Use of a Digital Medical Device to Improve Therapeutic Adherence in Patients with Hematological Malignancies: the MargheRITA Study

Alessandro Ferri, Sarena Dalto, Antonella Romanelli, Martina Violati, Carlotta Galeone, Davide Gaudesi, Francesca Sacchi, Massimo Beccaria, Mauro Moroni, Vittorio Montefusco

Submitted to: JMIR mHealth and uHealth
on: April 18, 2024

Table of Contents

Use of a Digital Medical Device to Improve Therapeutic Adherence in Patients with Hematological Malignancies: the MargheRITA Study

Alessandro Ferri[1]; Sarena Dalto[2]; Antonella Romanelli[2]; Martina Violati[2]; Carlotta Galeone[3]; Davide Gaudesi[1]; Francesca Sacchi[1]; Massimo Beccaria[1]; Mauro Moroni[4]; Vittorio Montefusco[2]

[1]Advice Pharma Group S.r.l. (Italy) Milano IT
[2]Hematology Division, ASST Santi Paolo e Carlo Milano IT
[3]Biostatistics & Outcome Research, Statinfo, Milan, Italy; Bicocca Applied Statistics Center (B-ASC), Universita degli Studi di Milano-Bicocca Milano IT
[4]Oncology Division, ASST Santi Paolo e Carlo Milano IT

Corresponding Author:
Alessandro Ferri
Advice Pharma Group S.r.l. (Italy)
Via G. Durando 38 20158 Milano c/o Polihub Politecnico di Milano
Milano
IT

Abstract

Background: Oncological conditions are a global health challenge, with a substantial number of deaths each year. Treatment adherence is crucial for improving patient outcomes in patients with hematological malignancies, but resource limitations and logistical challenges hinder optimal outpatient management. Digital health solutions, such as the Remote Intelligence for Therapeutic Adherence (RITA) software as medical device (SaMD), offer potential solutions by facilitating telemedicine visits and supporting patients in managing their treatment.

Objective: To evaluate the performance and safety of RITA SaMD in improving patient adherence to treatment protocols for hematological malignancies.

Methods: This prospective clinical investigation involved patients with hematological malignancies at ASST Santi Paolo e Carlo in Milan, Italy. The RITA SaMD Group used the RITA platform, while the Control Group comprised historical patients. The primary endpoint was therapeutic adherence to the prescribed drug treatment, defined as at least 80% of the prescribed dose intensity, at Month 3. Secondary endpoints included therapeutic adherence to the prescribed drug treatment at Month 1 and 2, emergency room (ER) visits, adverse events (AEs), and patient-reported outcomes (PROs). Multivariable logistic regression models were used to evaluate the effectiveness of RITA.

Results: Between July and December 2022, 119 patients were included in the analysis (57 in the RITA SaMD Group and 62 in the Control Group). The probability of being adherent to treatment tended to be higher at all time points in the RITA SaMD Group compared with the Control Group (82.1% vs 80.7% at Month 1, 81.1% vs 76.3% at Month 2, and 85.2% vs 77.1% at Month 3). Multivariable analysis confirmed significantly improved adherence in the RITA SaMD Group at Month 3 [odds ratio (OR): 3.0, 95% confidence interval (CI): 1.0–8.8, P=0.042]. A total of 1476 self-reported AEs were collected through RITA SaMD usage, the majority (N=1080) being Grade 1 events. During the study visits, a total of 20 AEs was recorded by the study physician, 16 in the RITA SaMD Group and 4 in the Control Group. Of the recorded AEs during study visits, 14 were SAEs (11 in the RITA SaMD Group and 3 in the Control Group). None of the reported AEs was considered related to RITA SaMD usage.

Conclusions: The MargheRITA clinical investigation showed that after 3 months of using the RITA SaMD, patients with hematological malignancies had 3 times higher OR of being adherent to the prescribed treatment than the Control Group. The use of RITA SaMD facilitated the reporting of AEs and PROs, reinforcing the role of mobile health apps and software in optimizing patient outcomes. Further research is needed to fully understand its interdisciplinary potential and long-term impact on patient outcomes. Clinical Trial: ClinicalTrials.gov Identifier NCT05260203

(JMIR Preprints 18/04/2024:59662)
DOI: https://doi.org/10.2196/preprints.59662

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.
No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**
Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Original Manuscript

Title

Use of a Digital Medical Device to Improve Therapeutic Adherence in Patients with Hematological Malignancies: the MargheRITA Study

Authors

Sarena Dalto[1], Antonella Romanelli[1], Martina Violati[1], Carlotta Galeone[2], Davide Gaudesi[3], Francesca Sacchi[3,] Massimo Beccaria[3], Mauro Moroni[4], Alessandro Ferri[3], Vittorio Montefusco[1]

Affiliations

[1] Hematology Division, ASST Santi Paolo e Carlo, Milano

[2] Biostatistics & Outcome Research, Statinfo, Milan, Italy; Bicocca Applied Statistics Center (B-ASC), Universita degli Studi di Milano-Bicocca, Milan, Italy

[3] Advice Pharma Group S.r.l. (Italy)

[4] Oncology Division, ASST Santi Paolo e Carlo, Milano

Abstract

Background: Oncological conditions are a global health challenge, with a substantial number of deaths each year. Treatment adherence is crucial for improving patient outcomes in patients with hematological malignancies, but resource limitations and logistical challenges hinder optimal outpatient management. Digital health solutions, such as the Remote Intelligence for Therapeutic Adherence (RITA) software as medical device (SaMD), offer potential solutions by facilitating telemedicine visits and supporting patients in managing their treatment.

Objective: To evaluate the performance and safety of RITA SaMD in improving patient adherence to treatment protocols for hematological malignancies.

Methods: This prospective clinical investigation involved patients with hematological malignancies at ASST Santi Paolo e Carlo in Milan, Italy. The RITA SaMD Group used the RITA platform, while the Control Group comprised historical patients. The primary endpoint was therapeutic adherence to the prescribed drug treatment, defined as at least 80% of the prescribed dose intensity, at Month 3. Secondary endpoints included therapeutic adherence to the prescribed drug treatment at Month 1 and 2, emergency room (ER) visits, adverse events (AEs), and patient-reported outcomes (PROs). Multivariable logistic regression models were used to evaluate the effectiveness of RITA.

