Cost-Effectiveness of eRAPID eHealth Intervention for Symptom Management During Chemotherapy

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ABSTRACT

PURPOSE A randomized controlled trial of online symptom monitoring during chemotherapy with electronic patient self-Reporting of Adverse-events: Patient Information and aDvice (eRAPID) system found improved symptom control and patient self-efficacy, without increasing hospital admissions and visits. The aim of this study was to evaluate the cost-effectiveness of the eRAPID eHealth intervention compared with usual care for patients receiving systemic treatment for colorectal, breast, or gynecologic cancers in the United Kingdom.

METHODS An embedded economic evaluation was conducted alongside the trial evaluating the effectiveness of eRAPID from health care provider and societal perspectives. Costs and quality-adjusted life-years (QALYs) of patients were compared over 18 weeks of the trial. Incremental cost-effectiveness ratios (ICERs) were estimated and compared with the National Institute for Health and Care Excellence cost-effectiveness threshold. Uncertainty around the ICER was explored using nonparametric bootstrapping and sensitivity analyses. Follow-up data were collected 12-months after random assignment for a subset of the study sample to conduct exploratory analysis of potential longer-term effects.

RESULTS Patients in the eRAPID group had the highest QALY gain and lowest costs over 18 weeks. Although differences were small and not statistically significant, eRAPID had a 55%-58% probability of being more cost-effective than usual care. Patient out-of-pocket costs were lower in the eRAPID group, indicating eRAPID may help patients access support needed within the National Health Service. Exploratory 12-months analysis showed small differences in costs and QALYs, with higher QALY gains in the eRAPID group but also higher costs. Exploratory subgroup analysis by disease status indicated that the eRAPID intervention was cost-effective for patients with early-stage cancers but not for patients with metastatic disease.

CONCLUSION Despite small differences in QALYs and costs, the analyses show potential cost-effectiveness of online symptom monitoring, when added to usual care, particularly during adjuvant systemic treatment for early-stage cancers.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Increasing numbers of patients with cancer receive systemic treatment for early and advanced disease, including traditional chemotherapy, and more recently, targeted agents (monoclonal antibodies and small molecules) and immunotherapy. These cancer treatments can cause acute and long-term adverse events with associated costs both to the patient and the health care system.[1] Almost one in five patients on chemotherapy attends emergency services for symptom management within 14 days of a scheduled treatment visit.[2-4] In the United Kingdom, the financial impact on cancer services to the National Health Service is estimated at >£5 billion.[5] Concurrently, patients face both out-of-pocket expenses and reduced personal or family income, and many report difficulties in paying bills.[6] Those younger than 60 years are particularly affected, suggesting loss of income from employment plays a substantial part in the financial burden when people are unable to work or need to reduce their hours.[6]

In routine oncology practice, treatment of adverse events and symptoms are typically monitored by health professionals via outpatient clinic visits and provision of emergency care in hospitals. eHealth approaches have the potential to improve delivery of cancer care. Patients can self-report symptoms and

CONTEXT

Key Objective

To evaluate the cost-effectiveness of the eRAPID eHealth intervention for online symptom monitoring of patients receiving systemic treatment for colorectal, breast, or gynecologic cancers in the United Kingdom.

Knowledge Generated

The eRAPID online system for symptom monitoring can lead to improved patient quality of life and reduced health care costs and patient out-of-pocket health care–related costs during cancer treatment. eRAPID may be a cost-effective addition to care for patients on chemotherapy, particularly those with early-stage disease.

Relevance

This study demonstrates the cost-effectiveness of online patient reported outcome measures monitoring during adjuvant chemotherapy for early-stage cancers, thus adding to existing evidence in metastatic disease.

toxicity online or via mobile devices using standardized questionnaires (known as patient-reported outcome measures [PROMs]). PROMs encompass questionnaire data reported directly by people about how they feel and function, including symptoms from their disease, side effects of treatment, as well as impact on their functioning and daily life.[7]

A growing number of studies show that when used during care delivery, electronic patient reported outcome measures (ePROMs) improve communication between clinicians and patients, improve symptom control and quality of life (QoL), and, in some cancer sites and health care systems, may improve service use and survival.[8-13] The wide penetration of the Internet and mobile devices in everyday life has facilitated the use of ePROMs and eHealth in real time to support patient monitoring and care.[14] Furthermore, online symptom monitoring with ePROMs has shown promise as a cost-effective way to improve patient outcomes.[10,15,16]

The electronic patient self-Reporting of Adverse-events: Patient Information and aDvice (eRAPID) is an online eHealth system, added to usual care, to help manage symptoms during cancer treatment. Patients self-report online, symptoms and side effects during treatment (items on the basis of the Common Toxicity Criteria for Adverse Events) and receive automated severity-dependent advice guiding self-management or medical contact (on the basis of an underlying clinical scoring algorithm), and their self-reports are displayed in their electronic patient records.[17] The randomized controlled trial (RCT) of eRAPID in patients during chemotherapy for breast, colorectal, and gynecologic cancers showed improved symptom control early during chemotherapy (6 and 12 weeks), with the effects observed in patients with early-stage cancers, treated with curative intent, but not in patients with metastatic disease. No increase in hospital workload (emergency admissions, hospital visits, or calls) was seen. Patients reported better self-efficacy and confidence in self-managing their symptoms, and improved QoL at the end of the chemotherapy.[18]

Here, we report the cost-effectiveness analysis of eRAPID compared with usual care over the 18-week trial, a key pre-planned secondary outcome. In addition, after the internal pilot of the trial, an exploratory cost-effectiveness analysis was added at 12 months after random assignment, with data collected for a subset of the study sample that reached 12 months within the funding period.

METHODS

The embedded economic evaluation was conducted alongside the eRAPID RCT (ISRCTN88520246). Full methods are available in the trial paper and the protocol[18,19] and the CONSORT diagram for the trial is included in Appendix Figure A1 (online only). Briefly, 508 patients with breast, colorectal, and gynecologic cancers starting systemic treatment were randomly assigned to usual care or usual care plus eRAPID (weekly online symptom reporting and advice for 18 weeks) to evaluate the impact of eRAPID on symptom control, hospital contacts and emergency admissions, and patient self-efficacy in managing side effects.

To evaluate cost-effectiveness of eRAPID compared with usual care, costs (direct and indirect) and outcomes of patients were compared over the 18 weeks of the trial. As the time frame was less than a year, discounting of costs and benefits was not required.[20,21] The primary analysis was conducted from the health care provider perspective, with additional analyses conducted from the societal perspective including patient out-of-pocket costs associated with their care. The analysis was guided by the recommendations of the National Institute for Health and Care Excellence (NICE) methods guide.[21]

Data Collection

Data to inform the economic evaluation were collected as part of the eRAPID trial from participants (self-reported questionnaires) and directly from hospital electronic records on

the use of hospital services. Patient questionnaires included EQ-5D-5L, EORTC QLQ-C30, and a trial-specific questionnaire on health care resource use (use of primary and secondary care services, prescription medications) and patient out-of-pocket costs (including travel to hospital, nonprescription medications, and other health care–related expenses). Questionnaires were administered by post at baseline, and 6, 12, and 18 weeks after random assignment; and at 12 months for a subset of the patient sample (ie, those participants reaching 12 months of follow-up before the end of the funding period).

