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THE MyPal Adult STUDY PROTOCOL: A RANDOMIZED CLINICAL TRIAL OF THE MyPal ePRO-BASED EARLY PALLIATIVE CARE SYSTEM IN ADULT PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

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4 **ePRO-BASED EARLY PALLIATIVE CARE SYSTEM IN ADULT PATIENTS WITH**
5 **HAEMATOLOGICAL MALIGNANCIES**
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Abstract

Introduction: The systematic collection of electronic patient-reported outcome (ePRO) information in the routine care of patients with chronic hematologic malignancies such as chronic lymphocytic leukaemia (CLL) and myelodysplastic syndromes (MDS) can constitute a very ambitious but worthwhile challenge. MyPal is a Horizon 2020 (H2020) Research & Innovation Action aiming to meet this challenge and foster palliative care for patients with CLL or MDS by leveraging ePRO systems to adapt to the personal needs of the patient and his/her caregiver(s).

Methods and analysis: In this interventional randomized controlled clinical trial, 300 patients diagnosed with CLL or MDS will be recruited across Europe. Patients will be randomly allocated to receive early palliative oncology care using the MyPal system (n=150) versus standard care which could include general palliative care if needed (n=150). Patients randomized to the experimental arm will be given access to the MyPal Digital Health Platform which consists of purposely-designed software available on smartphones and/or tablets. The platform entails different functionalities including physical and psycho-emotional symptom reporting via regular questionnaire completion, spontaneous self-reporting, motivational messages, medication management, and a personalized search engine that retrieves health information. Data on patients' activity information such as daily step count and sleep quality will be automatically collected via wearable devices (FitBit).

Ethics and dissemination: The integration of ePROs via mobile applications has raised ethical concerns regarding inclusion criteria, information provided to participants, free and voluntary consent, as well as respect for their autonomy. These have been carefully addressed by a multidisciplinary team. Data processing as well as the dissemination and exploitation of the study findings will take place in full compliance with EU data protection law. A participatory design was adopted in the development of the digital health platform involving focus groups and discussions with patients in order to identify needs and preferences.

Trial Registration Number: ClinicalTrials.gov: NCT04370457

Strengths and Limitations

Strengths

- MyPAL Adults is a multicentre randomized interventional study in palliative care using an innovative approach based on ePRO-based systems to improve the quality of life of patients with chronic lymphocytic leukaemia (CLL) or myelodysplastic syndromes (MDS).
- This is an international study involving 5 clinical sites with longstanding expertise in the management of patients with CLL and MDS.
- MyPal system developers have interacted extensively with end-users from its initial development and will continue until its evaluation, thus putting down the basis for successful user engagement.

Limitations

- Participation of sites from different countries can hinder the comparison of standard and interventional arms considering the diverse palliative care contexts.
- Considering the median age of diagnosis of about 70 years for both CLL and MDS, use of eHealth systems might be challenging, requiring comprehensive training and possibly leading to higher than expected attrition rate.
- COVID-19 pandemic has delayed study initiation and might require ad hoc adaptations to data collection processes during the study.

Introduction

Chronic lymphocytic leukaemia (CLL) and myelodysplastic syndromes (MDS) are two of the most frequent haematological malignancies in the Western world usually occurring in older individuals (median age at diagnosis of around 70 years) [1,2]. These diseases, though generally chronic, are considerably heterogeneous in underlying biology, presentation and clinical course, ranging from relatively indolent to extremely aggressive. Recent scientific advances have revolutionized the therapeutic landscape through the introduction of novel therapies, resulting in improved outcomes, including increased overall survival [3]. That said, both CLL and MDS remain essentially incurable and current therapies aim at controlling the disease long-term. Due to this, open issues abound regarding the impact of CLL and MDS and their treatment 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, especially considering the likely association with other comorbidities due to advanced age [4].

Evidence suggests that patients with CLL have poorer QoL compared to the general population, being significantly bothered by physical symptoms (81% reporting fatigue and 56% sleep disturbances) at treatment initiation [5]. Similarly, patients with MDS may suffer from a wide variety of symptoms, including fatigue, anxiety, and insomnia, amongst others, which result in impaired QoL [6,7]. This is highly relevant in light of the recent therapeutic shift from fixed duration intravenous chemoimmunotherapy to continuous oral therapies for which patient compliance and treatment adherence are key to obtaining long-lasting disease control. This evidence highlights a key role for palliative care, meant as the management of physical symptoms and psychosocial distress, also by means of cancer-specific care throughout the disease course.

Changes in the patients' experience across the illness trajectory can be captured and measured using patient-reported outcomes (PROs). PROs typically refer to the use of standardized, validated self-report questionnaires, and they could be considered the gold standard as far as subjective experiences are concerned [8,9]. PROs are typically employed as part of clinical trials, e.g. in order to support drug safety studies, and to this end, systematic reporting processes and specific terminologies are actively developed and investigated [10]. Furthermore, PROs have a major role in improving the quality, efficiency and availability of palliative care [11]. Their consideration along with clinical and laboratory data within the

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3 palliative care clinical setting can help provide patients with the most appropriate support
4 [12]. Specifically, in palliative care which can be offered from the diagnosis and throughout
5 the disease journey, even along with curative treatment, PROs can: (i) monitor changes in the
6 patients' health status; (ii) facilitate the identification of unmet needs which could have been
7 overlooked (psychological, social, physical etc.); (iii) provide information on the evolution of
8 disease and the impact of treatment interventions; (iv) promote patient/physician interaction
9 and communication; and (v) aid clinical decision making [13, 10].

15 The process of collecting PROs has progressed along technical advances, in particular through
16 the introduction of eHealth paradigm, defined as the use of information and communications
17 technology in support of health [14]. eHealth interventions might target the active capture of
18 measurements from the patients themselves, as is the case with the electronic
19 implementation of PROs (ePROs). In fact, ePROs have been found to contribute to improved
20 health outcomes in cancer patients e.g. improvement in physical activity **Error! Reference**
21 **source not found.**, reduction in anxiety and drowsiness **Error! Reference source not found.**,
22 lower levels of fatigue, nausea, insomnia **Error! Reference source not found.** and pain
23 intensity as well as significant improvement in emotional and social functioning **Error!**
24 **Reference source not found.**

31 The systematic collection of ePRO information in routine CLL and MDS practice can constitute
32 a very ambitious but worthwhile challenge. MyPal is a Horizon 2020 (H2020) Research &
33 Innovation Action aiming to meet this challenge and foster palliative care for patients with CLL
34 and MDS by leveraging ePRO systems to adapt to the personal needs of the patient and
35 his/her caregiver(s). MyPal aspires to empower patients and their caregivers in capturing
36 more accurately their symptoms/conditions, communicate them in a seamless and effective
37 way to their healthcare providers and, ultimately, foster action through advanced methods
38 of identification of important deviations relevant to the patient's state and QoL. MyPal will
39 evaluate the proposed intervention for adults with CLL and MDS through a carefully designed
40 randomized controlled trial (RCT) that will be conducted in diverse health care settings across
41 Europe.
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Methods and Analysis

Study Design

This is a multi-national randomised controlled trial, enrolling patients with CLL or MDS at 5 clinical sites in Europe. The methodological approach of the study involves patients' use of a mobile application with a range of functionalities as well as a FitBit smartwatch. Patients will be able to conveniently self-report via the MyPal mobile application using ePROs as outcome measures while the Fitbit will also be collecting data on patients' physical activity. 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 or MDS).

Objectives and Outcome measures

Primary objective

The main objective is to determine whether the MyPal ADULT intervention can lead to improved QoL compared to standard care as evidenced by statistically significant higher scores in the EORTC QLQ-C30 [19] General Questionnaire and the Euroqol EQ-5D [20].

Secondary objectives

To determine whether - compared to standard care - the MyPal system intervention can lead to the following outcomes in patients with CLL or MDS:

1. Improvement in physical and emotional functioning as evidenced by higher scores in the Integrated Palliative Care Outcome Scale (IPOS) [21] at prespecified timepoints (please refer to "Reporting Period")
2. Increase in satisfaction with care as evidenced by higher scores in the EORTC Patient Satisfaction with Cancer Care questionnaire (EORTC PATSAT C33) [22] at prespecified timepoints
3. Increase in overall survival as evidenced by longer survival times

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.

To determine whether the MyPal system intervention can lead to the following outcomes in patients with CLL or MDS over time:

- Reduced symptom burden as evidenced by lower scores in the Edmonton Symptom Assessment System (ESAS) [23] at prespecified timepoints
- Reduced pain score as evidenced by lower scores in the Brief Pain Inventory (BPI) [24] at prespecified timepoints
- Reduced emotional distress as evidenced by lower scores in the Emotion Thermometers (ET) [25] at prespecified timepoints
- Increase in patient engagement in care as evidenced by satisfactory adherence to reporting (e.g. 70% answered scheduled reports).

Patient recruitment

Patients (n=300) will be recruited from the following 5 clinical centres across 4 European countries:

1. Karolinska Institutet (Sweden)
2. Università Vita-Salute San Raffaele (Italy)
3. University Hospital of Heraklion, Crete (Greece)
4. University Hospital Brno (Czech Republic)
5. G. Papanicolaou Hospital of Thessaloniki (Greece)

All consecutive patients with CLL (as well as small lymphocytic lymphoma-SLL, a condition equivalent to CLL) or MDS who visit the participating centres will be screened and asked to participate in the MyPal study. Patients should fulfill the eligibility criteria highlighted in Box 1 for enrollment.

Box 1. Eligibility Criteria

Inclusion Criteria

1. Adults (≥ 18 years)
2. Diagnosed with CLL or small lymphocytic lymphoma (SLL), a condition equivalent to CLL, or 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/SLL or MDS
4. Able to understand and communicate in the respective language
5. Users of an Internet connected device (smartphone/tablet)

Exclusion Criteria

1. Patients who are already participating in another interventional study
2. Patients needing immediate referral for specialised palliative care
3. Any life-threatening illness, medical condition, or organ system dysfunction that, in the attending physician's opinion, could compromise the subject's safety or put the study outcomes at undue risk
4. Life expectancy < 3 months
5. For the CLL/SLL cohort: patients who have experienced Richter's transformation

Randomisation

Patients will be randomly assigned in a 1:1 fashion to receive early palliative oncology care using the MyPal Digital Health Platform (*intervention group*) versus standard care which could include general palliative care if needed (*control group*), stratified by cancer type (i.e. CLL/SLL vs MDS), using a computer-generated number sequence, based on blocked randomization approach [26]. The assignment of each patient will be conducted during his/her enrolment phase (Figure 1) with no prior knowledge for the enrolling clinicians, in order to avoid biases.

MyPal Digital Health Platform

The intervention consists of the use of the MyPal Digital Health Platform. The system will be used by the patients who participate in the intervention arm of the trial and by the participating HCPs, while patients participating in the control group (the standard arm of the trial) will not use the system. Access to the MyPal Digital Health Platform (Figure 2) will be granted to the patients for 12 months of continuous use right after their enrollment in the

trial. HCPs will have access to the system until the end of the trial. Patients will be informed that the MyPal eHealth system is not meant to be used as an emergency service and urgent issues have to be reported following standard care procedures.

The intervention focuses on the reporting of physical and psycho-emotional symptoms by the patient via the MyPal smartphone app installed on his/her personal smartphone or tablet (see sample screen in Figure 3a). Furthermore, the reported symptom-related information is immediately delivered to the HCP via the MyPal web app which is the main interface of the HCP to the system (see sample web app page in Figure 3b). Finally, the smart wristband, Fitbit Ionic™, a commercial activity tracking device that will be employed for monitoring the physical activity and the sleep quality of the patient, will be provided by the site personnel. Despite the fact that the presentation of the technical infrastructure is considered out of this paper's scope, it should be highlighted that the system backend infrastructure stores the collected data focusing on information security best practices.

The patient's perspective

From the patient's perspective, both system initiated functionalities (i.e., functionalities for which the system decides when they become available to the user) and user initiated functionalities (i.e., functionalities that the user has access to at all times) offered via the MyPal smartphone app can be seen in Table 1.

Table 1. The system and user initiated functionalities offered in the MyPal smartphone app.

System-Initiated Functionality	Description
PS1 Physical symptom questionnaires	Notifications to complete physical symptom questionnaires are issued once per week.
PS2 Psycho-emotional symptom questionnaires	Notifications to complete a psycho-emotional symptom questionnaire (are issued once per week.
PS3 Screener questionnaires	Notifications to complete a screener questionnaire concerning (1) the patient's ongoing engagement with the MyPal study, and (2) the risk of medication non-adherence. Responses will determine the motivational messages that patients will be receiving and the

		highest priority topics for the discussion guide presented to the HCP (issued at Month 0, 3 and 6).
PS4	Motivational messages	Tailored short motivational messages presented to the patient. Their content is determined based on a custom algorithm that receives input from patient responses (Issued twice weekly until Week 4, then once weekly until Week 24).
PS5	Medication reminders	Notifications that remind the patient to take their medication; determined by the patient via the medication management functionality.
User-Initiated Functionality		Description
PU1	Spontaneous symptom reporting	A form that is used by the patient to spontaneously report physical or psycho-emotional symptoms in a structured or unstructured way.
PU2	Medication management	An editable list of the patient's medication plan along with the dosage and the frequency of intake.
PU3	Personal health information recommender	A personalized search engine that retrieves health information related to health status of the patient.
PU4	Self-reported information review	A view that presents the patients's past responses to physical and psycho-emotional questionnaires.
PU5	Activity information review	A view that presents past daily step count and sleep quality indicators acquired by the commercial wristband.

The main phases for the enrolled patients point of view, include a registration phase, a main usage phase and a follow up phase and can be summarized as follows:

Registration Phase. This phase is completed the first time the patient uses the MyPal smartphone/tablet app, and aims at (1) registering the patient into the MyPal system, (2) initially setting a number of preferences, (3) collecting via self-reporting the baseline assessment of the patient's physical and psycho-emotional symptoms, and (4) screening for motivational targets and non-adherence risk. The smartphone app guides the patient throughout the entire registration process in a wizard-like fashion. In case needed, the patient

might get some help for completing the registration from a HCP (e.g., research nurse) participating in the study.

Main usage phase. This phase lasts 6 months (Month 1 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 and system-initiated ones. Two main types of notifications can be distinguished, 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).

Follow-up usage phase. The follow-up usage phase starts immediately after the completion of the main usage phase and it also lasts 6 months (Month 7 to Month 12 of the patient's participation). During this phase however, the smartphone app does not issue assessment notification monthly; instead it issues only one such notification at the end of Month 12.

The HCP's perspective

The functionalities offered via the HCP web app are reported in Table 2.

Table 2. 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. The summarized incoming information is automatically prioritized in the system backend with the help of custom algorithms and the pieces of incoming information that are assigned the highest priority and placed on the top of the list.
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 the trial. The information includes (1) patients' responses to the symptom questionnaires (2) the spontaneous symptom reports; (3) the self-reported medication via the smartphone app; (4) the appointment schedule; (5) the 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).

	Functionality	Description
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).
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.
H5	Information recommender repository update	A page used for editing the information that resides in the repository of the personal health Information recommender. The HCP can upload documents or specify web resources that containing valid medical information.
H6	HCP response log	A page 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.

The HCPs need to follow a simple registration process during their first entry in the MyPal web app. During the main usage of the MyPal web app, the HCPs get access to the data that are collected by (1) the MyPal smartphone app and (2) the commercial smart wristband. The collected data become available to the MyPal web app in a "live" fashion, as soon as they are stored. At an individual level, the HCP is authorized to access only the data of the patients of the associated clinical centre; however, access to aggregated and summarized data coming from all patients (descriptive statistics such as min, max, average and percentiles) will also be provided to all HCPs. HCPs are not actively notified by the MyPal system at any point in order to avoid "alert fatigue"-related issues and biases. The individual data of the participating patients of every clinical center are planned to be reviewed by the associated HCPs at least once every 72 hours. 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 information on the web interface (to be completed by the HCPs accessing the

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3 system), including review of reported symptoms and questionnaires by HCPs (audit trail) and
4 action taken by HCPS, if any.
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9 Data collection and analysis

10 Data collection

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12 Data collection will be undertaken by the MyPal Digital Health Platform, which consists of the
13 following modules:
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- 15 1. **The MyPal smartphone app.** This will be used by the patients assigned to the study
16 intervention group in order to report their physical and psycho-emotional symptoms
17 either spontaneously or periodically, as well as manage their medication intake,
18 review their own data (e.g., symptom trajectory), etc. Additionally, it will serve as the
19 hub for the transfer of activity level and sleep quality data acquired by a commercial
20 activity tracking device.
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- 22 2. **The MyPal web portal.** This will be used by the HCPs participating in the study in
23 order to monitor and periodically review the collected patient data, as well as to
24 register certain data pertaining to a patient (e.g. treatment plan, next appointment).
25 The portal will also be used sporadically by the patients assigned to the study control
26 group for answering the assessment ePRO questionnaires.
27
- 28 3. **The MyPal backend and storage module.** All patient data collected from the
29 smartphone app and the web portal will be synchronized to the MyPal backend and
30 storage module.
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45 Types of data

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47 Special categories of personal data collected during the study include:
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49 Data collected in both experimental and standard arms:

- 50 ▪ Demographic (e.g. age, gender);
- 51 ▪ Clinical information, including disease and treatment-related features, frequency of
52 appointments and events occurring during the observation time
53
- 54 ▪ Patient reported outcomes for study endpoint assessment (assessment
55 questionnaires) to allow for a comparison:
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- The EORTC QLQ-C30 which is a 30-item Quality of Life questionnaire, assessing important functioning domains, common cancer symptoms as well as the perceived financial impact of the disease and treatment
- The Euroqol, EQ-5D – 3L, a 25-item general measure evaluating patients with regards to the following dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
- The Integrated Palliative Outcome Scale (IPOS), a 10-item questionnaire, specific to palliative care, which measures patients' physical symptoms, psychological, emotional and spiritual, as well as information and support needs.
- The Satisfaction with Cancer Care developed by The European Organization for Research and Treatment of Cancer (EORTC) group which assesses patients' perception of the quality of medical and nursing care, as well as the organisation of care and services of an oncology department.

Data collected in the experimental arm only:

- FitBit-derived (e.g. activity and sleep patterns)
- Symptoms (through both spontaneous and scheduled reporting)
- Patient reported outcomes which are part of the intervention (intervention questionnaires) and will be deployed to monitor patient's condition in MyPal:
 - The Edmonton Symptom Assessment System (ESAS), a 10-item questionnaire assessing common symptoms experienced by patients with cancer.
 - The Brief Pain Inventory (BPI), a 9-item questionnaire designed to assess cancer pain intensity, pain relief treatment or medication as well as pain interference in activities.
 - The Emotional Thermometers, a tool which assesses emotional issues, namely distress, anxiety, depression and anger, as well as patients' need for help through 5 visual analogue scales (VAS).

Reporting period

After the patients are enrolled in the study, they are asked to complete the assessment ePROs on a monthly basis (both groups) and the intervention/symptom ePROs on a weekly basis (intervention group only) for 6 months (main phase). In the follow-up phase, the patients of the intervention group continue completing the intervention ePROs as before, while both groups complete the assessment ePROs once more in the end of the phase.

Data security

The privacy-by-design paradigm [27] has been employed to install appropriate data protection measures as early as possible in the development of the MyPal platform, in compliance with the General Data Protection Regulation (EU) 2016/679 (GDPR) [28]. To this end, the necessary Data Protection Impact Assessments 2 (DPIAs) were conducted. The first focusing on the management of data on local clinical sites (mobile apps etc.), and the second focusing on the management of aggregated data for further analysis (anonymization of data etc.) These were thoroughly reviewed by the respective Data Protection Officers (DPOs). The data protection security measures include (1) the storage of personally identifiable data only in the premises of clinical sites, (2) role-based data access, (3) password encryption, (4) use of the OAuth protocol (to minimize password-based authentication whenever possible), (5) network data transfer via the secure HTTPS protocol, etc.

Furthermore, adjusting the system architecture along the privacy-by-design paradigm, a decentralized deployment model of the MyPal platform has been adopted encompassing one local installations per participating clinical center in order to host personally identifiable information for all participating study subjects from the clinical center in its own IT infrastructure. However, one central installation at the site of the study sponsor has also been deployed to host the assessment ePRO responses from all centers after they have been completely deidentified.

Sample size calculation

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 with CLL or MDS at any ratio 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.

Data analysis plan

Descriptive statistics will be provided for demographic (gender, age group, origin, etc.) and clinical characteristics (diagnosis, disease stage, etc.) recorded at baseline. The aim of the analysis will be to evaluate the changes in outcome measures over time (1) in

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2
3 the experimental arm and (2) in the experimental arm in comparison with the standard arm,
4 using one-way and two-way repeated measures analysis of variance (ANOVA) (or a non-
5 parametric equivalent), respectively. Post-hoc analysis will be applied as appropriate.
6
7 Subgroup analysis of the outcome measures will also be performed at baseline, month 6 and
8
9 month 12 of the study using one, two and three-way ANOVA in order to detect potential
10
11 differences between specific groups of participants. The grouping variables that will be
12
13 employed are (a) the clinical centre (origin), (b) the country of residence, (c) the age group,
14
15 (d) the disease stage, and (e) the diagnosis (CLL, MDS). In the case an interaction effect is
16
17 observed, separate subgroup analyses in the CLL and MDS cohorts with repeated measures
18
19 ANOVA will be performed to assess the effect of intervention on quality of life and other the
20
21 outcome measures. The level of significance for all statistical tests is set to $\alpha=0.05$, in
22
23 accordance with the power calculations.

24 25 26 27 Monitoring

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29 The study includes a Data Monitoring Committee (DMC). The DMC will be an independent and
30
31 multidisciplinary committee consisting of 3-4 members such as clinicians who have expertise
32
33 in haematological cancers, ethics and palliative care, biostatisticians. They will have access to
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35 unblinded data and will monitor accumulating trial data at pre-specified intervals in terms of
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37 safety and efficacy and in particular: quality including completeness and attrition, recruitment
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39 across sites and evidence for differences in the main outcome measures between arms. Any
40
41 reports of serious adverse events such as safety or ethical issues will be brought to the
42
43 attention of the Principal Investigators.

44 45 46 47 Safety reporting

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49 Although no safety issues are foreseen, the PI will promptly notify all concerned investigators,
50
51 the Ethics Committee(s) and the regulatory authorities of possible findings that could affect
52
53 adversely the safety of patients, impact the conduct of the study, increase the risk of
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55 participation or otherwise alter the IEC's approval to continue the trial.

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57 As the study population consists of individuals facing life threatening illness, we would not
58
59 expect it to be an unusual occurrence for patients to be admitted to hospital while taking part
60
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

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2
3 considered to be part of routine care, and as such, we expect the risks to be limited. Filling in
4 questionnaires about physical and psychological symptoms, and quality of life may also be
5 upsetting for patients. However, we expect the risk to be limited as these are validated
6 questionnaires that address issues that are discussed in usual care.
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For peer review only

Discussion

Digital health technologies offer the potential for rapid and spontaneous reporting of symptoms, facilitating remote monitoring and communication between patients and HCPs. They have been increasingly implemented in routine practice in all areas of healthcare, especially during the COVID-19 pandemic. However, concerns remain about their acceptability to patients, especially older people, and the degree to which they may alter patient-clinician relationships in palliative care contexts [29]. Therefore, it is important to rigorously test these interventions using robust research designs, highlighting usability and patient acceptability as top priorities.

The MyPal project aspires to offer a personalised approach for improving the delivery of early palliative care in patients with cancer, including CLL and MDS that typically affect the elderly. This will be achieved by empowering patients and their caregivers to actively participate in the care process through the use of digital health tools for self-reporting symptoms and events, QoL as well as any kind of perceived changes in their daily patterns occurring throughout the disease trajectory. Hence, MyPal has the ambition to formally prove the advantage and substantial improvement of eHealth systems as compared to traditional methods of palliative care for cancer patients and promote self-control of health; and, foster active participation of patients in disease management, which may possibly inspire them into a more active participation in society as well. In parallel, through the use of the digital health tools offered by MyPal, healthcare providers are likely to experience improved communication with patients, more timely and accurate interventions, and an increase in knowledge on effective cancer patient management with patients featuring in an empowered role.

