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Digital remote monitoring plus usual care versus usual care in patients treated with oral anticancer agents: the randomized phase 3 CAPRI trial

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Strategies that individualize the care of cancer patients receiving oral anticancer agents offer opportunities to improve treatment adherence and patient care. However, the impact of digital remote monitoring systems in this setting has not been evaluated. Here, we report the results of a phase 3 trial (CAPRI, NCT02828462) to assess the impact of a nurse navigator-led program on treatment delivery for patients with metastatic cancer. Patients receiving approved oral anticancer agents were randomized (1:1) to an intervention combining a nurse navigator-led follow-up system and a web portal-smartphone application on top of usual care, or to usual symptom monitoring at the discretion of the treating oncologist, for a duration of 6 months. The primary objective included optimization of the treatment dose. Secondary objectives were grade ≥ 3 toxicities, patient experience, rates and duration of hospitalization, response and survival, and quality of life. In 559 evaluable patients the relative dose intensity was higher in the experimental arm (93.4% versus 89.4%, $P = 0.04$). The intervention improved the patient experience (Patient Assessment of Chronic Illness Care score, 2.94 versus 2.67, $P = 0.01$), reduced the days of hospitalization (2.82 versus 4.44 days, $P = 0.02$), and decreased treatment-related grade ≥ 3 toxicities (27.6% versus 36.9%, $P = 0.02$). These findings show that patient-centered care through remote monitoring of symptoms and treatment may improve patient outcomes and experience.

Remote patient monitoring has long been integrated into the management of chronic conditions such as heart failure, pain management, or depression^{1,2}, with the aim to improve quality of care, to reduce costs and supplement (or replace) in-hospital care, and to offer convenience and closer management of clinical events^{3,4}. In the field of oncology, retrospective studies have suggested that remote patient monitoring could help in the monitoring of chemotherapy-related adverse events⁵, and could improve adherence to oral anticancer agents^{6–8}. These retrospective studies involved nurse-led follow-up and the use of basic remote monitoring technologies (mostly phone calls and emails). However, a lack of rigorous methodology in such studies has limited the potential impact of these combined strategies.

Oral anticancer agents represent 38 of 228 (17%) US Food and Drug Administration-approved drugs (all diseases, all routes of administration) from 2016 to 2020 (ref. ⁹). In contrast with patients receiving intravenous chemotherapies (with frequent hospital visits for treatment every 1–3 weeks depending on the chemotherapy schedule), patients receiving oral anticancer agents are usually monitored during consultations scheduled less frequently (for prescription renewal and dose modifications). Hence, in the setting of oral anticancer therapy, the clinical challenges encompass not only the remote management of frequent clinical events (drug-related or

disease-related) and the need to incorporate nurse-led follow-up for optimal care), but also adherence issues, an underestimated cause of toxicity, decreased treatment efficacy and increased costs^{10–12}.

The tremendous uptake of connected devices during the past decade has paved the way for clinical trials implementing digital remote patient monitoring tools in oncology¹³. In a seminal randomized controlled trial, Basch et al.¹⁴ showed that digital reporting of patient-reported outcomes (using touchscreen tablet computers or freestanding computer kiosks in hospital, and/or weekly emails at home) improved outcomes in cancer patients receiving routine outpatient chemotherapy. In another randomized trial, Denis et al.¹⁵ reported earlier detection of relapse as well as survival improvement in lung cancer patients, using web-mediated monitoring.

In this context, the aim of this study (Impact of a Monitoring Device for Patients With Cancer Treated Using Oral Therapeutics; CAPRI) was to evaluate an intervention combining a nurse navigator-led follow-up and a mobile application for patients receiving oral anticancer agents on top of usual care, designed to pursue simultaneously three dimensions: improvement of the patient experience of care; improvement of the health of the target population; and reduction in the per capita cost of healthcare.

The primary endpoint was the relative dose intensity (RDI, defined as the ratio of the dose actually delivered over time to

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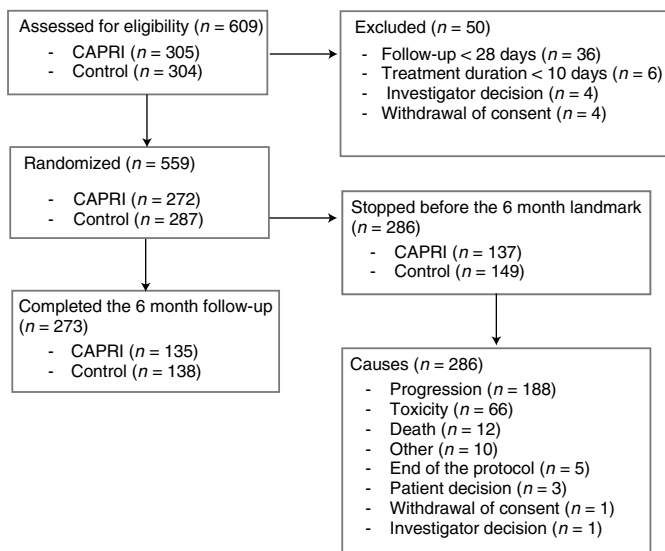


Fig. 1 | CONSORT diagram. This diagram shows the flow of the patients through the study. Of 559 evaluable patients, 286 (51.2%) did not complete the scheduled 6 month follow-up, mostly due to disease progression ($n=188$, 65.7%) and intolerable toxicity ($n=66$, 23.1%).

the prescribed dose intensity)¹⁶. We proposed that the nurse navigator-led intervention would enable earlier management of treatment-related adverse events, and therefore a higher RDI (due to less dose reductions or more dose increases¹⁷) than that observed with usual care. Secondary endpoints included adherence, toxicity, response and survival, quality of life, patient experience and economic estimation of the use of healthcare resources. A longitudinal analysis of the intervention was also pre-planned to study adoption issues by patients and healthcare professionals.

Results

From October 2016, 609 patients starting a new treatment line with oral anticancer agents were included (39% were receiving chemotherapy and 61% were receiving molecular-targeted therapies). As shown in Fig. 1, 50 patients were not evaluable due to early (<28 days from enrollment) progressive disease ($n=36$), treatment duration <10 days ($n=6$), investigator decision ($n=4$) or withdrawal of consent ($n=4$). The final analysis set totaled 559 patients: 272 in the CAPRI arm and 287 in the control arm. The study ended in May 2019 due to limited funding, without affecting the ability to address the primary endpoint (the observed RDI being higher than expected), but with decreased statistical power for exploratory analyses (for example, time to treatment interruptions, as shown below).

Baseline demographics and disease characteristics. Baseline demographics and disease characteristics were generally similar in both arms (Table 1). The median age was 62.0 years (range, 20.0–92.0 years), 155 patients (27.7%) were aged 65–74 years and 78 patients (14%) were aged ≥ 75 years. Performance status was 0–1 in 493 patients (88.2%), and 2 in the remaining 66 patients (11.8%). One hundred and forty-seven patients (27.8%) had received three or more prior lines of treatment. All patients were required to have access to phone and the internet, but no stratification was made based on previous experience with digital technology.

Nurse navigator-led clinical actions and use of the web app. After an initial assessment, nurse navigators linked the electronic patient record data with the CAPRI application, and each patient received a starter box, including the login data to gain access to the portal,

instructions for use and covering letters for healthcare providers. Through the CAPRI application (available in web or mobile version), patients had access to the app to record and track data, and could contact the nurse navigators via a secure messaging system, view therapy and side-effect information, or store documents. Several modules allowed them to report different symptoms (that is, fever, pain, appetite, weight, and specific criteria depending on their treatments; Extended Data Fig. 1a). The frequency of patient input was time dependent (once weekly during the first month, then once every other week from the second to the fourth months, and once every 3 weeks from the fifth month to the end of the study), and could be more frequent (daily) depending on the severity of the symptoms and the related alerts. The CAPRI application also included a dashboard for nurse navigators, allowing them to monitor the electronic medical records of patients (Extended Data Fig. 1b).

Last, the system generated automatic alerts that were sent to the patients and the nurse navigators (with a warning message indicating the times when nurse navigators could be contacted). The alerts and patient requests were generated in different ways: automatically, via the app; by the nurse navigators during follow-up; or by messaging or calling the patient or healthcare professionals. The nurse navigators assessed the alert grade based on clinical decision support tools, and determined the action to be taken according to navigation algorithms (Extended Data Fig. 4). Depending on the grade, the nurse navigators could give advice, refer the patient to his or her primary care physician or a Gustave Roussy professional (treating oncologist, other physicians and nurses; Fig. 2a), or contact the relevant departments to schedule hospitalization or consultations when needed.

Patients in the control arm had in-hospital follow-up visits (at the discretion of the treating oncologist, typically after 1 month, then every 2–3 months), but no interaction with the nurse navigators. In the experimental arm, remote follow-up on top of similar hospital visits encompassed a total of 3,445 interactions between patients and nurse navigators, as a result of either scheduled follow-up ($n=2,623$, 76.1%) or incoming alerts from the patients or their relatives ($n=822$, 23.9%). Of these 3,445 interactions, 2,062 (59.9%) led to a clinical intervention, of which 1,595 (77.4%) were performed by nurse navigators alone (that is, without having to refer to the treating oncologist). The pattern of such nurse navigator-led clinical interventions is shown in Fig. 2b.

After randomization in the CAPRI arm, 52% of patients downloaded the smartphone application while the remaining 48% used the web portal, emails and/or phone calls to interact with the nurse navigators. The proportion of patients who downloaded the smartphone application was age dependent, being highest in patients aged below 30 years (79%) and lowest in patients aged over 80 years (15%). The overall completion of scheduled remote (excluding in-hospital visits) follow-up (percentage of scheduled contacts effectively performed) was 87.4%, ranging from 77% in patients aged below 45 years to 90% for patients aged over 75 years. No missing interaction was observed during the first month of follow-up.

