Electronic self-reporting of adverse events for patients undergoing cancer treatment: the eRAPID research programme including two RCTs

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Scientific summary

The eRAPID research programme

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Scientific summary

Background

Cancer is treated using multiple modalities, including surgery, radiotherapy and systemic drugs. Treatments can cause acute and long-term adverse events that affect treatment delivery and quality of life. Typically, adverse events are recorded by clinical staff, but usual-care practices have a number of limitations. For example, patients can find it challenging to recall symptoms over longer time frames and can be unsure how to manage adverse events experienced at home. Clinical staff may not accurately record patients' experiences. Improved adverse-event reporting has the potential to benefit care through timely detection and management. Information technology offers potential for a feasible and cost-effective solution, but applied research is required.

Aims and objectives

This research programme developed and evaluated an electronic system called eRAPID (electronic patient self-Reporting of Adverse-events: Patient Information and aDvice). Key aims were to create a secure online system for cancer patients to self-report adverse events that could:

- be adapted for treatment settings
- allow patient reporting from home or hospital
- be integrated into routine care by documenting adverse events in electronic patient records in real time and generating clinician notifications
- provide patient advice to guide adverse event self-management or hospital contact.

The intervention was developed and tested in three treatment modalities (systemic therapy, pelvic radiotherapy and upper gastrointestinal surgery). The overall aim was to improve the safe delivery of treatment and enhance patient care.

Key research questions:

1. Is it feasible to collect routine adverse event data from patients' homes and clinics during cancer treatment and after discharge following cancer surgery?
2. Can eRAPID be implemented in different hospitals and treatment settings?
3. Will oncology health-care professionals review eRAPID reports during decision-making processes?
4. When added to usual care, will eRAPID lead to clinical benefits (improved adverse event/symptom control and patient safety) and better patient experiences?
5. Will eRAPID be cost-effective (systemic treatment only)?

Methods

Five work packages were applied across the treatment modalities:

- work package 1 – develop and implement the electronic platform across the hospitals
- work package 2 – patients: develop adverse event items and advice
- work package 3 – map health-care professionals and care pathways
- work package 4 – feasibility pilot studies to assess patient and clinician acceptability
- work package 5 – large-scale evaluation: a randomised controlled trial in systemic treatment to establish clinical effectiveness and cost-effectiveness.

Electronic platform

An electronic platform was developed, comprising an online questionnaire for self-reported adverse events and a web application for the transfer and display of adverse event data in electronic patient records. The platform was created at the Leeds site (Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK) and subsequently adapted for use at the Manchester (The Christie Hospital, The Christie NHS Foundation Trust, Manchester, UK) and Bristol sites (Bristol Royal Infirmary, University Hospitals Bristol NHS Foundation Trust, Bristol, UK).

Systemic treatment

During the development work, chemotherapy pathways were mapped and patient-reported adverse event items were developed. Consensus meetings with clinical teams and patients finalised adverse event reports, severity scoring and patient advice. Clinical usability testing was conducted.

A prospective, single-centre, randomised (1 : 1), two-arm, parallel-arm study with an internal pilot was conducted. Eligible patients were starting systemic treatment for breast, colorectal or gynaecological cancer. Participants were randomised to intervention (i.e. eRAPID) or usual care, stratified by cancer site/sex/previous chemotherapy. Usual care involved recently introduced acute oncology services, in which patients are typically reviewed before each treatment, most patients have specialist nurse support and all have 24 hours per day/7 days per week access to an emergency hotline. eRAPID was added to usual care. Intervention participants were asked to complete weekly symptom reports over 18 weeks.

The primary outcome was quality of life, measured using the Functional Assessment in Cancer Therapy Scale – General, Physical Well-Being subscale, assessed at 6, 12 and 18 weeks (primary time point). The main secondary outcomes were cost-effectiveness, assessed through comparison of health-care costs (including use of health-care services/patient expenses), and quality-adjusted life-years accruing to patients in the intervention and usual-care arms. Patient self-efficacy was assessed. End-of-study interviews and written feedback captured patient/staff views of eRAPID.

Radiotherapy

Development work (work packages 2 and 3) included a systematic review in prostate cancer, mapping of validated questionnaires, patient and clinician interviews, and a Delphi exercise to determine the best adverse event items. Symptom severity thresholds were established with clinical teams and management advice was prepared (guided by national/local resources). Patient pathways were mapped to determine time points for adverse event completions. A clinical usability study was carried out.