The clinical trial reported herein seeks to test the efficacy of the MyPal digital health platform using a newly designed smartphone app together with commonly used wearables to present ePROs to adults with CLL and MDS to determine if it helps communication with their healthcare professionals, compared to standard care. The strengths of this international study include the ability for patients in the intervention arm to spontaneously report on symptoms and concerns, in addition to regular reporting of symptoms when prompted by the app. In addition, this study will provide an opportunity to examine both the advantages and challenges of the MyPal system from the perspectives of the participating healthcare professionals and to assess the extent to which ePRO reporting can facilitate more effective

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3 and timely communication, and ultimately benefit patients by improvements in symptom
4 management.
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6 In summary, data from MyPal will be used to (1) identify QoL improvements compared to
7 usual care, (2) provide evidence of improvements in physical and emotional functioning
8 compared to usual care, and (3) acceptability and usefulness of the MyPal digital health
9 platform for HCPs. We anticipate being able to disseminate our findings by 2023.
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15
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41 Contributors

42 L.S., C.K., C.M., P.G., K.S. drafted the study protocol

43 L.S., C.K., J.D., C.P., C.M., P.G., S.P., K.S. drafted the manuscript

44 T.G., S.P., J.L., C.P., P.N. contributed to critical revisions of the study protocol and the
45 manuscript.
46

47 P.G., N.S., R.R., M.D., H.A.P. are the Site Chief Investigators and take overall responsibility for
48 all aspects of the study design, the protocol and the study conduct at the involved clinical
49 study sites.
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Competing interests

None declared.

Ethics approval

The MyPal-Adult study protocol has received ethical approval from the Ethics Committee of San Raffaele Hospital (05Feb2020, registry number 8/2020), the Ethics Committee of General Hospital of Thessaloniki 'George Papanikolaou' (20.5.2020, registry number 849), Ethics Committee of Karolinska Institutet (20.10.2020), Ethics Committee of the University General Hospital of Heraklion (07/15.4.2020) as well as the Ethics Committee of the University of Brno (01-120220/EK).

Provenance and peer review

Not commissioned; externally reviewed.

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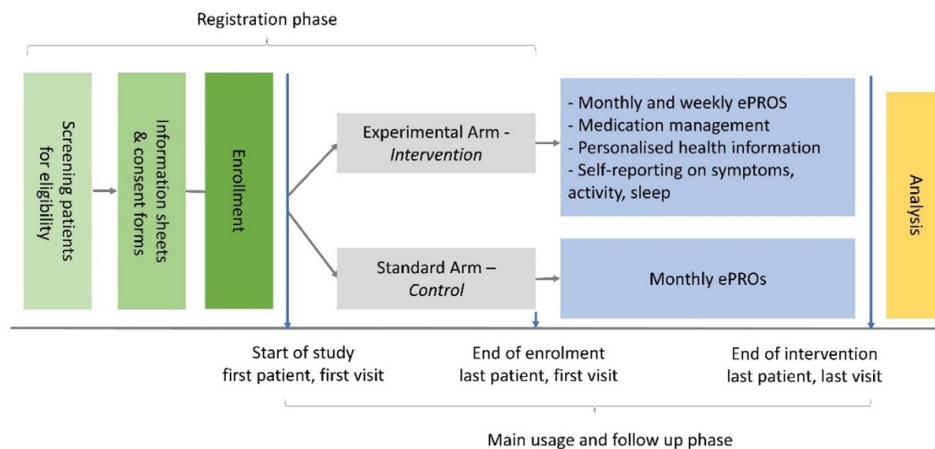


Figure 1. Schematic representation of the study design.

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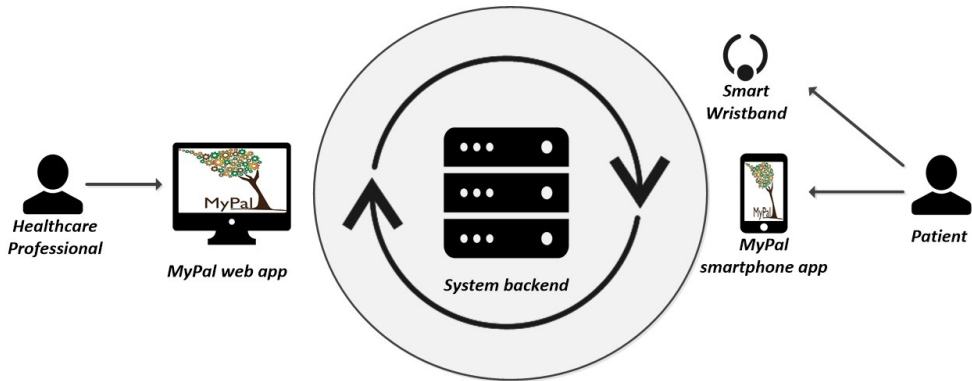


Figure 2. Software and hardware modules of the MyPal digital health platform.

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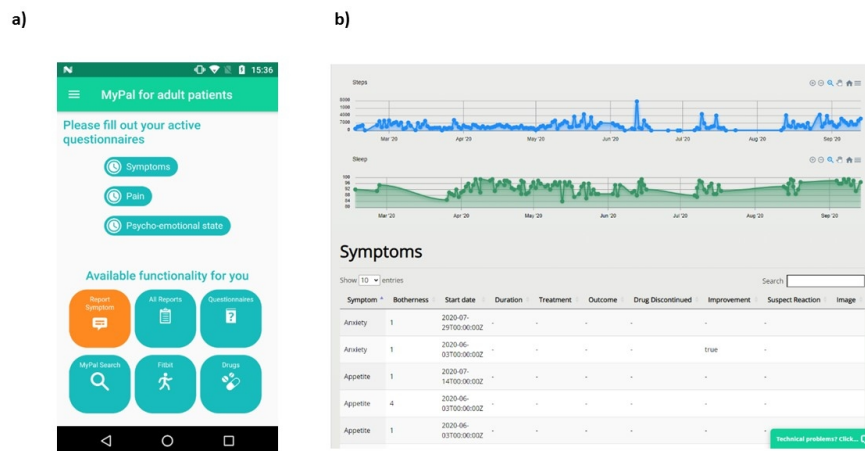


Figure 3. Sample graphical user interfaces of the MyPal eHealth system: (a) Screen of the MyPal smartphone app; (b) Page of the MyPal web app.

338x190mm (96 x 96 DPI)



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



1 Protocol Version 1.0 – 31.10.2019
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4 RESPONSIBILITIES

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29

30 **Responsible for all study-site related medical decisions:**

31 Prof. Paolo Ghia (UniSR/OSR); Prof. Heleni Papadaki (PAGNI); Dr. Michael Doubek FN BRNO); Prof.
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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	<ol style="list-style-type: none"> 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	<p>MyPal will operate according to the “palliative care” definition provided by the World Health Organization which states:</p> <p><i>‘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</i></p> <p>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 <i>specialist palliative care</i>, 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 <i>general palliative care</i> 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.</p> <p>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.</p>

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	<p>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).</p> <p><u>Primary Objective</u></p> <p>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-C30² General Questionnaire and EQ-5D³.</p> <p><u>Secondary Objectives</u></p> <p>To determine whether - compared to standard care - the MyPal system intervention can lead to the following outcomes in patients with hematological cancers (CLL/MDS):</p> <ol style="list-style-type: none"> 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] <p>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.</p> <p>And to determine whether the MyPal system intervention can lead to the following outcomes in patients with hematological cancers (CLL/MDS) over time:</p> <ol style="list-style-type: none"> 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]
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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.

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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.

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	<p>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]</p>																				
<p>Study Endpoints</p>	<table border="1"> <thead> <tr> <th data-bbox="470 398 933 430">Primary Endpoint</th> <th data-bbox="933 398 1383 430">Measure/Scale</th> </tr> </thead> <tbody> <tr> <td data-bbox="470 430 933 497">Improvement in quality of life</td> <td data-bbox="933 430 1383 497">EORTC QLQ-C30 General Questionnaire and EQ-5D</td> </tr> <tr> <th data-bbox="470 555 933 586">Secondary Endpoint</th> <th data-bbox="933 555 1383 586">Measure/Scale</th> </tr> <tr> <td data-bbox="470 586 933 654">Symptom reduction</td> <td data-bbox="933 586 1383 654">Edmonton Symptom Assessment System (ESAS)</td> </tr> <tr> <td data-bbox="470 654 933 685">Pain reduction</td> <td data-bbox="933 654 1383 685">Brief Pain Inventory (BPI) severity</td> </tr> <tr> <td data-bbox="470 685 933 730">Emotional distress reduction</td> <td data-bbox="933 685 1383 730">Emotion Thermometers (ET)</td> </tr> <tr> <td data-bbox="470 730 933 842">Improvement in psychological and physical functioning</td> <td data-bbox="933 730 1383 842">Integrated Palliative Care Outcome Scale (IPOS)</td> </tr> <tr> <td data-bbox="470 842 933 909">Increase in patient engagement in care</td> <td data-bbox="933 842 1383 909">Adherence to reporting (e.g.70% answered of scheduled reports)</td> </tr> <tr> <td data-bbox="470 909 933 976">Increase in satisfaction with care</td> <td data-bbox="933 909 1383 976">EORTC Satisfaction with Cancer Care questionnaire</td> </tr> <tr> <td data-bbox="470 976 933 1008">Overall survival</td> <td data-bbox="933 976 1383 1008">Event of death</td> </tr> </tbody> </table>	Primary Endpoint	Measure/Scale	Improvement in quality of life	EORTC QLQ-C30 General Questionnaire and EQ-5D	Secondary Endpoint	Measure/Scale	Symptom reduction	Edmonton Symptom Assessment System (ESAS)	Pain reduction	Brief Pain Inventory (BPI) severity	Emotional distress reduction	Emotion Thermometers (ET)	Improvement in psychological and physical functioning	Integrated Palliative Care Outcome Scale (IPOS)	Increase in patient engagement in care	Adherence to reporting (e.g.70% answered of scheduled reports)	Increase in satisfaction with care	EORTC Satisfaction with Cancer Care questionnaire	Overall survival	Event of death
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<p>Key Inclusion Criteria</p>	<ol style="list-style-type: none"> Adults (≥18 years) Diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or myelodysplastic syndrome (MDS) 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 Able to understand and communicate in the respective language Users of an Internet connected device (smartphone/tablet) 																				
<p>Key Exclusion Criteria</p>	<ol style="list-style-type: none"> Patients who are already participating in another experimental study Patients needing immediate referral for specialized palliative care 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 Patients unable to provide written informed consent Life expectancy <3 months For CLL cohort: patients who have experienced Richter transformation 																				
<p>Intervention</p>	<p>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.</p>																				



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<p>Study Duration</p>	<p>Total study duration: 25 months</p> <p>Study duration for each participant is expected to be 12 months.</p> <p>Study analysis: 3 months after the end of the study</p> <p>Expected First patient in date: 01.05.2020</p> <p>Expected Last patient in: 30.03.2021</p> <p>End of study: 30.03.2022</p>
<p>Efficacy Assessments</p>	<p>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.</p>
<p>Safety Assessments</p>	<p>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.</p>
<p>Statistical Methods and Planned Analyses</p>	<p>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 $\alpha=0.05$.</p> <p>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.</p>



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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 Plan¹⁰ and recommendations on digital interventions for health system strengthening⁹, respectively.

On top of that, WHO has produced a classification of digital health intervention to describe the various uses of digital health technology for health¹¹.

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 questions¹². 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 concerned¹³.

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 care¹⁴. 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>

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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.



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

7
8 For the MyPal ADULT clinical trial, measurements appropriate for use in palliative care with adults have
9 been selected. Multidimensional Patient Reported Outcomes Measures such as the Palliative care
10 Outcome Scale aiming to identify patients' needs, Edmonton Symptom Assessment Scale for
11 identification of common symptoms experienced by cancer patients. In terms of well-being, the EORTC
12 QLQ-C30 can be used to assess patients' cancer related quality of life. Generic measures such as the
13 EQ-5D assessing the overall physical, psychological and social quality of life will also be used. Please
14 section 4 on objectives and outcome measures¹².

16 1.1.3 Palliative care

17
18 According to the WHO definition (2002)¹ palliative care is “an approach that improves the quality of life
19 of patients and their families facing the problems associated with life threatening illness, through the
20 prevention and relief of suffering by means of early identification and impeccable assessment and
21 treatment of pain and other problems, physical, psychological and spiritual”. Definitions of palliative care
22 have changed from a focus on end-stage cancer to include the trajectory of all life-limiting conditions.
23 They remain both contested and poorly understood by healthcare professionals, and more importantly,
24 by patients and the public¹⁵ Palliative care is interdisciplinary in its approach and encompasses the
25 patient, the family and the community in its scope. Palliative care aims to assess and provide for the
26 needs of the patient wherever he or she is cared for, either at home or in a hospital, or other place.
27 Palliative care affirms life and regards dying as a normal process; it neither hastens nor postpones
28 death. It sets out to preserve the best possible quality of life until death. Palliative care focuses not only
29 on the patient but also his/her family. Furthermore, as the main purpose of palliative care is to improve
30 quality of life by supporting the patient not only through physical problems but other additional problems
31 of a social, psychological and spiritual nature. Palliative care can be offered to improve quality of life of
32 patients and their families who are receiving active treatment either curative or aiming at disease control.
33 Palliative care encompasses much more than just end-of-life or hospice care. Instead, palliative care is
34 an essential component of serious illness care, much further upstream from the terminal phase.
35 Therefore, palliative care should be viewed as a necessary component of care for patients with cancer
36 from the time of diagnosis. Palliative care begins at diagnosis and increases in “dosage” or focus as
37 needed throughout the continuum of illness. There is evidence from randomised control trials in the
38 USA of the benefits of early integration of palliative care into clinical care¹⁶ but this was not replicated in
39 Europe¹⁷.

54
55 ¹⁵ McIlfratrick S, Hasson F, McLaughlin D, Johnston G, Roulston A, Rutherford L, Noble H, Kelly S, Craig A, Kernohan WG.
56 Public awareness and attitudes toward palliative care in Northern Ireland. *BMC palliative care*. 2013 Dec;12(1):34.

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60 ¹⁷ Groenvold M, Petersen MA, Damkier A, Neergaard MA, Nielsen JB, Pedersen L, Sjøgren P, Strömberg AS, Vejlgård 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.



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5 1.1.4 Chronic lymphocytic leukemia

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

9
 10 CLL is a chronic leukemia, characterized by the clonal proliferation and accumulation of mature B-cells
 11 within the blood, bone marrow, lymph nodes, and spleen. CLL cells co-express the B-cell surface
 12 antigens CD19, CD20, CD23 and immunoglobulin as well as the T-cell antigen CD5^{21,22}. However, the
 13 expression of surface immunoglobulin, CD20, and CD79b are characteristically low compared to normal
 14 B cells^{23,24}.

15
 16 The disease has a highly variable clinical course and ranges from patients who do not require therapy
 17 for many years, if at all, to others who require treatment soon after diagnosis²⁵.

18
 19 In routine clinical practice, newly diagnosed low-risk patients with asymptomatic early-stage disease
 20 (Rai 0, Binet A^{26,27}; Table 1), should be monitored without therapy unless they have disease progression
 21 or symptomatic/active disease as defined by the International Workshop on CLL (iwCLL) guidelines²².
 22 Patients with active or symptomatic disease or with advanced Binet or Rai stages require therapy (iwCLL
 23 guidelines)²².

24
 25 In CLL many host- and tumor-related features with prognostic and/or predictive value have been
 26 identified over the years, assisting in the stratification of patients into subgroups with distinct clinical
 27 course and response to treatment. Amongst tumor-related biomarkers, those recommended by the
 28 iwCLL for predictive assessment prior to treatment initiation in both general practice and clinical trials
 29 pertain to the genomic background of the malignant clone, more particularly the TP53 gene that should
 30 be investigated for both deletions by Fluorescence in situ hybridization (FISH) and mutations by Sanger
 31 or Next-generation sequencing; and, the somatic hypermutation status (SHM) of the rearranged
 32 immunoglobulin heavy variable (IGHV) gene expressed by the clonotypic B cell receptor
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 46 ¹⁸ Hallek M. Chronic lymphocytic leukemia: 2015 Update on diagnosis, risk stratification, and treatment. *Am J Hematol*.
 2015;90(5):446-460.

47 ¹⁹ National Cancer Institute [Website]. Surveillance Epidemiology and End Results Cancer Statistics review. 2009. Available at:
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49 ²⁰ Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis,
 50 treatment and follow-up. *Ann Oncol*. 2015;26 Suppl 5:v78-84.

51 ²¹ Panovska A, Doubek M, Brychtova Y, Mayer J. Chronic lymphocytic leukemia and focusing on epidemiology and management
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56 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*.
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57 ²⁴ Moreau EJ, Matutes E, A'Hern RP, et al. Improvement of the chronic lymphocytic leukemia scoring system with the monoclonal
 58 antibody SN8 (CD79b). *Am J Clin Pathol*. 1997;108(4):378-382.

59 ²⁵ Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leukaemia. *Nature reviews. Disease primers*. 2017;3:16096.

60 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.



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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 CLL³³.

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 CLL²². 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.

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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.



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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 years³⁵. The annual incidence is approximately 4 cases per 100,000 people (reaching 40–50 per 100,000 after age 70 years)³⁵, with male predominance³⁶. 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 exertion³⁷. Fatigue is by far the most common symptom endorsed by patients and is not necessarily related to degree of anemia³⁸. 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 diagnosis³⁷. Many MDS patients also have immune disorders, including polyarthritis³⁷.

The diagnosis of MDS is generally suspected based on the presence of an abnormal complete blood cell count³⁴ 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 diagnosis³⁴. 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^{34,39}.

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 making⁴⁰. The most prevalent prognostic model in clinical use is the IPSS⁴¹ (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^{34,39}. 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.



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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^{34,39}.

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 $100 \times 10^9/L$; haemoglobin 100 g/L; absolute neutrophil count $1.8 \times 10^9/L$.

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 ($\times 10^9/L$)	≥100	50 to <100	<50
Absolute neutrophil count ($\times 10^9/L$)	≥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 illness⁴³.

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 initiation⁴⁸.

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 general⁴⁹, 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, Moynour 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.



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5 CLL-specific characteristics, comorbid conditions, and degree of fatigue all appear to have important
6 impact on the QOL of patients with CLL, with particular relevance on emotional QOL⁵⁰ Research
7 identifying effective interventions for patients with CLL is necessary to address this need.
8

9 **1.2.2 Myelodysplastic syndrome**

10 Patient-reported outcomes (PROs) have attracted much attention as a tool to gain more insight in the
11 burden of malignancy in patients' lives. By collecting data on quality of life, symptoms and the sense of
12 well-being, everyday functioning, disease and therapy perception, toxicities and adverse events as well
13 as patient evaluation of health care PROs can provide essential information to properly capture the
14 patient's condition⁴².
15

16 Cancer patients carry a substantial physical and psychosocial disease burden and are often obliged to
17 cope with disease and/ or treatment consequences which occur outside the hospital⁵¹. Yet there is an
18 increasing body of evidence suggesting that these consequences may go unnoticed by clinicians and
19 therefore not properly treated⁵². Recent studies have shown that routine follow-up of patients via PRO
20 monitoring can fill the gap in the patient-clinician communication, improve physician's awareness of
21 symptoms and result in better symptom management⁵³. Eventually this may exert a positive impact on
22 the quality of life and overall survival of patients with cancer⁵⁴.
23

24 As regards to MDS patients, they may suffer from a wide variety of symptoms, including fatigue, anxiety,
25 insomnia and dyspnea^{55,56}, which result in impaired quality of life⁵⁷. Notably, a study in which patients
26 with acute myeloid leukemia or advanced MDS were included has demonstrated that QOL is most
27 important to patients than the length of survival per se⁵⁸. Interestingly, hypomethylating agents, which
28 are mostly used in advanced MDS have been shown to improve QOL^{53,59}. Assessment of QOL as a
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42 ⁵⁰ Shanafelt TD, Bowen D, Venkat C, Slager SL, Zent CS, Kay NE, Reinalda M, Sloan JA, Call TG. Quality of life in chronic
43 lymphocytic leukemia: an international survey of 1482 patients. *Br J Haematol*. 2007;139(2):255-64.

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

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

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

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

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

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

60 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.



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relevant PRO⁶⁰⁶¹ has also showed that its impairment predicts an unfavorable clinical outcome^{62,63,64} and that it constitutes a parameter of response evaluation⁶⁵. Furthermore, apart from QOL, a recent report has also demonstrated that self-reported fatigue has prognostic value beyond standard MDS risk stratification systems⁶⁵.

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-C30² General Questionnaire and EQ-5D³.

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, Gerhing 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.



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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
-----	--------------



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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.

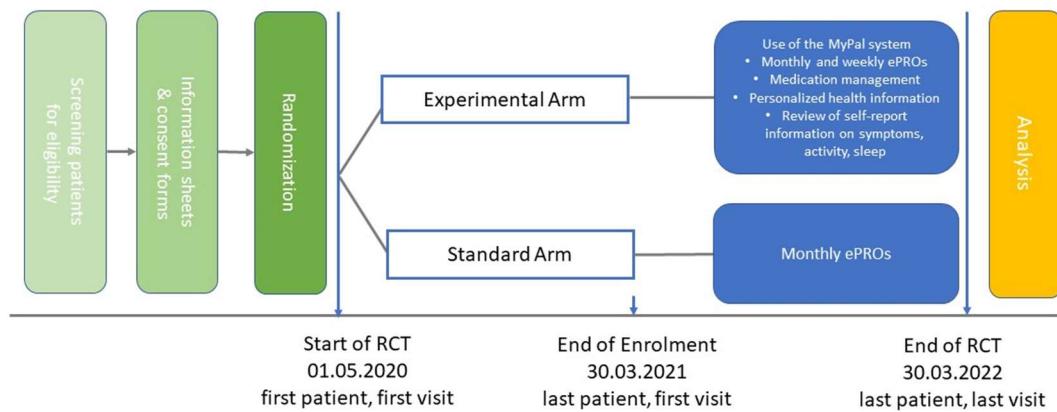


Figure 1. Schematic representation of the study design

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



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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.



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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



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5 respondent's pain on the day. The questionnaire is then composed of pain drawing diagrams,
6 four items about pain intensity (worst pain, least pain, average pain, pain right now), two items on
7 pain relief treatment or medication, and one item on pain interference, with seven sub-items
8 (general activity, mood, walking ability, normal walk, relations with other people, sleep, and
9 enjoyment of life).
10

- 11 3) The Emotional Thermometers, a tool for simple rapid detection of emotional issues through visual
12 analogue scales for four domains (distress, anxiety, depression, anger) as well as a need for help
13 domain. The tool constitutes a multidomain extension and adaptation of the American Distress
14 Thermometer adopted by the National Comprehensive Cancer Network and has been developed
15 for the assessment of psychological complications of cancer.
16

17 Patients in the experimental arm will also be able to report symptoms spontaneously through the MyPal
18 system. Apart from symptom reporting, which is an essential component of the MyPal intervention,
19 patients will be able to use the MyPal system to better manage their medication intake by registering
20 medication reminders. They will also be able to perform personalized searches in a repository developed
21 by medical experts and thus have access to valid medical information specific to their condition.
22 Furthermore, patients can review their own information such as physical or emotional symptoms
23 overtime, should they choose to do. Finally, at the start of the trial patients will be equipped with a fit-bit
24 watch which will allow monitoring of their physical activity and sleep quality. Information collected about
25 the patients through the MyPal system such as physical and psycho-emotional symptoms, physical
26 activity, sleep quality etc. will be monitored and periodically reviewed (every 72 hours maximum) by the
27 health-care professionals (HCPs). Appropriate actions will be taken according to the HCP's judgement
28 and medical expertise. These actions will be recorded by the HCPs via the MyPal system i.e. referral
29 for diagnostics, prescription of medication etc.
30
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32 As the MyPal eHealth system constitutes a complex intervention comprising of a number of individual
33 elements, the fidelity of the intervention implementation will be evaluated by collecting the following
34 information on the web interface (to be completed by the HCPs accessing the system):
35

- 36 - Symptom/questionnaire review by HCPs (audit trail)
- 37 - Action taken (yes vs no)
- 38

39 And competing and integrating them with the information reported in the clinical records.
40

41 **4 ELIGIBILITY**

42 **4.1 Inclusion Criteria**

- 43 1. Adults (≥ 18 years)
- 44 2. Diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or
45 myelodysplastic syndrome (MDS)
- 46 3. Scheduled to receive any line of treatment for CLL/SLL or MDS or who have been previously
47 exposed to any treatment for CLL or MDS
- 48 4. Able to understand and communicate in the respective language
- 49 5. Users of an Internet connected device (smartphone/tablet)
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56 **4.2 Exclusion Criteria**

- 57 1. Patients who are already participating in another interventional study
- 58 2. Patients needing immediate referral for specialized palliative care
- 59
- 60



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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.

