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Advancing strategies to increase adherence to oral therapies in onco-hematology: protocol for a randomized controlled study

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Original research

Advancing strategies to increase adherence to oral therapies in onco-hematology: protocol for a randomized controlled study

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ABSTRACT

Introduction The use of oral treatments is constantly growing in the area of onco-hematology, raising adherence and safety issues. There is an increasing body of literature highlighting the importance of patient empowerment in the self-management of cancer therapies. Within this scenario, the ONCO-TreC platform was customized and fine-tuned through a prospective multicenter training-validation study in cancer patients treated with oral anticancer drugs.

Methods and analysis This prospective randomized trial was designed to compare the effectiveness of two different strategies, ie, an electronic diary (ONCO-TreC) and a paper diary, for the management of oral cancer treatments in patients with solid and hematological tumors. *Ad hoc* strategies are planned to measure and monitor adherence to treatment and to assess usability and acceptability of the electronic diary. Informed consent will be obtained from all study participants.

Ethics and dissemination This innovative eHealth system is expected to contribute to increasing the adherence to and safety of cancer care, promoting patient empowerment and improving patient-doctor communication. Ethical approval was obtained from Romagna Ethics Committee (CEROM), study ID 2108, prot. n. IRST 100.28 of 10/04/2020. Findings will be disseminated through peer-reviewed journals, conferences and event presentations.

Trial registration number: ClinicalTrials.gov NCT04826458

Keywords

oral anticancer agents; home-based healthcare management; adherence; eHealth; patient empowerment

Strengths and limitations of this study

- This multicenter randomized study is the first to compare the efficacy of an electronic diary with that of standard clinical practice;
- ONCO-TreC is expected to contribute to improving the adherence and safety of cancer care, promoting patient empowerment and patient-doctor communication;
- The limited number of cancer centers involved in the trial could make it difficult to transfer the results to the general population;
- The organizational model that includes the presence of the counsellor may not be applicable to all cancer centers.

INTRODUCTION

The use of oral treatments is constantly increasing in the area of onco-hematology, raising adherence and safety issues.[1-5] Literature data show that there is enormous variability in adherence, with rates varying between 20% and 100%.[6] Given that poor adherence can have important consequences in terms of treatment efficacy and toxicity,[7] the concept of patient empowerment plays a key role in the self-management of therapies.[8,9]

Several trials have been carried out in recent years to evaluate interventions aimed at improving adherence to oral antineoplastic therapies, eg, educational support, treatment monitoring, pharmacy based and counselling programs, pre-filled pill boxes, and automated voice response systems.[5] To the best of our knowledge, no randomized trials have shown significant differences between intervention and control groups with respect to primary adherence outcomes. Two non-randomized cohort studies suggested a possible benefit in terms of adherence to oral antineoplastic therapy from their intervention programs with respect to retrospective control groups. In one study, a treatment monitoring program for patients undergoing erlotinib for advanced non small cell lung cancer was associated with significantly higher rates of adherence (as measured by both patient self report ($p=0.042$) and pill count ($p=0.002$)) and disease control ($p=0.037$).[10] In another trial, intensified multidisciplinary pharmaceutical care was associated with significantly higher mean daily adherence rates to oral capecitabine in a small cohort of patients with colorectal and breast cancer ($p=0.029$).[11]

In clinical practice, a program that includes the presence of a counsellor and the delivery of a paper diary is generally considered an adequate standard of care. Within this context, 2.0 web solutions such as telemedicine, mobile health devices and applications (apps)

might be useful to improve adherence to medication and to optimize shared management of oral agents between patient and healthcare providers.[10-17]

The Center for Communication and Information Technology of Fondazione Bruno Kessler (FBK-ICT) in Trento developed a monitoring system based on the TreC (CCC, Citizen Clinical Record) platform to deliver mobile health services in different chronic diseases, such as asthma, type 1 diabetes and hypertension.[18,19] The system was subsequently adapted for home management and remote monitoring of oral anticancer therapy (ONCO-TreC).

ONCO-TreC was customized, fine-tuned and validated through a prospective multicenter study in cancer patients treated with oral anticancer drugs [Passardi et al., *submitted*].[20] Forty patients were enrolled, and adherence to cancer treatment was >86%. The ability of the system to measure adherence to treatment was high, with a concordance of 97.3% (95 CI: 86.1%-99.9%) between investigator and system pill count. System usability and acceptability were also very high. However, the small sample size and absence of a control arm did not permit any definitive conclusions to be drawn about the efficacy of the system in improving adherence.

