BMJ open

Effect of enhanced recovery programmes on length of hospital stay in colorectal surgery: an overview and methodological assessment of systematic reviews

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005014
Article Type:	Research
Date Submitted by the Author:	07-Feb-2014
Complete List of Authors:	Chambers, Duncan; University of York, Centre for Reviews and Dissemination Paton, Fiona; University of York, Centre for Reviews and Dissemination Eastwood, Alison; University of York, Centre for Reviews and Dissemination Wilson, Paul; University of York, Centre for Reviews and Dissemination Craig, Dawn; University of York, Centre for Reviews and Dissemination Fox, Dave; University of York, Centre for Reviews and Dissemination Jayne, David; Leeds Teaching Hospitals, McGinnes, Erika; Leeds Teaching Hospitals,
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Research methods
Keywords:	SURGERY, Enhanced recovery after surgery, Fast track

Effect of enhanced recovery programmes on length of hospital stay in colorectal surgery: an overview and methodological assessment of systematic reviews

Duncan Chambers, Fiona Paton, Alison Eastwood, Paul Wilson, Dawn Craig, Dave Fox, David Jayne, Erika McGinnes

Centre for Reviews and Dissemination, University of York D Chambers, F Paton, P Wilson, A Eastwood, D Craig, D Fox

Leeds Teaching Hospitals NHS Trust, Leeds D Jayne, E McGinnes

Corresponding author: Duncan Chambers (duncan.chambers@york.ac.uk)

Abstract

Objectives: To identify and critically assess the extent to which systematic reviews of enhanced recovery programmes for patients undergoing colorectal surgery differ in their methodology and reported estimates of the effect.

Design: Review of published systematic reviews. We searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) Database from 1990 to March 2013. Systematic reviews of enhanced recovery programmes for patients undergoing colorectal surgery were eligible for inclusion.

Primary and secondary outcome measures: The primary outcome was length of hospital stay. We assessed changes in pooled estimates of treatment effect over time and how these might have been influenced by decisions taken by researchers as well as by the availability of new trials. The quality of systematic reviews was assessed using the CRD DARE critical appraisal process.

Results: Ten systematic reviews were included. Systematic reviews of RCTs have consistently shown a reduction in length of hospital stay with enhanced recovery compared with traditional care. The estimated effect tended to increase from 2006 to 2010 as more trials were published but has not altered significantly in the most recent review, despite the inclusion of several unique trials. The best estimate appears to be an average reduction of around 2.5 days in primary post-operative length of stay. Differences between reviews reflected differences in interpretation of inclusion criteria, searching and analytical methods or software.

Conclusions: Systematic reviews of enhanced recovery programmes show a high level of research waste, with multiple reviews covering identical or very similar groups of trials. Where multiple reviews exist on a topic, interpretation may require careful attention to apparently minor differences between reviews. Researchers can help readers by acknowledging existing reviews and through clear reporting of key decisions, especially on inclusion/exclusion and on statistical pooling.

Word count: 298

Strengths and limitations

- Systematic reviews of randomised trials have consistently shown that enhanced recovery programmes reduce length of hospital stay for patients undergoing colorectal surgery, compared with usual care. The strength of this study is that we have looked in some detail at the available reviews to identify differences between them and possible explanations, such as differences in intervention and outcome definitions and handling of missing data from included trials in meta-analyses.

- We found a high level of research waste, with multiple reviews covering identical or very similar groups of trials. Differences in pooled effect estimates across reviews reflected differences in interpretation of inclusion criteria, searching and analytical methods or software.

- Where multiple reviews exist on a topic, interpretation may require careful attention to apparently minor differences between reviews. Researchers can help readers by acknowledging existing reviews and through clear reporting of key decisions, especially on inclusion/exclusion and on statistical pooling.

- We identified limitations in reporting as one of the main barriers to understanding differences between reviews. These reporting issues often limited our ability to comment on whether decisions taken by review authors appear to be right' or 'wrong'.

Introduction

Reduction in length of stay in secondary care hospital settings provides a key potential opportunity to improve productivity in healthcare systems. There has been growing interest over recent years in the use of enhanced recovery programmes (also known as ERAS, fast track, multimodal, rapid or accelerated recovery programmes). The approach was pioneered in Denmark in the late 1990s for patients undergoing colorectal surgery and is now spreading to other surgical pathways such as musculoskeletal, urology and gynaecology.

The underlying aim of enhanced recovery programmes is to ensure that patients are in optimal condition for treatment (to minimise the risk of surgery being postponed or cancelled because of the patient's condition), receive innovative care during surgery and experience optimal post-surgical rehabilitation.(1) Programmes differ widely but share common elements such as patient education and involvement in preoperative planning processes, preoperative oral carbohydrates, improved anaesthetic and postoperative analgesic techniques to reduce the physical stress of the operation, early oral feeding and mobilisation.(2, 3) Enhanced recovery programmes have been delivered in the UK NHS since the early 2000s. Implementation has to date been variable despite the support of the Department of Health and more recently the Royal Colleges. It is likely that this variation reflects both the complexity of enhanced recovery programmes themselves and issues around implementing change in fundamental surgical procedures at a time when the NHS is facing severe funding constraints.

There are a substantial number of systematic reviews and economic evaluations that examine the effectiveness and cost-effectiveness of enhanced recovery programmes. We have used this evidence as the basis of a comprehensive rapid evidence synthesis relating to the effectiveness, cost effectiveness, implementation, delivery and impact of enhanced recovery programmes with particular reference to secondary care hospital settings in the NHS (Paton et al., in preparation). During the course of this project we became aware of significant methodological differences between systematic reviews of enhanced recovery programmes in colorectal surgery (by far the largest body of evidence for any surgical speciality). Reviews published at around the same time varied in the trials they included and in their estimates (derived by meta-analysis) of the reduction in length of stay associated with enhanced recovery programmes.

The objective of this study, therefore, is to provide a critical overview of the methodology of the available systematic reviews and their contribution to the development of the evidence base available to decision-makers. In particular, we will examine how numerical estimates of the benefit of enhanced recovery on length of hospital stay have changed over time and how these might have been influenced by decisions taken by systematic reviewers as well as by the availability of new trials.

Methods

Literature searches

This study was carried out following a rapid synthesis of evidence relating to enhanced recovery programmes in all types of surgery (Paton et al., in preparation). To identify systematic reviews, we searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) Database from 1990 to March 2013. See Appendix 1 for search strategies. The PROSPERO database was searched to identify any ongoing systematic reviews. Systematic reviews evaluating enhanced recovery programmes in patients undergoing any type of elective surgery in a hospital setting in the UK NHS or a comparable healthcare system were eligible for inclusion in the rapid evidence synthesis. Review authors' definitions of enhanced recovery programmes were accepted. Outcomes of interest were any measure of clinical outcomes, patient experience or resource use. Reviews had to compare enhanced recovery with usual/standard care without a structured multimodal enhanced recovery pathway. For this methodological study, only systematic reviews of enhanced recovery programmes for colorectal surgery were considered.

Study selection

We stored the literature search results in a reference management database (EndNote X6). Two researchers independently screened all titles and abstracts obtained through the searches for potentially relevant articles. Full manuscripts of potentially relevant articles were ordered and two researchers independently assessed the relevance of each article using the criteria stated above. Disagreements between researchers were resolved by discussion or by recourse to a third researcher where necessary.

Quality assessment

Quality assessment of systematic reviews was based on the CRD critical appraisal processes for DARE (http://www.crd.york.ac.uk/crdweb/HomePage.asp). Specific aspects assessed were adequacy of the search; assessment of quality/risk of bias of included studies; quality assessment results taken into account in the analysis; study details reported and differences between studies accounted for; investigation of statistical heterogeneity; were gaps in research identified; and were the review conclusions justified. The quality assessment was performed by one researcher and checked by a second. Discrepancies were resolved by discussion or by recourse to a third researcher.