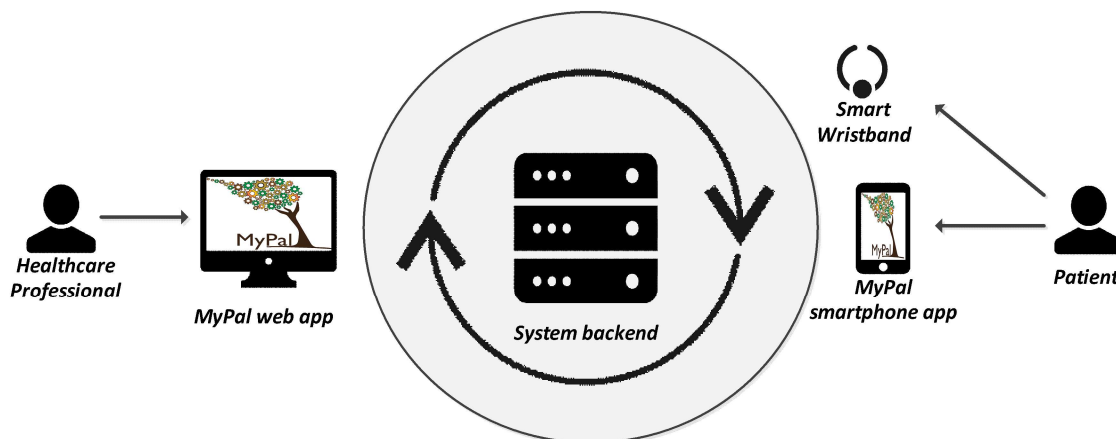


Figure 2. Software and hardware modules of the MyPal eHealth system

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:



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- **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.

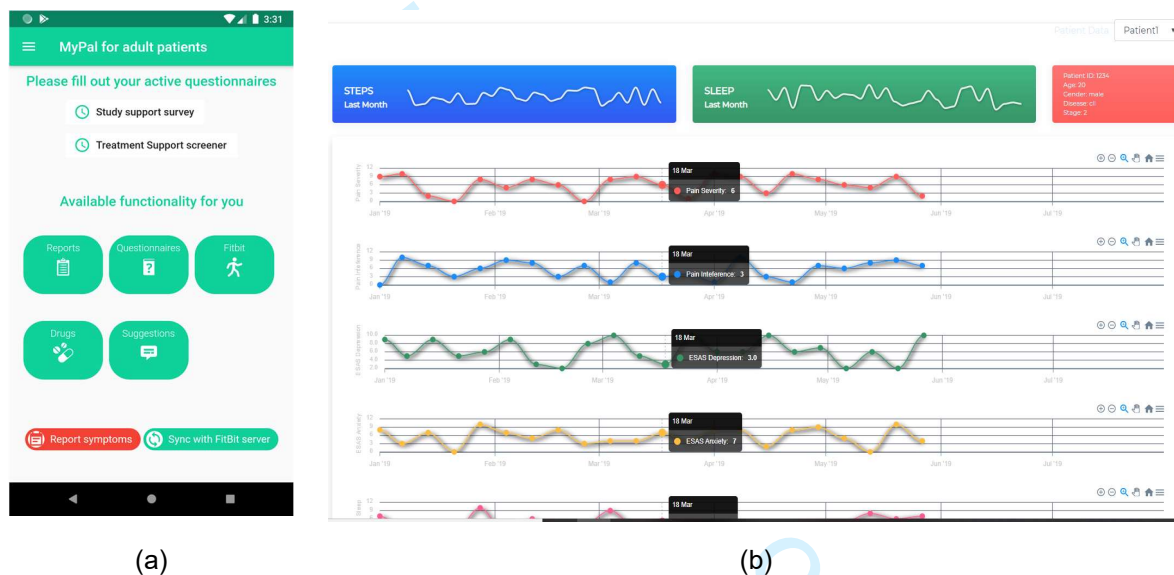


Figure 3. Sample graphical user interfaces of the MyPal eHealth system: (a) Screen of the MyPal smartphone app; (b) Page of the MyPal web app.





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.

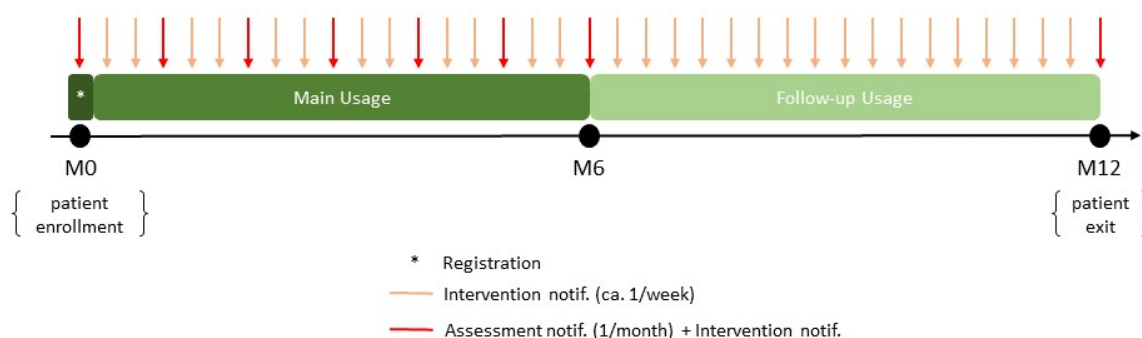


Figure 5. The 3 phases of the usage of the MyPal smartphone app by the patient.

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,



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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.

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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'.



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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

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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.



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5.2 Patient Completion & Withdrawal

6 Data collection will be considered complete for a participating patient if data available at 12 months after
7 enrolment have been recorded. For deceased and untraceable patients included in the study, the patient
8 will be censored at last observation.
9

10 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

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

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

28 Although no safety issues are foreseen, the PI will promptly notify all concerned investigators, the Ethics
29 Committee(s) and the regulatory authorities of possible findings that could affect adversely the safety of
30 patients, impact the conduct of the study, increase the risk of participation or otherwise alter the IEC's
31 approval to continue the trial.
32

33 In the occurrence of such an event the PI and the investigators will take appropriate urgent safety
34 measures to protect the patients against any immediate hazard. The local investigator will inform the
35 patients and local ethics or review committees according to hospital policy. The sponsor will inform any
36 other parties that are involved in the trial.
37
38

Safety reports

39 The PI will submit a first safety report to the IEC/IRB one year after the first approval date of the trial
40 and a second safety report one year after the last patient has completed protocol intervention.
41
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6.1.1 Adverse Events

44 An adverse event is any untoward medical occurrence that does not necessarily have a causal link to
45 the intervention studied.
46
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48

6.1.2 Serious Adverse Events

49 A serious adverse event (SAE) is any adverse event that: results in death, is life threatening, requires
50 hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or
51 incapacity, consists of a congenital anomaly or birth defect or anything else the Data Safety Monitoring
52 Board (DSMB) feels is significant. Given the nature of the intervention and the study population not all
53 of the SAE categories will be relevant to the MyPAL Adult study. In non-drug trials, SAEs that are
54 deemed to be related to the research procedure and are unexpected (referred to as SUSARs in drug
55 trials) are also recorded and reported.
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57

58 However, in MyPal Adult, it is difficult to predefine the serious risks of the MyPal eHealth system
59 intervention and to define the early stopping rules. The study population consists of individuals facing
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5 life threatening illness. We would not expect it to be an unusual occurrence for patients to be admitted
6 to hospital while taking part in the study.

7 We expect that the most likely serious risk of participating in the MyPal intervention is (serious) distress.
8 It should be noted however that symptom reporting is considered to be part of routine care, and as such,
9 we expect the risks to be limited. Filling in questionnaires about physical and psychological symptoms,
10 and quality of life may also be upsetting for patients. However, we expect the risk to be limited as these
11 are validated questionnaires that address issues that are discussed in usual care.
12
13

14 Definition of Serious Distress

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

17 Severe unresolved distress (e.g. unable to be comforted), self-reported self-harm or suicidal thoughts
18 or intent will be reported as SAEs in this study. An event that results in death, is life threatening or
19 requires hospitalization or prolongation of existing hospitalization associated with serious distress will
20 also be reported as an SAE. The DSMB will review all SAEs submitted and make recommendations
21 accordingly. MyPal Adult study partners and the DSMB take the possible occurrence of serious distress
22 due to participation in the trial very seriously.
23

24 No specific pregnancy reporting is required considering the nature of the study.
25
26

27 **6.2 Reporting Procedure**

28 **6.2.1 Adverse Events**

29 All adverse events will be systematically recorded in the CRF and the patient's source records,
30 regardless of seriousness or causality.
31

32 **6.2.2 Serious Adverse Events**

33 Hospital Site Responsibilities

34 Physicians and nurses in the trial hospitals must report serious negative reactions of patients who
35 participate in the study, using a predefined SAE form. The SAE form must be completed by the health
36 care professional with delegated responsibility and signed by the Principal Investigator* or delegated
37 medically qualified individual within 24 hours of becoming aware of the SAE. The form will then be
38 immediately sent to the (insert country) Chief Investigator* The initial form can be sent without the PI or
39 a delegated medically qualified individual's signature if the obtaining of a signature may cause delay in
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5 reporting. In this case, the form needs to be re-sent as soon as possible once it has been signed by the
6 PI or a delegated medically qualified individual.
7

8 The Principal Investigator or a delegated medically qualified individual will assess and document on the
9 SAE form whether they think the SAE is related to the intervention or not.
10

11 Follow up information regarding the SAE will be requested from the hospital research sites as necessary
12 to meet the requirements of the Chief Investigator and the DSMB. This will be submitted on the SAE
13 form.
14

15 All information sent from the hospital sites to the Chief Investigator must only contain the participant's
16 study number and date of birth. No personal identifiable information must be sent.
17

18 Chief Investigator Responsibilities

19 The Chief Investigator will review the SAE form, obtain further information from the study site as
20 necessary and liaise with the DSMB via the MyPal Adult study coordinating centre.
21

22 If the DSMB decides the SAE is related to the intervention and unexpected, the Chief Investigator will
23 report it to the Research Ethics Committee within 15 days as per (insert country) guidelines.
24

25 If the event is deemed unrelated to the trial intervention, no further safety reporting is required regardless
26 of the outcome. The Chief Investigator will inform the Principal Investigator of the DSMB decision in
27 writing.
28

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

39 The DSMB will evaluate the reported events, taking into account differences between intervention and
40 control hospitals. Based on this, the DSMB will recommend to continue, to modify or to stop the MyPal-
41 Adult RCT.
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45 **7 DATA HANDLING AND RECORD KEEPING**

46 *Case Report Forms*

47 Data will be collected on Case Report Forms (CRF) to document eligibility, safety and efficacy
48 parameters, compliance to intervention schedules and parameters necessary to evaluate the study
49 endpoints. Data collected on the CRF are derived from the protocol and will include at least:
50

- 51 1. Inclusion and exclusion criteria;
- 52 2. Baseline status of patient including medical history and stage of disease;
- 53 3. Timing of intervention;
- 54 4. Baseline concomitant diseases and adverse events;
- 55 5. Parameters for response evaluation;
- 56 6. Any other parameters necessary to evaluate the study endpoints;
- 57 7. Hospital visits, doctor visits, hospitalizations
- 58 8. Medications, treatments
- 59 9. Investigations (laboratory and imaging)
- 60



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

7 Each CRF page will be identified by a trial number, and a combination of patient study number (assigned
8 at registration) and hospital name.
9

10 The CRF will be completed on site by the local investigator or sub-investigator or an authorized staff
11 member. The CRF must be signed by the local investigator or sub-investigator upon completion. All
12 CRF entries must be based on source.
13
14

15 **Data Handling and Record keeping of data and documents**

16 The MyPal Adult clinical trial and its participants will conform to relevant national and EU legislation on
17 the protection of individuals with regard to the processing of personal data and on the free movement
18 of such data. All data (paper and electronic) will be treated as confidential. They will be stored securely
19 and they will be anonymised (where possible). Hard copy patient data will be stored in a secure place
20 (locked room, in a locked filing cabinet with limited access) and will be protected from the environment
21 (damp, mould and fire etc) or on a secure CERTH server.
22
23

24 Each clinical trial site will organise monitoring in the sense of examining whether data collection
25 processes and record keeping are executed properly locally (in study site files) and note all deviations
26 from standard operating procedures and study protocol requirements. In addition, the trial manager will
27 be responsible for oversight of trial documentation and record keeping.
28
29

30 *Archiving*

31 All of the studies essential¹ documents will be retained and archived for 10 years after completion of the
32 study. They will be stored securely and adequately protected from fire, flood, pest and extreme weather.
33 With respondents' permission, anonymised data collected during this study may be used for secondary
34 data analysis in future projects.
35
36
37

38 **8 REPORTING**

39 **8.1 Annual progress report**

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

41 The sponsor will submit a summary of the progress of the trial to the Ethic Committees once a year. The
42 first report is sent one year after the first approval date of the trial. The last report is sent one year after
43 the last patient has completed protocol treatment. Progress reports will include information regarding:
44
45

- 46 ▪ the date of inclusion of the first patient,
 - 47 ▪ numbers of patients included and numbers of patients that have completed the trial,
 - 48 ▪ screening failure and reasons for screening failure
 - 49 ▪ serious adverse events,
 - 50 ▪ any other issues and amendments.
- 51
52

53 **8.2 End of trial report**

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

56 In case the study is ended prematurely, the sponsor will notify the ECs and the competent authority
57 within 15 days, indicating the reasons for the premature termination.
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5 Within one year after the primary endpoint analysis of the trial, the sponsor will submit an end of study
6 report with the results of the study, including any publications/abstracts of the study, to the ECs and
7 the Competent Authority.
8

9 **9 QUALITY MANAGEMENT**

10 **9.1 Site Set-up and Initiation**

11 *Regulatory Documentation*

12 Regulatory and administrative documents will be provided by the PI (or delegated representative) and
13 require local Ethical Committee (EC) approval for each investigational site before enrolling the first
14 patient. The EC approval should be notified to the sponsor (or delegated representative). When all
15 requirements are met, each investigational site will be notified by the sponsor that enrolment started is
16 authorized.
17

18 *Registration*

19 Eligible patients should be registered before start of intervention.

20 All eligibility criteria will be checked with a checklist.

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

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

25 Data collected on the CRF will be verified for accuracy. If necessary, queries will be sent to the
26 investigational site to clarify the data on the CRF. The investigator should answer data queries within
27 the specified timeline.
28

29 **9.2 Audit and Inspection**

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

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

34 Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the
35 results of this study. The investigator should immediately notify the sponsor if they have been contacted
36 by a regulatory agency concerning an upcoming inspection.
37

38 **10 END OF TRIAL DEFINITION**

39 The end of the study will be the last data collection time point within the study for the last participating
40 patient.
41

42 **11 STATISTICAL CONSIDERATIONS**

43 **11.1 Sample Size**

44 Assuming relatively acceptable values for the attrition rate (i.e., 20%) and the missing data (i.e., 30%),
45 the sample size analysis concluded that 300 recruited patients providing one measure at enrolment
46 (baseline) and 7 repeated measures (at Months 1, 2, 3, 4, 5, 6 and 12) are sufficient for the power of
47 the intended statistical testing to be over 90% in all cases, given (a) a 0.05 significance level, and (b) an
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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*Power⁶⁷ 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 3, 4, 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 $\alpha=0.05$, in accordance with the power calculation. We will also perform

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



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

7 Patients will be followed for survival status until the end of the study. Overall survival (OS) will be
8 analyzed by Kaplan-Meier methodology using data from all enrolled patients. Median time survival will
9 be estimated and 0.95 confidence interval for the median time survival will be presented.
10

11 **11.3 Planned Sub Group Analyses**

12 Subgroup analysis of the outcome measures will also be performed at baseline, Month 6 and Month 12
13 of the study using one-, two- and three-way ANOVA in order to detect potential differences between
14 specific groups of participants. The grouping variables that will be employed are (a) the clinical center
15 (origin), (b) the country of residence, (c) the age group, (d) the disease stage, and (e) the diagnosis
16 (CLL, MDS). The level of significance for all statistical tests is set to $\alpha=0.05$, in accordance with the
17 power calculations. In the case an interaction effect is observed, separate subgroup analyses in the CLL
18 and MDS cohorts with repeated measures ANOVA will be performed to assess the effect of intervention
19 on quality of life and other the outcome measures.
20
21
22

23 **11.4 Planned Interim Analysis**

24 Since the present trial does not concern primary treatment (as it is the case for example for a
25 pharmacological trial), no substantial risks for the life and health of the study subjects are expected as
26 a result of the intervention or lack thereof. For this reason, interim statistics analysis of the results is not
27 needed and it will not be performed. Instead, the data monitoring committee will be responsible for
28 verifying the quality and completeness of the collected assessment data, using data science rather than
29 statistical methods. Every 3 months the data monitoring committee will be performing automated checks
30 via developed programming scripts for missing data based on predefined metrics that will assess the
31 extent of missing/incomplete data across several dimensions (percentage of missing data per study
32 participant, per assessment instrument, per assessment instrument component, per assessment
33 iteration, etc.)
34
35
36

37 **11.5 Planned Final Analyses**

38 The final analysis will take place after the end of the study (i.e., 30.03.2022) and it will be performed as
39 described in Analysis of Outcome Measures and the Planned Subgroup Analysis sections above. On
40 top of that, repeated measures multivariate ANOVA (MANOVA) will be applied with the quality of life
41 assessed by outcome measure 1 and 2 serving as the pair of dependent variables. The level of
42 significance for all statistical tests is set to $\alpha=0.05$, in accordance with the power calculations.
43
44
45

46 **12 TRIAL ORGANIZATIONAL STRUCTURE**

47 **12.1 Sponsor**

48 CERTH (partner 1, Greece) will be the Sponsor of the clinical trial, while the collaborating clinical sites
49 are the following:

50 Collaborators

51 CERTH (partner 1, Greece; through the affiliated G. Papanicolaou Hospital, Thessaloniki, Greece)

52 Karolinska Institutet (partner 6, Sweden)

53 Università Vita-Salute San Raffaele (partner 7, Italy)

54 University Hospital of Crete (partner 8, Greece)

55 University Hospital Brno (partner 10, Czech Republic)
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5 **12.2 Coordinating Centre**

6 The coordinating Centre will be Università Vita-Salute San Raffaele in Milan, Italy. It will be responsible
7 for overall data management, monitoring and communication among all sites, and general oversight of
8 the clinical trial conduct.
9

10 **12.3 Trial Management Committee**

11 The Trial Management Committee (TMC) will consist of a trial manager, the principal investigator and
12 representative investigators from each clinical site or/as well as other members of the trial team with
13 specific expertise i.e. Statistician, Health Economist, Database Programmer etc. Its main duty is to
14 manage the trial including clinical and practical aspects.
15

16 Specifically, to:

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

26 The TMC will virtually meet biweekly frequently during the set-up and start of the trial and quarterly until
27 the end of the trial.
28

29 **12.4 Data Monitoring Committee**

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

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

37 The DSMC will have access to unblinded data during the course of the trial and will monitor accumulating
38 data from the trial at pre-specified intervals. Any safety or ethical issues will be brought to the attention
39 of the investigators and the TSC. Meetings will be held every 6-12 months.
40

41 **12.5 Internal Ethics Committee**

42 It is the committee authorized by the Trial Management Committee to review documents (e.g. informed
43 consent) and tools (i.e. digital presentation of PROs), necessary for the conduct of the clinical trial. More
44 specifically, it is meant to safeguard the rights, safety, dignity and well-being of research participants. It
45 consists of three members, namely a chair expert in bioethics and two oncologists/ hematologists.
46

47 **12.6 Finance**

48 No individual per patient payment will be made to healthcare providers, Investigators or patients.
49
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2 3 4 5 **13 ETHICAL CONSIDERATIONS**

6
7 The protection of the autonomy of research participants with respect to their privacy, beneficence and
8 dignity is of paramount concern and an internal Ethics Committee will monitor this aspect of the trial
9 implementation in collaboration with the local investigator. Thus, the study will be conducted in
10 accordance with the ethical principles of the Declaration of Helsinki, the ICH-GCP Guidelines, the
11 General Data Protection Regulation (GDPR)⁶⁸, the EU Clinical Trial Directive (2001/20/EC)⁶⁹, the EU
12 Clinical Trials Regulation (EU No 536/2014)⁷⁰ and applicable regulatory requirements. The local
13 investigator is responsible for the proper conduct of the study at the study site.

14 15 **13.1 Scientific Advice / Protocol Assistance**

16
17 The following activities have been planned in the context of regulatory scientific advice or protocol
18 assistance:

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

25 26 27 **13.2 Screening**

28
29 MyPal will use a carefully-crafted, multicomponent, evidenced-based recruitment protocol fusing
30 evidence-based strategies with principles of “social marketing,” an approach involving the systematic
31 application of marketing techniques⁷¹. Main components will include (1) an inclusive triage algorithm,
32 (2) information booklets targeting particular stakeholders, (3) a specialized recruitment nurse, and (4)
33 standardization of wording across all study communications. Another key feature of our strategy pertains
34 to broad eligibility criteria within the selected hematologic cancers. The difficulties that may be
35 encountered in this study relate to the inherent problems being associated with palliative care research⁷².
36 To overcome these difficulties, the study will be multi-center in nature, involving centers of excellence
37 in the respective disease areas as well as expertise in the various aspects of such studies including
38 those related to ethics.

39 40 41 **13.3 Informed Consent**

42
43 Written informed consent of patients is required before enrolment in the trial and before any study related
44 procedures, and only after information has been provided to them regarding the voluntary character of
45 participation, the purpose of the study, the procedures involved, the management of possible risks or
46 incidental findings as well as ways to deal the safeguards for the protection of the participant’s personal
47 data and privacy and the right to withdraw at any time for the study. Before informed consent may be
48 obtained, the investigator should provide the patient time and opportunity to inquire about details of the
49 trial and to decide whether or not to participate in the trial. A copy of the informed consent form will be
50 given to the subject and the original will be kept at site. An entry must also be made in the subject's
51 dated source documents to confirm that informed consent was indeed obtained prior to any study-related
52 procedures and that the subject received a signed copy.

53
54
55
56 ⁶⁸ <https://www.eugdpr.org>

57 ⁶⁹ https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

58 ⁷⁰ https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

59 ⁷¹ LeBlanc TW, Lodato JE, Currow DC, Abernethy AP. Overcoming recruitment challenges in palliative care clinical trials.
60 *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.