The aim of the present study protocol and its primary endpoint is to compare the effectiveness of two different strategies, ie, electronic diary (ONCO-TreC) and paper diary, in improving adherence to oral cancer therapy in patients with solid and hematological tumors.

Secondary endpoints of the study are as follows: (i) to identify the reasons for non-adherence in each group of patients (eg, forgetting to take the pills, side-effects, misunderstanding of the prescription); (ii) to describe the satisfaction of patients and

healthcare professionals with the different strategies by means of brief questionnaires and semi-structured interviews; (iii) to evaluate the impact of the lack of therapeutic adherence in terms of both costs for medicines and overall healthcare costs (eg, hospitalizations, health services, access to Emergency Room).

METHODS AND ANALYSIS

Study design and participants

The research is a prospective randomized, interventional, non-pharmacological, multicenter study on cancer patients receiving anticancer oral treatment.

Inclusion and exclusion criteria

Inclusion criteria are defined as follows: adult ≥18 years old, either gender; Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2; life expectancy >12 weeks according to clinical judgment; patient candidate for treatment with an oral agent (adjuvant and advanced settings allowed); good understanding of the Italian language; ability to follow study procedures and manage mobile devices after a basic training course, at the investigator's discretion; written informed consent.

Patients receiving an intravenous anticancer treatment as well as experimental drugs will be excluded to reduce potential confounding in evaluating the strategies.

Recruitment

A total of 124 evaluable patients will be considered. Clinicians will identify potentially eligible patients, providing them with all the details pertaining to project participation, and

collecting the signed informed consent.

Randomization

After being approached for face-to-face screening and enrollment, participants will be randomized to the intervention or control group across sites (1:1 randomization) according to the following arms: A) electronic diary (ONCO-TreC APP); B) paper diary.

Patients assigned to the electronic diary group will be equipped with a dedicated APP (ONCO-TreC) and receive specific training on its use.

The researchers in charge of the randomization will not have any influence on the routine care of patients, and participation in the project does not imply any significant adjustment in the standard routine care.

Patient and public involvement

No patient involved.

ONCO-TreC

ONCO-TreC consists of a mobile application (APP) delivered to patients and a web-based dashboard managed by healthcare professionals. The APP contains a visual reminder of cancer therapy, a simplified adverse event reporting system, a section for vital signs entering, and a messaging system. Clinicians enter the details of oral treatment schedules through the dashboard, set reminders, monitor for adherence to treatment and reported adverse events, and can communicate with patients through the messaging system. A detailed description of the ONCO-TreC has been reported elsewhere.[20]

Counsellor

Patients of both arms will be followed by a trained healthcare professional (counsellor) who will be responsible for drug and diary delivery. The counsellor will also train the patient and/or caregiver at the very first treatment cycle with regard to (i) therapy (dosage, duration, storage methods, etc.) and (ii) issues/adverse events reporting. The healthcare staff will instruct the patient to return all the drug packs received, even if empty, at each cycle, for pill count. In addition, the counsellor will obtain information from patients about any concomitant drugs used at home. All these procedures will take place inside an adequate and dedicated room.

Study procedures

At the baseline visit, demographic data (age, sex, educational qualification and occupation), cancer history, and information on concomitant diseases and therapies will be collected; physical examination with vital signs and performance status assessment will be carried out. Patients assigned to arm A will be provided with the ONCO-TreC APP (installed on a smartphone or tablet), the oral drug for a treatment cycle and an appointment for the next cycle, and will be instructed on how to use the APP. Patients assigned to arm B will be provided with a paper diary, the oral medication and an appointment for the next cycle, and will be given instructions on how to use the paper diary.

During the patient's medical visits at each treatment cycle, adherence and adverse events will be reported in the patient's medical records, as per clinical practice. In addition, at each cycle the counsellor will check the patient's diary (paper or electronic), count any remaining tablets, and evaluate the need for retraining. Patients will also receive the drug

supply for a new treatment cycle, the appointment for the next cycle and, for those in arm B, a new paper diary.

The evaluation period will end after 6 cycles of therapy or before in the event of a change of therapy (for disease progression or unacceptable toxicity) or patient refusal. Each patient, once the planned 6-cycle phase is over, will continue the treatment, with visits and procedures as per clinical practice.

