Systematic review

Systematic review and meta-analysis of enhanced recovery programmes in surgical patients

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Background: **Enhanced recovery programmes (ERPs) have been developed over the past 10 years to improve patient outcomes and to accelerate recovery after surgery. The existing literature focuses on specific specialties, mainly colorectal surgery. The aim of this review was to investigate whether the effect of ERPs on patient outcomes varies across surgical specialties or with the design of individual programmes.**

Methods: **MEDLINE, Embase, CINAHL and the Cochrane Central Register of Controlled Trials were searched from inception to January 2013 for randomized or quasi-randomized trials comparing ERPs with standard care in adult elective surgical patients.**

Results: **Thirty-eight trials were included in the review, with a total of 5099 participants. Study design and quality was poor. Meta-analyses showed that ERPs reduced the primary length of stay (standardized mean difference −1·14 (95 per cent confidence interval −1·45 to −0·85)) and reduced the risk of all complications within 30 days (risk ratio (RR) 0·71, 95 per cent c.i. 0·60 to 0·86). There was no evidence of a reduction in mortality (RR 0·69, 95 per cent c.i. 0·34 to 1·39), major complications (RR 0·95, 0·69 to 1·31) or readmission rates (RR 0·96, 0·59 to 1·58). The impact of ERPs was similar across specialties and there was no consistent evidence that elements included within ERPs affected patient outcomes.**

Conclusion: **ERPs are effective in reducing length of hospital stay and overall complication rates across surgical specialties. It was not possible to identify individual components that improved outcome. Qualitative synthesis may be more appropriate to investigate the determinants of success.**

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Introduction

Approximately 234 million surgical operations are performed globally each year, with 8·1 million taking place in the UK[1]. Some 2·9 million operations require a general anaesthetic each year in the UK[2]. Demographic change, technological advances and the increasing burden of chronic disease have resulted in this high volume of surgery. This is likely to increase in coming years, placing a further demand on limited healthcare resources. Enhanced recovery programmes (ERPs) have been developed over the past 10 years. Their main aim is to improve patient outcomes and to accelerate recovery after surgery, with benefits to patients, staff and healthcare systems, as more patients are treated with the available resources[3,4].

ERPs are multifaceted approaches, involving intervention in all three phases of care: preoperative (assessment, counselling, avoidance of premedication, nutrition); intraoperative (minimally invasive surgery, regional anaesthesia, standardized anaesthetic protocol); and postoperative (early mobilization, nutrition, pain relief). The component interventions aim to maintain physiological function and to reduce the stress associated with surgery. Involvement of patients in decision-making and in their own recovery is a key feature of these programmes.

ERPs originally focused on colorectal surgery and this specialty still dominates the literature[5–7], but in practice all specialties are being encouraged to develop and apply such programmes[3]. Most of the existing studies and reviews focus on specific patient groups, the majority dealing with colorectal surgery. Evidence from specialties other than colorectal surgery, such as orthopaedics, aortic aneurysm repair or urogenital surgery, is provided largely by

Table 1 Checklist of potential elements in enhanced recovery programmes

Element	Examples of intervention
Preoperative	
Education/counselling/assessment	Patient being informed of surgical pathway, told what to expect after surgery, what they can do to prepare/help
	Discharge planning – possibly involving social therapists
	Optimized medical/health condition via preoperative assessment
Same-day admission/limited hospital stay	
Attention to fluid balance	Optimization of fluid hydration
Minimization of fasting period	Preoperative carbohydrate loading
Avoidance of premedication	Avoidance of long-acting sedatives, such as diazepam
Prophylaxis	Thromboprophylaxis, prophylactic antibiotics
Intraoperative	
Balanced/multimodal analgesia	Pre-emptive analgesia initiated before surgery
	Epidural anaesthesia
	Infiltration of wounds with local anaesthetic
	Intrathecal morphine
	Systemic local anaesthetic use
Use of short-acting anaesthetics	Intravenous and inhalational
Intravenous fluid replacement/restriction	Oesophageal Doppler technique
	Goal-directed fluid therapy
Minimally invasive techniques	For example transverse incisions, laparoscopy
Active prevention of hypothermia	
Avoidance of drains and lines	Including nasogastric tubes
High oxygen concentrations	Both intraoperative and perioperative
Postoperative	
Early mobilization	Walking from day 1 if possible
Early removal of drains, lines and urinary catheters	
Early oral intake	Immediate oral intake (liquids) and food from day 1
Balanced analgesia	Regional anaesthesia (local to surgical wound)
	Opioid-avoiding multimodal techniques – NSAIDs, paracetamol
	Continuation of epidural anaesthesia
	Peripheral opioid antagonist use
Prophylaxis against nausea and vomiting	Routine antiemetics
Use of prokinetics, laxatives or chewing gum	Routine use
Colorectal-specific	
Avoidance of bowel preparation	
Use of prebiotics and probiotics	

NSAID, non-steroidal anti-inflammatory drug.

observational studies[8]. This fragmented literature means that important overarching questions about ERPs have not been addressed and there is need for an overview of their impact on the recovery of patients across different surgical disciplines.

Using data from randomized clinical trials (RCTs), this systematic review aimed to describe the impact of ERPs compared with standard care in adult elective surgical patients on a range of outcomes, including mortality, complications and time to discharge from hospital. Specific research questions were whether the effect of ERPs is dependent on the type of surgical procedure or the components of the specific protocol.

Methods

The protocol for the systematic review was not published but is available from the corresponding author.

Eligibility criteria

Types of study considered for inclusion were RCTs and quasi-RCTs (in which the allocation to the intervention was decided by non-random means such as alternation, digits in date of birth or other identification number). Participants were required to be aged 16 years or over, undergoing any elective surgical operation, under either regional or general anaesthetic. An ERP was defined as one that included at least four elements from a checklist of 21 recognized elements, based on previous reviews and in consultation with local clinicians from a range of specialties (*Table 1*). A comparison programme had to have at least three elements fewer than the intervention group. Included studies reported one of the following outcomes: mortality within 30 days of surgery, non-fatal complications within 30 days of surgery (defined according to surgical procedure) or primary length of hospital stay (time from admission to first discharge).

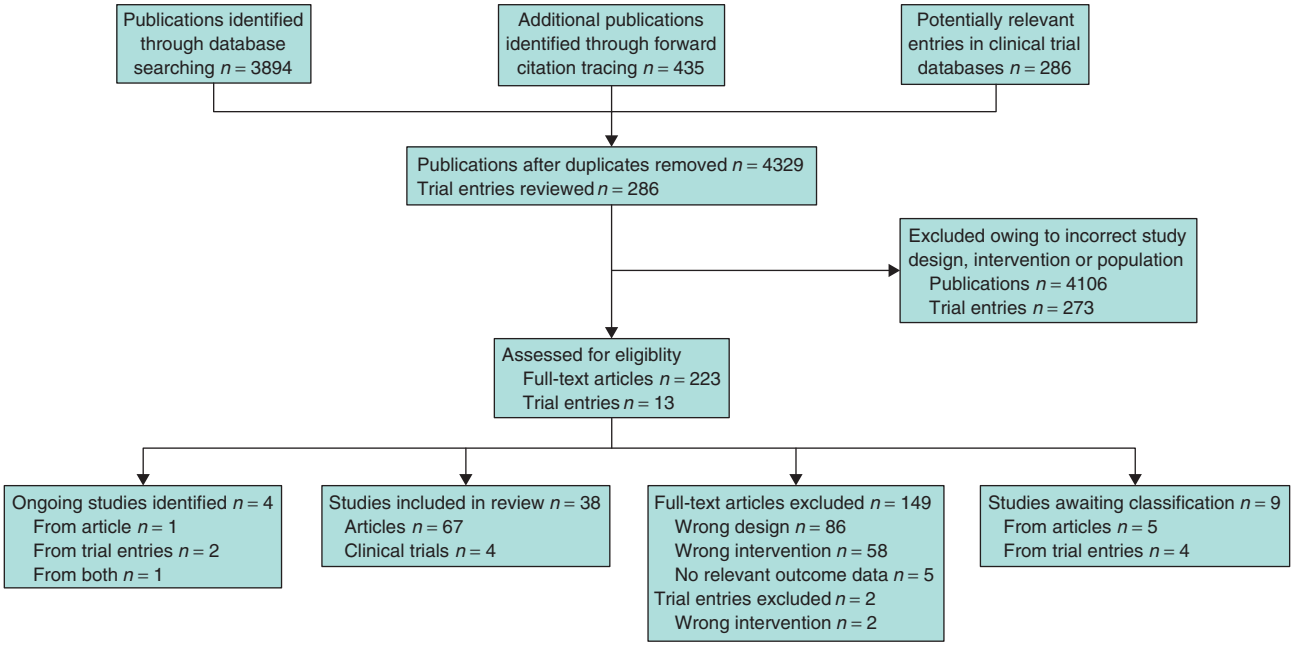

Fig. 1 Selection of articles for review

Search methods

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase (via Ovid), and Cumulative Index to Nursing and Allied Health Literature (CINAHL, via EBSCO) were searched from inception to 21 January 2013. The Cochrane highly sensitive filters for RCTs were applied in MEDLINE and Embase, and the SIGN filter for RCTs in CINAHL; no filters were used in CENTRAL. No language filters were applied. The search strategies are summarized in *Table S1* (supporting information). Forward citation tracking on three papers[9–11] identified as being important in the enhanced recovery literature, and backwards citation tracking by analysing the reference lists of six systematic reviews[5,8,12–15] was performed. Clinical trial registers (http://www.clinicaltrials.gov; http://www.controlled-trials.com) were searched in July 2012 using the terms 'fast track' and 'enhanced recovery'.

Selection of studies and data extraction

Two authors independently screened all titles and abstracts or clinical trial entries to remove studies unlikely to be eligible. The full texts of potentially relevant titles were reviewed and the checklist of potential components of the ERPs were completed to clarify eligibility. For trial entries identified as potentially eligible, available information and linked publications were used to complete the checklist. Trial investigators were contacted and, if necessary, asked to complete the checklist.

Two authors independently extracted data from eligible studies. If more than one publication was identified from the same study, a composite data set from all the eligible publications was created. If relevant information or data were not available in the paper, the lead author was contacted to request the additional details. Disagreements were resolved by discussion and, if necessary, consultation with a third investigator.