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

7 Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the informed
8 consent and all other forms of subject information related to the study (e.g., advertisements used to
9 recruit subjects) and any other necessary documents be reviewed by an independent Research Ethics
10 Committee (REC). The REC will review the ethical, scientific and medical appropriateness of the study
11 before it is conducted and the approval will be obtained prior to the initiation of the study in each study
12 site. Any amendments to the protocol including substantially revised informed consent forms and
13 information sheets will require new REC approval and approval by Regulatory Authority(ies), if required
14 by local regulations, prior to implementation of any changes made to the study design. Consequently,
15 the patient should be informed in a timely manner if new information becomes available that might be
16 relevant to the patient's willingness to continue participation in the trial. The communication of this
17 information should be documented.
18

19 The investigator will be required to submit, maintain and archive study essential documents according
20 to International Conference on Harmonization (ICH) GCP.
21
22

23 **13.4 Withdrawal of Informed Consent**

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

- 26 • The patient can refuse further participation and/or procedures according to protocol, while still
27 consenting with further follow up data collection.
- 28 • The patient can refuse further participation and/or procedures according to protocol, and
29 withdraw consent for further follow up data collection.
- 30 • The patient can refuse further participation and/or procedures according to protocol, withdraw
31 consent for further follow up data collection and withdraw consent to use any data in the study.
32
33
34

35 **14 CONFIDENTIALITY AND DATA PROTECTION**

36 **14.1 Patient Confidentiality**

37 Each patient is assigned a unique patient study number at enrolment. In trial documents the patient's
38 identity is coded by patient study number as assigned at enrolment. The data will be collected, stored
39 and accessed in a way that will ensure privacy of participants and compliance with data protection
40 legislation, in particular regulation 679/2016.
41

42 The local investigator will keep a subject enrolment and identification log that contains the key to the
43 code, i.e. a record of the personal identification data linked to each patient study number. This record is
44 filed at the investigational site and should only be accessed by the investigator and the supporting
45 hospital staff, and by representatives of the sponsor or a regulatory agency for the purpose of monitoring
46 visits or audits and inspections
47
48
49

50 **14.2 Filing of Essential Documents**

51 Essential Documents are defined as those documents that are needed to evaluate the conduct of a trial
52 and the quality of the data produced. The essential documents may be subject to, and should be
53 available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).
54

55 The investigator should file all essential documents relevant to the conduct of the trial on site. Essential
56 documents should be protected from accidental loss and should be easily retrieved for review.
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58
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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.

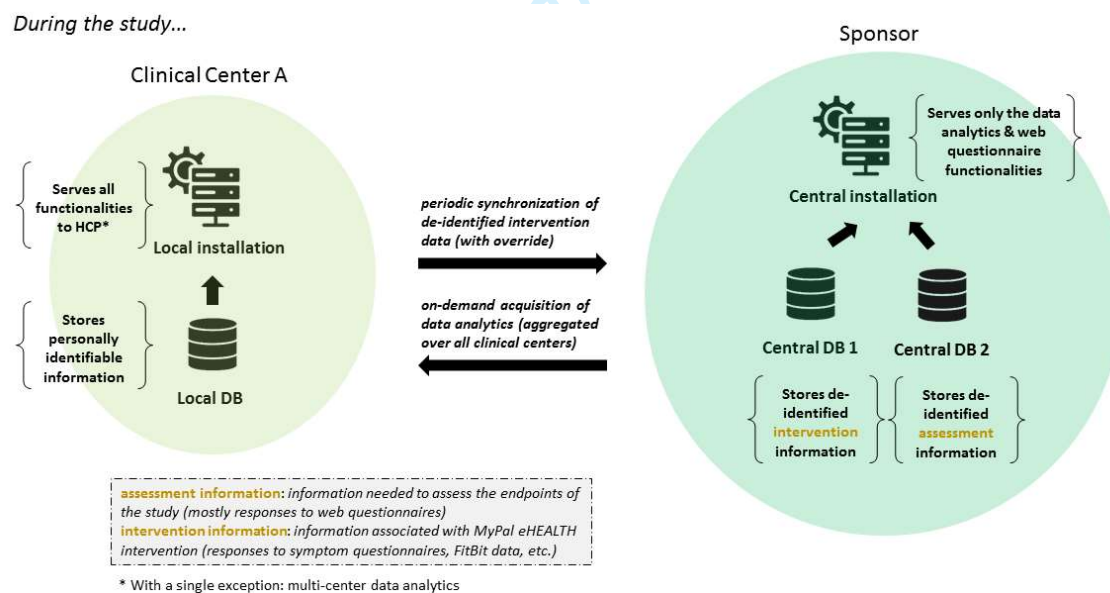


Figure 5. MyPal platform deployment

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,



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5 phone number, etc.) and clinical information (gender, disease stage/risk, treatment scheme, expected
6 outcome, functional impairment, etc.) is also stored in the local database. Concerning the clinical
7 information, the (a) age and (b) diagnosis of the study subject are categorized before storage.
8

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

- 11 (1) The provision of data analytics that pertain to the entire, multi-center group of study participants.
12 The functionality at hand aggregates de-identified intervention data coming from all the
13 participating clinical centers. At a predefined period (e.g., once per week), the local intervention
14 data are de-identified and subsequently synchronized with the central installation, where they
15 are stored in the 1st central database overwriting the previous data. De-identification is
16 performed by removing all the personal data and keeping among the clinical data only the
17 categorized age and diagnosis information. The provenance of the data (i.e., the clinical center
18 the data come from) is also retained. At the same time, the responsible modules of the central
19 installation calculate the study-wide aggregated data analytics and expose them to the local
20 installations, which consume them on demand.
21
22 (2) The hosting of the web-based questionnaires that are associated with the endpoints of the
23 study. The responses of the study subjects to these questionnaires constitute the core of the
24 assessment data of the MyPal platform. The latter are stored in the 2nd central database in a
25 completely de-identified manner. The assessment data of each study subject are accompanied
26 only by following pieces of information: provenance, categorized age, and categorized
27 diagnosis, which are intended for subgroup analysis and are already available to the central
28 installation for the purposes of the data analytics functionality.
29
30

31 **15 INSURANCE AND INDEMNITY**

32
33 Prior to the start of the trial, the Sponsor is responsible to ensure that adequate insurance for patients
34 participating to the trial is subscribed, in accordance with applicable laws and regulations. Proof of
35 insurance will be submitted to the Ethics Committee.
36
37

38 **16 PUBLICATION POLICY**

39 Results of the study will be owned by the Investigators. IPR management will be considered and
40 addressed within a dedicated IP Agreement, drafted and agreed as part of the Agreement prior to
41 commencing the study.
42

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

8 **Information Sheet for Adult Patients**

11 **MyPal: Fostering Palliative Care of Adults and Children with Cancer through Advanced Patient 12 Reported Outcome Systems**

15 We would like to invite you to participate in a study conducted by Dr and his/her team at the
16 University of Before you decide to take part in this study it is important that you understand why
17 it is being done and what it will involve. Please take time to read the following information carefully and
18 to decide whether or not you wish to take part.
19

21 **Aims of the study:** In this study (which is part of a larger project that will be conducted across four
22 European countries), we are interested in exploring the use of digital technology that will empower you
23 (and possibly members of your family) to communicate your condition more accurately and effectively
24 to your healthcare providers (i.e. oncologists, specialized physicians, psychologists, nurses). The aim is
25 to improve the quality of care by using modern methods of individualized information, communication
26 and support for patients with cancer and by promoting what we call a patient-centered approach through
27 the use of Patient Reported Outcome platforms. It is important for you to know that MyPal is not an alert
28 system and that doctors may not respond immediately as the study does not aim to provide or change
29 medical treatment. Supportive information provided by healthcare providers via the application (e.g. a
30 search engine for medication) does not imply legal liability.
31
32

34 **Why you have been chosen:** You have been chosen to participate in this study because you are over
35 18 years of age and because you have been diagnosed with chronic lymphocytic leukemia (CLL) or
36 myelodysplastic syndrome (MDS). Also, because you are fit to participate in the study and you are able
37 to use an Internet connected device. The feedback you provide will help us to adapt and improve the
38 acceptability and the performance of the various tools.
39

41 **What do you have to do:** If you volunteer to help us accomplish these aims, you will be randomly
42 assigned either to the intervention group which will use the MyPal system, or to the control group which
43 will receive the palliative care services normally provided. The study is a non-pharmacological ICTbased
44 (Information and Communications Technology) intervention and as such it does NOT involve collection
45 of biological samples or administration of any medication.
46
47

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

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

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

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

- 55 a) 4 self-report questionnaires at baseline, and then every month for the six following months,
56 b) the same 4 self-report questionnaires as a follow up at the end of the study, at the clinical site of the
57 research
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5 These 4 questionnaires are: two QOL questionnaires (the EORTC QoL and the Euroqol), the EORTC
6 satisfaction with cancer care questionnaire and the Integrated Palliative Care Outcome Scale.
7

8
9 Depending on the group on which you participate you may additionally have to respond to the Brief Pain
10 Inventory the Edmonton Symptom Assessment Scale and the Emotional Thermometers) in order to
11 evaluate your symptoms, the degree of your pain, your anxiety, the quality of your life during different
12 days or the satisfaction you get from your treatment. Your responses will provide the kind of information
13 that will enable the design and development of flexible tools responding to your different needs and
14 views.
15

16 If needed, a member of the research team will be available to help you complete the questionnaires.
17

18 **Will your taking part in this project be kept confidential?** Data protection is one of our most important
19 concerns in this study. National laws on personal data protection will be implemented in order to
20 guarantee the highest standards of personal data management. All procedures for protecting personal
21 information in this study are in accordance with the approved rules of the University of XXXXXXXX and
22 with the European legislation and the General Data Protection Regulation 2016/679. Only data that is
23 necessary for this research will be collected. Our technology partners will provide technical support and
24 tools regarding data security in order to mitigate data security risks. Any information that is obtained in
25 connection with this study and that can be identified with you will remain confidential. A computer
26 generated number, will be assigned to you at enrolment and your data will be pseudonymised. This
27 means that your name and other direct identifiers will be separated from the collected research data so
28 that your identity is protected and links to your identity will not be possible.
29

30
31 If you agree to take part in the study, we will use your data in the way needed to conduct the research
32 and analyze the research results. Your rights to access, change or move your information are limited,
33 as we need to manage your information in specific ways in order for the study to be reliable and accurate.
34

35 Data will be collected through a number of different tools: some of these have been already developed,
36 and some are new in this study. The data collected from the fit-bit wristwatch are stored on the FitBit
37 server and are retrieved from it by the MyPal app once per day to be stored in the My Pal server,
38 according to all data protection safeguards applying in this project. All medical data pertaining to your
39 care and treatment obtained during the project will be kept for 15 years in (name of the clinical site)
40 where they were collected or created. The data, however, that has been collected for the purposes of
41 the study, will be kept at the central installation of the sponsor of the study, CERTH, after having been
42 de-identified. De-identification is performed by removing all the personal data and keeping only the
43 categorized age, diagnosis information and the clinical centre where the data came from. This central
44 installation fulfills all technical and organizational requirements for the safety and the security of the
45 stored data. In case you have concerns or queries or you feel should lodge a complaint with Data
46 protection authorities, you can contact the Data Protection Officer of our Research Institution: Name of
47 the DPO, ... e-mail: ...
48
49

50
51 **Do you have to participate?** Participation is absolutely voluntary. If you decide to participate, you are
52 free to withdraw at any time without giving any reason and without there being any negative
53 consequences. Your decision whether or not to participate will not affect your relationship with the
54 researchers or with the team managing your care. With regard to the various questionnaires involved,
55 you can choose not to answer any particular question or questions. You can freely decide to withdraw
56 from the study once data collection has commenced, without giving a reason for withdrawal. Data
57 collected cannot be erased, but is anonymized and will be retained and included in the study in an
58 anonymized form. But no further data will be collected from you after your withdrawal. Once the research
59
60



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5 is complete, and the data analyzed, it is not possible to withdraw your data from the study. The whole
6 duration of the study will be 12 months.
7

8
9 **Are there possible disadvantages and/or risks in taking part?** The nature of this study means that
10 your participation does not entail any risk of physical discomfort, pain, injury, illness or disease. We do
11 not envisage any adverse or incidental findings, as these usually refer to medical problems discovered
12 in the course of a different type of research/clinical trial. However, if we come across an unexpected
13 finding, what we plan to do is to inform you, to discuss this in our team, and to consult with your treating
14 physician. If you have any concerns you are free to contact the Principal Investigator (see below for
15 details) and once again, we would like to remind you that your participation is entirely voluntary.
16

17
18 **What are the possible benefits of taking part?** You may not receive any personal benefits from
19 participating in this research. However, you may find your participation is a positive experience through
20 the use of the various tools and applications as well as contributing to the improvement of the role of
21 patients like yourself in the process of their treatment.
22

23
24 **Transfer of data:** data collected during the My Pal project will be shared among the collaborating
25 research teams but will never be transferred to countries outside of the European Union.
26

27
28 **What will happen to the results of the study?** The results will be used only for research purposes;
29 they may be reported in research publications and may be made available to other researchers in an
30 anonymized form. In every research output (papers, presentations, articles, reports) the total anonymity
31 of your data will be protected.
32

33
34 **Ethical approval:** This study has been approved by the Research Ethics Committee of the University
35 of....
36

37
38 **Contact for further information:** please do not hesitate to contact the Principal Investigator, Dr
39email.....

40 Tel: +XX(..) ... at any moment with questions or concerns about the study.
41
42
43
44
45
46
47

48 **Informed Consent Form for Adult Patients**

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

51 I understand that I will be randomly assigned to either:

- 52 • a group which will use the MyPal system, (called “the intervention group”) or to
- 53 • a group which will only receive usual palliative care if so desired (called the “control group”)

54
55
56
57 I consent:

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

59 to respond to the required burden of questionnaire completion and to complete
60



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- 5 a) 4 self-report questionnaires at baseline, and then every month for the six following months,
6 b) the same 4 self-report questionnaires as a follow up at the end of the study, in the site where the
7 study took place.

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

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

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

12 to respond to 3 questionnaires at baseline and every week until the end of the project - on physical
13 symptoms Brief Pain Inventory, Edmonton Symptom Assessment Scale and emotional symptoms the
14 Emotional Thermometers.
15
16
17

18 By ticking each box below I confirm that:

19 I am aware that NO biological samples will be collected.

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

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

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

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

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

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

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

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

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

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

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Name of Participant	Date	Signature
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Name of Researcher	Date	Signature

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THE MyPal Adult STUDY PROTOCOL: A RANDOMIZED CLINICAL TRIAL OF THE MyPal ePRO-BASED EARLY PALLIATIVE CARE SYSTEM IN ADULT PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

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1 **THE MyPal Adult STUDY PROTOCOL: A RANDOMIZED CLINICAL TRIAL OF THE MyPal**
2 **ePRO-BASED EARLY PALLIATIVE CARE SYSTEM IN ADULT PATIENTS WITH**
3 **HAEMATOLOGICAL MALIGNANCIES**

4
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1 Abstract

2 **Introduction:** The systematic collection of electronic patient-reported outcome (ePRO) in the
3 routine care of patients with chronic hematologic malignancies such as chronic lymphocytic
4 leukaemia (CLL) and myelodysplasia (MDS) can constitute a very ambitious but worthwhile
5 challenge. MyPal is a Horizon 2020 Research&Innovation Action aiming to meet this challenge
6 and foster palliative care for patients with CLL or MDS by leveraging ePRO systems to adapt
7 to the personal needs of patients and caregiver(s).

8 **Methods and analysis:** In this interventional randomized trial, 300 patients with CLL or MDS
9 will be recruited across Europe. Patients will be randomly allocated to early palliative care
10 using the MyPal system (n=150) versus standard care including general palliative care if
11 needed (n=150). Patients in the experimental arm will be given access to the MyPal Digital
12 Health Platform which consists of purposely-designed software available on smartphones
13 and/or tablets. The platform entails different functionalities including physical and psycho-
14 emotional symptom reporting via regular questionnaire completion, spontaneous self-
15 reporting, motivational messages, medication management, and a personalized search engine
16 for health information. Data on patients' activity (daily steps and sleep quality) will be
17 automatically collected via wearable devices.

18 **Ethics and dissemination:** The integration of ePROs via mobile applications has raised ethical
19 concerns regarding inclusion criteria, information provided to participants, free and voluntary
20 consent, and respect for their autonomy. These have been carefully addressed by a
21 multidisciplinary team. Data processing, dissemination and exploitation of the study findings
22 will take place in full compliance with EU data protection law. A participatory design was
23 adopted in the development of the digital platform involving focus groups and discussions
24 with patients to identify needs and preferences. The protocol was approved by the Ethics
25 Committees (EC) of San Raffaele (8/2020), Thessaloniki 'George Papanikolaou' Hospital (849),
26 Karolinska Institutet (20.10.2020), University General Hospital of Heraklion (07/15.4.2020)
27 and University of Brno (01-120220/EK).

28
29
30 Trial Registration Number: ClinicalTrials.gov: NCT04370457

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Strengths and limitations of this study

Strengths

- MyPAL Adults is a multicentre randomized interventional study in palliative care using an innovative approach based on ePRO-based systems to improve the quality of life of patients with chronic lymphocytic leukaemia (CLL) or myelodysplastic syndromes (MDS).
- This is an international study involving 5 clinical sites with longstanding expertise in the management of patients with CLL and MDS.
- MyPal system developers have interacted extensively with end-users from its initial development and will continue until its evaluation, thus putting down the basis for successful user engagement.

Limitations

- Considering the median age of diagnosis of about 70 years for both CLL and MDS, use of eHealth systems might be challenging, requiring comprehensive training and possibly leading to higher than expected attrition rate.
- COVID-19 pandemic has delayed study initiation and might require ad hoc adaptations to data collection processes during the study.

1 Introduction

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Chronic lymphocytic leukaemia (CLL) and myelodysplastic syndromes (MDS) are two of the most frequent haematological malignancies in the Western world usually occurring in older individuals (median age at diagnosis of around 70 years) [1,2]. These diseases, though generally chronic, are considerably heterogeneous in underlying biology, presentation and clinical course, ranging from relatively indolent to extremely aggressive. Recent scientific advances have revolutionized the therapeutic landscape through the introduction of novel therapies, resulting in improved outcomes, including increased overall survival [3]. That said, both CLL and MDS remain essentially incurable and current therapies aim at controlling the disease long-term. Due to this, open issues abound regarding the impact of CLL and MDS and their treatment 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, especially considering the likely association with other comorbidities due to advanced age [4].

Evidence suggests that patients with CLL have poorer QoL compared to the general population, being significantly bothered by physical symptoms (81% reporting fatigue and 56% sleep disturbances) at treatment initiation [5]. Similarly, patients with MDS may suffer from a wide variety of symptoms, including fatigue, anxiety, and insomnia, amongst others, which result in impaired QoL [6,7]. This is highly relevant in light of the recent therapeutic shift from fixed duration intravenous chemoimmunotherapy to continuous oral therapies for which patient compliance and treatment adherence are key to obtaining long-lasting disease control. Following this paradigm shift, palliative care, meant as the management of physical symptoms and psychosocial distress throughout the disease course, has come to play a key role.

Changes in the patients' experience across the illness trajectory can be captured and measured using patient-reported outcomes (PROs). PROs typically refer to the use of standardized, validated self-report questionnaires, and they could be considered the gold standard as far as subjective experiences are concerned [8,9]. PROs are typically employed as part of clinical trials, e.g. in order to support drug safety studies, and to this end, systematic reporting processes and specific terminologies are actively developed and investigated [10]. Furthermore, PROs have a major role in improving the quality of palliative care, like facilitating physician-patient communication and symptom management [11]. Their consideration along

1 with clinical and laboratory data within the palliative care clinical setting can help provide
2 patients with the most appropriate support [12]. Specifically, in palliative care throughout the
3 disease journey, PROs can: (i) monitor changes in the patients' health status; (ii) facilitate the
4 identification of unmet needs which could have been overlooked (psychological, social,
5 physical etc.); (iii) provide information on the evolution of disease and the impact of treatment
6 interventions; (iv) promote patient/physician interaction and communication; and (v) aid
7 clinical decision making [10,13].

8 The process of collecting PROs has progressed along technical advances, in particular through
9 the introduction of the eHealth paradigm, defined as the use of information and
10 communications technology in support of health [14]. eHealth interventions might target the
11 active capture of measurements from the patients themselves, as is the case with the
12 electronic implementation of PROs (ePROs). In fact, ePROs have been found to contribute to
13 improved health outcomes in cancer patients e.g. improvement in physical activity [15],
14 reduction in anxiety and drowsiness [16], lower levels of fatigue, nausea, insomnia [17] and
15 pain intensity as well as significant improvement in emotional and social functioning [18].

16 The systematic collection of ePRO information in routine CLL and MDS practice can constitute
17 a very ambitious but worthwhile challenge. MyPal is a Horizon 2020 (H2020) Research &
18 Innovation Action aiming to meet this challenge and foster palliative care for patients with CLL
19 and MDS by leveraging ePRO systems to adapt to the personal needs of the patient and
20 his/her caregiver(s). MyPal aspires to empower patients and their caregivers in capturing
21 more accurately their symptoms/conditions, communicate them in a seamless and effective
22 way to their healthcare providers and, ultimately, foster action through advanced methods
23 of identification of important deviations relevant to the patient's state and QoL. MyPal will
24 evaluate the proposed intervention for adults with CLL and MDS through a carefully designed
25 randomized controlled trial (RCT) that will be conducted in diverse health care settings across
26 Europe.

28 Methods and Analysis

29 Study Design

30 This is a multi-national randomised controlled trial, enrolling patients with CLL or MDS
31 at 5 clinical sites in Europe. The methodological approach of the study involves patients' use
32 of a mobile application with a range of functionalities as well as a FitBit smartwatch. Patients

1 will be able to conveniently self-report via the MyPal mobile application using ePROs as
2 outcome measures while the Fitbit will also be collecting data on patients' physical
3 activity. The main aim of the MyPal ADULT is to evaluate the effectiveness and cost-
4 effectiveness of use of the MyPal ePRO system as a novel, patient-centred, palliative care
5 intervention for patients with haematological malignancies (CLL or MDS).

7 Objectives and Outcome measures

8 Primary objective

9 The main objective is to determine whether the MyPal ADULT intervention can lead to
10 improved QoL compared to standard care as evidenced by statistically significant higher
11 scores in the EORTC QLQ-C30 [19] General Questionnaire and the Euroqol EQ-5D [20].

12 Secondary objectives

13 To determine whether - compared to standard care - the MyPal system intervention can lead
14 to the following outcomes in patients with CLL or MDS:

- 15 1. Improvement in physical and emotional functioning as evidenced by higher scores in
16 the Integrated Palliative Care Outcome Scale (IPOS) [21] at prespecified timepoints
17 (please refer to "Reporting Period")
- 18 2. Increase in satisfaction with care as evidenced by higher scores in the EORTC Patient
19 Satisfaction with Cancer Care questionnaire (EORTC PATSAT C33) [22] at prespecified
20 timepoints
- 21 3. Increase in overall survival as evidenced by longer survival times.