Outcomes

The primary outcome for the economic evaluation was quality-adjusted life-years (QALYs) gained, estimated from responses to the EQ-5D-5L questionnaire. In line with NICE guidance at the time of analysis, these responses were mapped to EQ-5D-3L utility values (representing QoL) using the Van Hout et al[22] crosswalk and multiplied by duration in each health state to generate QALYs.

Resource Use and Costs

Data on use of health care services were combined with relevant UK cost data at the time of analysis (price year 2018). Details of unit costs are available elsewhere.[23] Total costs for each patient were calculated in British pounds (£) as the sum of costs of use of hospital services, community health and social services, chemotherapy, alternative therapies, medications, and cost of the intervention. The intervention cost consisted of a patient manual, which provided training and guidance on using the eRAPID system, and a maintenance cost for the software (QTool; calculated for the 18 weeks of the trial on the basis of an annual maintenance cost of £10,000 divided by the number of patients in the eRAPID group). As the eRAPID system provides automated advice for self-management, no additional clinician time was included in the intervention cost as it was assumed that the use of eRAPID should reduce patient facing clinician time by reducing unnecessary consultations. Time taken off work by patients because of their condition was included in the societal perspective analysis using a human capital approach and a median hourly pay for UK adults of £11.31.[24] In the absence of additional information, patients who reported working full-time were assumed to work 7.5 hours per day and patients who reported working part-time were assumed to work 4 hours per day.

Missing Data

Multiple imputation methods (using chained equations and predictive mean matching) were used to generate missing EQ-5D-5L index scores and community health and social care cost values at each follow-up on the basis of the distribution of observed data.[25,26] Missing baseline EQ-5D-5L values were imputed using mean imputation to ensure imputed values were independent of treatment allocation.[25,27] The imputation was performed in Stata Version 15 (StataCorp LP, College Station, TX).

Multivariable Regression Analysis

Multivariable regression was used to analyze the difference in costs and QALYs between intervention and control groups. Variables were selected for inclusion in each regression model through analysis of univariable models and a stepwise approach to identify prognostic factors. Besides statistical significance, clinical considerations were also taken into account. Consequently, the difference in costs between treatment groups was analyzed controlling for age and sex. The difference in QALYs between groups was analyzed controlling for baseline QoL, age, and sex. In addition, a subsequent analysis was performed, which also controlled for clinical variables of interest: cancer site, whether the patient had received previous chemotherapy, and disease stage. This analysis is presented as a sensitivity analysis.

Cost-Effectiveness Analysis

The primary analysis consisted of a cost-utility analysis of the intention-to-treat (ITT) trial sample over the 18-week trial period, adjusting for baseline variables and imputing missing data. The incremental cost per QALY gained by patients using the eRAPID system compared with usual care was calculated. Incremental cost-effectiveness ratios (ICERs) were estimated and compared with the NICE cost-effectiveness threshold of £20,000-£30,000 per QALY gained; ICERs below this threshold indicate a cost-effective intervention.[21]

Secondary analysis was undertaken from the societal perspective, which, in addition to costs in the primary analysis, included costs to patients, such as travel expenses and over-the-counter medicines, and productivity losses. All other methods remained the same.

Uncertainty Analysis

Uncertainty around the ICER was explored using nonparametric bootstrapping to generate 10,000 estimates of incremental costs and benefits. These estimates were plotted on the cost-effectiveness plane to illustrate the uncertainty surrounding the cost-effectiveness point estimate.[28] A cost-effectiveness acceptability curve (CEAC) illustrating the probability that the eRAPID system is cost-effective at a range of threshold values (£0-£100,000) was also constructed using the bootstrapped samples.[29]

Sensitivity Analysis

Sensitivity analyses were conducted to explore the impact of assumptions made in the analysis on the results. Sensitivity analyses conducted were as follows: (1) analysis without adjustment for baseline characteristics; (2) analysis of complete data only, that is, without imputing missing data; (3) analysis

using EORTC QLQ-C30, a condition-specific tool to estimate health-related QoL, with calculated utility scores (EORTC-8D) as per Rowen et al[30]; (4) using the EQ-5D-5L value set rather than the 3L crosswalk[31]; and (5) controlling for additional clinical variables (cancer site, previous chemotherapy, and disease stage) in the analysis of costs and outcomes.

Exploratory Subgroup Analysis by Disease Stage

A planned exploratory subgroup analysis was undertaken to evaluate the effect of disease stage (early-stage cancers treated with curative intent and metastatic disease) on cost-effectiveness. In the main eRAPID trial, the planned subgroup analysis by disease stage showed differential impact—improved symptom control in early-stage cancers, but no statistically significant effect in metastatic cancers (one third of the sample). Here, the same methods as the main cost-effectiveness analysis were used, conducted separately for each of the subsamples.

Exploratory Analysis of 12-Month Follow-Up Data

In addition to the 18-week follow-up of the main trial, additional 12-month follow-up data were collected for a subsample of trial participants after the internal pilot. This was a planned a priori exploratory analysis of the cost-effectiveness of eRAPID in an attempt to evaluate potential longer-term impact beyond treatment. The exploratory hypothesis stated that if eRAPID leads to improved symptom control during treatment, patients would recover faster and would require fewer health care resources afterward. All methods used in the primary analysis were replicated for the exploratory 12-month analysis.

RESULTS

Sample

The data for the main trial were collected between January 22, 2015, and June 11, 2018, from 508 consented patients, whereas the subsample baseline data were collected from May 18, 2016 (started after the internal pilot) until September 1, 2017, with the 12-month follow-up ending on September 1, 2018. This subsample included 267 consented participants, but 22 withdrew and 40 died, so 12-month questionnaires were sent to 205 participants. The return rates of paper outcome questionnaires during the 18 weeks of the RCT have been published[18] (baseline 506/508, 99.6%; 6 weeks 441/483, 91.3%; 12 weeks 404/463, 87.3%; 18 weeks 380/447, 85.1%, without difference between eRAPID and usual care). Return rate at 12 months was 79.5% (163/205), with a small difference between eRAPID (76/98, 77.6%) and usual care (87/107, 82.3%), but with higher return rates by patients with metastatic disease (61/72, 84.7%) than those with early-stage cancers (102/133, 76.6%).

Sample characteristics of participants in the main trial (N = 508) and for the subsample with 12-month follow-up data (n = 267) are presented in Table 1. Although the samples are comparable on age, the subsample with 12-month data had a higher proportion of male patients, patients with metastatic disease, patients with previous chemotherapy, more patients with colorectal cancers, and less patients with breast cancer. Furthermore, the eRAPID group with 12-month follow-up had 55/135 (40.7%) patients with colorectal cancer in comparison with usual care (50/132 [37.9%]). Thus, the 12-month subsample is more representative of patients with advanced disease, with slightly worse baseline QoL, and who had less symptom control benefit from the eRAPID intervention than the main trial. Baseline EQ-5D-5L and EORTC-8D scores are lower in the 12-month subsample but balanced between the groups.