The following items were included in the data extraction form: patient group (age, demographic, type of surgical operation, healthcare setting), intervention and comparison (numbers and types of component), outcomes (outcomes collected and those reported in the publication). For each outcome, the definition, unit of measurement, method of ascertainment, timing, and number of participants assigned to each intervention group were recorded. For dichotomous outcomes (mortality, complications, readmission), totals and numbers of events within each randomization group were extracted if available. If risk ratios (RRs) only were reported, these were used in analyses. Studies that reported in-hospital or postoperative mortality or complications without precise length of follow-up were included, but not those in which a longer follow-up was specified or implied. Null values for mortality were included in the data extraction only

Table 2 Characteristics of included studies

Study	Lead reference	Patient group	Type of surgery	No. of patients		No. of ERP components used	
				ERP group	Control group	ERP group	Control group
Aizawa 2002	20	Genitourinary	Transurethral resection of prostate	32	37	5	0*
Anderson 2003	11	Colorectal	Open right/left hemicolectomy	14	11	11	0
Borgwardt 2009	21	Joint	Knee replacement	17	23	5	2
Cho 2011	22	Joint	Shoulder surgery	40	40	4	1
Delaney 2003	23	Colorectal	Open intestinal resection	31	33	4	0
Demanet 2011	24	Genitourinary	Radical nephrectomy	22	23	4	0*
Garcia-Botello 2011	25	Colorectal	Mixed laparopscopic and open (68%) colorectal	61	58	10	2
Gatt 2005	26	Colorectal	Open colorectal	19	20	11	2
Gooch 2009	27	Joint	Hip and knee replacement	1066	504	8	0*
Gralla 2007	28	Genitourinary	Laparoscopic radical prostatectomy	25	25	13	6
He 2010	29	Upper GI tract	Surgery for gastric cancer	41	41	13	0
Henriksen 2002	30	Colorectal	Colorectal; assume open	20	20	6	3
Ionescu 2009	31	Colorectal	Open colorectal	48	48	11	2
Khoo 2007	32	Colorectal	Colorectal; assume open	35	35	9	2
Kroon 2010	33	Genitourinary	Abdominal hysterectomy	27	26	7	2
LAFA	34	Colorectal	Colorectal open and laparoscopic procedures reported separately	193	207	13	4
Larsen 2008	35	Joint	Total knee or hip replacement	45	42	5	2
Lee 2011	36	Colorectal	Laparoscopic colonic resection	46	54	7	3
Liu 2008	37	Colorectal	Colorectal; assume open	44	39	6	0
Liu 2010	38	Upper GI tract	Surgery for gastric cancer	33	30	9	1
Muehling 2008a	39	Other	Abdominal aortic anuerysm repair	49	50	9	1
Muehling 2008b	40	Thoracic	Lung resection	30	28	7	2
Petersen 2006	41	Joint	Hip replacement	34	36	5	2
Recart 2005	42	Genitourinary	Laparoscopic nephrectomy	13	12	8	1
Ren 2012	43	Colorectal	Colorectal; assume open	299	298	11	3
Roig 2011	44	Colorectal	Mixed laparoscopic and open (60%) colorectal	69	39	8	2
Serclová 2009	45	Colorectal	Open colorectal	51	52	10	2
Shchepotin 2012	46	Upper GI tract	Pancreatoduodenal resection	11	10	8	0*
Sokouti 2011	47	Thoracic	Lung resection	30	30	4	0
Wang 2009	48	Upper GI tract	Surgery for gastric cancer	46	46	11	0
Wang 2010	49	Upper GI tract	Surgery for gastric cancer	45	47	11	0
Wang 2012a	50	Colorectal	Colorectal open and laparoscopic procedures reported separately	81	82	8	0
Wang 2012b	51	Colorectal	Laparoscopic colorectal resection	40	38	8	0
Xu 2007	52	Colorectal	Colorectal; assume open	34	34	8	0
Yang 2012	53	Colorectal	Open colorectal	32	30	10	5
Zhang 2010	54	Colorectal	Colorectal; assume open	43	43	6	0
Zhao 2010	55	Thoracic	Lung resection	38	36	11	1
Zhao 2012	56	Upper GI tract	Radical oesophageal surgery	34	34	9	0*

*Based on limited information. ERP, enhanced recovery programme; GI, gastrointestinal. LAFA, LAparoscopy and/or FAst track multimodal management trial.

for studies that actually specified there had been no deaths.

Complications were assessed where possible using the Clavien–Dindo classification[16], based on information available in the publication or with extra details obtained from authors. Complications were classified into all non-fatal (grade I–IV), and minor (I–II) and major (III–IV). Minor complications were those that were not life-threatening and could be treated without return to surgery, such as wound infections, ileus, anastomotic leaks that resolved without surgery and urinary retention. Major complications included deep vein thrombosis, pulmonary embolism, myocardial infarction and any requiring reoperation. If details were unclear, the study authors' classification into minor and major was accepted. Data were extracted, if possible, for both the number of patients with complications and the number of events. For analysis of numbers of patients with complications, those

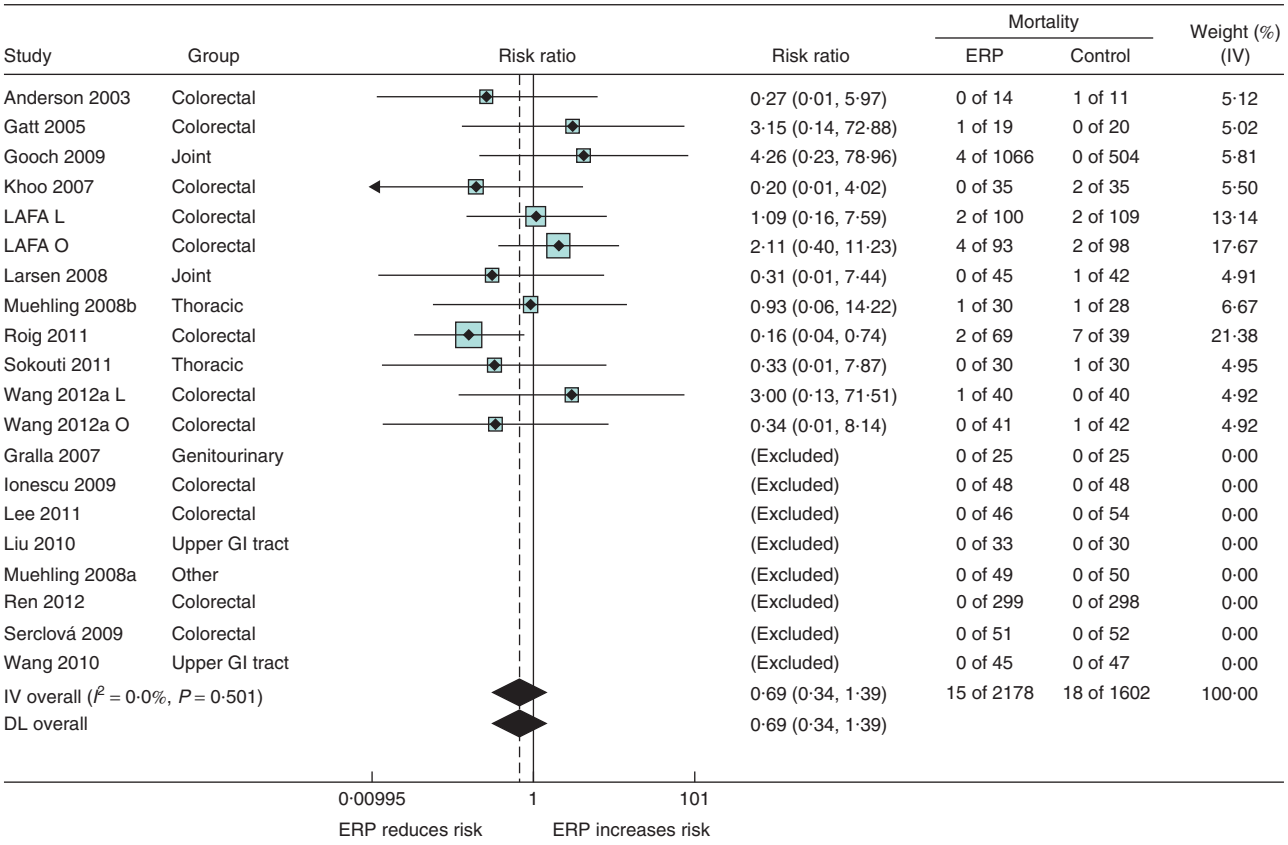

Fig. 2 Meta-analyses of mortality in enhanced recovery programme (ERP) *versus* control groups. Risk ratios are shown with 95 per cent confidence intervals. Overall effect estimates are shown for inverse-variance (IV) fixed-effect and DerSimonian and Laird (DL) random-effects models. LAFA, LAparoscopy and/or FAst track multimodal management *versus* standard care trial; L, laparoscopic; O, open; GI, gastrointestinal

who developed more than one complication were graded by the most serious event. Primary length of stay was converted into days. These data were used as mean(s.d.) wherever possible. Median and ranges were presented if means were not available.

Assessment of study quality

Study quality assessment was based on the Cochrane risk of bias tool[17] using the following domains: sequence generation and allocation concealment; performance and detection bias; incomplete outcome data; selective outcomes reporting; and other bias. It is not feasible to conduct fully blinded studies for this research question, as both the patients and staff know the nature of the intervention. Given these difficulties, if a study did not mention any blinding of staff or patients and it was not possible to contact the authors, the study was assumed to be unblinded and therefore at high risk of performance and detection bias. It was, however, possible for detection bias to be reduced by using standardized criteria for complications and discharge, and for outcome assessors to be unaware of the patients' allocation.

Statistical analysis

Data were entered into RevMan[18] and Stata® version 12 (StataCorp LP, College Station, Texas, USA) and pooled across all studies initially. Count data for complications were analysed by assuming standard follow-up time (30 days) unless stated otherwise and calculating a rate ratio for the intervention group[19]. Rate ratios were used in meta-analysis (metan command) using the generic inverse-variance method. Standardized mean differences (SMDs), expressed as a proportion of standard deviation (s.d.), were used in meta-analyses of length of stay to account for differences between operation type. Both fixed-effect (inverse-variance method) and random-effects (DerSimonian and Laird) models were run. Effect estimates are presented with 95 per cent confidence intervals (c.i).

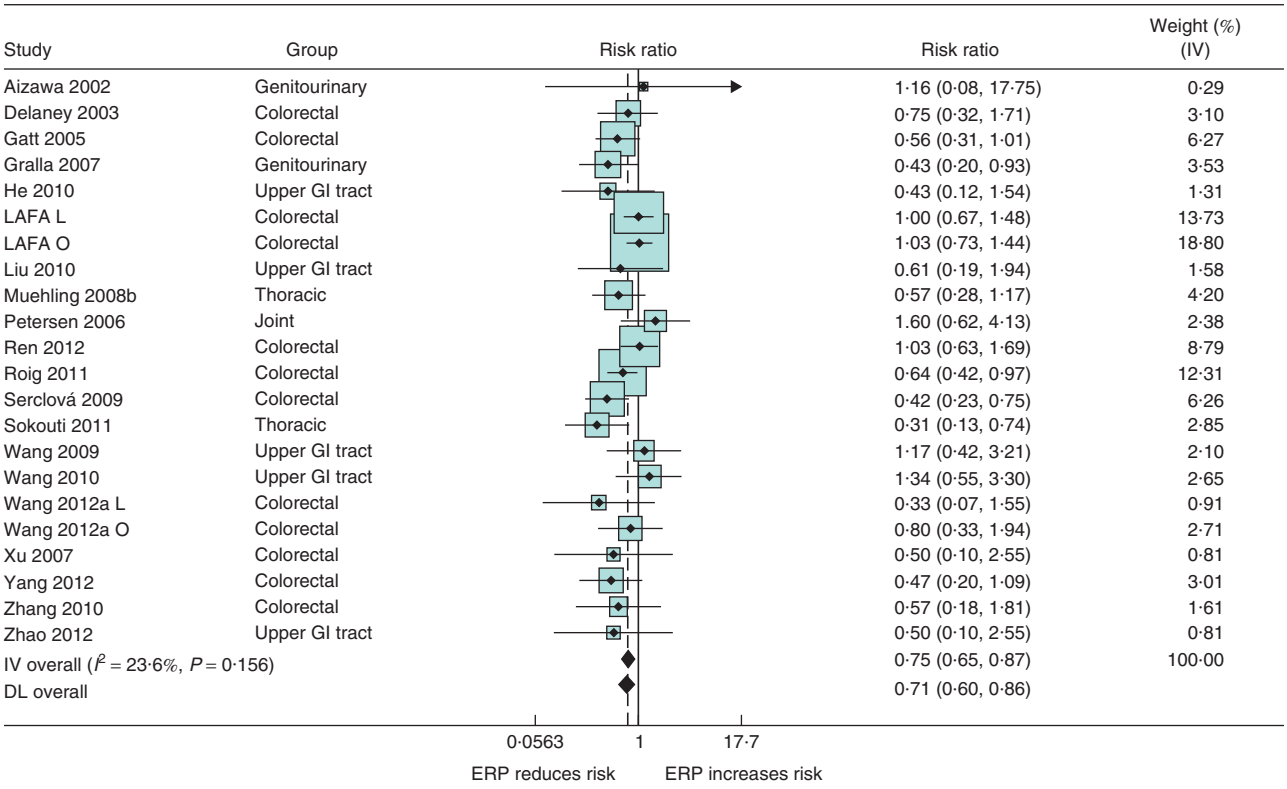

Fig. 3 Meta-analyses of all complications (by patient) in enhanced recovery programme (ERP) *versus* control groups. Risk ratios are shown with 95 per cent confidence intervals. Overall effect estimates are shown for inverse-variance (IV) fixed-effect and DerSimonian and Laird (DL) random-effects models. GI, gastrointestinal; LAFA, LAparoscopy and/or FAst track multimodal management *versus* standard care trial; L, laparoscopic; O, open

Funnel plots (metafunnel command) were prepared to assess the potential for publication bias if ten or more studies reported on a particular outcome. Visual assessment was supplemented by Egger's test for small-study effects for continuous variables and the Harbord test for dichotomous variables (metabias command). For each outcome, cumulative meta-analysis was carried out to describe the pattern of evidence over time.

Heterogeneity between studies due to the type of operation or the components included in ERPs (prespecified hypotheses) was investigated using subgroup analyses and meta-regression. The difference in effect sizes between subgroups was assessed using the test for heterogeneity between groups and by random-effects meta-regression models (metareg command), using the Hedges option and entering the meta-regression variable as dichotomous, categorical and linear variables as appropriate. Significance was assessed using the significance of the variable for linear or dichotomous variables, and the model fit for categorical variables.

Surgical procedures were grouped into: colorectal (including open and laparoscopic procedures); upper gastrointestinal tract surgery (including hepatic resection); joint (hip, knee and shoulder surgery); genitourinary (ranging from transurethral resection of prostate to radical cystectomy); thoracic (lung surgery); and other (spinal and aortic surgery). For colorectal surgery, studies were divided into laparoscopic, open or mixed approaches.

The total number of elements of ERPs in the intervention group was used both as a continuous and as a grouped variable (4–7, 8–10, 11 or more). The difference in number of elements in the intervention and control groups was calculated overall and for each phase of care. For subgroup analyses, studies were divided into groups based on the difference in number of elements, above or below the median.

Sensitivity analyses were carried out to assess the impact of study design and risk of bias on the results. Studies published in abstract form, quasi-randomized studies, and studies with variation in length of follow-up and presence or absence of standardized criteria for outcomes were considered.

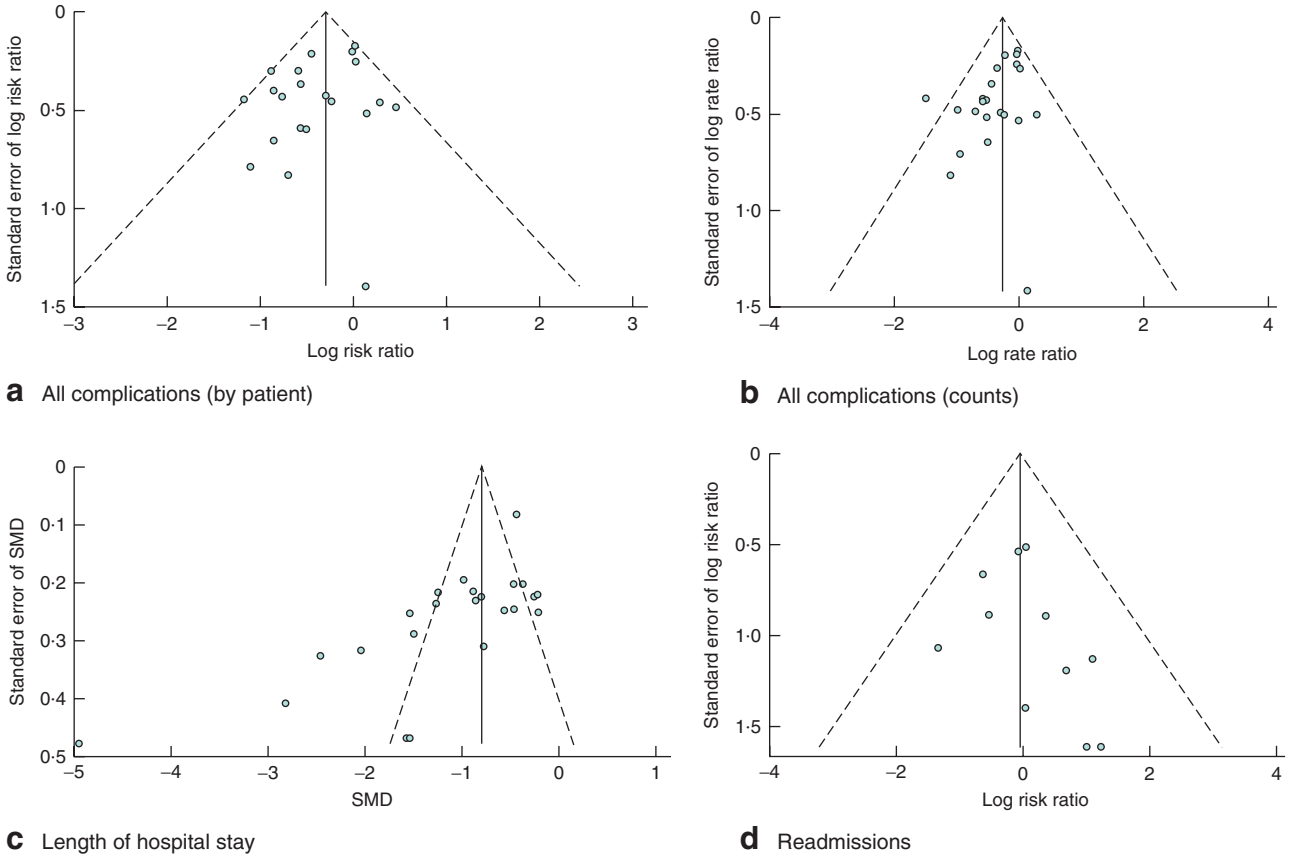

Fig. 4 Funnel plots with pseudo 95 per cent confidence intervals for: **a** all complications (by patient), **b** all complications (counts), **c** length of hospital stay and **d** readmissions. SMD, standardized mean difference

Results

Literature search

The results of the literature search are summarized in *Fig. 1*. Thirty-eight eligible studies with relevant outcomes[11,20–56] were found, including two quasi-randomized studies[22,44]. In total 67 papers on these studies were reviewed (*Appendix S1*, supporting information). Two studies[34,50] on patients undergoing colorectal surgery included both open and laparoscopic procedures, and reported separate results; these were entered as separate study populations in the meta-analyses. There were ten non-English language papers: eight[29,37,48,52,54–57] in Chinese, one[20] in Japanese and one[58] in German. Two studies[24,46] were reported in abstract form only.

Four ongoing studies were identified (2 published[59,60], 2 trial entries; *Table S2*, supporting information) and there were nine with insufficient information available to be clear about eligibility (5 published[61–65], 4 trial entries; *Table S3*, supporting information). Six studies[66–71], with four or more elements of ERP but a difference of only two elements between intervention and control groups, were excluded, including some studies that had been included in other reviews[67]. Three studies[72–74] that were otherwise eligible but did not present outcome data in a usable form were excluded from the analyses.

Characteristics of included studies

The 38 eligible studies, with a total of 5099 participants, are summarized in *Table 2* and *Table S4* (supporting information). The majority of studies investigated the use of ERPs in gastrointestinal surgery, with 18 studying colorectal surgery and six upper gastrointestinal surgery. Five studies investigated genitourinary surgery, five joint surgery, three lung surgery and one aortic aneurysm repair. Many study populations excluded vulnerable and frail patients. Common exclusions were more complicated surgery, inability to live independently at home, contraindications to early discharge, and psychiatric and serious physical ill health. The proportion of patients

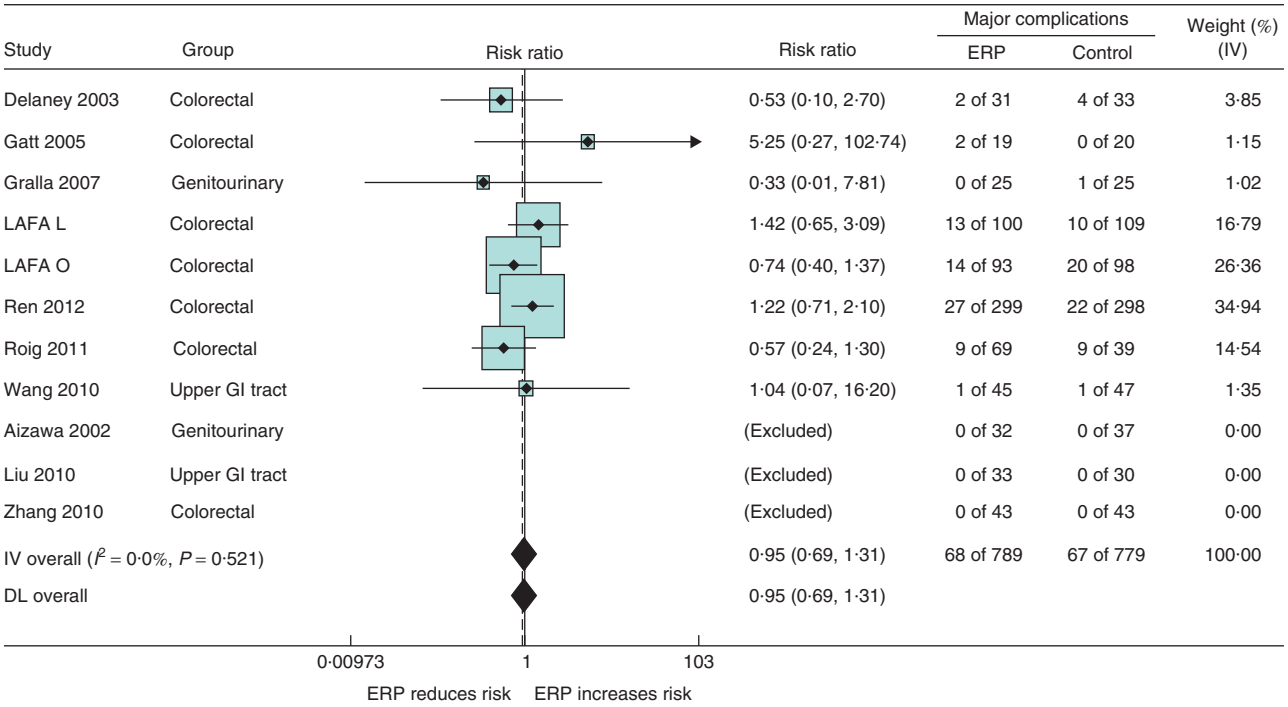

Fig. 5 Meta-analyses of major complications (by patient) in enhanced recovery programme (ERP) *versus* control groups. Risk ratios are shown with 95 per cent confidence intervals. Overall effect estimates are shown for inverse-variance (IV) fixed-effect and DerSimonian and Laird (DL) random-effects models. LAFA, LAparoscopy and/or FAst track multimodal management *versus* standard care trial; L, laparoscopic; O, open; GI, gastrointestinal

excluded was not always reported; it was given as 3 per cent by Larsen and colleagues[35], 17 per cent by Lee and co-workers[36] and 10 per cent by Wang *et al.*[50].

Most studies were of moderate size, typically with fewer than 100 subjects included. The median (i.q.r.) number of elements of ERPs in the intervention and control groups was 8 (6–11) and 1 (0–2) respectively. The median difference in number of elements between intervention and control group was 7·5 (5–8). Thirty-four of the 38 studies had elements of the intervention in all three phases of care, with 36 studies including preoperative elements, 29 intraoperative elements and all 38 including postoperative elements. The median difference in number of preoperative, intraoperative and postoperative elements was 2 (1–2), (1–3) and 3 (3–4) respectively.

Study quality

Overall the standard of reporting was low, with many Consolidated Standards of Reporting Trials (CONSORT) details not given. Two studies were quasi-randomized, with allocation depending on odd or even hospital numbers[22] or order on waiting list[44]. Only six studies[29,31,32,34,36,53] gave sufficiently full descriptions for them to be assessed as at low risk of bias for randomization and allocation concealment. Two studies[23,24] with unclear descriptions of randomization had baseline imbalances that may have affected the results.

None of the studies attempted to blind staff or patients to the allocation. Some[30,32,34,35,38,50] put intervention and control groups on different wards to avoid contamination bias, but in others the patients were treated on the same wards or no details were given. Diagnostic criteria or prespecified definitions for complications were not reported. Two studies[33,55] reporting some complications were not included in the analyses because of concerns that only selected complications had been reported. The majority of studies did not give details of who assessed complications. Ren and colleagues[43] stated that outcome assessors were blinded, whereas in the study by Serclová *et al.*[45] complications were assessed by independent physicians, but it was not clear whether they were blinded. One study[27] had an independent panel for outcomes, but this panel relied on data collected routinely on wards by staff who were aware of the allocation.

Twenty studies[11,21,23,25,26,31–36,38,39,41–43,49–51,53] reporting length of stay had standardized discharge criteria. In one[27] the criteria differed between intervention and

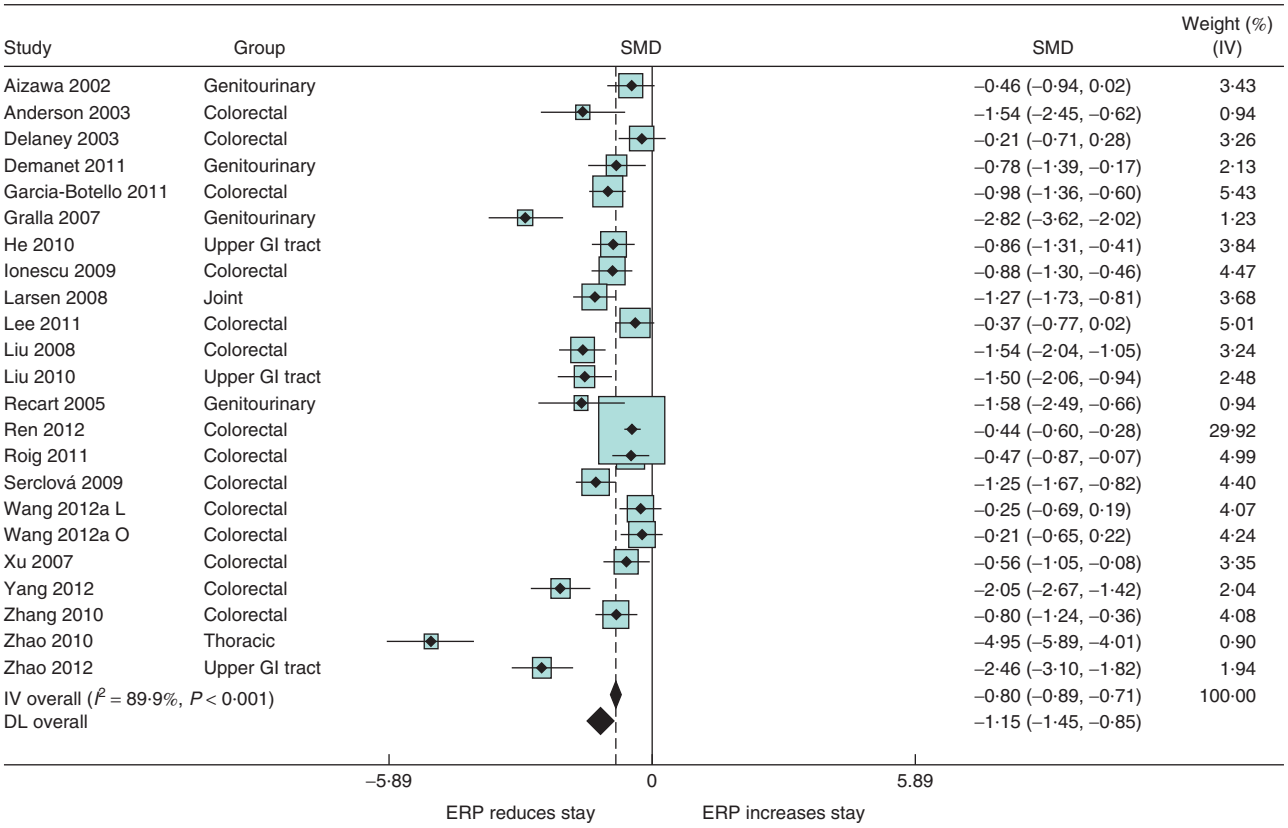

Fig. 6 Meta-analyses of length of primary hospital stay in enhanced recovery programme (ERP) *versus* control groups. Standardized mean differences (SMDs) are shown with 95 per cent confidence intervals. Overall effect estimates are shown for inverse-variance (IV) fixed-effect and DerSimonian and Laird (DL) random-effects models. GI, gastrointestinal; L, laparoscopic; O, open

control groups. In another study[28] length of stay was explicitly part of the intervention, with discharge planned for day 3 in the intervention group and day 6 for the control group. In most studies fitness for discharge was assessed by medical or nursing staff who were aware of the intervention. In three studies[41,42,75] an independent assessor decided on discharge, but in only one[41] was it clear that this assessor was blinded. Patient opinion and readiness for discharge appropriately often comprised part of the criteria for discharge. However, as patients were unblinded, this had the potential to introduce bias.

Twenty studies[11,20,21,23,25,26,28,31,32,34,36,37,38,39,41,42,45,49,53] reported readmission rates. No studies indicated that staff deciding on readmission were blinded to the allocation of patients or gave standardized criteria for readmission. As patients initiate readmission and were not blinded, this outcome was considered at high risk of detection bias. One study[25] specified that attendance at the emergency department was not classified as readmission. Most studies reported readmission within 30 or 28 days, but six[20,23,28,31,42,53] did not give a time frame and one[32] reported readmission within 14 days. One study[21] reported no readmission within 3 months of surgery, so these data were included.

In general, exclusions after randomization were appropriate and not a cause for concern. Many studies gave no details of funding, although three[30,34,41] reported partial funding from commercial sources but with no details of the involvement of these sponsors in the trial.

Effect of enhanced recovery programmes on outcomes

Twelve studies reported deaths and a further eight documented no deaths (*Fig. 2*). The pooled estimate of risk ratio of death within 30 days for the ERPs groups was 0·69 (95 per cent c.i. 0·34 to 1·39), a non-significant reduction. Event rates were low, with only 15 deaths (0·7 per cent) among 2178 patients in ERPs groups and 18 (1·1 per cent) of 1602 in control groups. There was no evidence of heterogeneity between studies. The funnel plot was symmetrical and there was no statistical evidence of small-study effects ($P = 0·929$).

Results for all complications were analysed separately by patient and by total number of complications. Results for the latter were converted into rate ratios. The results from both analyses were similar, with a significant reduction in complications in the intervention group. The pooled RR from the random-effects model was 0·71 (0·60 to 0·86) for the patient data (*Fig. 3*) and the pooled rate ratio was 0·77 (0·66 to 0·90) for the count data. There was no evidence of heterogeneity in either analysis. Both funnel plots showed asymmetry (*Fig. 4a*,*b*), and the Harbord and Egger tests for small-study effects had *P* values of 0·042 and 0·011 for patient and count data respectively.

Eleven studies[20,23,26,28,34,37,43,44,49,54] reported major complication events by patient and ten[23,27,30,34,39,40,43,47,49] reported count data, with an overlap of five studies. There was no evidence of a reduction in risk of major complications in ERPs in either analysis. The pooled RR from the random-effects model was 0·95 (0·69 to 1·31) for the patient data (*Fig. 5*), and the pooled rate ratio was 0·98 (0·74 to1·29) for the count data. These results do not exclude an increased risk of up to 30 per cent. There was no evidence of heterogeneity in either analysis ($I^2 = 0$ per cent in both patient and count models). There was no asymmetry in the funnel plots and the Harbord and Egger tests for small-study effects were not significant ($P = 0·756$ and $P = 0·254$ for patient and count data respectively).

Twenty-three studies reported data on primary length of hospital stay as mean(s.d.) (*Fig. 6*). The pooled estimate showed a significant reduction in stay for the intervention group: SMD −1·15 (95 per cent c.i. −1·45 to −0·85). However, there was extremely high level of heterogeneity between studies ($I^2 = 89·9$ per cent). The funnel plot showed extreme asymmetry, with a group of small studies showing a reduction in stay greater than the pooled estimate, but no small studies with a reduction smaller than the pooled estimate (*Fig. 4c*). The Egger test for small-study effects was highly significant ($P = 0·001$). A further 15 studies presented data as medians (*Table 3*). Ten of these reported a significant reduction in stay in the intervention group, three reported non-significant differences and two studies reported reduced stay in the intervention group but did not report significance tests.

Twenty studies reported readmission events, but nine of these had no events in either group. The pooled RR for readmission for ERPs groups compared with control groups was 0·96 (0·59 to 1·58) (*Fig. 7*). There was no evidence of heterogeneity between studies. The funnel plot showed some asymmetry, with the smaller studies being more likely to report an increased readmission rate (*Fig. 4d*) (Harbord test for small-study effects, $P = 0·094$).

Table 3 Length of hospital stay

Study	Study groups	Hospital stay (days)*	*P*‡
Borgwardt 2009	Accelerated *n* = 17	1 (1–3)	–
	Control *n* = 23	6 (4–7)	
Gatt 2005	Optimized *n* = 19	5 (4–9)†	0·027
	Control *n* = 20	7·5 (6–10)†	
Khoo 2007	Multimodal *n* = 35	5 (3–37)	< 0·001
	Control *n* = 35	7 (4–63)	
Kroon 2010	TIVA *n* = 27	2 (1–3)	< 0·001§
	PCA *n* = 26	3 (1–6)	
LAFA – open	Fast track *n* = 93	6 (4·5–10)†	0·032
	Standard care *n* = 98	7 (6–10·5)†	
LAFA – laparoscopic	Fast track *n* = 100	5 (4–7)†	0·020
	Standard care *n* = 109	6 (4–8·5)†	
Lee 2011	Rehab *n* = 46	7 (6–8)	0·65§
	Conventional *n* = 54	8 (7–9)	
Muehling 2008a	Fast track *n* = 49	10 (6–49)	0·741¶
	Conventional *n* = 50	11 (8–45)	
Muehling 2008b	Fast track *n* = 30	11 (8–33)	n.s.¶
	Conservative *n* = 28	11 (7–34)	
Petersen 2006	Intervention *n* = 27	7 (1–9)	0·019
	Control *n* = 30 (per-protocol analysis)	8 (1–10)	
Shchepotin 2012	Intervention *n* = 11	10	–
	Control *n* = 10	16	
Sokouti 2011	Fast track *n* = 30	7 (2–23)	0·03#
	Control *n* = 30	10 (4–22)	
Wang 2009	Fast track *n* = 46	6 (6·0–7·0)	< 0·050#
	Traditional *n* = 46	8 (7·0–8·3)	
Wang 2010	Fast track *n* = 45	6 (6–7)†	< 0·001
	Control *n* = 47	8 (7–8)†	
Wang 2012b	Fast track *n* = 40	5·5 (5–6)†	< 0·001
	Control *n* = 38	7 (7–8)†	

*Values are median range, except †median (i.q.r.). TIVA, total intravenous anaesthesia; PCA, patient-controlled anaesthesia; Rehab, rehabilitation programme; LAFA, LAparoscopy and/or FAst track multimodal management *versus* standard care trial. ‡Mann–Whitney *U* test, except §Wilcoxon rank-sum test, ¶Fisher's exact test and #unclear which test was used.

Cumulative meta-analyses for complications and mortality showed that pooled effect estimates were steady from 2003, with no evidence of a shift over time. The pooled estimate showed evidence of a progressively greater reduction in length of hospital stay over time.

Subgroup analyses

Given the similarity in results for complications for patient and count analyses, only patient-based complication outcomes were included in subgroup analyses. There was no evidence that the effect of ERPs on postoperative mortality, complications or readmission rate varied with type of surgery (*Table 4*). Similarly there was no indication that these outcomes differed between laparoscopic or open approaches in colorectal surgery studies. There was some evidence of a greater reduction in hospital stay in

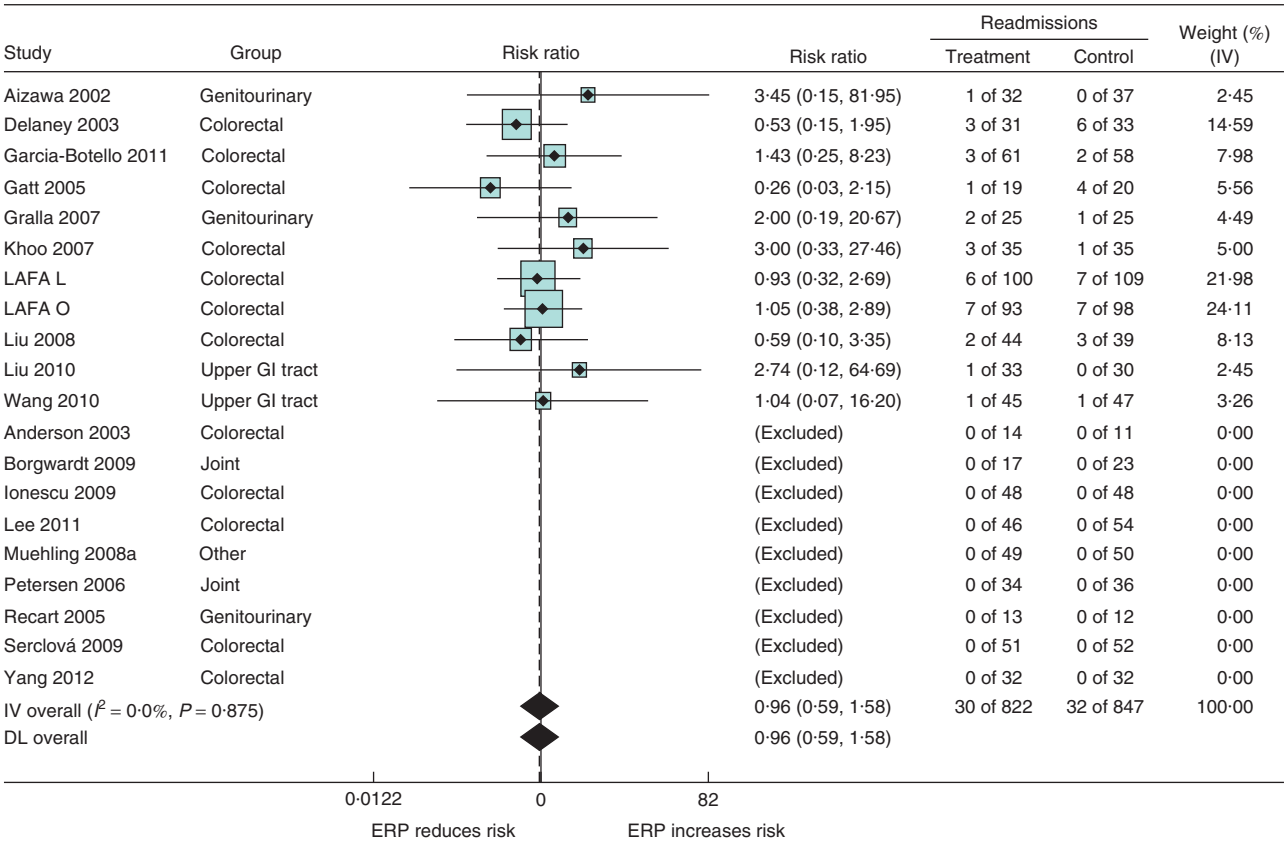

Fig. 7 Meta-analyses of readmissions in enhanced recovery programme (ERP) *versus* control groups. Risk ratios are shown with 95 per cent confidence intervals. Overall effect estimates are shown for inverse-variance (IV) fixed-effect and DerSimonian and Laird (DL) random-effects models. LAFA, LAparoscopy and/or FAst track multimodal management *versus* standard care trial; L, laparoscopic; O, open; GI, gastrointestinal

studies of thoracic and upper gastrointestinal surgery, but the estimate for thoracic surgery was based on only one study[55] that reported a large reduction in stay. There was no suggestion of a difference in reduction of length of stay between laparoscopic and open approaches in colorectal surgery, but only one study[51] reported length of stay for laparoscopic surgery.

In subgroup analyses to investigate the effect of the number of elements of ERPs, there was evidence that studies with fewer elements showed a greater reduction in mortality and complications (*Table 4*). The RR for mortality was 0·25 (0·09 to 0·74) in studies with a difference of less than seven between intervention and control groups, and 1·47 0·58 to 3·75) for studies with a difference of seven or more ($P = 0·036$ for t test of meta-regression variable). For all complications the corresponding RRs were 0·60 (0·47 to 0·77) and 0·80 (0·64 to 1·00) ($P = 0·145$).

Studies with 11 or more elements of ERPs showed a greater reduction in length of hospital stay, with a SMD of −1·84 (−2·78 to −0·90) ($P = 0·065$ for linear variable in meta-regression). For length of stay analyses the residual heterogeneity between studies remained extremely high: 95·8 per cent in studies with 11 elements or more in the ERPs ($P < 0·001$) and 90·2 per cent in the linear meta-regression model.

Sensitivity analyses

The exclusion of studies published in abstract form only[24,46] resulted in minimal changes to effect estimates for all outcomes. Similarly, the exclusion of quasi-randomized studies[22,44] did not change the effect estimates of complications, readmission or length of stay. The exclusion of the study by Roig and colleagues[44] did, however, alter the pooled estimate for mortality to 1·02 (0·46 to 2·25). This was due to the large reduction in mortality seen in the study (RR 0·16, 0·04 to 0·74).

Table 4 Subgroup analyses: random-effects meta-analysis models

	Mortality risk ratio	All complications (by patient) risk ratio	Major complication (by patient) risk ratio	SMD in hospital stay	Readmission risk ratio
Overall effect	0·69 (0·34,1·39)	0·71 (0·60, 0·86)	0·95 (0·69, 1·31)	−1·14 (−1·45, −0·85)	0·96 (0·59, 1·58)
Type of surgery					
Colorectal	0·66 (0·27, 1·63)	0·74 (0·60, 0·91)	0·95 (0·66, 1·37)	−0·78 (−1·03, −0·53)	0·86 (0·51, 1·47)
Genitourinary	–	0·46 (0·22, 0·98)	0·33 (0·01, 7·81)	−1·37 (−2·37, −0·37)	2·43 (0·37, 15·89)
Joint	1·24 (0·09, 16·38)	1·60 (0·62, 4·13)	–	−1·27 (−1·74, −0·81)	–
Thoracic	0·60 (0·08, 4·74)	0·45 (0·25, 0·80)	–	−4·95 (−5·89, −4·01)	–
Upper GI tract	–	0·85 (0·52, 1·41)	1·04 (0·07, 16·20)	−1·58 (−2·48, −0·69)	1·58 (0·20, 12·53)
Other	–	–	–	–	–
*P**	0·875	0·258	0·819	0·001	0·546
Colorectal surgical approach					
Open	0·95 (0·30, 2·96)	0·72 (0·55, 0·94)	0·97 (0·64, 1·49)	−0·85 (−1·15, −0·54)	0·78 (0·41, 1·50)
Laparoscopic	1·44 (0·27, 7·52)	0·75 (0·29, 1·92)	1·42 (0·65, 3·09)	−0·25 (−0·69, 0·19)	0·93 (0·33, 2·69)
Mixed	0·16 (0·04, 0·74)	0·64 (0·42, 0·98)	0·57 (0·25, 1·30)	−0·73 (−1·23, −0·23)	1·43 (0·25, 8·23)
*P**	0·200	0·811	0·439	0·609	0·817
No. of elements of ERP in intervention					
4–7	0·50 (0·09, 2·79)	0·66 (0·41, 1·04)	0·53 (0·11, 2·70)	−0·77 (−1·13, −0·41)	0·66 (0·25, 1·77)
8–10	0·51 (0·13, 2·05)	0·55 (0·42, 0·73)	0·57 (0·25, 1·30)	−1·09 (−1·53, −0·66)	2·01 (0·57, 7·10)
≥ 11	1·38 (0·46, 4·15)	0·88 (0·69, 1·12)	1·07 (0·75, 1·53)	−1·84 (−2·78, −0·90)	0·93 (0·49, 1·77)
P†	0·138	0·218	0·364	0·065	0·569
*P**	0·308	0·036	0·373	0·201	0·429
Difference in no. of elements between intervention and control					
Median or below (≤ 7)	0·25 (0·09, 0·74)	0·60 (0·47, 0·77)	0·54 (0·26, 1·12)	−1·07 (−1·48, −0·66)	0·95 (0·41, 2·20)
Above median (> 7)	1·47 (0·58, 3·75)	0·80 (0·64, 1·00)	1·09 (0·76, 1·55)	−1·23 (−1·68, −0·78)	0·97 (0·52, 1·78)
P†	0·143	0·341	0·350	0·223	0·676
P‡	0·036	0·145	0·142	0·707	0·972

Values in parentheses are 95 per cent confidence intervals. Results are shown for intervention group relative to control group. SMD, standardized mean difference; GI, gastrointestinal; ERP, enhanced recovery programme. Random-effects meta-regression models were used with meta-regression variable entered as *categorical, †linear and ‡dichotomized variable.

Table 5 Sensitivity analyses: random-effects meta-analysis models

	Mortality risk ratio	All complications (by patient) risk ratio	Major complication (by patient) risk ratio	SMD in hospital stay	Readmission risk ratio
Overall effect	0·69 (0·34, 1·39)	0·71 (0·60, 0·86)	0·95 (0·69, 1·31)	−1·14 (−1·45, −0·85)	0·96 (0·59, 1·58)
Sensitivity analysis					
Quality measure	In-hospital mortality or unspecified	Follow-up < 30 days or unspecified	Follow-up < 30 days or unspecified	No standardized discharge criteria	Follow-up < 30 days or unspecified
Higher quality	0·64 (0·10, 3·92)	0·80 (0·64, 1·00)	1·05 (0·75, 1·49)	−0·87 (−1·17, −0·57)	0·92 (0·51, 1·63)
Lower quality	0·71 (0·31, 1·39)	0·57 (0·44, 0·75)	0·55 (0·24, 1·23)	−1·47 (−2·03, −0·91)	1·10 (0·42, 2·87)
*P**	0·908	0·081	0·193	0·204	0·760

Values in parentheses are 95 per cent confidence intervals. Results are shown for intervention group relative to control group. SMD, standardized mean difference. *Random-effects meta-regression models were used with meta-regression variable entered as dichotomized variable.

When mortality and complication outcomes were analysed in subgroups depending on length of follow-up (*Table 5*), there was no difference in mortality risk in ERPs groups between studies with shorter or unspecified periods of follow-up and those with 30-day follow-up. For all and major complications, studies with follow-up of less than 30 days or an unclear follow-up period reported a greater reduction in risk, although this difference was not significant for major complications. Studies with standardized discharge criteria reported a smaller reduction in length of stay than studies without criteria: SMD −0·87 (−1·17 to 0·57) and −1·47 (−2·03 to −0·91) respectively. This was not a significant variable in meta-regression analyses and unexplained heterogeneity remained high at 89·1 per cent.

Table 6 Subgroup analyses after exclusion of lower-quality studies

	Mortality risk ratio	All complications (by patient) risk ratio	Major complication (by patient) risk ratio	SMD in hospital stay	Readmission risk ratio
No. of studies	11*	13†	0‡	12§	7¶
No. of elements of ERP in intervention					
4–7	0·50 (0·09, 2·79)	1·05 (0·50, 2·22)		−0·62 (−1·25, −0·01)	0·59 (0·10, 3·36)
8–10	0·99 (0·21, 4·55)	0·50 (0·34, 0·72)		−1·05 (−1·63, −0·47)	1·66 (0·36, 7·70)
≥ 11	1·38 (0·46, 4·15)	0·96 (0·78, 1·18)		−0·81 (−1·32, −0·30)	0·87 (0·45, 1·70)
P#	0·312	0·653		0·411	0·752
*P***	0·633	0·034		0·668	0·681
Difference in no. of elements between intervention and control					
Median or below (≤ 7)	0·40 (0·09, 1·77)	0·80 (0·41, 1·58)		−1·06 (−1·73, −0·38)	0·59 (0·10, 3·36)
Above median (> 7)	1·47 (0·58, 3·75)	0·80 (0·62, 1·03)		−0·75 (−1·08, −0·42)	0·97 (0·52, 1·78)
P#	0·378	0·912		0·897	0·842
P††	0·179	0·991		0·512	0·623

Values in parentheses are 95 per cent confidence intervals. Results are shown for intervention group relative to control group. *Only one quasi-randomized study was excluded. No studies published in abstract form were included in original analyses. Exclusion of studies with unspecified follow-up or in-hospital mortality left too few studies to model and this variable was not associated with a difference in effect. †Studies published in abstract form, quasi-randomized studies and studies with follow-up either unspecified or less than 30 days were excluded. ‡No studies published in abstract form or quasi-randomized studies were included in original analyses. Studies with follow-up either unspecified or less than 30 days were excluded. §Studies published in abstract form, quasi-randomized and studies with no standardized discharge criteria were excluded. ¶No studies published in abstract form or quasi-randomized studies were included in original analyses. Studies with follow-up either unspecified or less than 30 days were excluded. SMD, standardized mean difference; ERP, enhanced recovery programme. Random-effects meta-regression models were used with meta-regression variable entered as #linear, **categorical or ††dichotomized variable.

The subgroup analyses for number of elements of ERPs and differences between intervention and control groups were repeated with exclusion of studies reported in abstract form, quasi-randomized studies and those with shorter follow-up (*Table 6*). Differences between groups were reduced, particularly for length of stay.

Discussion

This meta-analysis of the impact of ERPs on surgical outcomes, including 38 studies across a range surgical specialties, has demonstrated that use of an ERP leads to a reduction in primary hospital stay (SMD 1·14 days) and a 30 per cent reduction in risk of complications in the 30 days after surgery. For a typical stay of 5 days with a standard deviation of 1 day (meaning that 70 per cent of patients stay between 4 and 6 days), an ERP will lead to a reduction in hospital stay of 1 day. There was no evidence for an increased risk of death, major complications or readmission, and the present results were consistent with ERPs leading to either an increased or decreased risk of these outcomes. The impact of ERPs was similar across studies of colorectal, upper gastrointestinal, thoracic and genitourinary surgery, with no indication of differences in effect between specialties. The outcomes of ERPs were similar in laparoscopic and open colorectal surgery. There was no consistent evidence that either the number of elements included in ERPs or the difference in number between intervention and control groups affected the outcomes of such programmes.

There is a large literature on ERPs, but study design and quality is poor. To improve study quality this review was restricted to randomized (or quasi-randomized) trials and involved a comprehensive search, including non-English language publications. However, the methodological challenges of ERPs studies have been recognized[13]. It is impossible to conduct double-blind RCTs for ERPs interventions, and performance bias is inevitable. It would be possible to minimize detection bias with assessment performed by observers unaware of patient allocation, although few studies used such methods. Sensitivity analyses for length of stay indicated a potentially important impact of detection bias, but the reduction remained significant after exclusion of high-risk studies. Few studies were designed or powered to study complication rates and the reporting of complications was generally poor, with unspecified lengths of follow-up, no definitions and few details of ascertainment methods. There was evidence of small-study bias, particularly for length of stay, with smaller studies reporting more benefits from use of ERPs. Despite these limitations in the included trials, the present review has demonstrated that ERPs are effective in reducing the length of hospital stay and overall complication rate. Many studies excluded dependent patients and those not able to cope independently, so

the present findings are relevant only to those living independently before surgery.

This review found no consistent evidence that the effect of ERPs differed according to type of operation; there was a significant reduction in hospital stay in all specialty subgroups except for laparoscopic colorectal surgery. The reduction in complications did not reach statistical significance in some surgical subgroups but there was no evidence of increased risk. The precise content of an ERP will vary with specialty, such as importance of bowel preparation and use of drains or nasogastric tubes, but the core principles are now being applied across many specialties. An enhanced recovery intervention in any specialty was required to have three or more components of care from a comprehensive checklist than the control. The interventions were not identical, but all studies were comparing an enhanced intervention with a less enhanced control.

It is perhaps surprising that it was not possible to show that programmes with more elements were more successful than those with fewer components. Studies with four to seven elements seemed to work as well as those with 11 or more. ERPs are a composite of effective interventions and it might be expected that more interventions might have greater effect. Studies with fewer than four components or only one or two additional elements were excluded from the review, but the inclusion criteria applied here were more generous than those in previous reviews[13,14]. This permitted the investigation of composition of ERPs over a wider range. The treatment in the control group was sometimes poorly reported, with some studies[20,24,27,46,56] providing little or no information. This will have led to overestimation of the difference, but these studies did not contribute to the group with 11 or more elements in the ERPs. Changes in standard practice over time might reduce the impact of ERPs as some components were incorporated into standard care. Cumulative meta-analyses did not support this, as there was no change or an increasing effect over time. Ideally, the effect of individual components would be assessed, but owing to collinearity and clustering this would have required meta-regression models with each component as a separate variable. The number of included studies did not support such models.

Substantial heterogeneity remained in all analyses of length of stay, suggesting that there are unexplained differences between the studies, and was not reduced when studies were grouped by type of surgery. Cultural differences were reported by some authors, with patients unwilling to leave hospital[36], but much of the variation between studies remained unexplained.

The exact nature of the successful intervention is therefore difficult to establish. The 14 studies that had ERPs with between four and seven elements all had postoperative components, but only five had intraoperative and 12 had preoperative elements. This suggests that intraoperative elements may be less important, but it was not possible to investigate this further as no studies had intraoperative components without postoperative ones. Other review authors[13] have suggested that the successful ingredient in ERPs may be a mind set or psychological approach among staff and patients[13]. Qualitative synthesis or realist review may be more appropriate to investigate the determinants of success.

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Disclosure

The authors declare no conflict of interest.

References

1 Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR *et al.* An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; **372**: 139–144.

2 Woodall NM, Cook TM. National census of airway management techniques used for anaesthesia in the UK: first phase of the Fourth National Audit Project at the Royal College of Anaesthetists. *Br J Anaesth* 2011; **106**: 266–271.

3 NHS Institute for Innovation and Improvement. *Enhanced Recovery Programme*. http://www.institute.nhs.uk/quality_and_service_improvement_tools/quality_and_service_improvement_tools/enhanced_recovery_programme.html [accessed 1 April 2012].

4 Wilmore DW, Kehlet H. Management of patients in fast track surgery. *BMJ* 2001; **322**: 473–476.

5 Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K *et al.* Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr* 2005; **24**: 466–477.

6 Kehlet H. Future perspectives and research initiatives in fast-track surgery. *Langenbecks Arch Surg* 2006; **391**: 495–498.

7 Kehlet H. Fast-track colorectal surgery. *Lancet* 2008; **371**: 791–793.

8 Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg* 2008; **248**: 189–198.

9 Dowsey MM, Kilgour ML, Santamaria NM, Choong PF. Clinical pathways in hip and knee arthroplasty: a prospective randomised controlled study. *Med J Aust* 1999; **170**: 59–62.

10 Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg* 2002; **183**: 630–641.

11 Anderson ADG, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. *Br J Surg* 2003; **90**: 1497–1504.

12 Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C *et al.*; Enhanced Recovery After Surgery (ERAS) Group. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg* 2009; **144**: 961–969.

13 Spanjersberg Willem R, Reurings J, Keus F, van Laarhoven Cornelis JHM. Fast track surgery *versus* conventional recovery strategies for colorectal surgery. *Cochrane Database Syst Rev* 2011; (2)CD007635.

14 Walter CJ, Collin J, Dumville JC, Drew PJ, Monson JR. Enhanced recovery in colorectal resections: a systematic review and meta-analysis. *Colorectal Dis* 2009; **11**: 344–353.

15 Wind J, Polle SW, Fung Kon Jin PH, Dejong CH, von Meyenfeldt MF, Ubbink DT *et al.*; Laparoscopy and/or Fast Track Multimodal Management *Versus* Standard Care (LAFA) Study Group; Enhanced Recovery after Surgery (ERAS) Group. Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg* 2006; **93**: 800–809.

16 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD *et al.* The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; **250**: 187–196.

17 Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD *et al.*; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.

18 The Cochrane Collaboration. *Review Manager (RevMan)*. 5.1 edn. The Cochrane Collaboration: Copenhagen, 2011.

19 Higgins JP, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0. The Cochrane Collaboration, 2011. http://www.cochrane-handbook.org [accessed 2 December 2013].

20 Aizawa T, Kin T, Kitsukawa SI, Mamiya Y, Akiyama A, Ohno Y *et al.* [Impact of a clinical pathway in cases of transurethral resection of the prostate.] *Nihon Hinyokika Gakkai Zasshi* 2002; **93**: 463–468.

21 Borgwardt L, Zerahn B, Bliddal H, Christiansen C, Sylvest J, Borgwardt A. Similar clinical outcome after unicompartmental knee arthroplasty using a conventional or accelerated care program: a randomized, controlled study of 40 patients. *Acta Orthop* 2009; **80**: 334–337.

22 Cho CH, Song KS, Min BW, Lee KJ, Ha E, Lee YC *et al.* Multimodal approach to postoperative pain control in patients undergoing rotator cuff repair. *Knee Surg Sports Traumatol Arthrosc* 2011; **19**: 1744–1748.

23 Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. *Dis Colon Rectum* 2003; **46**: 851–859.

24 Demanet J, Wattier JM, Colin P, Fantoni JC, Villers A, Lebuffe G. Feasibility of fast track strategy for patients undergoing radical nephrectomy: a prospective randomized study. *Eur J Anaesthesiol* 2011; **28**(Suppl 48): 120.

25 Garcia-Botello S, Canovas de Lucas R, Tornero C, Escamilla B, Espi-Macias A, Esclapez-Valero P *et al.* Implementation of a perioperative multimodal rehabilitation protocol in elective colorectal surgery. A prospective randomised controlled study. *Cir Esp* 2011; **89**: 159–166.

26 Gatt M, Anderson ADG, Reddy BS, Hayward-Sampson P, Tring IC, MacFie J. Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. *Br J Surg* 2005; **92**: 1354–1362.

27 Gooch K, Marshall DA, Faris PD, Khong H, Wasylak T, Pearce T *et al.* Comparative effectiveness of alternative clinical pathways for primary hip and knee joint replacement patients: a pragmatic randomized, controlled trial. *Osteoarthritis Cartilage* 2012; **20**: 1086–1094.

28 Gralla O, Haas F, Knoll N, Hadzidiakos D, Tullmann M, Romer A *et al.* Fast-track surgery in laparoscopic radical prostatectomy: basic principles. *World J Urol* 2007; **25**: 185–191.

29 He ZG, Tang Y, Wu HG, Wei B, Chen L, Li R. [Benefits of perioperative fast-track surgery program on clinical outcome in patients with gastric cancer.] *Chinese J Clin Nutr* 2010; **18**: 29–32.

30 Henriksen MG, Jensen MB, Hansen HV, Jespersen TW, Hessov I. Enforced mobilization, early oral feeding, and balanced analgesia improve convalescence after colorectal surgery. *Nutrition* 2002; **18**: 147–152.

31 Ionescu D, Iancu C, Ion D, Al-Hajjar N, Margarit S, Mocan L *et al.* Implementing fast-track protocol for colorectal surgery: a prospective randomized clinical trial. *World J Surg* 2009; **33**: 2433–2438.

