patients unable to provide written informed consent
5. Life expectancy <3 months
6. For CLL cohort: patients who have experienced Richter transformation

5 INTERVENTION DETAILS

5.1 MyPal Intervention

The MyPal eHealth system coincides with the MyPal intervention. The types of users of the MyPal eHealth system are specified in Table 10, while the software and hardware modules of the system are presented in Figure 2.

Table 10. Types of users of the MyPal eHealth system

User type	Description
Patients	Study participants assigned to the intervention arm of the trial (primary users); these are eligible adult cancer patients diagnosed with CLL or MDS and registered at the participating clinical centers
Healthcare professionals (HCP)	An interdisciplinary team of clinicians of the participating clinical centers that treat the patients (secondary users); the team can include oncologists, hematologists, nurses, psychologists, social workers, medical doctors of other specialties.

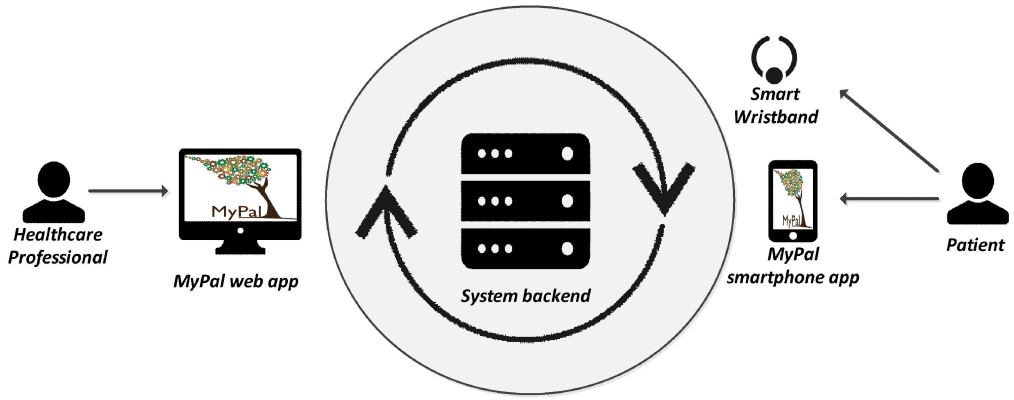
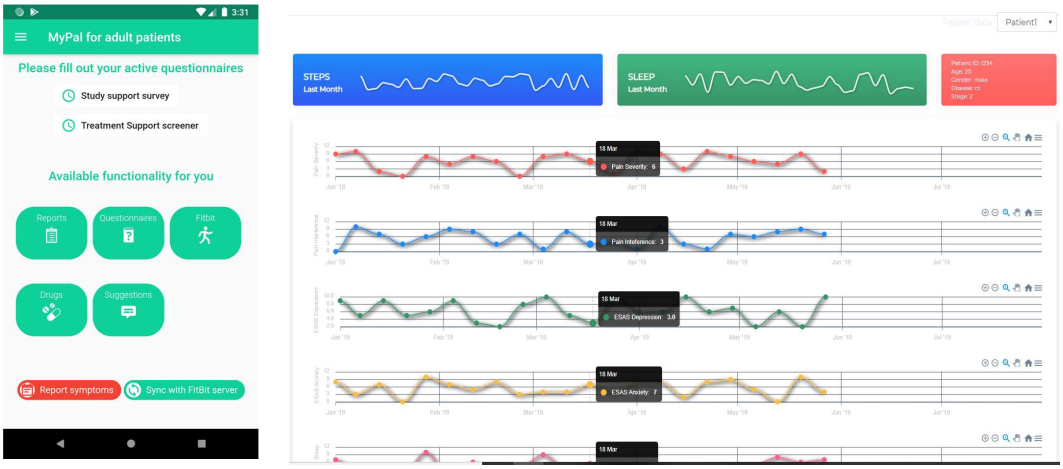


Figure 2. Software and hardware modules of the MyPal eHealth system

The system will be used primarily by the patients that participate in the intervention arm of the trial and secondarily by the participating healthcare professionals (HCP). Patients participating in the standard arm of the trial won't use the system. Access to the MyPal eHealth system will be granted to the patients and HCP right after their enrollment in the trial. Patients will have access to the system continuously for 12 months; HCP will have access to the system until the end of the trial.

The main modules (software and hardware) of the system are outlined below:

- **MyPal smartphone application (app)**. This is the interface of the patient to the system. The MyPal smartphone app is available for smartphones running on the Android and iOS operating systems and it is installed on the personal smartphone of the patient. A sample screen of smartphone app is provided in Figure 3a.
- **Commercial smart wristband**. This is a commercial activity tracking device that will be employed for monitoring the physical activity and the sleep quality of the patient, provided by the site personnel. Wearable to be worn. Ionic™ (Fitbit) will be employed by the trial as the smart wristband. A picture of Fitbit Ionic™ is presented in Figure 3.
- **MyPal web application (app).** This is the main interface of the HCP to the system. It is accessible as a web portal through any modern web browser. A sample page of web app is provided in Figure 3b.
- **System backend.** This module resides at the backend of the system and it is not directly accessible by the aforementioned types of users. The system backend interfaces the MyPal smartphone app and the MyPal web app.



(a) (b)

Figure 3. Sample graphical user interfaces of the MyPal eHealth system: (a) Screen of the MyPal smartphone app; (b) Page of the MyPal web app.

Figure 4. The smart wristband to be employed: Fitbit Ionic by Fitbit

In brief, the intervention revolves around the reporting by the patient of physical and psycho-emotional symptoms (via the MyPal smartphone app) and the immediate delivery of the reported symptom-related information to the HCP (via the MyPal web app). Of note, the reported symptom-related information becomes instantly available to the HCP in the MyPal web app; however, this does not imply that the HCP is guaranteed to review it at the same time. The intervention is described in more detailed below, first from the standpoint of the patient and then from that of the HCP.

5.1.1 Patient standpoint

The patients interact with the MyPal smartphone app in 3 sequential phases, which are visualized in Figure 5 and are presented below. Additionally, during the enrollment in the study, the patients are handed the commercial smart wristband and they are instructed to wear it as much as possible (also while sleeping) throughout their participation in the study.

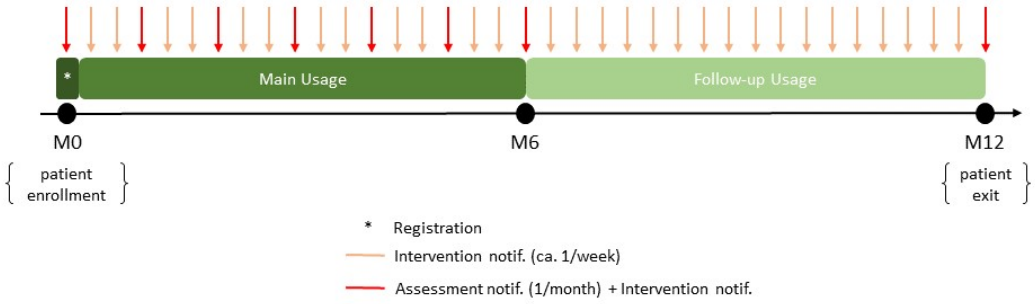


Figure 5. The 3 phases of the usage of the MyPal smartphone app by the patient.