Data extraction and analysis

Clinical effectiveness data for the rapid evidence synthesis were extracted into review software (EPPI Reviewer 4.0). An analysis plan for this methodological study was prepared in advance and additional methodological information was extracted into a Microsoft Excel spreadsheet. Data were extracted by one researcher and checked by another; discrepancies were resolved by consensus or where necessary by recourse to a third researcher.

Data extracted from the reviews included the systematic review inclusion criteria (particularly the definition of an ERAS programme); RCTs included (number and list); length of stay mean difference (MD) estimates and 95% confidence intervals (CIs) for each RCT as reported in the review; meta-analysis methods (e.g. type of model used); method used to handle missing means/SDs; definition of primary and total length of stay; pooled estimates of weighted MD (WMD) in length of stay between ERAS and control groups; and source of funding.

Extracted data were examined and tabulated to identify differences between reviews that may have influenced their conclusions and quantitative estimates of the effectiveness of enhanced recovery programmes compared with usual care. We focused on the outcome of length of primary hospital stay (and total length of stay including readmissions, where reported) because reduction of length of stay is a key objective of enhanced recovery programmes and because length of stay was a primary outcome of most included systematic reviews. Only length of stay data from randomised controlled trials (RCTs) were included in this analysis.

Results

The report by Paton et al. included 11 systematic reviews of ERAS programmes for colorectal surgery. One review(4) focused on quality of life and patient satisfaction and another on compliance and variations in practice(5), leaving nine reviews that reported length of stay, of which seven reported a pooled effect estimate (weighted mean difference (WMD) in days). The review by Zhuang et al.,(6) which was published too late to be fully discussed by Paton et al., is also included in this report, giving a total of ten systematic reviews that met the inclusion criteria for this methodological study (Table 1).

Most of the included reviews were reasonably well conducted and reported (Table 2). The reviews by Wind et al., (7) Walter et al. (8), Spanjersberg et al. (9) and Zhuang et al. (6) met all seven quality criteria and were considered at low risk of bias. Three other reviews met six criteria but all failed to take study quality into account in their synthesis.(10-12) Adamina et al. (13) and Lv et al. (14) failed to meet two of the criteria, while the paper by Rawlinson et al. (15) only clearly met two criteria and was considered potentially at high risk of bias.

Chronological development of the evidence base

Four systematic reviews were published in the years 2006–2009. At this stage only a few randomised trials were available. Wind et al. Wind 2006(7) included three trials; Eskicioglu et al. and Gouvas et al. four trials; and Walter et al. included just two trials (Table 1).

Four further reviews were published in 2010 and 2011. These all considered the same six trials, although one review chose to exclude two of these from its main analysis because the intervention did not meet the review definition of an ERAS programme. (9)

A systematic review by Lv et al. published in 2012 added one more trial, bringing the total to seven. However, just a year later Zhuang et al. published a systematic review with 13 included trials, among them four recent trials by Chinese investigators. With one exception,(16) the trials included in this review were identified and discussed by Paton et al. in our review of trials not included in the then-available systematic reviews.

The included reviews varied somewhat in the extent to which they cited previously published reviews of the field. However, in general reviews tended to cite most of the earlier reviews that would have been available at the time of writing. The first systematic review, by Wind et

al., was cited by eight of the nine subsequent reviews. Gouvas et al.'s review was cited by six of seven subsequent reviews and Varadhan et al. by four out of five (Table 3). The main exception was the paper by Rawlinson et al.,(15) which was not cited by three later reviews. Adamina et al. differed from other researchers in their use of Bayesian methodology and their work was only cited by one of the four later reviews. Zhuang et al. cited all the previous systematic reviews except that of Lv et al., which may have been published too late to be included.

Methodological differences between systematic reviews

The four early systematic reviews of ERAS for colorectal surgery showed a number of methodological differences. Although inclusion criteria appeared similar, Walter et al. excluded two trials that were included in the reviews by Eskicioglu et al. and Gouvas et al. In one case(17) this was reported to be because the trial included some patients who had undergone small bowel surgery; the reason for the other exclusion(18) was not reported. Walter et al. also differed from the other reviews in its definition of outcomes: length of stay was measured as total days of admission in this review and as days spent in hospital after surgery in the other reviews published in the same period.

In terms of data synthesis, Eskicioglu et al. was the only one of the four early reviews that did not perform a meta-analysis, on the grounds that data in the right form (means and standard deviations) were not available. The remaining three reviews elected to pool. Gouvas et al. and Wind et al. used random-effects models for their main meta-analysis, while Walter et al. used a fixed-effect model. Both Wind et al. and Walter et al. justified their choice on the basis of a random-effects model being more appropriate in the presence of some heterogeneity but neither stated a level of heterogeneity above which a random-effects model should be used. Wind et al. stated that trials without means and standard deviations were omitted from the analysis, while Gouvas et al. estimated from reported medians and ranges where necessary. Walter et al. did not report on this point.

Pooled estimates (WMD) of the effect of ERAS on primary length of stay varied substantially, being considerably higher and with a wider confidence interval in Walter et al. compared with the other reviews (Table 4). Wind et al. and Gouvas et al. provided almost identical WMDs, the only effect of an additional trial in Gouvas et al. being to slightly narrow the 95% confidence interval. Walter et al. reported no statistical heterogeneity while the other two reviews found some evidence of heterogeneity.

Overall, these reviews suggested considerable uncertainty about the magnitude of the effect of ERAS programmes in reducing length of hospital stay. Based on 95% confidence intervals, the effect could plausibly range from less than 0.5 days to almost 5 days.

The next group of systematic reviews to be published(9, 12, 13, 15) included up to six RCTs (additional RCTs by Muller et al. (19) and Serclova et al. (20) were now available). Spanjersberg et al. differed from other authors in treating length of stay as a secondary outcome of the review and more significantly by excluding two trials that were included in most other systematic reviews. The authors stated that Muller et al. and Delaney et al. (17) failed to meet the inclusion criterion of including at least seven elements in the ERAS intervention.

None of these reviews provided clear definitions of outcomes but Varadhan et al. and Spanjersberg et al. appeared to measure days in hospital after surgery (i.e., primary length of stay). Adamina et al. reported their outcome as length of hospital stay without definition or distinguishing between primary and total length of stay. The reviews also differed in their reported treatment of studies with missing data (mean/standard deviation): Varadhan et al. obtained data from original authors, Spanjersberg et al. calculated from median and range and Adamina et al. did not report their methods. Adamina et al. were the only authors who used Bayesian methods for meta-analysis, although few details were reported. (13) Rawlinson et al. (15) did not report an original meta-analysis but instead discussed the findings of Gouvas et al. and Varadhan et al.

Compared with the earlier reviews, this group of systematic reviews reported a substantially narrower range of effect estimates, all suggesting a reduction of 2.5 to 3 days in primary hospital stay associated with ERAS programmes (Table 1). The range of 95% confidence intervals was also narrower (approximately 1.1 to 3.9 days).

The 2012 review by Lv et al. added one additional RCT for a total of seven trials. (14) The new trial(21) compared ERAS with traditional care in patients undergoing both laparoscopic and open surgery and so was treated as two trials in the meta-analysis. The trial showed a 1 day reduction in length of stay in the laparoscopic setting but there was no difference in patients undergoing open surgery. Lv et al. also differed from most of the earlier reviews in defining length of stay as length of the index admission (rather than days in hospital after surgery). It is unclear whether this explains the discrepancy but Lv et al. reported a smaller reduction in length of stay compared with the reviews immediately preceding it (-1.88 days,

95% CI -2.91 to -0.86). However, this estimate was still compatible with a 'true' reduction of around 2 to 3 days in primary length of stay.