Feasibility pilot study

The pilot feasibility study was designed to establish feasibility and recruitment/attrition rates and select a primary outcome for a future randomised controlled trial. A prospective, two-centre, randomised (1 : 1) trial was conducted in two distinct treatment arms: (1) radical radiotherapy for early prostate cancer and (2) pelvic chemoradiotherapy for lower gastrointestinal (anal/rectal) and gynaecological (cervical/endometrial/vaginal) cancer(s). Participants allocated to the intervention reported adverse events/symptoms online for 12 weeks and at 18 and 24 weeks. We measured patient-reported outcomes (Functional Assessment in Cancer Therapy Scale – General, Physical Well-Being score/ European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire score), process of care (hospital contacts/admissions), EuroQol-5 Dimensions, five-level version, score and use of resources. End-of-study patient and staff interviews were conducted.

Surgery

eRAPID development (work packages 1–3) included:

- creation of an online symptom report from a review of European Organization for Research and Treatment of Cancer questionnaires, patient cognitive interviews and clinical opinion

- development of clinical algorithms triggering symptom severity-dependent patient advice and clinician alerts from (1) prospectively collected patient reported data, (2) stakeholder meetings and (3) patient interviews
- development of patient advice from clinician–patient consultations and patient interviews, hospital information and patient websites
- pathway mapping.

A pilot study (work package 4) evaluated the usability and feasibility of the intervention following cancer-related upper gastrointestinal surgery at two sites: the Bristol site and the Birmingham site (Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK). Participants completed the online symptom report at discharge, twice during week 1 and then weekly. Symptom report completeness, system alerts and barriers to the use of eRAPID were examined along with participant and clinician interviews.

Results

Systemic treatment

Online adverse event reports, severity thresholds/scoring algorithms and advice were finalised. Clinical usability testing of eRAPID was conducted (patients, $n = 12$; health-care professionals, $n = 10$), with the results used to refine the intervention.

Randomised controlled trial with internal pilot (January 2015–June 2018)

Overall, 1484 patients were assessed for eligibility, 702 were excluded pre approach and 92 after full eligibility assessment. Among the 690 fully eligible patients, 182 declined (26.4%) and 508 (73.6%) consented and were randomly assigned to the eRAPID intervention ($n = 256$) or usual care ($n = 252$). A total of 55 health-care professionals participated.

There was no statistically significant effect of the eRAPID intervention on the primary outcome at 18 weeks (pre-specified time point; adjusted difference least square means Functional Assessment in Cancer Therapy Scale – General, Physical Well-Being score 0.20; 95% confidence interval 0.81 to 1.20; $p = 0.6992$). There was a statistically significant intervention effect at the earlier time points of 6 weeks (adjusted difference least square means Functional Assessment in Cancer Therapy Scale – General, Physical Well-Being score 1.08, 95% confidence interval 0.12 to 2.05; $p = 0.0280$) and 12 weeks (adjusted difference least square means Functional Assessment in Cancer Therapy Scale – General, Physical Well-Being score 1.01, 95% confidence interval 0.05 to 1.98; $p = 0.0395$). The pre-planned exploratory subgroup analysis showed no effect in patients with metastatic disease ($n = 171$). In patients treated with curative intent ($n = 377$), a statistically significant positive effect was observed for the eRAPID intervention at 6 weeks (adjusted difference least square means Functional Assessment in Cancer Therapy Scale – General, Physical Well-Being score 1.45, 95% confidence interval 0.32 to 2.58; $p = 0.0112$) and 12 weeks (adjusted difference least square means Functional Assessment in Cancer Therapy Scale – General, Physical Well-Being score 1.13, 95% confidence interval 0.07 to 2.19; $p = 0.0362$), but not at 18 weeks (adjusted difference least square means Functional Assessment in Cancer Therapy Scale – General, Physical Well-Being score 0.04, 95% confidence interval −1.08 to 1.17; $p = 0.9430$).

No between-arm differences were found for admissions, calls/visits to acute oncology or chemotherapy delivery.

Within-trial cost-effectiveness analyses indicated that there were higher quality-adjusted life-year gains and lower costs in the eRAPID intervention arm than in the usual-care arm. Mean differences were small and not statistically significant. At the National Institute for Health and Care Excellence-recommended cost-effectiveness threshold of £20,000 per quality-adjusted life-year gained, the eRAPID intervention had a 55% probability of being cost-effective.

