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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 oncology, 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)

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4 might be useful to improve adherence to medication and to optimize shared management of
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6 oral agents between patient and healthcare providers.¹⁰⁻¹⁷
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9 The Center for Communication and Information Technology of Fondazione Bruno
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11 Kessler (FBK-ICT) in Trento developed a monitoring system based on the TreC (CCC,
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13 Citizen Clinical Record) platform to deliver mobile health services in different chronic
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15 diseases, such as asthma, type 1 diabetes and hypertension.^{18,19} The system was
16
17 subsequently adapted for home management and remote monitoring of oral anticancer
18
19 therapy (ONCO-TreC).
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23 ONCO-TreC was customized, fine-tuned and validated through a prospective
24
25 multicenter study in cancer patients treated with oral anticancer drugs [Passardi et al.,
26
27 *submitted*].²⁰ Forty patients were enrolled, and adherence to cancer treatment was >86%.
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29 The ability of the system to measure adherence to treatment was high, with a concordance
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31 of 97.3% (95 CI: 86.1%-99.9%) between investigator and system pill count. System
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33 usability and acceptability were also very high. However, the small sample size and
34
35 absence of a control arm did not permit any definitive conclusions to be drawn about the
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37 efficacy of the system in improving adherence.
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42 The aim of the present study protocol and its primary endpoint is to compare the
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44 effectiveness of two different strategies, ie, electronic diary (ONCO-TreC) and paper diary,
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46 in improving adherence to oral cancer therapy in patients with solid and hematological
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48 tumors.
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51 Secondary endpoints of the study are as follows: (i) to identify the reasons for non-
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53 adherence in each group of patients (eg, forgetting to take the pills, side-effects,
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55 misunderstanding of the prescription); (ii) to describe the satisfaction of patients and
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4 healthcare professionals with the different strategies by means of brief questionnaires and
5 semi-structured interviews; (iii) to evaluate the impact of the lack of therapeutic adherence
6 in terms of both costs for medicines and overall healthcare costs (eg, hospitalizations,
7 health services, access to Emergency Room).
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16 **METHODS AND ANALYSIS**

17 **Study design and participants**

18 The research is a prospective randomized, interventional, non-pharmacological, multicenter
19 study on cancer patients receiving anticancer oral treatment.
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27 **Inclusion and exclusion criteria**

28 Inclusion criteria are defined as follows: adult ≥ 18 years old, either gender; Eastern
29 Cooperative Oncology Group performance status (ECOG PS) ≤ 2 ; life expectancy > 12
30 weeks according to clinical judgment; patient candidate for treatment with an oral agent
31 (adjuvant and advanced settings allowed); good understanding of the Italian language;
32 ability to follow study procedures and manage mobile devices after a basic training course,
33 at the investigator's discretion; written informed consent.
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43 Patients receiving an intravenous anticancer treatment as well as experimental drugs will
44 be excluded to reduce potential confounding in evaluating the strategies.
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50 **Recruitment**

51 A total of 124 evaluable patients will be considered. Clinicians will identify potentially
52 eligible patients, providing them with all the details pertaining to project participation, and
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4 collecting the signed informed consent.
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8 9 **Randomization**

10 After being approached for face-to-face screening and enrollment, participants will be
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12 randomized to the intervention or control group across sites (1:1 randomization) according
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14 to the following arms: A) electronic diary (ONCO-TreC APP); B) paper diary.
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18 Patients assigned to the electronic diary group will be equipped with a dedicated APP
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20 (ONCO-TreC) and receive specific training on its use.
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23 The researchers in charge of the randomization will not have any influence on the
24
25 routine care of patients, and participation in the project does not imply any significant
26
27 adjustment in the standard routine care.
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30 31 32 **Patient and public involvement**

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34 No patient involved.
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38 39 **ONCO-TreC**

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41 ONCO-TreC consists of a mobile application (APP) delivered to patients and a web-based
42
43 dashboard managed by healthcare professionals. The APP contains a visual reminder of
44
45 cancer therapy, a simplified adverse event reporting system, a section for vital signs
46
47 entering, and a messaging system. Clinicians enter the details of oral treatment schedules
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49 through the dashboard, set reminders, monitor for adherence to treatment and reported
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51 adverse events, and can communicate with patients through the messaging system. A
52
53 detailed description of the ONCO-TreC has been reported elsewhere.²⁰
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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