Improvement of relative dose intensity. The primary objective of the study (that is, increase of the RDI) was met, despite its early ending. Mean (s.d.) RDI was 93.4% (25.9%) in the CAPRI arm and 89.4% (19.1%) in the control arm ($P=0.043$). This difference remained statistically significant when RDI was adjusted for treatment adherence (assessed using a dedicated questionnaire, see Methods section): mean (s.d.) RDI was 84.2% (26.3%) in the CAPRI arm and 80.0% (20.9%) in the control arm ($P=0.045$). As shown in Table 2, the proportion of patients with low adherence was lower in the CAPRI arm (5.9% versus 9.8%), but did not reach statistical significance ($P=0.10$). The number of treatment interruptions due to toxicity was similar in both arms: 72 (26.5%) in the

CAPRI arm and 69 (24.0%) in the control arm, but tended to occur earlier in the CAPRI arm (HR, 1.16; 95% CI: 0.83–1.61, $P=0.39$; Extended Data Fig. 2), possibly explaining the impact on grade ≥ 3 toxicity rates. Regarding treatment activity (a secondary endpoint of the study), 136 patients (58.9%) in the CAPRI arm and 137 patients (53.5%) in the control arm had stable disease or objective response as best response ($P=0.23$). There was no significant difference in progression-free survival or overall survival (Extended Data Fig. 3).

Effect on grade ≥ 3 toxicities and healthcare utilization. Regarding grade ≥ 3 toxicities (a pre-specified secondary endpoint of the study), 75 patients (27.6%) in the CAPRI arm had at least one treatment-related grade ≥ 3 adverse event (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, NCI-CTCAE v4.03, ref. ¹⁸), versus 106 (36.9%) in the control arm ($P=0.02$) (Table 3). The mean (s.d.) number of different toxicities was 0.5 (0.8) in the CAPRI arm and 0.7 (0.9) in the control arm ($P=0.01$).

The most commonly reported symptoms using the app were gastrointestinal disorders ($n=15$, 5.5%) and skin disorders ($n=10$, 3.7%), the latter being significantly lower than in the control arm ($n=22$, 7.7%, $P=0.04$), possibly due to early interventions on grade 1–2 toxicities (decreasing the likelihood of worsening to grade 3–4 toxicities).

Sixty-two patients (22.8%) in the CAPRI arm were hospitalized, versus 91 (31.7%) in the control arm ($P=0.02$, Table 3). The mean (s.d.) number of days of hospitalization (another secondary endpoint of the study) was 2.82 (6.96) days in the CAPRI arm versus 4.44 (9.60) days in the control arm ($P=0.02$). As an illustration, the remote follow-up of neuro-oncology patients enabled an early adjustment of the dose of corticosteroids in the case of symptoms suggestive of intracranial hypertension; four (2.9%) glioblastoma patients in the control arm were hospitalized in the emergency department for intracranial hypertension, versus none (0%) in the CAPRI arm. Finally, the number of visits to an emergency department (at our institution (Gustave Roussy Comprehensive Cancer Center) or another one) was significantly lower in the CAPRI arm: 41 (15.1%) versus 63 (22.0%) ($P=0.04$).

Increased use of supportive care and improved patient experience. Whereas 101 patients (35.2%) in the control arm had at least one ambulatory visit with supportive care teams during the study, 119 (43.8%) did so in the CAPRI arm ($P=0.04$). Specifically, a significant increase was seen in visits to nutritionists and dietitians (39 (14.3%) in the CAPRI arm versus 25 (8.7%) in the control arm, $P=0.04$) and to social workers (59, 21.7% versus 31, 10.8%, $P<0.01$). No difference was seen across age groups or engagement with the smartphone app. Mean (s.d.) global health scores (assessed with the EORTC QLQ-C30 quality of life questionnaire, ref. ¹⁹) at 3 months and at the end of the study were 56.3 (21.7) and 55.2 (21.6) in the CAPRI arm, and 54.7 (22.2) and 54.7 (23.7) in the control arm, and did not statistically differ ($P=0.56$ and 0.86, respectively). Finally, the CAPRI intervention improved the patient experience of care (another pre-specified secondary endpoint). The mean (s.d.) global Patient Assessment of Chronic Illness Care (PACIC) score was 2.94 (0.83) in the CAPRI arm and 2.67 (0.89) in the control arm ($P=0.01$). As shown in Table 4, significant differences were seen in problem-solving and coordination.

Discussion

This single-center randomized phase 3 trial comparing an intervention (CAPRI) combining nurse navigator-led follow-up and a mobile application on top of usual care versus usual care in patients with advanced cancers treated with oral anticancer agents met its primary endpoint, that is, a significant improvement of RDI. The CAPRI study, a digital, nurse navigator-led intervention, has been

Table 1 | Baseline patient demographics and disease characteristics

Variable	CAPRI <i>n</i> (%)	Control <i>n</i> (%)	Total <i>n</i> (%)	Statistics ^a
Gender				
No. of patients	272	287	559	$\chi^2=0.62$
Male	116 (42.6)	113 (39.4)	229 (41.0)	$P=0.43$
Female	156 (57.4)	174 (60.6)	330 (59.0)	
Age (years)				
No. of patients	272	287	559	$\chi^2=1.25$
<45	42 (15.4)	37 (12.9)	79 (14.1)	$P=0.87$
45–54	45 (16.5)	49 (17.1)	94 (16.8)	
55–64	70 (25.7)	83 (28.9)	153 (27.4)	
65–74	76 (27.9)	79 (27.5)	155 (27.7)	
≥ 75	39 (14.3)	39 (13.6)	78 (14.0)	
Marital status				
No. of patients	266	278	544	$\chi^2=0.03$
Not married	83 (31.2)	85 (30.6)	168 (30.9)	$P=0.87$
Married	183 (68.8)	193 (69.4)	376 (69.1)	
Employment				
No. of patients	95	94	189	$\chi^2=2.51$
Employed	64 (67.4)	73 (77.7)	137 (72.5)	$P=0.11$
Unemployed	31 (32.6)	21 (22.3)	52 (27.5)	
Performance status				
No. of patients	272	287	559	$\chi^2=0.09$
0	121 (44.5)	127 (44.3)	248 (44.4)	$P=0.96$
1	120 (44.1)	125 (43.6)	245 (43.8)	
2	31 (11.4)	35 (12.2)	66 (11.8)	
Primary tumor site				
No. of patients	272	287	559	$\chi^2=3.93$
Endocrine	51 (18.8)	47 (16.4)	98 (17.5)	$P=1.00$
Breast	48 (17.6)	55 (19.2)	103 (18.4)	
Digestive	43 (15.8)	48 (19.6)	91 (16.3)	
Renal	32 (11.8)	32 (11.1)	64 (11.4)	
CNS	27 (9.9)	26 (9.1)	53 (9.5)	
Sarcoma	21 (7.7)	24 (8.4)	45 (8.1)	
Gynecological	15 (5.5)	18 (6.2)	33 (5.9)	
Lung	14 (5.1)	17 (5.9)	31 (5.5)	
Hematological	6 (2.2)	6 (2.1)	12 (2.1)	
Melanoma	5 (1.8)	4 (1.4)	9 (1.6)	
Other	2 (0.7)	1 (0.3)	3 (0.5)	
Disease status at inclusion				
No. of patients	272	287	559	$\chi^2=0.3$
Locally advanced	50 (18.4)	58 (20.2)	108 (19.3)	$P=0.58$
Metastatic	222 (81.6)	229 (79.8)	451 (80.7)	
Prior treatment lines				
No. of patients	262	266	528	$\chi^2=1.7$
0	76 (29.0)	73 (27.4)	149 (28.2)	$P=0.79$
1	58 (22.1)	58 (21.8)	116 (22.0)	
2	48 (18.3)	54 (20.3)	102 (19.3)	
≥ 3	71 (27.1)	76 (28.6)	147 (27.8)	

Of 559 evaluable patients, 228 (41.7%) were aged 65 or over and 66 (11.8%) had a performance status of 2. Primary tumor sites, metastatic status and prior treatment lines were balanced between the two study arms. ^aThe chi-squared test was two-sided. CNS, central nervous system.