Registration Phase. This phase is completed the first time the patient uses the MyPal smartphone app, which take place right after the patient is enrolled in the study. The mission of this phase is (1) to register the patient into the MyPal system, (2) to initially set a number of preferences, (3) to collect via self-reporting the baseline assessment of the patient's physical and psycho-emotional symptom, and (4) to screen for motivational targets and non-adherence risk. The smartphone app guides the patient throughout the entire registration process in a wizard-like fashion, where the user has to provide some information (1)-(2) and complete certain questionnaires (3)-(4). The latter is elaborated in the next phase. The patient might get some help for completing the registration from a HCP participating in the study (e.g., research nurse).

Main usage phase. As soon as the registration phase is completed, the MyPal smartphone app enters into its main usage phase. This lasts 6 months (Month 0 to Month 6 of the patient's participation in the study) and, during this time, the patient is given access to a number of user-initiated functionalities (i.e., functionalities that the user has access to at all times) and system-initiated ones (i.e., functionalities for which the system decides when they become available to the user). More specifically, the functionalities of the second category are initiated via notifications that are presented by the smartphone app to the user. We can distinguish two main types of notifications, namely the *intervention notifications* (i.e., notifications associated with functionalities that are part of the interventions) and the assessment notifications (i.e., notifications informing the patient it's time to complete the assessment questionnaires that have been foreseen by the study protocol). The intervention notification frequency is once every week, while the assessment notifications are issued once per month (see Figure 5). Whenever possible,

messages concerning multiple functionalities are grouped in a single notification, either intervention notification (orange line in Figure 5) or mixed one (red line in Figure 5). The system-initiated and user-initiated functionalities of the MyPal smartphone app are presented in Table 11 and Table 12, respectively.

Table 11. System-initiated functionalities of the MyPal smartphone app.

	Functionality	Description
PS1	Physical symptom questionnaires	Intervention notifications that inform the patient about the need to complete physical symptom questionnaires (ESAS, BPI) and provide an option for opening the questionnaire; these are issued once per week.
PS2	Psycho-emotional symptom questionnaires	Intervention notifications that inform the patient about the need to complete a psycho-emotional symptom questionnaire (ET) and provide an option for opening the questionnaire; these are issued once per week.
PS3	Screener questionnaires	Intervention notifications that inform the patient about the need to complete a screener questionnaire concerning (1) the patient's ongoing engagement with the MyPal study, and (2) the risk of non-adherence, if prescribed medication for CLL or MDS. The responses of the patient to the first and second questionnaire will determine the motivational messages that they will be receiving (see PS4 below) and highest priority topics to discuss using the conversation guide that will be presented to the HCP (see H4 in Table 4), respectively; there are issued at Month 0 (belongs to the registration phase), 3 and 6.
PS4	Motivational messages	Tailored short motivational messages[66] that are presented to the patient either as intervention notifications issued by the smartphone app or as SMS. Their content is determined based on a custom algorithm that receives as input the responses of the patient in the previous screener questionnaire for motivational needs (see PS3); these are issued twice per week until Week 4, then once per week until Week 24.
PS5	Medication reminders	Intervention notifications that remind the patient to take their medication; the timing of these reminders is determined by the patient input in the medication management functionality (see PU2 in Table 3).

[66] *In order to personalize a series of messages designed to motivate patients to stay engaged with the MyPal intervention throughout the study period, a literature review of key patient factors related to engagement with digital behaviour change interventions was conducted. From those findings, a screener was designed to assess each individual's personal level of risk of non-engagement in the MyPal study (PS3). Their personal results from completing this screener will then be interpreted and prioritized in the MyPal platform, and stored in the patient's record in the MyPal database. Factors assessed in the screener* include motivation, expectations, emotional distress, self-efficacy and personal relevance. *Using these results, through the course of the study patients will receive a series of messages in a personalized sequence, targeting the highest priority factors in their screener results. The message content has been developed by health psychology specialists using established behaviour change techniques relevant to the factors assessed in the screener. For example a message targeting* motivation would be: 'Reporting your symptoms through the MyPal app each month can help your healthcare team obtain more up to date information about your condition'.

Table 12. User-initiated functionalities of the MyPal smartphone app.

	Functionality	Description
PU1	Spontaneous symptom reporting	A form that is used by the patient to spontaneous report physical or psycho-emotional symptoms. The form combines structured (list of symptoms to choose from, severity and bothersomeness rating of selected symptom, etc.) and unstructured (free-text description of the symptom experience) information; this functionality can be used at patient's will.
PU2	Medication management	An editable list of the patient's medication plan, where the patient can specify the medication they receive along with the dosage and the frequency of reception. The information that is provided by the patient in this functionality defined the timing and content of the medication reminders (see PS5 in Table 3); this functionality can be used at patient's will.
PU3	Personal health information recommender	A personalized search engine that retrieves health information related to health status of the patient. The search is performed in a repository of valid medical information and takes into account the medical record of the patient; this functionality can be used at patient's will.
PU4	Self-reported information review	A view that presents information reported by the patient. This information mainly includes past responses to physical and psycho-emotional questionnaires (see PS1 and PS2 in Table 2), which are properly visualized; this functionality can be used at patient's will.
PU5	Activity information review	A view that presents information acquired by the commercial wristband. This information mainly includes past daily step count and sleep quality indicators, which are properly visualized; this functionality can be used at patient's will.

Follow-up usage phase. The follow-up usage phase starts immediately after the completion of the main usage phase and it also last 6 months (Month 7 to Month 12 of the patient's participation). This phase is identical to the previous phase (all the previously described functionalities are available) with a single exception. This is that the smartphone app does not issue assessment notification monthly; instead it issues only one such notification at the end of Month 12.

5.1.2 HCP standpoint

In contrast to the case of the patients, the HCP interact with the MyPal web app (i.e., their interface to the MyPal system) in the same manner throughout their participation in the study (this is considered to be from the first to the last month of the study). The only exception to this (main usage) is a short procedure that registers them into the MyPal system; the registration takes place the first time the HCP accesses the MyPal web app.

