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Multicentre, interventional, single-arm study protocol of telemonitored circadian rhythms and patient-reported outcomes for improving mFOLFIRINOX safety in patients with pancreatic cancer (MultiDom, NCT04263948)

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In Memoriam

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ABSTRACT

Introduction Circadian clocks regulate cellular proliferation and drug effects. Tolerability and/or efficacy of anticancer therapies have been improved by their administration according to circadian rhythms, while being predicted by circadian robustness. The combination of leucovorin, fluorouracil, irinotecan and oxaliplatin (mFOLFIRINOX) is a standard treatment for pancreatic ductal adenocarcinoma (PDAC), that generates grades 3–4 adverse events in the majority of patients and an estimated 15%–30% emergency admission rate. The MultiDom study evaluates whether mFOLFIRINOX safety can be improved using a novel circadian-based telemonitoring-telecare platform in patients at home. The detection of early warning signals of clinical toxicities could guide their early management, possibly preventing emergency hospital admissions.

Methods and analysis This multicentre, interventional, prospective, longitudinal, single-arm study hypothesises that the mFOLFIRINOX-related emergency admission rate will be 5% (95% CI 1.7% to 13.7%), among 67 patients with advanced PDAC. Study participation is 7 weeks for each patient, including a reference week before chemotherapy onset and 6 weeks afterwards. Accelerometry and body temperature are measured q1-min using a continuously worn telecommunicating chest surface sensor, daily body weight is self-measured with a telecommunicating balance and 23 electronic patient-reported outcomes (e-PROs) are self-rated using a tablet. Hidden Markov model, spectral analyses and other algorithms automatically compute physical activity, sleep, temperature, body weight change, e-PRO severity and 12 circadian sleep/activity parameters, including the dichotomy index I<O (% activity 'in-bed' below median activity 'out-of-bed'), once to four times daily. Health professionals access visual displays of near-real time parameter dynamics and receive automatic alerts, with trackable digital follow-up.

Ethics and dissemination The study has been approved by the National Agency for Medication and Health Product Safety (ANSM) and Ethics Committee West V (2 July 2019; third amendment, 14 June 2022). The data will be disseminated at conferences and in peer-reviewed journals and will support large-scale randomised evaluation.

Trial registration numbers NCT04263948 and ID RCB-2019-A00566-51.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The main study endpoint is the rate of emergency hospital admissions for adverse events in patients receiving mFOLFIRINOX chemotherapy for pancreatic ductal adenocarcinoma at one of four oncology units.
⇒ Circadian rhythms in rest-activity and body temperature, body weight and electronic patient-reported outcomes (e-PROs) are telemonitored and automatically analysed in near real-time using an ad hoc mobile domomedicine platform system during the most 'at-risk' period corresponding to the initial three courses of chemotherapy.
⇒ An electronic alert generation and follow-up system notifies the occurrence of circadian disruption, fever, body weight loss or poor ePRO scores to the oncology team and tracks proactive care responses, thus complementing standard oncology decision-making based on q2 weekly clinical and biological data records.
⇒ Selected parameters from telemonitored data gathered through patient engagement complement those in the classical electronic clinical research file databases based on medical records.
⇒ The tested domomedicine platform system-based intervention is not compared with standard care within a randomised trial, and the planned study sample is limited to 67 patients.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the fourth-leading cause of cancer-related

death, with only 6% survivors at 5 years.[1 2] PDAC is most common in men aged 40–85 years. Early-stage PDAC is usually asymptomatic, with the diagnosis usually being made at an advanced stage, when chemotherapy is required for disease control.[1 2]

Clinical trials have established FOLFIRINOX (leucovorin, fluorouracil, irinotecan, oxaliplatin) as the standard chemotherapy protocol for patients with advanced PDAC.[3–5] In a retrospective pooled analysis, the median overall survival (OS) of patients with locally advanced PDAC was 24.2 months for those receiving FOLFIRINOX vs 6–13 months for those given gemcitabine.[4] The improved survival on mFOLFIRINOX compared with gemcitabine comes at the expense of higher drug-related toxicity, with grades 3–4 adverse events (AEs) affecting up 75% of patients.[3 4] Severe toxicities include haematological, digestive (diarrhoea, nausea/vomiting, anorexia), asthenia, weight loss and peripheral sensitive neuropathy.[3 4] For this reason, mFOLFIRINOX use is recommended for patients with WHO performance status 0 or 1. In practice, mFOLFIRINOX treatment is stopped in up to 25% of patients as soon as grades 3–4 clinical or haematological toxicities occur, as these may profoundly alter both performance status and quality of life (QoL).[4 5]