Usability and acceptability of ONCO-TreC and paper diary by patients will be assessed through 3 questionnaires: Q-pre and Q-post at baseline and at the end of observation (EoO); and the Italian version of the System Usability Scale (SUS) at EoO.[21] Q-pre and Q-post are *ad hoc* questionnaires developed to analyze patient expectations with regard to the system (Q-pre) and to evaluate system acceptability (Q-post) and communication between patients and cancer centers (Q-pre and Q-post). A subgroup of patients will also undergo semi-structured interviews by FBK-ICT sociologists at EoO. These interviews will be conducted by teleconference and will focus on healthcare practice and the use of the electronic or paper diary. FBK-ICT sociologists will also conduct semi-structured interviews with the oncologists, counsellors and healthcare professionals involved in the trial to evaluate the impact of the technology on the workload, as well as patient-hospital communication, adherence and adverse events management.

Data management

ONCO-TreC APP will communicate with a back-end service to store data on a central server. Researchers will be able to evaluate capability data through a web-based dashboard. Data entered into the system or paper diary by the patient will be compared with those

assessed by the oncologist and/or the counsellor. In particular, the adherence to treatment that emerges from diaries will be related to the number of residual pills returned during the hospital visit, and adverse events reported in the diaries will be compared to those reported to the oncologist and recorded in the medical records. Data will be registered in electronic case report forms, implemented using a relational database management system and a graphic user interface.

Statistical Analysis

Adherence will be assessed at each treatment cycle by counting the remaining pills. Any patient who takes at least 90% of the total planned drug dose as per study protocol will be defined as adherent. Patients who take fewer tablets than prescribed due to toxicity or medical decision will be considered adherent if this decision is recorded in the medical records. The effectiveness of each experimental strategy will be evaluated by comparing the proportion of adherent patients in the corresponding groups.

Patient perception about ONCO-TreC or paper diary will be assessed through questionnaires. Two specific questionnaires (Q-pre, Q-post) will be administered to evaluate patient expectations about the system, system acceptability, quality of care and patient-doctor communication. An internationally validated SUS will be used to investigate system usability in the experimental arm. The semi-structured interviews will be audio-recorded, transcribed and assessed by the template analysis, a structured technique for the evaluation of qualitative data.

The sample size was calculated assuming a percentage of non-adherence to oral therapy of 40% in arm B, and a 60% reduction in the percentage of non-adherent patients in arm A.

A sample consisting of 124 patients (62 patients for each arm) will provide 80% power to identify an absolute difference greater than 24 percentage points using a bilateral Fisher's exact test with a significance level of 0.05. Considering a dropout rate of 10%, approximately 136 total patients will have to be enrolled.

The hypothesis relating to the primary endpoint of the study will be tested using Fisher's exact test. The percentage of adherent patients in the 2 groups will be reported both as a point estimate and by means of 95% confidence intervals. Secondary endpoints will be reported through descriptive statistics: mean ± standard deviation (sd) or median and interquartile range for continuous variables, and absolute and relative frequency for categorical variables.

ETHICS AND DISSEMINATION

This Italian multicenter randomized study, approved by the Romagna Ethics Committee (CEROM), study ID 2108, prot. n. IRST 100.28 of 10/04/2020, will be conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Informed consent will be obtained from all individual study participants before enrollment.

Considering the impact of adherence to oral treatments in onco-hematology in terms of treatment efficacy and toxicity, the validation of reliable and easy-to-use tools to improve patients' self-management of therapies is essential.[9] Current literature supports the idea that multilayer approaches including educational support, treatment monitoring, pharmacy based and counselling programs are essential for improving adherence and, therefore, treatment efficacy.[5] An increasing level of acceptance to m-health technologies in oncology is being shown by patients and healthcare staff. However, despite the numerous studies

published on this issue, there is still a clear need to further promote the validation of technological, organizational and m-health platforms (eg, APP) to support patients' self-management, which is a key factor in sustaining proper treatment adherence.