In brief, during the main usage of the MyPal web app, the HCP get access to the data that are collected by (1) the MyPal smartphone app and (2) the commercial smart wristband and stored in the system backend. The collected data become available to the MyPal web app as soon as they are stored. At individual level, the HCP is authorized to access only the data of the patients of the associated clinical center; however, access to aggregated and summarized data coming from all the patients (descriptive statistics such as min, max, average and percentiles) will also be provided to all the HCP. In contrast to the notification-heavy approach that was adopted for the patients, the HCP are not actively notified by the MyPal system at any point. To compensate for this, the study protocol mandates that the individual data of the participating patients of a given clinical center are reviewed by the associated HCP at least once every 72 hours. The data review and any action related to this will be recorded through the web

interface. The absence of notifications means that all functionalities offered to the HCP are user-initiated. These are presented in Table 13.

Table 13. Functionalities of the MyPal web app.

	Functionality	Description
H1	Incoming information summary	A central page of the web app which lists the incoming patient information that has not been reviewed yet. Only a summary of the incoming patient information is presented through this functionality. The summarized incoming information is automatically prioritized in the system backed with the help of custom algorithms and the pieces of incoming information that are assigned the highest priority and place on the top of the list. Whenever the information associated with an item of the list is reviewed in full (see H2 below), the item is removed from the list. Evidently, the list aggregates information that concerns all the patient of a participating clinical center.
H2	Individual data dashboard	A page that presents, using a dashboard with modern visualizations, all the information that has been collected for a given patient since the beginning of their participation in the trial. The information includes (1) the responses of the patient to the symptom questionnaires (see PS1 and PS2 in Table 2); (2) the spontaneous symptom reports of the patient (see PU1 in Table 3); (3) the medication plan of the patient as reported by themselves in the smartphone app (see PU2 in Table 3); (4) the appointment schedule of the patient; (5) the activity of the patients (daily number of steps and sleep quality) as tracked by the commercial smart wristband; (6) relevant clinical information (age, gender, diagnosis, treatment-naïve/relapsed, stage or risk, treatment to be given, info on expected outcome, Karnofsky index at the time of inclusion, comorbidities). The appointment information can be edited by the HCP. The page is organized in a number of tabs or panes, one of which summarized the not yet reviewed incoming information.
H3	Aggregated data dashboard	A page that presents, using an analytics dashboard with modern visualizations, aggregated and summarized information coming from all patients that participate in the trial (descriptive statistics such a min, max, average and percentiles). The aggregation of information concerns the items (1), (2) and (5) of the list of individual information from the previous functionality (see H2 above). The page is organized in a number of tabs or panes.
H4	Discussion guide	A page that provides a personalized discussion guide to be used during an appointment with a patient to mitigate potential risk of non-adherence with the intervention. This will be available to the HCP through the web-interface before a patient's visit. The discussion guide is personalized to the patient's non-adherence risk screener results; the content and flow of the discussion guide is prioritized based on the responses of the given patient in the screener questionnaire for non-adherence risk (see PS3 in Table 2).
H5	Information recommender repository update	A page that is used for editing the information that resides in the repository of the personal health Information recommender (see PU3 in Table 3). The HCP can upload documents or specify web resources that containing valid medical information.
H6	HCP response log	A page that is used for logging potential responses of the HCP to the presented information of a specific patient. The HCP can log in a structured manner any actions taken after visiting individual data dashboard of a patient (see H2) – for instance, calling the patient and requesting blood test.

5.2 Patient Completion & Withdrawal

Data collection will be considered complete for a participating patient if data available at 12 months after enrolment have been recorded. For deceased and untraceable patients included in the study, the patient will be censored at last observation.

A patient will be withdrawn from the study in case of withdrawal of consent to continue on the study.

Follow up of patients withdrawn from protocol treatment

Investigators will make every reasonable effort to maintain each patient on study until all planned assessments have been performed. Study intervention may be discontinued in case the patient refuses to continue on the study. In case of premature termination, date and reason for early discontinuation will be noted in the source document and the corresponding CRF. All data available for the patient at the time of discontinuation from the study should be recorded in the CRF, and all reasons for discontinuation of study participation must be documented in patient records.

6 ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the appropriate competent authorities. Definitions of different types of AE are listed below. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the protocol.

6.1 Reporting Requirements

Although no safety issues are foreseen, the PI will promptly notify all concerned investigators, the Ethics Committee(s) and the regulatory authorities of possible findings that could affect adversely the safety of patients, impact the conduct of the study, increase the risk of participation or otherwise alter the IEC's approval to continue the trial.

In the occurrence of such an event the PI and the investigators will take appropriate urgent safety measures to protect the patients against any immediate hazard. The local investigator will inform the patients and local ethics or review committees according to hospital policy. The sponsor will inform any other parties that are involved in the trial.

Safety reports

The PI will submit a first safety report to the IEC/IRB one year after the first approval date of the trial and a second safety report one year after the last patient has completed protocol intervention.

6.1.1 Adverse Events

An adverse event is any untoward medical occurrence that does not necessarily have a causal link to the intervention studied.

6.1.2 Serious Adverse Events

A serious adverse event (SAE) is any adverse event that: results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, consists of a congenital anomaly or birth defect or anything else the Data Safety Monitoring Board (DSMB) feels is significant. Given the nature of the intervention and the study population not all of the SAE categories will be relevant to the MyPAL Adult study. In non-drug trials, SAEs that are deemed to be related to the research procedure and are unexpected (referred to as SUSARs in drug trials) are also recorded and reported.

However, in MyPal Adult, it is difficult to predefine the serious risks of the MyPal eHealth system intervention and to define the early stopping rules. The study population consists of individuals facing

life threatening illness. We would not expect it to be an unusual occurrence for patients to be admitted to hospital while taking part in the study.

We expect that the most likely serious risk of participating in the MyPal intervention is (serious) distress. It should be noted however that symptom reporting is considered to be part of routine care, and as such, we expect the risks to be limited. Filling in questionnaires about physical and psychological symptoms, and quality of life may also be upsetting for patients. However, we expect the risk to be limited as these are validated questionnaires that address issues that are discussed in usual care.

Definition of Serious Distress

We define serious distress as severe unresolved distress (e.g. unable to be comforted), self-reported self-harm or suicidal thoughts or intent.

Severe unresolved distress (e.g. unable to be comforted), self-reported self-harm or suicidal thoughts or intent will be reported as SAEs in this study. An event that results in death, is life threatening or requires hospitalization or prolongation of existing hospitalization associated with serious distress will also be reported as an SAE. The DSMB will review all SAEs submitted and make recommendations accordingly. MyPal Adult study partners and the DSMB take the possible occurrence of serious distress due to participation in the trial very seriously.

No specific pregnancy reporting is required considering the nature of the study.

6.2 Reporting Procedure

6.2.1 Adverse Events

All adverse events will be systematically recorded in the CRF and the patient's source records, regardless of seriousness or causality.