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

26 To determine whether the MyPal system intervention can lead to the following outcomes in
27 patients with CLL or MDS over time:

- 28 - Reduced symptom burden as evidenced by lower scores in the Edmonton Symptom
29 Assessment System (ESAS) [23] at prespecified timepoints
- 30 - Reduced pain score as evidenced by lower scores in the Brief Pain Inventory (BPI) [24]
31 at prespecified timepoints

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3 1 - Reduced emotional distress as evidenced by lower scores in the Emotion
4 2 Thermometers (ET) [25] at prespecified timepoints
5
6 3 - Increase in patient engagement in care as evidenced by satisfactory adherence to
7 4 reporting (e.g. 70% answered scheduled reports).
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10 Patient recruitment

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13 6 Patients (n=300) will be recruited from the following 5 clinical centres across 4 European
14 7 countries:

- 15
16 8 1. Karolinska Institutet (Sweden)
17
18 9 2. Università Vita-Salute San Raffaele (Italy)
19
20 10 3. University Hospital of Heraklion, Crete (Greece)
21
22 11 4. University Hospital Brno (Czech Republic)
23
24 12 5. G. Papanicolaou Hospital of Thessaloniki (Greece)

25 13 All consecutive patients with CLL (as well as small lymphocytic lymphoma-SLL, a condition
26 14 equivalent to CLL) or MDS who visit the participating centres will be screened and asked to
27 15 participate in the MyPal study. Patients should fulfill the eligibility criteria highlighted in Box
28 16 1 for enrollment. The patient recruitment started in January 2021 (first patient in 04Jan2021)
29 17 and it is planned to end by December 2021.
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33 34 35 19 **Box 1. Eligibility Criteria**

Inclusion Criteria

1. Adults (≥ 18 years)
2. Diagnosed with CLL or small lymphocytic lymphoma (SLL), a condition equivalent to CLL, or 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/SLL or MDS
4. Able to understand and communicate in the respective language
5. Users of an Internet connected device (smartphone/tablet)

Exclusion Criteria

1. Patients who are already participating in another interventional study
2. Patients needing immediate referral for specialised palliative care
3. Any life-threatening illness, medical condition, or organ system dysfunction that, in the attending physician's opinion, could compromise the subject's safety or put the study outcomes at undue risk
4. Life expectancy < 3 months
5. For the CLL/SLL cohort: patients who have experienced Richter's transformation

Randomisation

Patients will be randomly assigned in a 1:1 fashion to receive early palliative oncology care using the MyPal Digital Health Platform (*intervention group*) versus standard care which could include general palliative care if needed (*control group*), stratified by cancer type (i.e. CLL/SLL vs MDS), using a computer-generated number sequence, based on blocked randomization approach [26]. The assignment of each patient will be conducted during his/her enrolment phase (Figure 1) with no prior knowledge for the enrolling clinicians, in order to avoid biases.

MyPal Digital Health Platform

The intervention consists of the use of the MyPal Digital Health Platform. The system will be used by the patients who participate in the intervention arm of the trial and by the participating HCPs, while patients participating in the control group (the standard arm of the trial) will not use the system. Access to the MyPal Digital Health Platform (Figure 2) will be granted to the patients for 12 months of continuous use right after their enrollment in the trial. HCPs will have access to the system until the end of the trial. Patients will be informed

1 that the MyPal eHealth system is not meant to be used as an emergency service and urgent
2 issues have to be reported following standard care procedures.

3 The intervention focuses on the reporting of physical and psycho-emotional symptoms by the
4 patient via the MyPal smartphone app installed on his/her personal smartphone or tablet (see
5 sample screen in Figure 3a). Furthermore, the reported symptom-related information is
6 immediately delivered to the HCP via the MyPal web app which is the main interface of the
7 HCP to the system (see sample web app page in Figure 3b). Finally, the smart wristband, Fitbit
8 Ionic™, a commercial activity tracking device that will be employed for monitoring the physical
9 activity and the sleep quality of the patient, will be provided by the site personnel. Despite
10 the fact that the presentation of the technical infrastructure is considered out of this paper's
11 scope, it should be highlighted that the system backend infrastructure stores the collected
12 data focusing on information security best practices.

14 The patient's perspective

15 From the patient's perspective, both system initiated functionalities (i.e., functionalities for
16 which the system decides when they become available to the user) and user initiated
17 functionalities (i.e., functionalities that the user has access to at all times) offered via the
18 MyPal smartphone app can be seen in Table 1.

20 **Table 1.** The system and user initiated functionalities offered in the MyPal smartphone app.

System-Initiated Functionality	Description
PS1 Physical symptom questionnaires	Notifications to complete physical symptom questionnaires are issued once per week.
PS2 Psycho-emotional symptom questionnaires	Notifications to complete a psycho-emotional symptom questionnaire (are issued once per week.
PS3 Screener questionnaires	Notifications to complete a screener questionnaire concerning (1) the patient's ongoing engagement with the MyPal study, and (2) the risk of medication non-adherence. Responses will determine the motivational messages that patients will be receiving and the highest priority topics for the discussion guide presented to the HCP (issued at Month 0, 3 and 6).

		Tailored short motivational messages presented to the patient.
PS4	Motivational messages	Their content is determined based on a custom algorithm that receives input from patient responses (Issued twice weekly until Week 4, then once weekly until Week 24).
PS5	Medication reminders	Notifications that remind the patient to take their medication; determined by the patient via the medication management functionality.
User-Initiated Functionality		Description
PU1	Spontaneous symptom reporting	A form that is used by the patient to spontaneously report physical or psycho-emotional symptoms in a structured or unstructured way.
PU2	Medication management	An editable list of the patient's medication plan along with the dosage and the frequency of intake.
PU3	Personal health information recommender	A personalized search engine that retrieves health information related to health status of the patient.
PU4	Self-reported information review	A view that presents the patients's past responses to physical and psycho-emotional questionnaires.
PU5	Activity information review	A view that presents past daily step count and sleep quality indicators acquired by the commercial wristband.

The main phases for the enrolled patients point of view, include a registration phase, a main usage phase and a follow up phase and can be summarized as follows:

Registration Phase. This phase is completed the first time the patient uses the MyPal smartphone/tablet app, and aims at (1) registering the patient into the MyPal system, (2) initially setting a number of preferences, (3) collecting via self-reporting the baseline assessment of the patient's physical and psycho-emotional symptoms, and (4) screening for motivational targets and non-adherence risk. The smartphone app guides the patient throughout the entire registration process in a wizard-like fashion. In case needed, the patient might get some help for completing the registration from a HCP (e.g., research nurse) participating in the study.

Main usage phase. This phase lasts 6 months (Month 1 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 and system-initiated ones. Two main types of notifications can be distinguished, 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).

Follow-up usage phase. The follow-up usage phase starts immediately after the completion of the main usage phase and it also lasts 6 months (Month 7 to Month 12 of the patient's participation). During this phase however, the smartphone app does not issue assessment notification monthly; instead it issues only one such notification at the end of Month 12.

The HCP's perspective

The functionalities offered via the HCP web app are reported in Table 2.

Table 2. 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. The summarized incoming information is automatically prioritized in the system backend with the help of custom algorithms and the pieces of incoming information that are assigned the highest priority and placed on the top of the list.
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 the trial. The information includes (1) patients' responses to the symptom questionnaires (2) the spontaneous symptom reports; (3) the self-reported medication via the smartphone app; (4) the appointment schedule; (5) the 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).
H3	Aggregated data dashboard	A page that presents, using an analytics dashboard with modern visualizations, aggregated and summarized information coming from all

Functionality	Description
	patients that participate in the trial (descriptive statistics such a min, max, average and percentiles).
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.
H5 Information recommender repository update	A page used for editing the information that resides in the repository of the personal health Information recommender. The HCP can upload documents or specify web resources that containing valid medical information.
H6 HCP response log	A page 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.

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2 The HCPs need to follow a simple registration process during their first entry in the MyPal web
3 app. During the main usage of the MyPal web app, the HCPs get access to the data that are
4 collected by (1) the MyPal smartphone app and (2) the commercial smart wristband. The
5 collected data become available to the MyPal web app in a "live" fashion, as soon as they are
6 stored. At an individual level, the HCP is authorized to access only the data of the patients of
7 the associated clinical centre; however, access to aggregated and summarized data coming
8 from all patients (descriptive statistics such as min, max, average and percentiles) will also be
9 provided to all HCPs. HCPs are not actively notified by the MyPal system at any point in order
10 to avoid "alert fatigue"-related issues and biases. The individual data of the participating
11 patients of every clinical center are planned to be reviewed by the associated HCPs at least
12 once every 72 hours. Appropriate actions will be taken according to the HCP's judgement and
13 medical expertise. These actions will be recorded by the HCPs via the MyPal system i.e.
14 referral for diagnostics, prescription of medication etc.

15 As the MyPal eHealth system constitutes a complex intervention comprising of a number of
16 individual elements, the fidelity of the intervention implementation will be evaluated by
17 collecting the information on the web interface (to be completed by the HCPs accessing the
18 system), including review of reported symptoms and questionnaires by HCPs (audit trail) and
19 action taken by HCPs, if any.

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2 Data collection and analysis

3 Data collection

4 Data collection will be undertaken by the MyPal Digital Health Platform, which consists of the
5 following modules:

- 6 1. **The MyPal smartphone app.** This will be used by the patients assigned to the study
7 intervention group in order to report their physical and psycho-emotional symptoms
8 either spontaneously or periodically, as well as manage their medication intake,
9 review their own data (e.g., symptom trajectory), etc. Additionally, it will serve as the
10 hub for the transfer of activity level and sleep quality data acquired by a commercial
11 activity tracking device.
- 12 2. **The MyPal web portal.** This will be used by the HCPs participating in the study in
13 order to monitor and periodically review the collected patient data, as well as to
14 register certain data pertaining to a patient (e.g. treatment plan, next appointment).
15 The portal will also be used sporadically by the patients assigned to the study control
16 group for answering the assessment ePRO questionnaires.
- 17 3. **The MyPal backend and storage module.** All patient data collected from the
18 smartphone app and the web portal will be synchronized to the MyPal backend and
19 storage module.

21 Types of data

22 Special categories of personal data collected during the study include:

23 Data collected in both experimental and standard arms:

- 24 ▪ Demographic (e.g. age, gender);
- 25 ▪ Clinical information, including disease and treatment-related features, frequency of
26 appointments and events occurring during the observation time
- 27 ▪ Patient reported outcomes for study endpoint assessment (assessment
28 questionnaires) to allow for a comparison:
 - 29 - The EORTC QLQ-C30 which is a 30-item Quality of Life questionnaire,
30 assessing important functioning domains, common cancer symptoms as well
31 as the perceived financial impact of the disease and treatment

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- 1 - The Euroqol, EQ-5D – 3L, a 25-item general measure evaluating patients with
2 regards to the following dimensions: mobility, self-care, usual activities,
3 pain/discomfort and anxiety/depression.
- 4 - The Integrated Palliative Outcome Scale (IPOS), a 10-item questionnaire,
5 specific to palliative care, which measures patients' physical symptoms,
6 psychological, emotional and spiritual, as well as information and support
7 needs.
- 8 - The Satisfaction with Cancer Care developed by The European Organization
9 for Research and Treatment of Cancer (EORTC) group which assesses patients'
10 perception of the quality of medical and nursing care, as well as the
11 organisation of care and services of an oncology department.

12 Data collected in the experimental arm only:

- 13 ▪ FitBit-derived (e.g. activity and sleep patterns)
- 14 ▪ Symptoms (through both spontaneous and scheduled reporting)
- 15 ▪ Patient reported outcomes which are part of the intervention (intervention
16 questionnaires) and will be deployed to monitor patient's condition in MyPal:
 - 17 - The Edmonton Symptom Assessment System (ESAS), a 10-item questionnaire
18 assessing common symptoms experienced by patients with cancer.
 - 19 - The Brief Pain Inventory (BPI), a 9-item questionnaire designed to assess
20 cancer pain intensity, pain relief treatment or medication as well as pain
21 interference in activities.
 - 22 - The Emotional Thermometers, a tool which assesses emotional issues,
23 namely distress, anxiety, depression and anger, as well as patients' need for
24 help through 5 visual analogue scales (VAS).

25 Reporting period

26 After the patients are enrolled in the study, they are asked to complete the assessment ePROs
27 on a monthly basis (both groups) and the intervention/symptom ePROs on a weekly basis
28 (intervention group only) for 6 months (main phase). In the follow-up phase, the patients of
29 the intervention group continue completing the intervention ePROs as before, while both
30 groups complete the assessment ePROs once more in the end of the phase.

31 Data security

32 The privacy-by-design paradigm [27] has been employed to install appropriate data protection
33 measures as early as possible in the development of the MyPal platform, in compliance with

1 the General Data Protection Regulation (EU) 2016/679 (GDPR) [28]. To this end, the necessary
2 Data Protection Impact Assessments 2-(DPIAs, n=2) were conducted. The first focusing on the
3 management of data on local clinical sites (mobile apps etc.), and the second focusing on the
4 management of aggregated data for further analysis (anonymization of data etc.) These were
5 thoroughly reviewed by the respective Data Protection Officers (DPOs). The data protection
6 security measures include (1) the storage of personally identifiable data only in the premises
7 of clinical sites, (2) role-based data access, (3) password encryption, (4) use of the OAuth
8 protocol (to minimize password-based authentication whenever possible), (5) network data
9 transfer via the secure HTTPs protocol, etc.

10 Furthermore, adjusting the system architecture along the privacy-by-design paradigm, a
11 decentralized deployment model of the MyPal platform has been adopted encompassing one
12 local installations per participating clinical center in order to host personally identifiable
13 information for all participating study subjects from the clinical center in its own IT
14 infrastructure. However, one central installation at the site of the study sponsor has also been
15 deployed to host the assessment ePRO responses from all centers after they have been
16 completely deidentified. It should be clarified that the link between the ID of the patient used
17 in the context of MyPal study and the patient identification information (name, address, age
18 etc.) exists, but this link never leaves the local clinical site environment.

20 Sample size calculation

21 Assuming relatively acceptable values for the attrition rate (i.e., 20%) and the missing data
22 (i.e., 30%), the sample size analysis concluded that 300 recruited patients with CLL or MDS at
23 any ratio providing one measure at enrolment (baseline) and 7 repeated measures (at months
24 1, 2, 3, 4, 5, 6 and 12) are sufficient for the power of the intended statistical testing to be over
25 90% in all cases, given (a) a 0.05 significance level, and (b) an effect size of 0.2; the employed
26 value of the effect size was based on a priori knowledge of the domain.

28 Data analysis plan

29 Descriptive statistics will be provided for demographic (gender, age group, origin, etc.) and
30 clinical characteristics (diagnosis, disease stage, etc.) recorded at baseline. The aim of the
31 analysis will be to evaluate the changes in outcome measures over time (1) in
32 the experimental arm and (2) in the experimental arm in comparison with the standard arm,

1 using one-way and two-way repeated measures analysis of variance (ANOVA) (or a non-
2 parametric equivalent), respectively. Post-hoc analysis will be applied as appropriate.
3 Subgroup analysis of the outcome measures will also be performed at baseline, month 6 and
4 month 12 of the study using one, two and three-way ANOVA in order to detect potential
5 differences between specific groups of participants. The grouping variables that will be
6 employed are (a) the clinical centre (origin), (b) the country of residence, (c) the age group,
7 (d) the disease stage, and (e) the diagnosis (CLL, MDS). In the case an interaction effect is
8 observed, separate subgroup analyses in the CLL and MDS cohorts with repeated measures
9 ANOVA will be performed to assess the effect of intervention on quality of life and other the
10 outcome measures. The level of significance for all statistical tests is set to $\alpha=0.05$, in
11 accordance with the power calculations.

13 Monitoring

14 The study includes a Data Monitoring Committee (DMC). The DMC will be an independent and
15 multidisciplinary committee consisting of 3-4 members such as clinicians who have expertise
16 in haematological cancers, ethics and palliative care, biostatisticians. They will have access to
17 unblinded data and will monitor accumulating trial data at pre-specified intervals in terms of
18 safety and efficacy and in particular: quality including completeness and attrition, recruitment
19 across sites and evidence for differences in the main outcome measures between arms. Any
20 reports of serious adverse events such as safety or ethical issues will be brought to the
21 attention of the Principal Investigators.

23 Safety reporting

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

28 As the study population consists of individuals facing life threatening illness, we would not
29 expect it to be an unusual occurrence for patients to be admitted to hospital while taking part
30 in the study. We expect that the most likely serious risk of participating in the MyPal
31 intervention is (serious) distress. It should be noted however that symptom reporting is
32 considered to be part of routine care, and as such, we expect the risks to be limited. Filling in

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3 1 questionnaires about physical and psychological symptoms, and quality of life may also be
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5 2 upsetting for patients. However, we expect the risk to be limited as these are validated
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7 3 questionnaires that address issues that are discussed in usual care.
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For peer review only

1 Ethics and dissemination

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The integration of ePROs via mobile applications has raised ethical concerns regarding inclusion criteria, information provided to participants, free and voluntary consent, as well as respect for their autonomy. These have been carefully addressed by a multidisciplinary team, including experts in bioethics. Data processing as well as the dissemination and exploitation of the study findings will take place in full compliance with EU data protection law. A participatory design was adopted in the development of the digital health platform involving focus groups and discussions with patients in order to identify needs and preferences. The protocol (version 1.0 dated 16Dec2019, included in the Supplementary material) “has received ethical approval from the Ethics Committee of San Raffaele Hospital (05Feb2020, registry number 8/2020), the Ethics Committee of General Hospital of Thessaloniki ‘George Papanikolaou’ (20.5.2020, registry number 849), Ethics Committee of Karolinska Institutet (20.10.2020), Ethics Committee of the University General Hospital of Heraklion (07/15.4.2020) as well as the Ethics Committee of the University of Brno (01-120220/EK).

17 Patient and Public Involvement

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The definition of key research questions was based on thorough search of the literature where communication with the healthcare team and better understanding of health-related information were of paramount importance for informed decision-making by the patient [29]. A participatory design was adopted in the development of the digital health platform involving the established instrument of focus groups and discussions with patients in order to identify needs and preferences. In more detail, multiple focus groups have been organized in all MyPAL clinical sites and the results analysed by means of established qualitative research methods to main themes/topics concerning the user needs.

27 Discussion

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Digital health technologies offer the potential for rapid and spontaneous reporting of symptoms, facilitating remote monitoring and communication between patients and HCPs. They have been increasingly implemented in routine practice in all areas of healthcare,

1 especially during the COVID-19 pandemic. However, concerns remain about their
2 acceptability to patients, especially older people, and the degree to which they may alter
3 patient-clinician relationships in palliative care contexts [30]. Therefore, it is important to
4 rigorously test these interventions using robust research designs, highlighting usability and
5 patient acceptability as top priorities.

6 The MyPal project aspires to offer a personalised approach for improving the delivery of early
7 palliative care in patients with cancer, including CLL and MDS that typically affect the elderly.
8 This will be achieved by empowering patients and their caregivers to actively participate in
9 the care process through the use of digital health tools for self-reporting symptoms and
10 events, QoL as well as any kind of perceived changes in their daily patterns occurring
11 throughout the disease trajectory. Hence, MyPal has the ambition to formally prove the
12 advantage and substantial improvement of eHealth systems as compared to traditional
13 methods of palliative care for cancer patients and promote self-control of health.-By fostering
14 active participation of patients in disease management, our project may possibly inspire them
15 into a more active participation in society as well. In parallel, through the use of the digital
16 health tools offered by MyPal, healthcare providers are likely to experience improved
17 communication with patients, more timely and accurate interventions, and an increase in
18 knowledge on effective cancer patient management with patients featuring in an empowered
19 role.

20 The clinical trial reported herein seeks to test the efficacy of the MyPal digital health platform
21 using a newly designed smartphone app together with commonly used wearables to present
22 ePROs to adults with CLL and MDS to determine if it helps communication with their
23 healthcare professionals, compared to standard care. The strengths of this international study
24 include the ability for patients in the intervention arm to spontaneously report on symptoms
25 and concerns, in addition to regular reporting of symptoms when prompted by the app. In
26 addition, this study will provide an opportunity to examine both the advantages and
27 challenges of the MyPal system from the perspectives of the participating healthcare
28 professionals and to assess the extent to which ePRO reporting can facilitate more effective
29 and timely communication, and ultimately benefit patients by improvements in symptom
30 management.

31 In summary, data from MyPal will be used to (1) identify QoL improvements compared to
32 usual care, (2) provide evidence of improvements in physical and emotional functioning
33 compared to usual care, and (3) acceptability and usefulness of the MyPal digital health
34 platform for HCPs. We anticipate being able to disseminate our findings by 2023.

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13 at the clinical study sites who are essential to this study (patient recruitment, symptom
14 assessment and management and data collection). This work is dedicated to Vassilis Koutkias.

16 Author contributions

17 Lydia Scarfò, Christina Karamanidou, Christos Maramis, Paolo Ghia, Kostas Stamatopoulos
18 designed the study and drafted the study protocol.

19 Lydia Scarfò, Christina Karamanidou, Jana Didi, Charalampos Pontikoglou Christos Maramis,
20 Paolo Ghia, Sheila Payne, Kostas Stamatopoulos drafted the manuscript

21 Michael Doubek, Tina Garani-Papadatos, Julie Ling, Cathy Payne, Helen A. Papadaki, Richard
22 Rosenquist, Niki Stavroyianni, Pantelis Natsiavas, contributed to critical revisions of the study
23 protocol and the manuscript.

24 Paolo Ghia, Niki Stavroyianni, Richard Rosenquist, Michael Doubek, Helen A. Papadaki, are
25 the Site Chief Investigators and take overall responsibility for all aspects of the study design,
26 the protocol and the study conduct at the involved clinical study sites.

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1 2 **Competing interests**

3 None declared.

5 **Ethics approval**

6 The MyPal-Adult study protocol has received ethical approval from the Ethics Committee of
7 San Raffaele Hospital (05Feb2020, registry number 8/2020), the Ethics Committee of General
8 Hospital of Thessaloniki ‘George Papanikolaou’ (20.5.2020, registry number 849), Ethics
9 Committee of Karolinska Institutet (20.10.2020), Ethics Committee of the University General
10 Hospital of Heraklion (07/15.4.2020) as well as the Ethics Committee of the University of Brno
11 (01-120220/EK).

13 **Provenance and peer review**

14 Not commissioned; externally reviewed.

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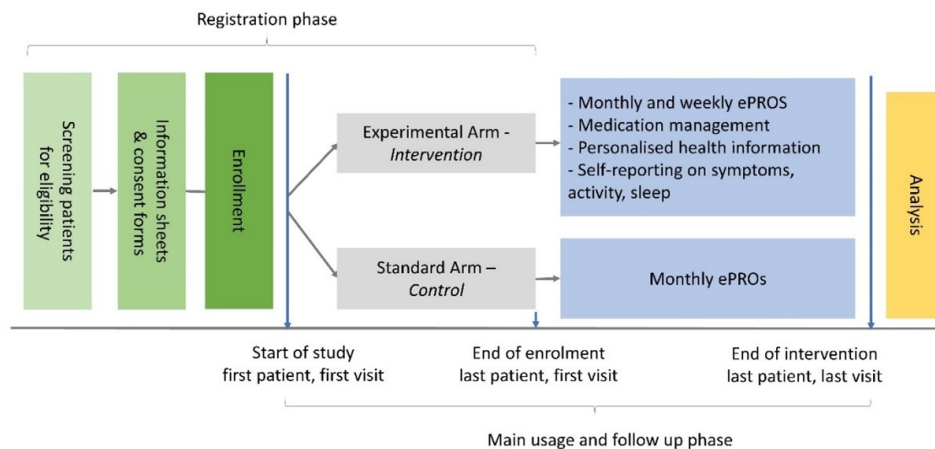


Figure 1. Schematic representation of the study design.

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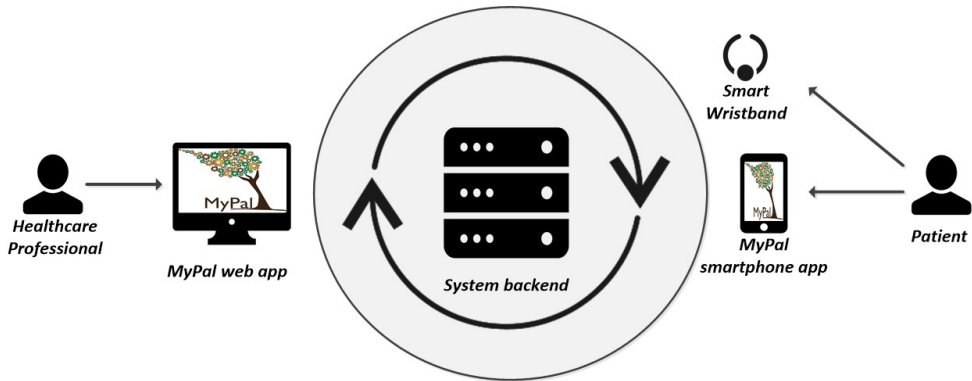


Figure 2. Software and hardware modules of the MyPal digital health platform.