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4 supply for a new treatment cycle, the appointment for the next cycle and, for those in arm
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6 B, a new paper diary.
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9 The evaluation period will end after 6 cycles of therapy or before in the event of a
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11 change of therapy (for disease progression or unacceptable toxicity) or patient refusal. Each
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13 patient, once the planned 6-cycle phase is over, will continue the treatment, with visits and
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15 procedures as per clinical practice.
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18 Usability and acceptability of ONCO-TreC and paper diary by patients will be assessed
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20 through 3 questionnaires: Q-pre and Q-post at baseline and at the end of observation (EoO);
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22 and the Italian version of the System Usability Scale (SUS) at EoO.²¹ Q-pre and Q-post are
23
24 *ad hoc* questionnaires developed to analyze patient expectations with regard to the system
25
26 (Q-pre) and to evaluate system acceptability (Q-post) and communication between patients
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28 and cancer centers (Q-pre and Q-post). A subgroup of patients will also undergo semi-
29
30 structured interviews by FBK-ICT sociologists at EoO. These interviews will be conducted
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32 by teleconference and will focus on healthcare practice and the use of the electronic or
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34 paper diary. FBK-ICT sociologists will also conduct semi-structured interviews with the
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36 oncologists, counsellors and healthcare professionals involved in the trial to evaluate the
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38 impact of the technology on the workload, as well as patient-hospital communication,
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40 adherence and adverse events management.
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48 **Data management**

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50 ONCO-TreC APP will communicate with a back-end service to store data on a central
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52 server. Researchers will be able to evaluate capability data through a web-based dashboard.
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54 Data entered into the system or paper diary by the patient will be compared with those
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4 assessed by the oncologist and/or the counsellor. In particular, the adherence to treatment
5 that emerges from diaries will be related to the number of residual pills returned during the
6 hospital visit, and adverse events reported in the diaries will be compared to those reported
7 to the oncologist and recorded in the medical records. Data will be registered in electronic
8 case report forms, implemented using a relational database management system and a
9 graphic user interface.
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20 **Statistical Analysis**

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22 Adherence will be assessed at each treatment cycle by counting the remaining pills. Any
23 patient who takes at least 90% of the total planned drug dose as per study protocol will be
24 defined as adherent. Patients who take fewer tablets than prescribed due to toxicity or
25 medical decision will be considered adherent if this decision is recorded in the medical
26 records. The effectiveness of each experimental strategy will be evaluated by comparing
27 the proportion of adherent patients in the corresponding groups.
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36 Patient perception about ONCO-TreC or paper diary will be assessed through
37 questionnaires. Two specific questionnaires (Q-pre, Q-post) will be administered to
38 evaluate patient expectations about the system, system acceptability, quality of care and
39 patient-doctor communication. An internationally validated SUS will be used to investigate
40 system usability in the experimental arm. The semi-structured interviews will be audio-
41 recorded, transcribed and assessed by the template analysis, a structured technique for the
42 evaluation of qualitative data.
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52 The sample size was calculated assuming a percentage of non-adherence to oral therapy
53 of 40% in arm B, and a 60% reduction in the percentage of non-adherent patients in arm A.
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4 A sample consisting of 124 patients (62 patients for each arm) will provide 80% power to
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6 identify an absolute difference greater than 24 percentage points using a bilateral Fisher's
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8 exact test with a significance level of 0.05. Considering a dropout rate of 10%,
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10 approximately 136 total patients will have to be enrolled.
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13 The hypothesis relating to the primary endpoint of the study will be tested using Fisher's
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15 exact test. The percentage of adherent patients in the 2 groups will be reported both as a
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17 point estimate and by means of 95% confidence intervals. Secondary endpoints will be
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19 reported through descriptive statistics: mean \pm standard deviation (sd) or median and
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21 interquartile range for continuous variables, and absolute and relative frequency for
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23 categorical variables.
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29 **ETHICS AND DISSEMINATION**