In all animal species including humans, cell proliferation, DNA repair and apoptosis, as well as drug metabolism and molecular targets are regulated by circadian clocks in healthy cells. As a result, circadian rhythms moderate drug pharmacokinetics and pharmacodynamics[6] and rhythmically regulate all stages of carcinogenesis, from initiation to progression.[7–9] Several randomised clinical trials have demonstrated that the administration of anticancer therapies at specific times, according to circadian rhythms, so-called chronotherapy or chronomodulated chemotherapy, can increase anticancer treatment efficacy and improve host cell tolerability.[6 10–13] Lévi *et al* reported that the toxicity and efficacy of more than 30 anticancer drugs varied by more than 50% in experimental models as a function of dose administration time.[6] Two circadian rhythm-based treatment strategies (known as chronotherapy) have been developed in oncology, particularly for advanced or metastatic digestive cancer: (1) the administration of drugs according to an average human circadian rhythm using a programmable in-time multichannel injector[6 10–14] and (2) the measurement of individual patient's circadian rhythms to determine the role of the circadian clock on QoL, tumour progression and survival, to develop personalised chronotherapy and to identify new chronotherapeutic targets.[6 15–19]

Circadian rhythms can be determined by measuring the rest-activity rhythm (RAR), which is a non-invasive biomarker of circadian function in mammals.[15] RAR is usually measured by actimetry using a wristwatch-like motion-sensing device.[16] In 2000, the team led by Lévi *et al* described a quantitatively relevant index of RAR in oncology, namely the dichotomy index (I<O).[15 16] This measures the perentage of activity per min while 'In bed' (I), which is less than the median activity 'out of bed' (O), over three or more consecutive days. I<O reaches 100% if the RAR is very ample and regular, with excellent sleep quality. In contrast, those patients whose I<O drops below 97.5% display clinically relevant circadian disruption.[15 16] I<O was identified as an independent prognostic factor for progression-free survival and OS in a meta-analysis of 436 patients with metastatic colorectal cancer.[16] Lower I<O values were also associated with worse fatigue, worse anorexia and sleep problems in 232 patients with metastatic colorectal cancer.[17] Disruption of RAR, as measured with I<O<97.5%, also proved an early indicator of chemotherapy toxicity, which has been significantly associated with lower survival.[18 19]

The integration of circadian rhythm data into oncological practice and their combination with current health status indicators in non-hospitalised cancer patients is part of the domomedicine concept, as proposed by the Academy of Technologies of France.[20]

In the context of the European project inCASA (FP7-ICT), Lévi *et al* participated in the conception and development of the first fixed internet e-health platform allowing the distant monitoring of RAR, body weight and self-evaluated symptoms (19 items of an electronic version of the core MD Anderson Symptoms Inventory questionnaire (MDASI)). These three parameters were measured daily for 30–180 days in 31 patients with metastatic or advanced digestive cancer, with individual compliance rates of 60%–90%. The data collected were teletransmitted daily by the patients themselves to a server via the internet, using a dedicated platform installed at home (domomedicine). Multidimensional analyses revealed that RAR disruption, jointly with symptoms and body weight loss, predicted emergency hospitalisation due to drug-related toxicity 3 days in advance, with an accuracy of 94%.[21] A recent analysis demonstrated that an I<O cut-off of 96% was more discriminating, with RAR displaying the most prominent weight in the model (unpublished data). In a further study by our group, 11 patients with colorectal cancer or PDAC received the chronomodulated administration of FOLFIRINOX at home, using a programmable-in-time pump. Remote follow-up of these patients using the inCASA platform demonstrated excellent tolerance of this protocol, with few alterations to their daily life, over the 26 treatment cycles administered.[22] However, the inCASA platform was fixed and wire-connected, a single circadian rhythm was measured, and parameters and dynamic changes were not computed and visualised in real time. The PiCADo mobile domomedecine platform system was then co-developed by our team, to respond to these limitations. It consists of a thoracic sensor that measures the number of accelerations per minute, three-dimensional (3D) orientation and chest surface temperature every minute[23] and teletransmits these measurements every 10 min via Bluetooth Low Energy (BLE) to a smartphone-like gateway. The infrared thermal probe measures chest surface temperature, whose rhythm disruption also represents an early marker of poor patient outcomes.[24 25] The gateway

also receives body weight measurements taken from BLE-connected scales and teletransmits all sensor data via GPRS to an approved health data hub up to every 6 hours. A GPRS-connected tablet also presents symptoms and QoL questionnaires to the patient, whose answers are teletransmitted in real time to the server. All data are analysed in near-real time, resulting in the daily computation and graphical displays of 12 circadian activity and sleep parameters and 23 symptom scores, with the potential to generate early alerts of toxicity.