32 Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing

elective colorectal resection for cancer. *Ann Surg* 2007; **245**: 867–872.
33 Kroon UB, Rådström M, Hjelthe C, Dahlin C, Kroon L. Fast-track hysterectomy: a randomised, controlled study. *Eur J Obstet Gynecol Reprod Biol* 2010; **151**: 203–207.
34 Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF *et al.*; LAFA study group. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). *Ann Surg* 2011; **254**: 868–875.
35 Larsen K, Sørensen OG, Hansen TB, Thomsen PB, Søballe K. Accelerated perioperative care and rehabilitation intervention for hip and knee replacement is effective: a randomized clinical trial involving 87 patients with 3 months of follow-up. *Acta Orthop* 2008; **79**: 149–159.
36 Lee TG, Kang SB, Kim DW, Hong S, Heo SC, Park KJ. Comparison of early mobilization and diet rehabilitation program with conventional care after laparoscopic colon surgery: a prospective randomized controlled trial. *Dis Colon Rectum* 2011; **54**: 21–28.
37 Liu Z, Wang XD, Li L. [Perioperative fast track programs enhance the postoperative recovery after rectal carcinoma resection.] *Zhonghua Wei Chang Wai Ke Za Zhi* 2008; **11**: 551–553.
38 Liu XX, Jiang ZW, Wang ZM, Li JS. Multimodal optimization of surgical care shows beneficial outcome in gastrectomy surgery. *JPEN J Parenter Enteral Nutr* 2010; **34**: 313–321.
39 Muehling BM, Halter G, Lang G, Schelzig H, Steffen P, Wagner F *et al.* Prospective randomized controlled trial to evaluate 'fast-track' elective open infrarenal aneurysm repair. *Langenbecks Arch Surg* 2008; **393**: 281–287.
40 Muehling BM, Halter GL, Schelzig H, Meierhenrich R, Steffen P, Sunder-Plassmann L *et al.* Reduction of postoperative pulmonary complications after lung surgery using a fast track clinical pathway. *Eur J Cardiothorac Surg* 2008; **34**: 174–180.
41 Petersen MK, Madsen C, Andersen NT, Søballe K. Efficacy of multimodal optimization of mobilization and nutrition in patients undergoing hip replacement: a randomized clinical trial. *Acta Anaesthesiol Scand* 2006; **50**: 712–717.
42 Recart A, Duchene D, White PF, Thomas T, Johnson DB, Cadeddu JA. Efficacy and safety of fast-track recovery strategy for patients undergoing laparoscopic nephrectomy. *J Endourol* 2005; **19**: 1165–1169.
43 Ren L, Zhu D, Wei Y, Pan X, Liang L, Xu J *et al.* Enhanced Recovery After Surgery (ERAS) program attenuates stress and accelerates recovery in patients after radical resection for colorectal cancer: a prospective randomized controlled trial. *World J Surg* 2012; **36**: 407–414.
44 Roig JV, Garcia-Fadrique A, Salvador A, Villalba FL, Tormos B, Lorenzo-Linan MA *et al.* Selective intestinal preparation in a multimodal rehabilitation program. Influence on preoperative comfort and the results after colorectal surgery. *Cir Esp* 2011; **89**: 167–174.
45 Serclová Z, Dytrych P, Marvan J, Nová K, Hankeová Z, Ryska O *et al.* Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456). *Clin Nutr* 2009; **28**: 618–624.
46 Shchepotin I, Lukashenko A, Kolesnik O, Vovk M. Efficacy of multimodal program 'fast track surgery' in the surgical treatment for pancreatic cancer patients. *HPB* 2012; **14**(Suppl S2): 227.
47 Sokouti M, Aghdam BA, Golzari SEJ, Moghadaszadeh M. A comparative study of postoperative pulmonary complications using fast track regimen and conservative analgesic treatment: a randomized clinical trial. *Tanaffos* 2011; **10**: 12–19.
48 Wang DS, Zhou YB, Kong Y, Wang QG, Wang H. [Observation of fast track surgery in patients with gastric cancer.] *Zhonghua Wei Chang Wai Ke Za Zhi* 2009; **12**: 462–466.
49 Wang D, Kong Y, Zhong B, Zhou X, Zhou Y. Fast-track surgery improves postoperative recovery in patients with gastric cancer: a randomized comparison with conventional postoperative care. *J Gastrointest Surg* 2010; **14**: 620–627.
50 Wang G, Jiang Z, Zhao K, Li G, Liu F, Pan H *et al.* Immunologic response after laparoscopic colon cancer operation within an enhanced recovery program. *J Gastrointest Surg* 2012; **16**: 1379–1388.
51 Wang Q, Suo J, Jiang J, Wang C, Zhao YQ, Cao X. Effectiveness of fast-track rehabilitation *vs* conventional care in laparoscopic colorectal resection for elderly patients: a randomized trial. *Colorectal Dis* 2012; **14**: 1009–1013.
52 Xu JM, Zhong YS, Zhu DX, Ren L, Wei Y, Xue ZG *et al.* [Application of the protocol of enhanced recovery after surgery in colorectal surgery.] *Zhonghua Wei Chang Wai Ke Za Zhi* 2007; **10**: 238–244.
53 Yang D, He W, Zhang S, Chen H, Zhang C, He Y. Fast-track surgery improves postoperative clinical recovery and immunity after elective surgery for colorectal carcinoma: randomized controlled clinical trial. *World J Surg* 2012; **36**: 1874–1880.
54 Zhang H, Cui MM, Liu DS, Feng Y, Chen CS. [Effect of fast track surgery on serum levels of CRP, IL-6 and insulin resistance in patients with colorectal cancer.] *World Chinese J Digestol* 2010; **18**: 3813–3817.
55 Zhao G, Huang Y, Chen X, Duan L, Ma Q, Yujie LEI *et al.* [Research on fast track surgery application in lung cancer surgery.] *Zhongguo Fei Ai Za Zhi* 2010; **13**: 102–106.
56 Zhao GB, Cao SQ, Zhang K, Dong Q, Cui J. [Effect of fast track surgery on insulin resistance indexes of esophageal cancer patients.] *Chinese J Clin Nutr* 2012; **20**: 78–83.
57 Tang Y, Wu XS, Wei B, Chen L, Li R. [Clinical application of perioperative fast-track and nutrition support program in elderly patients with gastric cancer.] *Chinese J Clin Nutr* 2010; **18**: 137–140.
58 Gralla O, Buchser M, Haas F, Anders E, Kramer J, Lein M *et al.* [Fast-track laparoscopic radical prostatectomy.] *Urologe A* 2008; **47**: 712–717.

59 Jones C, Kelliher L, Scott M, Dickinson M, Karajia N. Enhanced recovery in liver resection surgery: a single-blinded randomised controlled trial. *Br J Anaesth* 2012; **108**(Suppl 2): ii242–ii243.
60 Zhou JJ, Li J, Ying XJ, Song YM, Chen R, Chen G *et al.* Fast track multi-discipline treatment (FTMDT trial) *versus* conventional treatment in colorectal cancer – the design of a prospective randomized controlled study. *BMC Cancer* 2011; **11**: 494.
61 Brodner G, Van Aken H, Hertle L, Fobker M, Von Eckardstein A, Goeters C *et al.* Multimodal perioperative management – combining thoracic epidural analgesia, forced mobilization, and oral nutrition – reduces hormonal and metabolic stress and improves convalescence after major urologic surgery. *Anesth Analg* 2001; **92**: 1594–1600.
62 El-Sheikh S, El-Sayed S, Mostafa A, Hussein H. Enhanced recovery program safely improves the outcome of elective colorectal surgery. *Egyptian J Anaesth* 2010; **26**: 229–239.
63 Pellegrino L, Giraudo G, Donati D, Meineri M, Borghi Felice F. Fast track *versus* traditional peri-operative care after right hemicolectomy with intracorporeal anastomosis. *Tech Coloproctol* 2011; **15**: 251.
64 Rich-Ruiz M, Requena-Tapia M, Regueiro-López JC, López-Luque AJ, Muñoz-Gomáriz E, Prieto-Rodríguez M. Impact of a clinical pathway in cases of transurethral resection of the prostate and bladder.] *Enfermeria Clinica* 2006; **16**: 253–263.
65 Serclová Z, Dytrych P, Marvan J, Nova K, Hankeova Z, Ryska O *et al.* [Tolerance of accelerated postoperative rehabilitation following intestinal resections.] *Rozhl Chir* 2009; **88**: 178–184.
66 Basse L, Jakobsen DH, Bardram L, Billesbolle P, Lund C, Mogensen T *et al.* Functional recovery after open *versus* laparoscopic colonic resection – a randomized, blinded study. *Ann Surg* 2005; **241**: 416–423.
67 Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N; Zurich Fast Track Study Group. A fast-track program reduces complications and length of hospital stay after open colonic surgery. *Gastroenterology* 2009; **136**: 842–847.e841.
68 Tsunoda A, Shibusawa M, Takata M, Hiratsuka K, Shida K, Kusano M. Early oral feeding should be resumed following the resolution of gastric ileus. *Hepatogastroenterology* 2005; **52**: 775–779.
69 Nielsen PR, Jorgensen LD, Dahl B, Pedersen T, Tonnesen H. Prehabilitation and early rehabilitation after spinal surgery: randomized clinical trial. *Clin Rehabil* 2010; **24**: 137–148.
70 Olbert PJ, Baumann L, Hegele A, Schrader AJ, Hofmann R. [Fast-track concepts in the perioperative management of patients undergoing radical cystectomy and urinary diversion. Review of the literature and research results.] *Urologe A* 2009; **48**: 137–142.
71 Basse L, Madsen JL, Billesbølle P, Bardram L, Kehlet H. Gastrointestinal transit after laparoscopic *versus* open colonic resection. *Surg Endosc* 2003; **17**: 1919–1922.
72 Karl A, Buchner A, Weninger E, Becker A, Seitz M, Staehler M *et al.* A simple fast track regimen for patients undergoing radical cystectomy for bladder cancer. *J Urol* 2012; **187**(Suppl 1): e215–e216.
73 Mari G, Costanzi A, Maggioni A, Ferrari G, Citterio D, Origi M *et al.* Fast track *vs* conventional care in laparoscopic left hemicolectomy. A pilot prospective randomized study. *Surg Endosc* 2011; **25**(Suppl): pS2.
74 Susa A, Roveran A, Bocchi A, Carrer S, Tartari S. [FastTrack approach to major colorectal surgery.] *Chir Ital* 2004; **56**: 817–824.
75 Larsen K, Hansen TB, Thomsen PB, Christiansen T, Søballe K. Cost-effectiveness of accelerated perioperative care and rehabilitation after total hip and knee arthroplasty. *J Bone Joint Surg Am* 2009; **91**: 761–772.

Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Full list of articles from eligible studies (Word document)

Table S1 Search strategy (Word document)

Table S2 Characteristics of ongoing studies (Word document)

Table S3 Characteristics of trials awaiting classification (Word document)

Table S4 Elements included in enhanced recovery programme of included studies (Word document)