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31 This Italian multicenter randomized study, approved by the Romagna Ethics Committee
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33 (CEROM), study ID 2108, prot. n. IRST 100.28 of 10/04/2020, will be conducted in
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35 accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.
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37 Informed consent will be obtained from all individual study participants before enrollment.
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41 Considering the impact of adherence to oral treatments in onco-hematology in terms of
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43 treatment efficacy and toxicity, the validation of reliable and easy-to-use tools to improve
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45 patients' self-management of therapies is essential.⁹ Current literature supports the idea that
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47 multilayer approaches including educational support, treatment monitoring, pharmacy
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49 based and counselling programs are essential for improving adherence and, therefore,
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51 treatment efficacy.⁵ An increasing level of acceptance to m-health technologies in oncology
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53 is being shown by patients and healthcare staff. However, despite the numerous studies
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4 published on this issue, there is still a clear need to further promote the validation of
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6 technological, organizational and m-health platforms (eg, APP) to support patients' self-
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8 management, which is a key factor in sustaining proper treatment adherence.
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11 The present multicenter randomized study represents a unique contribution in this area
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13 in that it will be the first to compare the efficacy of an electronic diary with that of standard
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15 clinical practice. The technological platform adopted, ONCO-TreC, evaluated in a previous
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17 study,²⁰ is expected to contribute to further improving the adherence and safety of cancer
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19 care, and promoting patient empowerment and patient-doctor communication. In addition,
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21 the involvement of different stakeholders (eg, healthcare institutions, research centers)
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23 represents a key element in ensuring a correct evaluation of the present trial. A specific
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25 evaluation component has been designed to correctly assess the implementation of the
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27 technological platform and the organizational aspects behind it. At the same time, the study
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29 also has a number of limitations. The first concerns the small number of cancer centers
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31 involved in the trial, which could arguably restrict the generalizability of results. Secondly,
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33 the study design has been carefully adapted to the specific organizational contexts in which
34
35 the research will take place. Although this could represent a strength of the project in terms
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37 of feasibility, an organizational model where a pharmacist counsellor plays a key role may
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39 not be applicable or reproducible in all cancer centers.
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46 The present trial holds great promise for substantially impacting and benefitting a large
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48 audience. The results will be disseminated through peer-reviewed journals, conferences and
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50 event presentations.
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37 **Ethical statement:** This study was approved Ethical approval was obtained from Romagna
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39 Ethics Committee (CEROM), study ID 2108, prot. n. IRST 100.28 of 10/04/2020, will be
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41 conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice
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43 guidelines. Informed consent will be obtained from all individual study participants before
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45 enrollment.
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51 **Data availability:** Data sharing is not applicable to this article as no new data were created
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53 or analyzed.
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BMJ Open

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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	ONCOLOGY, ORAL MEDICINE

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4 1 Original research
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9 **3 Use of the ONCO-TreC electronic diary compared with a**
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12 **4 standard paper diary to improve adherence to oral cancer**
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15 **5 therapy in patients with solid and hematological tumors:**
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18 **6 protocol for a randomized controlled trial**
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4 33 **ABSTRACT**

5
6 34 **Introduction** ONCO-TreC platform consists of a mobile application delivered to patients
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8
9 35 as electronic diary and a web-based dashboard managed by healthcare professionals. We
10
11 36 aim to compare the effectiveness of ONCO-TreC electronic diary with a standard paper
12
13 37 diary, in improving adherence to oral cancer therapy in patients with solid and
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15
16 38 haematological tumors.

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18 39 **Methods and analysis** This is an open label, superiority, randomised controlled trial
19
20 40 conducted in 2 Italian Oncology Units. Patients will be randomized with a 1:1 ratio to
21
22 41 electronic or paper diary. For both groups a counsellor will be responsible for drug and
23
24 42 diary delivery. The evaluation period will end after 6 cycles of therapy. The primary aim is
25
26 43 to compare the proportion of non-adherent patients in the two arms. Adherence will be
27
28 44 measured through pill count; anyone who takes less than 90% of the total prescribed drug
29
30 45 dose will be considered non-adherent. Assuming a percentage of non-adherent patients to
31
32 46 oral therapy of 40% in arm B, and a 60% reduction in this percentage in arm A, a sample of
33
34 47 124 patients will provide 80% power to identify an absolute difference greater than 24
35
36 48 percentage points using a bilateral Fisher's exact test with a significance level of 0.05.
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38 49 Considering a dropout rate of 10%, approximately 136 patients will have to be enrolled.
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41 50 The primary analysis will be performed on the intention-to-treat population. Secondary
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43 51 aims are to describe the reasons for non-adherence, the level of satisfaction of patients and
44
45 52 healthcare professionals with the paper and electronic diary, and the impact of non-
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48 53 adherence in terms of healthcare costs.

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51 54 **Ethics and dissemination** Ethical approval was obtained from Romagna Ethics Committee
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53 55 (CEROM), study ID 2108, prot. n. IRST 100.28 of 10/04/2020. Informed consent will be
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4 56 obtained from all study participants. Findings will be disseminated through peer-reviewed
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6 57 journals, conferences and event presentations.
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11 59 **Protocol version:** V.2, 6 April 2021
12

13 60 **Trial registration number:** ClinicalTrials.gov NCT04826458
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17 62 **Keywords**

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20 63 oral anticancer agents; home-based healthcare management; adherence; eHealth; patient
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22 64 empowerment
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26 66 **Strengths and limitations of this study**