338x190mm (96 x 96 DPI)

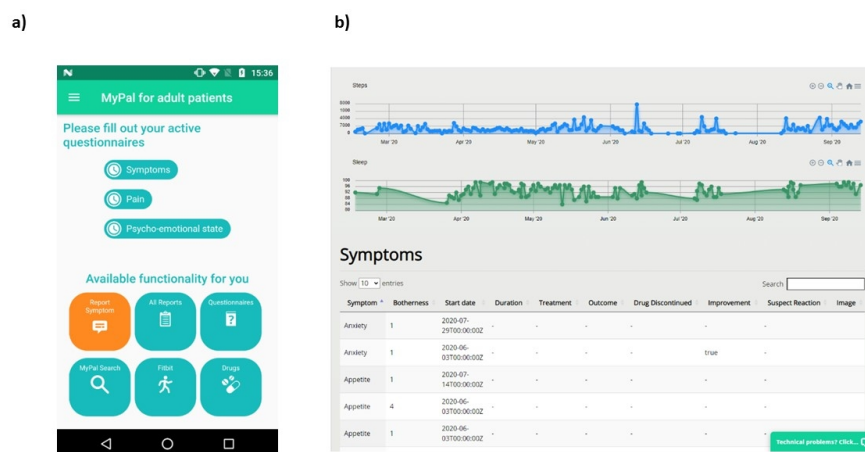


Figure 3. Sample graphical user interfaces of the MyPal eHealth system: (a) Screen of the MyPal smartphone app; (b) Page of the MyPal web app.

338x190mm (96 x 96 DPI)



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



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SIGNATURE PAGE

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

This protocol has been approved by:

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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.**

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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	<ol style="list-style-type: none"> 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	<p>MyPal will operate according to the “palliative care” definition provided by the World Health Organization which states:</p> <p><i>‘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</i></p> <p>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 <i>specialist palliative care</i>, 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 <i>general palliative care</i> 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.</p> <p>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.</p>

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.



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Study Objectives	<p>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).</p> <p><u>Primary Objective</u></p> <p>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-C30² General Questionnaire and EQ-5D³.</p> <p><u>Secondary Objectives</u></p> <p>To determine whether - compared to standard care - the MyPal system intervention can lead to the following outcomes in patients with hematological cancers (CLL/MDS):</p> <ol style="list-style-type: none"> 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] <p>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.</p> <p>And to determine whether the MyPal system intervention can lead to the following outcomes in patients with hematological cancers (CLL/MDS) over time:</p> <ol style="list-style-type: none"> 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]
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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.

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	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]																				
Study Endpoints	<table border="1"> <thead> <tr> <th>Primary Endpoint</th> <th>Measure/Scale</th> </tr> </thead> <tbody> <tr> <td>Improvement in quality of life</td> <td>EORTC QLQ-C30 General Questionnaire and EQ-5D</td> </tr> <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> </tbody> </table>	Primary Endpoint	Measure/Scale	Improvement in quality of life	EORTC QLQ-C30 General Questionnaire and EQ-5D	Secondary Endpoint	Measure/Scale	Symptom reduction	Edmonton Symptom Assessment System (ESAS)	Pain reduction	Brief Pain Inventory (BPI) severity	Emotional distress reduction	Emotion Thermometers (ET)	Improvement in psychological and physical functioning	Integrated Palliative Care Outcome Scale (IPOS)	Increase in patient engagement in care	Adherence to reporting (e.g.70% answered of scheduled reports)	Increase in satisfaction with care	EORTC Satisfaction with Cancer Care questionnaire	Overall survival	Event of death
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Standard care arm (n=150): no intervention besides general palliative care if required	General palliative care if required																				
Key Inclusion Criteria	<ol style="list-style-type: none"> Adults (≥ 18 years) Diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or myelodysplastic syndrome (MDS) 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 Able to understand and communicate in the respective language Users of an Internet connected device (smartphone/tablet) 																				
Key Exclusion Criteria	<ol style="list-style-type: none"> Patients who are already participating in another experimental study Patients needing immediate referral for specialized palliative care 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 Patients unable to provide written informed consent Life expectancy < 3 months For CLL cohort: patients who have experienced Richter transformation 																				
Intervention	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.																				



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<p>Study Duration</p>	<p>Total study duration: 25 months</p> <p>Study duration for each participant is expected to be 12 months.</p> <p>Study analysis: 3 months after the end of the study</p> <p>Expected First patient in date: 01.05.2020</p> <p>Expected Last patient in: 30.03.2021</p> <p>End of study: 30.03.2022</p>
<p>Efficacy Assessments</p>	<p>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.</p>
<p>Safety Assessments</p>	<p>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.</p>
<p>Statistical Methods and Planned Analyses</p>	<p>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 $\alpha=0.05$.</p> <p>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.</p>



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5 **1 BACKGROUND AND RATIONALE**

6 **1.1 Background**

7 **1.1.1 Digital health**

8 According to World Health Organization (WHO)⁹, digital health (also known as eHealth) is defined as
9 *the use of information and communications technology in support of health and health-related fields*.
10 Digital health has become a salient field of practice for employing a wide range of digital technologies
11 to address health needs. The technologies that are employed by digital health include both hardware
12 devices (such as mobile phones, wearable devices, remote monitoring sensors) and software products
13 and services (telemedicine services, text messages, email, web-based or smartphone applications). In
14 2018, the World Health Assembly Resolution on Digital Health, which was unanimously approved by
15 WHO Member States, recognized the value of digital technologies towards advancing universal health
16 coverage sustainable health care.
17

18 However, the enthusiasm for digital health has also led to a number of short-lived digital implementations
19 characterized by overwhelming diversity, limited understanding of their impact on health systems and
20 people's well-being. For this reason, both Food and Drug Administration (FDA) and WHO have
21 published guidelines for the development of high-quality, evidence-based digital health interventions
22 (i.e., discrete functionalities of digital technology that are applied to achieve health objectives), namely
23 the Digital Health Innovation Action Plan¹⁰ and recommendations on digital interventions for health
24 system strengthening⁹, respectively.
25

26 On top of that, WHO has produced a classification of digital health intervention to describe the various
27 uses of digital health technology for health¹¹.
28

29 **1.1.2 Patient reported outcome measures**

30 Cancer patients' experience is multi-faceted and can include a physical dimension relating to symptoms
31 or functional status, a psychological dimension relating to thoughts and feelings, a social dimension
32 relating to relationships or finances and a spiritual dimension relating to existential questions¹². Changes
33 in the patients' experience across the illness trajectory can be captured and measured using Patient-
34 Reported Outcome (PROs). PROs are standardized, validated self-report questionnaires, considered
35 the gold standard as far as subjective experiences are concerned¹³.
36

37 PROs have a major role to play in improving the quality, efficiency and availability of palliative care.
38 Their consideration along with biochemical and clinical data within the palliative care clinical setting can
39 help provide patients the most appropriate support at every stage of their care¹⁴. Specifically, in
40 palliative care PROs can: a) monitor changes in the patients' health status and b) facilitate the
41 identification and screening of unmet needs which could have been overlooked (psychological, social,
42 physical etc.) of patients and their families; c) provide information on the evolution of disease and the
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51 ⁹ World Health Organization. WHO guideline: recommendations on digital interventions for health system strengthening web
52 supplement 2: summary of findings and GRADE tables. World Health Organization; 2019.

53 ¹⁰ US Food and Drug Administration. Digital health innovation action plan. Available from
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55 ¹¹ World Health Organization. Classification of digital health interventions v1. 0: a shared language to describe the uses of digital
56 technology for health. World Health Organization; 2018.

57 ¹² Bausewein, C., Daveson, B., Benalia, H., Simon, S.T. and Higginson, I.J., 2011. Outcome measurement in palliative care: the
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59 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,
60 W. and Frank, E.S., 2012. Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness
61 research in adult oncology. J Clin Oncol, 30(34), pp.4249-4255.

62 ¹⁴ Antunes B, et al. Implementing patient-reported outcome measures in palliative care clinical practice: a systematic review of
63 facilitators and barriers. Palliat Med. 2014;28(2):158-75.



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

7
8 For the MyPal ADULT clinical trial, measurements appropriate for use in palliative care with adults have
9 been selected. Multidimensional Patient Reported Outcomes Measures such as the Palliative care
10 Outcome Scale aiming to identify patients' needs, Edmonton Symptom Assessment Scale for
11 identification of common symptoms experienced by cancer patients. In terms of well-being, the EORTC
12 QLQ-C30 can be used to assess patients' cancer related quality of life. Generic measures such as the
13 EQ-5D assessing the overall physical, psychological and social quality of life will also be used. Please
14 section 4 on objectives and outcome measures¹².

16 1.1.3 Palliative care

17
18 According to the WHO definition (2002)¹ palliative care is “an approach that improves the quality of life
19 of patients and their families facing the problems associated with life threatening illness, through the
20 prevention and relief of suffering by means of early identification and impeccable assessment and
21 treatment of pain and other problems, physical, psychological and spiritual”. Definitions of palliative care
22 have changed from a focus on end-stage cancer to include the trajectory of all life-limiting conditions.
23 They remain both contested and poorly understood by healthcare professionals, and more importantly,
24 by patients and the public¹⁵ Palliative care is interdisciplinary in its approach and encompasses the
25 patient, the family and the community in its scope. Palliative care aims to assess and provide for the
26 needs of the patient wherever he or she is cared for, either at home or in a hospital, or other place.
27 Palliative care affirms life and regards dying as a normal process; it neither hastens nor postpones
28 death. It sets out to preserve the best possible quality of life until death. Palliative care focuses not only
29 on the patient but also his/her family. Furthermore, as the main purpose of palliative care is to improve
30 quality of life by supporting the patient not only through physical problems but other additional problems
31 of a social, psychological and spiritual nature. Palliative care can be offered to improve quality of life of
32 patients and their families who are receiving active treatment either curative or aiming at disease control.
33 Palliative care encompasses much more than just end-of-life or hospice care. Instead, palliative care is
34 an essential component of serious illness care, much further upstream from the terminal phase.
35 Therefore, palliative care should be viewed as a necessary component of care for patients with cancer
36 from the time of diagnosis. Palliative care begins at diagnosis and increases in “dosage” or focus as
37 needed throughout the continuum of illness. There is evidence from randomised control trials in the
38 USA of the benefits of early integration of palliative care into clinical care¹⁶ but this was not replicated in
39 Europe¹⁷.

54
55 ¹⁵ McIlfratrick S, Hasson F, McLaughlin D, Johnston G, Roulston A, Rutherford L, Noble H, Kelly S, Craig A, Kernohan WG.
56 Public awareness and attitudes toward palliative care in Northern Ireland. *BMC palliative care*. 2013 Dec;12(1):34.

57 ¹⁶ Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF,
58 Billings JA. Early palliative care for patients with metastatic non-small-cell lung cancer. *New England Journal of Medicine*. 2010
59 Aug 19;363(8):733-42.

60 ¹⁷ Groenvold M, Petersen MA, Damkier A, Neergaard MA, Nielsen JB, Pedersen L, Sjøgren P, Strömberg AS, Vejlgård 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.



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5 1.1.4 Chronic lymphocytic leukemia

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

9
10 CLL is a chronic leukemia, characterized by the clonal proliferation and accumulation of mature B-cells
11 within the blood, bone marrow, lymph nodes, and spleen. CLL cells co-express the B-cell surface
12 antigens CD19, CD20, CD23 and immunoglobulin as well as the T-cell antigen CD5^{21,22}. However, the
13 expression of surface immunoglobulin, CD20, and CD79b are characteristically low compared to normal
14 B cells^{23,24}.

15
16 The disease has a highly variable clinical course and ranges from patients who do not require therapy
17 for many years, if at all, to others who require treatment soon after diagnosis²⁵.

18
19 In routine clinical practice, newly diagnosed low-risk patients with asymptomatic early-stage disease
20 (Rai 0, Binet A^{26,27}; Table 1), should be monitored without therapy unless they have disease progression
21 or symptomatic/active disease as defined by the International Workshop on CLL (iwCLL) guidelines²².
22 Patients with active or symptomatic disease or with advanced Binet or Rai stages require therapy (iwCLL
23 guidelines)²².

24
25 In CLL many host- and tumor-related features with prognostic and/or predictive value have been
26 identified over the years, assisting in the stratification of patients into subgroups with distinct clinical
27 course and response to treatment. Amongst tumor-related biomarkers, those recommended by the
28 iwCLL for predictive assessment prior to treatment initiation in both general practice and clinical trials
29 pertain to the genomic background of the malignant clone, more particularly the TP53 gene that should
30 be investigated for both deletions by Fluorescence in situ hybridization (FISH) and mutations by Sanger
31 or Next-generation sequencing; and, the somatic hypermutation status (SHM) of the rearranged
32 immunoglobulin heavy variable (IGHV) gene expressed by the clonotypic B cell receptor
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45 ¹⁸ Hallek M. Chronic lymphocytic leukemia: 2015 Update on diagnosis, risk stratification, and treatment. *Am J Hematol.*
46 2015;90(5):446-460.

47 ¹⁹ National Cancer Institute [Website]. Surveillance Epidemiology and End Results Cancer Statistics review. 2009. Available at:
48 <http://seer.cancer.gov/statfacts/html/clyl.html>. Last accessed January 26 2016.

49 ²⁰ Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis,
50 treatment and follow-up. *Ann Oncol.* 2015;26 Suppl 5:v78-84.

51 ²¹ Panovska A, Doubek M, Brychtova Y, Mayer J. Chronic lymphocytic leukemia and focusing on epidemiology and management
52 in everyday hematologic practice: recent data from the Czech Leukemia Study Group for Life (CELL). *Clin Lymphoma Myeloma*
53 *Leuk.* 2010;10(4):297-300.

54 ²² Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report
55 from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996
56 guidelines. *Blood.* 2008;111(12):5446-5456.

57 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.*
58 1998;51(5):364-369.

59 ²⁴ Moreau EJ, Matutes E, A'Hern RP, et al. Improvement of the chronic lymphocytic leukemia scoring system with the monoclonal
60 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.



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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 CLL³³.

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 CLL²². 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.



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5 **1.1.5 Myelodysplastic syndrome**

6 The myelodysplastic syndromes (MDS) consist of a heterogeneous group of malignant hematopoietic
7 stem cell disorders characterized by ineffective hematopoiesis resulting in blood cytopenias and a
8 variable risk of transformation to acute myeloid leukemia (AML)³⁴. Myelodysplastic syndromes are
9 generally diseases of older people, with a median age at diagnosis of 65–70 years³⁵. The annual
10 incidence is approximately 4 cases per 100,000 people (reaching 40–50 per 100,000 after age 70
11 years)³⁵, with male predominance³⁶. Notably, with an aging population and improved awareness of
12 disease, it is likely that the number of new patients diagnosed with MDS each year will increase in the
13 future.
14

15 As regards to clinical features, patients can be asymptomatic or, if anemia is more severe, can exhibit
16 pallor, weakness, loss of a sense of well-being and dyspnea on exertion³⁷. Fatigue is by far the most
17 common symptom endorsed by patients and is not necessarily related to degree of anemia³⁸. A small
18 proportion of patients have infections related to neutropenia or neutrophil dysfunction, or hemorrhage
19 related to severe thrombocytopenia or platelet dysfunction at the time of diagnosis³⁷. Many MDS patients
20 also have immune disorders, including polyarthritis³⁷.
21

22 The diagnosis of MDS is generally suspected based on the presence of an abnormal complete blood
23 cell count³⁴ and is confirmed by bone marrow analysis which usually reveals hypercellularity, dysplastic
24 cell morphology with or without excess of immature cells (blasts)³⁹. To complete the laboratory
25 evaluation of a patient with MDS, the analysis of bone marrow cytogenetics is required. An abnormal
26 karyotype is shown by conventional cytogenetic analysis in 40–50% of cases at diagnosis³⁴.
27 Cytogenetics have major impact in MDS, not only as regards to prognosis, but also in the choice of the
28 most effective treatment, at least in subset of patients^{34,39}.
29

30 The disease course and natural history varies significantly between MDS patients, thereby necessitating
31 the development of prognostication systems to estimate the probability of disease progression and
32 survival and enable clinical decision making⁴⁰. The most prevalent prognostic model in clinical use is
33 the IPSS⁴¹ (Table 1,2), which includes percent of blasts, number of cytopenias and cytogenetics.
34 Patients are thus assigned to one of 4 risk categories (Table 1,2) with significant differences in overall
35 survival and risk of clonal evolution to AML. The system has several limitations that have become
36 evident over the years. The IPSS-R includes different cut off points of cytopenias and incorporates the
37 new cytogenetic MDS score. Based on the total risk score, patients are assigned to one of five risk
38 groups.
39

40 Although MDS treatment has improved over the last years, it still remains challenging. The therapeutic
41 strategy is largely based on the IPSS^{34,39}. More precisely, in patients classified as high or intermediate
42 2 on the IPSS (higher risk) with median survival if untreated of only about 12 months, treatment should
43 aim at modifying the disease course, avoiding progression to acute myeloid leukemia, and extending
44 survival^{34,39}. In contrast, in those classified as low or intermediate 1 on the IPSS (lower risk), survival is
45 longer and many patients die from causes other than myelodysplastic syndromes. Therefore, their
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49 ³⁴ Ades L, Itzykson R, Fenaux P. Myelodysplastic syndromes. *Lancet*. 2014;383(9936):2239-52.

50 ³⁵ Neukirchen J, Schoonen WM, Strupp C, Gattermann N, Aul C, Haas R, et al. Incidence and prevalence of myelodysplastic
51 syndromes: data from the Dusseldorf MDS-registry. *Leukemia research*. 2011;35(12):1591-6.

52 ³⁶ Ma X. Epidemiology of myelodysplastic syndromes. *The American journal of medicine*. 2012;125(7 Suppl):S2-5.

53 ³⁷ Steensma DP, Bennett JM. The myelodysplastic syndromes: diagnosis and treatment. *Mayo Clinic proceedings*.
54 2006;81(1):104-30.

55 ³⁸ Steensma DP, Heptinstall KV, Johnson VM, Novotny PJ, Sloan JA, Camoriano JK, et al. Common troublesome symptoms
56 and their impact on quality of life in patients with myelodysplastic syndromes (MDS): results of a large internet-based survey.
57 *Leukemia research*. 2008;32(5):691-8.

58 ³⁹ Montalban-Bravo G, Garcia-Manero G. Myelodysplastic syndromes: 2018 update on diagnosis, risk-stratification and
59 management. *American journal of hematology*. 2018;93(1):129-47.

60 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.



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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^{34,39}.

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 $100 \times 10^9/L$; haemoglobin 100 g/L; absolute neutrophil count $1.8 \times 10^9/L$.

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 ($\times 10^9/L$)	≥100	50 to <100	<50
Absolute neutrophil count ($\times 10^9/L$)	≥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.



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	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 illness⁴³.

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 initiation⁴⁸.

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 general⁴⁹, 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, Moynour 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.



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5 CLL-specific characteristics, comorbid conditions, and degree of fatigue all appear to have important
6 impact on the QOL of patients with CLL, with particular relevance on emotional QOL⁵⁰ Research
7 identifying effective interventions for patients with CLL is necessary to address this need.
8

9 **1.2.2 Myelodysplastic syndrome**

10 Patient-reported outcomes (PROs) have attracted much attention as a tool to gain more insight in the
11 burden of malignancy in patients' lives. By collecting data on quality of life, symptoms and the sense of
12 well-being, everyday functioning, disease and therapy perception, toxicities and adverse events as well
13 as patient evaluation of health care PROs can provide essential information to properly capture the
14 patient's condition⁴².
15

16 Cancer patients carry a substantial physical and psychosocial disease burden and are often obliged to
17 cope with disease and/ or treatment consequences which occur outside the hospital⁵¹. Yet there is an
18 increasing body of evidence suggesting that these consequences may go unnoticed by clinicians and
19 therefore not properly treated⁵². Recent studies have shown that routine follow-up of patients via PRO
20 monitoring can fill the gap in the patient-clinician communication, improve physician's awareness of
21 symptoms and result in better symptom management⁵³. Eventually this may exert a positive impact on
22 the quality of life and overall survival of patients with cancer⁵⁴.
23

24 As regards to MDS patients, they may suffer from a wide variety of symptoms, including fatigue, anxiety,
25 insomnia and dyspnea^{55,56}, which result in impaired quality of life⁵⁷. Notably, a study in which patients
26 with acute myeloid leukemia or advanced MDS were included has demonstrated that QOL is most
27 important to patients than the length of survival per se⁵⁸. Interestingly, hypomethylating agents, which
28 are mostly used in advanced MDS have been shown to improve QOL^{53,59}. Assessment of QOL as a
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42 ⁵⁰ Shanafelt TD, Bowen D, Venkat C, Slager SL, Zent CS, Kay NE, Reinalda M, Sloan JA, Call TG. Quality of life in chronic
43 lymphocytic leukemia: an international survey of 1482 patients. *Br J Haematol*. 2007;139(2):255-64.

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

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

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

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

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

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

60 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.

61 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.

62 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.



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relevant PRO⁶⁰⁶¹ has also showed that its impairment predicts an unfavorable clinical outcome^{62,63,64} and that it constitutes a parameter of response evaluation⁶⁵. Furthermore, apart from QOL, a recent report has also demonstrated that self-reported fatigue has prognostic value beyond standard MDS risk stratification systems⁶⁵.

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-C30² General Questionnaire and EQ-5D³.

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, Gerhing 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.



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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
-----	--------------



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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.

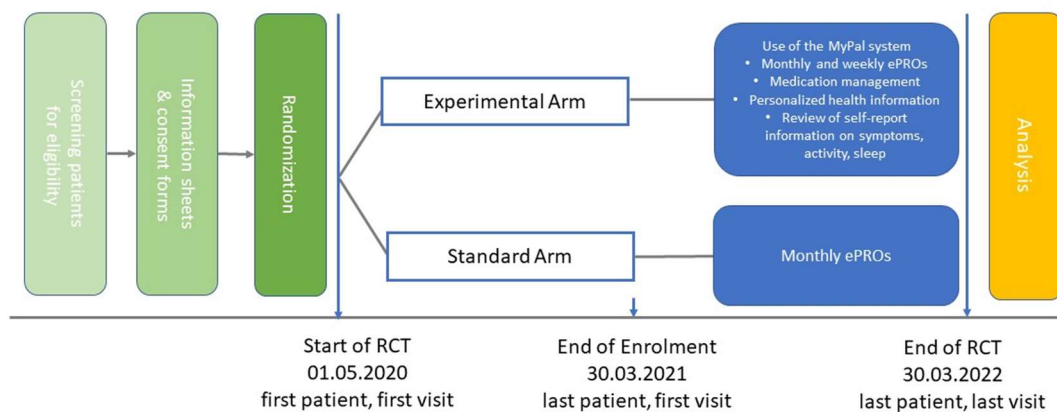


Figure 1. Schematic representation of the study design

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



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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.