The most recent systematic review that we are aware of was published in May 2013, too late to be considered in detail in the full report.(6) It is more comprehensive than the previous reviews, with 13 included trials (two with both open and laparoscopic arms) and 1910 participants. All except one(22) of the RCTs included in our report were also in this systematic review. However, Zhuang et al. also included one trial that we excluded.(16) In fact this publication is a single-centre report of results from the LAFA trial that was reported in full by Vlug et al.(21) so it is likely that there was double-counting of these patients in Zhuang et al.'s meta-analyses. However, this publication was not included in the meta-analysis of length of stay outcomes.

Some of the trials included for the first time in Zhuang et al.'s review, particularly that of Ionescu et al. (2009), were available to earlier systematic reviewers. Of the reviews published in 2010 or later, Varadhan et al. did not give references for any excluded studies. Adamina et al. gave references for excluded studies but did not list Ionescu et al., suggesting that their search did not locate this trial. Rawlinson et al. did not list excluded studies, while the Cochrane review by Spanjersberg et al. did not list Ionescu et al. among the excluded studies. Lv et al. excluded 26 out of 33 studies examined in full text but did not report any details.

There was a discrepancy between Zhuang et al. and Lv et al. in their data extraction of the trial by Vlug et al. There were also minor data extraction discrepancies between these reviews for two other trials but as they were in opposite directions in the two cases this is unlikely to have had a major impact on the overall meta-analysis results.

Like most included reviews, Zhuang et al. defined length of stay as time in hospital after surgery. The pooled estimate of a 2.44 day reduction in primary length of stay (95% CI 1.83 to 3.06) for ERAS relative to traditional care was very similar to those reported by Varadhan et al. (12) and Adamina et al. (13)

Discussion

Main findings

Systematic reviews of randomised trials have consistently shown a reduction in length of hospital stay with ERAS compared with traditional care. The estimated effect tended to increase over time from 2006 to 2010 as more trials were published but has not altered significantly in the most recent review, despite the inclusion of several unique trials. The best estimate appears to be an average reduction of around 2.5 days in primary post-operative length of hospital stay. However, there is considerable heterogeneity in most pooled estimates and the complexity of ERAS as an intervention means that the benefits achieved in routine practice may differ from those reported in clinical trials. These issues are discussed in the full project report (Paton et al., in preparation).

The published systematic reviews show a high level of redundancy, with multiple reviews covering identical or very similar groups of trials. Differences in pooled effect estimates across reviews reflect differences in interpretation of inclusion criteria, searching and analytical methods or software. A few data extraction discrepancies were observed but these are unlikely to have significantly affected review conclusions.

Findings in relation to previous studies

The existence of multiple systematic reviews covering the same topic was investigated by Siontis et al.(23) They found that of 73 systematic reviews (with meta-analysis) published in 2010, 49 (67%) had at least one other published meta-analysis on the same topic. A particularly striking example was the existence of 11 meta-analyses of statins to prevent atrial fibrillation after cardiac surgery; all except the first of these showed a large positive effect of the intervention. Our findings reinforce those of Siontis et al., although even where reviews included exactly the same trials their pooled estimates of effect were not necessarily identical. Enhanced recovery differs from an intervention like statins after cardiac surgery, being more complex and changing over time as more elements are incorporated into routine practice. This would tend to favour increased variation between reviews along the lines we observed.

A slightly different approach to investigating overlap between systematic reviews was taken by Woodman et al., who looked at the differences between eight reviews of community interventions to promote physical activity.(24) Across the eight reviews there were 28

included studies, of which 22 (79%) were only included in one review. There was little cross-citation between reviews. For most reviews, Woodman et al. could explain why primary data were not included, which was usually due to the reviews having a relatively narrow scope. Despite these issues, the review conclusions were similar. Comparing our results with those of Woodman et al., the enhanced recovery reviews had a higher degree of overlap although they differed with respect to inclusion of non-randomised studies (not discussed in this paper). The differences between the enhanced recovery and physical activity reviews probably reflect the fact that enhanced recovery, although a complex intervention, is more narrowly defined than interventions to increase physical activity

Implications

The findings of this study have implications for systematic reviewers, readers of systematic reviews and producers of systematic review-based evidence products. Systematic reviewers can help readers compare their reviews with other similar studies by clear reporting of key decisions, especially on inclusion/exclusion and on statistical pooling. Most of the reviews of enhanced recovery programmes performed a meta-analysis to calculate a WMD in length of stay between enhanced recovery and usual care groups. Calculating the WMD requires the means and standard deviations (SDs) of length of stay in each group in the included trials, but trials often report a different measure such as median and range (or interquartile range). Systematic reviews can deal with this situation in different ways, for example by using formulae to estimate the mean and SD, contacting the trial authors or omitting trials from any meta-analysis if mean and SD are not reported. The enhanced recovery reviews adopted all of these approaches but did not report which data were estimated rather than derived directly from trial reports. Improved reporting in this area would improve transparency and help readers to understand discrepancies between apparently similar meta-analyses. Length of stay outcomes were not always clearly defined or reported and differences between reviews may in part stem from the fact that they were measuring an outcome in different ways.

Readers of systematic reviews need to be aware of the existence of multiple systematic reviews for a high percentage of topics. This means they should not rely uncritically on the first review they find and underlines the importance of services that critically appraise systematic reviews and those that provide overviews of reviews across a topic area.(25, 26) As an aid to transparency, authors of new systematic reviews should also acknowledge the existence of any systematic reviews addressing the same or a similar question.

The use of systematic reviews to produce rapid evidence summaries to inform decision-making is an area where methodology is still developing, although some methodological frameworks have been published.(27, 28) Assessment of the quality and reliability of systematic reviews is an important part of this process but the present study suggests that conventional approaches to critical appraisal are not sufficient and careful attention should be paid to apparently minor differences between reviews. This may require increased extraction of methodological data even though the results may not be included in published evidence summaries aimed at decision-makers.

Strengths and limitations

The strength of this study is that we have looked in some detail at reviews of a complex clinical intervention to identify differences between them and possible explanations, such as differences in intervention and outcome definitions and handling of missing data from included trials in meta-analyses. We have identified limitations in reporting as one of the main barriers to understanding differences between reviews of the same topic. These reporting issues have often limited our ability to comment on whether decisions taken by review authors appear to be right' or 'wrong'. The discrepancies between reviews identified in this study sometimes arose from decisions where both options could be considered reasonable, for example whether or not to exclude the trial by Delaney et al.(17) because a small number of patients undergoing small bowel surgery were included.

Unanswered questions/further research

The current study suggests a need for further, more in-depth research into methods of quality assessment of systematic reviews; to make the best use of a cumulative evidence base for decision-making; and to identify methodological issues and decision points that may influence the eventual conclusions of a review. These issues are particularly important for researchers seeking to help decision-makers interpret and use systematic reviews. Enhanced recovery is a complex intervention with multiple components and its successful implementation is likely to be influenced by numerous background factors. Given this background, researchers and clinicians carrying out new systematic reviews should ensure that their chosen method of synthesis is appropriate for exploring intervention complexity. The recently published research agenda for reviews of complex interventions(29) provides timely guidance in this regard.

Systematic reviews of enhanced recovery programmes in colorectal surgery continue to be published and we are aware of at least two publications since our search was completed.(30, 31) The authors of one of these reviews refer to their paper as 'a substantial update from previous meta-analyses'(30) but in fact the included trials and overall findings are almost identical to those of Zhuang et al.(6) This is not the fault of the authors but represents an avoidable waste of research resources. Systematic reviews are now increasingly being registered prospectively at the outset on databases such as PROSPERO(32) and it will be interesting to see whether the production of overlapping reviews decreases over time.

Word count (main text): 3973

Disclaimer:

This report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and do not necessarily reflect those of the NIHR Health Services and Delivery Research programme or the Department of Health.

Acknowledgements: This project was funded as part of a programme of research funded by the NIHR Health Services and Delivery Research programme (Project ref: 11/1026/04).