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30 67 • This multicenter randomized study is the first to compare the efficacy of an electronic
31
32 68 diary with that of standard clinical practice.
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34 69 • The majority of cancer patients use smart phones or tablets on a regular basis.
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37 70 • Methodological strengths include sample size and randomization, rigorous
38
39 71 measurement of adherence, wide qualitative data deriving from questionnaires and semi
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41 72 structured interviews.
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44 73 • The limited number of cancer centers involved in the trial could make it difficult to
45
46 74 generalize the results to the general population.
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48 75 • The organizational model that includes the presence of the counsellor may not be
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50 76 applicable to all cancer centers.
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77 INTRODUCTION

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

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

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

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4 100 2.0 web solutions such as telemedicine, mobile health devices and applications (apps)
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6 101 might be useful to improve adherence to medication and to optimize shared management of
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9 102 oral agents between patient and healthcare providers.¹⁰⁻¹⁷

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11 103 The Center for Communication and Information Technology of Fondazione Bruno
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13 104 Kessler (FBK-ICT) in Trento developed a monitoring system based on the TreC (CCC,
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15 105 Citizen Clinical Record) platform to deliver mobile health services in different chronic
16
17 106 diseases, such as asthma, type 1 diabetes and hypertension.^{18,19} The system was
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19
20 107 subsequently adapted for home management and remote monitoring of oral anticancer
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22 108 therapy (ONCO-TreC).

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25 109 ONCO-TreC was customized, fine-tuned and validated through a prospective
26
27 110 multicenter study in cancer patients treated with oral anticancer drugs.²⁰ Forty patients were
28
29 111 enrolled, and adherence to cancer treatment was >86%. The ability of the system to
30
31 112 measure adherence to treatment was high, with a concordance of 97.3% (95 CI: 86.1%-
32
33 113 99.9%) between investigator and system pill count. System usability and acceptability were
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35 114 also very high. However, the small sample size and absence of a control arm did not permit
36
37 115 any definitive conclusions to be drawn about the efficacy of the system in improving
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39 116 adherence [Passardi et al., *submitted*].

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43 117 The aim of the present study is to compare the effectiveness of two different strategies,
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45 118 ie, electronic diary and paper diary, in improving adherence to oral cancer therapy in
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47 119 patients with solid and hematological tumors.

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123 **METHODS AND ANALYSIS**

124 **Study design and participants**

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

129 **Inclusion and exclusion criteria**

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

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

139 **Recruitment**

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

146 **Randomization**

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

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

159

160 **Patient and public involvement**

161 No patient involved.

162

163 **ONCO-TreC and paper diary**

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

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4 168 through the dashboard, set reminders, monitor for adherence to treatment and reported
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6 169 adverse events, and can communicate with patients through the messaging system. A
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9 170 detailed description of the ONCO-TreC has been reported elsewhere.²⁰
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11 171 Each study center will provide patients in the control arm with a paper diary according
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13 172 to clinical practice. This diary must contain some essential information, e.g. drug name,
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15 173 dosage, dates of administration. There is also a section for reporting any side effects and
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17 174 notes.
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22 176 **Counsellor**

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24 177 Patients of both arms will be followed by a trained healthcare professional (counsellor) who
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26 178 will be responsible for drug and diary delivery. The counsellor will also train the patient
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28 179 and/or caregiver at the very first treatment cycle with regard to (i) therapy (dosage,
29
30 180 duration, storage methods, etc.) and (ii) issues/adverse events reporting. The healthcare
31
32 181 staff will instruct the patient to return all the drug packs received, even if empty, at each
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34 182 cycle, for pill count. In addition, the counsellor will obtain information from patients about
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36 183 any concomitant drugs used at home. All these procedures will take place inside an
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38 184 adequate and dedicated room.
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45 186 **Study procedures**

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47 187 At the baseline visit, demographic data (age, sex, educational qualification and occupation),
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49 188 cancer history, and information on concomitant diseases and therapies will be collected;
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51 189 physical examination with vital signs and performance status assessment will be carried
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54 190 out. Patients assigned to arm A will be provided with the ONCO-TreC APP (installed on a
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4 191 smartphone or tablet), the oral drug for a treatment cycle and an appointment for the next
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6 192 cycle, and will be instructed on how to use the APP. Patients assigned to arm B will be
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9 193 provided with a paper diary, the oral medication and an appointment for the next cycle, and
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11 194 will be given instructions on how to use the paper diary.

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13 195 During the patient's medical visits at each treatment cycle, adherence and adverse events
14
15 196 will be reported in the patient's medical records, as per clinical practice. In addition, at each
16
17 197 cycle the counsellor will check the patient's diary (paper or electronic), count any
18
19 198 remaining tablets, and evaluate the need for retraining. Patients will also receive the drug
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21 199 supply for a new treatment cycle, the appointment for the next cycle and, for those in arm
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23 200 B, a new paper diary.