6.2.2 Serious Adverse Events

Hospital Site Responsibilities

Physicians and nurses in the trial hospitals must report serious negative reactions of patients who participate in the study, using a predefined SAE form. The SAE form must be completed by the health care professional with delegated responsibility and signed by the Principal Investigator* or delegated medically qualified individual within 24 hours of becoming aware of the SAE. The form will then be immediately sent to the (insert country) Chief Investigator* The initial form can be sent without the PI or a delegated medically qualified individual's signature if the obtaining of a signature may cause delay in

reporting. In this case, the form needs to be re-sent as soon as possible once it has been signed by the PI or a delegated medically qualified individual.

The Principal Investigator or a delegated medically qualified individual will assess and document on the SAE form whether they think the SAE is related to the intervention or not.

Follow up information regarding the SAE will be requested from the hospital research sites as necessary to meet the requirements of the Chief Investigator and the DSMB. This will be submitted on the SAE form.

All information sent from the hospital sites to the Chief Investigator must only contain the participant's study number and date of birth. No personal identifiable information must be sent.

Chief Investigator Responsibilities

The Chief Investigator will review the SAE form, obtain further information from the study site as necessary and liaise with the DSMB via the MyPal Adult study coordinating centre.

If the DSMB decides the SAE is related to the intervention and unexpected, the Chief Investigator will report it to the Research Ethics Committee within 15 days as per (insert country) guidelines.

If the event is deemed unrelated to the trial intervention, no further safety reporting is required regardless of the outcome. The Chief Investigator will inform the Principal Investigator of the DSMB decision in writing.

The Chief Investigator will contact the Research Ethics Committee by telephone within 24 hours and in writing within 3 days if urgent safety measures have had to be put in place in order to protect research participants against any immediate hazard to their health or safety. (*The Principal Investigator is the person responsible for the individual study research site. * The Chief Investigator is responsible for the conduct of the study in the country.)

DSMB Responsibilities

The DSMB will evaluate the reported events, taking into account differences between intervention and control hospitals. Based on this, the DSMB will recommend to continue, to modify or to stop the MyPal-Adult RCT.

7 DATA HANDLING AND RECORD KEEPING

Case Report Forms

Data will be collected on Case Report Forms (CRF) to document eligibility, safety and efficacy parameters, compliance to intervention schedules and parameters necessary to evaluate the study endpoints. Data collected on the CRF are derived from the protocol and will include at least:

1. Inclusion and exclusion criteria;
2. Baseline status of patient including medical history and stage of disease;
3. Timing of intervention;
4. Baseline concomitant diseases and adverse events;
5. Parameters for response evaluation;
6. Any other parameters necessary to evaluate the study endpoints;
7. Hospital visits, doctor visits, hospitalizations
8. Medications, treatments
9. Investigations (laboratory and imaging)

10. Survival status of patient;
11. Reason for end of protocol intervention.

Each CRF page will be identified by a trial number, and a combination of patient study number (assigned at registration) and hospital name.

The CRF will be completed on site by the local investigator or sub-investigator or an authorized staff member. The CRF must be signed by the local investigator or sub-investigator upon completion. All CRF entries must be based on source.

Data Handling and Record keeping of data and documents

The MyPal Adult clinical trial and its participants will conform to relevant national and EU legislation on the protection of individuals with regard to the processing of personal data and on the free movement of such data. All data (paper and electronic) will be treated as confidential. They will be stored securely and they will be anonymised (where possible). Hard copy patient data will be stored in a secure place (locked room, in a locked filing cabinet with limited access) and will be protected from the environment (damp, mould and fire etc) or on a secure CERTH server.

Each clinical trial site will organise monitoring in the sense of examining whether data collection processes and record keeping are executed properly locally (in study site files) and note all deviations from standard operating procedures and study protocol requirements. In addition, the trial manager will be responsible for oversight of trial documentation and record keeping.

Archiving

All of the studies essential[1] documents will be retained and archived for 10 years after completion of the study. They will be stored securely and adequately protected from fire, flood, pest and extreme weather. With respondents' permission, anonymised data collected during this study may be used for secondary data analysis in future projects.

8 REPORTING

8.1 Annual progress report

The study will be supervised by the independent Data, Safety and Monitoring Committee.

The sponsor will submit a summary of the progress of the trial to the Ethic Committees once a year. The first report is sent one year after the first approval date of the trial. The last report is sent one year after the last patient has completed protocol treatment. Progress reports will include information regarding:

- the date of inclusion of the first patient,
- numbers of patients included and numbers of patients that have completed the trial,
- screening failure and reasons for screening failure
- serious adverse events,
- any other issues and amendments.

8.2 End of trial report

The sponsor will notify the ECs and the Competent Authority of the end of the trial within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the ECs and the competent authority within 15 days, indicating the reasons for the premature termination.

Within one year after the primary endpoint analysis of the trial, the sponsor will submit an end of study report with the results of the study, including any publications/abstracts of the study, to the ECs and the Competent Authority.

9 QUALITY MANAGEMENT

9.1 Site Set-up and Initiation

Regulatory Documentation

Regulatory and administrative documents will be provided by the PI (or delegated representative) and require local Ethical Committee (EC) approval for each investigational site before enrolling the first patient. The EC approval should be notified to the sponsor (or delegated representative). When all requirements are met, each investigational site will be notified by the sponsor that enrolment started is authorized.

Registration

Eligible patients should be registered before start of intervention.

All eligibility criteria will be checked with a checklist.

Each patient will be given a unique patient study number (a sequence number by order of enrolment in the trial).

The accuracy and reliability of data are based first on the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator before the study.

Data collected on the CRF will be verified for accuracy. If necessary, queries will be sent to the investigational site to clarify the data on the CRF. The investigator should answer data queries within the specified timeline.

9.2 Audit and Inspection

In accordance with regulatory guidelines, audits may be carried out for this study. The investigator is required to facilitate an audit by means of a site visit.

These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

10 END OF TRIAL DEFINITION

The end of the study will be the last data collection time point within the study for the last participating patient.

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size

Assuming relatively acceptable values for the attrition rate (i.e., 20%) and the missing data (i.e., 30%), the sample size analysis concluded that 300 recruited patients providing one measure at enrolment (baseline) and 7 repeated measures (at Months 1, 2, 3, 4, 5, 6 and 12) are sufficient for the power of the intended statistical testing to be over 90% in all cases, given (a) a 0.05 significance level, and (b) an

effect size of 0.2; the employed value of the effect size was based on a priori knowledge of the domain. Power calculations were performed using the G*Power[67] statistical analysis software.