Contributors: All authors contributed to the design of this methodological study and commented on the analysis plan and/or draft manuscript. PW took overall responsibility for the rapid evidence synthesis and is guarantor. D Chambers and FP extracted additional methodological data. D Chambers wrote the first draft of the paper. All authors have seen and approved the final version.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. Enhanced Recovery Partnership Programme. Delivering enhanced recovery – Helping patients to get better sooner after surgery. London: Department of Health, 2010 March 31st.
2. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg. 2002 Jun;183(6):630-41.
3. Sturm L, Cameron AL. Brief review: Fast-track surgery and enhanced recovery after surgery (ERAS) programs. Melbourne: Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S), 2009 Contract No.: 3.
4. Khan S, Wilson T, Ahmed J, Owais A, MacFie J. Quality of life and patient satisfaction with enhanced recovery protocols. Colorectal Dis. 2010;12(12):1175-82.
5. Ahmed J, Khan S, Lim M, Chandrasekaran TV, MacFie J. Enhanced recovery after surgery protocols - compliance and variations in practice during routine colorectal surgery. Colorectal Dis. 2012;14(9):1045-51.
6. Cheng-Le Z, Xing-Zhao YX-D, Z., Bi-Cheng C, Zhen Y. Enhanced recovery after surgery programs versus traditional care for colorectal surgery: A meta-analysis of randomized controlled trials. Dis Colon Rectum. 2013;56:667-78.
7. Wind J, Polle SW, Fung Kon Jin PH, Dejong CH, Meyenfeldt MF, Ubbink DT, et al. Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg. 2006;93(7):800-9.
8. Walter CJ, Collin J, Dumville JC, Drew PJ, Monson JR. Enhanced recovery in colorectal resections: a systematic review and meta-analysis. Colorectal Dis. 2009 May;11(4):344-53.
9. Spanjersberg Willem R, Reurings J, Keus F, van Laarhoven Cornelis JHM. Fast track surgery versus conventional recovery strategies for colorectal surgery. Cochrane Database of Systematic Reviews. 2011 (2).
10. Eskicioglu C, Forbes SS, Aarts M-A, Okrainec A, McLeod RS. Enhanced Recovery after Surgery (ERAS) programs for patients having colorectal surgery: a meta-analysis of randomized trials. J Gastrointest Surg. 2009 Dec;13(12):2321-9.
11. Gouvas N, Tan E, Windsor A, Xynos E, Tekkis PP. Fast-track vs standard care in colorectal surgery: a meta-analysis update. Int J Colorectal Dis. 2009 Oct;24(10):1119-31.
12. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr. 2010;29(4):434-40.
13. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ, Delaney CP. Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. Surgery. 2011;149(6):830-40.
14. Lv L, Shao Y-f, Zhou Y-b. The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. Int J Colorectal Dis. 2012;27:1549–54.
15. Rawlinson A, Kang P, Evans J, Khanna A. A systematic review of enhanced recovery protocols in colorectal surgery. Ann R Coll Surg Engl. 2011;93(8):583-8.
16. van Bree SH, Vlug MS, Bemelman WA, Hollmann MW, Ubbink DT, Zwinderman AH, et al. Faster recovery of gastrointestinal transit after laparoscopy and fast-track care in patients undergoing colonic surgery. Gastroenterology. 2011 Sep;141(3):872-80.e1-4.
17. Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. Dis Colon Rectum. 2003 Jul;46(7):851-9.
18. Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. Ann Surg. 2007 Jun;245(6):867-72.

19. Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N, Zurich Fast Track Study G. A fast-track program reduces complications and length of hospital stay after open colonic surgery. Gastroenterology. 2009 Mar;136(3):842-7.
20. Serclova Z, Dytrych P, Marvan J, Nova K, Hankeova Z, Ryska O, et al. Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456). Clin Nutr. 2009 Dec;28(6):618-24.
21. Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg. 2011 Dec;254(6):868-75.
22. Lee TG, Kang SB, Kim DW, Hong S, Heo SC, Park KJ. Comparison of early mobilization and diet rehabilitation program with conventional care after laparoscopic colon surgery: a prospective randomized controlled trial. Dis Colon Rectum. 2011 Jan;54(1):21-8.
23. Siontis KC, Hernandez-Boussard T, Ioannidis JP. Overlapping meta-analyses on the same topic: survey of published studies. BMJ. 2013;347:f4501.
24. Woodman J, Thomas J, Dickson K. How explicable are differences between reviews that appear to address a similar research question? A review of reviews of physical activity interventions. Systematic reviews. 2012;1:37.
25. Chambers D, Wilson P, Thompson C, Hanbury A, Farley K, Light K. Maximizing the impact of systematic reviews in healthcare decision-making: a systematic scoping review of knowledge translation resources. Milbank Q. 2011;89(1):131-56.
26. Lavis JN. How can we support the use of systematic reviews in policymaking? PLoS Medicine. 2009;6(11):e1000141.
27. Chambers D, Wilson P. A framework for production of systematic review based briefings to support evidence-informed decision-making. Systematic reviews. 2012;1:32.
28. Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence summaries: the evolution of a rapid review approach. Systematic reviews. 2012;1:10.
29. Noyes J, Gough D, Lewin S, Mayhew A, Michie S, Pantoja T, et al. A research and development agenda for systematic reviews that ask complex questions about complex interventions. J Clin Epidemiol. 2013 Nov;66(11):1262-70.
30. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced Recovery Program in Colorectal Surgery: A Meta-analysis of Randomized Controlled Trials. World J Surg. 2013 Dec 25.
31. Gianotti L, Beretta S, Luperto M, Bernasconi D, Valsecchi MG, Braga M. Enhanced recovery strategies in colorectal surgery: is the compliance with the whole program required to achieve the target? Int J Colorectal Dis. 2013 Dec 13.
32. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, et al. PROSPERO at one year: an evaluation of its utility. Systematic reviews. 2013;2:4.
33. Anderson AD, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. Br J Surg. 2003 Dec;90(12):1497-504.
34. Gatt M, Anderson AD, Reddy BS, Hayward-Sampson P, Tring IC, MacFie J. Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. Br J Surg. 2005 Nov;92(11):1354-62.
35. Ionescu D, Iancu C, Ion D, Al-Hajjar N, Margarit S, Mocan L, et al. Implementing fast-track protocol for colorectal surgery: a prospective randomized clinical trial. World J Surg. 2009 Nov;33(11):2433-8.
36. Garcia-Botello S, Canovas de Lucas R, Tornero C, Escamilla B, Espi-Macias A, Esclapez-Valero P, et al. Implementation of a perioperative multimodal rehabilitation protocol in elective colorectal surgery. A prospective randomised controlled study. Cir Esp. 2011 Mar;89(3):159-66.
37. Ren L, Zhu D, Wei Y, Pan X, Liang L, Xu J, et al. Enhanced Recovery After Surgery (ERAS) program attenuates stress and accelerates recovery in patients after radical resection for colorectal cancer: a prospective randomized controlled trial. World J Surg. 2012 Feb;36(2):407-14.

38. Wang G, Jiang Z, Zhao K, Li G, Liu F, Pan H, et al. Immunologic response after laparoscopic colon cancer operation within an enhanced recovery program. J Gastrointest Surg. 2012 Jul;16(7):1379-88.
39. Wang Q, Suo J, Jiang J, Wang C, Zhao YQ, Cao X. Effectiveness of fast-track rehabilitation vs conventional care in laparoscopic colorectal resection for elderly patients: a randomized trial. Colorectal Dis. 2012 Aug;14(8):1009-13.
40. Yang D, He W, Zhang S, Chen H, Zhang C, He Y. Fast-track surgery improves postoperative clinical recovery and immunity after elective surgery for colorectal carcinoma: randomized controlled clinical trial. World J Surg. 2012 Aug;36(8):1874-80.