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28 29 202 **Outcome measures**

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31 203 The primary outcome of the trial is to compare the proportion of non-adherent patients in
32
33 204 the experimental and control arms. Adherence will be assessed at each treatment cycle by
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35 205 counting the remaining pills. Any patient who takes less than 90% of the total planned drug
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37 206 dose during the study period as per study protocol will be defined as non-adherent. Patients
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39 207 who take fewer tablets than prescribed due to toxicity or medical decision will be
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41 208 considered adherent if this decision is recorded in the medical records. The evaluation
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43 209 period will end after 6 cycles of therapy or earlier due to a therapy change for disease
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45 210 progression or unacceptable toxicity or patient refusal. Each patient, once the planned 6-
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47 211 cycle phase is over, will continue the treatment, with visits and procedures as per clinical
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49 212 practice.

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51 213 As for the secondary aims, the reasons for non-adherence (eg, forgetting to take the pills,
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4 214 side-effects, misunderstanding of the prescription) will be registered in the medical records
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6 215 by the counselor during each cycle visit and summarized through percentages (ie.
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9 216 percentage of non-adherent patients by cause and study arm).

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11 217 Usability and acceptability of ONCO-TreC and paper diary by patients will be assessed
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13 218 through 3 questionnaires: Q-pre and Q-post administered at baseline and at the end of
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15 219 observation (EoO); and the Italian version of the System Usability Scale (SUS) at EoO.²¹
16
17 220 Q-pre and Q-post are *ad hoc* questionnaires developed to analyze patient expectations with
18
19 221 regard to the system (Q-pre) and to evaluate system acceptability (Q-post) and
20
21 222 communication between patients and cancer centers (Q-pre and Q-post) through 4-point
22
23 223 Likert scale questions as well as open-ended questions. Answers will be reported in terms
24
25 224 of percentages. The data from SUS questionnaire will be summarized by first summing, for
26
27 225 each patient, the score contributions from each item. For items 1, 3, 5, 7, and 9 the score
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29 226 contribution is given by subtracting 1 to the scale position. For items 2, 4, 6, 8, and 10, the
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31 227 contribution is 5 minus the scale position. Then, multiplying by 2.5 the sum of the score
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33 228 contributions. The overall system usability level will be averaged over all patients
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35 229 randomized to Arm A.

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39 230 A subgroup of patients will also undergo semi-structured interviews by FBK-ICT
40
41 231 sociologists at EoO. These interviews will be conducted by teleconference and will focus
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43 232 on healthcare practice and the use of the electronic or paper diary. FBK-ICT sociologists
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45 233 will also conduct semi-structured interviews with the oncologists, counsellors and
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47 234 healthcare professionals involved in the trial to evaluate the impact of the technology on the
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49 235 workload, as well as patient-hospital communication, adherence and adverse events
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51 236 management. The semi-structured interviews will be audio-recorded, transcribed and
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4 237 assessed by the template analysis, a structured technique for the evaluation of qualitative
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6 238 data.

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9 239 The costs for medicines and for hospital resource utilization (eg, hospitalizations, access
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11 240 to the emergency room) will be assessed for patients enrolled at IRST and resident in the
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13 241 Emilia-Romagna Region only. Administrative sources such as the pharmacy dispensing
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15 242 database, hospital discharge cards, and the outpatient specialist assistance services database
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17 243 will be considered. The costs for healthcare procedures will be measured according to the
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19 244 regional Healthcare Range of Outpatients Fees, in order to estimate the cost actually
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21 245 incurred by the healthcare provider, while for inpatient setting, we will compute the entire
22
23 246 DRG (Diagnosis Related Group)-related costs. Unit costs for drugs will be acquired from
24
25 247 the national pharmaceutical formulary drafted by the Italian Medicines Agency (AIFA).
26
27 248 Costs will be assessed on a per-patient per-month (PPPM) basis and summarized as
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29 249 follows: (total amount of costs from the start of intervention start until its end/days from the
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31 250 start of intervention until its end) \times 30.
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39 252 **Data management**

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41 253 ONCO-TreC APP will communicate with a back-end service to store data on a central
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43 254 server. Researchers will be able to evaluate capability data through a web-based dashboard.
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45 255 Data entered into the system or paper diary by the patient will be compared with those
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47 256 assessed by the oncologist and/or the counsellor. In particular, the adherence to treatment
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49 257 that emerges from diaries will be related to the number of residual pills returned during the
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51 258 hospital visit, and adverse events reported in the diaries will be compared to those reported
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55 259 to the oncologist and recorded in the medical records. Data will be registered in electronic
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4 260 case report forms, implemented using a relational database management system and a
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6 261 graphic user interface (OpenClinica V.3.12.2).
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10 263 **Statistical Analysis**