The present multicenter randomized study represents a unique contribution in this area in that it will be the first to compare the efficacy of an electronic diary with that of standard clinical practice. The technological platform adopted, ONCO-TreC, evaluated in a previous study,[20] is expected to contribute to further improving the adherence and safety of cancer care, and promoting patient empowerment and patient-doctor communication. In addition, the involvement of different stakeholders (eg, healthcare institutions, research centers) represents a key element in ensuring a correct evaluation of the present trial. A specific evaluation component has been designed to correctly assess the implementation of the technological platform and the organizational aspects behind it. At the same time, the study also has a number of limitations. The first concerns the small number of cancer centers involved in the trial, which could arguably restrict the generalizability of results. Secondly, the study design has been carefully adapted to the specific organizational contexts in which the research will take place. Although this could represent a strength of the project in terms of feasibility, an organizational model where a pharmacist counsellor plays a key role may not be applicable or reproducible in all cancer centers.

The present trial holds great promise for substantially impacting and benefitting a large audience. The results will be disseminated through peer-reviewed journals, conferences and event presentations.

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Competing interests: None declared.

Ethical statement: This study was approved Ethical approval was obtained from Romagna Ethics Committee (CEROM), study ID 2108, prot. n. IRST 100.28 of 10/04/2020, will be conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Informed consent will be obtained from all individual study participants before enrollment.

Data availability: Data sharing is not applicable to this article as no new data were created or analyzed.

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Use of the ONCO-TreC electronic diary compared with a standard paper diary to improve adherence to oral cancer therapy in patients with solid and hematological tumors: protocol for a randomized controlled trial

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Original research

Use of the ONCO-TreC electronic diary compared with a standard paper diary to improve adherence to oral cancer therapy in patients with solid and hematological tumors: protocol for a randomized controlled trial

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ABSTRACT

Introduction ONCO-TreC platform consists of a mobile application delivered to patients as electronic diary and a web-based dashboard managed by healthcare professionals. We aim to compare the effectiveness of ONCO-TreC electronic diary with a standard paper diary, in improving adherence to oral cancer therapy in patients with solid and haematological tumors.

Methods and analysis This is an open label, superiority, randomised controlled trial conducted in 2 Italian Oncology Units. Patients will be randomized with a 1:1 ratio to electronic or paper diary. For both groups a counsellor will be responsible for drug and diary delivery. The evaluation period will end after 6 cycles of therapy. The primary aim is to compare the proportion of non-adherent patients in the two arms. Adherence will be measured through pill count; anyone who takes less than 90% of the total prescribed drug dose will be considered non-adherent. Assuming a percentage of non-adherent patients to oral therapy of 40% in arm B, and a 60% reduction in this percentage in arm A, a sample of 124 patients will provide 80% power to identify an absolute difference greater than 24 percentage points using a bilateral Fisher's exact test with a significance level of 0.05. Considering a dropout rate of 10%, approximately 136 patients will have to be enrolled. The primary analysis will be performed on the intention-to-treat population. Secondary aims are to describe the reasons for non-adherence, the level of satisfaction of patients and healthcare professionals with the paper and electronic diary, and the impact of non-adherence in terms of healthcare costs.

Ethics and dissemination Ethical approval was obtained from Romagna Ethics Committee (CEROM), study ID 2108, prot. n. IRST 100.28 of 10/04/2020. Informed consent will be

obtained from all study participants. Findings will be disseminated through peer-reviewed journals, conferences and event presentations.

Protocol version: V.2, 6 April 2021

Trial registration number: ClinicalTrials.gov NCT04826458

Keywords

oral anticancer agents; home-based healthcare management; adherence; eHealth; patient empowerment

Strengths and limitations of this study

- This multicenter randomized study is the first to compare the efficacy of an electronic diary with that of standard clinical practice.
- The majority of cancer patients use smart phones or tablets on a regular basis.
- Methodological strengths include sample size and randomization, rigorous measurement of adherence, wide qualitative data deriving from questionnaires and semi structured interviews.
- The limited number of cancer centers involved in the trial could make it difficult to generalize the results to the general population.
- The organizational model that includes the presence of the counsellor may not be applicable to all cancer centers.