Outcomes

Patients' QoL scores measured by EQ-5D-5L and EORTC-8D are presented in Appendix Table A1, expressed as utility scores. EQ-5D-5L scores decrease over the trial period in both arms, but scores were higher at each time point in the eRAPID arm. Multiple regression analysis indicated the difference in QALYs gained between groups were not statistically significant ($P > .05$; 95% CI, −0.004 to 0.011). EORTC-8D scores follow a similar pattern over the trial period, but baseline scores are slightly higher in the usual care arm.

Costs

A detailed breakdown of patient use of health care services and associated health care costs is available elsewhere.[23] Multiple regression analysis indicated that the difference in total costs over the 18-week trial between groups was not statistically significant ($P > .05$; 95% CI, −1,240.91 to 1,167.69).

Cost-Effectiveness Results

Cost-effectiveness results are presented in Table 2. In the primary analysis, the eRAPID group had both the highest QALY gain over the trial period and the lowest costs, but the cost-savings per person were relatively small (−£25). For analysis including societal perspective costs, the difference in costs between groups was larger than in the analysis of health care provider perspective (−£149). Overall, the results indicate the eRAPID system may be a cost-effective use of resources. This result was robust to all sensitivity analyses explored over the 18-week time horizon (ITT no adjustment for baseline, complete case analysis, EQ-5D-5L value set, EORTC-8D instead of EQ-5D-5L, controlling for additional clinical variables; Appendix Table A2).

Exploratory subgroup analysis by disease status indicated that the eRAPID intervention was cost-effective for patients with early-stage cancers but not for patients with metastatic disease. In the metastatic subgroup, the costs per patient were higher in the eRAPID group and the QALYs gained lower, that is, eRAPID was not cost-effective. However, in

TABLE 1. Sample Characteristics

Characteristic	Main Trial[a]		Subsample With 12-Month Follow-Up[b]	
	eRAPID	Usual Care	eRAPID	Usual Care
Sample, No.	256	252	135	132
Age at baseline, years				
Mean (SD)	55.95 (12.27)	56.06 (11.37)	56.4 (12.84)	56.59 (11.62)
Minimum-maximum	22-86	18-79	22-82	18-79
Males, No. (%)	51 (19.92)	51 (20.24)	33 (24.44)	29 (21.97)
Females, No. (%)	205 (80.08)	201 (79.76)	102 (75.56)	103 (78.03)
Cancer site, No. (%)				
Breast	117 (45.70)	116 (46.03)	49 (36.30)	51 (38.64)
Gynecologic	53 (20.70)	53 (21.0)	31 (24.03)	31 (23.48)
Colorectal	86 (33.59)	83 (32.94)	55 (40.74)	50 (37.88)
Had previous chemotherapy, No. (%)				
Yes	55 (21.48)	51 (20.24)	37 (27.41)	34 (25.76)
Disease stage, No. (%)				
Early-stage cancer	161 (62.89)	156 (61.90)	72 (53.33)	71 (53.79)
Metastatic disease	95 (37.11)	96 (38.10)	63 (46.66)	61 (46.21)
Baseline EQ5D[c]				
Mean (SD)	0.758 (0.185)	0.753 (0.180)	0.751 (0.185)	0.750 (0.191)
No.	250	248	129	130
Baseline EORTC-8D[d]				
Mean (SD)	0.827 (0.134)	0.827 (0.135)	0.821 (0.134)	0.823 (0.143)
No.	205	205	131	131

NOTE. Two hundred sixty-seven participants were consented during this period; however, only 205 questionnaires were sent as n = 22 participants withdrew and n = 40 died. Patients who died or withdrew were included in the final analysis (with 0 cost and 0 QALYs for those who died, and imputing missing values on the basis of available data on those who withdrew).

Abbreviations: QALYs, quality-adjusted life-years; SD, standard deviation.

[a]Data for the main trial were collected between January 22, 2015, and June 11, 2018.

[b]Data for the subsample were collected between May 18, 2016, and September 1, 2017.

[c]EQ-5D-5L responses were mapped to EQ-5D-3L utility values, using the Van Hout et al[22] crosswalk.

[d]EORTC Utility score (EORTC-8D) were calculated using the methodology by Rowen et al.[30]

the patients with early-stage cancer, the cost-savings per patient were significant (−£727) and the incremental QALYs were higher. Thus, the exploratory analysis by disease stage strongly suggests that the eRAPID intervention is cost-effective during treatment in early-stage patients with breast, ovarian, and colorectal cancers treated with adjuvant chemotherapy.

Similar to the main cost-effectiveness analysis, the exploratory 12-month analysis showed small differences in costs and QALYs between the eRAPID and usual care groups. However, while the higher QALYs gained in the eRAPID group were maintained over 12 months, costs were also higher. The subgroup analysis by disease stage in the 12-month sample indicated that patients with early cancers gained more QALYs than those in the usual care group but at higher cost, whereas those with metastatic cancers showed higher costs and lower QALYs for the eRAPID group. However, the results were not robust and the sensitivity analyses showed variable results, with complete case analysis of EQ-5D-5L and EORTC-8D suggesting that eRAPID dominates (higher QALYs, lower costs), whereas ITT analysis of EORTC-8D suggests that usual care dominates. The breakdown of health care costs (Appendix Tables A3-A6) shows the higher costs in the eRAPID group are largely because of the metastatic group having higher treatment costs and more use of hospital services, likely because they continued treatment.

Uncertainty Analysis

Figure 1A shows the bootstrapped estimates of the incremental costs and incremental effects plotted on the cost-effectiveness plane for the 18-week trial. The majority of the points lie to the right of the *y*-axis, indicating that the use of the eRAPID system is likely to increase QALYs gained. The spread of points both above and below the *x*-axis indicates the uncertainty around the impact of eRAPID on health care costs at 18 weeks. The CEAC for the 18-week trial (Fig 1B) indicates that at the NICE cost-effectiveness threshold of £20,000-£30,000 per QALY gained, eRAPID has a 55%-58% probability of being cost-effective compared with usual care.

