Department of Veterans Affairs
Health Services Research & Development Service

Evidence-based Synthesis Program

QUERI

Enhanced Recovery After Surgery (ERAS) Programs for Patients Undergoing Colorectal Surgery

August 2017

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Quality Enhancement Research Initiative
Health Services Research & Development Service
Washington, DC 20420

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

Recommended citation: Greer N, Sultan S, Shaukat A, Dahm P, Lee A, MacDonald R, McKenzie L, Ercan-Fang D, Wilt, TJ. Enhanced Recovery After Surgery (ERAS) Programs for Patients Undergoing Colorectal Surgery. VA ESP Project #09-009; 2017.

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the **Minneapolis VA Health Care System, Minneapolis, MN**, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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INTRODUCTION

Enhanced recovery after surgery (ERAS), also referred to as an enhanced recovery program, fast-track rehabilitation, multimodal management, or similar descriptors, is a multidisciplinary approach to perioperative care. A protocol of components related to preadmission, preoperative, intraoperative, and postoperative care is implemented with the goal of improving patient recovery, facilitating earlier discharge from the hospital, and potentially reducing health care costs without increasing complications or hospital readmissions.[1-3] The protocol components may contribute to minimizing, and/or improving the response to, physiological stress associated with surgery.[1,2]

The ERAS Society has published guidelines for implementing an ERAS program for colorectal surgery.[2,4] However, variation in the number and definition of protocol components contributes to difficulties in determining effectiveness. Little is known about implementation barriers and facilitators as well as components (or combinations of components) key for improved clinical outcomes. In addition, protocol compliance, when reported, may be measured by percentage of elements applied or completed without standardization across elements (timing, regimens, doses, *etc*).

Enhanced recovery protocols are not limited to colorectal surgery. ERAS Society guidelines are available for at least 15 procedures.[2] However, given that the largest volume of evidence for comparative effectiveness of enhanced recovery and usual care protocols is available for colorectal surgery, we limit our review to studies of enhanced recovery for colorectal surgery.

Preliminary literature searches for topic refinement identified published systematic reviews on the topic. An overview of 13 systematic reviews published between 2011 and 2017 is presented in Appendix A.[5-17] Three focused only on laparoscopic surgery.[11,15,16] None of the existing reviews reported on subgroups based on surgical approach (open or laparoscopic surgery) or colorectal condition. While several noted the enhanced recovery protocol components from the included studies, the standard care protocols were not documented. Only one systematic review formally rated the overall quality of evidence.[17] None commented on barriers or facilitators to implementation of an enhanced recovery program.

The defining components of an enhanced recovery program for colorectal surgery have been revised over time[2] and new trials have been published since the search dates of the existing reviews. We provide an updated review of randomized controlled trials (RCTs) and controlled clinical trials (CCTs), looking at comparative effectiveness and harms overall and by type of surgery, colorectal condition, and fidelity to an enhanced recovery protocol. We also review barriers and facilitators to implementation and provide a contextual discussion of compliance and outcomes.

With input from the topic nominator and a technical expert panel, we developed the following analytic framework (Figure 1); population, intervention, comparator, outcomes (PICO); and key questions.

PICO

Population: Adults (18 and over) undergoing elective colorectal surgery

Intervention: Enhanced recovery program (as defined by study authors)

Comparator: Usual care or subset of enhanced recovery components not meeting author definition of a full enhanced recovery program

Outcomes:

Final Health Outcomes: Length of stay (initial stay, total); overall morbidity; mortality; readmission rate; ileus; clinically important difference in pain scores; and clinically meaningful changes in quality of life

Intermediate: Gastrointestinal function (time to oral feeding, bowel function, nausea), intravenous fluid administration, mobilization, pain scale scores

Harms: Surgical complications (infection, anastomotic leakage), non-surgical complications (cardiovascular, respiratory, urinary tract infection), need for re-operation, bleeding, Foley catheter re-insertion and complications, aspiration pneumonia, readmission

Key Questions

KQ1: What is the comparative effectiveness of ERAS versus usual care or a subset of ERAS components for adults undergoing elective colorectal surgery?

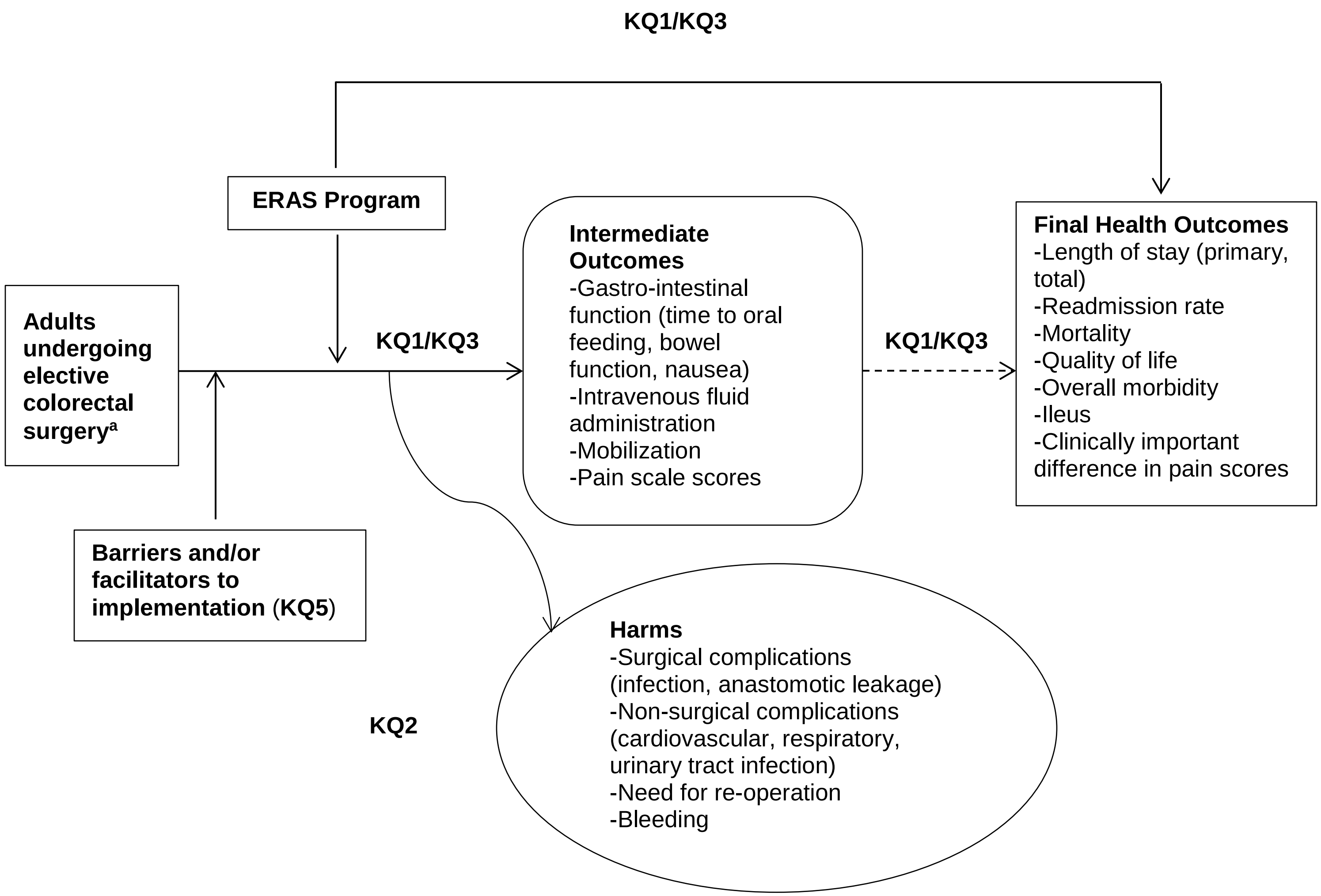
KQ2: What are the harms of ERAS versus usual care or a subset of ERAS components for adults undergoing elective colorectal surgery?

KQ3: Do comparative effectiveness and harms vary by fidelity to ERAS components?

KQ4: Do comparative effectiveness and harms vary by type of, and clinical conditions for, colorectal surgery (*eg*, anatomical site, laparoscopic versus open surgery, reasons for open surgery, *etc*)?

KQ5: What are the barriers to and facilitators of implementation of ERAS programs?

Figure 1. Analytic Framework



[a] Consider subgroups based on comorbidity status, mobility status, frailty index, age, patient size, right vs left side, laparoscopic vs open procedure, type of surgery **(KQ4)**

METHODS

TOPIC DEVELOPMENT

The topic was nominated for review by William Gunnar, MD, JD, National Director of Surgery.

SEARCH STRATEGY

We searched MEDLINE (Ovid) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) for English language publications from 2011 to July 2017. Search terms included terms used synonymously with ERAS (*eg*, fast track, multimodal, accelerated, enhanced) and terms for colorectal surgery (both open and laparoscopic). The search strategies are presented in Appendix B.

We obtained additional articles from reference lists of existing systematic reviews, reference lists of included studies, and suggestions from technical expert panel members.

STUDY SELECTION

Abstracts identified in the literature searches were independently reviewed by 2 researchers. Full-text review of potentially eligible studies was completed by one researcher with input from investigators. We included:

1) Studies of adults undergoing elective colorectal surgery (any colorectal procedure, open or laparoscopic surgery),

2) For effectiveness of ERAS programs (KQ1-KQ4):
   a. randomized controlled trial (RCT) or controlled clinical trial (CCT)
   b. comparator is usual care or subset of ERAS components (as defined by study authors),

3) For barriers to and facilitators of implementation (KQ5):
   a. any study design providing qualitative data on barriers and facilitators
   b. study conducted in healthcare system relevant to VA.

We excluded:

1) Non-English language publications,

2) Studies that compared laparoscopic and open surgery within an enhanced recovery protocol,

3) Studies reporting outcomes before and after implementation of an enhanced recovery protocol (*ie*, pre-post or case series with historical controls design); we included controlled clinical trials if data collection was concurrent,

4) Trials of single component of enhanced recovery,

5) Studies that included post-operative components only (often referred to as "Post-operative Rehabilitation" or "Controlled Rehabilitation").

DATA ABSTRACTION

For each eligible study for KQ1 to KQ4, we created a table indicating the included ERAS components.[2,4] We also noted which of the ERAS components were implemented as part of the usual care protocol.

We abstracted the following data onto evidence tables organized by type of surgery (open or laparoscopic):

1) Patient and study characteristics: study location (country); funding source; inclusion/exclusion criteria; length of follow-up; compliance with enhanced recovery protocol; patient age, gender, race/ethnicity, BMI or obesity status; comorbidity status; colorectal conditions; and surgical procedures

2) Outcomes (as defined above) for intervention and control groups

QUALITY ASSESSMENT

Risk of bias of RCTs and CCTs was assessed using a modified Cochrane approach considering sequence generation, allocation, blinding, incomplete outcome reporting, and selective outcome reporting. Each study was rated as high, medium, low, or unclear risk of bias.[18]

DATA SYNTHESIS

Tables were developed with studies pertaining to KQ1 and KQ2 noting outcomes reported by fidelity to enhanced recovery components (KQ3) or type of surgery (KQ4). If applicable, data for critical outcomes were pooled and analyzed using DerSimonian and Laird random-effects models[19] in Cochrane Collaboration Review Manager software, Version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). We calculated weighted mean differences (WMD) for length of stay and risk ratios (RR) for overall morbidity, all-cause mortality, readmissions, and surgical site infections. Peto odds ratios were applied when events were rare, such as mortality. Heterogeneity between studies was assessed by using the I^2 test, with a I^2 value greater than 50% considered substantial.[20] If length of stay data were reported in medians, data were extracted from previous systematic reviews or converted to estimates of means and standard deviations based on methods outlined by Hozo.[21]

We qualitatively summarized findings for KQ5 (enhanced recovery barriers and facilitators).

RATING THE BODY OF EVIDENCE

We evaluated the overall strength of evidence for our critical outcomes using a method developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group.(GRADEpro 2015 accessed at www.gradepro.org). The following domains were used to assess strength of evidence: 1) risk of bias; 2) consistency; 3) directness; and 4) precision. Strength of evidence ranges from high (indicating high confidence that the true effect lies close to that of the estimate of the effect) to very low (indicating very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate of effect).