INTRODUCTION

The use of oral treatments is constantly increasing in the area of onco-hematology, raising adherence and safety issues.[1-5] Literature data show that there is enormous variability in adherence, with rates varying between 20% and 100%.[6] Given that poor adherence can have important consequences in terms of treatment efficacy and toxicity,[7] the concept of patient empowerment plays a key role in the self-management of therapies.[8,9]

Several trials have been carried out in recent years to evaluate interventions aimed at improving adherence to oral antineoplastic therapies, eg, educational support, counselling programs, pre-filled pill boxes, and automated voice response systems.[5] To the best of our knowledge, no randomized trials have been performed to evaluate the difference between intervention and control groups with respect to primary adherence outcomes. Two non-randomized cohort studies showed a benefit in terms of adherence to oral antineoplastic therapy from their intervention programs with respect to retrospective control groups. In one study, a treatment monitoring program, where the patient and the caregiver were extensively informed about drug characteristics and potential side effects and trained in their management, was provided to patients undergoing erlotinib for advanced non small cell lung cancer; this intervention was associated with significantly higher rates of adherence - as measured by both patient self report (p=0.042) and pill count (p=0.002) - and disease control (p=0.037).[10] In another trial, intensified multidisciplinary pharmaceutical care was associated with significantly higher mean daily adherence rates to oral capecitabine in a small cohort of patients with colorectal and breast cancer (p=0.029).[11]

In clinical practice, a program that includes the presence of a counsellor and the delivery of a paper diary is generally considered an adequate standard of care. Within this context,

2.0 web solutions such as telemedicine, mobile health devices and applications (apps) might be useful to improve adherence to medication and to optimize shared management of oral agents between patient and healthcare providers.[10-17]

The Center for Communication and Information Technology of Fondazione Bruno Kessler (FBK-ICT) in Trento developed a monitoring system based on the TreC (CCC, Citizen Clinical Record) platform to deliver mobile health services in different chronic diseases, such as asthma, type 1 diabetes and hypertension.[18,19] The system was subsequently adapted for home management and remote monitoring of oral anticancer therapy (ONCO-TreC).

ONCO-TreC was customized, fine-tuned and validated through a prospective multicenter study in cancer patients treated with oral anticancer drugs.[20] Forty patients were enrolled, and adherence to cancer treatment was >86%. The ability of the system to measure adherence to treatment was high, with a concordance of 97.3% (95 CI: 86.1%-99.9%) between investigator and system pill count. System usability and acceptability were also very high. However, the small sample size and absence of a control arm did not permit any definitive conclusions to be drawn about the efficacy of the system in improving adherence [Passardi et al., *submitted*].

The aim of the present study is to compare the effectiveness of two different strategies, ie, electronic diary and paper diary, in improving adherence to oral cancer therapy in patients with solid and hematological tumors.

METHODS AND ANALYSIS

Study design and participants

The research is an Italian prospective open label, superiority, randomized, interventional, non-pharmacological, multicenter clinical study on cancer patients receiving anticancer oral treatment.

Inclusion and exclusion criteria

Inclusion criteria are defined as follows: adult ≥18 years old, either gender; Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2; life expectancy >12 weeks according to clinical judgment; patient candidate for treatment with an oral agent (adjuvant and advanced settings allowed); good understanding of the Italian language; ability to follow study procedures and manage mobile devices after a basic training course, at the investigator's discretion; written informed consent.

Patients receiving an intravenous anticancer treatment as well as experimental drugs will be excluded to reduce potential confounding in evaluating the strategies.

Recruitment

This study will be jointly conducted at 2 Italian cancer care and research centers: IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola; Oncology Unit of the Azienda Provinciale per i Servizi Sanitari (APSS) in Trento. Clinicians will identify potentially eligible patients, providing them with all the details pertaining to project participation, and collecting the signed informed consent. Recruitment started in May 2021 and is expected to last 24 months. Total study duration is 36 months.

Randomization

After being approached for face-to-face screening and enrollment, participants will be randomized to the intervention or control group across sites (1:1 ratio), according to the following arms: A) electronic diary (ONCO-TreC APP); B) paper diary. A permuted block unstratified randomization procedure, with block sizes randomly varying between 4 and 6, will be used. The randomization sequence will be computer-generated by the Biostatistics and Clinical Trials Unit of IRST and implemented using centralized controlled website randomization service and electronic data capture system (OpenClinica V.3.12.2). The investigators will not have access to the randomization list.

Patients assigned to the electronic diary group will be equipped with a dedicated APP (ONCO-TreC) and receive specific training on its use. The researchers in charge of the randomization will not have any influence on the routine care of patients, and participation in the project does not imply any significant adjustment in the standard routine care.

Patient and public involvement

No patient involved.