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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



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5 respondent's pain on the day. The questionnaire is then composed of pain drawing diagrams,
6 four items about pain intensity (worst pain, least pain, average pain, pain right now), two items on
7 pain relief treatment or medication, and one item on pain interference, with seven sub-items
8 (general activity, mood, walking ability, normal walk, relations with other people, sleep, and
9 enjoyment of life).
10

- 11 3) The Emotional Thermometers, a tool for simple rapid detection of emotional issues through visual
12 analogue scales for four domains (distress, anxiety, depression, anger) as well as a need for help
13 domain. The tool constitutes a multidomain extension and adaptation of the American Distress
14 Thermometer adopted by the National Comprehensive Cancer Network and has been developed
15 for the assessment of psychological complications of cancer.
16

17 Patients in the experimental arm will also be able to report symptoms spontaneously through the MyPal
18 system. Apart from symptom reporting, which is an essential component of the MyPal intervention,
19 patients will be able to use the MyPal system to better manage their medication intake by registering
20 medication reminders. They will also be able to perform personalized searches in a repository developed
21 by medical experts and thus have access to valid medical information specific to their condition.
22 Furthermore, patients can review their own information such as physical or emotional symptoms
23 overtime, should they choose to do. Finally, at the start of the trial patients will be equipped with a fit-bit
24 watch which will allow monitoring of their physical activity and sleep quality. Information collected about
25 the patients through the MyPal system such as physical and psycho-emotional symptoms, physical
26 activity, sleep quality etc. will be monitored and periodically reviewed (every 72 hours maximum) by the
27 health-care professionals (HCPs). Appropriate actions will be taken according to the HCP's judgement
28 and medical expertise. These actions will be recorded by the HCPs via the MyPal system i.e. referral
29 for diagnostics, prescription of medication etc.
30
31

32 As the MyPal eHealth system constitutes a complex intervention comprising of a number of individual
33 elements, the fidelity of the intervention implementation will be evaluated by collecting the following
34 information on the web interface (to be completed by the HCPs accessing the system):
35

- 36 - Symptom/questionnaire review by HCPs (audit trail)
- 37 - Action taken (yes vs no)
- 38

39 And competing and integrating them with the information reported in the clinical records.
40

41 **4 ELIGIBILITY**

42 **4.1 Inclusion Criteria**

- 43 1. Adults (≥ 18 years)
- 44 2. Diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or
45 myelodysplastic syndrome (MDS)
- 46 3. Scheduled to receive any line of treatment for CLL/SLL or MDS or who have been previously
47 exposed to any treatment for CLL or MDS
- 48 4. Able to understand and communicate in the respective language
- 49 5. Users of an Internet connected device (smartphone/tablet)
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56 **4.2 Exclusion Criteria**

- 57 1. Patients who are already participating in another interventional study
- 58 2. Patients needing immediate referral for specialized palliative care
- 59
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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.

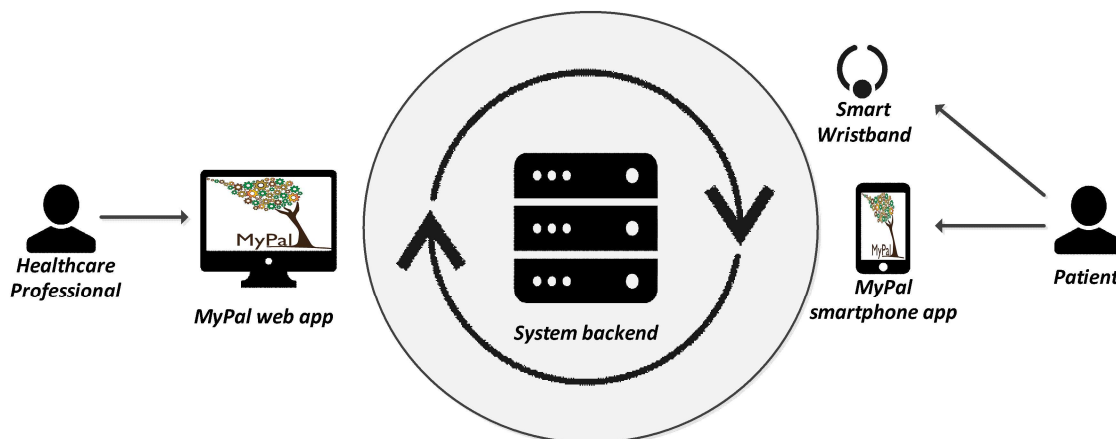


Figure 2. Software and hardware modules of the MyPal eHealth system

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:



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- **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.

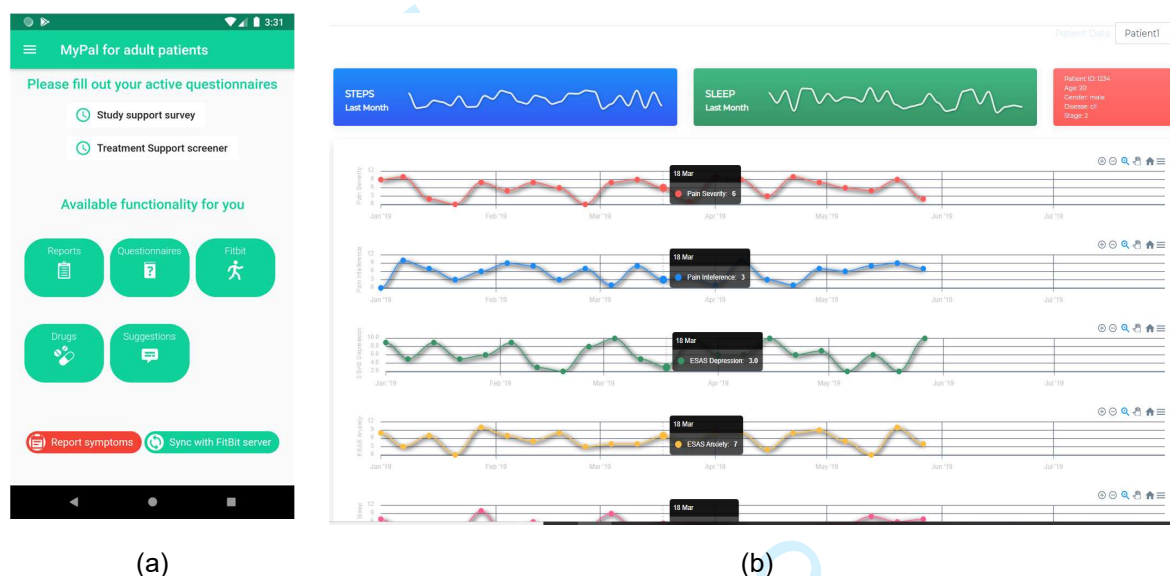


Figure 3. Sample graphical user interfaces of the MyPal eHealth system: (a) Screen of the MyPal smartphone app; (b) Page of the MyPal web app.





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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.

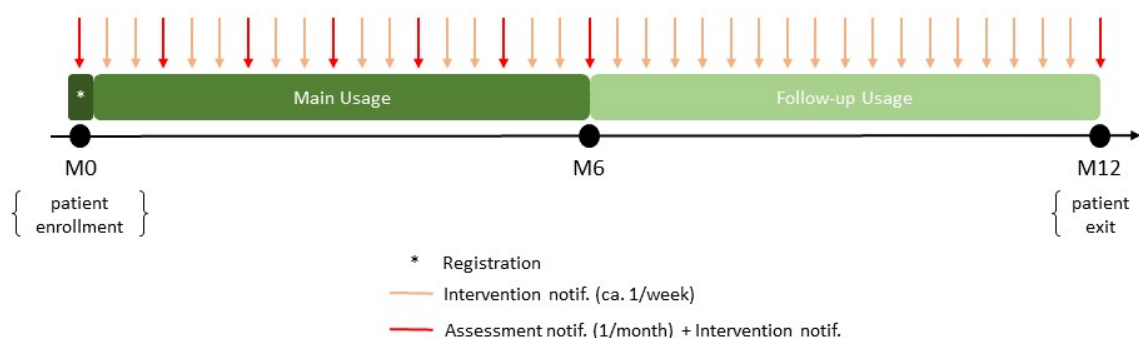


Figure 5. The 3 phases of the usage of the MyPal smartphone app by the patient.

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,



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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.

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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'.



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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

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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.



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5 **5.2 Patient Completion & Withdrawal**

6 Data collection will be considered complete for a participating patient if data available at 12 months after
7 enrolment have been recorded. For deceased and untraceable patients included in the study, the patient
8 will be censored at last observation.
9

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

11 ***Follow up of patients withdrawn from protocol treatment***

12 Investigators will make every reasonable effort to maintain each patient on study until all planned
13 assessments have been performed. Study intervention may be discontinued in case the patient refuses
14 to continue on the study. In case of premature termination, date and reason for early discontinuation will
15 be noted in the source document and the corresponding CRF. All data available for the patient at the
16 time of discontinuation from the study should be recorded in the CRF, and all reasons for discontinuation
17 of study participation must be documented in patient records.
18
19

20 **6 ADVERSE EVENT REPORTING**

21 The collection and reporting of Adverse Events (AEs) will be in accordance with the appropriate
22 competent authorities. Definitions of different types of AE are listed below. The Investigator should
23 assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should
24 be documented in the source data) with reference to the protocol.
25
26

27 **6.1 Reporting Requirements**

28 Although no safety issues are foreseen, the PI will promptly notify all concerned investigators, the Ethics
29 Committee(s) and the regulatory authorities of possible findings that could affect adversely the safety of
30 patients, impact the conduct of the study, increase the risk of participation or otherwise alter the IEC's
31 approval to continue the trial.
32

33 In the occurrence of such an event the PI and the investigators will take appropriate urgent safety
34 measures to protect the patients against any immediate hazard. The local investigator will inform the
35 patients and local ethics or review committees according to hospital policy. The sponsor will inform any
36 other parties that are involved in the trial.
37
38

39 *Safety reports*

40 The PI will submit a first safety report to the IEC/IRB one year after the first approval date of the trial
41 and a second safety report one year after the last patient has completed protocol intervention.
42
43

44 **6.1.1 Adverse Events**

45 An adverse event is any untoward medical occurrence that does not necessarily have a causal link to
46 the intervention studied.
47
48

49 **6.1.2 Serious Adverse Events**

50 A serious adverse event (SAE) is any adverse event that: results in death, is life threatening, requires
51 hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or
52 incapacity, consists of a congenital anomaly or birth defect or anything else the Data Safety Monitoring
53 Board (DSMB) feels is significant. Given the nature of the intervention and the study population not all
54 of the SAE categories will be relevant to the MyPAL Adult study. In non-drug trials, SAEs that are
55 deemed to be related to the research procedure and are unexpected (referred to as SUSARs in drug
56 trials) are also recorded and reported.
57

58 However, in MyPal Adult, it is difficult to predefine the serious risks of the MyPal eHealth system
59 intervention and to define the early stopping rules. The study population consists of individuals facing
60



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

7 We expect that the most likely serious risk of participating in the MyPal intervention is (serious) distress.
8 It should be noted however that symptom reporting is considered to be part of routine care, and as such,
9 we expect the risks to be limited. Filling in questionnaires about physical and psychological symptoms,
10 and quality of life may also be upsetting for patients. However, we expect the risk to be limited as these
11 are validated questionnaires that address issues that are discussed in usual care.
12
13

14 Definition of Serious Distress

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

17 Severe unresolved distress (e.g. unable to be comforted), self-reported self-harm or suicidal thoughts
18 or intent will be reported as SAEs in this study. An event that results in death, is life threatening or
19 requires hospitalization or prolongation of existing hospitalization associated with serious distress will
20 also be reported as an SAE. The DSMB will review all SAEs submitted and make recommendations
21 accordingly. MyPal Adult study partners and the DSMB take the possible occurrence of serious distress
22 due to participation in the trial very seriously.
23

24 No specific pregnancy reporting is required considering the nature of the study.
25
26

27 **6.2 Reporting Procedure**

28 **6.2.1 Adverse Events**

29 All adverse events will be systematically recorded in the CRF and the patient's source records,
30 regardless of seriousness or causality.
31

32 **6.2.2 Serious Adverse Events**

33 Hospital Site Responsibilities

34 Physicians and nurses in the trial hospitals must report serious negative reactions of patients who
35 participate in the study, using a predefined SAE form. The SAE form must be completed by the health
36 care professional with delegated responsibility and signed by the Principal Investigator* or delegated
37 medically qualified individual within 24 hours of becoming aware of the SAE. The form will then be
38 immediately sent to the (insert country) Chief Investigator* The initial form can be sent without the PI or
39 a delegated medically qualified individual's signature if the obtaining of a signature may cause delay in
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5 reporting. In this case, the form needs to be re-sent as soon as possible once it has been signed by the
6 PI or a delegated medically qualified individual.
7

8 The Principal Investigator or a delegated medically qualified individual will assess and document on the
9 SAE form whether they think the SAE is related to the intervention or not.
10

11 Follow up information regarding the SAE will be requested from the hospital research sites as necessary
12 to meet the requirements of the Chief Investigator and the DSMB. This will be submitted on the SAE
13 form.
14

15 All information sent from the hospital sites to the Chief Investigator must only contain the participant's
16 study number and date of birth. No personal identifiable information must be sent.
17

18 Chief Investigator Responsibilities

19 The Chief Investigator will review the SAE form, obtain further information from the study site as
20 necessary and liaise with the DSMB via the MyPal Adult study coordinating centre.
21

22 If the DSMB decides the SAE is related to the intervention and unexpected, the Chief Investigator will
23 report it to the Research Ethics Committee within 15 days as per (insert country) guidelines.
24

25 If the event is deemed unrelated to the trial intervention, no further safety reporting is required regardless
26 of the outcome. The Chief Investigator will inform the Principal Investigator of the DSMB decision in
27 writing.
28

29 The Chief Investigator will contact the Research Ethics Committee by telephone within 24 hours and in
30 writing within 3 days if urgent safety measures have had to be put in place in order to protect research
31 participants against any immediate hazard to their health or safety. (*The Principal Investigator is the
32 person responsible for the individual study research site. * The Chief Investigator is responsible for the
33 conduct of the study in the country.)
34
35
36
37

38 DSMB Responsibilities

39 The DSMB will evaluate the reported events, taking into account differences between intervention and
40 control hospitals. Based on this, the DSMB will recommend to continue, to modify or to stop the MyPal-
41 Adult RCT.
42
43
44

45 **7 DATA HANDLING AND RECORD KEEPING**

46 *Case Report Forms*

47 Data will be collected on Case Report Forms (CRF) to document eligibility, safety and efficacy
48 parameters, compliance to intervention schedules and parameters necessary to evaluate the study
49 endpoints. Data collected on the CRF are derived from the protocol and will include at least:
50

- 51 1. Inclusion and exclusion criteria;
- 52 2. Baseline status of patient including medical history and stage of disease;
- 53 3. Timing of intervention;
- 54 4. Baseline concomitant diseases and adverse events;
- 55 5. Parameters for response evaluation;
- 56 6. Any other parameters necessary to evaluate the study endpoints;
- 57 7. Hospital visits, doctor visits, hospitalizations
- 58 8. Medications, treatments
- 59 9. Investigations (laboratory and imaging)
60



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

7 Each CRF page will be identified by a trial number, and a combination of patient study number (assigned
8 at registration) and hospital name.
9

10 The CRF will be completed on site by the local investigator or sub-investigator or an authorized staff
11 member. The CRF must be signed by the local investigator or sub-investigator upon completion. All
12 CRF entries must be based on source.
13
14

15 **Data Handling and Record keeping of data and documents**

16 The MyPal Adult clinical trial and its participants will conform to relevant national and EU legislation on
17 the protection of individuals with regard to the processing of personal data and on the free movement
18 of such data. All data (paper and electronic) will be treated as confidential. They will be stored securely
19 and they will be anonymised (where possible). Hard copy patient data will be stored in a secure place
20 (locked room, in a locked filing cabinet with limited access) and will be protected from the environment
21 (damp, mould and fire etc) or on a secure CERTH server.
22
23

24 Each clinical trial site will organise monitoring in the sense of examining whether data collection
25 processes and record keeping are executed properly locally (in study site files) and note all deviations
26 from standard operating procedures and study protocol requirements. In addition, the trial manager will
27 be responsible for oversight of trial documentation and record keeping.
28
29

30 *Archiving*

31 All of the studies essential¹ documents will be retained and archived for 10 years after completion of the
32 study. They will be stored securely and adequately protected from fire, flood, pest and extreme weather.
33 With respondents' permission, anonymised data collected during this study may be used for secondary
34 data analysis in future projects.
35
36
37

38 **8 REPORTING**

39 **8.1 Annual progress report**

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

41 The sponsor will submit a summary of the progress of the trial to the Ethic Committees once a year. The
42 first report is sent one year after the first approval date of the trial. The last report is sent one year after
43 the last patient has completed protocol treatment. Progress reports will include information regarding:
44
45

- 46 ▪ the date of inclusion of the first patient,
 - 47 ▪ numbers of patients included and numbers of patients that have completed the trial,
 - 48 ▪ screening failure and reasons for screening failure
 - 49 ▪ serious adverse events,
 - 50 ▪ any other issues and amendments.
- 51
52

53 **8.2 End of trial report**

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

56 In case the study is ended prematurely, the sponsor will notify the ECs and the competent authority
57 within 15 days, indicating the reasons for the premature termination.
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5 Within one year after the primary endpoint analysis of the trial, the sponsor will submit an end of study
6 report with the results of the study, including any publications/abstracts of the study, to the ECs and
7 the Competent Authority.
8

9 QUALITY MANAGEMENT

10 9.1 Site Set-up and Initiation

11 *Regulatory Documentation*

12 Regulatory and administrative documents will be provided by the PI (or delegated representative) and
13 require local Ethical Committee (EC) approval for each investigational site before enrolling the first
14 patient. The EC approval should be notified to the sponsor (or delegated representative). When all
15 requirements are met, each investigational site will be notified by the sponsor that enrolment started is
16 authorized.
17

18 *Registration*

19 Eligible patients should be registered before start of intervention.

20 All eligibility criteria will be checked with a checklist.

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

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

25 Data collected on the CRF will be verified for accuracy. If necessary, queries will be sent to the
26 investigational site to clarify the data on the CRF. The investigator should answer data queries within
27 the specified timeline.
28

29 9.2 Audit and Inspection

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

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

34 Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the
35 results of this study. The investigator should immediately notify the sponsor if they have been contacted
36 by a regulatory agency concerning an upcoming inspection.
37

38 10 END OF TRIAL DEFINITION

39 The end of the study will be the last data collection time point within the study for the last participating
40 patient.
41

42 11 STATISTICAL CONSIDERATIONS

43 11.1 Sample Size

44 Assuming relatively acceptable values for the attrition rate (i.e., 20%) and the missing data (i.e., 30%),
45 the sample size analysis concluded that 300 recruited patients providing one measure at enrolment
46 (baseline) and 7 repeated measures (at Months 1, 2, 3, 4, 5, 6 and 12) are sufficient for the power of
47 the intended statistical testing to be over 90% in all cases, given (a) a 0.05 significance level, and (b) an
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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*Power⁶⁷ 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 3, 4, 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 $\alpha=0.05$, in accordance with the power calculation. We will also perform

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



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

7 Patients will be followed for survival status until the end of the study. Overall survival (OS) will be
8 analyzed by Kaplan-Meier methodology using data from all enrolled patients. Median time survival will
9 be estimated and 0.95 confidence interval for the median time survival will be presented.
10

11 **11.3 Planned Sub Group Analyses**

12 Subgroup analysis of the outcome measures will also be performed at baseline, Month 6 and Month 12
13 of the study using one-, two- and three-way ANOVA in order to detect potential differences between
14 specific groups of participants. The grouping variables that will be employed are (a) the clinical center
15 (origin), (b) the country of residence, (c) the age group, (d) the disease stage, and (e) the diagnosis
16 (CLL, MDS). The level of significance for all statistical tests is set to $\alpha=0.05$, in accordance with the
17 power calculations. In the case an interaction effect is observed, separate subgroup analyses in the CLL
18 and MDS cohorts with repeated measures ANOVA will be performed to assess the effect of intervention
19 on quality of life and other the outcome measures.
20
21
22

23 **11.4 Planned Interim Analysis**

24 Since the present trial does not concern primary treatment (as it is the case for example for a
25 pharmacological trial), no substantial risks for the life and health of the study subjects are expected as
26 a result of the intervention or lack thereof. For this reason, interim statistics analysis of the results is not
27 needed and it will not be performed. Instead, the data monitoring committee will be responsible for
28 verifying the quality and completeness of the collected assessment data, using data science rather than
29 statistical methods. Every 3 months the data monitoring committee will be performing automated checks
30 via developed programming scripts for missing data based on predefined metrics that will assess the
31 extent of missing/incomplete data across several dimensions (percentage of missing data per study
32 participant, per assessment instrument, per assessment instrument component, per assessment
33 iteration, etc.)
34
35
36

37 **11.5 Planned Final Analyses**

38 The final analysis will take place after the end of the study (i.e., 30.03.2022) and it will be performed as
39 described in Analysis of Outcome Measures and the Planned Subgroup Analysis sections above. On
40 top of that, repeated measures multivariate ANOVA (MANOVA) will be applied with the quality of life
41 assessed by outcome measure 1 and 2 serving as the pair of dependent variables. The level of
42 significance for all statistical tests is set to $\alpha=0.05$, in accordance with the power calculations.
43
44
45

46 **12 TRIAL ORGANIZATIONAL STRUCTURE**

47 **12.1 Sponsor**

48 CERTH (partner 1, Greece) will be the Sponsor of the clinical trial, while the collaborating clinical sites
49 are the following:

50 Collaborators

51 CERTH (partner 1, Greece; through the affiliated G. Papanicolaou Hospital, Thessaloniki, Greece)

52 Karolinska Institutet (partner 6, Sweden)

53 Università Vita-Salute San Raffaele (partner 7, Italy)

54 University Hospital of Crete (partner 8, Greece)

55 University Hospital Brno (partner 10, Czech Republic)
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5 **12.2 Coordinating Centre**

6 The coordinating Centre will be Università Vita-Salute San Raffaele in Milan, Italy. It will be responsible
7 for overall data management, monitoring and communication among all sites, and general oversight of
8 the clinical trial conduct.
9

10 **12.3 Trial Management Committee**

11 The Trial Management Committee (TMC) will consist of a trial manager, the principal investigator and
12 representative investigators from each clinical site or/as well as other members of the trial team with
13 specific expertise i.e. Statistician, Health Economist, Database Programmer etc. Its main duty is to
14 manage the trial including clinical and practical aspects.
15

16 Specifically, to:

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

26 The TMC will virtually meet biweekly frequently during the set-up and start of the trial and quarterly until
27 the end of the trial.
28

29 **12.4 Data Monitoring Committee**

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

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

37 The DSMC will have access to unblinded data during the course of the trial and will monitor accumulating
38 data from the trial at pre-specified intervals. Any safety or ethical issues will be brought to the attention
39 of the investigators and the TSC. Meetings will be held every 6-12 months.
40

41 **12.5 Internal Ethics Committee**

42 It is the committee authorized by the Trial Management Committee to review documents (e.g. informed
43 consent) and tools (i.e. digital presentation of PROs), necessary for the conduct of the clinical trial. More
44 specifically, it is meant to safeguard the rights, safety, dignity and well-being of research participants. It
45 consists of three members, namely a chair expert in bioethics and two oncologists/ hematologists.
46

47 **12.6 Finance**

48 No individual per patient payment will be made to healthcare providers, Investigators or patients.
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5 **13 ETHICAL CONSIDERATIONS**

7 The protection of the autonomy of research participants with respect to their privacy, beneficence and
8 dignity is of paramount concern and an internal Ethics Committee will monitor this aspect of the trial
9 implementation in collaboration with the local investigator. Thus, the study will be conducted in
10 accordance with the ethical principles of the Declaration of Helsinki, the ICH-GCP Guidelines, the
11 General Data Protection Regulation (GDPR)⁶⁸, the EU Clinical Trial Directive (2001/20/EC)⁶⁹, the EU
12 Clinical Trials Regulation (EU No 536/2014)⁷⁰ and applicable regulatory requirements. The local
13 investigator is responsible for the proper conduct of the study at the study site.
14

15 **13.1 Scientific Advice / Protocol Assistance**

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

- 19 – The study will incorporate scientific advice and follow relevant scientific guidelines on palliative
20 care (mentioned in Section 1.2.3);
- 21 – The study investigators will contact regulators at national level when appropriate;
- 22 – The PI will check relevant submission timelines and deadlines;
- 23 – The study will incorporate regulatory input by EMA and the local authorities throughout the
24 project and at all stages of the intervention.
25

26 **13.2 Screening**

27 MyPal will use a carefully-crafted, multicomponent, evidenced-based recruitment protocol fusing
28 evidence-based strategies with principles of “social marketing,” an approach involving the systematic
29 application of marketing techniques⁷¹. Main components will include (1) an inclusive triage algorithm,
30 (2) information booklets targeting particular stakeholders, (3) a specialized recruitment nurse, and (4)
31 standardization of wording across all study communications. Another key feature of our strategy pertains
32 to broad eligibility criteria within the selected hematologic cancers. The difficulties that may be
33 encountered in this study relate to the inherent problems being associated with palliative care research⁷².
34 To overcome these difficulties, the study will be multi-center in nature, involving centers of excellence
35 in the respective disease areas as well as expertise in the various aspects of such studies including
36 those related to ethics.
37

38 **13.3 Informed Consent**

39 Written informed consent of patients is required before enrolment in the trial and before any study related
40 procedures, and only after information has been provided to them regarding the voluntary character of
41 participation, the purpose of the study, the procedures involved, the management of possible risks or
42 incidental findings as well as ways to deal the safeguards for the protection of the participant’s personal
43 data and privacy and the right to withdraw at any time for the study. Before informed consent may be
44 obtained, the investigator should provide the patient time and opportunity to inquire about details of the
45 trial and to decide whether or not to participate in the trial. A copy of the informed consent form will be
46 given to the subject and the original will be kept at site. An entry must also be made in the subject's
47 dated source documents to confirm that informed consent was indeed obtained prior to any study-related
48 procedures and that the subject received a signed copy.
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56 ⁶⁸ <https://www.eugdpr.org>

57 ⁶⁹ https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

58 ⁷⁰ https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

59 ⁷¹ LeBlanc TW, Lodato JE, Currow DC, Abernethy AP. Overcoming recruitment challenges in palliative care clinical trials.
60 *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.