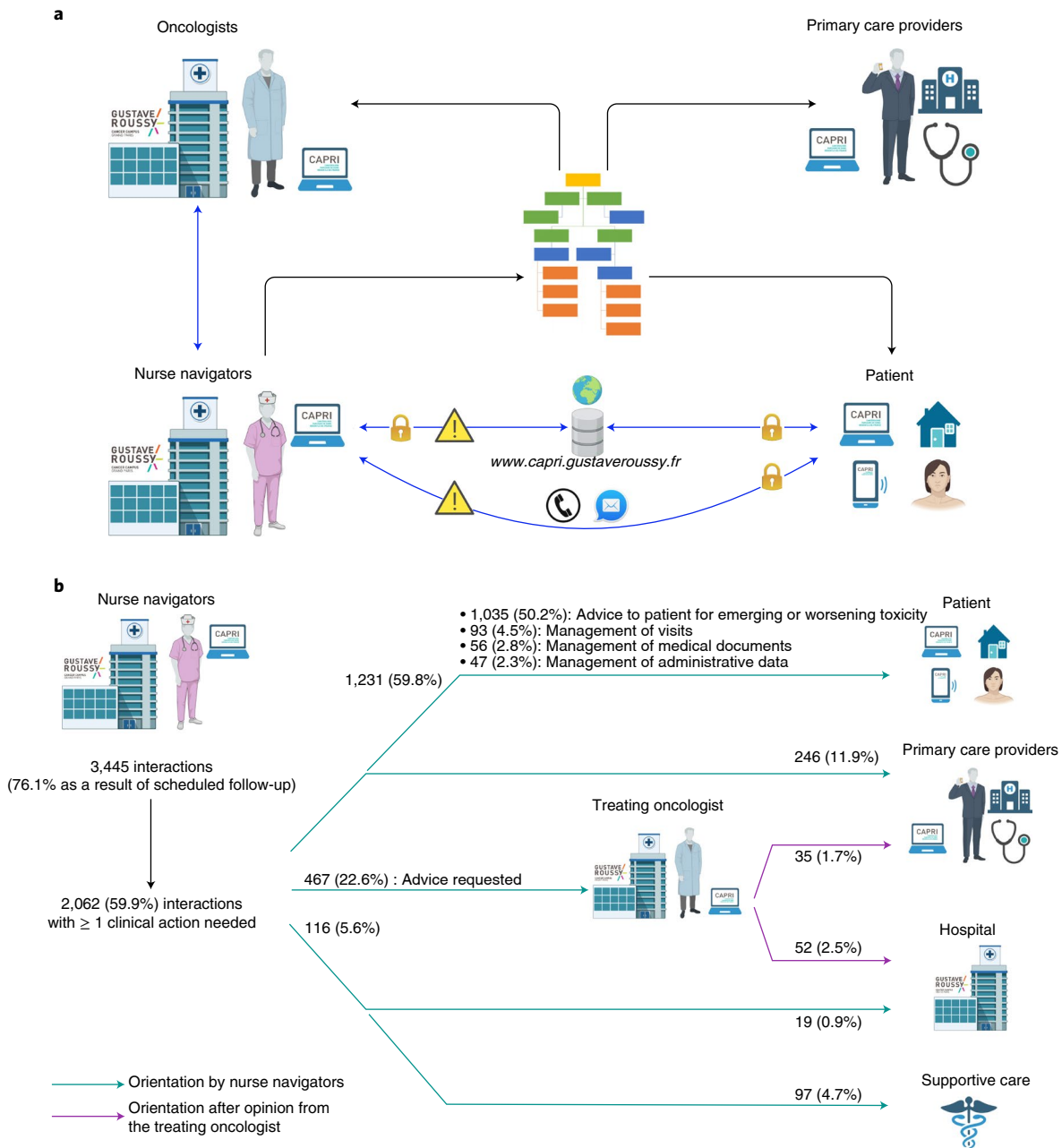


Fig. 2 | CAPRI intervention design and nurse-led clinical interventions. **a**, Schematic diagram of the interactions between nurse navigators and patients through the CAPRI platform; depending on predefined decision trees, primary healthcare providers or the treating oncologist could be contacted to inform decision-making or provide guidance and, if needed, prescriptions. **b**, Outcomes of the 3,445 interactions between the nurse navigators and patients enrolled in the CAPRI arm.

able to show a positive effect on the triple aims of healthcare interventions²⁰ through an improvement of patient experience of care (that is, the PACIC score); the health of the target population (that is, a decrease of grade ≥ 3 toxicities from 36.9% of patients to 27.6% of patients); and cost control (that is, a decrease in days of hospitalization from a mean (s.d.) of 4.44 (9.60) to 2.82 (6.96)).

In previous randomized studies on remote monitoring of cancer patients, the patients were under intravenous chemotherapy (that is, with more frequent hospital visits)^{14,15}, and analyses were restricted to a limited number of tumor types¹⁵. The CAPRI trial, however, was dedicated to the remote monitoring of patients under oral treatment, including all advanced solid tumor types.

Importantly, nurse navigators were able to manage 77.4% of clinical interventions without having to refer to the treating oncologist. These results derived from a prolonged design process prior to the initiation of the study²¹, a critical phase that requires a sound methodological basis. It seems likely that such a remote patient monitoring system represents not only a technological advance using digital tools, but also (and most importantly) an organizational innovation that includes the recruitment of nurse navigators with clinical and managerial skills, and the definition of institutionally approved algorithms for clinical decision-making for patient assessment and orientation. The adoption rate of the smartphone application was 52% in 272 patients randomized in the CAPRI arm, of whom 42.2% were aged 65 years or over. This rate is in line with those

Table 2 | Treatment disposition and outcomes

Variable	CAPRI	Control	Total	Statistics ^a
RDI (until study discontinuation)				
No. of patients	272	287	559	$t = 4.38$
Mean (s.d.)	0.9344 (0.2590)	0.8943 (0.1914)	0.9138 (0.2275)	$P = 0.0426$
95% CI	0.9035–0.9653	0.8720–0.9165	0.8949–0.9327	
Min–Max	0.20–2.00	0.00–1.51	0.00–2.00	
Median	1.00	1.00	1.00	
Q1–Q3	0.80–1.00	0.80–1.00	0.80–1.00	
RDI (until study discontinuation) adjusted for global adherence				
No. of patients	255	265	520	$t = 4.07$
Mean (s.d.)	0.8417 (0.2632)	0.7998 (0.2090)	0.8204 (0.2378)	$P = 0.0451$
95% CI	0.8093–0.8742	0.7745–0.8251	0.7999–0.8408	
Min–Max	0.0–2.0	0.0–1.3	0.0–2.0	
Median	0.9	0.8	0.9	
Q1–Q3	0.7–1.0	0.7–1.0	0.7–1.0	
Adherence, <i>n</i> (%)				
No. of patients	255	265	520	$\chi^2 = 2.76$
High/Medium	240 (94.1)	239 (90.2)	479 (92.1)	$P = 0.10$
Low	15 (5.9)	26 (9.8)	41 (7.9)	
Treatment interruptions, <i>n</i> (%)				
No. of patients	272	287	559	$\chi^2 = 0.28$
0	182 (66.9)	198 (69.0)	380 (68.0)	$P = 0.60$
≥1	90 (33.1)	89 (31.0)	179 (32.0)	
Cause of treatment interruptions, <i>n</i> (%)				
No. of patients	272	287	559	
Toxicity	72 (26.5)	69 (24.0)	141 (25.2)	$P = 0.51$
Patient decision	8 (2.9)	4 (1.4)	12 (2.1)	$P = 0.21$
Other	23 (8.5)	27 (9.4)	50 (8.9)	$P = 0.69$
Planned	1 (0.4)	1 (0.3)	2 (0.4)	$P = 1.00$
Duration of treatment interruption (days)				
No. of patients	130	123	253	$t = 0.16$
Mean (s.d.)	13.2 (11.9)	13.9 (14.7)	13.5 (13.3)	$P = 0.69$
95% CI	11.1–15.3	11.3–16.5	11.9–15.2	
Treatment received				
No. of patients	272	287	559	$\chi^2 = 0.26$
Oral chemotherapy	109 (40.1%)	109 (38.0%)	218 (39.0%)	$P = 0.61$
Molecular-targeted agents	162 (59.6%)	177 (61.7%)	339 (61.0%)	

The primary objective of the study was met, given that the mean RDI was 93.4% (± 25.9) in the CAPRI arm, which was significantly higher than in the control arm (89.4% ± 19.1 , $P = 0.0426$). This difference remained statistically significant when adjusted for adherence. The main reason for treatment interruptions was treatment-related toxicity ($n = 141$, 25.2%). ^aThe chi-squared test and the t-test were two-sided.

expected in Western countries in the present decade^{22–24}. However, the proportion of patients who downloaded the smartphone application was low in patients aged over 80 years (15%), suggesting an age-dependent digital divide²⁴.

Although the RDI was higher in the CAPRI arm, there was no significant difference in terms of clinical benefit rates (stable disease or objective responses) or survival. An RDI > 85% seems to be associated with a favorable impact on survival²⁵, but in the present study the control arm outperformed historical data on RDI^{25,26}, with a mean (s.d.) RDI of 89.4% (19.1%), suggesting that further studies are needed to better assess the impact of maintaining planned treatment dose intensity on outcomes in metastatic solid tumors.

As far as medico-economic endpoints are concerned, the decrease in days of hospitalization associated with the CAPRI intervention appears critical. Indeed, the economic gain associated with improved coordination varies according to the perspective adopted to calculate this gain^{27–29}. The inclusion of indirect costs (loss of productivity, family assistance), and even intangible costs (pain, psychosocial burden of the disease) in addition to direct costs, varies the impact of the program^{30–32}. On top of the improvement of the quality and patient experience of care, the economic gain we observed suggests that the CAPRI program can be considered as an intervention that offers cancer care value, and could therefore be the subject of new payment models.

Table 3 | Grade ≥ 3 toxicities and hospitalizations per treatment arm

Variable	CAPRI	Control	Total	Statistics ^a
At least one toxicity, <i>n</i> (%)				
No. of patients	272	287	559	$\chi^2 = 5.59$
No	197 (72.4)	181 (63.1)	378 (67.6)	<i>P</i> = 0.02
Yes	75 (27.6)	106 (36.9)	181 (32.4)	
No. of toxicity groups				
No. of patients	272	287	559	<i>t</i> = 6.29
Mean (s.d.)	0.4 (0.7)	0.5 (0.9)	0.5 (0.8)	<i>P</i> = 0.01
95% CI	0.3–0.5	0.4–0.6	0.4–0.5	
Min–Max	0.0–4.0	0.0–5.0	0.0–5.0	
Hematological and lymphatic system disorders, <i>n</i> (%)				
No. of patients	272	287	559	$\chi^2 = 0.12$
No	246 (90.4)	262 (91.3)	508 (90.9)	<i>P</i> = 0.73
Yes	26 (9.6)	25 (8.7)	51 (9.1)	
Gastrointestinal disorders, <i>n</i> (%)				
No. of patients	272	287	559	$\chi^2 = 0.75$
No	257 (94.5)	266 (92.7)	523 (93.6)	<i>P</i> = 0.39
Yes	15 (5.5)	21 (7.3)	36 (6.4)	
Respiratory disorders, <i>n</i> (%)				
No. of patients	272	287	559	$\chi^2 = 1.9$
No	272 (100.0)	285 (99.3)	557 (99.6)	<i>P</i> = 0.17
Yes	0	2 (0.7)	2 (0.4)	
General disorders, <i>n</i> (%)				
No. of patients	272	287	559	$\chi^2 = 1.47$
No	258 (94.9)	265 (92.3)	523 (93.6)	<i>P</i> = 0.23
Yes	14 (5.1)	22 (7.7)	36 (6.4)	
Infections and infestations, <i>n</i> (%)				
No. of patients	272	287	559	$\chi^2 = 1.1$
No	265 (97.4)	275 (95.8)	540 (96.6)	<i>P</i> = 0.29
Yes	7 (2.6)	12 (4.2)	19 (3.4)	
Nervous system disorders, <i>n</i> (%)				
No. of patients	272	287	559	$\chi^2 = 0.28$
No	271 (99.6)	285 (99.3)	556 (99.5)	<i>P</i> = 0.59
Yes	1 (0.4)	2 (0.7)	3 (0.5)	
Skin disorders, <i>n</i> (%)				
No. of patients	272	287	559	$\chi^2 = 4.12$
No	262 (96.3)	265 (92.3)	527 (94.3)	<i>P</i> = 0.04
Yes	10 (3.7)	22 (7.7)	32 (5.7)	
Vascular disorders, <i>n</i> (%)				
No. of patients	272	287	559	$\chi^2 = 1.25$
No	266 (97.8)	276 (96.2)	542 (97.0)	<i>P</i> = 0.26