ONCO-TreC and paper diary

ONCO-TreC consists of a mobile application (APP) delivered to patients and a web-based dashboard managed by healthcare professionals. The APP contains a visual reminder of cancer therapy, a simplified adverse event reporting system, a section for vital signs entering, and a messaging system. Clinicians enter the details of oral treatment schedules

through the dashboard, set reminders, monitor for adherence to treatment and reported adverse events, and can communicate with patients through the messaging system. A detailed description of the ONCO-TreC has been reported elsewhere.[20]

Each study center will provide patients in the control arm with a paper diary according to clinical practice. This diary must contain some essential information, e.g. drug name, dosage, dates of administration. There is also a section for reporting any side effects and notes.

Counsellor

Patients of both arms will be followed by a trained healthcare professional (counsellor) who will be responsible for drug and diary delivery. The counsellor will also train the patient and/or caregiver at the very first treatment cycle with regard to (i) therapy (dosage, duration, storage methods, etc.) and (ii) issues/adverse events reporting. The healthcare staff will instruct the patient to return all the drug packs received, even if empty, at each cycle, for pill count. In addition, the counsellor will obtain information from patients about any concomitant drugs used at home. All these procedures will take place inside an adequate and dedicated room.

Study procedures

At the baseline visit, demographic data (age, sex, educational qualification and occupation), cancer history, and information on concomitant diseases and therapies will be collected; physical examination with vital signs and performance status assessment will be carried out. Patients assigned to arm A will be provided with the ONCO-TreC APP (installed on a

smartphone or tablet), the oral drug for a treatment cycle and an appointment for the next cycle, and will be instructed on how to use the APP. Patients assigned to arm B will be provided with a paper diary, the oral medication and an appointment for the next cycle, and will be given instructions on how to use the paper diary.

During the patient's medical visits at each treatment cycle, adherence and adverse events will be reported in the patient's medical records, as per clinical practice. In addition, at each cycle the counsellor will check the patient's diary (paper or electronic), count any remaining tablets, and evaluate the need for retraining. Patients will also receive the drug supply for a new treatment cycle, the appointment for the next cycle and, for those in arm B, a new paper diary.

Outcome measures

The primary outcome of the trial is to compare the proportion of non-adherent patients in the experimental and control arms. Adherence will be assessed at each treatment cycle by counting the remaining pills. Any patient who takes less than 90% of the total planned drug dose during the study period as per study protocol will be defined as non-adherent. Patients who take fewer tablets than prescribed due to toxicity or medical decision will be considered adherent if this decision is recorded in the medical records. The evaluation period will end after 6 cycles of therapy or earlier due to a therapy change for disease progression or unacceptable toxicity or patient refusal. Each patient, once the planned 6-cycle phase is over, will continue the treatment, with visits and procedures as per clinical practice.

As for the secondary aims, the reasons for non-adherence (eg, forgetting to take the pills,

side-effects, misunderstanding of the prescription) will be registered in the medical records by the counselor during each cycle visit and summarized through percentages (ie. percentage of non-adherent patients by cause and study arm).

Usability and acceptability of ONCO-TreC and paper diary by patients will be assessed through 3 questionnaires: Q-pre and Q-post administered at baseline and at the end of observation (EoO); and the Italian version of the System Usability Scale (SUS) at EoO.[21.] Q-pre and Q-post are *ad hoc* questionnaires developed to analyze patient expectations with regard to the system (Q-pre) and to evaluate system acceptability (Q-post) and communication between patients and cancer centers (Q-pre and Q-post) through 4-point Likert scale questions as well as open-ended questions. Answers will be reported in terms of percentages. The data from SUS questionnaire will be summarized by first summing, for each patient, the score contributions from each item. For items 1, 3, 5, 7, and 9 the score contribution is given by subtracting 1 to the scale position. For items 2, 4, 6, 8, and 10, the contribution is 5 minus the scale position. Then, multiplying by 2.5 the sum of the score contributions. The overall system usability level will be averaged over all patients randomized to Arm A.

A subgroup of patients will also undergo semi-structured interviews by FBK-ICT sociologists at EoO. These interviews will be conducted by teleconference and will focus on healthcare practice and the use of the electronic or paper diary. FBK-ICT sociologists will also conduct semi-structured interviews with the oncologists, counsellors and healthcare professionals involved in the trial to evaluate the impact of the technology on the workload, as well as patient-hospital communication, adherence and adverse events management. The semi-structured interviews will be audio-recorded, transcribed and

assessed by the template analysis, a structured technique for the evaluation of qualitative data.