11.2 Data Analysis Plan

11.2.1 Descriptive Analysis

Descriptive statistics will be provided for demographic (gender, age group, origin, etc.) and clinical characteristics (diagnosis, disease stage, etc.) recorded at baseline. All baseline summary statistics will be based on characteristics prior to the initiation of study, unless otherwise stated.

11.2.2 Analysis of Outcome Measures

In alignment with the objectives of the trial, the following outcome measures will be considered in the statistical analysis:

Table 14. Primary and secondary outcome measures

	Outcome measure	**Measured parameter**	**Primary/Secondary**
1	Score in EORTC QLQ-C30 General Questionnaire assessment scale	Quality of life	Primary
2	Score in EQ-5D assessment scale	Quality of life	Primary
3	Score in ESAS assessment scale	Symptom burden	Secondary
4	Score in BPI assessment scale	Symptom burden (pain)	Secondary
5	Score in ET assessment scale	Emotional Distress	Secondary
6	Score in IPOS assessment scale	Physical and emotional functioning	Secondary
7	Score in EORTC PATSAT C33 assessment scale	Satisfaction with cancer care	Secondary
8	Percentage in adherence to reporting	Patient engagement in care	Secondary
9	Days from MyPal enrolment to death by any cause	Overall survival	Secondary

To evaluate the changes in outcome measures 1, 2, 6,7 and 8 over time (1) in the experimental arm and (2) in the experimental arm in comparison with the standard arm, one-way and two-way repeated measures analysis of variance (ANOVA) will be applied (or a non-parametric equivalent), respectively. For the outcome measures 34, 5, only one-way ANOVA will be applied, since these outcomes are not measure in the control group. Post-hoc analysis will be applied as appropriate. The level of significance for all statistical tests is set to a=0.05, in accordance with the power calculation. We will also perform

[67] http://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower.html

analysis that will control for baseline criterion scores and potential confounders such as age group and gender, which may be imbalanced between groups and associated with outcomes of interest.

Patients will be followed for survival status until the end of the study. Overall survival (OS) will be analyzed by Kaplan-Meier methodology using data from all enrolled patients. Median time survival will be estimated and 0.95 confidence interval for the median time survival will be presented.

11.3 Planned Sub Group Analyses

Subgroup analysis of the outcome measures will also be performed at baseline, Month 6 and Month 12 of the study using one-, two- and three-way ANOVA in order to detect potential differences between specific groups of participants. The grouping variables that will be employed are (a) the clinical center (origin), (b) the country of residence, (c) the age group, (d) the disease stage, and (e) the diagnosis (CLL, MDS). The level of significance for all statistical tests is set to a=0.05, in accordance with the power calculations. In the case an interaction effect is observed, separate subgroup analyses in the CLL and MDS cohorts with repeated measures ANOVA will be performed to assess the effect of intervention on quality of life and other the outcome measures.

11.4 Planned Interim Analysis

Since the present trial does not concern primary treatment (as it is the case for example for a pharmacological trial), no substantial risks for the life and health of the study subjects are expected as a result of the intervention or lack thereof. For this reason, interim statistics analysis of the results is not needed and it will not be performed. Instead, the data monitoring committee will be responsible for verifying the quality and completeness of the collected assessment data, using data science rather than statistical methods. Every 3 months the data monitoring committee will be performing automated checks via developed programming scripts for missing data based on predefined metrics that will assess the extent of missing/incomplete data across several dimensions (percentage of missing data per study participant, per assessment instrument, per assessment instrument component, per assessment iteration, etc.)

11.5 Planned Final Analyses

The final analysis will take place after the end of the study (i.e., 30.03.2022) and it will be performed as described in Analysis of Outcome Measures and the Planned Subgroup Analysis sections above. On top of that, repeated measures multivariate ANOVA (MANOVA) will be applied with the quality of life assessed by outcome measure 1 and 2 serving as the pair of dependent variables. The level of significance for all statistical tests is set to a=0.05, in accordance with the power calculations.

12 TRIAL ORGANIZATIONAL STRUCTURE

12.1 Sponsor

CERTH (partner 1, Greece) will be the Sponsor of the clinical trial, while the collaborating clinical sites are the following:
Collaborators
CERTH (partner 1, Greece; through the affiliated G. Papanicolaou Hospital, Thessaloniki, Greece)
Karolinska Institutet (partner 6, Sweden)
Università Vita-Salute San Raffaele (partner 7, Italy)
University Hospital of Crete (partner 8, Greece)
University Hospital Brno (partner 10, Czech Republic)

12.2 Coordinating Centre

The coordinating Centre will be Università Vita-Salute San Raffaele in Milan, Italy. It will be responsible for overall data management, monitoring and communication among all sites, and general oversight of the clinical trial conduct.

12.3 Trial Management Committee

The Trial Management Committee (TMC) will consist of a trial manager, the principal investigator and representative investigators from each clinical site or/as well as other members of the trial team with specific expertise i.e. Statistician, Health Economist, Database Programmer etc. Its main duty is to manage the trial including clinical and practical aspects.

Specifically, to:

- oversee the overall conduct and progress of the trial
- finalize protocols and supervise their submission to local Ethics committees
- review Standard Operating Procedures (SOPs) and clinical staff training and ensure these are adhered to.
- supervise selection and recruitment
- provide clinical and other expert guidance to the clinical trial team on clinical and practical queries
- coordinate implementation and day-to-day management of the trial
- monitor and track project milestones to ensure project runs within timelines

The TMC will virtually meet biweekly frequently during the set-up and start of the trial and quarterly until the end of the trial.

12.4 Data Monitoring Committee

The DSMC will be an independent and multidisciplinary committee consisting of 3-4 members such as clinicians who have experts in hematological cancer, ethics and palliative care, biostatisticians etc. It will be responsible for the data emerging from the clinical trial in terms of safety and efficacy. Specifically, to:

- Monitor data quality including completeness
- Monitor evidence for differences in the main outcome measures between arms
- Assess results of the interim analysis

The DSMC will have access to unblinded data during the course of the trial and will monitor accumulating data from the trial at pre-specified intervals. Any safety or ethical issues will be brought to the attention of the investigators and the TSC. Meetings will be held every 6-12 months.

12.5 Internal Ethics Committee

It is the committee authorized by the Trial Management Committee to review documents (e.g. informed consent) and tools (i.e. digital presentation of PROs), necessary for the conduct of the clinical trial. More specifically, it is meant to safeguard the rights, safety, dignity and well-being of research participants. It consists of three members, namely a chair expert in bioethics and two oncologists/ hematologists.

12.6 Finance

No individual per patient payment will be made to healthcare providers, Investigators or patients.

13 ETHICAL CONSIDERATIONS

The protection of the autonomy of research participants with respect to their privacy, beneficence and dignity is of paramount concern and an internal Ethics Committee will monitor this aspect of the trial implementation in collaboration with the local investigator. Thus, the study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, the ICH-GCP Guidelines, the General Data Protection Regulation (GDPR)[68], the EU Clinical Trial Directive (2001/20/EC)[69], the EU Clinical Trials Regulation (EU No 536/2014)[70] and applicable regulatory requirements. The local investigator is responsible for the proper conduct of the study at the study site.

13.1 Scientific Advice / Protocol Assistance

The following activities have been planned in the context of regulatory scientific advice or protocol assistance:

- The study will incorporate scientific advice and follow relevant scientific guidelines on palliative care (mentioned in Section 1.2.3);
- The study investigators will contact regulators at national level when appropriate;
- The PI will check relevant submission timelines and deadlines;
- The study will incorporate regulatory input by EMA and the local authorities throughout the project and at all stages of the intervention.

13.2 Screening

MyPal will use a carefully-crafted, multicomponent, evidenced-based recruitment protocol fusing evidence-based strategies with principles of “social marketing,” an approach involving the systematic application of marketing techniques[71]. Main components will include (1) an inclusive triage algorithm, (2) information booklets targeting particular stakeholders, (3) a specialized recruitment nurse, and (4) standardization of wording across all study communications. Another key feature of our strategy pertains to broad eligibility criteria within the selected hematologic cancers. The difficulties that may be encountered in this study relate to the inherent problems being associated with palliative care research[72.] To overcome these difficulties, the study will be multi-center in nature, involving centers of excellence in the respective disease areas as well as expertise in the various aspects of such studies including those related to ethics.

13.3 Informed Consent

Written informed consent of patients is required before enrolment in the trial and before any study related procedures, and only after information has been provided to them regarding the voluntary character of participation, the purpose of the study, the procedures involved, the management of possible risks or incidental findings as well as ways to deal the safeguards for the protection of the participant’s personal data and privacy and the right to withdraw at any time for the study. Before informed consent may be obtained, the investigator should provide the patient time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. A copy of the informed consent form will be given to the subject and the original will be kept at site. An entry must also be made in the subject's dated source documents to confirm that informed consent was indeed obtained prior to any study-related procedures and that the subject received a signed copy.

[68] https://www.eugdpr.org
[69] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
[70] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
[71] LeBlanc TW, Lodato JE, Currow DC, Abernethy AP. Overcoming recruitment challenges in palliative care clinical trials. Journal of oncology practice. 2013 Oct 15;9(6):277-82.
[72] Aoun SM, Kristjanson LJ. Challenging the framework for evidence in palliative care research. Palliative Medicine. 2005 Sep;19(6):461-5.

Patient information and consenting should comply with relevant regulation (e.g. The Oviedo Convention, ICH-GCP and the GDPR) (See Appendix for Information Sheet and Consent Form).

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an independent Research Ethics Committee (REC). The REC will review the ethical, scientific and medical appropriateness of the study before it is conducted and the approval will be obtained prior to the initiation of the study in each study site. Any amendments to the protocol including substantially revised informed consent forms and information sheets will require new REC approval and approval by Regulatory Authority(ies), if required by local regulations, prior to implementation of any changes made to the study design. Consequently, the patient should be informed in a timely manner if new information becomes available that might be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

The investigator will be required to submit, maintain and archive study essential documents according to International Conference on Harmonization (ICH) GCP.

13.4 Withdrawal of Informed Consent

If a patient withdraws his/her consent to participate in the study, the investigator should attempt to verify and record the patient's intent in the medical records:

- The patient can refuse further participation and/or procedures according to protocol, while still consenting with further follow up data collection.
- The patient can refuse further participation and/or procedures according to protocol, and withdraw consent for further follow up data collection.
- The patient can refuse further participation and/or procedures according to protocol, withdraw consent for further follow up data collection and withdraw consent to use any data in the study.

14 CONFIDENTIALITY AND DATA PROTECTION

14.1 Patient Confidentiality

Each patient is assigned a unique patient study number at enrolment. In trial documents the patient's identity is coded by patient study number as assigned at enrolment. The data will be collected, stored and accessed in a way that will ensure privacy of participants and compliance with data protection legislation, in particular regulation 679/2016.

The local investigator will keep a subject enrolment and identification log that contains the key to the code, i.e. a record of the personal identification data linked to each patient study number. This record is filed at the investigational site and should only be accessed by the investigator and the supporting hospital staff, and by representatives of the sponsor or a regulatory agency for the purpose of monitoring visits or audits and inspections

14.2 Filing of Essential Documents

Essential Documents are defined as those documents that are needed to evaluate the conduct of a trial and the quality of the data produced. The essential documents may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

The investigator should file all essential documents relevant to the conduct of the trial on site. Essential documents should be protected from accidental loss and should be easily retrieved for review.

14.3 Record Retention

Essential documents should be retained in a secure environment at each participating clinical site for 15 years after the end of the trial or as longer as needed in accordance with applicable laws and regulations. Essential documentation (Trial Master File) includes, but is not limited to, signed protocols and amendments, IRB/REB/IEC approval letters (dated), signed ICFs (including subject confidentiality information), signed dated and completed case report forms (CRFs), and documentation of CRF corrections, any SAE and notification of SAEs and related reports, source documentation, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

Source documents (i.e. medical records) of patients should be retained for at least 15 years after the end of the trial or as longer as needed in accordance with applicable laws and regulations. Record retention and destruction after this time is subject to the site's guidelines regarding medical records.

In the design of the MyPal platform special care has been taken to ensure the de-identification of the personal information that is collected. This is reflected in the deployment of the MyPal platform, which is visualized in Figure 5. The deployment of the MyPal platform encompassed a number of *local installations*, one per participating clinical center and one *central installation* at the site of the sponsor.

14.4 Digital Data Storage & Transfer

In the design of the MyPal platform special care has been taken to ensure the de-identification of the personal information that is collected. This is reflected in the deployment of the MyPal platform, which is visualized in Figure 5. The deployment of the MyPal platform encompasses a number of *local installations*, one per participating clinical center and one *central installation* at the site of the sponsor.