TABLE 2. Cost-Effectiveness Results

Treatment Group	Cost,[a] Mean (SE)	Incremental Cost[b]	QALY,[a] Mean (SE)	Incremental QALY[b]	ICER (£/QALY)[c]
Analysis over the 18-week follow-up					
Primary analysis: health care provider perspective—ITT with adjustment for baseline					
Usual care (n = 252)	£8,330.36 (435.23)		0.255 (0.004)		eRAPID dominates
eRAPID (n = 256)	£8,305.08 (450.5)	−£25.28	0.259 (0.004)	0.003	
Secondary analysis: societal perspective					
Usual care (n = 252)	£9,811.67 (453.53)		0.255 (0.004)		eRAPID dominates
eRAPID (n = 256)	£9,662.24 (463.3)	−£149.42	0.259 (0.004)	0.003	
Exploratory subgroup analysis by disease stage					
Patients with early-stage cancer (primary or local recurrence)					
Usual care (n = 156)	£8,336.15 (568.09)		0.262 (0.004)		
eRAPID (n = 161)	£7,609.02 (484.16)	−£727.13	0.269 (0.003)	0.005	eRAPID dominates
Patients with metastatic disease					
Usual care (n = 96)	£8,320.95 (676.83)		0.243 (0.007)		
eRAPID (n = 95)	£9,484.73 (885.38)	£1,163.78	0.242 (0.008)	−0.001	Usual care dominates
Exploratory analysis for the subsample with 12-month follow-up					
Exploratory analysis: health care provider perspective—ITT					
Usual care (n = 132)	£10,023.78 (641.66)		0.663 (0.021)		
eRAPID (n = 135)	£10,635.43 (699.15)	£611.65	0.673 (0.022)	0.009	£64,455.74
Exploratory analysis: societal perspective					
Usual care (n = 132)	£11,467.41 (669.27)		0.663 (0.021)		
eRAPID (n = 135)	£11,843.72 (707.83)	£376.31	0.673 (0.022)	0.009	£39,662.81
Exploratory subgroup analysis by disease stage					
Patients with early cancer (primary or local recurrence)					
Usual care (n = 71)	£8,720.69 (748.11)		0.754 (0.020)		
eRAPID (n = 72)	£9,231.23 (915.78)	£510.54	0.772 (0.015)	0.022	£22,737.31
Patients with metastatic disease					
Usual care (n = 61)	£11,540.51 (1,055.39)		0.557 (0.035)		
eRAPID (n = 63)	£12,240.24 (1,043.24)	£699.73	0.560 (0.038)	−0.006	Usual care dominates

NOTE. As negative ICERs can indicate either a negative or positive result, in the case of negative ICERs, a statement of which option dominates is presented instead, indicating which option is less costly and more effective.
Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality-adjusted life-year.
[a]Unadjusted values in mean (SE).
[b]Incremental values from regression output (controlling for baseline variables unless stated).
[c]ICERs are presented as cost per QALY gained with eRAPID compared with usual care, denoted (£/QALY).

Figures 1C and 1D present the uncertainty analysis for the subsample with 12-month follow-up data. eRAPID is likely to increase QALYs gained, indicated by the majority of the points being to the right of the *y*-axis. However, the majority of points lie above the *x*-axis, indicating health care costs are likely to be higher with eRAPID. The probability eRAPID is cost-effective compared with usual care is 36%-40%.

DISCUSSION

Use of online and mobile symptom monitoring has been growing exponentially, further encouraged during the COVID-19 pandemic. The use of this technology now features in national guidelines.[32,33] Internationally, the European Society for Medical Oncology was the first to publish clinical practice guidelines on the role of PROMs in the continuum of cancer clinical care.[34] However, the evidence of the cost-effectiveness of this approach in cancer is sparse.[32-34] A recent review[14] identified only two cost-effectiveness studies using online ePROMs, including symptom monitoring. Both were focused on patients with advanced or metastatic cancers, and both suggested there was value in their use: improving QALYs relative to cost in Canada[16] and reduced follow-up costs in France.[15] The eRAPID study expands this evidence base to another country and health care system, providing data from the United Kingdom and importantly including new evidence in early-stage cancers, treated with adjuvant chemotherapy with curative intent. To the best of our knowledge, this is the first cost-effectiveness analysis of online PROMs during adjuvant chemotherapy internationally and in the United Kingdom.

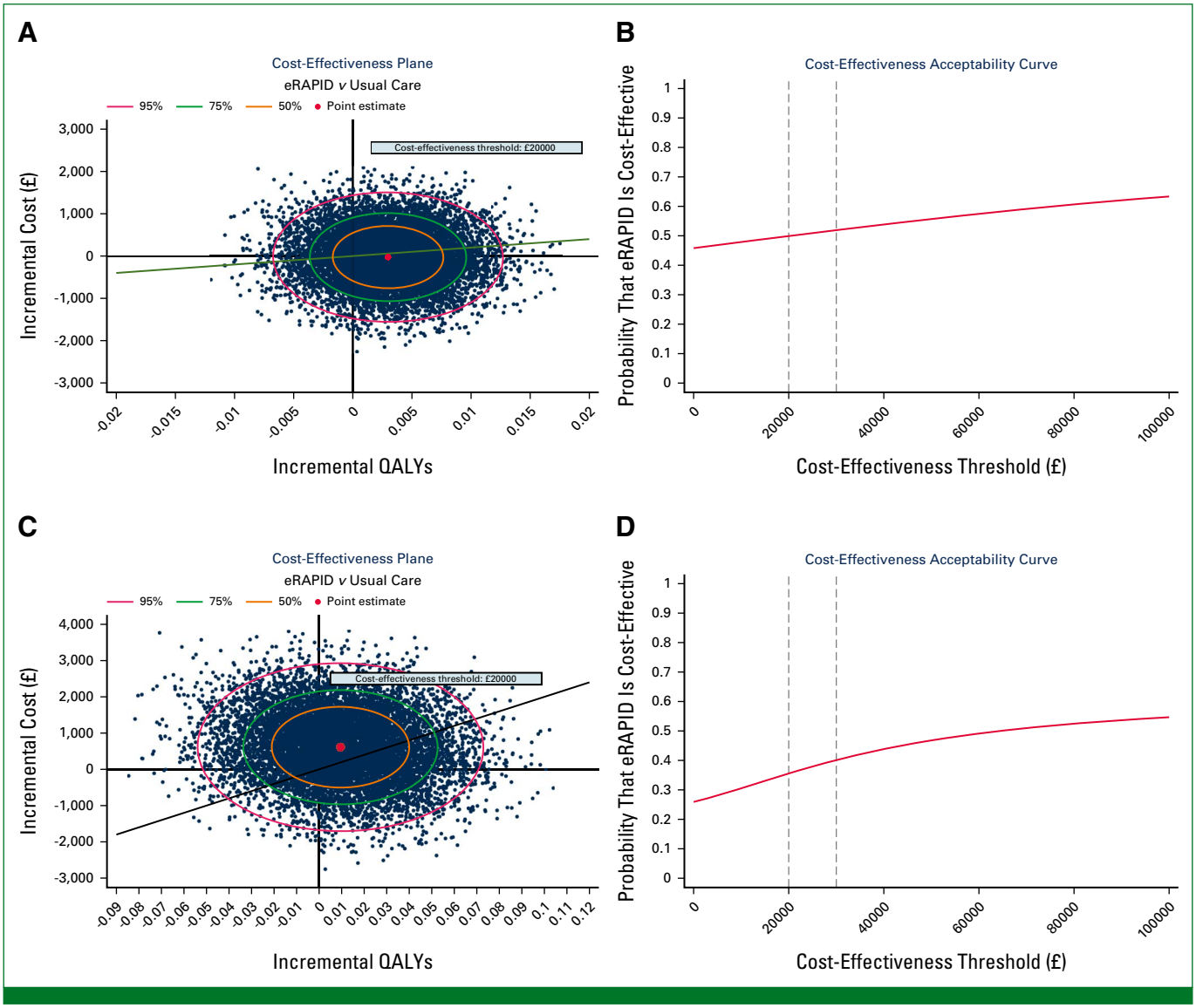

FIG 1. (A) Cost-effectiveness plane, 18-week analysis. (B) CEAC, 18-week analysis. (C) Cost-effectiveness plane, 12-month analysis. (D) CEAC, 12-month analysis. CEAC, cost-effectiveness acceptability curve; QALYs, quality-adjusted life-years.