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

7 Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the informed
8 consent and all other forms of subject information related to the study (e.g., advertisements used to
9 recruit subjects) and any other necessary documents be reviewed by an independent Research Ethics
10 Committee (REC). The REC will review the ethical, scientific and medical appropriateness of the study
11 before it is conducted and the approval will be obtained prior to the initiation of the study in each study
12 site. Any amendments to the protocol including substantially revised informed consent forms and
13 information sheets will require new REC approval and approval by Regulatory Authority(ies), if required
14 by local regulations, prior to implementation of any changes made to the study design. Consequently,
15 the patient should be informed in a timely manner if new information becomes available that might be
16 relevant to the patient's willingness to continue participation in the trial. The communication of this
17 information should be documented.
18

19 The investigator will be required to submit, maintain and archive study essential documents according
20 to International Conference on Harmonization (ICH) GCP.
21
22

23 **13.4 Withdrawal of Informed Consent**

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

- 26 • The patient can refuse further participation and/or procedures according to protocol, while still
27 consenting with further follow up data collection.
- 28 • The patient can refuse further participation and/or procedures according to protocol, and
29 withdraw consent for further follow up data collection.
- 30 • The patient can refuse further participation and/or procedures according to protocol, withdraw
31 consent for further follow up data collection and withdraw consent to use any data in the study.
32
33
34

35 **14 CONFIDENTIALITY AND DATA PROTECTION**

36 **14.1 Patient Confidentiality**

37 Each patient is assigned a unique patient study number at enrolment. In trial documents the patient's
38 identity is coded by patient study number as assigned at enrolment. The data will be collected, stored
39 and accessed in a way that will ensure privacy of participants and compliance with data protection
40 legislation, in particular regulation 679/2016.
41

42 The local investigator will keep a subject enrolment and identification log that contains the key to the
43 code, i.e. a record of the personal identification data linked to each patient study number. This record is
44 filed at the investigational site and should only be accessed by the investigator and the supporting
45 hospital staff, and by representatives of the sponsor or a regulatory agency for the purpose of monitoring
46 visits or audits and inspections
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50 **14.2 Filing of Essential Documents**

51 Essential Documents are defined as those documents that are needed to evaluate the conduct of a trial
52 and the quality of the data produced. The essential documents may be subject to, and should be
53 available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).
54

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

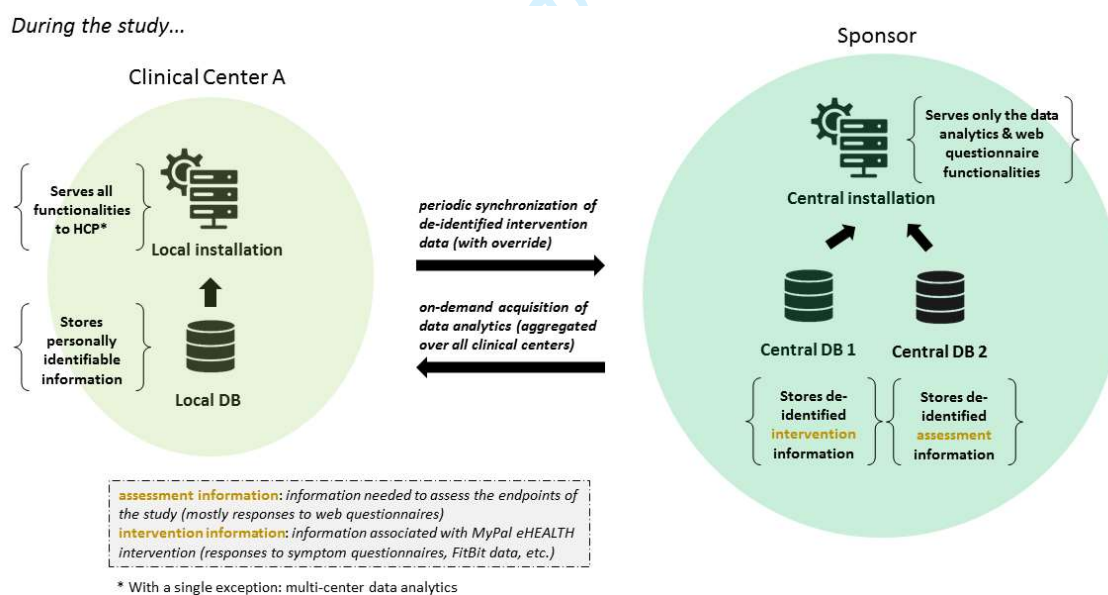


Figure 5. MyPal platform deployment

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,



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5 phone number, etc.) and clinical information (gender, disease stage/risk, treatment scheme, expected
6 outcome, functional impairment, etc.) is also stored in the local database. Concerning the clinical
7 information, the (a) age and (b) diagnosis of the study subject are categorized before storage.
8

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

- 11 (1) The provision of data analytics that pertain to the entire, multi-center group of study participants.
12 The functionality at hand aggregates de-identified intervention data coming from all the
13 participating clinical centers. At a predefined period (e.g., once per week), the local intervention
14 data are de-identified and subsequently synchronized with the central installation, where they
15 are stored in the 1st central database overwriting the previous data. De-identification is
16 performed by removing all the personal data and keeping among the clinical data only the
17 categorized age and diagnosis information. The provenance of the data (i.e., the clinical center
18 the data come from) is also retained. At the same time, the responsible modules of the central
19 installation calculate the study-wide aggregated data analytics and expose them to the local
20 installations, which consume them on demand.
21
22 (2) The hosting of the web-based questionnaires that are associated with the endpoints of the
23 study. The responses of the study subjects to these questionnaires constitute the core of the
24 assessment data of the MyPal platform. The latter are stored in the 2nd central database in a
25 completely de-identified manner. The assessment data of each study subject are accompanied
26 only by following pieces of information: provenance, categorized age, and categorized
27 diagnosis, which are intended for subgroup analysis and are already available to the central
28 installation for the purposes of the data analytics functionality.
29
30

31 **15 INSURANCE AND INDEMNITY**

32
33 Prior to the start of the trial, the Sponsor is responsible to ensure that adequate insurance for patients
34 participating to the trial is subscribed, in accordance with applicable laws and regulations. Proof of
35 insurance will be submitted to the Ethics Committee.
36
37

38 **16 PUBLICATION POLICY**

39 Results of the study will be owned by the Investigators. IPR management will be considered and
40 addressed within a dedicated IP Agreement, drafted and agreed as part of the Agreement prior to
41 commencing the study.
42

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

8 **Information Sheet for Adult Patients**

11 **MyPal: Fostering Palliative Care of Adults and Children with Cancer through Advanced Patient 12 Reported Outcome Systems**

15 We would like to invite you to participate in a study conducted by Dr and his/her team at the
16 University of Before you decide to take part in this study it is important that you understand why
17 it is being done and what it will involve. Please take time to read the following information carefully and
18 to decide whether or not you wish to take part.
19

21 **Aims of the study:** In this study (which is part of a larger project that will be conducted across four
22 European countries), we are interested in exploring the use of digital technology that will empower you
23 (and possibly members of your family) to communicate your condition more accurately and effectively
24 to your healthcare providers (i.e. oncologists, specialized physicians, psychologists, nurses). The aim is
25 to improve the quality of care by using modern methods of individualized information, communication
26 and support for patients with cancer and by promoting what we call a patient-centered approach through
27 the use of Patient Reported Outcome platforms. It is important for you to know that MyPal is not an alert
28 system and that doctors may not respond immediately as the study does not aim to provide or change
29 medical treatment. Supportive information provided by healthcare providers via the application (e.g. a
30 search engine for medication) does not imply legal liability.
31
32

34 **Why you have been chosen:** You have been chosen to participate in this study because you are over
35 18 years of age and because you have been diagnosed with chronic lymphocytic leukemia (CLL) or
36 myelodysplastic syndrome (MDS). Also, because you are fit to participate in the study and you are able
37 to use an Internet connected device. The feedback you provide will help us to adapt and improve the
38 acceptability and the performance of the various tools.
39

41 **What do you have to do:** If you volunteer to help us accomplish these aims, you will be randomly
42 assigned either to the intervention group which will use the MyPal system, or to the control group which
43 will receive the palliative care services normally provided. The study is a non-pharmacological ICTbased
44 (Information and Communications Technology) intervention and as such it does NOT involve collection
45 of biological samples or administration of any medication.
46
47

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

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

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

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

- 55 a) 4 self-report questionnaires at baseline, and then every month for the six following months,
56 b) the same 4 self-report questionnaires as a follow up at the end of the study, at the clinical site of the
57 research
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5 These 4 questionnaires are: two QOL questionnaires (the EORTC QoL and the Euroqol), the EORTC
6 satisfaction with cancer care questionnaire and the Integrated Palliative Care Outcome Scale.
7

8
9 Depending on the group on which you participate you may additionally have to respond to the Brief Pain
10 Inventory the Edmonton Symptom Assessment Scale and the Emotional Thermometers) in order to
11 evaluate your symptoms, the degree of your pain, your anxiety, the quality of your life during different
12 days or the satisfaction you get from your treatment. Your responses will provide the kind of information
13 that will enable the design and development of flexible tools responding to your different needs and
14 views.
15

16 If needed, a member of the research team will be available to help you complete the questionnaires.
17

18 **Will your taking part in this project be kept confidential?** Data protection is one of our most important
19 concerns in this study. National laws on personal data protection will be implemented in order to
20 guarantee the highest standards of personal data management. All procedures for protecting personal
21 information in this study are in accordance with the approved rules of the University of XXXXXXXX and
22 with the European legislation and the General Data Protection Regulation 2016/679. Only data that is
23 necessary for this research will be collected. Our technology partners will provide technical support and
24 tools regarding data security in order to mitigate data security risks. Any information that is obtained in
25 connection with this study and that can be identified with you will remain confidential. A computer
26 generated number, will be assigned to you at enrolment and your data will be pseudonymised. This
27 means that your name and other direct identifiers will be separated from the collected research data so
28 that your identity is protected and links to your identity will not be possible.
29

30
31 If you agree to take part in the study, we will use your data in the way needed to conduct the research
32 and analyze the research results. Your rights to access, change or move your information are limited,
33 as we need to manage your information in specific ways in order for the study to be reliable and accurate.
34

35 Data will be collected through a number of different tools: some of these have been already developed,
36 and some are new in this study. The data collected from the fit-bit wristwatch are stored on the FitBit
37 server and are retrieved from it by the MyPal app once per day to be stored in the My Pal server,
38 according to all data protection safeguards applying in this project. All medical data pertaining to your
39 care and treatment obtained during the project will be kept for 15 years in (name of the clinical site)
40 where they were collected or created. The data, however, that has been collected for the purposes of
41 the study, will be kept at the central installation of the sponsor of the study, CERTH, after having been
42 de-identified. De-identification is performed by removing all the personal data and keeping only the
43 categorized age, diagnosis information and the clinical centre where the data came from. This central
44 installation fulfills all technical and organizational requirements for the safety and the security of the
45 stored data. In case you have concerns or queries or you feel should lodge a complaint with Data
46 protection authorities, you can contact the Data Protection Officer of our Research Institution: Name of
47 the DPO, ... e-mail: ...
48
49

50
51 **Do you have to participate?** Participation is absolutely voluntary. If you decide to participate, you are
52 free to withdraw at any time without giving any reason and without there being any negative
53 consequences. Your decision whether or not to participate will not affect your relationship with the
54 researchers or with the team managing your care. With regard to the various questionnaires involved,
55 you can choose not to answer any particular question or questions. You can freely decide to withdraw
56 from the study once data collection has commenced, without giving a reason for withdrawal. Data
57 collected cannot be erased, but is anonymized and will be retained and included in the study in an
58 anonymized form. But no further data will be collected from you after your withdrawal. Once the research
59
60



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5 is complete, and the data analyzed, it is not possible to withdraw your data from the study. The whole
6 duration of the study will be 12 months.
7

8
9 **Are there possible disadvantages and/or risks in taking part?** The nature of this study means that
10 your participation does not entail any risk of physical discomfort, pain, injury, illness or disease. We do
11 not envisage any adverse or incidental findings, as these usually refer to medical problems discovered
12 in the course of a different type of research/clinical trial. However, if we come across an unexpected
13 finding, what we plan to do is to inform you, to discuss this in our team, and to consult with your treating
14 physician. If you have any concerns you are free to contact the Principal Investigator (see below for
15 details) and once again, we would like to remind you that your participation is entirely voluntary.
16
17

18 **What are the possible benefits of taking part?** You may not receive any personal benefits from
19 participating in this research. However, you may find your participation is a positive experience through
20 the use of the various tools and applications as well as contributing to the improvement of the role of
21 patients like yourself in the process of their treatment.
22
23

24 **Transfer of data:** data collected during the My Pal project will be shared among the collaborating
25 research teams but will never be transferred to countries outside of the European Union.
26
27

28 **What will happen to the results of the study?** The results will be used only for research purposes;
29 they may be reported in research publications and may be made available to other researchers in an
30 anonymized form. In every research output (papers, presentations, articles, reports) the total anonymity
31 of your data will be protected.
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34 **Ethical approval:** This study has been approved by the Research Ethics Committee of the University
35 of....
36
37

38 **Contact for further information:** please do not hesitate to contact the Principal Investigator, Dr
39email.....
40

41 Tel: +XX(..) ... at any moment with questions or concerns about the study.
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48 **Informed Consent Form for Adult Patients**

49 I confirm that I have read and understood the information sheet explaining the above research project
50 and I have had the opportunity to ask questions about it.
51

52 I understand that I will be randomly assigned to either:

- 53 • a group which will use the MyPal system, (called “the intervention group”) or to
- 54 • a group which will only receive usual palliative care if so desired (called the “control group”)
- 55
- 56

57 I consent:

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

59 to respond to the required burden of questionnaire completion and to complete
60



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- 5 a) 4 self-report questionnaires at baseline, and then every month for the six following months,
6 b) the same 4 self-report questionnaires as a follow up at the end of the study, in the site where the
7 study took place.

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

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

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

12 to respond to 3 questionnaires at baseline and every week until the end of the project - on physical
13 symptoms Brief Pain Inventory, Edmonton Symptom Assessment Scale and emotional symptoms the
14 Emotional Thermometers.
15
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17

18 By ticking each box below I confirm that:

19 I am aware that NO biological samples will be collected.

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

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

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

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

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

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

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

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

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

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

For peer review only



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <input checked="" type="checkbox"/> Page 1 row 1 of the manuscript and Page 1 row 19 of the synopsis
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <input checked="" type="checkbox"/> Page 3 row 29 of the manuscript
	2b	All items from the World Health Organization Trial Registration Data Set <input checked="" type="checkbox"/> Page 1 and 2 of the Synopsis
Protocol version	3	Date and version identifier <input checked="" type="checkbox"/> Page 1 of the Synopsis
Funding	4	Sources and types of financial, material, and other support <input checked="" type="checkbox"/> Not applicable
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <input checked="" type="checkbox"/> Page 1 row 41 of the Synopsis
	5b	Name and contact information for the trial sponsor <input checked="" type="checkbox"/> Page 2 row 8 of the Synopsis
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities <input checked="" type="checkbox"/> Page 30 row 50 of the Protocol
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) <input checked="" type="checkbox"/> Page 2 row 26 of the Synopsis
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention <input checked="" type="checkbox"/> Page 6 row 17 of the manuscript and Page 3 row 7 of the Protocol

1			
2		6b	Explanation for choice of comparators <input checked="" type="checkbox"/> Page 9 of the Protocol
3			
4	Objectives	7	Specific objectives or hypotheses <input checked="" type="checkbox"/> Page 7 row 8 of the manuscript and Page 11 row 26 of the Protocol
5			
6			
7	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) <input checked="" type="checkbox"/> Page 6 row 30 “Study Design” of the manuscript and Page 12 row 24 of the Protocol
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Methods: Participants, interventions, and outcomes

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16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained <input checked="" type="checkbox"/> Page 8 row 3 of the manuscript “Patient recruitment”
17			
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22	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) <input checked="" type="checkbox"/> Page 8 row 17 of the manuscript (Box 1: Eligibility criteria) and Page 16 row 42 of the Protocol
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29	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered <input checked="" type="checkbox"/> Page 9 row 3 of the manuscript and Page 17 row 14 of the Protocol
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33		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) <input checked="" type="checkbox"/> Page 24 row 5 of the Protocol
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39		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) <input checked="" type="checkbox"/> Page 13 Table 2 “Discussion guide” of the manuscript and Page 5 row 16 of the Protocol
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45		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial <input checked="" type="checkbox"/> Not applicable
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48	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended <input checked="" type="checkbox"/> Page 7 row 10 of the manuscript and Page 11 row 31 of the Protocol
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2	Participant	13	Time schedule of enrolment, interventions (including any run-ins and
3	timeline		washouts), assessments, and visits for participants. A schematic
4			diagram is highly recommended (see Figure) <input checked="" type="checkbox"/> Figure 1 of the
5			manuscript and Page 13 Figure 1 of the Protocol
6			
7	Sample size	14	Estimated number of participants needed to achieve study objectives
8			and how it was determined, including clinical and statistical
9			assumptions supporting any sample size calculations <input checked="" type="checkbox"/> Page 16
10			row 19 of the manuscript and Page 28 row 54 of the Protocol
11			
12			
13	Recruitment	15	Strategies for achieving adequate participant enrolment to reach
14			target sample size <input checked="" type="checkbox"/> Not applicable
15			

Methods: Assignment of interventions (for controlled trials)

Allocation:

20			
21	Sequence	16a	Method of generating the allocation sequence (eg, computer-
22	generation		generated random numbers), and list of any factors for stratification.
23			To reduce predictability of a random sequence, details of any
24			planned restriction (eg, blocking) should be provided in a separate
25			document that is unavailable to those who enrol participants or
26			assign interventions <input checked="" type="checkbox"/> Page 9 row 3 of the manuscript
27			
28	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
29	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
30	mechanism		describing any steps to conceal the sequence until interventions are
31			assigned <input checked="" type="checkbox"/> Not applicable
32			
33			
34	Implementatio	16c	Who will generate the allocation sequence, who will enrol
35	n		participants, and who will assign participants to interventions <input checked="" type="checkbox"/> Page
36			9 row 6 of the manuscript
37			
38	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
39	(masking)		participants, care providers, outcome assessors, data analysts), and
40			how <input checked="" type="checkbox"/> Not applicable
41			
42			
43		17b	If blinded, circumstances under which unblinding is permissible, and
44			procedure for revealing a participant's allocated intervention during
45			the trial <input checked="" type="checkbox"/> Not applicable
46			

Methods: Data collection, management, and analysis

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49	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
50	methods		trial data, including any related processes to promote data quality
51			(eg, duplicate measurements, training of assessors) and a
52			description of study instruments (eg, questionnaires, laboratory tests)
53			along with their reliability and validity, if known. Reference to where
54			data collection forms can be found, if not in the protocol <input checked="" type="checkbox"/> Page 14
55			row 3 of the manuscript
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2		18b	Plans to promote participant retention and complete follow-up,
3			including list of any outcome data to be collected for participants who
4			discontinue or deviate from intervention protocols <input checked="" type="checkbox"/> Page 24 row 5
5			of the Protocol
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8	Data	19	Plans for data entry, coding, security, and storage, including any
9	management		related processes to promote data quality (eg, double data entry;
10			range checks for data values). Reference to where details of data
11			management procedures can be found, if not in the protocol <input checked="" type="checkbox"/> Page
12			15 row 31 of the manuscript and Page 34 row 25 of the Protocol,
13			Page 30 row 30 of the Protocol, Page 31 row 39 of the Protocol
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16	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
17	methods		Reference to where other details of the statistical analysis plan can
18			be found, if not in the protocol <input checked="" type="checkbox"/> Page 16 row 27 of the manuscript
19			and Page 28 row 52 of the Protocol
20			
21		20b	Methods for any additional analyses (eg, subgroup and adjusted
22			analyses) <input checked="" type="checkbox"/> Page 30 row 12 of the Protocol
23			
24		20c	Definition of analysis population relating to protocol non-adherence
25			(eg, as randomised analysis), and any statistical methods to handle
26			missing data (eg, multiple imputation) <input checked="" type="checkbox"/> Page 30 row 24 of the
27			Protocol
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30	Methods: Monitoring		
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32	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its
33			role and reporting structure; statement of whether it is independent
34			from the sponsor and competing interests; and reference to where
35			further details about its charter can be found, if not in the protocol.
36			Alternatively, an explanation of why a DMC is not needed <input checked="" type="checkbox"/> Page 17
37			row 10 of the manuscript
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40		21b	Description of any interim analyses and stopping guidelines,
41			including who will have access to these interim results and make the
42			final decision to terminate the trial <input checked="" type="checkbox"/> Page 30 row 24 of the
43			Protocol
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46	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
47			spontaneously reported adverse events and other unintended effects
48			of trial interventions or trial conduct <input checked="" type="checkbox"/> Page 17 row 20 of the
49			manuscript and Page 24 row 21 of the Protocol
50			
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52	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
53			whether the process will be independent from investigators and the
54			sponsor <input checked="" type="checkbox"/> Page 28 row 35 of the Protocol
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57	Ethics and dissemination		
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2	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval <input checked="" type="checkbox"/> Page 21 row 1 of the manuscript
3			
4			
5	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) <input checked="" type="checkbox"/> Page 33 row 13 of the Protocol
6			
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10	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) <input checked="" type="checkbox"/> Page 32 row 41 of the Protocol
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15		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable <input checked="" type="checkbox"/> Not applicable
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19	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial <input checked="" type="checkbox"/> Page 33 row 36 of the Protocol
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25	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site <input checked="" type="checkbox"/> Page 20 row 29 of the manuscript
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29	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators <input checked="" type="checkbox"/> Not applicable
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34	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation <input checked="" type="checkbox"/> Not applicable
35			
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38	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions <input checked="" type="checkbox"/> Page 3 row 18 of the manuscript and Page 14 Table 8 of the Protocol, Page 35 row 38 of the Protocol
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47		31b	Authorship eligibility guidelines and any intended use of professional writers <input checked="" type="checkbox"/> Not applicable
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50		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code <input checked="" type="checkbox"/> Not applicable
51			
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54	Appendices		
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56	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates <input checked="" type="checkbox"/> Page 36 of the Protocol Appendix
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2 Biological 33 Plans for collection, laboratory evaluation, and storage of biological
3 specimens genetic or molecular analysis in the current trial and
4 for future use in ancillary studies, if applicable **Not applicable**
5

6 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
7 Explanation & Elaboration for important clarification on the items. Amendments to the
8 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
9 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"
10 license.
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