Table 1: Overview of systematic reviews of ERAS for colorectal surgery

Review	Minimum definition of ERAS intervention	Search cut-off date	Included RCTs
Wind 2006(7)	At least four elements required	December 2005	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34)
Eskicioglu 2009(10)	Not stated	May 2008	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18)
Gouvas 2009(11)	At least four elements required	July 2008	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18)
Walter 2009(8)	At least five elements required (pre-, peri- and post-operative)	January 2007	Anderson 2003(33); Gatt 2005(34)
Varadhan 2010(12)	At least four elements required (pre-, peri- and post-operative)	November 2009	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20)
Adamina 2011(13)	Documented compliance with at least four of five key elements	June 2010	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20)
Rawlinson 2011(15)	At least four elements required (pre-, peri- and post-operative)	February 2011	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20)
Spanjersberg 2011(9)	At least seven elements required	Unclear (January 2011?)	Anderson 2003(33); Gatt 2005(34); Khoo 2007(18); Serclova 2009(20)
Lv 2012(14)	Not stated	April 2012	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20); Vlug 2011(21)
Zhuang 2013.(6)	At least seven elements required	July 2012	Anderson 2003(33); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20); Ionescu 2009(35); Vlug 2011(21)Garcia-Botello 2011(36); Bree 2011(16); Ren 2012(37); G Wang 2012(38); Q Wang 2012(39); Yang 2012(40)

Table 2: Risk of bias in included systematic reviews

Review	Adequate search	Risk of bias assessed	Quality score accounted for in analysis	Study details reported and differences accounted for	Statistical heterogeneity investigated	Gaps in research identified	Conclusions justified
Wind 2006(7)	✓	✓	✓	✓	✓	✓	✓
Eskicioglu 2009(10)	✓	✓	X	✓	✓	✓	✓
Gouvas 2009(11)	✓	✓	X	✓	✓	✓	✓
Walter 2009(8)	✓	✓	✓	✓	✓	✓	✓
Varadhan 2010(12)	✓	✓	X	✓	✓	✓	✓
Adamina 2011(13)	✓	✓	UC	✓	UC	✓	✓
Rawlinson 2011(15)	✓	X	X	✓	UC	X	UC
Spanjersberg 2011(9)	✓	✓	✓	✓	✓	✓	✓
Lv 2012(14)	✓	✓	X	X	✓	✓	✓
Zhuang 2013.(6)	✓	✓	✓	✓	✓	✓	✓

UC, unclear

Table 3: Cross-citation among included systematic reviews

Review	Reviews cited	Cited by subsequent reviews
Wind 2006(7)	NA	Eskicioglu 2009(10); Gouvas 2009(11); Walter 2009(8); Varadhan 2010(12); Adamina 2011(13); Rawlinson 2011(15); Spanjersberg 2011(9); Zhuang 2013.(6)
Eskicioglu 2009(10)	Wind 2006(7)	Varadhan 2010(12); Rawlinson 2011(15); Zhuang 2013.(6)
Gouvas 2009(11)	Wind 2006(7)	Varadhan 2010(12); Adamina 2011(13); Rawlinson 2011(15); Spanjersberg 2011(9); Lv 2012(14); Zhuang 2013.(6)
Walter 2009(8)	Wind 2006(7)	Varadhan 2010(12); Spanjersberg 2011(9); Lv 2012(14); Zhuang 2013.(6)
Varadhan 2010(12)	Wind 2006(7); Eskicioglu 2009(10); Gouvas 2009(11); Walter 2009(8)	Rawlinson 2011(15); Spanjersberg 2011(9); Lv 2012(14); Zhuang 2013.(6)
Adamina 2011(13)	Wind 2006(7); Gouvas 2009(11)	Zhuang 2013.(6)
Rawlinson 2011(15)	Wind 2006(7); Eskicioglu 2009(10); Gouvas 2009(11); Varadhan 2010(12)	Not cited
Spanjersberg 2011(9)	Wind 2006(7); Gouvas 2009(11); Walter 2009(8); Varadhan 2010(12)	Lv 2012(14); Zhuang 2013.(6)
Lv 2012(14)	Gouvas 2009(11); Walter 2009(8); Varadhan 2010(12); Spanjersberg 2011(9)	Not cited
Zhuang 2013.(6)	Wind 2006(7); Eskicioglu 2009(10); Gouvas 2009(11); Walter 2009(8); Varadhan 2010(12); Adamina 2011(13); Spanjersberg 2011(9)	NA

NA, not applicable

Table 4: Summary of meta-analyses for length of stay

Review	Definition of primary length of stay	Meta-analysis model	Pooled effect estimate for primary length of stay	Pooled effect estimate for total length of stay
Wind 2006(7)	Days in hospital after surgery	Random	WMD -1.89 (-3.61 to -0.18) I^2 = 63.4%	Not calculated
Eskicioglu 2009(10)	Days in hospital after surgery	NA	Not calculated (authors stated pooling was not feasible)	
Gouvas 2009(11)	Days in hospital after surgery	Random	WMD -1.88 (-3.35 to -0.41) I^2 = 45%	WMD -1.73 (-3.50 to 0.04) I^2 = 0%
Walter 2009(8)	Days in hospital during index admission	Fixed	WMD -3.64 (-4.98 to -2.29) I^2 = 0%	WMD -3.75 (-5.11 to -2.40) I^2 = 0%
Varadhan 2010(12)	Not explicitly defined but appears to be days in hospital after surgery	Random	WMD -2.51 (-3.54 to -1.47) I^2 = 55%	Not calculated
Adamina 2011(13)	Length of stay outcome not explicitly defined	Bayesian	Mean difference for 'length of stay' -2.5 (95% CrI -3.92 to -1.11) I^2 not reported	
Rawlinson 2011(15)	Not defined	NA	Not calculated (authors cited findings from Gouvas and Varadhan)	
Spanjersberg 2011(9)	Not explicitly defined but appears to be days in hospital after surgery	Fixed	WMD -2.94 (-3.69 to -2.19) I^2 = 0%	Not calculated
Lv 2012(14)	Days in hospital during index admission	Random	WMD -1.88 (-2.91 to -0.86) I^2 = 75%	Not calculated
Zhuang 2013.(6)	Days in hospital after surgery	Random	WMD -2.44 (-3.06 to -1.83) I^2 = 88%	WMD -2.39 (-3.70 to -1.09) I^2 = 85%

NA, not applicable

Appendix 1: Search strategy for systematic reviews

#1 ERAS:ti,ab
#2 ((enhanced or early or accelerated or fast track or fast-track or rapid) near/1 (recover* or rehabilitat* or convalesc* or mobil* or ambulat* or walk* or feed* or nutrition* or eat*) near/3 (surger* or program* or protocol* or pathway*)):ti,ab
#3 ((multimodal or optimised or optimized) near/1 (recover* or rehabilitat* or convalesc*)):ti,ab
#4 #1 or #2 or #3
#5 MeSH descriptor: [Receptors, Endothelin] explode all trees
#6 #4 not #5

BMJ Open

An overview and methodological assessment of systematic reviews and meta-analyses of enhanced recovery programmes in colorectal surgery.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005014.R1
Article Type:	Research
Date Submitted by the Author:	30-Apr-2014
Complete List of Authors:	Chambers, Duncan; University of York, Centre for Reviews and Dissemination Paton, Fiona; University of York, Centre for Reviews and Dissemination Wilson, Paul; University of York, Centre for Reviews and Dissemination Eastwood, Alison; University of York, Centre for Reviews and Dissemination Craig, Dawn; University of York, Centre for Reviews and Dissemination Fox, Dave; University of York, Centre for Reviews and Dissemination Jayne, David; Leeds Teaching Hospitals, McGinnes, Erika; Leeds Teaching Hospitals,
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Research methods
Keywords:	SURGERY, Enhanced recovery after surgery, Fast track

An overview and methodological assessment of systematic reviews and meta-analyses of enhanced recovery programmes in colorectal surgery

Duncan Chambers, Fiona Paton, Paul Wilson, Alison Eastwood, Dawn Craig, Dave Fox, David Jayne, Erika McGinnes

Centre for Reviews and Dissemination, University of York D Chambers, F Paton, P Wilson, A Eastwood, D Craig, D Fox

Leeds Teaching Hospitals NHS Trust, Leeds D Jayne, E McGinnes

Corresponding author: Duncan Chambers (duncan.chambers@york.ac.uk)

Abstract

Objectives: To identify and critically assess the extent to which systematic reviews of enhanced recovery programmes for patients undergoing colorectal surgery differ in their methodology and reported estimates of effect.