The primary (from the health care provider perspective) and secondary (from the societal perspective) cost-effectiveness analyses indicated that the eRAPID intervention may be cost-effective for the management of symptoms and adverse events in patients receiving systemic treatment for colorectal, breast, or gynecologic cancers. Higher QALY gains and lower costs were seen in the eRAPID group than the usual care group during 18 weeks of the trial (ie, during treatment). The CEAC showed that eRAPID had a 55%-58% probability of being cost-effective at the NICE recommended threshold. The mean differences in QALY gain and costs per patient between eRAPID and usual care were relatively small. Such small differences might be expected for an intervention such as eRAPID, which was added to usual care to aid with the management of treatment only (ie, the scope for benefits may be smaller than an intervention offering a new treatment). As such, finding consistently positive results in the main analysis is encouraging. Much lower costs per patient were observed in the societal perspective analysis, indicating that eRAPID may have an additional positive impact on the wider societal costs associated with cancer care. The main RCT analysis showed that the majority (82%) of the eRAPID reports generated self-management advice plus patients reported improved self-efficacy in symptom management, which may lead to lower out-of-pocket costs. This pattern of results is compatible with the observed measurable benefits and cost-savings for patients and society.[18]

In patients with early-stage disease (>60% of the sample), the incremental QALY gain was higher and the costs per patient a lot lower, demonstrating the cost-effectiveness of eRAPID in this group. This is consistent with the main trial showing significant improvement in symptom control, which

was predominantly seen in patients with early-stage cancers, with low baseline symptom burden, subsequent mild or moderate symptoms leading to self-management advice, who adhered >70% to the online monitoring and whose clinicians explicitly used reports. To the best of our knowledge, these are the first data showing that online symptom monitoring with patient advice during adjuvant treatment is cost-effective from both health care provider and societal perspectives. Another multinational European trial showed similar benefit for mobile symptom monitoring during adjuvant treatments, but cost-effectiveness analysis is not yet available.[35]

Conversely, in patients with metastatic disease, the main trial did not find improved symptom control from the eRAPID intervention. The cost-effectiveness analysis is consistent with this lack of primary effect, with no positive increment in QALYs and higher costs, suggesting that eRAPID is not cost-effective during treatment for metastatic cancers. The higher costs were due to an increased use of hospital services and treatment costs. These findings are in contrast with other trials in United States and France, which showed better symptom monitoring, improved QoL and survival, and confirmed cost-effectiveness of follow-up monitoring in lung cancer, on the basis of online symptom reporting.[10,15] Possible explanations for the differences include the longer symptom monitoring in those trials covering the follow-up period, as well as having dedicated nurse teams supporting patients on the symptom monitoring pathway, plus lower hospital costs as ePROMs replaced the 6-monthly monitoring with computer tomography. The exploratory (although preplanned) nature of this subgroup analysis by disease stage should be noted, which led to a smaller sample size of the metastatic subgroup and thus unlikely to detect small differences in outcomes. The effect of disease stage on the effectiveness of electronic symptom management is an important topic for further evaluation in future research.

Exploratory analysis using data from a subsample with 12-month follow-up data also found small differences in costs and QALYs between groups; however, while higher QALY gains in the eRAPID group were maintained, higher costs were also observed, driving down the probability that eRAPID is cost-effective over this time horizon and for this subsample. This exploratory analysis involved all consecutive patients randomly assigned to the study over a period of 16 months (limited because of existing funding), leading to a smaller sample and different population characteristics with a predominance of patients with metastatic cancer. In metastatic disease, the effect of disease progression and the need for further treatment would have a greater effect on the costs than the effect of the previous eRAPID intervention. Indeed, the costs over 12 months were driven by the treatments and the use of hospital services. However, higher costs were also observed in patients with early disease, where improved QALYs were maintained. It is plausible that improved self-efficacy may have led to patients seeking more help for symptoms after treatment, or that patients who returned the questionnaires were more motivated to self-manage their health. It is also possible that patients who recovered faster were less likely to return 12-month questionnaires than patients with longer-lasting side effects (eg, as a way to report what was happening to them). The observed lower 12-month return rate for patients with early-stage disease is consistent with this hypothesis. However, the main limitation of the 12-month analysis is the smaller unbalanced sample. The uncertainty in estimates of cost-effectiveness is clearly demonstrated in the cost-effectiveness plane (Fig 1), which shows a spread of points across all four quadrants. Given the small differences in costs and QALYs observed between treatment groups, other factors such as patient and health care provider acceptability of the system are also likely to be important in decisions about wider implementation.

A strength of the study is the preplanned, within-trial cost-effectiveness analysis, which enabled the collection of good-quality data at prespecified time points during the 18-week duration of the main trial. However, the 12-month data collection point was added after the internal pilot phase to examine a hypothesis that the intervention may have a carryover effect and allow faster recovery after treatment. This resulted in a subsample of the main trial population who reached 12 months after baseline within the funded period of the trial. All eligible consecutively randomly assigned patients were sent 12-month questionnaires, but at the analysis stage, it became apparent that there were important differences between this subsample and the main trial population (see above). The predominance of metastatic disease may explain the higher costs in the 12-month analysis and likely make the results of the 18-week and 12-month analyses incomparable.

The use of linked hospital electronic records provided real-life data on use of cancer services. As such, the analysis benefitted from robust data on cancer treatments, outpatient clinics, cancer-related hospital admissions, and other hospital contacts. However, the lack of a completely connected system for all health care records between the cancer center and the community services meant that self-reported data were collected on use of nonhospital health care services. Although the self-reported health care resource use questionnaires were simplified and improved with patient partners' input, there were still a lot of missing fields, and this problem increased over the trial period. This resulted in a large proportion of patients with missing community health care use data.

The costs associated with the eRAPID intervention included a system maintenance cost for eRAPID, which was divided by the trial patients in the eRAPID group to give an estimate of the cost per patient within the trial. However, in practice, the cost of system maintenance would cover a larger patient group, meaning the per-patient cost may be overestimated.

In conclusion, the health economic analysis of the eRAPID trial confirmed that the eHealth intervention is cost-effective

during treatment in patients with early-stage cancer treated with adjuvant chemotherapy, with both cost-savings and maintaining better QoL. The inconsistencies in results of the 12-month analysis attributed to differences in sample characteristics show that the benefits of eHealth interventions could be disease-, setting-, and context-specific. This underlines the importance of adaptation and robust evaluation of eHealth interventions in different settings to ensure their appropriate use and implementation to maximize benefits for the patients with cancer and the health care services.