Continued

Table 3 | Grade ≥ 3 toxicities and hospitalizations per treatment arm (Continued)

Variable	CAPRI	Control	Total	Statistics ^a
Yes	6 (2.2)	11 (3.8)	17 (3.0)	
Metabolic and nutritional disorders, <i>n</i> (%)				
No. of patients	272	287	559	$\chi^2 = 0.96$
No	267 (98.2)	278 (96.9)	545 (97.5)	<i>P</i> = 0.33
Yes	5 (1.8)	9 (3.1)	14 (2.5)	
No. of hospitalizations				
No. of patients	272	287	559	<i>t</i> = 3.06
Mean (s.d.)	0.33 (0.69)	0.44 (0.76)	0.39 (0.73)	<i>P</i> = 0.08
95% CI	0.25–0.41	0.35–0.53	0.33–0.45	
Min–Max	0.0–4.0	0.0–4.0	0.0–4.0	
Median	0.0	0.0	0.0	
Q1–Q3	[0.0; 0.0]	[0.0; 1.0]	[0.0; 1.0]	
Days of hospitalization per patient				
No. of patients	272	287	559	<i>t</i> = 5.19
Mean (s.d.)	2.82 (6.96)	4.44 (9.60)	3.65 (8.45)	<i>P</i> = 0.02
95% CI	1.99–3.65	3.32–5.55	2.95–4.35	
Min–Max	0.0–39.0	0.0–72.0	0.0–72.0	
Median	0.0	0.0	0.0	
Q1–Q3	0.0–0.0	0.0–6.0	0.0–3.0	
Duration of hospitalization (days)				
No. of patients	89	124	213	<i>t</i> = 1.82
Mean (s.d.)	8.45 (7.29)	10.02 (9.04)	9.36 (8.37)	<i>P</i> = 0.18
95% CI	6.91–9.98	8.41–11.62	8.23–10.49	
Min–Max	1.0–38.0	0.0–44.0	0.0–44.0	
Median	7.0	7.5	7.0	

During the study period, 181 of 559 evaluable patients had at least one grade ≥ 3 treatment-related toxicity. The number of toxicity groups per patient ranged from 0 to 5, and the most frequent toxicity groups are listed. The number of days of hospitalization per patient was significantly lower in the CAPRI arm (2.82 ± 6.96 versus 4.44 ± 9.60 , *P* = 0.02). ^aThe chi-squared test and the *t*-test were two-sided.

The external validity of the findings relies on the prospective, randomized design of the trial, with a patient population as close as possible to that of routine practice (for example, all solid tumor types, approved oral treatment, 11.8% of patients with a performance status of 2 and 14% aged ≥ 75 years). However, CAPRI was a single-center study, and nurse navigators were located in our institution (thereby facilitating interactions with the treating oncologists whenever needed, through emails, phone calls or direct contact). The full-time employment of two nurse navigators represents a sizeable expense for most community oncology practices, and must be balanced against the expected positive impact on hospital direct costs and medical time savings. In our institution, the nurse navigator positions were funded by the study budget; however, recent changes in the French healthcare financial laws now allow for the reimbursement of remote monitoring of patients with cancer (as other care activities performed in hospitals), making this approach sustainable³³.

The limitations of the present study encompass the single-center design and the inclusion of patients receiving oral therapy excluding hormone therapy alone. Regarding the latter, durations of treatment

Table 4 | Patient experience (PACIC score) per treatment arm

Dimension	CAPRI	Control	Total	Statistics ^a
Patient activation				
Missing, <i>n</i> (%)	100 (36.76)	124 (43.21)	224 (40.07)	
No. of patients	172	163	335	<i>t</i> = 0.82
Mean (s.d.)	3.46 (1.14)	3.35 (1.11)	3.40 (1.13)	<i>P</i> = 0.37
95% CI	3.29–3.63	3.17–3.52	3.28–3.52	
Min–Max	1.00–5.00	1.00–5.00	1.00–5.00	
Median	3.67	3.67	3.67	
Q1–Q3	2.33–4.33	2.33–4.33	2.33–4.33	
Delivery system design				
Missing, <i>n</i> (%)	106 (38.97)	127 (44.25)	233 (41.68)	
No. of patients	166	160	326	<i>t</i> = 2.48
Mean (s.d.)	3.23 (0.95)	3.06 (1.05)	3.15 (1.00)	<i>P</i> = 0.12
95% CI	3.09–3.38	2.89–3.22	3.04–3.25	
Min–Max	1.00–5.00	1.00–5.00	1.00–5.00	
Median	3.00	3.00	3.00	
Q1–Q3	2.33–4.00	2.33–3.67	2.33–3.67	
Goal setting				
Missing, <i>n</i> (%)	118 (43.38)	135 (47.04)	253 (45.26)	
No. of patients	154	152	306	<i>t</i> = 0.95
Mean (s.d.)	2.53 (1.04)	2.41 (1.01)	2.47 (1.03)	<i>P</i> = 0.33
95% CI	2.36–2.69	2.25–2.58	2.36–2.59	
Min–Max	1.00–5.00	1.00–5.00	1.00–5.00	
Median	2.40	2.40	2.40	
Q1–Q3	1.80–3.20	1.60–3.00	1.80–3.00	
Problem-solving				
Missing, <i>n</i> (%)	131 (48.16)	144 (50.17)	275 (49.19)	
No. of patients	141	143	284	<i>t</i> = 5
Mean (s.d.)	3.19 (1.17)	2.86 (1.29)	3.02 (1.24)	<i>P</i> = 0.03
95% CI	2.99–3.38	2.64–3.07	2.88–3.17	
Min–Max	1.00–5.00	1.00–5.00	1.00–5.00	
Median	3.25	2.75	3.00	
Q1–Q3	2.50–4.00	1.75–4.00	2.00–4.00	
Coordination				
Missing, <i>n</i> (%)	125 (45.96)	129 (44.95)	254 (45.44)	
No. of patients	147	158	305	<i>t</i> = 25.96
Mean (s.d.)	2.54 (0.86)	2.02 (0.93)	2.27 (0.94)	<i>P</i> < 0.0001
95% CI	2.40–2.68	1.87–2.16	2.17–2.38	
Min–Max	1.00–5.00	1.00–5.00	1.00–5.00	
Median	2.60	1.80	2.20	
Q1–Q3	1.80–3.20	1.40–2.40	1.60–3.00	

Continued

Table 4 | Patient experience (PACIC score) per treatment arm (continued)

Dimension	CAPRI	Control	Total	Statistics ^a
Global score				
Missing, <i>n</i> (%)	148 (54.41)	166 (57.84)	314 (56.17)	
No. of patients	124	121	245	<i>t</i> = 6.34
Mean (s.d.)	2.94 (0.83)	2.67 (0.89)	2.81 (0.87)	<i>P</i> = 0.01
95% CI	2.80–3.09	2.51–2.83	2.70–2.92	
Min–Max	1.00–5.00	1.00–5.00	1.00–5.00	
Median	2.85	2.50	2.70	
Q1–Q3	2.38–3.53	2.05–3.20	2.15–3.40	

The global PACIC score, an instrument used to evaluate the chronic care experiences of patients, was improved in the CAPRI arm compared with the control arm, the largest differences being observed in problem-solving and coordination items. ^aThe *t*-test was two-sided.

in the present study were shorter than in adjuvant hormone therapy trials, and adherence issues related to treatment duration³⁴ might have been underestimated. Also, the CAPRI intervention was combined with usual care (scheduled hospital visits with the treating oncologist), and did not facilitate exploration of whether remote monitoring per se could decrease the frequency of hospital visits.

Future directions for the CAPRI program encompass (but are not restricted to) possible upgrades of the digital tool, a better identification of the patient subpopulations who derive the most benefit from this program, and implementation of the program in specific therapeutic areas. For instance, neuro-oncology patients, in whom disease-related cognitive disorders might impair the optimal use of first-line oral treatments (for example, temozolomide), represent credible candidates for this approach, and the CAPRI remote monitoring program has already become a standard of care for neuro-oncology patients at our institution. Future research will also need to address the issue of psychological or emotional secondary outcomes. Furthermore, the development of electronic onco-geriatric evaluations and dedicated programs for patients included in clinical trials represent fields of application with potentially rapid implementation in view of the retrospective studies already published^{35,36}, with the possible implementation of electronic patient-reported outcomes, which were a feasible approach in recent trials^{37,38}. Finally, we have reported the implementation of the CAPRI program to monitor COVID-19 infections in cancer patients³⁹, suggesting that nurse navigator-led digital interventions deserve further prospective assessment in other non-oncological conditions.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-022-01788-1>.

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References

- Chaudhry, S. I. et al. Telemonitoring in patients with heart failure. *N. Engl. J. Med.* **363**, 2301–2309 (2010).
- Kroenke, K. et al. Effect of telecare management on pain and depression in patients with cancer: a randomized trial. *JAMA* **304**, 163–171 (2010).