Design: Review of published systematic reviews. We searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) Database from 1990 to March 2013. Systematic reviews of enhanced recovery programmes for patients undergoing colorectal surgery were eligible for inclusion.

Primary and secondary outcome measures: The primary outcome was length of hospital stay. We assessed changes in pooled estimates of treatment effect over time and how these might have been influenced by decisions taken by researchers as well as by the availability of new trials. The quality of systematic reviews was assessed using the CRD DARE critical appraisal process.

Results: Ten systematic reviews were included. Systematic reviews of RCTs have consistently shown a reduction in length of hospital stay with enhanced recovery compared with traditional care. The estimated effect tended to increase from 2006 to 2010 as more trials were published but has not altered significantly in the most recent review, despite the inclusion of several unique trials. The best estimate appears to be an average reduction of around 2.5 days in primary post-operative length of stay. Differences between reviews reflected differences in interpretation of inclusion criteria, searching and analytical methods or software.

Conclusions: Systematic reviews of enhanced recovery programmes show a high level of research waste, with multiple reviews covering identical or very similar groups of trials. Where multiple reviews exist on a topic, interpretation may require careful attention to apparently minor differences between reviews. Researchers can help readers by acknowledging existing reviews and through clear reporting of key decisions, especially on inclusion/exclusion and on statistical pooling.

Word count: 298

Strengths and limitations

- Systematic reviews of randomised trials have consistently shown that enhanced recovery programmes reduce length of hospital stay for patients undergoing colorectal surgery, compared with usual care. The strength of this study is that we have looked in some detail at the available reviews to identify differences between them and possible explanations, such as differences in intervention and outcome definitions and handling of missing data from included trials in meta-analyses.

- We found a high level of research waste, with multiple reviews covering identical or very similar groups of trials. Differences in pooled effect estimates across reviews reflected differences in interpretation of inclusion criteria, searching and analytical methods or software.

- Where multiple reviews exist on a topic, interpretation may require careful attention to apparently minor differences between reviews. Researchers can help readers by acknowledging existing reviews and through clear reporting of key decisions, especially on inclusion/exclusion and on statistical pooling.

- We identified limitations in reporting as one of the main barriers to understanding differences between reviews. These reporting issues often limited our ability to comment on whether decisions taken by review authors appear to be right' or 'wrong'.

Introduction

Reduction in length of stay in secondary care hospital settings provides a key potential opportunity to improve productivity in healthcare systems. There has been growing interest over recent years in the use of enhanced recovery programmes (also known as ERAS, fast track, multimodal, rapid or accelerated recovery programmes). The approach was pioneered in Denmark in the late 1990s for patients undergoing colorectal surgery and is now spreading to other surgical pathways such as musculoskeletal, urology and gynaecology.

The underlying aim of enhanced recovery programmes is to ensure that patients are in optimal condition for treatment (to minimise the risk of surgery being postponed or cancelled because of the patient's condition), receive innovative care during surgery and experience optimal post-surgical rehabilitation.(1) Programmes differ widely but share common elements such as patient education and involvement in preoperative planning processes, preoperative oral carbohydrates, improved anaesthetic and postoperative analgesic techniques to reduce the physical stress of the operation, early oral feeding and mobilisation.(2, 3) Enhanced recovery programmes have been delivered in the UK NHS since the early 2000s. Implementation has to date been variable despite the support of the Department of Health and more recently the Royal Colleges. It is likely that this variation reflects both the complexity of enhanced recovery programmes themselves and issues around implementing change in fundamental surgical procedures at a time when the NHS is facing severe funding constraints.

There are a substantial number of systematic reviews and economic evaluations that examine the effectiveness and cost-effectiveness of enhanced recovery programmes. We have used this evidence as the basis of a comprehensive rapid evidence synthesis relating to the effectiveness, cost effectiveness, implementation, delivery and impact of enhanced recovery programmes with particular reference to secondary care hospital settings in the NHS (Paton et al., in preparation). During the course of this project we became aware of significant methodological differences between systematic reviews of enhanced recovery programmes in colorectal surgery (by far the largest body of evidence for any surgical speciality). Reviews published at around the same time varied in the trials they included and in their estimates (derived by meta-analysis) of the reduction in length of stay associated with enhanced recovery programmes.

The objective of this study, therefore, is to provide a critical overview of the methodology of the available systematic reviews and their contribution to the development of the evidence base available to decision-makers. In particular, we will examine how numerical estimates of the benefit of enhanced recovery on length of hospital stay have changed over time and how these might have been influenced by decisions taken by systematic reviewers as well as by the availability of new trials.

Methods

Literature searches

This study was carried out following a rapid synthesis of evidence relating to enhanced recovery programmes in all types of surgery (Paton et al., in preparation). To identify systematic reviews, we searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) Database from 1990 to March 2013. See Appendix 1 for search strategies. The PROSPERO database was searched to identify any ongoing systematic reviews. Systematic reviews evaluating enhanced recovery programmes in patients undergoing any type of elective surgery in a hospital setting in the UK NHS or a comparable healthcare system were eligible for inclusion in the rapid evidence synthesis. Review authors' definitions of enhanced recovery programmes were accepted. Outcomes of interest were any measure of clinical outcomes, patient experience or resource use. Reviews had to compare enhanced recovery with usual/standard care without a structured multimodal enhanced recovery pathway. For this methodological study, only systematic reviews of enhanced recovery programmes for colorectal surgery were considered.

Study selection

We stored the literature search results in a reference management database (EndNote X6). Two researchers independently screened all titles and abstracts obtained through the searches for potentially relevant articles. Full manuscripts of potentially relevant articles were ordered and two researchers independently assessed the relevance of each article using the criteria stated above. Disagreements between researchers were resolved by discussion or by recourse to a third researcher where necessary.

Quality assessment

Quality assessment of systematic reviews was based on the CRD critical appraisal processes for DARE (http://www.crd.york.ac.uk/crdweb/HomePage.asp). Specific aspects assessed were adequacy of the search; assessment of quality/risk of bias of included studies; quality assessment results taken into account in the analysis; study details reported and differences between studies accounted for; investigation of statistical heterogeneity; were gaps in research identified; and were the review conclusions justified. The quality assessment was performed by one researcher and checked by a second. Discrepancies were resolved by discussion or by recourse to a third researcher.

Data extraction and analysis

Clinical effectiveness data for the rapid evidence synthesis were extracted into review software (EPPI Reviewer 4.0). An analysis plan for this methodological study was prepared in advance and additional methodological information was extracted into a Microsoft Excel spreadsheet. Data were extracted by one researcher and checked by another; discrepancies were resolved by consensus or where necessary by recourse to a third researcher.

Data extracted from the reviews included the systematic review inclusion criteria (particularly the definition of an ERAS programme); RCTs included (number and list); length of stay mean difference (MD) estimates and 95% confidence intervals (CIs) for each RCT as reported in the review; meta-analysis methods (e.g. type of model used); method used to handle missing means/SDs; definition of primary and total length of stay; pooled estimates of weighted MD (WMD) in length of stay between ERAS and control groups; and source of funding.

Extracted data were examined and tabulated to identify differences between reviews that may have influenced their conclusions and quantitative estimates of the effectiveness of enhanced recovery programmes compared with usual care. We focused on the outcome of length of primary hospital stay (and total length of stay including readmissions, where reported) because reduction of length of stay is a key objective of enhanced recovery programmes and because length of stay was a primary outcome of most included systematic reviews. Only length of stay data from randomised controlled trials (RCTs) were included in this analysis.