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DISCLAIMER

The views expressed are those of the author(s) and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

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Cost-Effectiveness of eRAPID eHealth Intervention for Symptom Management During Chemotherapy

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APPENDIX

TABLE A1. EQ-5D-5L and EORTC-8D Scores Over the 18-Week Trial and the 12-Month Follow-Up (complete data only)

	Sample With Data Over 18 Weeks						Sample With Data Over 12 Months					
	eRAPID			Usual Care			eRAPID			Usual Care		
Time Point	Sample	Mean (SD)	Minimum-Maximum	Sample	Mean (SD)	Minimum-Maximum	Sample	Mean (SD)	Minimum-Maximum	Sample	Mean (SD)	Minimum-Maximum
EQ-5D-5L scores (mapped to 3L)[a]												
Baseline	250	0.758 (0.185)	0.066-1	248	0.753 (0.18)	0.066-1	129	0.751 (0.185)	0.066-1	130	0.750 (0.191)	0.66-1
6 weeks	213	0.776 (0.175)	−0.161 to 1	226	0.752 (0.197)	−0.012 to 1	109	0.781 (0.192)	−0.161 to 1	118	0.760 (0.215)	−0.012 to 1
12 weeks	202	0.747 (0.192)	0-1	210	0.734 (0.18)	−0.038 to 1	103	0.733 (0.219)	0-1	111	0.726 (0.192)	0-1
18 weeks	189	0.739 (0.216)	−0.043 to 1	202	0.708 (0.213)	−0.134 to 1	96	0.736 (0.252)	−0.043 to 1	106	0.676 (0.255)	−0.134 to 1
12 months							102	0.565 (0.360)	0-1	104	0.590 (0.354)	−0.245 to 1
EORTC-8D scores[b]												
Baseline	205	0.827 (0.134)	0.397-1	205	0.827 (0.135)	0.392-1	131	0.821 (0.134)	0.407-1	131	0.823 (0.143)	0.446-1
6 weeks	168	0.796 (0.123)	0.392-1	180	0.770 (0.141)	0.291-1	104	0.806 (0.119)	0.392-1	112	0.780 (0.142)	0.291-1
12 weeks	161	0.781 (0.116)	0.443-1	171	0.744 (0.134)	0.291-1	98	0.779 (0.119)	0.443-1	108	0.744 (0.144)	0.291-1
18 weeks	148	0.778 (0.129)	0.408-1	162	0.751 (0.155)	0.316-1	90	0.793 (0.124)	0.443-1	98	0.750 (0.165)	0.316-1
12 months	–	–	–	–	–	–	73	0.843 (0.125)	0.371-1	86	0.807 (0.156)	0.318-1

Abbreviation: QoL, quality of life.

[a]QoL (utility) scores generated from responses to the EQ-5D-5L questionnaire, mapped to the 3L value set using the Van Hout et al[22] crosswalk.

[b]QoL (utility) scores generated from responses to the EORTC-QLQC30.

TABLE A2. Sensitivity Analyses of Cost-Effectiveness for 18 Weeks and 12 Months

Treatment Group	Cost,[a] Mean (SE)	Incremental Cost[b]	QALY,[a] Mean (SE)	Incremental QALY[b]	ICER (£/QALY)[c]
Analysis over the 18-week follow-up (N = 508)					
Primary analysis: health care provider perspective—ITT with adjusting for baseline					
Usual care (n = 252)	£8,330.36 (435.23)		0.255 (0.004)		eRAPID dominates
eRAPID (n = 256)	£8,305.08 (450.5)	−£25.28	0.259 (0.004)	0.003	
Sensitivity analysis: ITT—no adjustment for baseline					
Usual care (n = 252)	£8,330.36 (435.23)		0.255 (0.004)		eRAPID dominates
eRAPID (n = 256)	£8,305.08 (450.5)	−£25.28	0.259 (0.004)	0.004	
Sensitivity analysis: complete case					
Usual care (n = 109)	£11,069.05 (7,400.83)		0.254 (0.051)		eRAPID dominates
eRAPID (n = 86)	£10,971.14 (8,242.43)	−£97.90	0.264 (0.044)	0.003	
Sensitivity analysis: alternative measures of HRQoL—EORTC-8D					
Usual care (n = 252)	£8,330.60 (435.16)		0.264 (0.003)		eRAPID dominates
eRAPID (n = 256)	£8,307.04 (450.54)	−£23.55	0.268 (0.003)	0.004	
Sensitivity analysis: using EQ-5D-5L value set					
Usual care (n = 252)	£8,331.48 (435.17)		0.278 (0.003)		eRAPID dominates
eRAPID (n = 256)	£8,307.11 (450.44)	−£24.37	0.282 (0.003)	0.003	
Sensitivity analysis: controlling for additional clinical variables (cancer site, previous chemotherapy, disease stage)					
Usual care (n = 252)	£8,330.36 (435.23)		0.255 (0.004)		
eRAPID (n = 256)	£8,305.08 (450.5)	£31.30	0.259 (0.004)	0.003	£11,115.01
Exploratory analysis for the subsample with 12-month follow-up (n = 267)					
Exploratory analysis: health care provider perspective: ITT					
Usual care (n = 132)	£10,023.78 (641.66)		0.663 (0.021)		
eRAPID (n = 135)	£10,635.43 (699.15)	£611.65	0.673 (0.022)	0.009	£64,455.74
Sensitivity analysis: complete case					
Usual care (n = 81)	£9,923.68 (6,909.49)		0.706 (0.207)		eRAPID dominates
eRAPID (n = 69)	£9,603.93 (7,341.43)	−£635.86	0.738 (0.187)	0.015	
Sensitivity analysis: using EQ-5D-5L value set					
Usual care (n = 132)	£10,025.51 (641.62)		0.725 (0.021)		
eRAPID (n = 135)	£10,636.22 (699.686)	£610.71	0.732 (0.022)	0.005	£118,815.99
Sensitivity analysis: alternative measures of HRQoL—EORTC-8D, ITT sample					
Usual care (n = 132)	£10,023.12 (641.84)		0.716 (0.018)		Usual care dominates
eRAPID (n = 135)	£10,637.44 (699.67)	£614.32	0.707 (0.020)	-0.008	
Sensitivity analysis: alternative measures of HRQoL—EORTC-8D, complete case					
Usual care (n = 77)	£9,919.67 (7,023.03)		0.748 (0.173)		eRAPID dominates
eRAPID (n = 67)	£9,713.63 (7,406.84)	−£206.04	0.769 (0.173)	0.004	
Sensitivity analysis: controlling for additional clinical variables (cancer site, previous chemotherapy, disease stage)					
Usual care (n = 132)	£10,023.78 (641.66)		0.663 (0.021)		
eRAPID (n = 135)	£10,635.43 (699.15)	£702.96	0.673 (0.022)	0.009	£81,341.58

NOTE. As negative ICERs can indicate either a negative or positive result, in the case of negative ICERs, a statement of which option dominates is presented instead, indicating which option is less costly and more effective.

Abbreviations: HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality-adjusted life-year.

[a]Unadjusted values in mean (SE).

[b]Incremental values from regression output (controlling for baseline variables unless stated).

[c]ICERs are presented as cost per QALY gained with eRAPID compared with usual care, denoted (£/QALY).