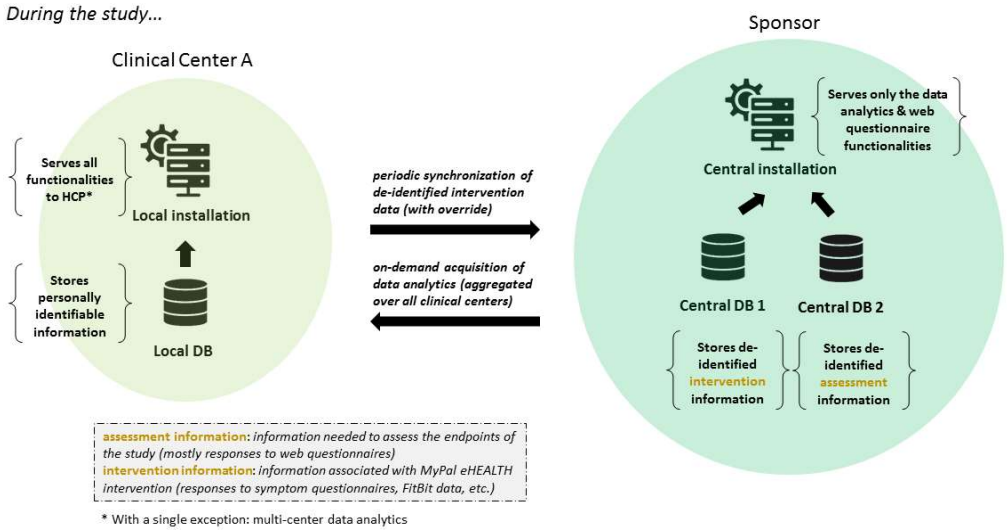


Figure 5. MyPal platform deployment

Each local installation runs the software modules needed to serve all the functionalities and features that are addressed to the corresponding HCP with a single exception (i.e., a part of the data analytics functionality; see item 1 below). In the backend of the local installation there is an integrated *local database* which stores personally identifiable information for all the participating study subjects of the clinical center at hand. This corresponds to the intervention data, i.e., the dataset associated with the delivered MyPal eHEALTH intervention, including the responses to symptom questionnaires, spontaneous symptom reporting forms, FitBit data, etc. On top of that, personal (patient name, email,

phone number, etc.) and clinical information (gender, disease stage/risk, treatment scheme, expected outcome, functional impairment, etc.) is also stored in the local database. Concerning the clinical information, the (a) age and (b) diagnosis of the study subject are categorized before storage.

The central installation resides at the side of the sponsor of the study and it serves two functionalities during the study:

(1) The provision of data analytics that pertain to the entire, multi-center group of study participants. The functionality at hand aggregates de-identified intervention data coming from all the participating clinical centers. At a predefined period (e.g., once per week), the local intervention data are de-identified and subsequently synchronized with the central installation, where they are stored in the 1st central database overwriting the previous data. De-identification is performed by removing all the personal data and keeping among the clinical data only the categorized age and diagnosis information. The provenance of the data (i.e., the clinical center the data come from) is also retained. At the same time, the responsible modules of the central installation calculate the study-wide aggregated data analytics and expose them to the local installations, which consume them on demand.

(2) The hosting of the web-based questionnaires that are associated with the endpoints of the study. The responses of the study subjects to these questionnaires constitute the core of the assessment data of the MyPal platform. The latter are stored in the 2nd central database in a completely de-identified manner. The assessment data of each study subject are accompanied only by following pieces of information: provenance, categorized age, and categorized diagnosis, which are intended for subgroup analysis and are already available to the central installation for the purposes of the data analytics functionality.

15 INSURANCE AND INDEMNITY

Prior to the start of the trial, the Sponsor is responsible to ensure that adequate insurance for patients participating to the trial is subscribed, in accordance with applicable laws and regulations. Proof of insurance will be submitted to the Ethics Committee.

16 PUBLICATION POLICY

Results of the study will be owned by the Investigators. IPR management will be considered and addressed within a dedicated IP Agreement, drafted and agreed as part of the Agreement prior to commencing the study.

For multicenter studies, it is mandatory that the first publication will be based on data from all analyzed subjects; investigators participating in multicenter studies must agree not to present data gathered individually or by subgroup of centers prior to the full initial publication, unless this has been agreed by study chairs. Any formal presentation or publication of data from this trial will be considered as a joint publication by the Investigators. The results of this study will be submitted for publication in peer reviewed journals and for presentation at appropriate scientific meetings. No publication of results will occur without the agreement of the principal investigator.

Protocol Version 1.0 – 31.10.2019

APPENDIX

Information Sheet for Adult Patients

MyPal: Fostering Palliative Care of Adults and Children with Cancer through Advanced Patient Reported Outcome Systems

We would like to invite you to participate in a study conducted by Dr …….. and his/her team at the University of …….. Before you decide to take part in this study it is important that you understand why it is being done and what it will involve. Please take time to read the following information carefully and to decide whether or not you wish to take part.

Aims of the study: In this study (which is part of a larger project that will be conducted across four European countries), we are interested in exploring the use of digital technology that will empower you (and possibly members of your family) to communicate your condition more accurately and effectively to your healthcare providers (i.e. oncologists, specialized physicians, psychologists, nurses). The aim is to improve the quality of care by using modern methods of individualized information, communication and support for patients with cancer and by promoting what we call a patient-centered approach through the use of Patient Reported Outcome platforms. It is important for you to know that MyPal is not an alert system and that doctors may not respond immediately as the study does not aim to provide or change medical treatment. Supportive information provided by healthcare providers via the application (e.g. a search engine for medication) does not imply legal liability.

Why you have been chosen: You have been chosen to participate in this study because you are over 18 years of age and because you have been diagnosed with chronic lymphocytic leukemia (CLL) or myelodysplastic syndrome (MDS). Also, because you are fit to participate in the study and you are able to use an Internet connected device. The feedback you provide will help us to adapt and improve the acceptability and the performance of the various tools.

What do you have to do: If you volunteer to help us accomplish these aims, you will be randomly assigned either to the intervention group which will use the MyPal system, or to the control group which will receive the palliative care services normally provided. The study is a non-pharmacological ICTbased (Information and Communications Technology) intervention and as such it does NOT involve collection of biological samples or administration of any medication.

If you participate, you will be asked to do the following:

Use the MyPal app, a smartphone application, with many functionalities through Internet connected devices, such as smart phone, tablet or computer.

Wear a commercially available smart wristband to monitor your physical activity & quality of sleep. This will be provided by the research team

Complete on repeated occasions (which may change due to the needs of the study) a variety of questionnaires appropriate for use in palliative care with adults:

a) 4 self-report questionnaires at baseline, and then every month for the six following months,

b) the same 4 self-report questionnaires as a follow up at the end of the study, at the clinical site of the research

These 4 questionnaires are: two QOL questionnaires (the EORTC QoL and the Euroquol), the EORTC satisfaction with cancer care questionnaire and the Integrated Palliative Care Outcome Scale.

Depending on the group on which you participate you may additionally have to respond to the Brief Pain Inventory the Edmonton Symptom Assessment Scale and the Emotional Thermometers) in order to evaluate your symptoms, the degree of your pain, your anxiety, the quality of your life during different days or the satisfaction you get from your treatment. Your responses will provide the kind of information that will enable the design and development of flexible tools responding to your different needs and views.