Results

The report by Paton et al. included 11 systematic reviews of ERAS programmes for colorectal surgery. One review(4) focused on quality of life and patient satisfaction and another on compliance and variations in practice(5), leaving nine reviews that reported length of stay, of which seven reported a pooled effect estimate (weighted mean difference (WMD) in days). The review by Zhuang et al.,(6) which was published too late to be fully discussed by Paton et al., is also included in this report, giving a total of ten systematic reviews that met the inclusion criteria for this methodological study (Table 1).

Most of the included reviews were reasonably well conducted and reported (Table 2). The reviews by Wind et al., (7) Walter et al. (8), Spanjersberg et al. (9) and Zhuang et al. (6) met all seven quality criteria and were considered at low risk of bias. Three other reviews met six criteria but all failed to take study quality into account in their synthesis.(10-12) Adamina et al. (13) and Lv et al. (14) failed to meet two of the criteria, while the paper by Rawlinson et al. (15) only clearly met two criteria and was considered potentially at high risk of bias.

Chronological development of the evidence base

Four systematic reviews were published in the years 2006–2009. At this stage only a few randomised trials were available. Wind et al. Wind 2006(7) included three trials; Eskicioglu et al. and Gouvas et al. four trials; and Walter et al. included just two trials (Table 1).

Four further reviews were published in 2010 and 2011. These all considered the same six trials, although one review chose to exclude two of these from its main analysis because the intervention did not meet the review definition of an ERAS programme. (9)

A systematic review by Lv et al. published in 2012 added one more trial, bringing the total to seven. However, just a year later Zhuang et al. published a systematic review with 13 included trials, among them four recent trials by Chinese investigators. With one exception,(16) the trials included in this review were identified and discussed by Paton et al. in our review of trials not included in the then-available systematic reviews.

The included reviews varied somewhat in the extent to which they cited previously published reviews of the field. However, in general reviews tended to cite most of the earlier reviews that would have been available at the time of writing. The first systematic review, by Wind et

al., was cited by eight of the nine subsequent reviews. Gouvas et al.'s review was cited by six of seven subsequent reviews and Varadhan et al. by four out of five (Table 3). The main exception was the paper by Rawlinson et al.,(15) which was not cited by three later reviews. Adamina et al. differed from other researchers in their use of Bayesian methodology and their work was only cited by one of the four later reviews. Zhuang et al. cited all the previous systematic reviews except that of Lv et al., which may have been published too late to be included.

Methodological differences between systematic reviews

The four early systematic reviews of ERAS for colorectal surgery showed a number of methodological differences. Although inclusion criteria appeared similar, Walter et al. excluded two trials that were included in the reviews by Eskicioglu et al. and Gouvas et al. In one case(17) this was reported to be because the trial included some patients who had undergone small bowel surgery; the reason for the other exclusion(18) was not reported. Walter et al. also differed from the other reviews in its definition of outcomes: length of stay was measured as total days of admission in this review and as days spent in hospital after surgery in the other reviews published in the same period.

In terms of data synthesis, Eskicioglu et al. was the only one of the four early reviews that did not perform a meta-analysis, on the grounds that data in the right form (means and standard deviations) were not available. The remaining three reviews elected to pool. Gouvas et al. and Wind et al. used random-effects models for their main meta-analysis, while Walter et al. used a fixed-effect model. Both Wind et al. and Walter et al. justified their choice on the basis of a random-effects model being more appropriate in the presence of some heterogeneity but neither stated a level of heterogeneity above which a random-effects model should be used. Wind et al. stated that trials without means and standard deviations were omitted from the analysis, while Gouvas et al. estimated from reported medians and ranges where necessary. Walter et al. did not report on this point.

Pooled estimates (WMD) of the effect of ERAS on primary length of stay varied substantially, being considerably higher and with a wider confidence interval in Walter et al. compared with the other reviews (Figure 1 and Table 4). Wind et al. and Gouvas et al. provided almost identical WMDs, the only effect of an additional trial in Gouvas et al. being to slightly narrow the 95% confidence interval. Walter et al. reported no statistical heterogeneity while the other two reviews found some evidence of heterogeneity.

Overall, these reviews suggested considerable uncertainty about the magnitude of the effect of ERAS programmes in reducing length of hospital stay. Based on 95% confidence intervals, the effect could plausibly range from less than 0.5 days to almost 5 days.

The next group of systematic reviews to be published(9, 12, 13, 15) included up to six RCTs (additional RCTs by Muller et al. (19) and Serclova et al. (20) were now available). Spanjersberg et al. differed from other authors in treating length of stay as a secondary outcome of the review and more significantly by excluding two trials that were included in most other systematic reviews. The authors stated that Muller et al. and Delaney et al. (17) failed to meet the inclusion criterion of including at least seven elements in the ERAS intervention.

None of these reviews provided clear definitions of outcomes but Varadhan et al. and Spanjersberg et al. appeared to measure days in hospital after surgery (i.e., primary length of stay). Adamina et al. reported their outcome as length of hospital stay without definition or distinguishing between primary and total length of stay. The reviews also differed in their reported treatment of studies with missing data (mean/standard deviation): Varadhan et al. obtained data from original authors, Spanjersberg et al. calculated from median and range and Adamina et al. did not report their methods. Adamina et al. were the only authors who used Bayesian methods for meta-analysis, although few details were reported. (13) Rawlinson et al. (15) did not report an original meta-analysis but instead discussed the findings of Gouvas et al. and Varadhan et al.

Compared with the earlier reviews, this group of systematic reviews reported a substantially narrower range of effect estimates, all suggesting a reduction of 2.5 to 3 days in primary hospital stay associated with ERAS programmes (Table 1). The range of 95% confidence intervals was also narrower (approximately 1.1 to 3.9 days).

The 2012 review by Lv et al. added one additional RCT for a total of seven trials. (14) The new trial(21) compared ERAS with traditional care in patients undergoing both laparoscopic and open surgery and so was treated as two trials in the meta-analysis. The trial showed a 1 day reduction in length of stay in the laparoscopic setting but there was no difference in patients undergoing open surgery. Lv et al. also differed from most of the earlier reviews in defining length of stay as length of the index admission (rather than days in hospital after surgery). It is unclear whether this explains the discrepancy but Lv et al. reported a smaller reduction in length of stay compared with the reviews immediately preceding it (-1.88 days,

95% CI -2.91 to -0.86). However, this estimate was still compatible with a 'true' reduction of around 2 to 3 days in primary length of stay.

The most recent systematic review that we are aware of was published in May 2013, too late to be considered in detail in the full report.(6) It is more comprehensive than the previous reviews, with 13 included trials (two with both open and laparoscopic arms) and 1910 participants. All except one(22) of the RCTs included in our report were also in this systematic review. However, Zhuang et al. also included one trial that we excluded.(16) In fact this publication is a single-centre report of results from the LAFA trial that was reported in full by Vlug et al.(21) so it is likely that there was double-counting of these patients in Zhuang et al.'s meta-analyses. However, this publication was not included in the meta-analysis of length of stay outcomes.

Some of the trials included for the first time in Zhuang et al.'s review, particularly that of Ionescu et al. (2009), were available to earlier systematic reviewers. Of the reviews published in 2010 or later, Varadhan et al. did not give references for any excluded studies. Adamina et al. gave references for excluded studies but did not list Ionescu et al., suggesting that their search did not locate this trial. Rawlinson et al. did not list excluded studies, while the Cochrane review by Spanjersberg et al. did not list Ionescu et al. among the excluded studies. Lv et al. excluded 26 out of 33 studies examined in full text but did not report any details.

There was a discrepancy between Zhuang et al. and Lv et al. in their data extraction of the trial by Vlug et al. There were also minor data extraction discrepancies between these reviews for two other trials but as they were in opposite directions in the two cases this is unlikely to have had a major impact on the overall meta-analysis results.