The mobile domomedecine platform system has been validated in 228 healthy subjects and its clinical potential has been demonstrated in 37 cancer patients in France and the UK along study sessions of 4 days to 4 weeks.[23 26–28]

The current study will carry out a prospective evaluation of the potential role of such a domomedicine platform system in patients with advanced PDAC receiving first-line mFOLFIRINOX chemotherapy. The aim is to provide a near-real time qualitative and quantitative assessment of this active yet toxic chemotherapeutic protocol on the daily life of such patients. The system should enable the identification of early warning signals of deterioration or improvement in the remote patients' health status. In turn, medical alerts would trigger proactive interventions whenever necessary, in order to avoid a rapid deterioration in general status resulting in toxicity-related emergency hospitalisation and the possible halt of an effective treatment.

METHODS

Study design

This national, multicentre, interventional, non-comparative, prospective, longitudinal, single-arm study is sponsored by Ramsay-Santé Research-and-Education Group, Paris, France. The regulatory submissions, amendments, monitoring and final analyses are prepared by ECTEN (European Clinical Trial Experts Network), La Rochette, France.

The study is taking place at four oncology units in France (Mousseau Clinic, Ramsay-Santé, Evry; St Jean Clinic, Melun; Digestive and Medical Oncology Unit, Paul Brousse Hospital, Villejuif; Private Hospital, Ramsay-Santé, Antony).

Sixty-seven patients will be recruited over 30 months. Each patient will participate for 7 and up to 10 weeks, starting 1 week before the first course of mFOLFIRINOX and finishing 2 weeks after the third course. The total duration of the study will be 32 months.

The study protocol has been designed in order for the results to be reported according to Standard Protocol Items: Recommendations for Interventional Trials guidelines 2013. It has been registered as www.clinicaltrials.gov NCT04263948 (registered on 11 February 2020) and under registration number ID RCB-2019-A00566-51. The first participant was recruited on 8 June 2021. Study recruitment completion is expected by December 2023.

Patient and public involvement

The development of the research question and outcome measures in MultiDom was based on prior extensive experience of individual cancer patients' evaluations throughout the development of earlier versions of the current domomedicine platform. Patients' evaluations and recommendations were gathered through face-to-face interviews by nurses, psychologists and physicians. Anonymised questionnaires regarding technology (Service User Technology Acceptability Questionnaire, SUTAQ) and participation in research experience (Research Participation Questionnaire, RRPQ) have been administered to 68 patients with cancer in three studies[20 21 23 27] and are also collected in MultiDom. Although patients are not involved in recruitment to the study, their engagement is essential since they are providing the daily multidimensional physiological and symptoms data that serve to trigger early warning signals aimed at proactive interventions. The daily changes in physiological and symptoms parameters are shown to the patients on user-friendly screens when they attend the clinics. It is not planned to disseminate the study results to the participants, but we will do so to the public at large.

Eligibility and recruitment

Patients will be enrolled in the study if they have: (1) a histological or cytological diagnosis of ductal adenocarcinoma, (2) local unresectable or metastatic PDAC, (3) with or without previous pancreas resection, (4) WHO performance status 0 or 1, (5) age 18–85 years (note that we elected to include patients with age criteria similar to those used for the main (m)FOLFIRINOX trials in pancreatic cancer, and this was approved by the regulatory authorities and ethical committees.), (6) no previous chemotherapy or radiotherapy for PDAC, (7) absence of confirmed deep vein or arterial thrombosis, (8) absence of cardiopathy or another disease poorly controlled by current treatments, (9) serum bilirubin<1.5 upper reference limit, (10) haematological, renal and hepatic investigations allowing mFOLFIRINOX administration and (10) patients affiliated to or beneficiary of a social security regime

Exclusion criteria include: (1) readily resectable PDAC, (2) other cancer except skin carcinoma diagnosed or treated during past 5 years, (3) total deficiency of dihydropyrimidine dehydrogenase activity, (4) participation in another interventional clinical study, (5) protected patient: adult under guardianship or other legal protection, deprived of liberty by judicial or administrative decision and (6) pregnancy or breast feeding.