3. McLean, S., Protti, D. & Sheikh, A. Telehealthcare for long term conditions. *BMJ* **342**, d120 (2011).
4. Mecklai, K. et al. Remote patient monitoring: overdue or overused? *N. Engl. J. Med.* **384**, 1384–1386 (2021).
5. McCann, L., Maguire, R., Miller, M. & Kearney, N. Patients' perceptions and experiences of using a mobile phone-based advanced symptom management system (ASyMS) to monitor and manage chemotherapy related toxicity. *Eur. J. Cancer Care (Engl.)* **18**, 156–164 (2009).
6. Schneider, S. M., Hess, K. & Gosselin, T. Interventions to promote adherence with oral agents. *Semin. Oncol. Nurs.* **27**, 133–141 (2011).
7. Sun, W. et al. Novel tool to monitor adherence to oral oncolytics: a pilot study. *JCO Clin. Cancer Inform.* **5**, 701–708 (2021).
8. Doolin, J. W. et al. Implementing electronic patient-reported outcomes for patients with new oral chemotherapy prescriptions at an academic site and a community site. *JCO Clin. Cancer Inform.* **5**, 631–640 (2021).
9. US Food and Drug Administration. *Novel Drug Approvals for 2020* <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020> (accessed 28 July 2021).
10. Agboola, S. et al. Improving outcomes in cancer patients on oral anti-cancer medications using a novel mobile phone-based intervention: study design of a randomized controlled trial. *JMIR Res. Protoc.* **3**, e79 (2014).
11. Weingart, S. N. et al. Oral chemotherapy safety practices at US cancer centres: questionnaire survey. *BMJ* **334**, 407 (2007).
12. Ruddy, K., Mayer, E. & Partridge, A. Patient adherence and persistence with oral anticancer treatment. *CA Cancer J. Clin.* **59**, 56–66 (2009).
13. Garg, S., Williams, N. L., Ip, A. & Dicker, A. P. Clinical integration of digital solutions in health care: an overview of the current landscape of digital technologies in cancer care. *JCO Clin. Cancer Inform.* **2**, 1–9 (2018).
14. Basch, E. et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. *J. Clin. Oncol.* **34**, 557–565 (2016).
15. Denis, F. et al. Randomized trial comparing a web-mediated follow-up with routine surveillance in lung cancer patients. *J. Natl Cancer Inst.* **109**, (2017).
16. Nielson, C. M. et al. Relative dose intensity of chemotherapy and survival in patients with advanced stage solid tumor cancer: a systematic review and meta-analysis. *Oncologist* **26**, 1609–1618 (2021).
17. Weaver, A. et al. A pilot study: dose adaptation of capecitabine using mobile phone toxicity monitoring – supporting patients in their homes. *Support. Care Cancer* **22**, 2677–2685 (2014).
18. National Cancer Institute, Division of Cancer Treatment and Diagnosis. *CTEP: Cancer Therapy Evaluation Program* https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm (accessed 12 January 2022).
19. Groenvold, M. et al. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. *J. Clin. Epidemiol.* **50**, 441–450 (1997).
20. Berwick, D. M., Nolan, T. W. & Whittington, J. The triple aim: care, health, and cost. *Health Aff. (Millwood)* **27**, 759–769 (2008).
21. Ferrua, M. et al. How to design a remote patient monitoring system? A French case study. *BMC Health Serv. Res.* **20**, 434 (2020).
22. Dicker, A. P. & Jim, H. S. L. Intersection of digital health and oncology. *JCO Clin. Cancer Inform.* **2**, 1–4 (2018).
23. Potdar, R. et al. Access to internet, smartphone usage, and acceptability of mobile health technology among cancer patients. *Support. Care Cancer* **28**, 5455–5461 (2020).
24. Girault, A. et al. Internet-based technologies to improve cancer care coordination: current use and attitudes among cancer patients. *Eur. J. Cancer* **51**, 551–557 (2015).
25. Havrilesky, L. J., Reiner, M., Morrow, P. K., Watson, H. & Crawford, J. A review of relative dose intensity and survival in patients with metastatic solid tumors. *Crit. Rev. Oncol. Hematol.* **93**, 203–210 (2015).
26. Wildiers, H. & Reiser, M. Relative dose intensity of chemotherapy and its impact on outcomes in patients with early breast cancer or aggressive lymphoma. *Crit. Rev. Oncol. Hematol.* **77**, 221–240 (2011).
27. Bergmo, T. S. Can economic evaluation in telemedicine be trusted? A systematic review of the literature. *Cost Eff. Resour. Alloc.* **7**, 18 (2009).
28. Husereau, D. et al. Consolidated health economic evaluation reporting standards (CHEERS) – explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health* **16**, 231–250 (2013).
29. van Hezewijk, M., van den Akker, M. E., van de Velde, C. J. H., Scholten, A. N. & Hille, E. T. M. Costs of different follow-up strategies in early breast cancer: a review of the literature. *Breast* **21**, 693–700 (2012).
30. Dávalos, M. E., French, M. T., Burdick, A. E. & Simmons, S. C. Economic evaluation of telemedicine: review of the literature and research guidelines for benefit–cost analysis. *Telemed. J. E Health* **15**, 933–948 (2009).
31. Rauh, S. S., Wadsworth, E. B., Weeks, W. B. & Weinstein, J. N. The savings illusion: why clinical quality improvement fails to deliver bottom-line results. *N. Engl. J. Med.* **365**, e48 (2011).
32. Lairson, D. R., Huo, J., Ball Ricks, K. A., Savas, L. & Fernández, M. E. The cost of implementing a 2-1-1 call center-based cancer control navigator program. *Eval. Program Plann.* **39**, 51–56 (2013).
33. Légifrance. *LAW no. 2017-1836 of December 30, 2017 on the financing of social security for 2018 (1)* https://www.legifrance.gouv.fr/jorf/article_jo/JORFARTI000036339172 (accessed 12 January 2022).
34. Pistilli, B. et al. Serum detection of nonadherence to adjuvant tamoxifen and breast cancer recurrence risk. *J. Clin. Oncol.* **38**, 2762–2772 (2020).
35. Guerard, E. et al. Electronic geriatric assessment: is it feasible in a multi-institutional study that included a notable proportion of older African American patients? (Alliance A171603). *JCO Clin. Cancer Inform.* **5**, 435–441 (2021).
36. Liu, J. F. et al. Technology applications: use of digital health technology to enable drug development. *JCO Clin. Cancer Inform.* **2**, 1–12 (2018).
37. Basch, E. et al. Clinical utility and user perceptions of a digital system for electronic patient-reported symptom monitoring during routine cancer care: findings from the PRO-TECT trial. *JCO Clin. Cancer Inform.* **4**, 947–957 (2020).
38. Maguire, R. et al. Real time remote symptom monitoring during chemotherapy for cancer: European multicentre randomised controlled trial (eSMART). *BMJ* **374**, n1647 (2021).
39. Ferrua, M. et al. Nurse navigators' telemonitoring for cancer patients with COVID-19: a French case study. *Support. Care Cancer* **29**, 4485–4492 (2021).

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Methods

Trial status and ethics. The clinical trial number (NCT02828462) is posted on www.clinicaltrials.gov/. The study was conducted in agreement with applicable laws and regulations and the Declaration of Helsinki, and was approved by an ethics committee (CPP Paris-Ile-de-France IV no. 2016/20SC, US Department of Health and Human Services approved IRB no. 00003835).

The study protocol has been previously published elsewhere⁴⁰. In brief, the recruitment took place at the Gustave Roussy Comprehensive Cancer Center and was open to patients with advanced or metastatic cancer started on approved oral chemotherapy and/or molecular-targeted therapy, not eligible for enrollment in another clinical trial (according to the treating oncologist's judgment). No compensation was offered to participants. The first patient was included on 24 October 2016 and the last patient on 24 April 2019.

Eligibility criteria. All participants had to speak French, to be aged 18 years or older, to have a performance status ≤ 2 , and to have a life expectancy of at least 6 months (according to investigator judgment). Exclusion criteria included hormone therapy alone, not having a referring general practitioner, having neither internet nor phone access at home, and being deprived of liberty.

Sample size calculation. Given the previous reports suggesting that RDI varies from 60% to 95% for oral anticancer agents^{41,42}, with an RDI lower than 85% being associated with worse outcomes²⁵, and considering that a difference of 6–20% was found between different treatment options or between different cancer types, we expected a sizeable effect of the CAPRI intervention on RDI (a +5% difference from the control group). Therefore, 393 individuals per group ($n = 786$ in total) were estimated as sufficient to detect a difference in RDI (from 85% to 90%) between the CAPRI intervention and usual care, assuming a significance threshold set at 5% ($\alpha = 0.05$), power at 80%, and a standard deviation of 25% for the distribution of mean change. In agreement with CONSORT guidelines⁴³, randomization occurred once participants had completed their consent form. Given the potential difference in adherence and socioeconomic status between the different cancer types^{44,45}, stratified randomization was used to minimize these differences between and within groups. This randomization was performed using computer software and was completed by an independent researcher (Gustave Roussy randomization department). A randomization number was allocated to each participant, and results of the randomization were sent to both the treating oncologist and the nurse navigators. Participants included in the intervention arm were given immediate access to the CAPRI program, including access to their personalized online portal.

Intervention: the CAPRI program. Throughout the course of the study, participants from the control group received usual care (consultations with the treating oncologist at Gustave Roussy, mainly for prescription renewals and dose modifications), while participants from the intervention group benefited (for 6 months) from the CAPRI program on top of similar usual care. Two nurse navigators ensured the remote follow-up of patients randomized to the CAPRI arm, scheduled as follows: once weekly during the first month, then once every other week from the second to the fourth months, and once every 3 weeks from the fifth month to the end of the study. Nurse navigators could be contacted (by phone or internet) from Monday to Friday, during office hours only (09:00–17:00 hours). Out of hours, the patients received the instruction to contact the emergency department of our institution. Nurse navigators provided the link between hospital professionals, patients and primary care professionals (general practitioner, private nurse, pharmacist and so on) identified by the patient. The web portal provided a unique interface through which healthcare professionals were able to connect with patients (each program stakeholder having his or her own login for access to a dedicated portal). The web portal included a dashboard for nurse navigators, enabling them to monitor the records of all patients enrolled in the program. Following each contact with a patient, nurse navigators created 'interaction reports' detailing what they had done or discussed, and shared the information with other healthcare professionals involved, tracked in the medical record. These healthcare professionals could log on to the portal to communicate with nurse navigators online, and access information regarding the patients they cared for. The system also generated automatic alerts to patients or nurse navigators. Alerts and patient requests could be generated in various ways: automatically, through the web portal, for instance while reporting follow-up measures (that is, if the patient measures are below or above predefined thresholds); by the nurse navigators during scheduled follow-up; or by a message or call from the patient or healthcare professionals.