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13 264 The sample size was calculated assuming a percentage of non-adherence to oral therapy of
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15 265 40% in arm B, and a 60% reduction in the percentage of non-adherent patients in arm A. A
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17 266 sample consisting of 124 patients (62 patients for each arm) will provide 80% power to
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19 267 identify an absolute difference greater than 24 percentage points using a bilateral Fisher's
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21 268 exact test with a significance level of 0.05. Considering a dropout rate of 10%,
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23 269 approximately 136 total patients will have to be enrolled.
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27 270 The main study hypothesis will be tested using Fisher's exact test. The percentage of
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29 271 non-adherent patients in the 2 groups will be reported both as a point estimate and by
30
31 272 means of 95% confidence intervals in the intention-to-treat population. Secondary
32
33 273 outcomes will be reported through descriptive statistics: mean \pm standard deviation (sd) or
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35 274 median and interquartile range for continuous variables, and absolute and relative
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37 275 frequency for categorical variables. Such descriptive statistics will be computed on the
38
39 276 overall population, by patient randomization arm, and other clinical characteristics, as
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41 277 appropriate.
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46 279 **ETHICS AND DISSEMINATION**

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49 280 This Italian multicenter randomized study, approved by the Romagna Ethics Committee
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51 281 (CEROM), study ID 2108, prot. n. IRST 100.28 of 10/04/2020, will be conducted in
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53 282 accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.
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4 283 Informed consent will be obtained from all individual study participants before enrollment.
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6 284 The results will be disseminated through peer-reviewed journals, conferences and event
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8 285 presentations. All information and documentation provided to investigators are considered
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10 286 confidential and cannot be given or disclosed to third parties. The investigators will prepare
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12 287 and maintain adequate and accurate source documents designed to record all observations
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14 288 and other pertinent data for each patient. Only the study promoter staff will have access to
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16 289 the final dataset containing pseudonymized data.
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20 290 Any study modification will be notified to the pertinent Ethics Committee through an
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22 291 amendment.
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27 293 **DISCUSSION**

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29 294 Considering the impact of adherence to oral treatments in onco-hematology in terms of
30
31 295 treatment efficacy and toxicity, the validation of reliable and easy-to-use tools to improve
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33 296 patients' self-management of therapies is essential.⁹ Current literature supports the idea that
34
35 297 multilayer approaches including educational support, treatment monitoring, pharmacy
36
37 298 based and counselling programs are essential for improving adherence and, therefore,
38
39 299 treatment efficacy.⁵ An increasing level of acceptance to m-health technologies in oncology
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42 300 is being shown by patients and healthcare staff. However, despite the numerous studies
43
44 301 published on this issue, there is still a clear need to further promote the validation of
45
46 302 technological, organizational and m-health platforms (eg, APP) to support patients' self-
47
48 303 management, which is a key factor in sustaining proper treatment adherence²².
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52 304 The present multicenter randomized study represents a unique contribution in this area
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54 305 in that it will be the first to compare the efficacy of an electronic diary with that of standard
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4 306 clinical practice. Nowadays, the majority of cancer patients, even the elderly, use smart
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6 307 phones or tablets on a regular basis. The technological platform adopted, ONCO-TreC,
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8 308 evaluated in a previous study,²⁰ is expected to contribute to further improving the adherence
9
10 309 and safety of cancer care, and promoting patient empowerment and patient-doctor
11
12 310 communication. The methodological strengths of the present trial include the sample size
13
14 311 and randomization of patients, a rigorous measurement of adherence, and the analysis of
15
16 312 qualitative data deriving from questionnaires and semi structured interviews. In addition,
17
18 313 the involvement of different stakeholders (eg, healthcare institutions, research centers)
19
20 314 represents a key element in ensuring a correct evaluation of the present trial. At the same
21
22 315 time, the study also has a number of limitations. The first concerns the small number of
23
24 316 cancer centers involved in the trial, which could arguably restrict the generalizability of
25
26 317 results. Secondly, the study design has been carefully adapted to the specific organizational
27
28 318 contexts in which the research will take place. Although this could represent a strength of
29
30 319 the project in terms of feasibility, an organizational model where a pharmacist counsellor
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32 320 plays a key role may not be applicable or reproducible in all cancer centers.
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6
7 321 **Acknowledgements:** The authors would like to acknowledge all their colleagues from the
8
9 322 different institutions who contributed to the study protocol.