Patient intervention adherence levels were high: 3314 online symptom reports were completed (median compliance per patient 72.2%). Emergency alerts were activated in 29 out of 3314 online completions (0.9%), and serious symptoms not requiring immediate medical attention were reported on 163 out of 3314 occasions (4.9%). The majority of completions triggered self-management advice (2714/3314; 81.9%). Clinician engagement was variable. Post hoc exploratory analyses indicated that better patient adherence was associated with clinician use of the data, higher baseline Functional Assessment in Cancer Therapy Scale – General, Physical Well-Being score and older age. Patients with high levels of adherence had better Functional Assessment in Cancer Therapy Scale – General, Physical Well-Being scores over time than those with lower levels of adherence (eRAPID intervention: adjusted mean 21.7, 95% confidence interval 21.0 to 22.5; usual care: adjusted mean 20.2, 95% confidence interval 19.4 to 21.0; $p < 0.0001$).

The Self-Efficacy for Managing Chronic Diseases 6-item Scale scores showed a significant difference in mean self-efficacy score in favour of the intervention (0.48, 95% confidence interval 0.13 to 0.83; $p = 0.0073$). No differences were observed for Cancer Behaviour Inventory–Brief Version or Patient Activation Measure scores.

No between-arm differences were found for Functional Assessment in Cancer Therapy Scale – General and EuroQol-5 Dimensions, five-level version, scores. European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire summary scores suggested better symptom control at 12 weeks in the intervention arm ($p = 0.0111$). The EuroQol-5 Dimensions visual analogue scale showed better health in patients allocated to eRAPID at 12 weeks (difference in means 3.50, 95% confidence interval 0.35 to 6.66; $p = 0.0302$) and 18 weeks (difference in means 4.48, 95% confidence interval 1.11 to 7.86; $p = 0.0095$) but not at 6 weeks (difference in means 1.36, 95% confidence interval −1.66 to 4.39; $p = 0.3773$).

Radiotherapy

The systematic review found that patient-reported outcome measures were rarely used in acute toxicity reporting. The Male Pelvic Questionnaire and Female Pelvic Questionnaire had the best adverse event coverage for prostate, lower gastrointestinal and gynaecological cancers. Additional items were drawn from the Expanded Prostate Cancer Index Composite, European Organization for the Research and Treatment of Cancer and eRAPID adverse events. A total of 26 cancer health-care professionals, 48 patients and nine carers were interviewed. Final items were agreed through a Delphi consensus procedure. Final symptom reports included 51 items (prostate cancer, $n = 25$; gynaecological cancer, $n = 29$; anorectal cancer, $n = 47$). The usability testing involved 10 prostate cancer patients from the Leeds site, 10 gynaecology patients from the Manchester site and 12 health-care professionals.

Feasibility pilot study (December 2016–June 2018)

A total of 502 patients were screened for eligibility; 228 were approached and 167 provided informed consent (73.2%) and were randomised to the eRAPID intervention ($n = 83$) or usual care ($n = 84$) (prostate cancer, $n = 87$; gynaecological cancer, $n = 45$; lower gastrointestinal cancer, $n = 34$). The number of withdrawals was small (16/167, 9.6%; intervention, $n = 10$; usual care, $n = 6$). Patient adherence to weekly online reporting was 82% at week 1, 63% at week 12 and 40% at week 24. Prostate radiotherapy patients had high levels of adherence [93% at weeks 1 and 2 and 69% at week 12, but only 43% post treatment (i.e. at week 24)]. The adherence level was lower in chemoradiotherapy patients (between 74% and 52%, and down to 31% post treatment). The algorithms activated alerts for severe symptoms (4% for chemoradiotherapy patients and 0.5% for prostate cancer patients). Patient-reported outcomes suggested a trend in the eRAPID chemoradiotherapy arm towards reporting less deterioration over time than in the usual-care arm, with greater differences at 6 weeks for Functional Assessment in Cancer Therapy – General, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire summary score, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire global health score, EuroQol-5 Dimensions visual analogue scale scores. In the prostate radiotherapy arm, there were no changes over time and no differences between the eRAPID

intervention and usual care. However, these data should be interpreted with caution because of the small numbers, wide 95% confidence intervals and an imbalance in the outcome measures at baseline. Interviews revealed that the eRAPID intervention was acceptable to patients and staff. Clinicians felt that a longer monitoring period would be valuable to capture late effects.