Patients will be recruited by the consulting oncologist investigators at the four oncology units, where a weekly screening for potential patients will be implemented.

Patient withdrawal from study

Patients can leave the study at any time by withdrawing their consent. If a patient is lost to follow-up, the investigator will make every attempt to contact them before they

are withdrawn from the study. In both cases above, the observation file will be completed up until the date where the patient is no longer taking part.

The investigator will terminate the participation of a patient temporarily or definitively if they think that it is in their best interest, namely unacceptable toxicity of mFOLFIRINOX revealed by the occurrence of a severe AE (SAE) justifying the withdrawal of treatment or rapid disease progression. Other reasons for premature withdrawal from the study will be: hospitalisation for >2 weeks (irrespective of the reason) or patient death. The reasons for premature withdrawal from the study will be reported by the investigator in an observation file.

Sample size calculation

The incidence of grades 3–4 toxicities on FOLFIRINOX or mFOLFIRINOX for pancreatic cancer is high, consistently ranging between 60% and 76% of patients.[4 29–31] The rate of emergency admissions for Adverse Events over the initial two treatment months has been estimated to exceed 15% on standard patient management, based on reported rates of grade 4 toxicities of 10%–15% and rates of clinical grade 3 toxicities of >20%. Thus, a sample size of 60 evaluable patients was adequate to test the hypothesis of a 5% rate of emergency hospital admissions for toxicity with a precision of ±2.5%, resulting into a bilateral 95% CI with a total width of 12% (1.7% to 13.7%), according to Wilson's method.[32] We considered that seven patients (10.5%) might not be evaluable in the trial, hence our target sample size is 67 patients. Such an estimate was based on our previous studies in a total of 37 patients with gastrointestinal cancer using a fixed telemonitoring platform (InCASA) or an earlier version of the current mobile platform (Pilot for Circadian And Domomedicine, PiCADo; and, Identification of DEterminants of Altered circadian rhythm study, IDEAs), where the drop-out rate of consenting patients was <5%, with a median overall compliance with the study protocol of 98%.[21–23 27]

Intervention protocol

The intervention consists of the use of the upgraded PiCADo domomedicine mobile platform by patients receiving conventional administration of mFOLFIRINOX, and nurses, oncologists, scientists and biomedical engineers involved in their care.

One week before the administration of the first course of mFOLFIRINOX, a nurse provides the patient with the PiCADo system kit and trains him or her on its use. The intervention in each patient will last for 7–10 weeks, depending on the frequency of the initial three treatment courses.

All patients will receive the conventional mFOLFIRINOX protocol,[29] namely: oxaliplatin (85 mg/m^2, as a 2-hour intravenous infusion on day 1; irinotecan 180 mg/m^2, as a 90 min intravenous infusion on day 1; leucovorin 400 mg/m^2, as a 2-hour intravenous infusion on day 1 and 5-fluorouracil 2400 mg/m^2, as a continuous intravenous infusion via a pump for 46 hours, starting on dy 1 (visit 2)). The mFOLFIRINOX courses will be repeated every 2 weeks at visits 3 and 4 (table 1) depending on AES, biology and tumour response.

PiCADo mobile platform

The PiCADo platform system involves the measurement of multidimensional data from sensors which are transmitted via BLE to a mobile data collection and teletransmission device the size of a smartphone (EeleoCare; Eeleo, Angers, France). The measurements are then teletransmitted via a secure web interface (GPRS) to the Clinikali Platform (Altran, Cap Gemini), which is harboured within the National Health Data Hub. Raw data, automatically computed parameters and their graphical displays are visualised, in near-real time by the study investigators through personalised access to the MultiDom website (figure 1).

The participants are asked to continuously wear specially designed medical underwear (Thuasne, St Etienne, France) containing a modified telecommunicating chest surface sensor (Move3; Movisens, Karlsruhe, Germany). Following activation, the sensor automatically measures activity and 3D orientation via an accelerometer, and body temperature via an infrared thermal probe, every min. Medical grade sensor-containing T-shirts and bras have been designed to minimise any skin sensitivity or discomfort, as they are made of cloth material for patients with severe burns. The data are automatically transmitted to the data collection device (EeleoCare) via BLE every 5 min.