TABLE A3. Health Care Cost Breakdown During the Main Trial Over 18 Weeks by Disease Stage

	Usual Care		eRAPID	
Total Cost	Mean (SD)	Minimum-Maximum	Mean (SD)	Minimum-Maximum
Early cancer				
Community health and social services	£236.82 (174.81), n = 67	0-920	£265.16 (250.91), n = 60	15.4-1,270.35
Hospital services	£1,305.89 (2,091.91), n = 156	0-18,968.84	£1,279.34 (1,902.49), n = 161	0-10,346.64
Chemotherapy	£4,614.83 (2,129.83), n = 156	429-11,056	£4,362.75 (2,143.2), n = 161	514-11,858
Alternative therapies (hormonotherapy and targeted treatments)	£2,125.93 (5,248.76), n = 156	0-27,226.52	£1,618.79 (4,542.17), n = 161	0-22,995
Prescription medications	£67.62 (143.56), n = 146	0-1,275.17	£49.53 (60.4), n = 154	0.35-345.35
Intervention cost	£0 (0), n = 156	0-0	£15.59 (0), n = 161	15.59-15.59
Out-of-pocket costs	£261.79 (300.04), n = 156	0-2,122.72	£385.63 (943.72), n = 161	0-9,200
Time out of work	£1,447.02 (2,331.53), n = 154	0-10,687.95	£1,359.34 (2,116.24), n = 161	0-9,670.05
Total cost (health care provider)	£9,334.54 (7,340.98), n = 66	2,522.76-31,883.43	£7,887.3 (6,324.76), n = 59	2,390.9-31,668.26
Total cost (societal)	£11,612.68 (7,464.01), n = 66	3,503.17-34,759	£10,591.75 (6,616.46), n = 59	3,209.51-31,799.86
Metastatic cancer		0-0		0-0
Community health and social services	£292.66 (274.68), n = 47	0-1,798	£309.34 (232.6), n = 37	0-1,314.75
Hospital services	£2,156.55 (3,031.86), n = 96	0-17,342.93	£3,009.1 (5,104.27), n = 95	0-31,094.81
Chemotherapy	£4,533.81 (2,995.82), n = 96	0-24,120	£4,633.67 (3,001.24), n = 95	526-15,229
Alternative therapies (hormonotherapy and targeted treatments)	£1,247.45 (3,973.34), n = 96	0-20,383.44	£1,430.04 (4,832.56), n = 95	0-27,226.52
Prescription medications	£90.8 (135.24), n = 88	0-769.74	£73.72 (101.17), n = 77	0-525.8
Intervention cost	£0 (0), n = 96	0-0	£15.59 (0), n = 95	15.59-15.59
Out-of-pocket costs	£398.78 (817.12), n = 96	0-5,340	£228.72 (394.52), n = 95	0-2,853.47
Time out of work	£742.98 (1,789.86), n = 96	0-9,161.1	£471.21 (1,434.59), n = 95	0-7,634.25
Total cost (health care provider)	£8,627.67 (6,683.87), n = 46	2,656.8-41,196.16	£9,845.86 (10,061.3), n = 34	1,871.53-43,064.25
Total cost (societal)	£10,062.58 (7,144.88), n = 46	2,895.93-41,652.16	£11,244.77 (10,073.71), n = 34	1,879.52-43,198.25

Abbreviation: SD, standard deviation.

TABLE A4. Hospital Services Use 18 Weeks by Disease Stage

	Usual Care		eRAPID	
Item	Mean (SD)	Minimum-Maximum	Mean (SD)	Minimum-Maximum
Early cancer				
Inpatient visits	2.746 (1.713), n = 63	1-8	2.869 (2.766), n = 61	1-15
Inpatient days	5.508 (5.962), n = 63	1-44	5.59 (5.084), n = 61	1-24
Hospital consultation	2.03 (1.549), n = 66	1-8	2.029 (1.782), n = 69	1-11
Outgoing phone consultation	2.547 (3.01), n = 53	1-20	2.485 (1.996), n = 68	1-9
Incoming phone consultation	1.375 (0.619), n = 16	1-3	1.412 (1.004), n = 17	1-5
CNS helpline	1 (0), n = 4	1-1	1.4 (0.548), n = 5	1-2
Other outpatient visit (assessment)	1.833 (1.028), n = 60	1-5	1.698 (1.087), n = 63	1-7
A&E	1 (0), n = 10	1-1	1 (0), n = 6	1-1
Metastatic cancer				
Inpatient visits	2.769 (1.926), n = 52	1-9	3.157 (2.221), n = 51	1-11
Inpatient days	8.058 (7.075), n = 52	1-37	11.196 (13.13), n = 51	1-71
Hospital consultation	2.057 (1.571), n = 35	1-8	3.049 (2.626), n = 41	1-12
Outgoing phone consultation	2.643 (2.093), n = 42	1-8	3.5 (2.651), n = 40	1-12
Incoming phone consultation	1.944 (2.155), n = 18	1-9	2.571 (2.563), n = 14	1-10
CNS helpline	1.667 (0.577), n = 3	1-2	4 (5.196), n = 3	1-10
Other outpatient visit (assessment)	1.787 (1.25), n = 47	1-6	1.818 (1.04), n = 44	1-5
A&E	1.25 (0.5), n = 4	1-2	1 (0), n = 7	1-1

Abbreviations: A&E, accident and emergency; SD, standard deviation.

TABLE A5. Cost Breakdown for 12-Month Data by Disease Stage (which includes the costs during the 18-week trial)

	Usual Care		eRAPID	
Total Cost	Mean (SD)	Minimum-Maximum	Mean (SD)	Minimum-Maximum
Early cancer				
Community health and social services	£258.74 (221.97), n = 64	0-1,057.1	£249.89 (288.71), n = 62	0-1,789.95
Hospital services	£2,639.59 (3,137.41), n = 71	0-18,968.84	£2,425.91 (3,085.52), n = 72	0-16,169.78
Chemotherapy	£4,343.11 (1,722.67), n = 71	429-10,542	£4,553.76 (2,199.77), n = 72	858-11,056
Alternative therapies	£1,300.18 (4,365.18), n = 71	0-27,226.52	£1,807.98 (4,727.94), n = 72	0-18,208.22
Prescription medications	£84.66 (186.2), n = 69	1.12-1,280.11	£60.87 (70.6), n = 70	0.56-345.35
Intervention cost	£0 (0), n = 71	0-0	£15.59 (0), n = 72	15.59-15.59
Out-of-pocket costs	£306.94 (309.3), n = 71	0-1,429.99	£551.71 (1,411.79), n = 72	0-9,450
Time out of work	£1,566.51 (2,475.25), n = 71	0-10,687.95	£1,163.63 (1,955.03), n = 72	0-7,634.25
Total cost (health care provider)	£9,148.74 (6,431.88), n = 63	2,690.44-40,646.32	£9,733.95 (8,133.71), n = 61	1,448.48-38,316.27
Total cost (societal)	£11,214.74 (6,883.1), n = 63	3,778.24-44,101.07	£11,628.37 (8,407.63), n = 61	1,460.38-38,558.77
Metastatic cancer	£0 (0)	0-0	£0 (0)	0-0
Community health and social services	£255.98 (261.42), n = 60	0-1,306.3	£244.01 (250.96), n = 59	0-1,314.75
Hospital services	£5,739.66 (6,291.72), n = 61	0-22,710.15	£6,255.46 (5,980.94), n = 63	0-30,557.66
Chemotherapy	£4,277.56 (2,969.13), n = 61	0-24,120	£4,610.02 (2,570.69), n = 63	526-14,568
Alternative therapies	£1,082.99 (3,396.02), n = 61	0-16,512.41	£992.41 (3,651.31), n = 63	0-18,684.82
Prescription medications	£97.74 (135.4), n = 59	0-544.06	£58.34 (70.25), n = 52	2.23-366
Intervention cost	£0 (0), n = 61	0-0	£15.59 (0), n = 63	15.59-15.59
Out-of-pocket costs	£343.81 (557.02), n = 61	0-2,997	£227.12 (314.74), n = 63	0-1,396.4
Time out of work	£599.52 (1,460.05), n = 61	0-7,634.25	£401.68 (1,297.11), n = 63	0-7,634.25
Total cost (health care provider)	£11,894.01 (8,211.65), n = 58	2,023.48-42,308.61	£12,594.55 (8,539.73), n = 50	4,308.18-39,292.59
Total cost (societal)	£12,886.14 (8,415.21), n = 58	2,023.48-42,886.61	£13,383.2 (8,461.68), n = 50	4,426.25-40,324.84