The nurse navigator then evaluated the alert level using algorithms (based on the NCI-CTCAE v4.03 classification⁴⁶) and determined the clinical action to implement, in line with the navigation decision trees developed at our institution through a collaboration between physicians, nurse navigators and CAPRI investigators. An example (hand-foot skin reaction) is shown in Extended Data Fig. 4. Depending on level, nurse navigators could give advice, refer the patient to their primary care physician or to a professional at Gustave Roussy, or contact the dedicated services to organize a hospitalization or schedule an appointment for the patient. The nurse navigators' responses to alert notifications were also tracked and reported in the medical record.

Nurse navigators involved in the study were trained internally with the hospital discharge platform developed in Gustave Roussy and described elsewhere⁴⁷, they had a clinical experience of ≥ 1 year, and had obtained a university diploma in nursing care in clinical oncology (100 h over 1 year) from our institution.

Impact evaluation. The primary endpoint of the study was a significant increase in the delivery of oral treatment, measured by RDI (defined as the ratio of the dose actually delivered over time to the prescribed dose intensity). We proposed that, thanks to earlier management of treatment-related adverse events, patients in the intervention arm would have a significant increase in RDI compared with those in the control group. Secondary endpoints were patient adherence to oral anticancer therapy (measured with a dedicated questionnaire⁴⁸ and/or the Medication Event Monitoring System (MEMs)), quality of life (EORTC QLQ-C30 questionnaire¹⁹), patient experience (PACIC score⁴⁹), tumor response, progression-free survival, overall survival (evaluated by investigators, using RECIST 1.1)⁵⁰ and grade ≥ 3 toxicities (graded according to the NCI-CTCAE v4.03 classification⁴⁶). We expected that patients in the intervention arm, compared with controls, would have significantly greater improvements in secondary outcome measures. Demographic, socioeconomic and clinical variables were assessed and adjusted for in the study results. Outcomes were collected by a clinical research associate at baseline, and each month until the end of the program (after 6 months), except for patient quality of life (at baseline, after 3 months and at the end of the program) and for patient experience (at the end of the program). The instruments used to collect data from participants, including primary and secondary outcomes, are detailed elsewhere⁴⁰.

Economic evaluation. The economic evaluation of the CAPRI program adopted a societal perspective, assessing intervention, medical and non-medical costs. All resources used by the patients included in the study were considered in the frame of a cost-effectiveness study. We expected that in comparison with usual care, the CAPRI intervention would result in cost-effective care with improvement in patient adherence to oral anticancer therapy. Cost data were collected monthly using retrospective self-questionnaires for non-hospital costs. For hospital costs, medico-administrative data were collected. The resources used and included in the cost-effectiveness study, and their value units, are detailed elsewhere⁴⁰.

Process evaluation. Data on access to, and use of, the web portal were extracted from the web portal records. In addition, focus groups with nurse navigators were conducted monthly throughout the study. Last, semi-structured interviews with patients, relatives and healthcare professionals engaged in the program were conducted by the research team at the end of the trial.

Statistical analysis. Appropriate descriptive statistics enabled presentation and comparison of sample characteristics at baseline, and at each evaluation time point. The primary analyses used a between-group design (CAPRI versus control groups) at six time points (each month). Significant changes in treatment delivery were measured using RDI, calculated with the dedicated questionnaire⁴⁷ and/or the MEMs results. If the data distribution was normal, Student's *t*-test was used to compare the RDI means, as well as the secondary outcomes designed as continuous variables. If not, a Mann-Whitney test was used. A chi-squared or Fisher's test was used to compare secondary outcomes designed as binary variables. All tests were two-sided. Baseline data were examined to analyze the probability of attrition bias.

Software. Data were collected and analyzed using Microsoft Excel 2016, and Fig. 2 was designed using the BioRender.com Premium portal.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The datasets generated and/or analyzed in this study are considered commercially sensitive and, therefore, are not publicly available. However, to ensure independent interpretation of clinical study results the authors will consider requests for data supporting the findings in this study. These data are available to be shared on request after publication. Bona fide, qualified scientific and medical researchers are eligible to request access to the clinical study data. Prior to providing access, clinical study documents and data will be examined and, if necessary, redacted and de-identified to protect the personal data of the study participants, to respect the boundaries of the informed consent of the study participants. Data might be shared in the form of aggregate data summaries and via a data transfer agreement. Individual participant-level raw data containing confidential or identifiable patient information are subject to patient privacy and cannot be shared. Requests should be made by email to E.M. (etienne.minvielle@gustaveroussy.fr) and will be reviewed individually on a quarterly basis.

Code availability

The decision trees (algorithms) used by the nurse navigator are also the intellectual property of Gustave Roussy. An example is shared in Extended Data Fig. 4, but

others are not publically available. However, to ensure independent interpretation of clinical study results the authors will consider requests for data supporting the findings in this study. Bona fide, qualified scientific and medical researchers are eligible to request access to other examples of the decision trees, which might be shared via a data transfer agreement. These data are available to be shared on request after publication. Requests should be made by email to E.M. (etienne.minville@gustaveroussy.fr) and will be reviewed individually on a quarterly basis.

References

40. Gervès-Pinquier, C. et al. Impacts of a navigation program based on health information technology for patients receiving oral anticancer therapy: the CAPRI randomized controlled trial. *BMC Health Serv. Res.* **17**, 133 (2017).
41. Porta, C. et al. Impact of adverse events, treatment modifications, and dose intensity on survival among patients with advanced renal cell carcinoma treated with first-line sunitinib: a medical chart review across ten centers in five European countries. *Cancer Med* **3**, 1517–1526 (2014).
42. Banna, G. L. et al. Anticancer oral therapy: emerging related issues. *Cancer Treat. Rev.* **36**, 595–605 (2010).
43. Moher, D., Schulz, K. F. & Altman, D. G. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* **357**, 1191–1194 (2001).
44. Ward, E. et al. Cancer disparities by race/ethnicity and socioeconomic status. *CA Cancer J. Clin.* **54**, 78–93 (2004).
45. Clegg, L. X. et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. *Cancer Causes Control* **20**, 417–435 (2009).
46. National Cancer Institute, Division of Cancer Treatment and Diagnosis. *CTEP: Cancer Therapy Evaluation Program* https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm (accessed 28 July 2021).
47. Yatim, F. et al. Analysis of nurse navigators' activities for hospital discharge coordination: a mixed method study for the case of cancer patients. *Support. Care Cancer* **25**, 863–868 (2017).
48. Morisky, D. E., Green, L. W. & Levine, D. M. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med. Care* **24**, 67–74 (1986).
49. Glasgow, R. E. et al. Development and validation of the Patient Assessment of Chronic Illness Care (PACIC). *Med. Care* **43**, 436–444 (2005).
50. Eisenhauer, E. A. et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* **45**, 228–247 (2009).

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Author contributions

All authors were involved in data interpretation and the review and writing of the manuscript. M.F., A.F., D.Mat., A.D.-B., M.G., V.P., M.d.P. and E.M. designed the study.

O.M., D.Mat., A.D.-B., S.Du., E.B., S.De., D.Mal., L.A., P.P., C.R., D.P., S.d.B., F.L., M.A., M.G., V.P. and M.d.P. collected the data. O.M., M.F., A.F., F.S., M.d.P. and E.M. analyzed the data.

Competing interests

O.M. has received consultancy fees from Amgen, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Ipsen, Lundbeck, Merck Sharpe & Dohme, Pfizer, Roche, Servier and Vifor Pharma, and has been an employee of Amgen since 1 February 2022. F.S. has received honoraria from Amgen, Biogaran, Bristol Myers Squibb, Helsinn, Leo Pharma, Merck Sharpe & Dohme, Mundi Pharma, Mylan, Pfizer, Pierre Fabre Oncology and Vifor Pharma. F.L. has been an employee of AstraZeneca France since 1 May 2019. E.B. has received honoraria from Novartis, Ipsen and Pfizer, research grants from Novartis, and is a member of Ipsen and Novartis speaker's bureau. S.De. declares grants from F. Hoffmann-La Roche/Genentech during the conduct of the study and grants from Pfizer, Novartis, AstraZeneca, Lilly, Puma, Myriad, Orion, Amgen, Sanofi, Genomic Health, GE, Servier, Merck Sharp & Dohme and Bristol Myers Squibb outside of the submitted work; non-financial support from Pfizer, AstraZeneca and F. Hoffmann-La Roche/Genentech; and personal fees from AstraZeneca. D.Mal. declares competing interests with Agios, Amgen, Bayer, BMS, HaliDx, Incyte, Merck Serono, MSD, Pierre Fabre Oncologie, Roche, Sanofi, Servier and Shire. L.A. reports research funding from BMS (Institution) and advisory roles (Institution) for Astellas-AstraZeneca, BMS, Corvus Pharmaceuticals, Ipsen, Janssen, Merck & Co., MSD, Novartis, Pfizer and Eisai. P.P. has received consultancy fees from AstraZeneca, GSK and Clovis Oncology. C.R. has received consultancy fees from Amgen, Bristol Myers Squibb, Merck, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche and Sanofi. D.P. reports personal fees from AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, Prime Oncology, Peer CME, Roche and Samsung, outside the submitted work; and clinical trials research (as principal investigator or co-investigator): AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmune, Sanofi-Aventis, Taiho Pharma, Novocure and Daiichi Sankyo. S.d.B. has received research funding and served on an advisory board for Agios; participated in speakers' bureaus and served on advisory boards for AbbVie, Bristol Myers Squibb and Janssen; served on an advisory board and provided consultancy to Pierre Fabre; and served on advisory boards for Astellas, Bayer, Daiichi-Sankyo, Forma, Novartis, Pfizer, Servier and Syros. All other authors have no competing interests. The CAPRI academic system is owned by Gustave Roussy; none of the authors is involved financially with CAPRI. After this study, a commercial solution has been derived from CAPRI by RESILIENCE. None of the authors is involved financially with CAPRI or RESILIENCE.

Additional information

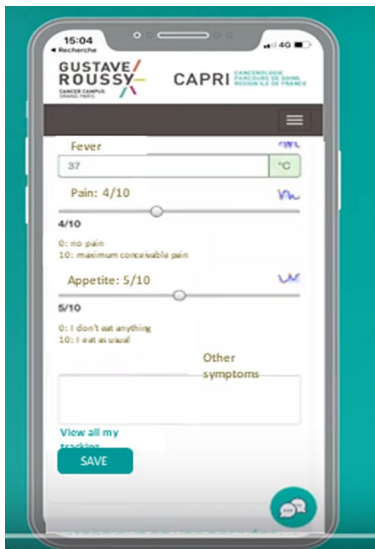
Extended data are available for this paper at <https://doi.org/10.1038/s41591-022-01788-1>.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41591-022-01788-1>.

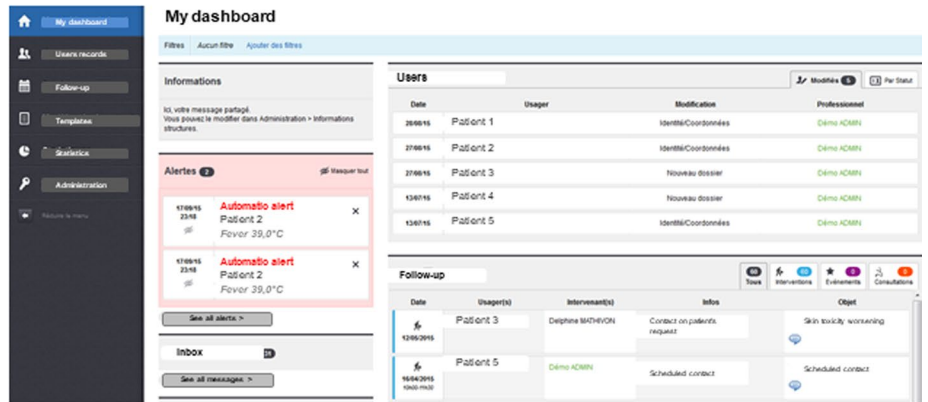
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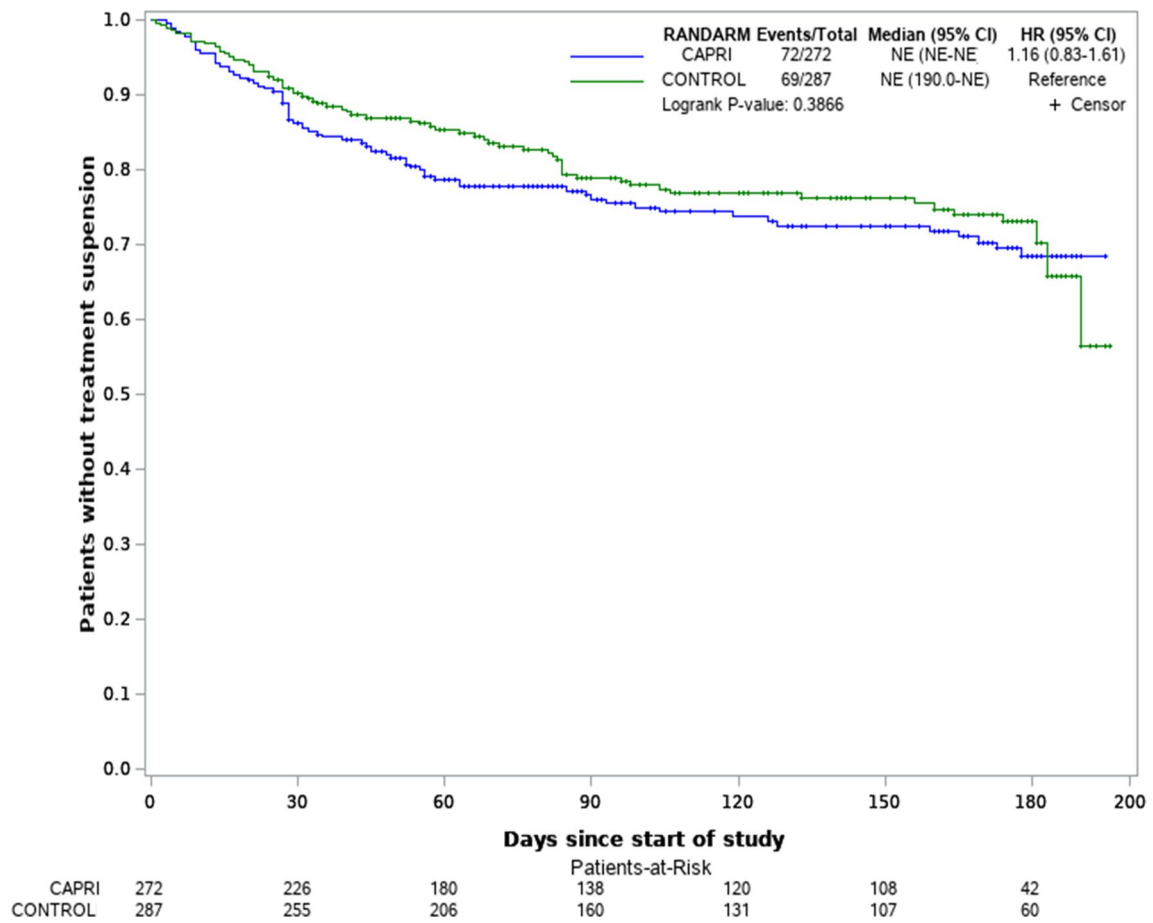


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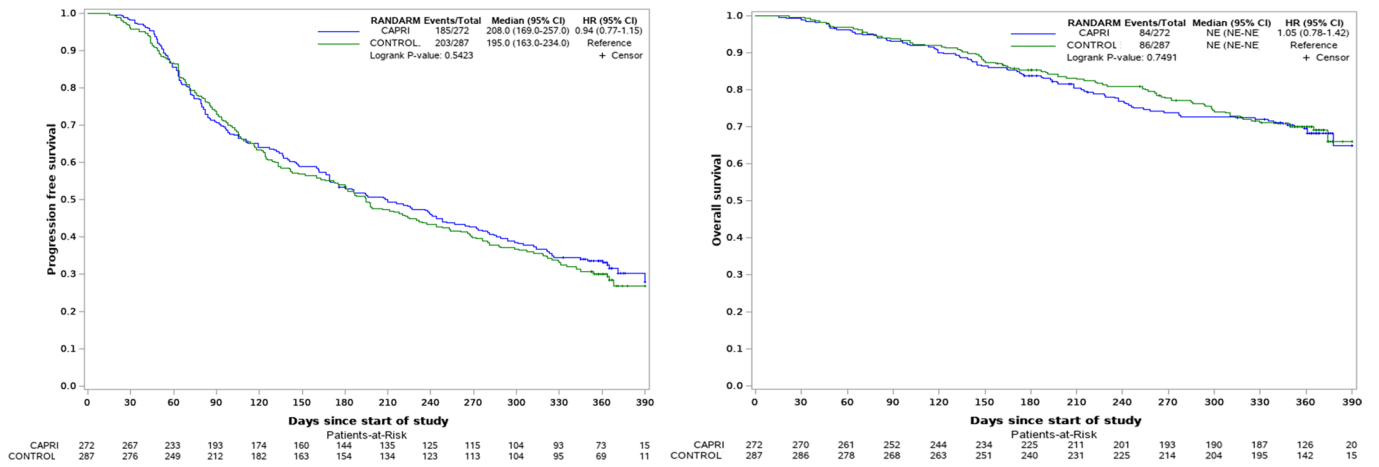


B

Extended Data Fig. 1 | Screenshots of the patient smartphone app (panel a) and nurse navigators dashboard (panel b).



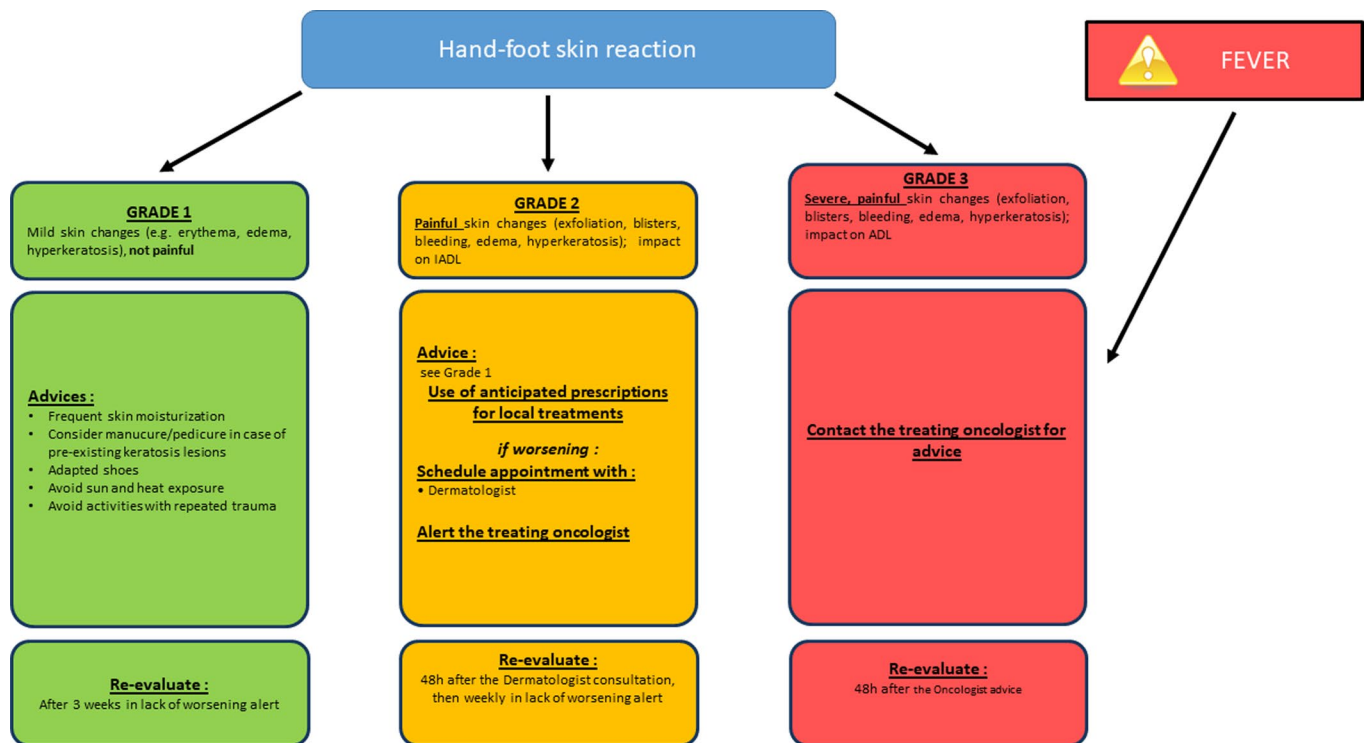
Extended Data Fig. 2 | Time to first treatment interruption due to toxicity.



a – Progression-free survival

b – Overall survival

Extended Data Fig. 3 | Progression-free survival (panel a) and overall survival (panel b).



Extended Data Fig. 4 | Example of a decisional tree used by the nurse navigators (for example hand-foot skin reaction).

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Software and code

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Data collection

Softwares used : Microsoft Excel 2016, BioRender.com
Scores and algorithms used : NCI CTC v.043, EORTC QLQ-C30, PACIC score, CONSORT 2010, RECIST 1.1

Data analysis

Appropriate descriptive statistics allowed presentation and comparison of sample characteristics at baseline, and at each evaluation time point. The primary analyses used a between-group design (CAPRI versus control groups) at six time points (each month). Significant changes in treatment delivery were measured on the RDI ratio, calculated with the dedicated questionnaire 9 and/or the Medication Event Monitoring System (MEMS) results. If distribution was normal, a Student t-test was used to compare RDI means, as well as secondary outcomes designed as continuous variables. If not, a Mann-Whitney test was used. Chi2 or Fisher's test were used to compare secondary outcomes designed as binary variables. All tests were two-sided. Baseline data were examined to analyze probability of attrition bias.

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The datasets generated and/or analyzed in this study are considered commercially sensitive and, therefore, are not publicly available. However, to ensure

independent interpretation of clinical study results, the authors will consider requests for data supporting findings in the manuscript.

These data are available to be shared on request after publication of the primary manuscript. Bona fide, qualified scientific and medical researchers are eligible to request access to the clinical study data. Prior to providing access, clinical study documents and data will be examined, and, if necessary, redacted and de-identified to protect the personal data of the study participants, in order to respect the boundaries of the informed consent of the study participants. Data might be shared in the form of aggregate data summaries and via a data transfer agreement. Individual participant-level raw data containing confidential or identifiable patient information are subject to patient privacy and cannot be shared.

Requests should be made by e-mail to Professor Etienne Minvielle (Etienne.minvielle@gustaveroussy.fr) and will be reviewed individually on a quarterly basis.

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Life sciences Behavioural & social sciences Ecological, evolutionary & environmental sciences

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Since previous reports suggesting that Relative Dose Intensity (RDI) varies from 60% to 95% for oral anticancer agents, with a RDI lower than 85% being associated with worse outcomes, and considering that a difference of 6% to 20% was found between different treatment options or between different cancer types, we expected a sizeable effect of the CAPRI intervention on RDI (+5% difference with the control group). Therefore, 393 individuals per group were estimated as sufficient to detect a difference in RDI between the CAPRI intervention and usual care, assuming a significance threshold set at 5% ($\alpha=0.05$), power at 80%, and a standard deviation of 25% for the distribution of mean change.
Data exclusions	As shown in the CONSORT diagram, 50 patients were excluded, for the following reasons : - Follow-up < 28 days (n=36) - Treatment duration < 10 days (n=6) - Investigator decision (n=4) - Withdrawal of consent (n=4)
Replication	No replication was made, since this is a randomized clinical trial with limited funding. However, the external validity of the study may be questioned, and an attempt to replicate our findings is ongoing in separate studies conducted at other institutions (i.e. Hematology patients, based on Compaci G, Ysebaert L, Obéric L, Derumeaux H, Laurent G. Effectiveness of telephone support during chemotherapy in patients with diffuse large B cell lymphoma: the Ambulatory Medical Assistance (AMA) experience. <i>Int J Nurs Stud.</i> 2011 Aug;48(8):926-32. doi: 10.1016/j.ijnurstu.2011.01.008. Epub 2011 Feb 23. PMID: 21349519.)
Randomization	In agreement with CONSORT guidelines, randomization occurred once participants had completed their consent form. Given the potential difference in adherence and socioeconomic status among the different cancer types, stratified randomization was used in order to minimize these differences between and within groups. This randomization was performed using computer software, and completed by an independent researcher (Gustave Roussy randomization department). A randomization number was allocated to each participant, and results of the randomization was sent to both the treating oncologist and the nurse navigators. Participants included in the intervention arm were given immediate access to the CAPRI program, including access to their personalized online portal.
Blinding	No blinding process was used, since this is an open-label, randomized study.

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We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

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<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants
<input type="checkbox"/>	<input checked="" type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
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Human research participants

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Population characteristics	<p>All participants had to speak French, to be aged 18 years or older, to have a performance status ≤ 2, and their life expectancy had to be of at least 6 months (according to investigator's judgement). Exclusion criteria included: hormone therapy alone, not having a referring general practitioner (GP), having neither internet nor phone access at home, and being deprived of liberty.</p> <p>609 patients (59% females) initiating a new treatment line with oral anticancer agents were included (39% were receiving chemotherapy, and 61% molecular targeted therapies). Baseline demographics and disease characteristics were generally similar in both arms (Table 1). Median age was 62.0 years (range: 20.0-92.0), 155 patients (27.7%) were aged 65-74 and 78 patients (14%) were aged over 75. Performance status was 0-1 in 493 patients (88.2%), and 2 in the remaining 66 patients (11.8%). One hundred forty-seven patients (27.8%) had received three or more prior lines of treatment.</p>
Recruitment	<p>All patients initiating an approved oral anticancer treatment (chemotherapy or molecular targeted agent) were invited to participate, after having excluded a possible inclusion in another clinical trial (phase 1-3).</p> <p>There is a possible selection bias, since around 20% of patients in our tertiary institution are enrolled in therapeutic clinical trials (phase 1-3), but also reflects the study population (real life oncology outside clinical trials).</p> <p>Self selection bias was limited since the attrition of participants was limited, with the overall completion of scheduled remote (excluding in-hospital visits) follow-up (percentage of scheduled contacts effectively performed) being 87.4%.</p>
Ethics oversight	<p>Ethics Committee (CPP Paris-Ile-de-France IV no. 2016/20SC, US Department of Health and Human Services approved IRB no. 00003835).</p>

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

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Clinical trial registration	Clinicaltrials.gov NCT02828462
Study protocol	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5307879/
Data collection	<p>The study was conducted from October 2016 to May 2019 (The first patient was included on October 24th, 2016 and the last patient on April 24th, 2019) at the Gustave Roussy Comprehensive Cancer Center (located in Villejuif, France).</p> <p>Data analysis was performed in February 2020.</p>
Outcomes	<p>The primary endpoint of the study was significant increase in the delivery of oral treatment, measured by RDI (defined as the ratio of the dose actually delivered over time to the prescribed dose intensity). Our hypothesis was that, thanks to earlier management of treatment-related adverse events, patients in the intervention arm would experience a significant increase in RDI, in comparison with those from the control group. Secondary endpoints were patient adherence to oral anticancer therapy [measured with a dedicated questionnaire 9 and/or Medication Event Monitoring System (MEMs)], quality of life (EORTC QLQ-C30 10), patient experience (PACIC score), tumor response, Progression Free Survival (PFS), Overall Survival (OS) (evaluated by investigators, using RECIST 1.1) and grade ≥ 3 toxicities (graded according to NCI-CTCAE v4.03 classification 8). We expected that patients in the intervention arm, by comparison with controls, would demonstrate significantly greater improvements in secondary outcomes measures. Demographic, socio-economic and clinical variables were assessed and considered in order to adjust the study results. Outcomes were collected by a clinical research associate at baseline, and each month until the end of the program (after 6 months), excepted for patient quality of life (at baseline, after 3 months and at the end of the program) and for patient experience (at the end of the program). Instruments used to collect data from participants, including primary and secondary outcomes, are detailed elsewhere (Gervès-Pinquier, C. et al. Impacts of a navigation program based on health information technology for patients receiving oral anticancer therapy: the CAPRI randomized controlled trial. BMC Health Serv Res 17, 133 (2017).)</p> <p>Economic evaluation. The economic evaluation of the CAPRI program adopted a societal perspective, assessing intervention, medical and non-medical costs. All resources used by patients included in the study were considered in the frame of a cost-effectiveness study. We expected that in comparison with usual care, the CAPRI intervention would result in cost-effective care with improvement in patients' adherence to oral anticancer therapy. Cost data were collected monthly using retrospective self-questionnaires for non-hospital costs. For hospital costs, medico-administrative data were collected. The resources used to be included in the cost-effectiveness study, and their value units are detailed elsewhere (Gervès-Pinquier, C. et al. Impacts of a navigation program based on health information technology for patients receiving oral anticancer therapy: the CAPRI randomized controlled trial. BMC Health Serv Res 17, 133 (2017).)</p> <p>Process evaluation. Data on access to, and use of, the web portal were extracted from the web portal records. In addition, focus groups with NNs were conducted monthly throughout the study. Lastly, semi-structured interviews with patients, relatives and healthcare professionals engaged in the program were conducted by the research team at the end of the trial.</p>