PEER REVIEW

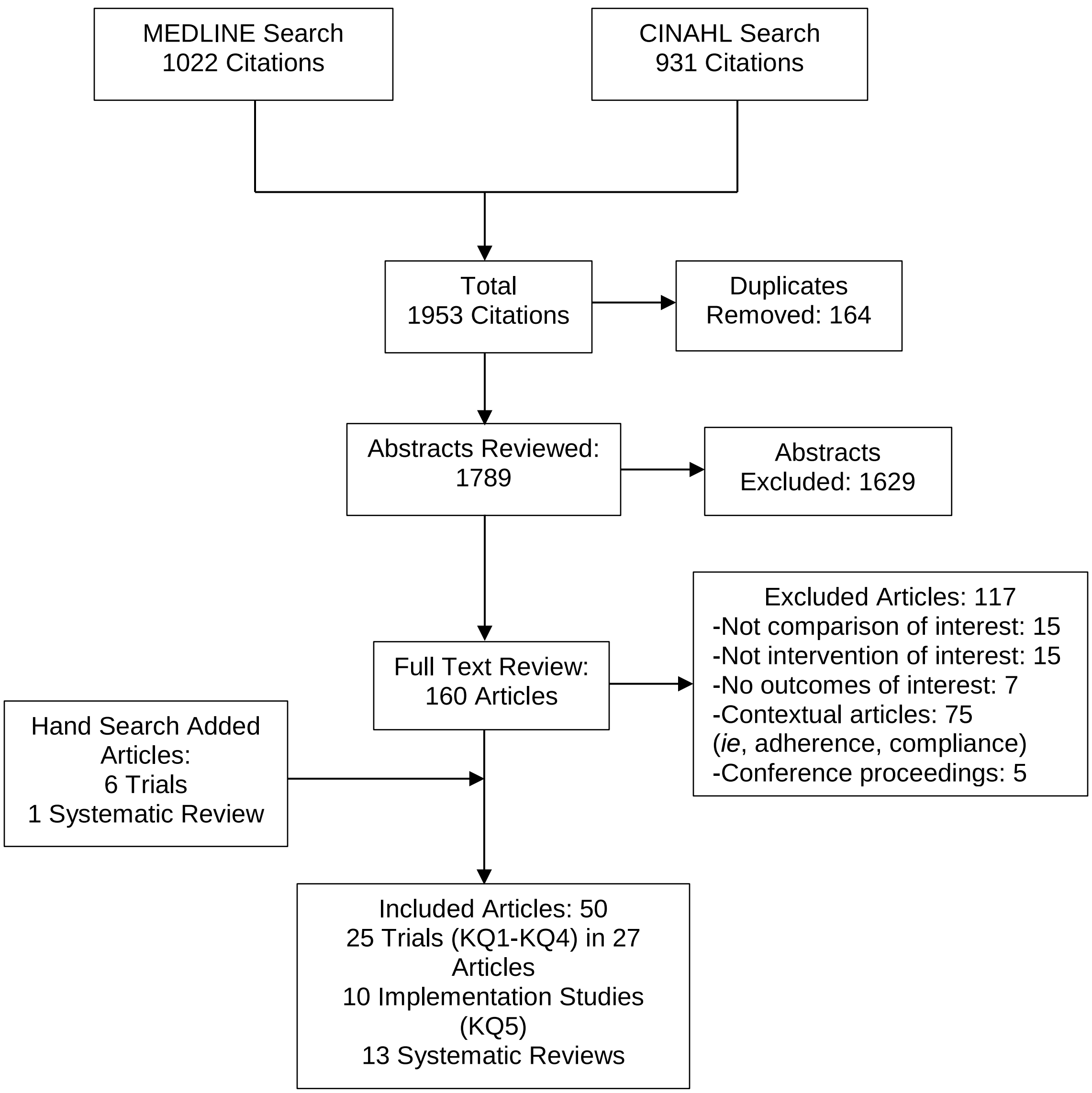
A draft version of this report was reviewed by content experts as well as clinical leadership. Reviewer comments and our responses are presented in Appendix C and the report was modified as needed.

RESULTS

LITERATURE FLOW

The literature searches yielded 1022 citations in MEDLINE and 931 citations in CINAHL. Combining the results and removing duplicates yielded 1789 citations. We excluded 1629 studies at the abstract stage and another 117 after full-text review. Many of the excluded studies were observational studies that provided contextual information about adherence or compliance but did not meet inclusion criteria. We added 7 articles (including 6 trials published prior to 2011 identified from existing systematic reviews) resulting in a total of 50 included articles: 25 trials reported in 27 articles, 10 with information about implementation barriers and facilitators, and 13 systematic reviews.

Figure 2: Literature Flow Chart



KEY QUESTION 1: What is the comparative effectiveness of ERAS versus usual care or a subset of ERAS components for adults undergoing elective colorectal surgery?

Overview of Studies

Open Surgery Studies

Sixteen studies (15 RCTs, 1 CCT) compared open surgery with an enhanced recovery protocol to open surgery with a conventional (usual care) protocol.[22-37] Three of these studies also reported results for laparoscopic surgery with an enhanced recovery protocol compared to laparoscopic surgery with a conventional protocol (see below).[25,34,35] We rated 4 studies low risk of bias, 4 medium risk of bias, 3 high risk of bias, and 5 unclear risk of bias. Study details are provided in Appendix D, Table 1.

No studies were conducted in the US. There were 6 from China,[23,27,32,35-37] 3 from the United Kingdom,[22,24,28] and one each from Italy,[31] India,[30] Greece,[25] the Netherlands,[34] Romania,[26] Switzerland,[29] and the Czech Republic.[33]

Seven studies included patients undergoing elective surgery for colorectal cancer.[23,26-28,32,36,37] Three studies reported the percentage of colon and rectal surgeries.[23,26,28] One study enrolled patients age 70 and older.[27] Sample sizes in the colorectal cancer studies ranged from 62[37] to 597.[32] Mean or median ages ranged from 55 to 73 years; in the study of elderly patients, the mean age was 75 years. The study population was more than 55% male in all but one study.[28] Three studies reported BMI with values of 22,[37] 22.5,[32] and 24.[23] No study included participants with preoperative American Society of Anesthesiologists (ASA) physical status classification IV.

Five studies included mixed groups of patients – colorectal cancer or benign conditions,[22,24,29,34,35] though the majority of participants underwent surgery for colon cancer. Sample sizes in these studies ranged from 25[22] to 191[34] with mean or median ages ranging from 55 to 68 years. In all but one study,[22] more than 50% of participants were male. All 5 studies reported BMI with mean or median values of 27 or lower. As with the colorectal cancer studies, no colorectal cancer/benign condition study included participants with preoperative ASA score IV.

Two studies included patients undergoing rectal cancer surgery.[25,31] Both enrolled fewer than 100 patients. Mean ages were 67[31] and 64[25] years and more than 50% were male. Mean BMI was 28 in one study;[25] the other reported that 38% had a BMI less than 25.[31] In one study, 88% were ASA I or II;[25] in the other, 90% were ASA II or III.

The remaining 2 studies enrolled patients undergoing colorectal surgery that was primarily non-cancer related. In the study from India, 3% of participants had a cancer diagnosis[30] while in the study from the Czech Republic,[33] 7% had a cancer diagnosis and 78% had Crohn's disease. Sample sizes in the 2 studies were 60 and 103, respectively, with mean ages of 34 and 36 years. Approximately 50% were male in both studies; neither reported BMI or ASA scores.

Laparoscopic Studies

Eleven studies (8 RCTs, 3CCTs) compared an enhanced recovery program to usual care in patients undergoing laparoscopic surgery for colorectal conditions.[25,34,35,38-46] Three of these studies also reported results for open surgery (see above).[25,34,35] Five studies were from China[35,38,44-46] and 3 were from Italy,[40,41,43] with one each from Japan,[42] Greece,[25] and The Netherlands.[34] Three were rated unclear risk of bias, 5 medium risk of bias, 2 high risk of bias, and one low risk of bias. Study details are provided in Appendix D, Table 1.

Five studies included patients with colon cancer[35,44,45] or colorectal cancer.[42,46] Sample sizes ranged from 78[46] to 320.[42] One study enrolled patients over 65 years; median ages were 71 in the enhanced recovery group and 72 in the usual care group.[46] In the other 4 studies, mean or median ages were in the 50s[35,44,45] or 60s.[42] Across the 4 studies, 47%[45] to 66%[35] were male and in 3 studies reporting BMI, means or medians were 22 to 24.[35,44,45] No study reporting ASA included grade IV; 2 studies excluded ASA III or IV.[42,45]

One study included 209 patients with cancer and benign conditions[34] and 2 included patients with cancer (69%-75%) or diverticular disease (25%-31%).[40,41] In the study with cancer and benign conditions, mean age was 57 years, 58% were male, and mean BMI was 26.[34] Patients with ASA IV were excluded. In the studies with cancer and diverticular disease, the mean or median ages were 66 years, approximately 50% were male, and mean BMI was 26.5.[40,41] ASA IV was also an exclusion criterion. A subgroup analysis of one of these studies included only patients 70 years of age and older.[39]

Two studies enrolled patients exclusively with rectal cancer.[25,38] Mean ages were 55 years in a study of 116 patients[38] and 66 years in a study of 75 patients.[25] In one study the populations was 66% male with a mean BMI of 22.[38] In the second study, the population was 44% male with a mean BMI of 28.[25] One study excluded patients with ASA III or IV[38]; in the other study there were no patients with ASA IV.[25]

One study enrolled 227 women with bowel endometriosis.[43] Mean age was 35 years and mean BMI was 22.

We identified one additional report of laparoscopic surgery with enhanced recovery compared to usual perioperative care in elderly patients with colorectal cancer.[47] However, the authenticity of the paper has been questioned.[48] We do not report findings from this study.

Mixed Open and Laparoscopic Study

One low risk of bias RCT included 324 patients who underwent either open or laparoscopic surgery (the surgeon's choice) for colon (46%) or rectal (54%) disease.[49,50] Overall, 79% of cases were malignant. Median ages were 65 (ERAS group) and 66 (usual care group), 54% were male, and 63% were ASA II. A subgroup analysis divided patients into 3 age groups: ≤65 years, 66 to 79 years, and ≥80 years.[49]

Enhanced Recovery Components

Ljungqvist et al organized the ERAS components into 4 phases: preadmission, preoperative, intraoperative, and postoperative.[2] We merged the ERAS components from this recent description with those from 2013 guidelines.[2,4] We charted the enhanced recovery protocol components specified in the enhanced recovery protocols and usual care protocols for each of the studies included in our review (Appendix E). Some studies used identical protocols resulting in 24 unique protocols (13 for open surgery, 10 for laparoscopic surgery, and one for open or laparoscopic surgery). We tracked 3 preadmission components, 8 preoperative components, 6 intraoperative components, and 9 postoperative components.

We found wide variation in the number of enhanced recovery components contained in the study protocols. Of 26 possible enhanced recovery components, enhanced recovery group protocols were found to include between 4 and 18 enhanced recovery components (4 studies with fewer than 10 components, 10 studies with 10-12 components, 8 studies with 13-15 components, and 2 studies with more than 15 components). The standard care group protocols included between 0 and 10 enhanced recovery components (16 with 0-2 components, 4 with 3-6 components, and 4 with more than 6 components).

The number of studies including each component (in either the enhanced recovery protocol or the usual care protocol) is presented in Table 1. No study included the preadmission components. Of the preoperative components, the most frequently included in enhanced recovery protocols were carbohydrate treatment, no routine use of mechanical bowel preparation, and a fasting protocol allowing clear fluids until 2 hours before surgery and solid until 6 hours before surgery. Eight protocols from our included studies had 2 or fewer of the 8 preoperative components, 2 had 3 components, 6 had 4 components, 6 had 5 components, and 2 had 6 components.

Of the 6 intraoperative components, the most frequently included were removal of nasogastric tubes before reversal of anesthesia (and no routine use of nasogastric tubes) and a standardized anesthesia protocol. One study protocol included only one intraoperative component. Most protocols included between 3 and 5 components. One protocol from a study of laparoscopic surgery included all 6 components.

Among the 9 postoperative components, early intake of oral fluids and solids was included in all enhanced recovery protocols. Other frequently included components were early mobilization, multimodal approach to opioid-sparing pain control, and early removal of urinary catheters and intravenous fluids. One protocol included only one postoperative component. The rest included at least 2 of the 9 components, with most including between 4 and 6 components.