10
11 323 **Contributors:** PS, AP, RV and SF conceived the idea for the study; AP, PS, RV, CM, OC,
12
13 324 EP and SF designed the study; AP, EMP and PS took care of questionnaires and semi
14
15 325 structured interviews; RV, CE and MD contributed to ONCO-TreC fine-tuning and
16
17 326 implementations; CM, AC, EB and VB contributed to the definition of roles and
18
19 327 responsibilities of the counselor; VG, GB, FS and CA critically reviewed and revised the
20
21 328 protocol drafts; EP performed the statistical analyses. The first draft of the manuscript was
22
23 329 jointly written by AP, EP and LG. All authors participated in the organization of the study.
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26 330 All authors contributed to editing subsequent drafts and all read and approved the final
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28 331 manuscript for submission.

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32 332 **Ethical statement:** This study was approved Ethical approval was obtained from Romagna
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34 333 Ethics Committee (CEROM), study ID 2108, prot. n. IRST 100.28 of 10/04/2020, will be
35
36 334 conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice
37
38 335 guidelines. Informed consent will be obtained from all individual study participants before
39
40 336 enrollment.

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42
43 337 **Competing interests:** None declared.

44
45
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47
48 339 commercial or not-for-profit sectors.

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er review only



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

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- 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**

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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
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Methods: Participants, interventions, and outcomes

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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
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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
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Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 10
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2		11b	Criteria for
3			discontinuing or
4			modifying allocated
5			interventions for a
6			given trial participant
7			(eg, drug dose
8			change in response to
9			harms, participant
10			request, or
11			improving/worsening
12			disease)
13			
14			
15			
16		11c	Strategies to improve
17			adherence to
18			intervention protocols,
19			and any procedures
20			for monitoring
21			adherence (eg, drug
22			tablet return,
23			laboratory tests)
24			
25			
26			
27		11d	Relevant concomitant
28			care and interventions
29			that are permitted or
30			prohibited during the
31			trial
32			
33			
34	Outcomes	12	Primary, secondary,
35			and other outcomes,
36			including the specific
37			measurement variable
38			(eg, systolic blood
39			pressure), analysis
40			metric (eg, change
41			from baseline, final
42			value, time to event),
43			method of
44			aggregation (eg,
45			median, proportion),
46			and time point for
47			each outcome.
48			Explanation of the
49			clinical relevance of
50			chosen efficacy and
51			harm outcomes is
52			strongly
53			recommended
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Page 10, the observation period will end earlier than planned for disease progression, unacceptable toxicity or patient refusal (lines 222-225)

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.

Page 8

Pages 11-13

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	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.
16 17 18 19 20 21 22 23 24 25 26 27 28 29	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
30 31 32 33 34 35 36 37 38 39	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:

1				
2	Sequence	16a	Method of generating	Page 9
3	generation		the allocation	
4			sequence (eg,	
5			computer-generated	
6			random numbers),	
7			and list of any factors	
8			for stratification. To	
9			reduce predictability	
10			of a random	
11			sequence, details of	
12			any planned	
13			restriction (eg,	
14			blocking) should be	
15			provided in a	
16			separate document	
17			that is unavailable to	
18			those who enrol	
19			participants or assign	
20			interventions	
21				
22				
23				
24				
25				
26	Allocation	16b	Mechanism of	Page 9
27	concealment		implementing the	
28	mechanism		allocation sequence	
29			(eg, central	
30			telephone;	
31			sequentially	
32			numbered, opaque,	
33			sealed envelopes),	
34			describing any steps	
35			to conceal the	
36			sequence until	
37			interventions are	
38			assigned	
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42				
43	Implementation	16c	Who will generate the	Page 9
44			allocation sequence,	
45			who will enrol	
46			participants, and who	
47			will assign	
48			participants to	
49			interventions	
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2	Blinding	17a	Who will be blinded	Page 8, this is an open label trial
3	(masking)		after assignment to	
4			interventions (eg, trial	
5			participants, care	
6			providers, outcome	
7			assessors, data	
8			analysts), and how	
9				
10				
11		17b	If blinded,	NA
12			circumstances under	
13			which unblinding is	
14			permissible, and	
15			procedure for	
16			revealing a	
17			participant's allocated	
18			intervention during	
19			the trial	
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Methods: Data collection, management, and analysis