The patients are asked to weigh themselves daily on a telecommunicating balance (A&D-321-PBT-C) and to self-rate 23 electronic patient-reported outcomes (e-PROs) using a tablet for 1 week before (baseline) and 6 weeks after the first mFOLFIRINOX course. Completion of these questionnaires takes 3–8 min daily.

Additional e-questionnaires will also be presented to the patients for self-assessment of their morningness-eveningness orientation (Horne-Ostberg) at inclusion, and their overall sleep quality (Pittsburgh) both at inclusion and at study completion. An electronic version of the EORTC-QLQ-C30 QoL questionnaire is presented for self-assessment every 2 weeks: this questionnaire evaluates 18 symptoms and 6 items assessing their impact on daily life. At the end of their study participation, the patients are asked to fill out electronic versions of the SUTAQ and the RRPQ.

Hidden Markov, spectrum and other algorithms automatically compute physical activity, sleep, temperature, body weight change, e-PRO severity, dichotomy index I<O of the circadian RAR (% activity 'in-bed' below median activity 'Out-of-bed'), and 11 other circadian, sleep and activity parameters once to four times daily.

Data collection, management and analysis

All data, including the responses to the questionnaires, will be transmitted electronically from the sensors or

Table 1 Schedule of enrolments, interventions and assessments (SPIRIT 2013)

	Study period					
	Screening and enrolment		Intervention and evaluation			
Time point	Days 28–8	Visit 1 Day 8	Visit 2 Day 1	Visit 3 Day 15	Visit 4 Day 29	Visit 5 Day 43
Enrolment:						
Collection of informed consent	✓					
Demographics	✓					
Medical history and history of pancreatic cancer	✓					
Clinical examination*	✓		✓	✓	✓	✓
Biological tests† ‡	✓		✓	✓	✓	✓
Interventions:						
Education and installation of the PiCADo sensor§		✓				
Assessments and therapy:						
Questionnaire Horne-Ostberg (Chronotype)		✓				
Questionnaire Pittsburgh (Sleep)		✓				✓
Questionnaire EORTC QLQ-C30		✓		✓	✓	✓
Questionnaire e-PRO (MDASI, 23 items)		✓	(Daily until visit 5)			
Rest-activity circadian rhythm		✓	(Continuously until visit 5)			
Chest surface temperature rhythm		✓	(Continuously until visit 5)			
mFOLFIRINOX chemotherapy course¶			✓	✓	✓	
Medical imaging	✓					✓
Recording of adverse events			✓	✓	✓	✓
Concomitant treatments (drugs, doses, times)	✓	✓	✓	✓	✓	✓
SUTAQ questionnaire (satisfaction)						✓
RRPQ§						✓

*Clinical examination: performance status, evaluation of pain (Visual Analog Scale), other symptoms experienced by the patient, description of the physical examination.
†Biological tests: whole blood cell and platelet counts, complete renal and hepatic function tests, glycaemia, C reactive protein, carcinoembryonic antigen and CA19.9.
‡Additional biological tests will be carried out on day 8 (±2 days), day 21 (±2 days) and day 35 (±2 days).
§PiCADo monitoring: from day 8 and for the duration of the study, the patient will weigh themselves daily on connected electronic scales, evaluate their symptoms (MDASI) using the touch screen of the tablet, and continuously wear, on their thorax, the telecommunicating sensor that measures accelerometry, body position and temperature.
¶The patient will visit the hospital to receive mFOLFIRINOX (day 1–day 3) as an outpatient. Following treatment initiation in the outpatient clinic on day 1, the 5-fluorouracil infusion at a constant rate over 46 hours is delivered at home using a pump.
EORTC, European Organisation for Research and Treatment of Cancer; e-PRO, electronic patient-reported outcome; MDASI, MD Anderson Symptoms Inventory; RRPQ, Research Participation Questionnaire; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; SUTAQ, Service User Technology Acceptability Questionnaire.

tablet via BLE to the home-based data collection and teletransmission device (EeleoCare) and then transmitted every 6 hours to the Clinikali platform via a secure SSL connection. The usual clinical data are collected and saved in an electronic clinical research file, which will be deidentified by giving each patient a unique identification number.