Results: Between July and December 2022, 119 patients were included in the analysis (57 in the RITA SaMD Group and 62 in the Control Group). The probability of being adherent to treatment tended to be higher at all time points in the RITA SaMD Group compared with the Control Group (82.1% vs 80.7% at Month 1, 81.1% vs 76.3% at Month 2, and 85.2% vs 77.1% at Month 3). Multivariable analysis confirmed significantly improved adherence in the RITA SaMD Group at Month 3 [odds ratio (OR): 3.0, 95% confidence interval (CI): 1.0–8.8, *P*=0.042]. A total of 1476 self-reported AEs were collected through RITA SaMD usage, the majority (N=1080) being Grade 1

events. During the study visits, a total of 20 AEs was recorded by the study physician, 16 in the RITA SaMD Group and 4 in the Control Group. Of the recorded AEs during study visits, 14 were SAEs (11 in the RITA SaMD Group and 3 in the Control Group). None of the reported AEs was considered related to RITA SaMD usage.

Conclusion: The MargheRITA clinical investigation showed that after 3 months of using the RITA SaMD, patients with hematological malignancies had 3 times higher OR of being adherent to the prescribed treatment than the Control Group. The use of RITA SaMD facilitated the reporting of AEs and PROs, reinforcing the role of mobile health apps and software in optimizing patient outcomes. Further research is needed to fully understand its interdisciplinary potential and long-term impact on patient outcomes.

Clinical Investigation Registration: ClinicalTrials.gov Identifier NCT05260203

Keywords

Medical device software; software as a medical device; digital health; therapy adherence; mobile health

Introduction

Oncological conditions continue to pose significant challenges to healthcare systems, with an increasing incidence observed in recent years; according to the World Health Organization (WHO), cancer stands as a prominent contributor to global mortality, responsible for nearly 10 million fatalities in the year 2020, equating to approximately one out of every six deaths.[1] One of the pivotal factors influencing the long-term outcomes of patients facing these complex diseases is their adherence to treatment regimens and completion of the treatment protocol in a defined period.[1-4] Improved therapy adherence positively correlates with enhanced prognosis and overall well-being.[1]

Global incident cases of hematologic malignancies have been increasing since 1990, surpassing 1343 thousand in 2019. Still, the age-standardized death rate for all types of hematologic malignancies has been declining.[5] This implies more extended patient management for the healthcare system.

Treatment adherence is a critical factor in the management of patients with hematological malignancies, since poor adherence can result in the emergence of resistance.[6, 7] Often occurs that the mild drug- or disease-related symptoms that the patient perceives during the treatment period are underestimated, leading to a more severe symptomatology later on that could further impair the patient's adherence to treatment.[3] In addition, many anti-tumor therapies are now continuous treatments, making therapeutic adherence particularly relevant for patient outcomes. For instance, in a real-world study comparing ibrutinib and acalabrutinib, two drugs used to treat chronic lymphocytic leukemia, patients were more likely to be adherent to treatment (defined as ≥80% adherence) if they were being treated with ibrutinib, which is administered once daily, than if they were being treated with acalabrutinib, which needs to be administered twice daily.[8] Similarly, a study assessing adherence to imatinib treatment in a resource-constrained environment showed that adherence during continuous treatment was related to molecular responses in patients with chronic

myeloid leukemia.[9] These data underline the importance of developing innovative approaches to improve therapeutic adherence in patients with hematological malignancies.

Efforts to address the management of oncology patients have spurred the development of outpatient care models, offering patients the benefits of home-based treatments.[5] However, the healthcare system must grapple with resource limitations exacerbated by factors such as the aging population and improvements in survival rates.[5] These factors present formidable challenges to achieving optimal outpatient management.

In response to these challenges, innovative solutions have emerged in the form of digital health systems designed to complement traditional outpatient care, such as the use of software as a medical device (SaMD).[10] These systems can potentially democratize access to oncological treatments for a wider audience of patients, bridging geographical and logistical barriers.[10]

The onset of the COVID-19 pandemic underscored the urgency of streamlining outpatient management processes.[11-13] Among the most promising strategies to address this need is the development of specific SaMD for oncology, which facilitates telemedicine visits and provides ongoing support for patients in their daily management of the disease, its associated complications, and treatment regimens.[11-13] Compared to non-medical device software and healthcare applications (apps), SaMD that is developed following International Organization for Standardization (ISO) 13485 and the European Medical Devices Regulation (EU MDR) 2017/745 (where it is known as medical device software) ensures patient safety and is an essential tool for improving healthcare quality.[14, 15]

With this in mind, a SaMD called RITA (Remote Intelligence for Therapeutic Adherence) was developed to serve as a communication platform between doctor and patient and support the patient in his or her therapeutic journey.

This manuscript briefly describes the RITA SaMD and reports the findings of the MargheRITA clinical investigation, which evaluated the performance and safety of the RITA SaMD in improving therapeutic adherence to treatment protocols in patients with hematological malignancies.

Methods

Study Design

This was a pre-market, pivotal, confirmatory, prospective, and interventional clinical investigation in patients with hematological malignancies. Patients were screened in a single center in Italy. The study was conducted in accordance with the clinical investigation plan (CIP) and international guidelines, including the most recent versions of the Declaration of Helsinki, the International Conference on Harmonisation guidelines for Good Clinical Practice, EU MDR 2017/745, and ISO 14155, as well as all applicable local laws and regulations. The CIP was approved by the local ethics committee (Milano Area 1 IEC prot. #0019486 21 Apr. 2022) and the Italian Ministry of Health (prot.#2028 3 May 2022). Signed informed consent was obtained from all patients. The clinical investigation is registered at ClinicalTrials.gov (NCT05260203).