Table 1. Count of ERAS Components in Study Protocols for ERAs and Standard Care

Phases	ERAS Components	ERAS Protocol	Standard Care Protocol
PREADMISSION	Smoking/alcohol cessation	0	0
	Nutritional screening/support	0	0
	Medical optimization of chronic disease	0	0
PREOPERATIVE	Structured information/patient and caretaker engagement	12	0
	Bowel preparation (no routine use of mechanical bowel prep)	16	2
	Pre-operative fasting (clear fluids to 2 hours and solids to 6 hours before surgery)	16	3
	Carbohydrate treatment	18	0
	Thrombosis prophylaxis	4	2
	Infection prophylaxis and/or skin preparation with chlorhexidine-alcohol	11	8
	Nausea and vomiting prophylaxis	5	2
	Pre-anesthetic sedative medication (no routine use)	3	0
INTRAOPERATIVE	Minimal invasive surgical techniques	2+10 Lap	0+10 Lap
	Standardized anesthesia protocol – may use thoracic epidural blocks with local anesthetics and low-dose opioids for open surgery and spinal analgesia or patient-controlled morphine as alternative to thoracic epidural for laparoscopic surgery	16	9
	Maintain fluid balance; vasopressors for blood pressure control	14	3
	Restrictive use of surgical site drains	15	5
	Remove nasogastric tubes before reversal of anesthesia (and no routine use)	21	5
	Control of body temperature	9	4
POSTOPERATIVE	Early mobilization	22	4
	Early intake of oral fluids and solids	23	1
	Early removal of urinary catheters and intravenous fluids	18	2
	Chewing gum, laxatives, peripheral opioid-blocking agents	7	1
	Protein and energy-rich nutritional supplements	11	0
	Glucose control	1	0
	Multimodal approach to opioid-sparing pain control – consider thoracic epidural analgesia (open surgery) or spinal analgesia (laparoscopic surgery); also NSAIDS and paracetamol	21	6
	Multimodal approach to control of nausea and vomiting	0	0
	Prepare for early discharge	2	1

Overview of Outcomes

Table 2 provides an overview of outcomes reported. An “up arrow” (-) indicates a statistically significant benefit with the enhanced recovery protocol compared to the usual care protocol. A “side-to-side arrow” («) indicates results were not significantly different between the enhanced recovery protocol and the usual care protocol. A “down arrow” (¯) indicates a significantly worse outcome with the enhanced recovery protocol compared to the usual care protocol. Complete outcomes data are provided in Appendix D, Tables 2-6. Outcome reporting varied across studies. No study reported on all our outcomes. All studies reported a measure of length of stay. Most studies reported on mortality, perioperative complications (including overall morbidity), hospital readmissions, and some aspect of gastrointestinal function. Few studies reported on clinically meaningful changes in quality of life or pain.

Table 2. Summary of Outcomes (Enhanced Recovery vs Usual Care)

Author Year Population	Length of Stay	Overall Mortality	Overall Morbidity	Readmissions	Quality of Life (Clinically Meaningful Change)	Pain (Clinically Meaningful Change)	Gastrointestinal Function			Surgical Complications				Non-Surgical Complications	
							Ileus	Time to Oral Solid Foods	Other (*eg*, Flatus, Bowel Movement)	Surgical Site Infection	Bleeding	Need for Re-operation	Other Surgical Complication	Foley Catheter Re-insertion/ Complication	Aspiration Pneumonia/ Pulmonary Infection
OPEN SURGERY STUDIES															
Feng 2016[23] Colorectal cancer	-[b]		-				«	-	-	«	«		«		«
Pappalardo 2016[31] Rectal cancer	-	«							-				«		
Jia 2014[27] Colorectal cancer (elderly)	-	«							-	«			«		-
Nanavati 2014[30] Gastrointestinal surgery (3% cancer)	-	«		«			«		-	«		«	«		
Gouvas 2012[25] *CCT* Rectal cancer	-[c]	«	«	«			-		-		«	«	«		-
Ren 2011[32] Colorectal cancer	-	«	«						-	«			«		
Wang 2012[35] Colon cancer	-[a]	«	«	«									«		
Yang 2012[37] Colorectal cancer	-		«	«				-	-	«			«		«

Author Year Population	Length of Stay	Overall Mortality	Overall Morbidity	Readmissions	Quality of Life (Clinically Meaningful Change)	Pain (Clinically Meaningful Change)	Gastrointestinal Function			Surgical Complications				Non-Surgical Complications	
							Ileus	Time to Oral Solid Foods	Other (*eg*, Flatus, Bowel Movement)	Surgical Site Infection	Bleeding	Need for Re-operation	Other Surgical Complication	Foley Catheter Re-insertion/ Complication	Aspiration Pneumonia/ Pulmonary Infection
Vlug 2011[34] Cancer and benign disease	- [c]	«	«	«			«	-	-	«		«	«		
Wang 2011[36] Colorectal cancer	-	«	-	«					-	«		«	«	«	
Ionescu 2009[26] Rectosigmoid (58%) or colon (42%) cancer	-			«				-	-	«		«	«		
Muller 2009[29] Colon surgery (87% malignant) with primary anastomosis	-		-	«			«			«	«		«		«
Šerclová 2009[33] Intestinal resection (78% Crohn's disease, 7% cancer)	-	«	-	«		-		-	-				-		
Khoo 2007[28] Colon (67%) or rectal (33%) cancer	- [c]	«		«				-	-				«	«	
Gatt 2005[24] Colon surgery (69% malignant)	- [c]	«	«	«			«	-		«					«

Author Year Population	Length of Stay	Overall Mortality	Overall Morbidity	Readmissions	Quality of Life (Clinically Meaningful Change)	Pain (Clinically Meaningful Change)	Gastrointestinal Function			Surgical Complications				Non-Surgical Complications	
							Ileus	**Time to Oral Solid Foods**	**Other (*eg,* Flatus, Bowel Movement)**	**Surgical Site Infection**	**Bleeding**	**Need for Re-operation**	**Other Surgical Complication**	**Foley Catheter Re-insertion/ Complication**	**Aspiration Pneumonia/ Pulmonary Infection**
Anderson 2003[22] Colon surgery (72% malignant)	-	«		«			«	-		«					
LAPAROSCPIC SURGERY STUDIES															
Ota 2017[42] CCT Colorectal cancer	-	«		«			«	-	-	«	mixed	«	«		
Scioscia 2017[43] Bowel endometriosis	-			«							«	«			
Mari 2016[40] Colorectal cancer (75%) or diverticular disease (25%)	-	«	«				«	-	mixed	«	«		«		«
Wang 2015[45] *CCT* Colon cancer	-	«	«		«	«	«		-	«			«		«
Feng 2014[38] Rectal cancer	-	«	-	«			«		-	«		«	«		«
Mari 2014[41] Colon cancer (69%) or diverticular disease (31%)	-	«	«	«				-	-				«		
Gouvas 2012[25] *CCT* Rectal cancer	-	«	-	«			«		-		«	«	«		«

Author Year Population	Length of Stay	Overall Mortality	Overall Morbidity	Readmissions	Quality of Life (Clinically Meaningful Change)	Pain (Clinically Meaningful Change)	Gastrointestinal Function			Surgical Complications				Non-Surgical Complications	
							Ileus	Time to Oral Solid Foods	Other (*eg*, Flatus, Bowel Movement)	Surgical Site Infection	Bleeding	Need for Re-operation	Other Surgical Complication	Foley Catheter Re-insertion/ Complication	Aspiration Pneumonia/ Pulmonary Infection
Wang 2012[35] Colon cancer	- [a]	«	«	«									«		
Wang 2012[44] Colon cancer	- [a]	«	«	«				-	-	«		«	«	«	
Wang 2012[46] Colorectal cancer (elderly)	-		-						-	«			«		«
Vlug 2011[34] Cancer and benign disease	-	«	«	«			«	-	-	«		«	«		
MIXED OPEN AND LAPAROSCOPIC SURGERY STUDIES															
Forsmo 2016[50] Colorectal cancer and benign disease	-	«	«	«			«	«	-	«		«	«		«

- =benefit with enhanced recovery protocol
« =no difference between enhanced recovery protocol and usual care protocol
‾ =poorer outcome with enhanced recovery protocol
mixed=more than one outcome and results varied
[a] total length of stay
[b] calculated P value
[c] median values (reported in study) indicate benefit with enhanced recovery protocol; calculated means (Figure 3) indicate no benefit

Length of Stay

All but one of the included studies reported mean or median length of stay. In most studies, this was the "initial" length of stay following the surgery date. In 2 studies, one of which provided data for both open surgery and laparoscopic surgery, readmissions were also considered providing a "total" length of stay.[35,44] Excluding those 2 studies, mean length of stay ranged from 3.0 to 8.5 days in the enhanced recovery group and 6.0 to 13.2 days in the control group. All studies found a reduced length of stay in the enhanced recovery group compared to the usual care group. Pooling results from the studies reporting initial length of stay yielded a mean difference of -2.59 days (95% CI -3.22, -1.97) (Figure 3). Statistical heterogeneity was high (I^2=92%). Quality of evidence for reduced length of stay with enhanced recovery protocols compared to usual care protocols was rated as moderate (Table 3 and Appendix F).

The remaining study reported the day on which patients met discharge criteria (*ie*, normal oral feeding, complete canalization, drains and catheters removed, no fever, no need for intravenous therapy).[31] The study included patients with rectal cancer undergoing open surgery. Overall, patients in the enhanced recovery protocol group achieved discharge status sooner than those in the traditional care group (P<.05) with 68% of the enhanced recovery group patients and 16% of the traditional care group meeting criteria on post-operative day 4. All of the enhanced recovery group patients met discharge criteria by post-operative day 6 while 28% of the traditional care group did not meet criteria until post-operative day 7 or longer.

Figure 3. Pooled Analysis for Length of Stay

	ERAS			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Yang 2012 (37)	6	1	32	11.7	3.8	30	4.0%	-5.70 [-7.10, -4.30]
Ota 2017-CCT (42)	8.5	6	159	14	6.5	161	4.1%	-5.50 [-6.87, -4.13]
Jia 2014 (27)	9	1.8	117	13.2	1.3	116	5.0%	-4.20 [-4.60, -3.80]
Scioscia 2017 (43)	3	2.3	62	7	4.8	165	4.6%	-4.00 [-4.93, -3.07]
Gouvas 2012-CCT lap (25)	4	2.3	42	8	3.8	33	4.0%	-4.00 [-5.47, -2.53]
Muller 2009 (29)	6.7	4.8	76	10.3	4.9	75	3.9%	-3.60 [-5.15, -2.05]
Anderson 2003 (22)	4	1.8	14	7	2.1	11	3.9%	-3.00 [-4.56, -1.44]
Serclová 2009 (33)	7.4	1.3	51	10.4	3.1	52	4.6%	-3.00 [-3.92, -2.08]
Mari 2014 (41)	4.7	2.4	25	7.7	2.4	25	4.1%	-3.00 [-4.33, -1.67]
Ionescu 2009 (26)	6.4	3.4	48	9.2	2.7	48	4.2%	-2.80 [-4.03, -1.57]
Nanavati 2014 (30)	4.7	1.3	30	7.3	1.4	30	4.8%	-2.60 [-3.28, -1.92]
Wang 2015 (CCT)	6.1	1.7	57	8.7	2.8	60	4.7%	-2.60 [-3.43, -1.77]
Wang 2011 (36)	5.1	3.1	106	7.6	4.8	104	4.4%	-2.50 [-3.60, -1.40]
Gatt 2005 (24)	6.6	4.4	19	9	4.6	20	2.5%	-2.40 [-5.22, 0.42]
Mari 2016 (40)	5	2.6	70	7.2	3	70	4.6%	-2.20 [-3.13, -1.27]
Khoo 2007 (28)	5	8.5	35	7	14.8	35	1.0%	-2.00 [-7.65, 3.65]
Forsmo 2016 (50)	5	8	154	7	7.6	153	3.6%	-2.00 [-3.75, -0.25]
Feng 2014 (38)	5.1	1.4	57	7	2.3	59	4.8%	-1.90 [-2.59, -1.21]
Wang 2012 (46)	5.5	1	40	7	1.8	38	4.8%	-1.50 [-2.15, -0.85]
Feng 2016 (23)	7.5	2.2	116	8.6	2.8	114	4.8%	-1.10 [-1.75, -0.45]
Gouvas 2012-CCT open (25)	7	2.3	36	8	4	45	4.1%	-1.00 [-2.39, 0.39]
Vlug 2011 lap (34)	5	2.9	100	6	2.9	109	4.7%	-1.00 [-1.79, -0.21]
Ren 2011 (32)	5.7	1.6	299	6.6	2.4	298	5.0%	-0.90 [-1.23, -0.57]
Vlug 2011 open (34)	7	4.4	93	7	5.2	98	4.1%	0.00 [-1.36, 1.36]
Total (95% CI)			**1838**			**1949**	**100.0%**	**-2.59 [-3.22, -1.97]**

Heterogeneity: Tau² = 1.97; Chi² = 270.86, df = 23 (P < 0.00001); I² = 92%
Test for overall effect: Z = 8.19 (P < 0.00001)

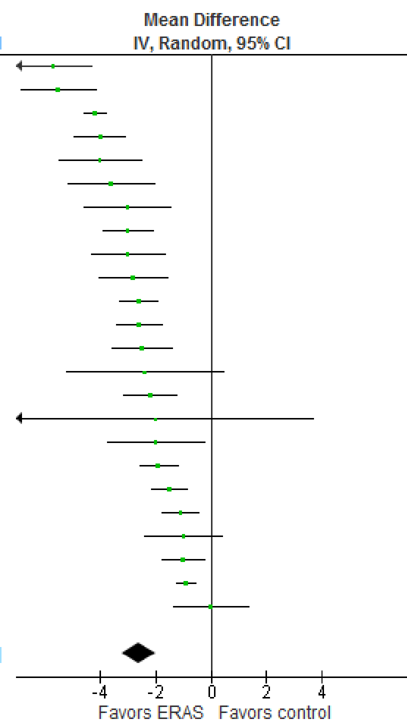


Table 3. Summary of Findings for ERAS Compared to Control for Colorectal Surgeries

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without ERAS	**With ERAS**	**Difference**		
Length of stay № of participants: 3787 (24 RCTs)				MD **2.6 days lower** (3.2 lower to 2.0 lower)	⊕⊕⊕◯ MODERATE [a,b]	Duration of hospital stay was lower with ERAS in both open and laparoscopic procedure groups compared with respective control groups. Subgroup results based on condition were comparable to the overall findings.
Mortality № of participants: 3255 (22 RCTs)	**OR 1.79** (0.81 to 3.95)	0.6%	**1.0%** (0.4 to 2.1)	**0.4% more** (0.1 fewer to 1.6 more)	⊕⊕◯◯ LOW [a,c]	No statistically significant differences between groups.
Perioperative morbidity № of participants: 2919 (19 RCTs)	**RR 0.66** (0.54 to 0.80)	29.1%	**19.2%** (15.7 to 23.3)	**9.9% fewer** (13.4 fewer to 5.8 fewer)	⊕⊕⊕◯ MODERATE [a]	Fewer complications in both open and laparoscopic ERAS groups versus respective controls. Subgroup results based on condition were comparable to the overall findings.
Readmissions № of participants: 2515 (19 RCTs)	**RR 1.11** (0.82 to 1.50)	6.4%	**7.1%** (5.2 to 9.6)	**0.7% more** (1.1 fewer to 3.2 more)	⊕⊕◯◯ LOW [a,d]	No statistically significant differences between groups.
Surgical site infection № of participants: 2880 (17 RCTs)	**RR 0.75** (0.52 to 1.07)	4.8%	**3.6%** (2.5 to 5.1)	**1.2% fewer** (2.3 fewer to 0.3 more)	⊕⊕◯◯ LOW [a,d]	No statistically significant differences between groups.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Mostly moderate, high or unclear risk of bias
b. I-square indicated substantial statistical heterogeneity although all but 2 studies reported lower duration with ERAS. Strong association observed.
c. Wide confidence intervals and very few events
d. Wide confidence intervals

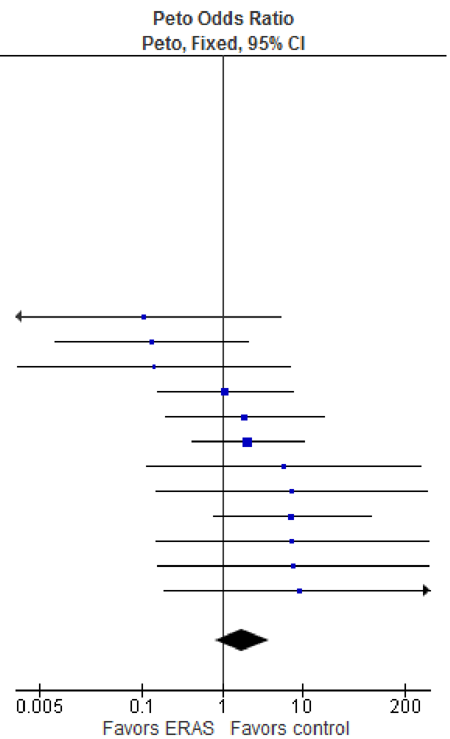
All-cause Mortality

All-cause mortality, typically assessed until 30 days post-surgery, was reported in 19 studies. Three of the studies[25,34,35] reported results for both open and laparoscopic surgery, resulting in a total of 22 comparisons of enhanced recovery and usual care protocols. Mortality was generally infrequent (approximately 1%) with 10 studies reporting no deaths.[27,30-33,38,40-42,45] No study reported a significant difference in mortality between the enhanced recovery and usual care protocols. The pooled odds ratio was 1.79 (95% CI 0.81, 3.95) (Figure 4). Quality of evidence for no difference in all-cause mortality with enhanced recovery or usual care protocols was rated as low (Table 3 and Appendix F).

Figure 4. Pooled Analysis for Mortality

Study or Subgroup	ERAS Events	ERAS Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Pappalardo 2016 (31)	0	25	0	25		Not estimable
Mari 2016 (40)	0	70	0	70		Not estimable
Mari 2014 (41)	0	25	0	25		Not estimable
Ren 2011 (32)	0	299	0	298		Not estimable
Jia 2014 (27)	0	117	0	116		Not estimable
Wang 2015 (CCT)	0	57	0	60		Not estimable
Serclová 2009 (33)	0	51	0	52		Not estimable
Ota 2017-CCT (42)	0	159	0	161		Not estimable
Nanavati 2014 (30)	0	30	0	30		Not estimable
Feng 2014 (38)	0	57	0	59		Not estimable
Anderson 2003 (22)	0	14	1	11	4.0%	0.10 [0.00, 5.34]
Khoo 2007 (28)	0	35	2	35	8.0%	0.13 [0.01, 2.14]
Wang 2012 open (35)	0	41	1	42	4.1%	0.14 [0.00, 6.99]
Vlug 2011 lap (34)	2	100	2	109	16.0%	1.09 [0.15, 7.87]
Wang 2011 (36)	2	106	1	104	12.1%	1.92 [0.20, 18.69]
Vlug 2011 open (34)	4	93	2	98	23.7%	2.09 [0.41, 10.60]
Gouvas 2012-CCT lap (25)	1	42	0	33	4.0%	5.96 [0.12, 309.26]
Wang 2012 lap (35)	1	40	0	40	4.1%	7.39 [0.15, 372.38]
Forsmo 2016 (50)	3	154	0	153	12.1%	7.44 [0.77, 72.04]
Wang 2012 (44)	1	49	0	50	4.1%	7.54 [0.15, 380.14]
Gatt 2005 (24)	1	19	0	20	4.1%	7.79 [0.15, 393.02]
Gouvas 2012-CCT open (25)	1	36	0	45	4.0%	9.49 [0.18, 489.97]
Total (95% CI)		**1619**		**1636**	**100.0%**	**1.79 [0.81, 3.95]**
Total events	16		9			

Heterogeneity: Chi² = 11.40, df = 11 (P = 0.41); I² = 4%
Test for overall effect: Z = 1.45 (P = 0.15)



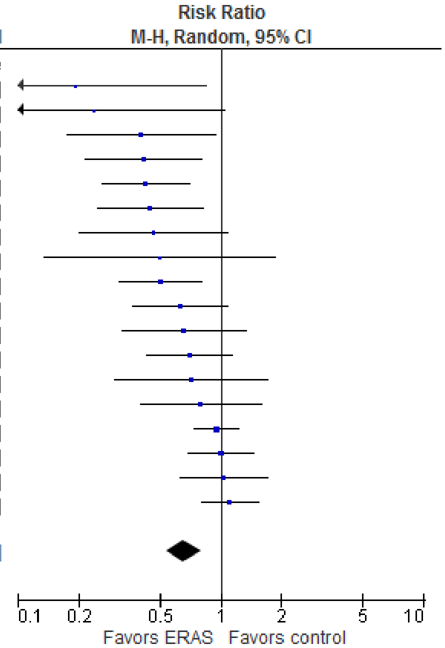
Overall Morbidity

Perioperative morbidity was reported in 17 studies. The 3 studies reporting outcomes for both open and laparoscopic surgery reported morbidity resulting in a total of 20 comparisons of enhanced recovery and usual care protocols. One study noted no major complications in either group.[41] In 11 of the remaining comparisons of enhanced recovery and usual care protocols, no significant difference in morbidity was observed. In 7 comparisons, overall morbidity was significantly lower in the enhanced recovery protocol groups compared to usual care. The pooled risk ratio was 0.66 (95% CI 0.54, 0.80) (Figure 5). One additional study reported the proportion of patients with one or more complications, finding no significant difference between the enhanced recovery and usual care protocols.[44] Quality of evidence for reduced overall morbidity with enhanced recovery protocols compared to usual care protocols was rated as moderate (Table 3 and Appendix F).

Figure 5. Pooled Analysis for Morbidity

Study or Subgroup	ERAS Events	ERAS Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Mari 2014 (41)	0	25	0	25		Not estimable
Feng 2014 (38)	2	59	10	57	1.6%	0.19 [0.04, 0.84]
Wang 2012 (46)	2	40	8	38	1.6%	0.24 [0.05, 1.05]
Feng 2016 (23)	7	116	17	114	3.9%	0.40 [0.17, 0.94]
Gouvas 2012-CCT lap (25)	9	42	17	33	5.2%	0.42 [0.21, 0.81]
Muller 2009 (29)	16	76	37	75	7.0%	0.43 [0.26, 0.70]
Serclová 2009 (33)	11	51	25	52	5.8%	0.45 [0.25, 0.81]
Yang 2012 (37)	6	32	12	30	3.8%	0.47 [0.20, 1.09]
Wang 2012 lap (35)	3	40	6	40	1.9%	0.50 [0.13, 1.86]
Wang 2011 (36)	20	106	39	104	7.3%	0.50 [0.32, 0.80]
Gatt 2005 (24)	9	19	15	20	6.5%	0.63 [0.37, 1.08]
Wang 2015 (CCT)	10	57	16	60	4.9%	0.66 [0.33, 1.33]
Gouvas 2012-CCT open (25)	14	36	25	45	7.1%	0.70 [0.43, 1.14]
Wang 2012 open (35)	7	41	10	42	3.7%	0.72 [0.30, 1.70]
Mari 2016 (40)	12	70	15	70	5.0%	0.80 [0.40, 1.58]
Forsmo 2016 (50)	65	154	68	153	10.1%	0.95 [0.74, 1.23]
Vlug 2011 lap (34)	34	100	37	109	8.4%	1.00 [0.69, 1.46]
Ren 2011 (32)	29	299	28	298	7.0%	1.03 [0.63, 1.69]
Vlug 2011 open (34)	43	93	41	98	9.2%	1.11 [0.80, 1.52]
Total (95% CI)		**1456**		**1463**	**100.0%**	**0.66 [0.54, 0.80]**
Total events	299		426			

Heterogeneity: Tau² = 0.09; Chi² = 36.88, df = 17 (P = 0.003); I² = 54%
Test for overall effect: Z = 4.12 (P < 0.0001)



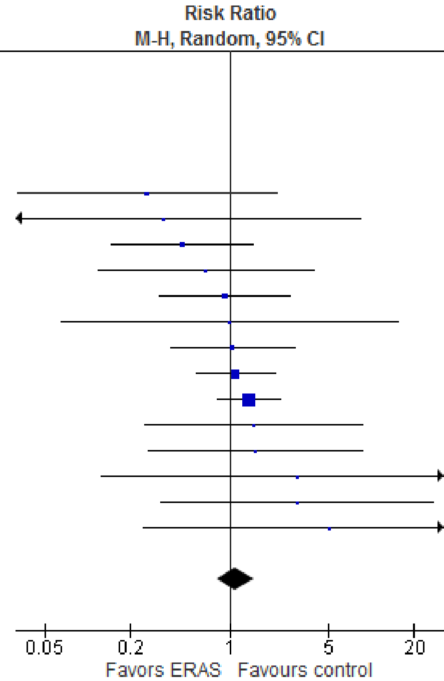
Readmissions

Eighteen studies (21 comparisons) reported readmissions. In one study with both open surgery and laparoscopic surgery results, readmission rates ranged from 9.5% to 15% but were not reported by group.[25] The authors reported that differences between groups were not significant. The pooled risk ratio for studies reporting readmission rates by study group is presented in Figure 6. Five studies reported no readmissions.[22,26,33,37,41] The pooled estimate was 1.11 (95% CI 0.82, 1.50) (absolute difference =-0.7%, 95% CI -1.1, 3.2), indicating no significant difference in risk of readmission following colorectal surgery with an enhanced recovery protocol compared to a usual care protocol. Quality of evidence for no significant difference in readmissions between enhanced recovery and usual care protocols was rated as low (Table 3 and Appendix F).

Figure 6. Pooled Analysis for Readmissions

Study or Subgroup	ERAS Events	ERAS Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Serclová 2009 (33)	0	51	0	52		Not estimable
Ionescu 2009 (26)	0	48	0	48		Not estimable
Mari 2014 (41)	0	25	0	25		Not estimable
Anderson 2003 (22)	0	19	0	20		Not estimable
Yang 2012 (37)	0	32	0	30		Not estimable
Gatt 2005 (24)	1	19	4	20	2.1%	0.26 [0.03, 2.15]
Feng 2014 (38)	0	57	1	59	0.9%	0.34 [0.01, 8.29]
Wang 2011 (36)	4	106	9	110	7.1%	0.46 [0.15, 1.45]
Wang 2012 (44)	2	49	3	50	3.1%	0.68 [0.12, 3.90]
Vlug 2011 lap (34)	6	100	7	109	8.4%	0.93 [0.32, 2.69]
Nanavati 2014 (30)	1	30	1	30	1.3%	1.00 [0.07, 15.26]
Vlug 2011 open (34)	7	93	7	98	9.2%	1.05 [0.38, 2.89]
Scioscia 2017 (43)	11	62	26	162	22.7%	1.11 [0.58, 2.10]
Forsmo 2016 (50)	29	154	21	153	35.2%	1.37 [0.82, 2.30]
Muller 2009 (29)	3	76	2	75	3.0%	1.48 [0.25, 8.61]
Wang 2012 open (35)	3	41	2	42	3.1%	1.54 [0.27, 8.73]
Wang 2012 lap (35)	1	40	0	40	0.9%	3.00 [0.13, 71.51]
Khoo 2007 (28)	3	35	1	35	1.9%	3.00 [0.33, 27.46]
Ota 2017-CCT (42)	2	159	0	161	1.0%	5.06 [0.24, 104.62]
Total (95% CI)		**1196**		**1319**	**100.0%**	**1.11 [0.82, 1.50]**
Total events	73		84			

Heterogeneity: Tau² = 0.00; Chi² = 8.01, df = 13 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)



Pain and Quality of Life

Few studies reported pain or quality of life outcomes (Appendix D, Tables 3 and 4). One study comparing enhanced recovery and usual care protocols associated with open surgery for benign conditions (78% Crohn's disease) reported clinically significant lower pain for the enhanced recovery group on post-operative days 0 to 5.[33] A difference of one point on a visual analog pain scale of 0 to 10 was considered a clinically important difference. Scores ranged from 1.6 for the enhanced recovery group and 3.2 for the usual care group on the day of surgery to 0 and 1, respectively, on post-surgery day 5 (Appendix D, Table 4).

Another study, enrolling patients with colon cancer undergoing laparoscopic surgery, reported European Organization for Research and Treatment of Cancer (EORTC OLQ-C30) scores for pain and quality of life.[45] The scale was administered pre-operatively and post-operatively and change scores were reported. A change of at least 5 points on a 0 to 100 scale was considered clinically significant with further gradations for "little," "moderate," or "very much" change (either better or worse). For pain, changes from before surgery to 3 days post-surgery did not differ significantly between the enhanced recovery and usual care protocol groups. Both groups experienced changes of greater than 20 points ("very much" worse pain). At post-operative day 28, the change from baseline pain was "little" worse for the enhanced recovery group and "moderate" worse for the usual care group (P=.05).

For quality of life, the change from baseline to post-operative day 3 was "moderate" for both the enhanced recovery and usual care groups but the difference between groups was significant (P<.001). By post-operative day 28, both groups rated quality of life similar to pre-surgery levels (P=.11 between groups).

Several studies reported pain scale scores without assessing whether clinically meaningful changes were observed (Appendix D, Table 4). A study of both open and laparoscopic surgery for colon cancer and benign disease reported that SF-36 Bodily Pain Scale scores returned to baseline at 4 weeks after surgery with no significant differences between enhanced recovery and usual care protocols.[34] Another study reported no difference between groups in pain scores.[24]

Three studies reported pain scores during the post-operative period. One study of open colon surgery (72% malignant) reported that median pain scores at rest, on movement, and on coughing were significantly higher in the usual care protocol group on post-operative day 1 but by day 7, only pain on coughing was significantly higher.[22] Two studies of laparoscopic surgery reported significantly higher pain in the enhanced recovery protocol group in the immediate post-operative period[41] or on post-operative days 1 and 3.[38] The first study, enrolling patients with colon cancer or diverticular disease, found the difference was not significant at 5 hours post-surgery. The enhanced recovery group experienced lower pain (although not significantly) starting on post-operative day 1.[41] The second study, enrolling patients with rectal cancer, found higher pain in the enhanced recovery group persisted on post-operative day 3 but was not significantly different from the usual care group at post-operative day 5.[38]

One study of open rectal surgery reported quality of life scores from the EORTC OLQ-C38.[31] The authors administered the questionnaire prior to discharge and at the 1 month follow-up but did not identify the time point associated with the reported scores. Overall, there was no significant difference between enhanced recovery and traditional care groups with 56% and 48%, respectively, reporting excellent quality of life and only 4% in each group (1 patient) reporting poor quality of life.

Gastrointestinal Function

Most studies reported measures of gastrointestinal function. Twelve studies (14 comparisons) reported ileus (Appendix D, Table 3). One study found significantly lower incidence of ileus in the enhanced recovery protocol group with open surgery but a non-significant difference between protocols for laparoscopic surgery.[25] The remaining studies found no significant difference between enhanced recovery and usual care protocols for open surgery,[22-24,29,30,34] laparoscopic surgery,[34,38,40,42,45] or mixed open and laparoscopic surgery.[50]

Twenty studies (22 comparisons) reported significantly shorter time to flatus and/or first bowel movement in the enhanced recovery protocol group compared to the usual care protocol group (Appendix D, Table 4). The difference was observed for open surgery,[23,25-28,30-34,36,37] laparoscopic surgery,[25,34,38,40-42,44-46] and mixed surgery approaches[50] across colorectal conditions.

The time to oral intake of solid foods was also significantly shorter following surgery with an enhanced recovery protocol compared to a usual care protocol in 8 open surgery[22-24,26,28,33,34,37] and 5 laparoscopic surgery[34,40-42,44] studies (Appendix D, Table 4). The study with mixed open and laparoscopic surgery found median days until able to tolerate solid food did not differ significantly between the enhanced recovery protocol group (2 days, range 0-9) and standard care group (1 day, range 0-12).[50]

KEY QUESTION 2: What are the harms of ERAS versus usual care or a subset of ERAS components for adults undergoing elective colorectal surgery?

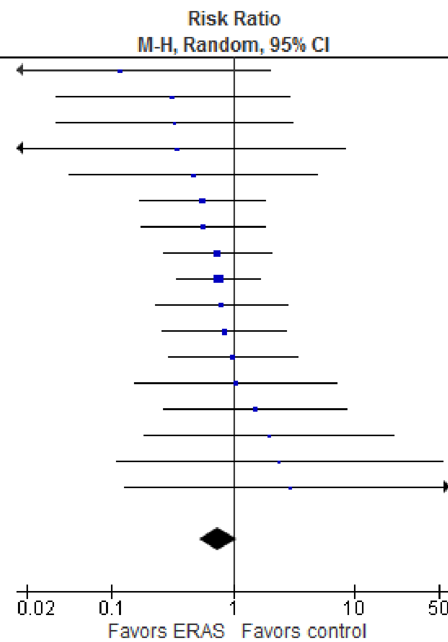
Surgical Site Infections

Surgical site infection rates were reported in 18 studies (19 comparisons of enhanced recovery and usual care protocols) and typically infrequent in both groups (Appendix D, Table 5). No study found a significant difference in surgical site infections between the 2 protocols. One study reported total number of infections for both open surgery and laparoscopic surgery with no difference between enhanced recovery and usual care protocols within the surgery types.[34] The remaining studies reported infection rates. Pooled results indicate no difference in the risk of surgical site infection with enhanced recovery or usual care protocols (RR 0.75 [95% CI 0.52, 1.07]) (Figure 7). Quality of evidence for no significant difference in surgical site infections between enhanced recovery and usual care protocols was rated as low (Table 3 and Appendix F).

Figure 7. Pooled Analysis for Surgical Site Infection

Study or Subgroup	ERAS Events	ERAS Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Gatt 2005 (24)	0	19	4	20	1.6%	0.12 [0.01, 2.03]
Wang 2012 (46)	1	40	3	38	2.6%	0.32 [0.03, 2.91]
Feng 2016 (23)	1	116	3	114	2.5%	0.33 [0.03, 3.10]
Feng 2014 (38)	0	57	1	59	1.3%	0.34 [0.01, 8.29]
Yang 2012 (37)	1	32	2	30	2.3%	0.47 [0.04, 4.91]
Wang 2011 (36)	4	106	7	104	9.0%	0.56 [0.17, 1.86]
Muller 2009 (29)	4	76	7	75	9.2%	0.56 [0.17, 1.85]
Jia 2014 (27)	6	117	8	116	12.2%	0.74 [0.27, 2.08]
Forsmo 2016 (50)	10	154	13	153	20.5%	0.76 [0.35, 1.69]
Ionescu 2009 (26)	4	48	5	48	8.2%	0.80 [0.23, 2.80]
Ota 2017-CCT (42)	5	159	6	161	9.5%	0.84 [0.26, 2.71]
Ren 2011 (32)	5	299	5	298	8.5%	1.00 [0.29, 3.41]
Wang 2015 (CCT)	2	57	2	60	3.5%	1.05 [0.15, 7.22]
Wang 2012	3	49	2	50	4.2%	1.53 [0.27, 8.77]
Mari 2016 (40)	2	70	1	70	2.3%	2.00 [0.19, 21.56]
Anderson 2003 (22)	1	14	0	11	1.3%	2.40 [0.11, 53.77]
Nanavati 2014 (30)	1	30	0	30	1.3%	3.00 [0.13, 70.83]
Total (95% CI)		**1443**		**1437**	**100.0%**	**0.75 [0.52, 1.07]**
Total events	50		69			

Heterogeneity: Tau² = 0.00; Chi² = 6.53, df = 16 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)



Other Harms (Appendix D, Tables 5 and 6)

Few bleeding events were observed with no significant differences between enhanced recovery and usual care protocol groups for either open or laparoscopic surgery.[23,25,29,40,42,43] Need for re-operation was reported on 10 studies (11 comparisons) with no significant differences between protocol groups for either surgery type.[25,26,30,34,36,38,42-44,50]

Many studies reported anastomotic leakage with no differences between enhanced recovery and usual care protocols for either open or laparoscopic surgery.[23,25-32,34,36-38,40-42,44-46,50] Unspecified surgical complications either were not significantly different between enhanced recovery and usual care protocol groups[25,35,42] or were significantly lower in the enhanced recovery protocol group.[33]

Foley catheter re-insertion was reported in 3 studies with no significant difference between enhanced recovery protocols and usual care protocols for open surgery[28,36] or laparoscopic surgery.[44] Pneumonia and other chest infections were reported in 11 studies (12 comparisons). Two open surgery studies found a significantly lower incidence in the enhanced recovery protocol group[25,27] while 4 found no difference between the enhanced recovery and usual care protocols.[23,24,29,37] Five laparoscopic studies[25,38,40,45,46] and one study with mixed open and laparoscopic procedures[50] found no significant difference in pulmonary infections between enhanced recovery and usual care protocol groups.

Five open surgery studies and one laparoscopic surgery study reported post-operative nausea, vomiting, or diarrhea with no significant difference between the enhanced recovery and usual care protocol groups.[24,26,32,33,35,40] One study of elderly patients (70 to 88 years old) undergoing open surgery for colorectal cancer found post-operative delirium was significantly less likely in the enhanced recovery protocol group.[27] Two other studies found no difference between protocol groups for delirium or post-operative confusion.[42,50] Other commonly reported non-surgical complications with no significant differences between protocol groups included intestinal obstruction,[25,27,32,36,44,46] urinary tract infection,[22,24,26-29,36,38,44,50] urinary retention,[23,25,29,34,36,38,40,50] deep vein thrombosis or pulmonary embolism,[24-27,36,38,42,44,50] and cardiovascular and/or cerebrovascular complications.[22,27-29,31,32,34,36,37,40,42,44,45,50]

KEY QUESTION 3: Do comparative effectiveness and harms vary by fidelity to ERAS components?

Adherence to Specific Enhanced Recovery Components

Four studies reported adherence or compliance data. A CCT from Japan with predominantly laparoscopic surgery for colorectal cancer reported compliance (*ie*, the component was "applied") with enhanced recovery components.[42] Across 17 components, the average compliance was 85%. Seven of the 17 components were also applied in more than 50% of the conventional care group including avoidance of fluid overload, no use of drains, antimicrobial prophylaxis, epidural anesthesia, early removal of nasogastric tubes, routine postoperative laxative, and ambulation on post-operative day 1. The study reported significantly shorter length of stay in the enhanced recovery group with no differences in mortality, readmissions, or surgical site infections. Among enhanced recovery group patients, increased adherence to the protocol was associated with shorter length of stay (P=.01) but not overall rate of complications (P=.29).

In a 4-arm study with enhanced recovery and usual care groups for both open and laparoscopic surgery (mainly for colorectal cancer), 15 enhanced recovery components were evaluated for each patient.[34] Successful application of each component was noted. A mean of 11.2 (SD 2.2) of the 15 components were applied in the laparoscopic surgery with enhanced recovery group (n=100) and 11.1 (SD 2.2) components in the open surgery with enhanced recovery group. The authors noted that "applied" does not mean that the component was successfully achieved. Vlug et al found no significant differences in mortality, overall morbidity, or hospital readmissions with enhanced recovery for either open or laparoscopic surgery. Length of stay was significantly shorter in the enhanced recovery groups compared to the usual care groups for both open and laparoscopic surgery.[34]

A study of open or laparoscopic surgery (surgeon's decision) for colorectal cancer or benign conditions reported adherence to 22 enhanced recovery components for both the enhanced recovery and standard care group.[50] Adherence was similar in the 2 groups for 7 components: omission of bowel preparation, no preoperative fasting, no premedication, antimicrobial prophylaxis, thoracic epidural analgesia, prevention of hypothermia, and intra-operative fluid loading level. The study reported significantly shorter length of stay in the enhanced recovery group compared to standard care with no differences in overall morbidity, mortality, readmissions, or surgical site infections.

A fourth study monitored adherence to 5 enhanced recovery components (intraoperative intravenous intake, first 24-hour intravenous intake, effective epidural analgesia, mobilization time on post-operative day 1, and oral nutrition on post-operative days 1 and 4) during open surgery, mainly for colorectal cancer.[29] The authors noted significant differences between the enhanced recovery and usual care protocol groups in median intraoperative intravenous intake, first 24-hour median intravenous intake, and oral nutrition on post-operative days 1 and 4 as evidence of "excellent compliance." The 2 protocol groups did not differ significantly on "effective" epidural analgesia or median mobilization time on day 1. Muller et al found no difference in surgical site infections or readmissions but did report a reduction in length of stay and overall morbidity in the enhanced recovery group versus usual care.

Inclusion of Recommended ERAS Components in a Perioperative Protocol

We used our charting of ERAS components in the enhanced recovery and standard care protocols of each of the included RCTs and CCTs to identify studies that best differentiated an enhanced recovery protocol from a standard care protocol. We looked at a) overlap of enhanced recovery components between the 2 protocols and b) inclusion of 2 enhanced recovery components that require a multidisciplinary team to successfully execute (intra-operative standardized anesthesia protocol and post-operative multimodal approach to opioid-sparing pain control). Based on these 2 criteria, we identified 11 studies (of the 25 included in the review) that appeared to best differentiate an enhanced recovery protocol from a usual care protocol.[22,23,27,28,32,33,35,36,40,44,46] We pooled data from these 11 studies (provided they reported outcomes of interest in a way that permitted pooling) and from the remaining studies for 2 critical outcomes – length of stay (Figure 8) and overall morbidity (Figure 9). The results were similar to the overall pooled estimates with no interaction for the subgroup analysis for either outcome. Heterogeneity was substantial for the length of stay analysis (I^2 values ≥84%) but nearly all studies favored the enhanced recovery protocol.

Figure 8. Pooled Analysis for Length of Stay in Studies with More vs Less Definitive Differentiation of ERAS vs Control Protocols

	ERAS			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
1.4.1 Best differentiation of ERAS protocol versus control								
Jia 2014 (27)	9	1.8	117	13.2	1.3	116	5.0%	-4.20 [-4.60, -3.80]
Anderson 2003 (22)	4	1.8	14	7	2.1	11	3.9%	-3.00 [-4.56, -1.44]
Serclová 2009 (33)	7.4	1.3	51	10.4	3.1	52	4.6%	-3.00 [-3.92, -2.08]
Wang 2011 (36)	5.1	3.1	106	7.6	4.8	104	4.4%	-2.50 [-3.60, -1.40]
Mari 2016 (40)	5	2.6	70	7.2	3	70	4.6%	-2.20 [-3.13, -1.27]
Khoo 2007 (28)	5	8.5	35	7	14.8	35	1.0%	-2.00 [-7.65, 3.65]
Wang 2012 (46)	5.5	1	40	7	1.8	38	4.8%	-1.50 [-2.15, -0.85]
Feng 2016 (23)	7.5	2.2	116	8.6	2.8	114	4.8%	-1.10 [-1.75, -0.45]
Ren 2011 (32)	5.7	1.6	299	6.6	2.4	298	5.0%	-0.90 [-1.23, -0.57]
Subtotal (95% CI)			**848**			**838**	**38.0%**	**-2.27 [-3.37, -1.17]**
Heterogeneity: Tau² = 2.40; Chi² = 173.85, df = 8 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 4.04 (P < 0.0001)								
1.4.2 Less definitive differentiation of ERAS protocol versus control								
Yang 2012 (37)	6	1	32	11.7	3.8	30	4.0%	-5.70 [-7.10, -4.30]
Ota 2017-CCT (42)	8.5	6	159	14	6.5	161	4.1%	-5.50 [-6.87, -4.13]
Scioscia 2017 (43)	3	2.3	62	7	4.8	165	4.6%	-4.00 [-4.93, -3.07]
Gouvas 2012-CCT lap (25)	4	2.3	42	8	3.8	33	4.0%	-4.00 [-5.47, -2.53]
Muller 2009 (29)	6.7	4.8	76	10.3	4.9	75	3.9%	-3.60 [-5.15, -2.05]
Mari 2014 (41)	4.7	2.4	25	7.7	2.4	25	4.1%	-3.00 [-4.33, -1.67]
Ionescu 2009 (26)	6.4	3.4	48	9.2	2.7	48	4.2%	-2.80 [-4.03, -1.57]
Nanavati 2014 (30)	4.7	1.3	30	7.3	1.4	30	4.8%	-2.60 [-3.28, -1.92]
Wang 2015 (CCT)	6.1	1.7	57	8.7	2.8	60	4.7%	-2.60 [-3.43, -1.77]
Gatt 2005 (24)	6.6	4.4	19	9	4.6	20	2.5%	-2.40 [-5.22, 0.42]
Forsmo 2016 (50)	5	8	154	7	7.6	153	3.6%	-2.00 [-3.75, -0.25]
Feng 2014 (38)	5.1	1.4	57	7	2.3	59	4.8%	-1.90 [-2.59, -1.21]
Gouvas 2012-CCT open (25)	7	2.3	36	8	4	45	4.1%	-1.00 [-2.39, 0.39]
Vlug 2011 lap (34)	5	2.9	100	6	2.9	109	4.7%	-1.00 [-1.79, -0.21]
Vlug 2011 open (34)	7	4.4	93	7	5.2	98	4.1%	0.00 [-1.36, 1.36]
Subtotal (95% CI)			**990**			**1111**	**62.0%**	**-2.79 [-3.53, -2.05]**
Heterogeneity: Tau² = 1.67; Chi² = 89.52, df = 14 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 7.43 (P < 0.00001)								
Total (95% CI)			**1838**			**1949**	**100.0%**	**-2.59 [-3.22, -1.97]**
Heterogeneity: Tau² = 1.97; Chi² = 270.86, df = 23 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 8.19 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.59, df = 1 (P = 0.44), I² = 0%								

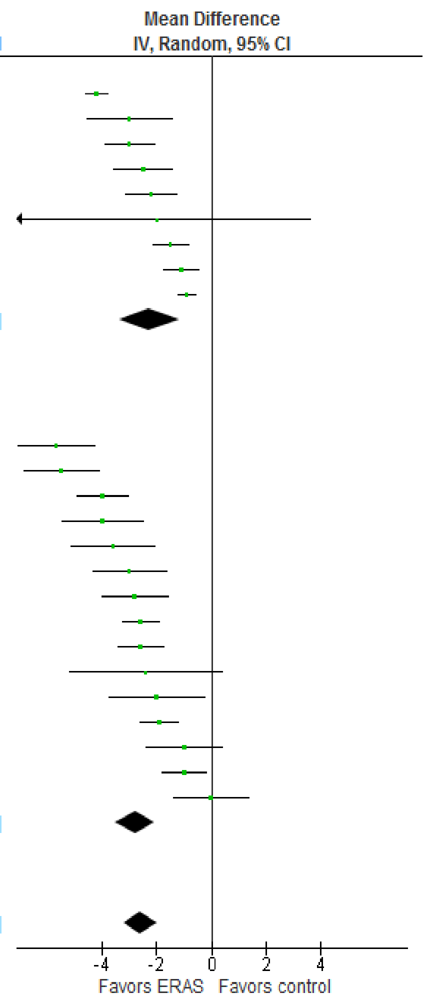
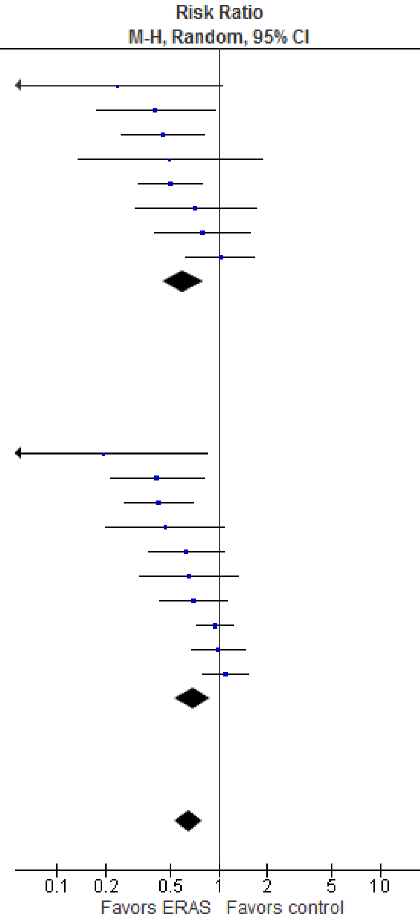


Figure 9. Pooled Analysis for Morbidity in Studies with More vs Less Definitive Differentiation of ERAS vs Control Protocols

Study or Subgroup	ERAS Events	ERAS Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Best differentiation of ERAS protocol versus control						
Wang 2012 (46)	2	40	8	38	1.6%	0.24 [0.05, 1.05]
Feng 2016 (23)	7	116	17	114	3.9%	0.40 [0.17, 0.94]
Serclová 2009 (33)	11	51	25	52	5.8%	0.45 [0.25, 0.81]
Wang 2012 lap (35)	3	40	6	40	1.9%	0.50 [0.13, 1.86]
Wang 2011 (36)	20	106	39	104	7.3%	0.50 [0.32, 0.80]
Wang 2012 open (35)	7	41	10	42	3.7%	0.72 [0.30, 1.70]
Mari 2016 (40)	12	70	15	70	5.0%	0.80 [0.40, 1.58]
Ren 2011 (32)	29	299	28	298	7.0%	1.03 [0.63, 1.69]
Subtotal (95% CI)		**763**		**758**	**36.2%**	**0.60 [0.45, 0.80]**
Total events	91		148			
Heterogeneity: Tau² = 0.04; Chi² = 9.33, df = 7 (P = 0.23); I² = 25%						
Test for overall effect: Z = 3.43 (P = 0.0006)						
1.8.2 Less definitive differentiation of ERAS protocol versus control						
Mari 2014 (41)	0	25	0	25		Not estimable
Feng 2014 (38)	2	59	10	57	1.6%	0.19 [0.04, 0.84]
Gouvas 2012-CCT lap (25)	9	42	17	33	5.2%	0.42 [0.21, 0.81]
Muller 2009 (29)	16	76	37	75	7.0%	0.43 [0.26, 0.70]
Yang 2012 (37)	6	32	12	30	3.8%	0.47 [0.20, 1.09]
Gatt 2005 (24)	9	19	15	20	6.5%	0.63 [0.37, 1.08]
Wang 2015 (CCT)	10	57	16	60	4.9%	0.66 [0.33, 1.33]
Gouvas 2012-CCT open (25)	14	36	25	45	7.1%	0.70 [0.43, 1.14]
Forsmo 2016 (50)	65	154	68	153	10.1%	0.95 [0.74, 1.23]
Vlug 2011 lap (34)	34	100	37	109	8.4%	1.00 [0.69, 1.46]
Vlug 2011 open (34)	43	93	41	98	9.2%	1.11 [0.80, 1.52]
Subtotal (95% CI)		**693**		**705**	**63.8%**	**0.69 [0.54, 0.90]**
Total events	208		278			
Heterogeneity: Tau² = 0.09; Chi² = 23.74, df = 9 (P = 0.005); I² = 62%						
Test for overall effect: Z = 2.81 (P = 0.005)						
Total (95% CI)		**1456**		**1463**	**100.0%**	**0.66 [0.54, 0.80]**
Total events	299		426			
Heterogeneity: Tau² = 0.09; Chi² = 36.88, df = 17 (P = 0.003); I² = 54%						
Test for overall effect: Z = 4.12 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.51, df = 1 (P = 0.47), I² = 0%						



KEY QUESTION 4: Do comparative effectiveness and harms vary by type of, and clinical conditions for, colorectal surgery (*eg*, anatomical site, laparoscopic versus open surgery, reasons for open surgery, *etc*)?