Data collection will be conducted in a predefined standard sequence with the main assessments conducted at inclusion (day 1), day 15, day 29 and day 42 (tables 1 and 2). Alerts are automatically generated and sent to an electronic coordination platform for health professionals, with trackable follow-up.

Outcome measures

The primary outcome is the proportion of patients undergoing one or more emergency hospital admissions as a result of toxicity during the 6 weeks following the start of mFOLFIRINOX.

Secondary outcomes include: (1) hospitalisation-free survival, evaluated from the date of starting the first course of mFOLFIRINOX to the date of the first hospitalisation

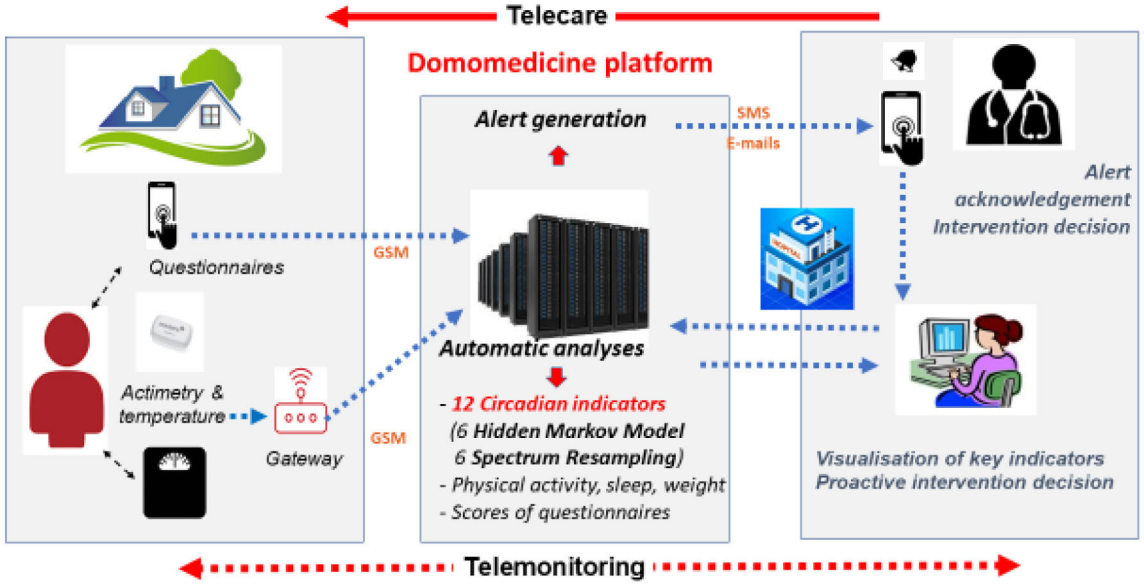

Figure 1 Diagram showing the connectivity between the thoracic monitor, the scales, the home-based data collection device, the electronic tablet in the patient's environment (left panel), the central data hub, with its resident automatic programs (middle panel), and the oncology team (right panel). GSM, Global System for Mobile communications; SMS, Short Message Service.

for toxicity if any, or the date of completed participation; (2) Quality of Life, evaluated using EORTC QLQ-C30, at inclusion, on day 15, day 29 and day 43; (3) Adverse Events (AEs), categorised according to grade for each type of AE using the CTCAE V.5.0 grid. The incidence of grades 2–4 and 3–4 toxicities per patient will be calculated for all toxicities observed, in particular: leucopenia, neutropenia, anaemia, thrombocytopaenia, diarrhoea, asthenia, anorexia and weight loss; (4) disruption of circadian RAR and dynamics of recovery, based on the dichotomy index decreasing to between 97.5% and 96% or below 96%; (5) disruption of the circadian rhythm of body temperature and dynamics of recovery, evaluated as the incidence of absence of rhythms with a period ranging between 28 hours and 20 hours (circadian) or between 14 hours and 10 hours (circahemidian) based on 'Spectrum Resampling' analysis of 3-day temperature time series, staggered over 6 hours during the 6 weeks following the first course of mFOLFIRINOX; (6) severity of symptoms linked to mFOLFIRINOX will be self-evaluated daily by the patients using the MDASI e-PROs questionnaire; (7) number of courses, doses and dose intensities of mFOLFIRINOX, evaluated from the patients' case report forms; (8) early response within the month following the third course of mFOLFIRINOX, evaluated by CT scans, and/or MRI, and/or positron emission tomography scans, according to RECIST V.1.1 criteria, 6–10 weeks after the first course of mFOLFIRINOX; (9) proactive interventions following alerts generated by the PiCADo telemonitoring system, measured both qualitatively and quantitatively and (10) patient satisfaction, evaluated using the SUTAQ (technological aspects) and RRPQ (research participation) at the end of the study.