Patients

The investigation enrolled individuals followed at ASST Santi Paolo e Carlo in Milan who met the following inclusion criteria: comprehension of the investigation's objectives and procedures, as well as acceptance to voluntarily sign an informed consent form before any investigation-related activities. In addition, participants needed to be at least 18 years old and have a diagnosis of a hematological malignancy (encompassing conditions such as symptomatic multiple myeloma, solitary plasmacytoma, amyloidosis, chronic myeloid leukemia, chronic lymphocytic leukemia, lymphocytic lymphoma, Hodgkin lymphoma, B-cell non-Hodgkin lymphoma, T-cell non-Hodgkin lymphoma, acute myeloid leukemia, myelodysplasia, and chronic myeloproliferative disorder). Eligibility also required prior receipt of standard-of-care therapy, irrespective of the administration method, and was open to patients at various therapy stages, with a minimum life expectancy of more

than six months. Exclusion criteria were established to ensure investigation integrity and participant well-being, excluding patients who had solely received radiotherapy, those with clinical conditions hindering treatment adherence, individuals unable to use smartphones or computers, those with major psychopathological conditions or cognitive impairments potentially affecting participation, and patients enrolled in another clinical investigation or in a clinical trial at the time of recruitment.

RITA SaMD

The RITA SaMD (Advice Pharma Group S.r.l., Milano, Italy) was designed and developed in accordance with ISO 13485 and the EU MDR 2017/745. It is classified as a class IIa medical device intended to increase treatment adherence in onco-hematological therapeutic regimens.

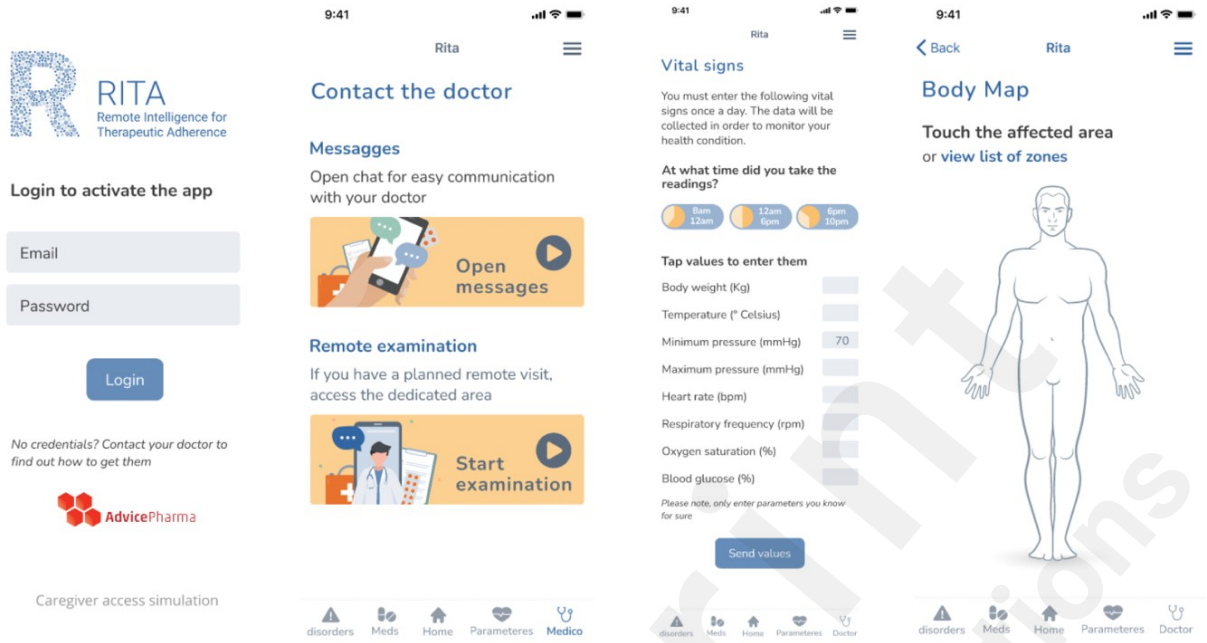
It was designed on the doctor's side as a support for the management of the onco-hematological patient and, on the patient's side, as a first aid tool for the management of the most common problems, as well as an efficient and "non-invasive" means of communication with their doctor. The system also includes the caregiver and general practitioner in the communication group.

RITA SaMD is also designed to communicate and receive information on the quality of life (QoL) and side effects, thus making the medical doctor aware of the health status in his or her patient population.

Using RITA SaMD, patients could notify their daily physical condition. RITA SaMD collects patient complaints with a proprietary grading system, which is modeled on Common Terminology Criteria for Adverse Events. In this way, physicians could manage and resolve mild to moderate symptoms during treatment.

RITA SaMD database has been developed on an Electronic Data Capture technology (ICE®, Advice Pharma), compliant with the regulations for clinical data management to facilitate the study data analysis. Patients could use the RITA SaMD on a smartphone or a tablet (see Figure 1).

Figure 1 – Example screenshots of the RITA SaMD



Physicians were able to access the RITA SaMD directly from a computer using a web-based interface.

Study Interventions

Patients with hematological malignancies were prospectively enrolled; the study physician (Principal Investigator) granted access to the RITA SaMD application to each patient in this group (RITA SaMD Group). The follow-up visits occurred 1, 2, and 3 months after enrollment. The follow-up visits at 3 months coincided with the end of the investigation visit. Each follow-up visit was a routine standard-of-care visit; no investigation-specific assessment was performed. During this visit, the physician paid particular attention to the patient's reported adverse events (AEs)/serious adverse events (SAEs). In each follow-up visit, the physician evaluated the delivered dose intensity.

A Control Group was also established; this group included patients with hematological malignancies treated in the same hospital in the past three years. Each patient in the RITA SaMD Group was paired in a 1:1 ratio with a patient in the Control Group of the same gender, pathology, treatment, and of the closest possible age.

Endpoints

The primary endpoint was the evaluation of the therapeutic adherence to the prescribed drug treatment, measured as at least the 80% of the relative dose intensity, at Month 3. Dose intensity was defined as the ratio of delivered dose intensity to the prescribed referenced dose intensity (expressed as a percentage) during the investigation period. The effectiveness of RITA SaMD use was evaluated by comparing results of therapeutic adherence with the Control Group.