For critical outcomes, we grouped studies by surgery type (open or laparoscopic) and by colorectal condition (colorectal cancer, rectal cancer, a mix of colorectal cancer and benign conditions, or benign conditions alone). Findings for other outcomes, including pain, quality of life, gastrointestinal function, and harms as described under Key Questions 1 and 2 (above), did not appear to differ between studies of open surgery and studies of laparoscopic surgery. We did not find outcomes reported for other subgroups of interest: comorbidity status, mobility status, frailty index, age, patient size, or right- versus left-side surgery.

Length of Stay

Length of stay reductions due to ERAS did not significantly differ by type of, or clinical condition for, surgery. We pooled results separately for studies using laparoscopic techniques and studies using open surgery. The resulting estimates for mean difference were similar to that of the overall mean difference for both groups (Appendix G, Figure 1). The interaction was not significant (P=.69).

We also pooled results separately for studies of surgery for different colorectal conditions (colorectal cancer, rectal cancer, a mix of colorectal cancer and benign conditions, or benign conditions alone). Pooled estimates for the mean differences were similar to that of the overall mean difference for all 4 groups (Appendix G, Figure 2). The interaction was not significant (P=.29).

All-cause Mortality

We found no difference in mortality between enhanced recovery and usual care protocols observed in studies performing open surgery or in studies performing laparoscopic surgery (Appendix G, Figure 3). The interaction was not significant (P=.43).

Across colorectal conditions, there was no difference in mortality between enhanced recovery and usual care protocols for colorectal cancer, rectal cancer, or a mix of colorectal cancer and benign conditions (Appendix G, Figure 4). The interaction was not significant (P=.42). There were no deaths in the 2 studies of benign conditions alone.[30,33]

Overall Morbidity

Perioperative morbidity reduction between enhanced recovery and usual care protocols did not differ in studies performing open surgery and in studies performing laparoscopic surgery (Appendix G, Figure 5). The risk ratios were similar to the overall risk ratio. The interaction was not significant (P=.79).

The effect of ERAS on overall morbidity also did not vary by clinical condition (P for interaction=0.13). Perioperative morbidity was significantly lower in the enhanced recovery groups compared to usual care (Appendix G, Figure 6).

Readmissions

No difference in risk of readmission between enhanced recovery and usual care protocols was observed in studies regardless of surgical approach (open or laparoscopic surgery) (P for interaction =.65) (Appendix G, Figure 7). The pooled risk ratio for each subset of studies was similar to the overall risk ratio.

Across colorectal conditions, risk of readmission was not significantly different between enhanced recovery and usual care protocols for colorectal cancer, rectal cancer, a mix of colorectal cancer and benign conditions, or benign conditions alone (Appendix G, Figure 8). The interaction was not significant (P=.87).

Surgical Site Infections

No difference in surgical site infection rates between enhanced recovery and usual care protocols was observed in studies performing open surgery or in studies performing laparoscopic surgery (Appendix G, Figure 9). The pooled estimates were similar to the overall risk ratio and the interaction was not significant (P=.54).

Across colorectal conditions, risk of surgical site infection did not differ significantly between enhanced recovery and usual care protocols for colorectal cancer, rectal cancer, or a mix of colorectal cancer and benign conditions (Appendix G, Figure 10). The interaction was not significant (P=.81).

KEY QUESTION 5: What are the barriers to and facilitators of implementation of ERAS programs?

We identified 10 studies that provided information on barriers and facilitators to implementing an enhanced recovery program. Five of the 7 studies interviewed representatives from a multidisciplinary team,[51-55] 2 interviewed patients,[56,57] 2 surveyed surgeons,[58,59] and one interviewed nurses.[60] The studies were conducted in the US,[51,59] Canada,[53,55] Australia/New Zealand,[54,58] the Netherlands,[52] and the UK.[56,57,60] Table 4 provides an overview of the studies.

Table 4. Studies of Barriers and Facilitators

Author, year Country	Hospital type	ERAS protocol in place at time of interview/survey?	Persons interviewed/surveyed
Alawadi 2016[51] US	Safety net hospital (single site)	No	Colorectal care surgeons, anesthesiologists, nurses; colorectal surgery patients
Keller 2016[59] US	Not applicable	70% of responders did not have an enhanced recovery protocol at their institution; 42% reported using enhanced recovery concepts	Surgeons, members of Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)
Pearsall 2015[55] Canada	University-affiliated adult teaching hospitals (7 sites)	No	Surgeons, anesthesiologists, ward nurses (not limited to colorectal care)
Conn 2015[53] Canada	Academic hospitals (15 sites)	Yes; 8 sites with experience; 7 sites with limited experience	Colorectal care surgeon champions, anesthesiologist champions, nurse champions, coordinators
Lyon 2014[54] Australia	Quaternary referral hospital (single site)	Yes	Colorectal care surgeons, stoma therapist, dietetics, physiotherapist medical administration
Ament 2014[52] Netherlands	Hospitals that successfully implemented ERAS[a] (10 sites)	Yes	Gastrointestinal surgeons, physician assistants, coordinators, nurses
Kahokehr 2011[58] New Zealand and Australia	Not applicable	45% of responders routinely or "sometimes" followed a formalized ERAS pathway	Colorectal surgeons (members of Colorectal Surgical Society of Australia and New Zealand)
Jeff 2014[60] United Kingdom	District general hospital	Yes	Ward nurses
Bernard 2014[56] United Kingdom	Not specified	Yes	Patients
Taylor 2011[57] United Kingdom	Tertiary colorectal unit	Yes	Patients

[a] Success defined as median length of stay of 6 days or less and protocol adherence rates above 70%

Adapting the framework reported by Alawadi et al,[51] barriers and facilitators reported in the studies are organized by staff-related factors, organizational factors, and patient factors. Commonly reported barriers to implementation include time, resources, and acceptability/feasibility of protocols to clinical staff and patients. Facilitators include organizational support, sufficient staff and electronic medical record resources, clear communication that is receptive to staff/patient feedback, and standardized yet adaptable and feasible protocols.

Staff-related Factors

Frequently mentioned staff-related barriers to implementation included difficulty adapting to change and perceived resistance to change by co-workers and colleagues from other specialty areas (Table 5). Other barriers included lack of agreement with the enhanced recovery recommendations (including a sense that there wasn't sufficient evidence to support some components) and lack of staff or staff time.

Staff-related facilitators to implementation included strong team collaboration and communication, support from leadership, ongoing staff education, and engagement of ERAS coordinators and physician champions.

Table 5. Staff-related Barriers and Facilitators

Barriers	Facilitators
Resistance to "cook book" approach[51]	Team cohesion/collaboration (problem solving, addressing barriers, support)[51,53,55,60]
Difficulty adapting to change (culture, personal preferences, resistance); need to change staff attitudes and behavior[51,53-55,60]	Good communication among team members; especially if there is need to modify the protocol for specific patient needs[51,54,55]
Perceived reluctance of others to adopt components of ERAS and to work cooperatively; lack of colleague or co-specialty support[51,55,58-60]	Creation of opportunities to build relationships across departments; avoid sense of coercion or "top-down" approach[53]
Need for flexibility to address special needs of patients[51,54,60]	Leadership team builds a "community of practice" with other centers (networking, shared best practices)[53]
Shortened preoperative fasting may require cases to be cancelled if a patient is moved forward on the operative schedule[55]	Physician champions[55]
Setting shortened discharge date might discourage patient if goal is not achieved[55]	An ERAS coordinator responsible for systematic checks and monitoring of outcomes and adherence[52-55]
Lack of agreement with recommendations, don't believe in it, not enough evidence[53,55,58,60]	Support from institution and departmental leaders[53,55,60]
Lack of staff to implement ERAS components (*eg,* more frequent mobilization)[55]	Staff education (ongoing) on the evidence behind change in practice; knowledge of program[52,54,55,60]
Lack of time[55,58]	
Lack of weekend staffing for some components (*eg,* stoma therapy nurse) delays discharge[54]	
Lack of individual confidence in following ERAS; concern about adverse consequences of accelerated patient discharge[60]	
Nurses not perceiving themselves as having ownership and ability to foster development of the program[60]	
Staff education[59]	
Lack of awareness about enhanced recovery[59]	

Organizational Factors

At the organizational level, commonly mentioned barriers include lack of institutional or departmental support, lack of resources, issues with staff scheduling, and difficulty coordinating across different departments (Table 6).

Facilitators of implementation of an enhanced recovery program included evidence-based pathways and standardized order sets, administrative reminders and/or integration of the enhanced recovery components into computer order entry systems, and use of outcomes data to build interest in the program. Setting performance targets, audit and feedback, and periodic updates were suggested as beneficial for sustaining a program.

Table 6. Organizational Barriers and Facilitators

Barriers	Facilitators
Need department-level "buy-in"; lack of institutional support[55,58,59]	ERAS pathway provides evidence-based standard of care; standardized order sets would reduce variation in practice[51,53,55]
Integration of ERAS with staff scheduling[53]	Protocol endorsed by a national organization[59]
Rotating residents could be a challenge to establishing consistency of practice[51]	Availability and use of data to drive effective implementation; provide updates to build and sustain interest in the ERAS program (*eg,* data reports with uptake, outcomes)[52,53,59]
Coordinating ERAS across different departments; need for education for entire perioperative multidisciplinary team, patients, and families[51,55]	Audit and feedback to sustain program[52,53,55]
Inconsistencies with partners or covering physicians following the same protocol[59]	Integration of ERAS into computer order entry systems[53]
Satisfaction with current results[58]	Administrative reminders integrated in daily practice (*eg,* checklists in patient files)[54]
Limited resources: equipment, staff, space[51,55,59,60]	Embed ERAS components in local protocols and performance targets for sustainability[52]
Lack of discharge resources (*ie,* rural areas may lack specialist experience and facilities required to care for patients after discharge)[54]	Cluster ERAS patients in a specific department or room[52]
	Uniformity in procedure for planning and discussing timing of discharge[52]
	Reaching the point where ERAS becomes the standard of care[53]

Patient Factors

Three studies interviewed patients,[51,56,57] and several others mentioned patient factors related to implementation of an enhanced recovery program (Table 7). Potential barriers included the characteristics of the patient population (potentially limiting early discharge and compliance with recommendations), patient preferences and expectations (particularly related to home recovery), and concern about availability of support and community resources following discharge. Patient and family/caregiver education and early communication of expectations were mentioned as facilitators of patient acceptance of an enhanced recovery program.

Table 7. Patient Factors

Barriers	Facilitators
Characteristics of patient population served by facility (*eg,* high comorbidity rate, advanced disease at presentation, social support, health literacy)[51,54]	Patient education component may increase patient satisfaction and compliance with care; family involvement[51,55,57]
Patient preferences and expectations (reflective of culture and values) might affect acceptance of ERAS program[54,55]	Early communication with the patient about expectations and discharge[52,54,57]
Amount of patient information provided and level of complexity may need to be tailored to individual patient preferences[56]	Frequent contact with multidisciplinary team can improve patient confidence in the rehabilitation process[57]
Lack of quiet and privacy hinders patient recovery[51]	Patients welcomed early mobilization and speedier recovery/release[51,56,57]
Concerns about protocol being too difficult for all patients[56]	Patient appreciation of earlier return to usual activities following discharge[57]
Concerns about pain control options[57]	
Recovery at home hindered by inadequate instructions and education on what to expect during home recovery and difficulty contacting specialist support[51,57]	
Need for support of family and friends after discharge[56]	
Patient fear that early release could be unsafe (*eg,* complications, pain management) particularly if no social support or community resources not available[51,56]	

SUMMARY AND DISCUSSION

KEY FINDINGS AND QUALITY OF EVIDENCE

1) Enhanced recovery protocols significantly reduced length of stay (mean reduction 2.6 days) following colorectal surgery compared to usual care protocols (Quality of Evidence: Moderate). Length of stay reductions occurred across surgical approach (open and laparoscopic) as well as clinical indication (*ie*, colorectal cancer, rectal cancer, a mix of colorectal cancer and benign conditions, or benign conditions alone).