Other parameters will also be calculated from the continuous recordings of rest-activity (rhythm index, midpoint of the sleep phase, etc)[22] or using questionnaires: (1) sleep quality (problems and their severity) will be evaluated on day 8 and day 43 (Pittsburgh questionnaire);

Table 2 Standard sequence used for remote patient assessment

Compulsory	Frequency
Body weight using the connected electronic scales	Once daily before breakfast from day −8 to day 43
Chest sensor (RAR, temperature, 3D orientation) in dedicated underwear	24 hours/24 hours from day −8 to day 43
Questionnaires	**Frequency**
e-PROs (MDASI)	Once daily after 16:00 hours from day −8 to day 43
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - C30 (EORTC QLQ-C30)	On day −8, day 15, day 29, day 43 (or study termination)
Morningness-eveningness (Horne-Ostberg)	Once on day −8
Sleep quality (Pittsburgh)	On day −8 and day 43
Service User Satisfaction (SUTAQ)	Once on day 43
Research participation experience (RRPQ)	Once on day 43

An independent data monitoring committee involves two oncologists, a mathematician and a health technologist, and will meet every 3–6 months.
3D, three dimensional; e-PROs, electronic patient-reported outcomes; MDASI, MD Anderson Symptoms Inventory; RAR, rest-activity rhythm; RRPQ, Research Participation Questionnaire; SUTAQ, Service User Technology Acceptability Questionnaire.

(2) morningness-eveningness (ie, chronotype: morning, intermediate or evening) will be determined on day 8 (Horne-Ostberg questionnaire); (3) evaluation of health-related technologies by the patients will be determined on day 43 using the SUTAQ; (4) the motivations and experience of the patients during their participation in the research will be evaluated using the RRPQ on day 43 or on completion of study participation (table 1).

Safety and medical alerts

There are no anticipated Serious AEs (SAEs) linked to the use of the PiCADo platform.

The SAEs (grades 3–5) linked to mFOLFIRINOX toxicity or disease progression will be evaluated during consultations every 2 weeks or more frequently if needed and classified as: (1) death (whose cause will be specified by the oncologist (tumour progression, toxicity or both)); (2) rapid worsening of the general state of the patient, noted either during a scheduled oncological consultation (every 2 weeks) or by the PiCADo system and (3) emergency hospitalisation, following either a scheduled oncological consultation or due to an alert by the PiCADo system, and confirmation of the severity by the oncological team after a telephone conversation with the patient and/or the decision of the emergency department.

All AEs and SAEs will be recorded in the patients' medical files. Any unexpected or new SAEs will be declared to the relevant authority (regional pharmacovigilance centre).

The following changes to data recording or to a patient's clinical or physical well-being will result in the intervention of an oncologist or a nurse: (1) questionnaire MDASI completed daily by the patient from day −8 to day 43: any symptom score ≥7 (scale of 0–10) and/or absence of evaluation for 48 hours; (2) PiCADo: I<O over 3 days ≤96% (calculated from data recorded over the last 3 days: wait for another 24 hours to calculate the next index, if ≤96% alert medical staff; (3) temperature ≥2°C compared with the reference temperature for the same patient; (4) temperature ≤2°C compared with the reference temperature for the same patient (mean value measured each min between day −7 and day 0 for each patient); (5) absence of data from the monitor for ≥6 hours, (6) detection of monitor removal for ≥6 hours; (7) increase or decrease in body weight of >5% in 1 week or less compared with the median weight measured from day −8 to day 0 and (8) absence of measurement of body weight for 48 hours.

In the case of an alert, the e-platform will send an SMS and email message to the nurse or the oncologist according to the alert type, with its main characteristic and the deidentification code for the patient. The type of action taken by the nurse/oncologist will then be registered on the platform as: (1) no action taken, (2) call to the patient without any need for follow-up, (3) call to the patient with prescription of treatment, (4) call to the patient with an appointment and (5) call to the oncologist.