Secondary endpoints were based on comparisons between the RITA SaMD Group and the Control Group and included evaluation of the therapeutic adherence to the prescribed drug treatment at Months 1 and 2; emergency room (ER) visits for minor and severe complications; average hospital stay, and mean therapeutic adherence at Months 1, 2, and 3. Safety secondary endpoints included physician-reported AEs during the study visits in the RITA SaMD Group vs the Control Group. Other safety secondary endpoints were only evaluated in the RITA SaMD Group and included self-reported AEs and adverse device effects (ADEs) through RITA SaMD usage.

Patient-reported outcomes (PROs) were collected at Months 1, 2, and 3 in the RITA SaMD Group. Among the questionnaires used were the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) descriptive system[16], the EuroQol visual analog scale (EQ-VAS)[17], the Instrumental Activities of Daily Living (IADL) scale[18], and the Activities of Daily Living (ADL) scale.[19]

Statistical Analysis

The clinical investigation planned a sample size of 112 patients (56 patients in the RITA SaMD Group and 56 in the Control Group) to provide an 80% power to detect a 20% improvement in treatment adherence after 3 months of RITA SaMD usage, with a one-sided type I error rate of 0.05. The enrollment of 124 patients (62 patients per group) was set as a goal to account for a drop-out rate of 10%.

In the primary analysis, all patients observed until the end of the investigation were included. The patient demographics were reported using descriptive analyses by tabulating frequencies and

percentages for categorical variables, and mean and median values, standard deviations (SD), quartiles and extreme values for continuous variables. Comparisons of continuous data between RITA SaMD and Control groups were analyzed using a two-sided Student's t-test, after verifying that the data were normally distributed (based on the Shapiro-Wilk test) and a two-sided Wilcoxon's rank-sum test otherwise. For categorical data, comparisons between groups were performed using the Chi-square or Fisher's exact test, as appropriate.

The effectiveness of the RITA SaMD was compared between the RITA SaMD Group and the Control Group using multivariable logistic regression models including as main confounders the following factors (chosen a priori): age, gender, comorbidities, and disease severity; adjusted odds ratios (ORs) and the corresponding 95% confidence intervals (CI) were estimated and reported.

AEs occurring during the investigation follow-up were also described.

The statistical significance limit was accepted as 5%, and the results below this value (P <.05) were considered statistically significant. Statistical analyses were performed using SAS system software (version 9.4).

Results

Patient Characteristics

Between July 4, 2022 and December 16, 2022, a total of 62 patients were enrolled in the RITA SaMD Group and matched to an equal number of patients in the Control Group. From the 62 patients enrolled in the RITA SaMD Group, 5 did not complete the study: 1 patient was lost to follow-up, 3 patients died from causes not related to the investigation, and 1 patient discontinued treatment after an SAE not related to the investigational device.

Thus, 119 patients were analyzed for the primary endpoint: 57 patients in the RITA SaMD Group and 62 in the Control Group. Baseline patient characteristics are reported in Table 1.

Table 1 – Baseline patient characteristics

	RITA SaMD Group	Control Group	*P*-value
Male; n (%)	37 (59.7%)	30 (48.4%)	0.207
Female; n (%)	25 (40.3%)	32 (51.6%)	
Age; mean (SD)	69.3 (15.1)	73.57 (9.9)	0.161
Pathology			
Monoclonal gammopathy	22 (35.5%)	20 (32.3%)	0.999
Chronic myeloid leukemia	4 (6.5%)	22 (35.5%)	
Chronic lymphocytic leukemia / lymphocytic lymphoma	9 (14.5%)	9 (14.5%)	
Hodgkin lymphoma	3 (4.8%)	3 (4.8%)	
B-cell non-Hodgkin lymphoma	12 (19.4%)	13 (21.0%)	
T-cell non-Hodgkin lymphoma	3 (4.8%)	3 (4.8%)	
Acute myeloid leukemia	2 (3.2%)	2 (3.2%)	
Myelodysplasia	3 (4.8%)	4 (4.5%)	
Chronic myeloproliferative syndrome	4 (4.5%)	4 (4.5%)	
Treatment phase			
1st line	52 (83.8%)	38 (61.3%)	0.005
2nd line or more	10 (16.1%)	24 (38.7%)	

Performance – Primary Endpoint

In the primary endpoint analysis, some patients in the RITA SaMD Group had missing data at the follow-up study visits. Therefore, the analyses included 115 patients at Month 3.

The probability of being treatment compliant – that is, ≥80% adherent to treatment – seemed higher in the RITA SaMD Group than in the Control Group at all time points (82.1 % vs 80.7% at Month 1, 81.1% vs 76.3% at Month 2, and 85.2% vs 77.1% at Month 3) (Table 2).

Table 2 – Treatment adherence to therapy

	RITA SaMD Group	Control Group	*P*-value
Month 1			
Yes	46 (82.1%)	50 (80.7%)	0.835
Month 2			
Yes	43 (81.1%)	45 (76.3%)	0.531
Month 3			
Yes	46 (74.2%)	47 (78.8%)	0.268

In terms of treatment adherence, univariable analyses revealed that differences between the two groups were not statistically significant. A multivariable analysis, adjusted for potential confounders

(gender, age, number of concomitant pathologies and treatment line), was performed. At Month 3, the OR of the RITA SaMD Group to be adherent to treatment was 3 times higher than the Control Group (adjusted OR: 3.0, 95% CI: 1.0–8.8, P=0.042) (Table 3).

Table 3 –Multivariable logistic regression analysis on the risk of being adherent to therapy over 3 months

	Adjusted OR (95% CI)	***P*-value**
Use of RITA SaMD application at Month 3 (Yes vs No)	**3.0 (1.0–8.8)**	**0.042**
Sex (F vs M)	1.4 (0.5–3.8)	0.533
Age, yrs (60-79 vs 60)	2.5 (0.6–10.6)	0.232
Age, yrs (≥80 vs 60)	2.2 (0.5–10.3)	0.302
Nr of concomitant pathologies (1-2 vs 0)	0.9 (0.1–5.3)	0.882
Nr of concomitant pathologies (≥3 vs 0)	0.5 (0.1–2.3)	0.353
Nr of treatment lines (≥1 vs 1)	**6.8 (1.4–33.3)**	**0.018**

Performance – Secondary Endpoints

Treatment adherence was analyzed in 118 patients at Month 1 and 112 patients at Month 2. The multivariable analysis with adjustment for potential confounders showed that the differences between the two groups in terms of treatment adherence were not statistically significant in the first two months, with an OR of 1.7 (95% CI: 0.61–4.9) at Month 1 and an OR of 2.0 (95% CI: 0.8–5.6) at Month 2.

Regarding ER Visits, there were no visits in either group for minor complications. At the end of the study period, there were 9 ER visits in the RITA SaMD Group requiring hospitalization and 3 in the Control Group, totaling 12 ER visits for severe complications. The average hospital stay was 25.3 days (SD 22.7) in the RITA SaMD Group and 8.3 days (SD 2.1) in the Control Group. Due to the small number of events, no statistical test was performed for these endpoints.

At Month 1, the mean therapeutic adherence was similar between the RITA SaMD and the Control groups, with 95.4% vs 95.0%, respectively. At Month 2 and Month 3, the mean therapeutic

adherence in the RITA SaMD Group tended to be slightly higher than in the Control Group, although not statistically significant (P=0.415 and P=0.456, respectively) (Table 4).

Table 4 – Mean therapeutic adherence

	RITA SaMD Group; mean (SD)	**Control Group; mean (SD)**	***P*-value**
Month 1	95.4 (15.5)	95.0 (10.6)	0.504
Month 2	96.1 (8.8)	93.2 (12.5)	0.415
Month 3	94.0 (17.1)	91.6 (16.5)	0.426

Note: For the *P*-value, data were not normally distributed; two-sided Wilcoxon's rank-sum was used

Safety **– Secondary Endpoints**

In the RITA SaMD Group, there were 16 AEs reported by the physicians during the study visits (Table 5), most of them Grade 2, while in the Control Group there were 4 AEs reported. During the study, a total of 14 SAEs occurred, 11 of which in the RITA SaMD Group. None of the recorded AEs was related to RITA SaMD usage; therefore, there were no ADEs.

Table 5 – Summary of AEs recorded at study visits

	Parameter	RITA SaMD Group	Control Group
AE	*Yes*	16	4
SAE	*Yes*	11	3
	No	5	1
Severity (Grade)	*1*	1	0
	2	8	1
	3	3	3
	4	2	0
	5	2	0
Related to RITA SaMD usage	*Yes*	0	0
	No	16	4

Table 6 – AEs recorded by the physician during the study visits – RITA SaMD Group

Body System Organ Class	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
Cardiac disorders	**0 (0.0%)**	**3 (75.0%)**	**1 (25.0%)**	**0 (0.0%)**	**0 (0.0%)**	**4**
Cardiac failure	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1

congestive						
Cardiac failure	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Atrial fibrillation	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2
General disorders and administration site conditions	**0 (0.0%)**	**3 (60.0%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (40.0%)**	**5**
Asthenia	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2
Disease progression	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)	2
Pyrexia (fever)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Infections and infestations	**0 (0.0%)**	**2 (50.0%)**	**1 (25.0%)**	**1 (25.0%)**	**0 (0.0%)**	**4**
COVID-19 infection	0 (0.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	2
Infection (not specified)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Septic shock	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	1
Respiratory, thoracic and mediastinal disorders	**0 (0.0%)**	**0 (0.0%)**	**1 (100.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1**
Interstitial lung disease (interstitial pneumonia)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1
Vascular disorders	**1 (50.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (50.0%)**	**0 (0.0%)**	**2**
Hypotensive syncope (anemia lipothymia)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Cardiovascular disorder (recurrence of circulatory decompensation)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	1
Total	**1**	**8**	**3**	**2**	**2**	**16**

Table 7 – AEs recorded by the physician during the study visits – Control Group

Body System Organ Class	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Blood and lymphatic system disorders	**0 (0.0%)**	**0 (0.0%)**	**1 (100.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1**
Neutropenia	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1
General disorders and administration site conditions	**0 (0.0%)**	**1 (100.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1**
Asthenia	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Hepatobiliary disorders	**0 (0.0%)**	**0 (0.0%)**	**1 (100.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1**
Hyperbilirubinemia	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1
Respiratory, thoracic and mediastinal disorders	**0 (0.0%)**	**0 (0.0%)**	**1 (100.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1**
Dyspnea (persistent fever and difficulty breathing)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1
Total	**0**	**1**	**3**	**0**	**0**	**4**

Regarding self-reported AEs, a total of 1,476 AEs were recorded through RITA SaMD usage (Table 8). There were 1080 minor (Grade 1) events, with tiredness being the most frequently reported Grade 1 event (n=720).

Table 8 – Self-reported AEs in the RITA SaMD Group

Body System Organ Class	Grade 1	Grade 2	Grade 3	Total
Cardiac disorders	3 (60.0%)	2 (40.0%)	0 (0.0%)	**5**
Palpitations	3 (60.0%)	2 (40.0%)	0 (0.0%)	**5**
Eye disorders	0 (0.0%)	90 (90.9%)	9 (9.1%)	**99**
Vision decreased (decrease of vision)	0 (0.0%)	90 (90.9%)	9 (9.1%)	**99**
Gastrointestinal disorders	41 (82.0%)	7 (14%)	2 (4%)	**50**
Diarrhea	27 (84.4%)	4 (12.5%)	1 (3.1%)	**32**
Constipation	7 (70.0%)	3 (30.0%)	0 (0.0%)	**10**
Stomatitis (oral cavity mucositis)	6 (100.0%)	0 (0.0%)	0 (0.0%)	**6**
Dyspepsia (difficult digestion)	0 (0.0%)	0 (0.0%)	1 (100.0%)	**1**
Gastric dilatation (stomach distension)	1 (100.0%)	0 (0.0%)	0 (0.0%)	**1**
General disorders and administration site conditions	773 (80.9%)	172 (18.0%)	10 (1.1%)	**955**
Fatigue (tiredness)	720 (83.9%)	129 (15.0%)	9 (1.1%)	**858**
Peripheral swelling (swelling in the legs)	12 (28.6%)	30 (71.4%)	0 (0.0%)	**42**
Pain (ache)	17 (56.7%)	12 (40.0%)	1 (3.3%)	**30**
Pyrexia (fever)	24 (96.0%)	1 (4.0%)	0 (0.0%)	**25**
Infections and infestations	36 (87.8%)	5 (12.2%)	0 (0.0%)	**41**
Flu symptoms	35 (89.7%)	4 (10.3%)	0 (0.0%)	**39**
Conjunctivitis	1 (50.0%)	1 (50.0%)	0 (0.0%)	**2**
Musculoskeletal and connective tissue disorders	3 (100.0%)	0 (0.0%)	0 (0.0%)	**3**
Gait disturbance (walking disorders)	3 (100.0%)	0 (0.0%)	0 (0.0%)	**3**
Nervous system disorders	44 (42.7%)	59 (57.3%)	0 (0.0)	**103**
Insomnia	6 (10.9%)	49 (89.1%)	0 (0.0%)	**55**
Anxiety	21 (72.4%)	8 (27.6%)	0 (0.0%)	**29**
Taste disorder	13 (92.9%)	1 (7.1%)	0 (0.0%)	**14**
Tremors	3 (100.0%)	0 (0.0%)	0 (0.0%)	**3**
Cognitive disorder	1 (50.0%)	1 (50.0%)	0 (0.0%)	**2**
Psychiatric disorders	13 (92.9%)	1 (7.1%)	0 (0.0%)	**14**
Nervousness	13 (92.9%)	1 (7.1%)	0 (0.0%)	**14**
Renal and urinary disorders	14 (100.0%)	0 (0.0%)	0 (0.0%)	**14**
Pollakiuria (urinate often)	13 (100.0%)	0 (0.0%)	0 (0.0%)	**13**
Urinary incontinence	1 (100.0%)	0 (0.0%)	0 (0.0%)	**1**
Respiratory, thoracic and mediastinal disorders	17 (44.7%)	17 (44.7%)	4 (10.5%)	**38**
Cough	16 (44.4%)	17 (47.2%)	3 (8.3%)	**36**
Dyspnea (difficulty breathing)	0 (0.0%)	0 (0.0%)	1 (100.0%)	**1**
Hiccups	1 (100.0%)	0 (0.0%)	0 (0.0%)	**1**

Skin and subcutaneous tissue disorders	129 (88.4%)	16 (11.0%)	1 (0.7%)	**146**
Pruritus (itching)	110 (90.2%)	11 (9.0%)	1 (0.8%)	**122**
Paresthesia (tingling feeling)	17 (81.0%)	4 (19.0%)	0 (0.0%)	**21**
Skin alterations	2 (66.7%)	1 (33.3%)	0 (0.0%)	**3**
Vascular disorders	7 (87.5%)	1 (12.5%)	0 (0.0%)	**8**
Epistaxis – nosebleed	7 (87.5%)	1 (12.5%)	0 (0.0%)	**8**
Total	**1080**	**370**	**26**	**1476**

Note: Percentages are based on the total number of cases for each row.

Patient-Reported Outcomes

In the RITA SaMD Group, 1 patient had complete questionnaires at all time points and 17 patients had complete questionnaires at Month 1 and Month 2. For each questionnaire, some patients were not considered in the analysis because their assessments were done out of the specified time frame, they reported incorrect values, or data were missing (Table 9).

Table 9 – Patient-reported outcomes

		No change	Improved	Worsened
EQ-5D-5L	Mobility item	6	2	3
	Self-care item	9	1	1
	Usual activities item	9	1	1
	Pain/discomfort	2	3	6
	Anxiety/ depression	4	1	6
Other	EQ-VAS Scale	2	5	3
	IADL Scale	NA	1	2
	ADL Scale	8	NA	1

Discussion

In this clinical investigation of patients with hematological malignancies, patients using the RITA SaMD device were more frequently compliant to treatment (85.2% vs 77.1%) and had a 3-fold higher risk of being adherent to treatment compared with nonusers after 3 months of use. According to WHO, adherence to log-term therapy for chronic illnesses is about 50% in developed countries,

which is a major challenge in the management of hematological malignancies.[3, 20] Previous research in the area of mobile health has shown that the use of information and communication platforms can increase the patients' sense of autonomy and facilitate the disease management, resulting in higher QoL and adherence to treatment.[21] One interesting finding in our study was the impact of the number of previous treatment lines on the odds of being adherent to treatment, with patients who underwent more than 1 line of treatment having a much higher likelihood of adhering to the prescribed drug treatment. This is somewhat in contradiction to what was found by Seal *et al.*, who described how adherence declines with increasing lines of treatment, but only for oral medications, not intravenous ones.[22] Given that the number of available oral formulations of both chemotherapy and biologic therapies is rising, and that patients tend to prefer oral therapy, it is worth to further explore the role of mobile health and SaMD in the factors influencing adherence, such as forgetfulness or loss of motivation.[23, 24]

A total of 1476 AEs were self-reported in the RITA SaMD Group with SaMD usage occurrence, the majority of them (73.2%) Grade 1, showing that app usage facilitated collection of such events and may improve the recording of low-grade AEs compared with traditional methods (namely, AE recording only during medical visits). During the study visits, 20 AEs were recorded by the physician, 16 in the RITA SaMD Group and 4 in the Control Group. Of the collected AEs during the study visits, 14 were considered SAEs (11 in the RITA SaMD Group and 4 in the Control Group). None of the collected AEs was considered to be related with RITA SaMD usage. In a recent study evaluating the factors impacting medication adherence in patients with hematologic malignancies who have undergone allogeneic hematopoietic stem cell transplants, although the AEs associated with medication did not directly impact adherence to treatment, they increased the patients' psychological distress.[25] Interestingly, the same study referred that caregiver and clinician support, as well as tools to aid medication management, were factors that facilitated treatment adherence.[25]

RITA SaMD can therefore help alleviate stress by providing a way for patients to report their ailments and feel they have clinician support.

RITA SaMD allowed the collection of PROs, including QoL data. Although the collected data were insufficient to analyze differences in therapeutic adherence relative to self-reported changes in the questionnaires' items, the fact that RITA SaMD enables the collection of PROs is an added value and may be further explored in the future. Unrecorded PROs are still sadly familiar in the literature; any SaMD that strives to help both patients and physicians to work better with the healthcare system cannot overlook PRO recording and the real-world data it generates.[17, 26]

Previous research has identified necessary features in mobile health apps and software, such as symptoms and medication tracking.[27] Patients themselves also refer that features that facilitate information exchange with their clinicians are important.[28] Our results in patients with hematological malignancies illustrate how RITA SaMD can help any oncology setting to promote patients' therapeutic adherence, while limiting healthcare resources used in patient management and contribute to optimal patient care.

Strengths and Limitations

Our clinical investigation has some limitations. The study was undertaken in a single center, which, along with the lack of randomization and unblinded nature, might limit the generalizability of the results. The short follow-up time precludes any conclusion regarding long-term adherence to treatment, despite the promising results.

Our study also had important strengths. To our knowledge, this is the first clinical investigation showing the effectiveness of a SaMD application in improving therapeutic adherence in patients with hematological malignancies. High-quality methods were implemented, including prospective registration in a publicly available clinical trial database and the use of a control group.

Conclusion

The MargheRITA clinical investigation revealed that after 3 months of using the RITA SaMD, patients with hematological malignancies were 3 times more likely of being adherent to the prescribed treatment than the Control Group. The use of RITA SaMD facilitated the reporting of AEs and (to a minor extent) of PROs, reinforcing the role of mobile health apps and software in optimizing patient outcomes.

This initial clinical investigation has confirmed the performance and safety of RITA SaMD; future studies are needed to prove its interdisciplinary application.

Acknowledgments

Francesca Paoloni (Senior Biostatistician) ran the statistical analysis. Laura C Collada Ali (Senior Medical Writing Consultant) and Diana Ribeiro (Medical Writer) provided editorial assistance in preparing this article. Advice Pharma Group S.r.l., Italy, funded support for these services. The investigators thank researchers and the clinical investigation patients for their involvement.

Funding

The present clinical investigation has been funded and sponsored by Advice Pharma Group S.r.l. (Italy).

Conflicts of Interest

Alessandro Ferri, President of Advice Pharma Group, Davide Gaudesi, Massimo Beccaria and Francesca Sacchi, employees of Advice Pharma Group S.r.l. (Italy). All remaining authors have no potential conflicts of interest concerning this article's research, authorship, and/or publication.

Author Contributions

All authors adhere to the following guidelines for authorship: ICMJE, Defining the Role of Authors and Contributors, Transparency in authors' contributions and responsibilities to promote integrity in scientific publication, McNutt at all, PNAS February 27, 2018.

Conceptualization: all authors; writing – original draft preparation: VM; MM; CG; DG; FS; AF; review and editing: VM; MM; CG; DG; FS; AF; MB; all authors have read and agreed to the published version of the manuscript.

References

1. Cancer. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer.

2. Ganesan P, Ganesan TS, Radhakrishnan V, Sagar TG, Kannan K, Dhanushkodi M, et al. Chronic Myeloid Leukemia: Long-Term Outcome Data in the Imatinib Era. Indian Journal of Hematology and Blood Transfusion. 2019 2019/01/01;35(1):37-42. doi: 10.1007/s12288-018-1009-y.

3. Solano M, Daguindau E, Faure C, Loriod P, Pain C, Maes A-C, et al. Oral therapy adherence and satisfaction in patients with multiple myeloma. Annals of Hematology. 2021 2021/07/01;100(7):1803-13. doi: 10.1007/s00277-021-04543-7.

4. Hochhaus A. Educational session: managing chronic myeloid leukemia as a chronic disease. Hematology Am Soc Hematol Educ Program. 2011;2011:128-35. PMID: 22160024. doi: 10.1182/asheducation-2011.1.128.

5. Zhang N, Wu J, Wang Q, Liang Y, Li X, Chen G, et al. Global burden of hematologic malignancies and evolution patterns over the past 30 years. Blood Cancer J. 2023 May 17;13(1):82. PMID: 37193689. doi: 10.1038/s41408-023-00853-3.

6. Collins Jt, Stump SE, Heiling H, Muir M, Deal A, Proco D, et al. Impact of adherence to ibrutinib on clinical outcomes in real-world patients with chronic lymphocytic leukemia. Leuk Lymphoma. 2022 Aug;63(8):1823-30. PMID: 35249442. doi: 10.1080/10428194.2022.2045597.

7. Williams AM, Baran AM, Casulo C, Reagan P, Friedberg JW, Helber M, et al. Ibrutinib Dose Adherence and Therapeutic Efficacy in Non-Hodgkin Lymphoma: A Single-Center Experience. Clin Lymphoma Myeloma Leuk. 2019 Jan;19(1):41-7. PMID: 30409718. doi: 10.1016/j.clml.2018.10.005.

8. Lu X, Emond B, Morrison L, Kinkead F, Lefebvre P, Lafeuille MH, et al. Real-World Comparison of First-Line Treatment Adherence Between Single-Agent Ibrutinib and Acalabrutinib in Patients with Chronic Lymphocytic Leukemia. Patient Prefer Adherence. 2023;17:2073-84. PMID: 37641660. doi: 10.2147/ppa.S417180.

9. Yanamandra U, Malhotra P, Sahu KK, Sushma Y, Saini N, Chauhan P, et al. Variation in Adherence Measures to Imatinib Therapy. J Glob Oncol. 2018 Sep;4:1-10. PMID: 30241224. doi: 10.1200/jgo.2016.007906.