2) Enhanced recovery protocols significantly reduced overall perioperative morbidity (mean absolute reduction 10%) associated with colorectal surgery compared to usual care protocols (Quality of Evidence: Moderate). Reductions due to enhanced recovery protocols did not significantly vary by type of, or clinical condition for, surgery.

3) Mortality, hospital readmissions, and surgical site infections were similar following colorectal surgery with an enhanced recovery protocol or a usual care protocol (Quality of Evidence for Mortality: Low) (Quality of Evidence for Readmissions: Low) (Quality of Evidence for Surgical Site Infections: Low). Outcomes were similar across surgical approach and clinical indication for surgery.

4) Few studies reported on clinically meaningful differences in pain or quality of life, though most studies noted an improvement in gastrointestinal function (typically passing flatus or bowel movement).

5) Enhanced recovery protocols varied across studies, little information was provided regarding component compliance, and evidence is insufficient regarding key components.

6) Commonly reported barriers to implementation include time, resources and acceptability/feasibility of protocols to clinical staff and patients. Facilitators include organizational support, sufficient staff and electronic medical record resources, clear communication that is receptive to staff/patient feedback, and standardized yet adaptable and feasible protocols.

DISCUSSION

Our review of 25 RCTs and CCTs (with 28 comparisons of enhanced recovery and standard care protocols) found moderate quality evidence of significantly reduced length of stay and overall morbidity in enhanced recovery protocol groups compared to standard care protocol groups. Mortality, readmissions, and surgical site infections were similar in the 2 groups (low quality evidence). Among other outcomes assessed, measures of gastrointestinal function (*eg*, time to first oral solid foods, flatus, and first bowel movement) were improved with enhanced recovery protocols compared to standard care protocols. Ileus, other surgical complications, and non-surgical complications were similar. Few studies reported on clinically meaningful change in pain or quality of life scores. Results were similar for open surgery and laparoscopic surgery and regardless of colorectal condition. We found insufficient evidence on whether the effects of enhanced recovery protocols vary by components, whether certain components are essential, or if certain components are unnecessary and perhaps burdensome. Our review also describes commonly reported barriers and facilitators to implementation.

Of the existing systematic reviews (Appendix A), the review by Greco et al[8] had the greatest overlap of included studies with our review. The review was limited to RCTs published to June 2012 with no language restrictions. Sixteen RCTs were included, 5 of which were rated high risk of bias. As in our review, no significant differences were observed between the enhanced recovery group and the standard treatment group for mortality, surgical complications (limited to surgical site infections in our review), and readmissions. Overall morbidity and length of stay were significantly reduced in the enhanced recovery group compared to the control group. In the Greco review, findings were similar when only low and medium risk of bias studies were included. The number of enhanced recovery components in the included studies ranged from 4 to 13. No measure of compliance was reported and no subgroup analyses based on enhanced recovery components were performed.[8]

A critical overview of the methodology used in 10 systematic reviews and meta-analyses (to March 2013) of ERAs programs for colorectal surgery was published in 2014.[61] Differences in study inclusion criteria (type of surgery allowed, number of enhanced recovery components), methods for meta-analyses, definitions of outcomes (particularly length of stay), handling of missing data, accuracy of extraction of data components, and reporting of key decisions in the review methodology are likely responsible for observed differences in pooled estimates across systematic reviews. The authors noted a high level of redundancy and encouraged readers of systematic reviews (particularly those seeking input for decision-making) to look for multiple reviews and to assess the quality of the review as one means of understanding differences in findings between reviews.

IMPLICATIONS FOR PRACTICE

Few studies addressed compliance with the enhanced recovery protocols.[62] Only 4 of the trials included in our review addressed fidelity to the ERAs protocol.[29,34,42,50] Only one related adherence to critical outcomes.[42] Our analysis of studies with higher differentiation or lesser differentiation of enhanced recovery protocols from standard care protocols found results similar to the overall pooled estimates with no interaction for the subgroup analysis for either length of stay or overall morbidity.

Representative data from recent observational studies (*not systematically reviewed*) suggest that outcomes vary depending on compliance with the enhanced recovery protocol.[63-66] A Canadian study included 347 patients, 66% with cancer, who underwent bowel resection.[64] A laparoscopic approach was used in 72%. The enhanced recovery protocol included 23 components, each with defined criteria for adherence. Adherence to the individual components ranged from 26% to 100% with only 2 components less than 50%. Patients were adherent to a median of 18 components (range 16-20). Adherence was significantly associated with successful recovery, a composite outcome with length of day 4 days or less, no 30-day post-operative complications, and no hospital readmissions (OR 1.39 [95% CI 1.24, 1.57] for every additional protocol component). Adherence was inversely associated with length of stay. A study from Poland with 251 patients who underwent laparoscopic resection for colorectal cancer under a 16-item enhanced recovery protocol created 3 groups of patients: those with >90% compliance (defined as "interventions fulfilled"), those with 70-90% compliance, and those with <70% compliance.

Length of stay was significantly lower (mean of 4.5 days) in the >90% compliance group than in the <70% compliance group (mean of 7.8 days).[65] A multi-nation database (Europe and New Zealand) with over 2,300 patients who underwent resection for colorectal cancer included data on compliance with 13 enhanced recovery components. Compliance was inversely associated with length of stay (median of 6 days with greater than 90% compliance; median of 8 days with less than 50% compliance) and development of complications (33% of those with greater than 90% compliance; 48% of those with less than 50% compliance).[63] An analysis of data from over 4,300 colorectal surgery patients in the UK found a weak but significant inverse correlation between length of stay and compliance with 19 enhanced recovery components ($r = -0.18$, $P<.001$).[66] The median length of stay was 7 days if compliance was 70% or higher and 9 days if compliance was less than 50% ($P<.001$).

Furthermore, although observational studies have attempted to identify key components or subsets of components (see, for example, Loftus et al,[67] Pecorelli et al,[64] ERAS Compliance Group 2015[63]) there is no consensus on how many, or which specific, components are necessary to implement to achieve improved patient outcomes. There may be a specific “bundle” of practices that would improve care and patient outcomes, a concept identified by the Institute for Healthcare Improvement to describe an approach to reduce variation in practice, develop a collaborative environment, and ultimately improve outcomes.[68]

Only one of our included trials reported cost data.[32] The study was done in China with all patients undergoing open surgery for colorectal cancer. The total cost of the procedure was $2,441 per patient in the enhanced recovery protocol group and $2,711 per patient in control group ($P<.001$). The postoperative expenses were $548 per patient in the enhanced recovery protocol group and $804 per patient in the control group ($P<.001$). The study did not provide details about what was included in the reported costs. Although not part of our systematic review, we identified one study that modeled costs of implementing an enhanced recovery program in a colorectal surgery program at The Johns Hopkins Hospital.[69] Total first year costs were $117,875 and $552,783 for 100 and 500 cases per year, respectively or approximately $1,100 per patient. Net savings based on 500 cases per year and 1.9 day average reduction in length of stay were over $395,000. We also identified a second study from the US that reported total actual costs (including labor, supplies, and facilities) for patients undergoing colorectal surgery before and after implementation of a perioperative consult service with enhanced recovery components.[70] Median total cost per patient decreased by 17% from pre-implementation to the extended follow-up period (5 to 14 months following implementation) ($P<.05$). During the same time period, median length of stay decreased from 4.2 days to 3.3 days ($P<.01$). Readmission and reoperation rates were not significantly different from pre- to post-implementation. The authors noted that the combination of decreased length of stay and costs achieved post-implementation meant that 4 patients could be cared for in the same time as 3 patients pre-implementation at significantly reduced cost.

Other concerns in practice include workload and sustainability of the intervention. We identified 3 studies (again, not part of our systematic review) that provide information on these topics. A study from Switzerland used a standardized point system for measuring nursing tasks associated with patient care before and after implementation of an enhanced recovery protocol.[71] Compliance with the 21 component enhanced recovery protocol was also tracked. Nursing workload was significantly lower following introduction of the enhanced recovery protocol (point values: 61.2 before implementation, 51.6 in the year after implementation, P<.002). Relative to pre-implementation, the average time saving per patient each day was 48 minutes. There was a significant inverse correlation between nursing workload and compliance with the enhanced recovery protocol (r =-0.42, P<.001).

A study from the Netherlands reported sustainability at 3 to 5 years after implementing an enhanced recovery protocol.[72] The analysis included data from 10 hospitals that were initially successful in implementing the protocol with success defined as length of stay 6 days or lower and protocol adherence greater than 70%. Length of stay increased from 5.25 days to 6.0 days (P>.05). Overall protocol compliance decreased from 75% to 67% (P<.01). Variation among the hospitals was noted. A study from Switzerland assessed sustainability using data from consecutive patients undergoing elective colorectal surgery at an academic hospital during the implementation process and for 3 years after.[73] Median length of stay, readmissions, and complications (including mortality) did not differ significantly over time and were similar to pre-implementation values. Functional recovery components (day of first passage of flatus, day at which oral pain control is achieved, and mobilization of 4 hours or more on post-operative day 1) were also unchanged over the implementation and post-implementation period. Adherence to components of the enhanced recovery protocol increased from 41% before implementation to 73% during implementation and 77% during year 3. Adherence decreased significantly, however, from year 3 to year 4 (P<.05).

LIMITATIONS

Although there is evidence from randomized controlled trials comparing enhanced recovery protocols to standard care, many studies were rated high or unclear risk of bias as methods of sequence generation, allocation concealment, and blinding were often not reported. Differences in the characteristics of the individual trials limits the interpretation and application of findings.

Observed differences in outcomes across studies might be due to implementation of different enhanced recovery protocols.[62] In the RCTs and CCTs included in our review, we found enhanced recovery group protocols included between 4 and 18 enhanced recovery components while standard care group protocols included between 0 and 10 enhanced recovery components.

Other differences across studies include implementation of enhanced recovery in different healthcare systems and with different procedures (including discharge protocols), different patient populations (*eg*, exclusion of patients with ASA grades III or IV), and different outcome definitions.[62]

APPLICABILITY OF FINDINGS TO THE VA POPULATION

None of the trials and only 2 of the qualitative studies of barriers to and facilitators of implementation were done in the US. There is no direct evidence of the effectiveness or harms of an enhanced recovery protocol for colorectal surgery in the US or at VHA facilities. Hospital length of stay, readmissions, and surgical complication rates from reported studies may not reflect US settings including those at VHA facilities. Resource needs, sustainability, or patient and provider acceptance of ERAS protocols are also not well-known. Before widely implementing an enhanced recovery protocol, discussions are needed with key staff, patients, and system groups. Although there are real potential benefits of enhanced recovery programs, particularly in reduced length of stay and possibly morbidity, rolling out a new protocol in "total quality improvement" fashion with evaluation and refinement might be the best approach due to limited applicability of existing RCT data, rapidly evolving standard practice, limited full understanding of implementation/adherence/standardization of enhanced recovery components, and possible barriers. Two recent publications describe implementation of an enhanced recovery program across multiple sites within a health care system in Canada[74] and the US.[75]

RESEARCH GAPS/FUTURE RESEARCH

There is a need for data from the US, and, for the purpose of making decisions relevant to Veteran care, RCTs or quality improvement program processes with real time evaluation across varying VHA facilities. While we found no empiric evidence, our key content experts and consultants suggest that many of the enhanced recovery components have been or, over time, are being adopted into standard perioperative care for colorectal surgery. A recent commentary described enhanced recovery as modern perioperative care tailored to individual patients.[76] The author noted that some components of surgical practice are not typically included in enhanced recovery protocols including the concept of "prehabilitation."

Studies designed to evaluate the benefits and harms of enhanced recovery protocols should provide detailed information describing enhanced recovery components and specifically how they are implemented and compliance is assessed in the intervention and control groups. Compliance should be documented for each patient with details of the anesthesiology and analgesia protocol (*eg*, specific medications and doses used, timing of administration), timing of pre- and post-operative solids and fluids intake, degree of mobilization, etcetera. Surgeon experience and surgical volume should be considered. Outcomes should include patient and/or caregiver experiences.[62]

CONCLUSIONS

Implementation of enhanced recovery protocols for elective colorectal surgery resulted in reduced length of stay and overall perioperative morbidity versus standard care protocols. Mortality, readmissions, and surgical site infections were similar between the groups. However, the enhanced recovery and standard care protocols varied across studies in number of components and combinations of components with few trials reporting compliance with the protocols. There is no reliable evidence on enhanced recovery components, alone or in combination, that are key to improving patient outcomes. The value of investing time and resources into implementing all of the enhanced recovery components remains largely unknown.

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