If needed, a member of the research team will be available to help you complete the questionnaires.

Will your taking part in this project be kept confidential? Data protection is one of our most important concerns in this study. National laws on personal data protection will be implemented in order to guarantee the highest standards of personal data management. All procedures for protecting personal information in this study are in accordance with the approved rules of the University of XXXXXXX and with the European legislation and the General Data Protection Regulation2016/679 Only data that is necessary for this research will be collected. Our technology partners will provide technical support and tools regarding data security in order to mitigate data security risks. Any information that is obtained in connection with this study and that can be identified with you will remain confidential. A computer generated number, will be assigned to you at enrolment and your data will be pseudonymised. This means that your name and other direct identifiers will be separated from the collected research data so that your identify is protected and links to your identity will not be possible.

If you agree to take part in the study, we will use your data in the way needed to conduct the research and analyze the research results. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the study to be reliable and accurate.

Data will be collected through a number of different tools: some of these have been already developed, and some are new in this study. The data collected from the fit-bit wristwatch are stored on the FitBit server and are retrieved from it by the MyPal app once per day to be stored in the My Pal server, according to all data protection safeguards applying in this project. All medical data pertaining to your care and treatment obtained during the project will be kept for 15 years in (name of the clinical site) where they were collected or created. The data, however, that has been collected for the purposes of the study, will be kept at the central installation of the sponsor of the study, CERTH, after having been de-identified. De-identification is performed by removing all the personal data and keeping only the categorized age, diagnosis information and the clinical centre where the data came from. This central installation fulfills all technical and organizational requirements for the safety and the security of the stored data. In case you have concerns or queries or you feel should lodge a complaint with Data protection authorities, you can contact the Data Protection Officer of our Research Institution: Name of the DPO, … e-mail:…

Do you have to participate? Participation is absolutely voluntary. If you decide to participate, you are free to withdraw at any time without giving any reason and without there being any negative consequences. Your decision whether or not to participate will not affect your relationship with the researchers or with the team managing your care. With regard to the various questionnaires involved, you can choose not to answer any particular question or questions. You can freely decide to withdraw from the study once data collection has commenced, without giving a reason for withdrawal. Data collected cannot be erased, but is anonymized and will be retained and included in the study in an anonymized form. But no further data will be collected from you after your withdrawal. Once the research

is complete, and the data analyzed, it is not possible to withdraw your data from the study.The whole duration of the study will be 12 months.

Are there possible disadvantages and/or risks in taking part? The nature of this study means that your participation does not entail any risk of physical discomfort, pain, injury, illness or disease. We do not envisage any adverse or incidental findings, as these usually refer to medical problems discovered in the course of a different type of research/clinical trial. However, if we come across an unexpected finding, what we plan to do is to inform you, to discuss this in our team, and to consult with your treating physician. If you have any concerns you are free to contact the Principal Investigator (see below for details) and once again, we would like to remind you that your participation is entirely voluntary.

What are the possible benefits of taking part? You may not receive any personal benefits from participating in this research. However, you may find your participation is a positive experience through the use of the various tools and applications as well as contributing to the improvement of the role of patients like yourself in the process of their treatment.

Transfer of data: data collected during the My Pal project will be shared among the collaborating research teams but will never be transferred to countries outside of the European Union.

What will happen to the results of the study? The results will be used only for research purposes; they may be reported in research publications and may be made available to other researchers in an anonymized form. In every research output (papers, presentations, articles, reports) the total anonymity of your data will be protected.

Ethical approval: This study has been approved by the Research Ethics Committee of the University of….

Contact for further information: please do not hesitate to contact the Principal Investigator, Dr ……..email…..

Tel: +XX(..) … at any moment with questions or concerns about the study.

Informed Consent Form for Adult Patients

I confirm that I have read and understood the information sheet explaining the above research project and I have had the opportunity to ask questions about it.

I understand that I will be randomly assigned to either:

• a group which will use the MyPal system, (called “the intervention group”) or to

• a group which will only receive usual palliative care if so desired (called the “control group”)

I consent:

to use Internet connected devices, e.g. smart phone, tablet or computer

to respond to the required burden of questionnaire completion and to complete

a) 4 self-report questionnaires at baseline, and then every month for the six following months,

b) the same 4 self-report questionnaires as a follow up at the end of the study, in the site where the study took place.

These 4 questionnaires are: two QOL questionnaires (the EORTC QoL and the Euroquol), the EORTC satisfaction with cancer care questionnaire and the Integrated Palliative Care Outcome Scale.

If I belong to the first group (the intervention group) I additionally consent:

to wear a commercially available wristband that will track my activity and my sleep

to respond to 3 questionnaires at baseline and every week until the end of the project - on physical symptoms Brief Pain Inventory, Edmonton Symptom Assessment Scale and emotional symptoms the Emotional Thermometers.

By ticking each box below I confirm that:

I am aware that NO biological samples will be collected.

I am also aware that the study does NOT entail the administration of any medication and that supportive information provided by healthcare providers via the application (e.g. a search engine for medication) does not imply legal liability

I have been informed that the study does not entail any foreseeable risks of discomfort, pain, injury, illness or disease brought about by the methods and procedures of this research and that no adverse events are expected from participating in the study. In the unlikely case they do, I have been informed of the procedure to be followed.

I have been informed that the MyPal system does not act as an alert system to ask for help in an emergency.

I understand that my participation is absolutely voluntary and that I am free to withdraw at any time without giving any reason and without there being any negative consequences regarding my treatment, my relationship with my health care providers and with the research team.

If I withdraw from the study after some data have been collected about me, I understand that these data will continue to be analyzed in an anonymized form but that no new data will be collected after my withdrawal.

I have been informed about data protection issues and appropriate organizational and security measures that will be taken in order to guarantee the protection of my personal data. Also, that my data will be pseudonymized, so that linkage to my identity is not possible. I understand that data collected during My Pal project will never be transferred to countries outside of the European Union. I have beeninformed that the data collected from this project will be stored by the research team for 15 years in

(name of the clinical site) where they were collected or created. The data that has been collected for the purposes of the study, will be kept at the central installation of the sponsor of the study after having been de-identified.

It has been confirmed to me that in every research outputs (e.g. papers, presentations, articles, reports) the total anonymity of my data will be protected.

I have been provided with contact details of the Data Protection Officer responsible, in case I have concerns or queries.

I have read this form and I have been provided with information regarding the research study. I have been given a copy of the information sheet and of this consent form and another copy will be retained for record keeping by the project.

Protocol Version 1.0 – 31.10.2019

For any further questions or concerns, I may contact Dr …..(Principal Investigator, e-mail…..). Tel: + XX (..) …

I agree to participate in the study described here.

Name of Participant	Date	Signature
Name of Researcher	Date	Signature