The costs for medicines and for hospital resource utilization (eg, hospitalizations, access to the emergency room) will be assessed for patients enrolled at IRST and resident in the Emilia-Romagna Region only. Administrative sources such as the pharmacy dispensing database, hospital discharge cards, and the outpatient specialist assistance services database will be considered. The costs for healthcare procedures will be measured according to the regional Healthcare Range of Outpatients Fees, in order to estimate the cost actually incurred by the healthcare provider, while for inpatient setting, we will compute the entire DRG (Diagnosis Related Group)-related costs. Unit costs for drugs will be acquired from the national pharmaceutical formulary drafted by the Italian Medicines Agency (AIFA). Costs will be assessed on a per-patient per-month (PPPM) basis and summarized as follows: (total amount of costs from the start of intervention start until its end/days from the start of intervention until its end) × 30.

Data management

ONCO-TreC APP will communicate with a back-end service to store data on a central server. Researchers will be able to evaluate capability data through a web-based dashboard. Data entered into the system or paper diary by the patient will be compared with those assessed by the oncologist and/or the counsellor. In particular, the adherence to treatment that emerges from diaries will be related to the number of residual pills returned during the hospital visit, and adverse events reported in the diaries will be compared to those reported to the oncologist and recorded in the medical records. Data will be registered in electronic

case report forms, implemented using a relational database management system and a graphic user interface (OpenClinica V.3.12.2).

Statistical Analysis

The sample size was calculated assuming a percentage of non-adherence to oral therapy of 40% in arm B, and a 60% reduction in the percentage of non-adherent patients in arm A. A sample consisting of 124 patients (62 patients for each arm) will provide 80% power to identify an absolute difference greater than 24 percentage points using a bilateral Fisher's exact test with a significance level of 0.05. Considering a dropout rate of 10%, approximately 136 total patients will have to be enrolled.

The main study hypothesis will be tested using Fisher's exact test. The percentage of non-adherent patients in the 2 groups will be reported both as a point estimate and by means of 95% confidence intervals in the intention-to-treat population. Secondary outcomes will be reported through descriptive statistics: mean ± standard deviation (sd) or median and interquartile range for continuous variables, and absolute and relative frequency for categorical variables. Such descriptive statistics will be computed on the overall population, by patient randomization arm, and other clinical characteristics, as appropriate.

ETHICS AND DISSEMINATION

This Italian multicenter randomized study, approved by the Romagna Ethics Committee (CEROM), study ID 2108, prot. n. IRST 100.28 of 10/04/2020, will be conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Informed consent will be obtained from all individual study participants before enrollment. The results will be disseminated through peer-reviewed journals, conferences and event presentations. All information and documentation provided to investigators are considered confidential and cannot be given or disclosed to third parties. The investigators will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each patient. Only the study promoter staff will have access to the final dataset containing pseudonymized data.

Any study modification will be notified to the pertinent Ethics Committee through an amendment.

DISCUSSION

Considering the impact of adherence to oral treatments in onco-hematology in terms of treatment efficacy and toxicity, the validation of reliable and easy-to-use tools to improve patients' self-management of therapies is essential.[9] Current literature supports the idea that multilayer approaches including educational support, treatment monitoring, pharmacy based and counselling programs are essential for improving adherence and, therefore, treatment efficacy.[5] An increasing level of acceptance to m-health technologies in oncology is being shown by patients and healthcare staff. However, despite the numerous studies published on this issue, there is still a clear need to further promote the validation of technological, organizational and m-health platforms (eg, APP) to support patients' self-management, which is a key factor in sustaining proper treatment adherence[22].

The present multicenter randomized study represents a unique contribution in this area in that it will be the first to compare the efficacy of an electronic diary with that of standard

clinical practice. Nowadays, the majority of cancer patients, even the elderly, use smart phones or tablets on a regular basis. The technological platform adopted, ONCO-TreC, evaluated in a previous study,[20] is expected to contribute to further improving the adherence and safety of cancer care, and promoting patient empowerment and patient-doctor communication. The methodological strengths of the present trial include the sample size and randomization of patients, a rigorous measurement of adherence, and the analysis of qualitative data deriving from questionnaires and semi structured interviews. In addition, the involvement of different stakeholders (eg, healthcare institutions, research centers) represents a key element in ensuring a correct evaluation of the present trial. At the same time, the study also has a number of limitations. The first concerns the small number of cancer centers involved in the trial, which could arguably restrict the generalizability of results. Secondly, the study design has been carefully adapted to the specific organizational contexts in which the research will take place. Although this could represent a strength of the project in terms of feasibility, an organizational model where a pharmacist counsellor plays a key role may not be applicable or reproducible in all cancer centers.