10. Raffenaud A, Gurupur V, Fernandes SL, Yeung T. Utilizing telemedicine in oncology settings: Patient favourability rates and perceptions of use analysis using Chi-Square and neural networks. Technol Health Care. 2019;27(2):115-27. PMID: 30664510. doi: 10.3233/thc-181293.

11. Shirke MM, Shaikh SA, Harky A. Implications of Telemedicine in Oncology during the COVID-19 Pandemic. Acta Biomed. 2020 Sep 7;91(3):e2020022. PMID: 32921719. doi: 10.23750/abm.v91i3.9849.

12. Lewis GD, Hatch SS, Wiederhold LR, Swanson TA. Long-Term Institutional Experience With Telemedicine Services for Radiation Oncology: A Potential Model for Long-Term Utilization. Adv Radiat Oncol. 2020 Jul-Aug;5(4):780-2. PMID: 32391444. doi: 10.1016/j.adro.2020.04.018.

13. Portnoy J, Waller M, Elliott T. Telemedicine in the Era of COVID-19. J Allergy Clin Immunol Pract. 2020 May;8(5):1489-91. PMID: 32220575. doi: 10.1016/j.jaip.2020.03.008.

14. Alotaibi YK, Federico F. The impact of health information technology on patient safety. Saudi Med J. 2017 Dec;38(12):1173-80. PMID: 29209664. doi: 10.15537/smj.2017.12.20631.

15. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA relevance.). OJ L. 2017 2017/04/05/;117.

16. EQ-5D-5L. Available from: https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/.

17. Feng Y, Parkin D, Devlin NJ. Assessing the performance of the EQ-VAS in the NHS PROMs programme. Qual Life Res. 2014 Apr;23(3):977-89. PMID: 24081873. doi: 10.1007/s11136-013-0537-z.

18. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969 Autumn;9(3):179-86. PMID: 5349366.

19. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. STUDIES OF ILLNESS IN THE AGED. THE INDEX OF ADL: A STANDARDIZED MEASURE OF BIOLOGICAL AND PSYCHOSOCIAL FUNCTION. Jama. 1963 Sep 21;185:914-9. PMID: 14044222. doi: 10.1001/jama.1963.03060120024016.

20. Chaudri NA. Adherence to Long-term Therapies Evidence for Action. Ann Saudi Med. 2004 May-Jun;24(3):221-2.

21. Collado-Borrell R, Escudero-Vilaplana V, Ribed A, Gonzalez-Anleo C, Martin-Conde M, Romero-Jimenez R, et al. Effect of a Mobile App for the Pharmacotherapeutic Follow-Up of Patients

With Cancer on Their Health Outcomes: Quasi-Experimental Study. JMIR Mhealth Uhealth. 2020 Oct 16;8(10):e20480. PMID: 33064100. doi: 10.2196/20480.

22. Seal BS, Anderson S, Shermock KM. Factors Associated with Adherence Rates for Oral and Intravenous Anticancer Therapy in Commercially Insured Patients with Metastatic Colon Cancer. J Manag Care Spec Pharm. 2016 Mar;22(3):227-35. PMID: 27003552. doi: 10.18553/jmcp.2016.22.3.227.

23. Hess LM, Louder A, Winfree K, Zhu YE, Oton AB, Nair R. Factors Associated with Adherence to and Treatment Duration of Erlotinib Among Patients with Non-Small Cell Lung Cancer. J Manag Care Spec Pharm. 2017 Jun;23(6):643-52. PMID: 28530522. doi: 10.18553/jmcp.2017.16389.

24. O'Neill VJ, Twelves CJ. Oral cancer treatment: developments in chemotherapy and beyond. Br J Cancer. 2002 Oct 21;87(9):933-7. PMID: 12434279. doi: 10.1038/sj.bjc.6600591.

25. Amonoo HL, Deary EC, Wang A, Newcomb RA, Daskalakis E, Weber D, et al. Medication Adherence in Patients with Hematologic Malignancies Who Are Hematopoietic Stem Cell Transplantation Survivors: A Qualitative Study. Transplant Cell Ther. 2023 Oct;29(10):620.e1-.e11. PMID: 37516379. doi: 10.1016/j.jtct.2023.07.019.

26. Au H-J, Ringash J, Brundage M, Palmer M, Richardson H, Meyer RM. Added value of health-related quality of life measurement in cancer clinical trials: the experience of the NCIC CTG. Expert Review of Pharmacoeconomics & Outcomes Research. 2010 2010/04/01;10(2):119-28. doi: 10.1586/erp.10.15.

27. Vaffis S, Whaley S, Axon DR, Hall-Lipsy E, Hincapie A, Slack M, et al. Features of Cancer mHealth Apps and Evidence for Patient Preferences: Scoping Literature Review. JMIR Cancer. 2023 Apr 28;9:e37330. PMID: 37115587. doi: 10.2196/37330.

28. Richards R, Kinnersley P, Brain K, Staffurth J, Wood F. The Preferences of Patients With Cancer Regarding Apps to Help Meet Their Illness-Related Information Needs: Qualitative Interview Study. JMIR Mhealth Uhealth. 2019 Jul 31;7(7):e14187. PMID: 31368446. doi: 10.2196/14187.

Abbreviations

ADEs: adverse device effects

ADL: Activities of Daily Living

AEs: adverse events

ASST: Aziende Socio Sanitarie Territoriali

CI: confidence interval

CIP: clinical investigation plan

EQ-5D-5L: EuroQol-5 Dimensions-5 Levels

EQ-VAS: EuroQol visual analog scale

ER: emergency room

EU MDR: European Medical Devices Regulation

IADL: Instrumental Activities of Daily Living

OR: odds ratio

PROs: patient-reported outcomes

QoL: quality of life

RITA: Remote Intelligence for Therapeutic Adherence

SAEs: serious adverse events

SaMD: software as medical device

SD: standard deviation

WHO: World Health Organization

Supplementary Files

CONSORT (or other) checklists

CONSORT checklist.
URL: http://asset.jmir.pub/assets/f208d63e60ec6cdfc7a1cd786d26a54c.pdf