



# 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 haematological tumours: protocol for a randomised 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 tumours.

**Methods and analysis** This is an open label, superiority, randomised controlled trial conducted in two Italian oncology units. Patients will be randomised 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 six 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** Version 2, 6 April 2021.

## Strengths and limitations of this study

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

**Trial registration number** NCT04826458.

## INTRODUCTION

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

Several trials have been carried out in recent years to evaluate interventions

aimed at improving adherence to oral antineoplastic therapies, for example, educational support, counselling programmes, pre-filled pill boxes and automated voice response systems.<sup>5</sup> To the best of our knowledge, no randomised trials have been performed to evaluate the difference between intervention and control groups with respect to primary adherence outcomes. Two non-randomised cohort studies showed a benefit in terms of adherence to oral antineoplastic therapy from their intervention programmes with respect to retrospective control groups. In one study, a treatment monitoring programme, 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 ( $p=0.037$ ).<sup>10</sup> 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 ( $p=0.029$ ).<sup>11</sup>

In clinical practice, a programme 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 optimise shared management of oral agents between patient and healthcare providers.<sup>10–17</sup>

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

ONCO-TreC was customised, fine-tuned and validated through a prospective multicentre study in patients with cancer treated with oral anticancer drugs.<sup>20</sup> 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% to 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, that is, electronic diary and paper diary, in improving adherence to oral cancer therapy in patients with solid and haematological tumours.

## METHODS AND ANALYSIS

### Study design and participants

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

### Inclusion and exclusion criteria

Inclusion criteria are defined as follows: adult  $\geq 18$  years old, either gender; Eastern Cooperative Oncology Group performance status  $\leq 2$ ; life expectancy >12 weeks according to clinical judgement; 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 two Italian cancer care and research centres: IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) 'Dino Amadori', Meldola; Oncology Unit of the Azienda Provinciale per i Servizi Sanitari 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.

### Randomisation

After being approached for face-to-face screening and enrolment, participants will be randomised to the intervention or control group across sites (1:1 ratio), according to the following arms: arm A—electronic diary (ONCO-TreC APP); arm B—paper diary. A permuted block unstratified randomisation procedure, with block sizes randomly varying between 4 and 6, will be used. The randomisation sequence will be computer-generated by the Biostatistics and Clinical Trials Unit of IRST and implemented using centralised controlled website randomisation service and electronic data capture system (OpenClinica V.3.12.2). The investigators will not have access to the randomisation 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 randomisation 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.<sup>20</sup>

Each study centre will provide patients in the control arm with a paper diary according to clinical practice. This diary must contain some essential information, for example, 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 six cycles of therapy or earlier due to a therapy change for disease progression or unacceptable toxicity or patient refusal. Each patient, once the planned six-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 counsellor during each cycle visit and summarised 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 three 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.<sup>21</sup> Q-pre and Q-post are ad hoc questionnaires developed to analyse patient expectations with regard to the system (Q-pre) and to evaluate system acceptability (Q-post) and communication between patients and cancer centres (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 summarised 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 randomised 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 utilisation (eg, hospitalisations, 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 basis and summarised 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 with 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 two groups will be reported both as a point estimate and by means of 95% CIs in the intention-to-treat population. Secondary outcomes will be reported through descriptive statistics: mean ± SD or median and IQR for continuous variables, and absolute and relative frequency for categorical variables. Such descriptive statistics will be computed on the overall population, by patient randomisation arm and other clinical characteristics, as appropriate.

### ETHICS AND DISSEMINATION

This Italian multicentre randomised 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 enrolment.

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 pseudonymised 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-haematology 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.<sup>9</sup> Current literature supports the idea that multilayer approaches including educational support, treatment monitoring, pharmacy based and counselling programmes are essential for improving adherence and, therefore, treatment efficacy.<sup>5</sup> 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, organisational and m-health platforms (eg, APP) to support patients' self-management, which is a key factor in sustaining proper treatment adherence.<sup>22</sup>

The present multicentre randomised 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 patients with cancer, even the elderly, use smart phones or tablets on a regular basis. The technological platform adopted, ONCO-TreC, evaluated in a previous study,<sup>20</sup> 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 randomisation 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 centres) 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 centres involved in the trial, which could arguably restrict the generalisability of results. Second, the study design has been carefully adapted to the specific organisational contexts in which the research will take place. Although this could represent a strength of the project in terms of feasibility,

an organisational model where a pharmacist counsellor plays a key role may not be applicable or reproducible in all cancer centres.

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