Surgery

Item development, including interviews with 18 patients, identified 35 symptom report items. The prospective study of patient self-reported symptoms to inform clinical algorithms identified 130 eligible patients among 300 (43%) screened patients. A total of 61 (47%) patients consented to participate and 59 (97%) provided 444 complete self-reports. Self-report data ($n = 27$ patients), 66 patient interviews ($n = 59$ patients) and two stakeholder meetings informed advice/alert development. Comparisons between eRAPID symptom-report data, telephone consultations and clinical events/outcomes ($n = 27$ patients) further refined clinical algorithms. A total of 15 telephone consultations, seven patient interviews and review of 28 patient information leaflets and three websites identified self-management advice for 22 symptoms.

In the pilot, 29 (71%) out of 41 eligible patients screened in the Bristol site and 11 (55%) out of 22 eligible patients screened in the Birmingham site consented. Symptom report response rates at key assessment time points were high (range 63–100%). Out of 197 Bristol site eRAPID completions analysed, 76 (39%) triggered self-management advice, 72 (36%) trigged advice to contact a clinician, nine (5%) triggered a clinician alert and 40 (20%) did not require advice. A total of 63 Birmingham site eRAPID completions were analysed, of which 36 (57%) triggered self-management advice, 20 (32%) triggered advice to contact a clinician, one (2%) triggered a clinician alert and six (10%) did not require advice. Participants found eRAPID reassuring, providing timely information and recovery advice. All relevant clinicians participated in accessing and acting on alerts triggered by eRAPID. Clinicians regarded the system as a valuable adjunct to care.

Limitations

The systemic randomised controlled trial, 1 : 1 trial design and pilot studies in radiotherapy and surgery led to small patient numbers simultaneously using the intervention. Consequently, staff saw limited numbers of patients using eRAPID and did not have regular opportunities to review adverse event symptoms reports. This may have had a negative impact on clinician engagement. There was a potential for contamination bias because staff saw patients across both study arms. The direction of the bias is towards reducing the intervention effect and, therefore, could potentially explain the relatively limited impact of eRAPID. The health economic results may also have been limited by levels of missing patient outcome data (use of resources and EuroQol-5 Dimensions, five-level version, scores) and the fixed data collection points, as fluctuations in patient health may have be missed. The cost-effectiveness may be underestimated, as the software costs were split only across patients allocated to the eRAPID intervention and not across a much larger patient group, resulting in a higher cost per patient.

Conclusions

This programme of online symptom monitoring in oncology was successfully delivered over 7 years. A wide range of intervention development and evaluation activities across three main cancer treatment modalities were conducted.

Systemic treatment

Online adverse event monitoring during chemotherapy, using self-reporting with severity-tailored advice, did not lead to significant improvement in patient symptom control at 18 weeks. A small positive effect was observed early within the treatment period (6 and 12 weeks) and mainly in the

subgroup treated with curative intent, consisting of patients receiving (neo-)adjuvant treatment (chemotherapy naive). There was no increase in hospital workload (hospital admissions, contacts or chemotherapy delivery). The intervention was added to already good usual care with 24 hours per day/7 days per week acute oncology services, and importantly did not increase the use of NHS resources. Health economic analysis indicated eRAPID was less costly and more effective in the management of adverse events than usual care, although mean differences were small and not statistically significant. eRAPID supported patient self-efficacy and many reported how useful and reassuring they found the intervention and management advice. Engagement from both patients and clinicians is vital to maximise intervention effectiveness.

Radiotherapy

The systematic review and Delphi process informed the content of the pelvic radiotherapy symptom reports. The two-centre pilot eRAPID randomised controlled trial confirmed recruitment feasibility and intervention acceptability. Consent rates of > 70%, a withdrawal rate of < 10% and adherence rates to online completions of 60–70% in prostate cancer and anorectal cancer patients are encouraging and justify further studies to explore online monitoring during treatment. The eRAPID approach may not be suitable for women aged < 40 years receiving intensive chemotherapy for advanced cervical cancer.

Surgery

The pilot study confirmed that the newly developed eRAPID information technology system for remote symptom monitoring in patients recovering from upper gastrointestinal cancer surgery is feasible and acceptable. A definitive study is planned to evaluate the impact of the system on patient recovery.

We implemented and maintained an innovative secure electronic system for the online reporting of adverse events in three hospitals. Our solution was one of the first to allow patient online symptom reporting (via a public-facing website), with data securely transferred in real time to electronic patient records to support patient care.

Trial registration

The systemic randomised controlled trial is registered as ISRCTN88520246. The radiotherapy trial is registered as ClinicalTrials.gov NCT02747264.

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