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24				
25				
26	Data collection	18a	Plans for assessment	Study procedures (Page 11) and
27	methods		and collection of	data management (Pages 13-14).
28			outcome, baseline,	
29			and other trial data,	
30			including any related	
31			processes to promote	
32			data quality (eg,	
33			duplicate	
34			measurements,	
35			training of assessors)	
36			and a description of	
37			study instruments (eg,	
38			questionnaires,	
39			laboratory tests) along	
40			with their reliability	
41			and validity, if known.	
42			Reference to where	
43			data collection forms	
44			can be found, if not in	
45			the protocol	
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2		18b	Plans to promote
3			participant retention
4			and complete follow-
5			up, including list of
6			any outcome data to
7			be collected for
8			participants who
9			discontinue or deviate
10			from intervention
11			protocols
12			
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14			
15	Data	19	Plans for data entry,
16	management		coding, security, and
17			storage, including any
18			related processes to
19			promote data quality
20			(eg, double data
21			entry; range checks
22			for data values).
23			Reference to where
24			details of data
25			management
26			procedures can be
27			found, if not in the
28			protocol
29			
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32			
33	Statistical	20a	Statistical methods for
34	methods		analysing primary and
35			secondary outcomes.
36			Reference to where
37			other details of the
38			statistical analysis
39			plan can be found, if
40			not in the protocol
41			
42			
43			
44		20b	Methods for any
45			additional analyses
46			(eg, subgroup and
47			adjusted analyses)
48			
49			
50		20c	Definition of analysis
51			population relating to
52			protocol non-
53			adherence (eg, as
54			randomised analysis),
55			and any statistical
56			methods to handle
57			missing data (eg,
58			multiple imputation)
59			
60			

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 window not too short and not too long. Reasons for early termination are collected in the eCRFs.

Page 13 (Data management)

Page 14

NA

Page 14

1
2 **Methods: Monitoring**

3			
4	Data monitoring	21a	Composition of data
5			monitoring committee
6			(DMC); summary of
7			its role and reporting
8			structure; statement
9			of whether it is
10			independent from the
11			sponsor and
12			competing interests;
13			and reference to
14			where further details
15			about its charter can
16			be found, if not in the
17			protocol. Alternatively,
18			an explanation of why
19			a DMC is not needed
20			
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24		21b	Description of any
25			interim analyses and
26			stopping guidelines,
27			including who will
28			have access to these
29			interim results and
30			make the final
31			decision to terminate
32			the trial
33			
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36	Harms	22	Plans for collecting,
37			assessing, reporting,
38			and managing
39			solicited and
40			spontaneously
41			reported adverse
42			events and other
43			unintended effects of
44			trial interventions or
45			trial conduct
46			
47			
48			
49	Auditing	23	Frequency and
50			procedures for
51			auditing trial conduct,
52			if any, and whether
53			the process will be
54			independent from
55			investigators and the
56			sponsor
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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.

NA, no interim analyses were planned

NA

NA

Ethics and dissemination

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4	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
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11	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)
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28	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
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38		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
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47	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
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2	Declaration of	28	Financial and other	Page 17
3	interests		competing interests	
4			for principal	
5			investigators for the	
6			overall trial and each	
7			study site	
8				
9				
10	Access to data	29	Statement of who will	Page 15
11			have access to the	
12			final trial dataset, and	
13			disclosure of	
14			contractual	
15			agreements that limit	
16			such access for	
17			investigators	
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21	Ancillary and	30	Provisions, if any, for	NA
22	post-trial care		ancillary and post-trial	
23			care, and for	
24			compensation to	
25			those who suffer harm	
26			from trial participation	
27				
28				
29	Dissemination	31a	Plans for investigators	Page 15
30	policy		and sponsor to	
31			communicate trial	
32			results to participants,	
33			healthcare	
34			professionals, the	
35			public, and other	
36			relevant groups (eg,	
37			via publication,	
38			reporting in results	
39			databases, or other	
40			data sharing	
41			arrangements),	
42			including any	
43			publication restrictions	
44				
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48		31b	Authorship eligibility	Authorship will be proportional to the
49			guidelines and any	accrual of each center. No professional
50			intended use of	writer will be used.
51			professional writers	
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2 31c Plans, if any, for [See IPD statement on clinicaltrials.gov](https://clinicaltrials.gov)
3 granting public access
4 to the full protocol,
5 participant-level
6 dataset, and statistical
7 code
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9

10 Appendices

11
12 Informed consent 32 Model consent form [This information can be found](#)
13 materials and other related [in the study protocol but not in the](#)
14 documentation given [manuscript.](#)
15 to participants and
16 authorised surrogates
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18
19 Biological 33 Plans for collection, [NA](#)
20 specimens laboratory evaluation,
21 and storage of
22 biological specimens
23 for genetic or
24 molecular analysis in
25 the current trial and
26 for future use in
27 ancillary studies, if
28 applicable
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