Acknowledgements: The authors would like to acknowledge all their colleagues from the different institutions who contributed to the study protocol.

Contributors: PS**,** AP, RV and SF conceived the idea for the study; AP, PS, RV, CM, OC, EP and SF designed the study; AP, EMP and PS took care of questionnaires and semi structured interviews; RV, CE and MD contributed to ONCO-TreC fine-tuning and implementations; CM, AC, EB and VB contributed to the definition of roles and responsibilities of the counselor; VG, GB, FS and CA critically reviewed and revised the protocol drafts; EP performed the statistical analyses. The first draft of the manuscript was jointly written by AP, EP and LG. All authors participated in the organization of the study. All authors contributed to editing subsequent drafts and all read and approved the final manuscript for submission.

Ethical statement: This study was approved Ethical approval was obtained from Romagna Ethics Committee (CEROM), study ID 2108, prot. n. IRST 100.28 of 10/04/2020, will be conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Informed consent will be obtained from all individual study participants before enrollment.

Competing interests: None declared.

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

Section/item	ItemNo	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	The Title is structured accordingly (page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	ClinicalTrials.gov NCT04826458 (Page 4)
Protocol version	3	Date and version identifier	Page 4
Funding	4	Sources and types of financial, material, and other support	Page 17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1
	5b	Name and contact information for the trial sponsor	NA, this is a non-industry-sponsored trial

	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	NA, this is a non-industry-sponsored trial
	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)	IRST is the coordinating centre of this study; the chief and co-chief investigators are Dr. Patrizia Serra (senior clinical research coordinator) and Dr. Alessandro Passardi (clinician). The coordinating centre has a core facility for the design and conduction of clinical trials, that is, the Biostatistics and Clinical Trials Unit. This unit is composed by study coordinators, monitors, and biostatisticians who support the principal investigators from the design of the study until its closure.
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	Pages 6,7
	6b	Explanation for choice of comparators	Pages 6,7
Objectives	7	Specific objectives or hypotheses	Page 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)	Page 7 (in Methods and Analysis), lines 138-40
Methods: Participants, interventions, and outcomes			
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	Page 9 (in Methods and Analysis) lines 153-155
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)	Page 8, lines 143-150
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 10

		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)	Page 10, the observation period will end earlier than planned for disease progression, unacceptable toxicity or patient refusal (lines 222-225)
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Pages 10,11. Patients will be closely monitored and trained by the clinician or the counsellor at the beginning of the study as well as, if necessary, at the following clinical visits.
		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8
	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	Pages 11-13

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Pages 10-11. Other than a description of enrolment and study duration as well as of intervention and timing of the study visits, already reported in the paper, the original protocol contains a flow-chart table of the study.
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	The eligibility criteria are wide favouring enrolment (target number and timing) of the target population and the pragmatic nature of the study itself. As for every new study activated by the coordinating centre, a feasibility check has been carried out during the protocol writing.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 9

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 8, this is an open label trial
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Study procedures (Page 11) and data management (Pages 13-14).

		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	This aspect was taken into account during the trial design, especially with respect to the definition of duration of follow-up. That is, defining an intervention widow not too short and not too long. Reasons for early termination are collected in the eCRFs.
	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 13 (Data management)
	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 14
		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 14

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Given the nature of the study, eg. not testing a new drug, not having serious safety concerns or unknown risks (the intervention under study here is an electronic diary), not having any regulatory approval intent, the DMC was not included.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA, no interim analyses were planned
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 15
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)	Page 15. Ethical committee approval is required before any protocol amendment is implemented.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 9 (recruitment)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA, no ancillary studies are planned
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	Page 15

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 17
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	Page 15
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	NA
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	Page 15
	31b	Authorship eligibility guidelines and any intended use of professional writers	Authorship will be proportional to the accrual of each center. No professional writer will be used.

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	See IPD statement on clinicaltrials.gov
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	This information can be found in the study protocol but not in the manuscript.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA