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original reports abstract

Phase III Randomized Controlled Trial of eRAPID eHealth Intervention During Chemotherapy

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PURPOSE Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice (eRAPID) is an online eHealth system for patients to self-report symptoms during cancer treatment. It provides automated severity-dependent patient advice guiding self-management or medical contact and displays the reports in electronic patient records. This trial evaluated the impact of eRAPID on symptom control, healthcare use, patient self-efficacy, and quality of life (QOL) in a patient population treated predominantly with curative intent.

METHODS Patients with colorectal, breast, or gynecological cancers commencing chemotherapy were randomly assigned to usual care (UC) or the addition of eRAPID (weekly online symptom reporting for 18 weeks). Primary outcome was symptom control (Functional Assessment of Cancer Therapy-General, Physical Well-Being subscale [FACT-PWB]) assessed at 6, 12, and 18 weeks. Secondary outcomes were processes of care (admissions or chemotherapy delivery), patient self-efficacy, and global quality of life (Functional Assessment of Cancer Therapy–General, EQ5D-VAS, and EORTC QLQ-C30 summary score). Multivariable mixed-effects repeated-measures models were used for analyses. Trial registration: ISRCTN88520246.

RESULTS Participants were 508 consenting patients (73.6% of 690 eligible) and 55 health professionals. eRAPID compared to UC showed improved physical well-being at 6 ($P = .028$) and 12 ($P = .039$) weeks and no difference at 18 weeks (primary end point) ($P = .69$). Fewer eRAPID patients (47%) had clinically meaningful physical well-being deterioration than UC (56%) at 12 weeks. Subgroup analysis found benefit in the non-metastatic group at 6 weeks ($P = .0426$), but not in metastatic disease. There were no differences for admissions or chemotherapy delivery. At 18 weeks, patients using eRAPID reported better self-efficacy ($P = .007$) and better health on EQ5D-VAS ($P = .009$). Average patient compliance with weekly symptom reporting was 64.7%. Patient adherence was associated with clinician's data use and improved FACT-PWB at 12 weeks.

CONCLUSION Real-time monitoring with electronic patient-reported outcomes improved physical well-being (6 and 12 weeks) and self-efficacy (18 weeks) in a patient population predominantly treated with curative intent, without increasing hospital workload.

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ASSOCIATED CONTENT

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INTRODUCTION

Patients with cancer experience a range of physical symptoms, which can significantly affect their quality of life (QOL). The symptoms can be due to the cancer itself, treatment side effects (reported as adverse events in clinical trials), or coexisting conditions. Chemotherapy and other systemic anticancer treatments cause symptomatic acute adverse events that affect treatment delivery and can be severe or life-threatening requiring emergency hospitalisations.[1,2] Better monitoring and management of adverse events can improve treatment delivery and reduce patients' physical distress. Here, we refer to symptoms as an umbrella term encompassing symptoms because of the cancer or coexisting conditions (disease-related symptoms) and adverse events because of treatment (treatment-related symptoms).

The use of standardized questionnaires in oncology practice (known as patient-reported outcome measures [PROMs]) for symptom monitoring can improve symptom management.[3,4] Systematic reviews of trials evaluating PROMs showed improved physician-patient communication, symptom control, supportive care, and patient satisfaction.[5,6] The reviews recommended further studies in patient safety, patient adherence, clinician burden, and healthcare implementation. Recent randomized trials in advanced cancers, using electronic or web-based symptom reporting, confirmed improved symptom control, better survival, and reduced healthcare usage.[7-9] Fewer data are available on early cancers, treated with curative intent.[10,11] Self-management education interventions in cancer can also reduce symptom burden and improve QOL.[12] A combined

CONTEXT

Key Objective

Can we control better treatment- and disease-related symptoms during chemotherapy by introducing online monitoring with patient-reported outcome measures, uniquely combined with automated algorithm-driven severity-dependent patient advice?

Knowledge Generated

In a patient population treated predominantly with curative intent, online monitoring plus immediate patient advice improved physical well-being early during the chemotherapy (6 and 12 weeks), without increasing healthcare utilization. Patients reported better self-efficacy and confidence in self-managing their symptoms.

Relevance

These findings extend the evidence of benefits from online symptom monitoring in advanced cancers to the curative treatment setting. This approach offers an alternative model of care delivery during curative chemotherapy, supporting patients with cancer experiencing mild to moderate symptoms and potentially reducing hospital visits. The COVID-19 pandemic has precipitated a shift to remote technology-enabled care. Online symptom monitoring is a feasible strategy to be implemented in routine cancer care.

approach of symptom self-reporting plus tailored self-care advice may reduce symptom distress.[13]

The Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice (eRAPID) system was designed to combine secure online symptom self-reporting with an innovative bespoke clinical algorithm, generating automated severity-based advice to patients to support self-management or prompt hospital contact. Immediate integration of the self-reports in electronic patient records (EPRs) facilitated clinical use.[14]

This trial aimed to evaluate the potential benefits of eRAPID for patients and clinicians when added to usual care (UC) during chemotherapy in a population of predominantly early-stage cancer treated with curative intent. The hypothesis was that adding eRAPID would improve symptom control, reduce hospital contacts or emergency admissions, and increase patient self-efficacy in managing side effects.

METHODS

Study Design and Participants

Patients initiating systemic treatment (chemotherapy with or without targeted therapies) for colorectal, breast, or gynecological cancers at Leeds Cancer Centre (United Kingdom) were enrolled in a prospective, randomized two-arm parallel group study over 18 weeks. An internal pilot assessing intervention feasibility met recruitment and attrition targets. The study was approved by the National Research Ethics Service Leeds East Committee (14/YH/1066) (trial registration: ISRCTN88520246 [September 11, 2014]).

Trial procedures are described in the Protocol (online only).[15] Patients were eligible if they planned to receive chemotherapy for colorectal, breast, or gynecological cancers, had internet access at home or via mobile devices, were fluent in English, did not participate in clinical trials with PROMS, and did not exhibit cognitive dysfunction. Patients were approached by their clinician. Consenting patients were randomly assigned 1:1 to UC or intervention (eRAPID added to UC) stratified by cancer site, sex, and previous chemotherapy in random permuted blocks (variable block sizes 4, 6, and 8) (Data Supplement, online only). Random assignment of clinicians was not possible because of the established team structures; therefore, staff saw patients in both arms. Random assignment was performed by University of Leeds Clinical Trials Research Unit via an automated 24-hour system.

Procedures

Usual care. Patients saw an oncologist to decide commencement of systemic treatment and received verbal and written information on treatment-related symptoms. During treatment, patients were regularly assessed by oncologists or nurses in clinics or by telephone (approximately 50% of occasions) for toxicity and to prescribe next treatment. Treatment could be modified or delayed depending on symptom severity. Medical problems during chemotherapy were managed via dedicated acute oncology services. Patients contacted the hospital via a 24/7 emergency hotline. The reported symptoms were documented on an acute triage form.[16] Acute admissions were directly to oncology, bypassing emergency rooms.

Intervention. eRAPID was added to UC. Participants completed online symptom questions from home, using their own PC or mobile device, over 18 weeks (at least weekly plus when having symptoms). Reminders were sent weekly via text or e-mail.[15] Participants received immediate severity-dependent advice on symptom management or a prompt to contact the hospital. The symptom reports were displayed in real time in EPR. Alerts for severe symptom reports were sent to each clinical team shared e-mail address, monitored by nurses (Data Supplement).

The symptom questions and advice were developed using participatory design involving patients and clinicians.[14,17]

Working with each cancer team, the key treatment-related symptoms were selected, severity levels agreed, and the clinical algorithm for patient advice and e-mail alerts developed[18] (Data Supplement).

We educated clinicians how to access patients' self-reported symptoms within the EPR and encouraged them to discuss the information when reviewing patients.[19] No recommendations for specific actions were made. Training included presentations at team meetings plus individual ad hoc training in clinics. Later, an eLearning program was developed accessible via a hyperlink from the EPR.

Outcome Measures

Symptom reporting by eRAPID patients was entirely online; however, all outcome PROMs at 6, 12, and 18 weeks were completed in both arms on paper to ensure equality in mode of outcomes assessment. Baseline questionnaires were completed prior to random assignment.

Primary outcome was symptom control measured by using the Functional Assessment of Cancer Therapy Scale-General Physical Well-Being subscale (FACT-PWB, scores 0-28, high scores = better symptoms) measured at 6, 12, and 18 weeks after baseline.[20] The seven items cover common symptoms during chemotherapy and their impact on patients' functioning (lack of energy, pain, nausea, bothered by side effects, feeling ill, spending time in bed, and not meeting family needs). A cumulative effect of the intervention was anticipated, and hence, a timepoint of 18 weeks (end of chemotherapy) was selected as the primary end point, with 6 and 12 weeks being secondary end points.

Main secondary outcomes were impacts on hospital services (process of care measures) and cost-effectiveness. Data on process of care were downloaded from the EPR on acute admissions, patient-initiated calls to the hotline, other hospital calls, and cancer treatment delivery (delays, dose modifications, and interruptions).

Secondary patient-reported outcomes included measures of self-efficacy and health-related QOL (see Table 1 for instrument details). Self-efficacy measures were included to evaluate the hypothesized impact of the intervention on patient education, expecting that the tailored information and advice would increase their confidence to manage the treatment-related symptoms.

Symptom reports were downloaded from the online software (completions, symptom severity, and activated algorithms). Clinicians completed a feedback form after each consultation with eRAPID patients.[9] A qualitative substudy, to be reported separately, explored patient and staff experiences.

Statistical Analysis

Five hundred and four patients were needed to detect a 2-point change in FACT-PWB at 18 weeks (small-medium effect size 0.3), with 80% power and 5% significance, allowing for 30% attrition.[27]

Patient-Reported Outcomes

For the primary outcome of FACT-PWB, a multivariable mixed-effects repeated-measures model (using unstructured correlation) was used to compare the differences in FACT-PWB scores between the arms over time. The model was adjusted for stratification factors (cancer site, sex, and previous chemotherapy), time, study arm, arm-time interaction, baseline FACT-PWB, and age as fixed effects. Participant and participant*time interaction were random effects. Time was modeled as discrete, adjusted differences in least squares means at 6, 12, and 18 weeks were summarized.[28] A planned exploratory subgroup analysis was performed for patients with metastatic and early-stage disease. Similar models were fitted for all secondary PROMs. Multiple imputation using chained equations was used for missing FACT-PWB scores, using predictive mean matching (Data Supplement). The unimputed observed data were modeled as a sensitivity analysis.

To aid the clinical interpretation of the results, a post hoc descriptive responder analysis of FACT-PWB change scores at individual level was performed.[29,30] FACT-PWB change scores of 2-points were considered a minimal clinically important difference.[27] The change from baseline to follow-up scores for each participant was categorized as follows: improved (change score ≥ 2), deteriorated (change score ≤ -2), and stable (-1.9 to 1.9). Proportions of patients in each category were calculated.

Process of care outcomes. A negative binomial model was fitted to process measures (admissions and hospital calls) because of overdispersion.[31]

Adherence to eRAPID intervention (subgroup analysis of the intervention arm). We examined patient adherence by (1) proportions of participants completing self-reports per protocol once a week (adjusting for withdrawals or deaths) and (2) the total number of reports per participant, including extra completions. Factors associated with participant adherence and correlations with primary outcome FACT-PWB were examined in post hoc regression analyses (Data Supplement).

Analyses used SAS version 9 on intention-to-treat population. No adjustments were made for multiple testing.

RESULTS

Between January 22, 2015, and June 11, 2018, 782 patients were identified. Ninety-two were ineligible, 182 of 690 fully eligible patients declined participation (26.4%), and 508 of 690 patients (73.6%) consented and were randomly assigned to eRAPID (n = 256) or UC (n = 252) (Fig 1). Forty-nine participants withdrew, 37 of 256 (14.5%) from eRAPID and 12 of 252 (4.8%) from UC. Ten patients died during the trial (5/arm).

Fifty-five clinicians participated, 19 saw > 10 eRAPID patients, and 36 were oncologists on training rotations or

TABLE 1. List of Secondary Outcomes: Patient-Reported Outcome Measures and Measures of Intervention Adherence

Outcome	Instrument or Method	Item Information or Data Collection	Score Range	Interpretation of Higher Score	Time Points
Patient self-efficacy					
Self-management	Self-Efficacy Scale for managing chronic disease questionnaire[21] General measure that covers symptom control, role function, emotional functioning, and communicating with physicians.	6 items with 10-point question response scale from 1 to 10 (not at all confident-totally confident).	0-10	Better outcome	Baseline and 18 weeks
Coping with cancer	CBI-B questionnaire[22] Cancer-specific scale, includes coping with physical changes, asking questions, and expressing feelings about cancer	14 items used from the 33-item measure. Response scale from 1 (not at all confident) to 9 (totally confident).	14-126	Better outcome	Baseline and 18 weeks
Patient engagement in their own healthcare	Patient Activation Measure[23] Assesses general patient engagement with their healthcare. It was included for a PhD project as a predictor of adherence.	13 items 5-Point response scale from 1 (disagree strongly) to 5 (strongly agree).	0-100	Better outcome	Baseline, 18 weeks, and 12 months[a]
Cost-effectiveness measures	EQ-5D-5L[24]	5 items 5-point response scale from no problems to extreme problems.	Utility score 0-1	Better outcome	Baseline, 6, 12, and 18 weeks, and 12 months[a]
	QLU-C10D-multiattribute utility measure[25] [5] based on EORTC QLQ-C30 (symptom and functional scales)[26,b]	30 items 4-point response scale from 1 (not at all) to 4 (very much).	0-100	Better outcome	Baseline, 6, 12, and 18 weeks, and 12 months[a]
Health-related QOL					
Cancer-related QOL	FACT-G questionnaire (physical, social, emotional, and functional well-being scales)[20]	27 items 5-point response scale from 0 (not at all) to 4 (very much).	0-108	Better outcome	Baseline, 6, 12, and 18 weeks, and 12 months[a]
Self-rated overall health	EQ-5D VAS[24]	Vertical 100-point response scale From 0 (worst health you can imagine) to 100 (best health you can imagine).	0-100	Better outcome	Baseline, 6, 12, and 18 weeks, and 12 months[a]
Cancer-related QOL	EORTC QLQ-C30[26,b]	30 items 4-Point response scale from 1 (not at all) to 4 (very much). Summary score analyzed	0-100	Better outcome	Baseline, 6, 12, and 18 weeks, and 12 months[a]
Adherence to eRAPID intervention or fidelity	Patient adherence to online reporting.	Downloaded from the online software (QTool).	0%-100%		During the 18-week study period
	Type, frequency, and severity of self-reported symptoms.	Downloaded from the online software (QTool).	0%-100%		During the 18-week study period
	Frequency of activated clinical algorithms and alerts.	Downloaded from the online software (QTool).	0%-100%		During the 18-week study period
	Clinicians' use of eRAPID during consultations Clinician Feedback Form[9]	Including: Did you look at the patient's eRAPID symptom information before or during the consultation? Did you use the eRAPID symptom information in the clinic discussion?	5-point scale from very much to not at all		At 3, 6, 9, 12, and 18 weeks (if the patient had a hospital visit)

Abbreviations: CBI-B, Cancer Behavior Inventory-Brief; eRAPID, Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice; FACT-G, Functional Assessment of Cancer Therapy–General; QOL, quality of life.

[a]12-month data were collected for extended cost-effectiveness analysis to be presented separately.

[b]Collected in the main trial only.

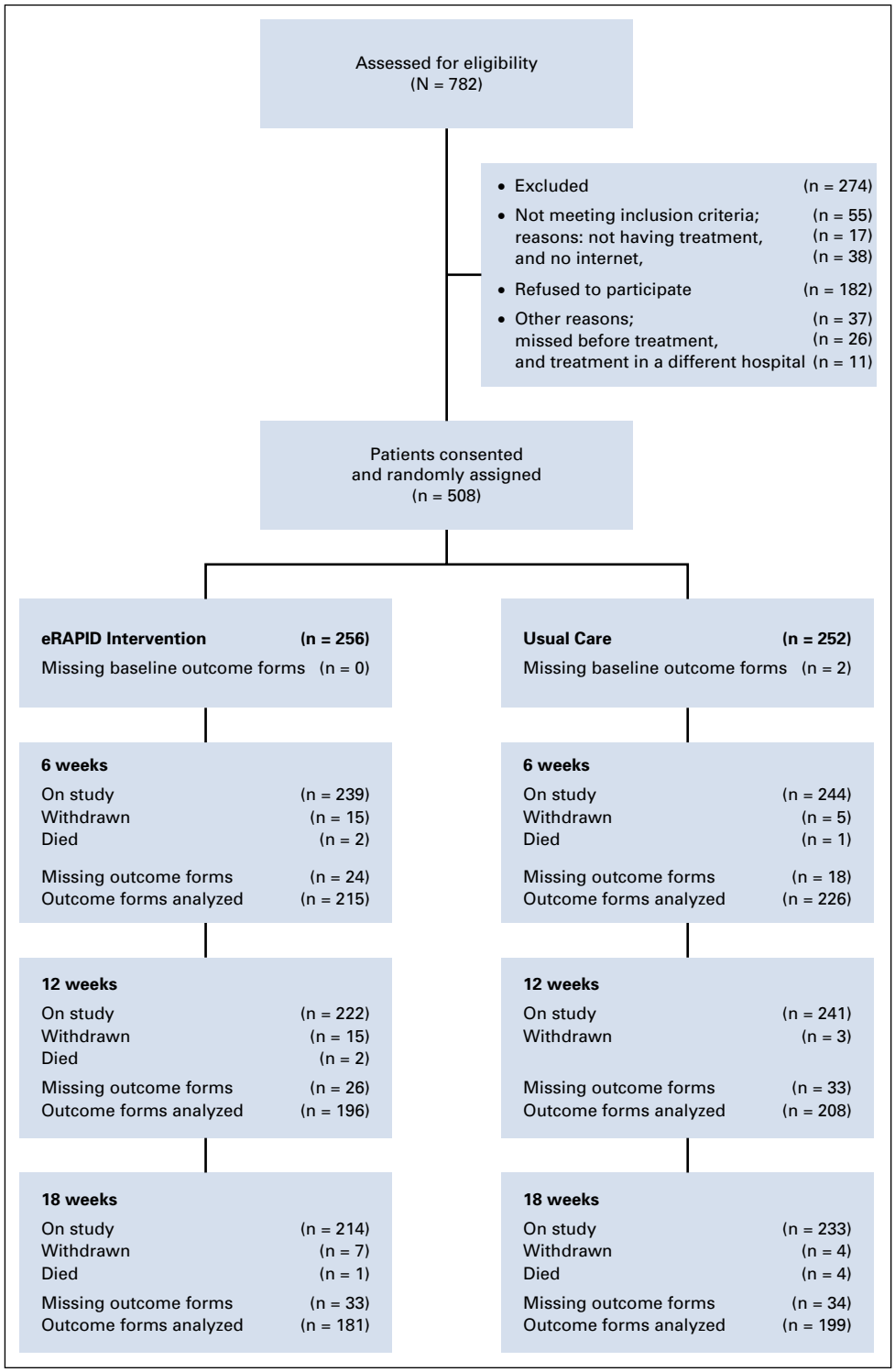


FIG 1. CONSORT diagram. eRAPID, Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice.

temporary staff seeing between one and eight patients assigned to eRAPID (median = 2).

Table 2 presents patients' baseline demographic and clinical characteristics. The majority of patients (n = 317/508, 62.4%) had early-stage cancer treated with curative intent: breast (220 of 317, 69.4%), colorectal (80 of 317, 25.2%), and gynecological (17 of 317, 5.4%). The remainder of the patients (n = 191/508, 37.6%) had metastatic cancers: colorectal (89 of 191, 46.6%), gynecological (89 of 191, 46.6%), and breast (13 of 191, 6.8%).

TABLE 2. Baseline Patient Characteristics

Patient Characteristic	eRAPID Intervention (n = 256)	UC (n = 252)	Total (N = 508)
Age in years			
Mean (SD)	55.9 (12.2)	56.0 (11.3)	56.0 (11.8)
Median (range)	56.0 (22.0-86.0)	56.0 (18.0-79.0)	56.0 (18.0-86.0)
Sex			
Male	51 (19.9%)	51 (20.2%)	102 (20.1%)
Female	205 (80.1%)	201 (79.8%)	406 (79.9%)
Education level			
Basic school education	86 (33.6%)	81 (32.1%)	167 (32.9%)
Beyond basic school education	60 (23.4%)	53 (21.0%)	113 (22.2%)
University or professional education	103 (40.2%)	108 (42.9%)	211 (41.5%)
Missing	7 (2.7%)	10 (4.0%)	17 (3.3%)
FACT-FWB baseline			
Mean (SD)	23.4 (4.54)	23.2 (4.61)	23.2 (4.57)
Median (range)	25.0 (2.33-28.0)	25.0 (5.0-28.0)	25.0 (2.33-28.0)
Clinical characteristics			
Cancer site			
Breast	117 (45.7%)	116 (46.0%)	233 (45.9%)
Gynecological	53 (20.7%)	53 (21.0%)	106 (20.9%)
Colorectal	86 (33.6%)	83 (32.9%)	169 (33.3%)
Previous chemotherapy			
Yes	55 (21.5%)	51 (20.2%)	106 (20.9%)
Disease stage			
Primary or local disease	161 (62.9%)	156 (61.9%)	317 (62.4%)[a]
Metastatic	95 (37.1%)	96 (38.1%)	191 (37.6%)
Chemotherapy intention			
Adjuvant or neoadjuvant	169 (66.0%)	168 (66.7%)	337 (66.3%)[a]
Palliative	87 (34.0%)	84 (33.3%)	171 (33.7%)
Number of baseline comorbidities[b]			
0	128 (50.0%)	139 (55.2%)	267 (52.6%)
1	86 (33.6%)	71 (28.2%)	157 (30.9%)
2	35 (13.7%)	31 (12.3%)	66 (13.0%)
3 or more	7 (2.7%)	11 (4.4%)	18 (3.5%)
Most common comorbidities			
Cardiovascular—hypertension	52 (20.3%)	49 (19.4%)	101 (19.9%)
Respiratory—asthma	21 (8.2%)	17 (6.7%)	38 (7.5%)
Endocrine—diabetes	19 (7.4%)	18 (7.1%)	37 (7.3%)
Endocrine—hypothyroidism	14 (5.5%)	10 (4.0%)	24 (4.7%)
Cardiovascular—previous myocardial infarction	10 (3.9%)	5 (2.0%)	15 (3.0%)
Previous malignancy	23 (9.0%)	25 (9.9%)	48 (9.4%)

Abbreviations: eRAPID, Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice; SD, standard deviation; UC, usual care.

[a]n = 20 patients with metastatic disease had (neo-)adjuvant chemotherapy: n = 16 colorectal patients with solitary liver metastasis, 3 patients with adjuvant gynecological cancers (postsurgery FIGO 3A), and 1 patient with neoadjuvant breast cancer (stage IV supraclavicular nodal disease).

[b]Measured by ACE27. (Kallogjeri D, et al: Comparison of scoring methods for ACE-27: Simpler is better. J Geriatr Oncol 3:238-245, 2012).

Primary Outcome Physical Well-Being

Significant positive effects of eRAPID were observed at 6 ($P = .0280$) and 12 weeks ($P = .0395$), but there was no significant difference at the primary end point of 18 weeks ($P = .6992$) (Table 3, Fig 2A). Higher baseline FACT-PWB scores were associated with better physical well-being ($P < .0001$). Sensitivity analysis on the unimputed data yielded similar estimated differences (Data Supplement).

The preplanned exploratory subgroup analysis by disease stage showed no evidence of eRAPID effect in the metastatic subgroup, which had only 191 patients. In the early-stage subgroup, there was a positive effect for eRAPID at 6 weeks ($P = .0426$) and no effect at 12 weeks ($P = .0550$) or 18 weeks ($P = .9955$) (Data Supplement).

In the responder analysis, at 6 and 12 weeks a smaller proportion of eRAPID patients had physical well-being deterioration (Fig 2B). For example, at 12 weeks, 47% of patients assigned to eRAPID had deterioration greater than minimal clinically important difference versus 56% in UC or eRAPID prevented deterioration in 9% of patients. More eRAPID patients maintained stable physical well-being (39% *v* 32%).

Process of Care

No between-arm differences were found for chemotherapy delivery, hospital admissions, acute oncology assessments, or emergency hotline calls (Table 4, Data Supplement).

Patient Self-Efficacy

The Self-Efficacy for Managing Chronic Disease scale (measured at 18 weeks) showed an increase in self-efficacy in the eRAPID arm ($P = .0073$) (Table 5, Data Supplement). No impact was found for Cancer Behavior Inventory-Brief or Patient Activation Measure.

Health-Related QOL (Table 5)

On the EQ-VAS scale, eRAPID patients reported better overall health at 18 weeks ($P = .0095$) and 12 weeks ($P = .0302$), but no difference at 6 weeks ($P = .3773$). No between-group differences were found for Functional Assessment of Cancer Therapy-General (FACT-G) and EQ-5D-5L utility scores at 6, 12, and 18 weeks. EORTC QLQ-C30 summary score showed an increase in symptom control only at 12 weeks in eRAPID arm ($P = .0111$) and no difference at 6 and 18 weeks. These are results from secondary analyses on observed data and should be interpreted with caution.

Adherence to eRAPID Intervention

Average adherence to weekly completions was 64.6% (71.8% [184/256] week 1; 58.1% [125/215] week 18). Per participant completions were 0-117 reports, mean 12.7 (SD 12.6) and median 14.0 (Data Supplement).

A total of 3,314 online reports were completed, reporting 18,867 individual symptoms: severe 323 (1.7%) and

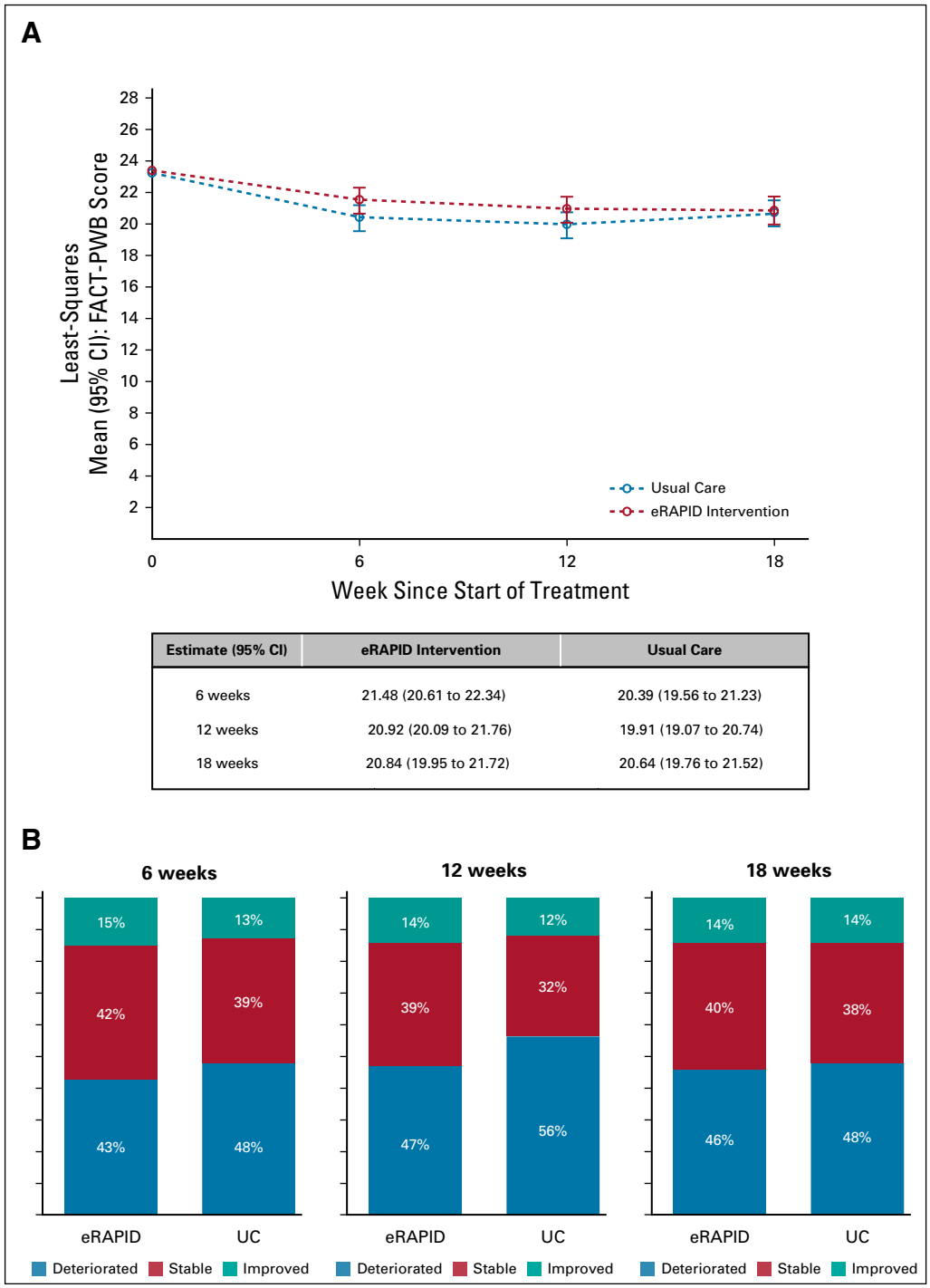
TABLE 3. Multivariable Multilevel Mixed-Effects Repeated-Measures Model for FACT-PWB Score at 6, 12, and 18 Weeks and Adjusted Difference in Least Squares Mean FACT-PWB Scores (N = 508*25)—Imputed Data

Adjusted Difference in Least Squares Mean FACT-PWB Score at Each Time Point	DF	Difference of Least Squares Means	SE	95% CI	*t* Value	*Pr* > |t|
Intervention effect (eRAPID *v* UC) at 6 weeks (secondary end point)	3,169.9	1.08	0.49	0.12 to 2.05	2.20	.0280
Intervention effect (eRAPID *v* UC) at 12 weeks (secondary end point)	527.68	1.01	0.49	0.05 to 1.98	2.06	.0395
Intervention effect (eRAPID *v* UC) at 18 weeks (primary end point)	650.37	0.20	0.51	−0.81 to 1.20	0.39	.6992

Model Parameter	DF	Parameter Estimates	SE	95% CI	*t* Value	*P*
Intercept	720.22	7.17	1.49	4.26 to 10.09	4.83	< .0001
Intervention effect eRAPID *v* UC (at 6 weeks)[a]	3,169.9	1.08	0.49	0.12 to 2.05	2.20	.0280
Time: week 12 *v* week 6	478.1	−0.49	0.39	−1.26 to 0.28	−1.24	.2154
Time: week 18 *v* week 6	568.86	0.24	0.41	−0.56 to 1.05	0.59	.5539
Time * intervention: eRAPID *v* UC at 12 weeks compared with 6 weeks	424.66	−0.07	0.56	−1.16 to 1.03	−0.12	.9034
Time * intervention: eRAPID *v* UC at 18 weeks compared with 6 weeks	340.69	−0.88	0.60	−2.07 to 0.30	−1.47	.1435
Baseline PWB score	433.2	0.45	0.05	0.35 to 0.54	9.35	< .0001
Age at study entry	1,341.3	0.02	0.02	−0.01 to 0.06	1.25	.2113
Cancer site: gynecological *v* breast	598.7	1.77	0.58	0.62 to 2.91	3.02	.0026
Cancer site: colorectal *v* breast	665.37	2.12	0.62	0.91 to 3.33	3.45	.0006
Sex: male *v* female	903.27	0.84	0.67	−0.48 to 2.16	1.25	.2101
Previous chemotherapy: yes *v* no	1,768.2	−0.34	0.51	−1.34 to 0.66	−0.67	.5046

Abbreviations: eRAPID, Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice; UC, usual care.

[a]When time is modeled as a discrete variable and baseline is controlled for, it is not possible to estimate change overtime compared with baseline timepoint. A limitation of using imputed data sets is the inability to robustly combine type III global effects.



Estimate (95% CI)	eRAPID Intervention	Usual Care
6 weeks	21.48 (20.61 to 22.34)	20.39 (19.56 to 21.23)
12 weeks	20.92 (20.09 to 21.76)	19.91 (19.07 to 20.74)
18 weeks	20.84 (19.95 to 21.72)	20.64 (19.76 to 21.52)

FIG 2. Primary outcome results and FACT-PWB scores. (A) Repeated measures model for imputed data: Least squares mean FACT-PWB score. (B) All participants. Responder analysis of FACT-PWB change scores at individual level (imputed data). Proportion of patients with change score deterioration (≤ -2) and stability or improvement (≥ 2). eRAPID, Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice; FACT-PWB, Functional Assessment of Cancer Therapy–General, Physical Well-being scale; UC, usual care.

moderately severe 4,342 (23.0%). The most common moderate or severe symptoms were fatigue, physical activity limitations, pain, anorexia, and nausea (Data Supplement).

The clinical algorithms activated emergency alerts to the nursing team in 29 of 3,314 cases (0.9%) and serious symptoms not requiring immediate medical attention or ≥ 3 moderate symptoms were reported in 461 of 3,314

TABLE 4. Process of Care Measures

Process of Care Measures	eRAPID Intervention (n = 256), Number (%)	UC (n = 252), Number (%)	OR (95% CI)[a]	*P*
Chemotherapy delivery[b]				
Patients with delays to chemotherapy	102/256 (39.8)	104/252 (41.3)	0.93 (0.64 to 1.35)	.7013
Patients with dose reductions	100/256 (39.1)	106/252 (42.1)	0.86 (0.58 to 1.26)	.4356
Patients with chemotherapy drug changes	35/256 (13.7)	29/252 (11.5)	1.23 (0.72 to 2.11)	.4470
Chemotherapy discontinuation	51/256 (19.9)	43/252 (17.1)	1.22 (0.76 to 1.97)	.4120
	eRAPID Intervention (n = 256), Number (%)	**UC (n = 252), Number (%)**	**IRR (95% CI)[c]**	***P***
Acute admissions				
Total number of admissions	133	121	1.14 (0.84 to 1.53)	.4003
Number of patients who had an admission	86/256 (33.6)	84/252 (33.3)		
Number with suspected sepsis	59/86 (68.6)	44/84 (52.4)		
Calls to the emergency hotline				
Total number of calls	518	527	1.05 (0.84 to 1.31)	.6516
Number of patients who called	152/256 (59.4)	142/252 (56.3)		
Number assessed on acute oncology ward	113/256 (44.1)	109/252 (43.3)		
Assessment leading to admission	39/113 (34.5)	37/109 (33.9)		

Abbreviations: eRAPID, Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice; IRR, incidence rate ratio; OR, odds ratio; UC, usual care.

[a]OR and *P* value from adjusted multivariable logistic regression with covariates age, sex, previous chemotherapy, and cancer site.

[b]Main reasons for chemotherapy modifications were adverse events. Patients with breast cancer on (neo-)adjuvant treatments had less chemotherapy modifications than those with colorectal and gynecological cancers.

[c]IRR and *P* value from adjusted multivariable negative binomial regression analysis.

occasions (13.9%). The majority of self-reported symptoms triggered self-management advice: 2,714 of 3,314 (81.9%), and 110 of 3,314 (3.3%) reported no problems. The website was accessed at least once by 123 of 256 (48%) of patients (Data Supplement).

Clinicians completed expected feedback forms (n = 787/1,314, 59.9%). They reviewed reports on 641 of 787 occasions (81.4%). The post hoc analysis showed positive associations between patient adherence and clinicians' use of eRAPID ($P = .0227$) and higher baseline FACT-PWB scores ($P = .0406$) (Data Supplement).

Patients with high adherence had better physical well-being at 12 weeks ($P = .0055$), but not at 6 and 18 weeks (Data Supplement).

DISCUSSION

Online symptom monitoring with severity-tailored patient advice via the eRAPID system improved physical well-being and self-efficacy in a population of patients predominantly treated with curative intent, without increasing hospital workload. Previous research has demonstrated clinical benefits of ePROM monitoring in highly symptomatic patients with metastatic cancers,[7,8] while evidence has been limited in the curative setting, where patients are relatively asymptomatic at baseline and receive toxic therapy transiently. The goal of symptom monitoring is to identify and manage treatment-related symptoms early to enable treatment delivery. Previous studies have included early stage cancers (predominantly breast) but had smaller numbers and no stage-specific analysis.[10,11,13,33,34] In our trial, most patients were treated with curative intent (> 60%). Clinically meaningful benefits in patients' physical well-being were seen at the early period of the toxic treatment (weeks 6 and 12), when it is expected to see challenges controlling side effects. Symptoms stabilized by week 18 in both arms, when patients reach a steady state of supportive medications or chemotherapy dose adjustments. The findings of this trial extend the evidence from the metastatic setting, demonstrating benefits on symptom control (measured by FACT-PWB) during curative (neo)adjuvant chemotherapy, particularly early in the course of treatment.

The results supported the secondary hypothesis that eRAPID increased patient self-efficacy to manage treatment-related symptoms. We believe that this is the first trial to provide immediate, algorithm-driven patient self-management advice for mild or moderate symptoms. A systematic review of electronic systems to monitor or manage treatment-related symptoms identified two smaller studies evaluating self-efficacy.[35] Our results provide the most robust evidence so far that targeted patient education or advice during treatment supported patient self-efficacy.[36]

TABLE 5. Secondary Outcomes—Self-Efficacy (Prespecified Hypothesis) and Health-Related Quality of Life (Exploratory Analysis)

Secondary Patient-Reported Outcome Measures	eRAPID Intervention (n = 256), Mean (SD)	UC (n = 252), Mean (SD)	Adj. Differences in Least Squares Means (95% CI) eRAPID *v* UC	*P*
6-item self-efficacy scale (score range 1-10, high score = high self-efficacy)[a]				
Baseline	6.85 (1.90) n = 252	6.74 (1.94) n = 247		
Week 18	7.55 (1.83) n = 186	6.96 (2.07) n = 196	0.48 (0.13 to 0.83)	.0073[b]
Cancer Behavior Inventory (14-item score range 14-126, higher scores = greater coping efficacy)				
Baseline	99.6 (18.4) n[c] = 239	97.8 (19.9) n = 233		
Week 18	102.0 (18.4) n = 181	97.5 (20.7) n = 189	2.83 (−0.53 to 6.18)	.0986
Patient activation measure (score range 0-100 higher scores = higher patient activation)				
Baseline	66.7 (14.6) n = 251	66.1 (16.1) n = 243		
Week 18	64.8 (14.1) n = 182	63.5 (15.7) n = 197	0.30 (−2.34 to 2.94)	.8249
EQ5D-VAS (score range 0-100, 0 = worst possible health; 100 = best possible health)[d]				
Baseline	76.3 (18.1) n = 255	75.2 (18.6) n = 248		
Week 6	74.0 (17.3) n = 213	71.4 (19.5) n = 225	1.36 (−1.66 to 4.39)	.3773
Week 12	74.0 (16.6) n = 199	68.9 (19.8) n = 209	3.50 (0.35 to 6.66)	.0302
Week 18	75.6 (18.0) n = 184	68.7 (20.4) n = 199	4.48 (1.11 to 7.86)	.0095
EORTC QLQ-C30 summary score (range 0-100, high = better)[d]				
Baseline	79.2 (15.6) n = 207	79.9 (15.0) n = 205		
Week 6	77.7 (13.0) n = 170	75.3 (16.8) n = 185	1.05 (−1.62 to 3.73)	.4420
Week 12	76.3 (13.3) n = 160	71.7 (16.7) n = 168	3.62 (0.84 to 6.40)	.0111
Week 18	76.0 (15.4) n = 148	72.1 (17.9) n = 164	1.91 (−1.17 to 5.00)	.2255
FACT-G (score range 0-108, high = better well-being)[d]				
Baseline	82.9 (14.1) n = 251	81.9 (14.1) n = 241		
Week 6	80.0 (15.6) n = 209	76.6 (15.7) n = 226	1.46 (−0.88 to 3.80)	.2218
Week 12	79.2 (15.0) n = 191	74.3 (16.1) n = 204	2.19 (−0.15 to 4.54)	.0679
Week 18	78.8 (16.2) n = 181	75.7 (16.6) n = 200	0.96 (−1.64 to 3.55)	.4712

(continued on following page)

TABLE 5. Secondary Outcomes—Self-Efficacy (Prespecified Hypothesis) and Health-Related Quality of Life (Exploratory Analysis) (continued)

Secondary Patient-Reported Outcome Measures	eRAPID Intervention (n = 256), Mean (SD)	UC (n = 252), Mean (SD)	Adj. Differences in Least Squares Means (95% CI) eRAPID *v* UC	*P*
Eq. 5D5L utility measure (utility score range 0-1 high = better)[d]				
Baseline	0.83 (0.15) n = 250	0.82 (0.15) n = 248		
Week 6	0.85 (0.13) n = 211	0.82 (0.17) n = 225	0.02 (−0.01 to 0.04)	.1249
Week 12	0.83 (0.15) n = 198	0.80 (0.16) n = 209	0.01 (−0.01 to 0.04)	.3230
Week 18	0.82 (0.15) n = 184	0.79 (0.17) n = 197	0.01 (−0.01 to 0.04)	.3066

Abbreviations: eRAPID, Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice; FACT-G, Functional Assessment of Cancer Therapy–General; SD, standard deviation; UC, usual care.

[a]Multivariable linear model (observed data).

[b]Responder analysis a larger proportion of eRAPID patients (67 of 256, 26.2%) had an improvement of over ½ standard deviation in self-efficacy (defined as clinically meaningful[32]) than UC (53 of 252, 21.0%).

[c]Number of completed questionnaires. Reduced sample for Cancer Behavior Inventory-Brief (14 items), as the scoring guide of Cancer Behavior Inventory-Brief does not provide instructions on dealing with missing items.

[d]Multivariable mixed-effects repeated-measures model (observed data).

We captured detailed metrics that are key to understanding the results and feasibility for implementation. Participants who benefitted most were those with mild or moderate symptom burden at baseline and early during treatment, receiving self-management advice, who adhered to > 70% of the weekly reports and whose clinicians explicitly discussed the self-reports. For the first time, using quantitative methods, we showed that the engagement of clinicians during routine encounters was important. The immediate advice increased patient confidence in managing the mild or moderate treatment-related symptoms, which can significantly affect patients' QOL and treatment adherence.[37] eRAPID can provide an alternative model of care to support this larger group of early stage cancers, facilitating clinical management.

The target population was heterogenous (all stages of breast, colorectal, and gynecological cancers), which is a strength, enhancing generalizability of the results. However, in the smaller group of patients with metastatic disease (n = 191), we did not observe a significant intervention effect. These results are at odds with international trials (eg, in the United States and France), which showed patient benefit in advanced cancers improving symptom management, QOL, and survival.[7,8,38] Our analysis by disease stage was preplanned but exploratory, and the metastatic subgroup was underpowered to detect smaller differences. Also, our trial was only during treatment (18 weeks/4.5 months) in comparison with 6 to 24 months.[7,8] Longer monitoring beyond treatment in metastatic disease captures disease recurrence symptoms and allows earlier initiation of further treatment, leading to improvements in QOL and survival.

Our trial collected robust data on emergency admissions and hospital contacts, showing no increase of hospital workload, no differences in chemotherapy delivery, low level of alerts (< 1%), and no compromise of patient safety. Other trials and real-world data showed reductions in emergency room visits and hospitalisations.[7,39] The lack of effect on treatment disruptions and emergency admissions could be due to our predominant population of patients treated with curative intent, experiencing mild or moderate symptoms not needing treatment modifications. The analysis of hospital workload showed that improved patients' physical well-being in the curative treatment setting can be achieved in a cost-effective way. These results provide reassurance to clinicians and help overcome the most significant implementation barrier, namely, concerns of increased workload.

This trial should be interpreted in the context of several limitations. Patient adherence to weekly reporting (average 64.7%) is comparable with other studies (73% reported by Basch et al[7] and 75% by Denis et al[38]). The eRAPID intervention focused only on online home reporting, without in-clinic reporting. Supplementing online home reporting with in-clinic reporting (similar to Basch et al[7]) would widen patient eligibility and increase engagement.

The chosen primary outcome FACT-PWB scale included a combination of key treatment-related symptoms and functional items, and therefore, there was a possibility that improvements in symptoms might be diluted by limited changes in functions. A granular symptom-based questionnaire, capturing all 12 core cancer symptoms, may have been a better outcome measure.[40]

This was a single center trial, but it was a large pragmatic study in a tertiary cancer center, screening all patients considered for chemotherapy and achieving good recruitment (73.5%) and retention rate. The range of patients, 18-86 years of age, supports the feasibility of this approach among older adults with cancer. We enrolled approximately 50% of the total chemotherapy population and engaged over 50 clinicians (oncologists, trainees, and nurses).

Engaging all clinicians in a parallel-arm randomized trial introduced a contamination bias. As clinicians saw patients in both arms, the symptom reports may have sensitized providers to interact differently and conduct in-depth symptom assessments with UC patients.[9] An alternative effect was also observed: 36 of 55 clinicians saw only a few patients assigned to eRAPID and needed frequent reminders to review and use the reports during encounters. In both scenarios, the direction of the contamination bias is toward reducing the intervention effect and could potentially explain the relatively limited impact of eRAPID.

The COVID-19 pandemic precipitated a rapid shift to remote technology-enabled care, reducing hospital visits. The American Medical Association encouraged the use of technology.[41] The need to speed up the adoption of e-PROMs and eHealth interventions for safe delivery of cancer care is highlighted.[42,43] Ongoing multicenter trials, addressing a similar eHealth approach, would contribute to the growing evidence on eHealth innovations in cancer care.[44] Within the existing evidence on online symptom monitoring, our findings are a step toward defining the parameters within which this approach may provide more versus less benefits, suggesting where future research and clinical use should focus. The eRAPID approach offers a model for alternative care delivery during curative chemotherapy and support for patients with cancer experiencing mild to moderate symptoms.

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Phase III Randomized Controlled Trial of eRAPID: eHealth Intervention During Chemotherapy

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