Abbreviation: SD, standard deviation.

TABLE A6. Hospital Services Use Over 12 Months by Disease Stage (including data during the 18-week trial)

	Usual Care		eRAPID	
Item	Mean (SD)	Minimum-Maximum	Mean (SD)	Minimum-Maximum
Early cancer				
Inpatient visits	2.429 (1.555), n = 49	1-6	3.159 (4.345), n = 44	1-23
Inpatient days	5.755 (7.12), n = 49	1-44	5.432 (6.453), n = 44	1-29
Hospital consultation	1.931 (2.42), n = 58	0-10	2.208 (2.421), n = 53	0-8
Phone consultation	3.603 (4.837), n = 58	0-31	3.528 (4.466), n = 53	0-24
CNS helpline	0.207 (1.196), n = 58	0-9	0.17 (0.643), n = 53	0-4
Other outpatient visit (assessment)	2.458 (1.841), n = 24	1-9	1.609 (1.406), n = 23	1-7
Metastatic cancer				
Inpatient visits	4.255 (3.047), n = 47	1-13	5.143 (3.055), n = 49	1-11
Inpatient days	15.149 (13.492), n = 47	1-47	16.306 (12.398), n = 49	1-68
Hospital consultation	2.867 (3.888), n = 45	0-20	3 (3.709), n = 50	0-13
Phone consultation	4.422 (4.887), n = 45	0-22	4.02 (4.897), n = 50	0-21
CNS helpline	0.222 (0.704), n = 45	0-4	0.32 (1.571), n = 50	0-11
Other outpatient visit (assessment)	2.78 (2.151), n = 41	1-9	2.349 (1.717), n = 43	1-9

Abbreviation: SD, standard deviation.

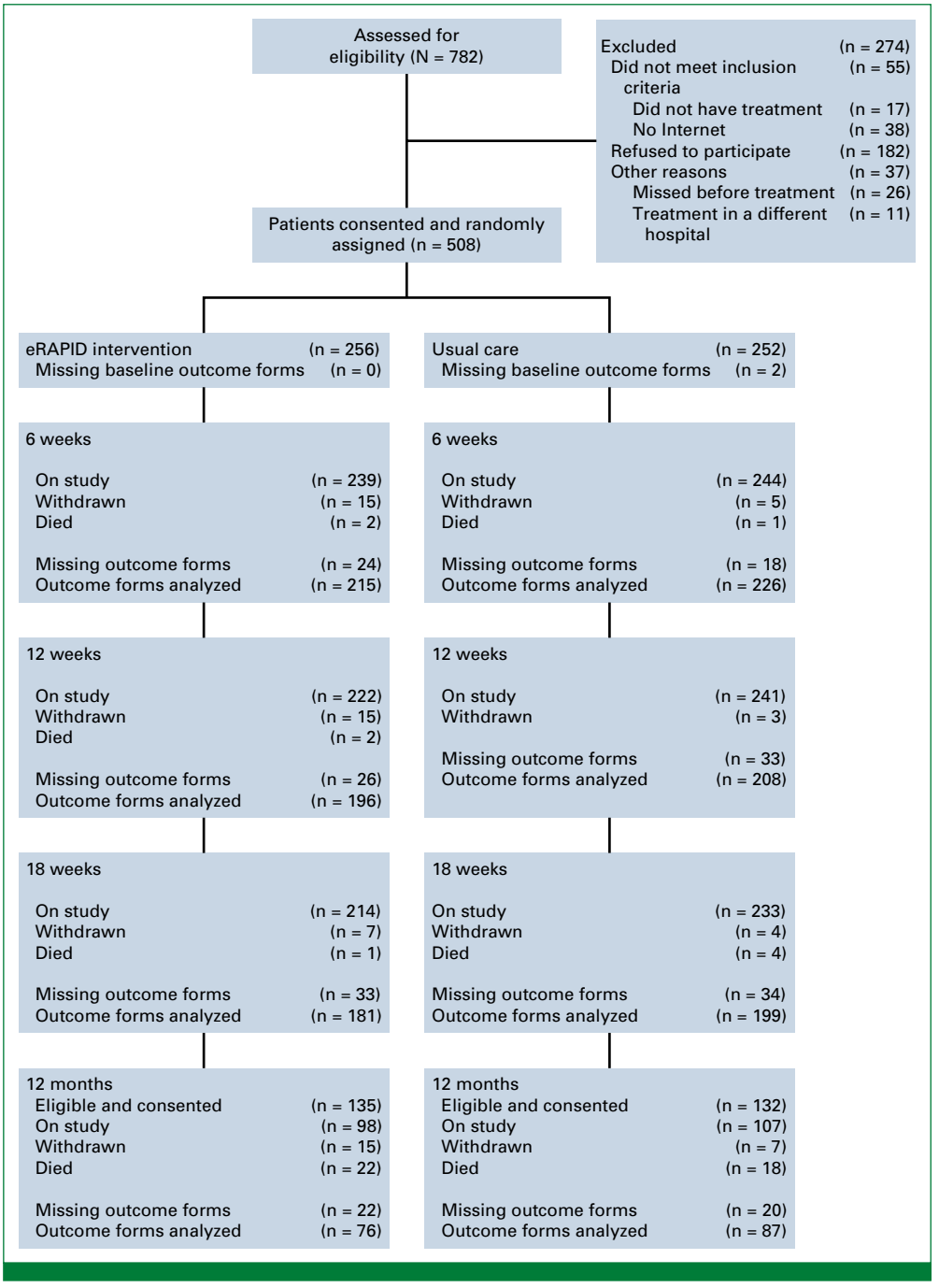

FIG A1. CONSORT Diagram.