Statistical analysis

The statistician and both chief investigators will have access to the final trial data set. The statistical analysis will concern all patients included in the study (intention-to-treat (ITT) population) and all patients for whom at least 30% of the expected data are teletransmitted over the duration of their participation in the study (per-protocol (PP) analysis). Patients with more missing data will not be replaced and will not be considered in the final analysis.

Quantitative variables will be described as number of values observed, mean, SD, median, range (min–max), first and third quartiles, number of missing data and 95% CIs, where appropriate.

Qualitative variables will be described as number of values observed, absolute and relative frequencies for each class, number of missing data and (95% CI). Patients with missing data will not be included in the calculation of percentages.

The incidence of emergency hospital admissions, SAEs and telemonitored alerts will also be described in relation to both the actual chemotherapy dose given during the course preceding the event and the dose intensities over the planned study participation of the patient.

All statistical tests will be bilateral with an alpha risk of 5%.

The time series data parameters will be transferred to the statistician in charge of the analysis and integrated in the database. The analyses will be performed using SAS V.9.4 or later.

The sponsor and funder have no role in the design, collection, management, analysis, interpretation of data or writing of the report.

ETHICS AND DISSEMINATION

The study has been approved by the National Agency for Medication and Health Product Safety (ANSM) and by the Ethics Committee West V on 2 July 2019, with three successive amendments on 7 July /2020, 11 June 2021 and 14 June 2022. The study conforms to the Declaration of Helsinki (http://www.wma.net), French law (no 2004–806 of 9 August 2004) and with Good Clinical Practice (I.C.H. version 4 of 1 May 1996 and decision of 24 November 2006). The data from the study will be disseminated in peer-reviewed journals and presented at international conferences.

DISCUSSION

This study is designed to evaluate the clinical relevance of a new domomedicine platform, PiCADo, for the remote monitoring of patients with local unresectable or metastatic PDAC. In 2016, a first European study evaluated the inCASA fixed domomedicine platform in patients with metastatic cancer receiving chemotherapy. Results showed that daily telemonitoring of body weight, circadian RAR and ePROs (MDASI score) was feasible and clinically relevant, predicting emergency hospital admission

due to toxicity within 3 days from the event, with an accuracy of 94%.[21] Full compliance rate was 59.7% and the patients were satisfied with the home use of the platform. However, the inCASA platform was fixed, involved no wireless connection and provided no parameter computation or advanced graphical displays.

The new domomedicine platform, PiCADo, takes into account these limitations. Accelerometry and body temperature are measured q1-min using a continuously worn telecommunicating chest surface sensor, body weight is self-measured with a telecommunicating balance and 23 e-PROs are self-rated using a tablet for 1 week before (baseline) and 6 weeks after the first mFOLFIRINOX course. The data are transmitted via BLE to a home-based data collection device the size of a mobile phone (EleoCare; Eleo), and then via a secure web interface (General Packet Radio Service, GPRS) to a centralised server (Altran/Cap Gemini), where a set of automatic programmes compute and visually display the dynamics of 12 circadian parameters, 23 e-PROs and body weight changes in near-real time, which can be visualised by the oncology team for decision-making. The size of the home-based data receiver makes it readily portable should a patient leave home for any reason (work, holiday, etc), ensuring the continuity of data collection.

The strength of the study is the e-medicine platform itself, which is designed to collect, analyse and graphically display in near-real time both longitudinal physiological time series and e-PROs from remote cancer patients at risk of SAEs, and to involve the oncology teams in the proactive management of remote patients. The platform should identify patients at risk of imminent SAEs allowing swift proactive interventions, preventing the patient from being admitted to hospital as an emergency. Earlier identification of an altered patient's condition before SAEs become obvious should improve the efficacy of anticancer treatments through the prevention of treatment withdrawal. A further reduction of patient-related costs would also benefit the healthcare system through preventing emergency hospital admissions. The relatively short duration of the study (7–10 weeks for each patient) and the fact that the use of the PiCADo platfom system could prevent patients from being admitted to hospital should contribute to increase compliance with potentially toxic yet effective treatment protocols such as mFOLFIRINOX.

The data obtained from this study will further lay the grounds for personalised chronotherapy and care of patients with PDAC, in order to reduce treatment morbidity and enhance patient QoL and survival. The data will support the design of a randomised trial comparing standard PDAC care with personalised mFOLFIRINOX chronotherapy, with chemotherapy timing being tailored to the individual patient's rhythms.[12 13 16 33]

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