Like most included reviews, Zhuang et al. defined length of stay as time in hospital after surgery. The pooled estimate of a 2.44 day reduction in primary length of stay (95% CI 1.83 to 3.06) for ERAS relative to traditional care was very similar to those reported by Varadhan et al. (12) and Adamina et al. (13)

Discussion

Main findings

Systematic reviews of randomised trials have consistently shown a reduction in length of hospital stay with ERAS compared with traditional care. The estimated effect tended to increase over time from 2006 to 2010 as more trials were published but has not altered significantly in the most recent review, despite the inclusion of several unique trials. The best estimate appears to be an average reduction of around 2.5 days in primary post-operative length of hospital stay. However, there is considerable heterogeneity in most pooled estimates and the complexity of ERAS as an intervention means that the benefits achieved in routine practice may differ from those reported in clinical trials. These issues are discussed in the full project report (Paton et al., in preparation).

The published systematic reviews show a high level of redundancy, with multiple reviews covering identical or very similar groups of trials. Differences in pooled effect estimates across reviews reflect differences in interpretation of inclusion criteria, searching and analytical methods or software. A few data extraction discrepancies were observed but these are unlikely to have significantly affected review conclusions.

Findings in relation to previous studies

The existence of multiple systematic reviews covering the same topic was investigated by Siontis et al.(23) They found that of 73 systematic reviews (with meta-analysis) published in 2010, 49 (67%) had at least one other published meta-analysis on the same topic. A particularly striking example was the existence of 11 meta-analyses of statins to prevent atrial fibrillation after cardiac surgery; all except the first of these showed a large positive effect of the intervention. Our findings reinforce those of Siontis et al., although even where reviews included exactly the same trials their pooled estimates of effect were not necessarily identical. Enhanced recovery differs from an intervention like statins after cardiac surgery, being more complex and changing over time as more elements are incorporated into routine practice. This would tend to favour increased variation between reviews along the lines we observed.

A slightly different approach to investigating overlap between systematic reviews was taken by Woodman et al., who looked at the differences between eight reviews of community interventions to promote physical activity.(24) Across the eight reviews there were 28

included studies, of which 22 (79%) were only included in one review. There was little cross-citation between reviews. For most reviews, Woodman et al. could explain why primary data were not included, which was usually due to the reviews having a relatively narrow scope. Despite these issues, the review conclusions were similar. Comparing our results with those of Woodman et al., the enhanced recovery reviews had a higher degree of overlap although they differed with respect to inclusion of non-randomised studies (not discussed in this paper). The differences between the enhanced recovery and physical activity reviews probably reflect the fact that enhanced recovery, although a complex intervention, is more narrowly defined than interventions to increase physical activity

Implications

The findings of this study have implications for systematic reviewers, readers of systematic reviews and producers of systematic review-based evidence products. Systematic reviewers can help readers compare their reviews with other similar studies by clear reporting of key decisions, especially on inclusion/exclusion and on statistical pooling. Most of the reviews of enhanced recovery programmes performed a meta-analysis to calculate a WMD in length of stay between enhanced recovery and usual care groups. Calculating the WMD requires the means and standard deviations (SDs) of length of stay in each group in the included trials, but trials often report a different measure such as median and range (or interquartile range). Systematic reviews can deal with this situation in different ways, for example by using formulae to estimate the mean and SD, contacting the trial authors or omitting trials from any meta-analysis if mean and SD are not reported. The enhanced recovery reviews adopted all of these approaches but did not report which data were estimated rather than derived directly from trial reports. Improved reporting in this area would improve transparency and help readers to understand discrepancies between apparently similar meta-analyses. Length of stay outcomes were not always clearly defined or reported and differences between reviews may in part stem from the fact that they were measuring an outcome in different ways.

Readers of systematic reviews need to be aware of the existence of multiple systematic reviews for a high percentage of topics. This means they should not rely uncritically on the first review they find and underlines the importance of services that critically appraise systematic reviews and those that provide overviews of reviews across a topic area.(25, 26) As an aid to transparency, authors of new systematic reviews should also acknowledge the existence of any systematic reviews addressing the same or a similar question.

The use of systematic reviews to produce rapid evidence summaries to inform decision-making is an area where methodology is still developing, although some methodological frameworks have been published.(27, 28) Assessment of the quality and reliability of systematic reviews is an important part of this process but the present study suggests that conventional approaches to critical appraisal are not sufficient and careful attention should be paid to apparently minor differences between reviews. This may require increased extraction of methodological data even though the results may not be included in published evidence summaries aimed at decision-makers.

Strengths and limitations

The strength of this study is that we have looked in some detail at reviews of a complex clinical intervention to identify differences between them and possible explanations, such as differences in intervention and outcome definitions and handling of missing data from included trials in meta-analyses. We have identified limitations in reporting as one of the main barriers to understanding differences between reviews of the same topic. These reporting issues have often limited our ability to comment on whether decisions taken by review authors appear to be 'right' or 'wrong'. The discrepancies between reviews identified in this study sometimes arose from decisions where both options could be considered reasonable, for example whether or not to exclude the trial by Delaney et al.(17) because a small number of patients undergoing small bowel surgery were included.

This study only considered length of stay outcomes. Length of stay was selected as the primary outcome because of its importance for the health service at a time of acute financial pressure and because it was an outcome considered in all the included systematic reviews. Other important outcomes, including morbidity and mortality, are discussed in the full report (Paton et al., in preparation).

Unanswered questions/further research

The current study suggests a need for further, more in-depth research into methods of quality assessment of systematic reviews; to make the best use of a cumulative evidence base for decision-making; and to identify methodological issues and decision points that may influence the eventual conclusions of a review. These issues are particularly important for researchers seeking to help decision-makers interpret and use systematic reviews. Enhanced recovery is a complex intervention with multiple components and its successful implementation is likely to be influenced by numerous background factors. Given this

background, researchers and clinicians carrying out new systematic reviews should ensure that their chosen method of synthesis is appropriate for exploring intervention complexity. The recently published research agenda for reviews of complex interventions(29) provides timely guidance in this regard. Ideally, systematic reviews of emerging complex interventions (for example, interventions to support integration of health and social care) should use standardised methods and outcome definitions and be regularly updated, although this may be difficult to achieve in practice.

Systematic reviews of enhanced recovery programmes in colorectal surgery continue to be published and we are aware of at least two publications since our search was completed.(30, 31) The authors of one of these reviews refer to their paper as 'a substantial update from previous meta-analyses'(30) but in fact the included trials and overall findings are almost identical to those of Zhuang et al.(6) This is not the fault of the authors but represents an avoidable waste of research resources. Systematic reviews are now increasingly being registered prospectively at the outset on databases such as PROSPERO(32) and it will be interesting to see whether the production of overlapping reviews decreases over time.

Word count (main text): 3973

Contributors: All authors contributed to the design of this methodological study and commented on the analysis plan and/or draft manuscript. PW took overall responsibility for the rapid evidence synthesis and is guarantor. D Chambers and FP extracted additional methodological data. D Chambers wrote the first draft of the paper. All authors have seen and approved the final version.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Disclaimer:

This report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and do not necessarily reflect those of the NIHR Health Services and Delivery Research programme or the Department of Health.

Acknowledgements: This project was funded as part of a programme of research funded by the NIHR Health Services and Delivery Research programme (Project ref: 11/1026/04).

Data sharing: No additional data available.

Figure legend
Figure 1: Summary of pooled results for primary length of stay

References

1. Enhanced Recovery Partnership Programme. Delivering enhanced recovery – Helping patients to get better sooner after surgery. London: Department of Health, 2010 March 31st.
2. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg. 2002 Jun;183(6):630-41.
3. Sturm L, Cameron AL. Brief review: Fast-track surgery and enhanced recovery after surgery (ERAS) programs. Melbourne: Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S), 2009 Contract No.: 3.
4. Khan S, Wilson T, Ahmed J, et al. Quality of life and patient satisfaction with enhanced recovery protocols. Colorectal Dis. 2010;12(12):1175-82.
5. Ahmed J, Khan S, Lim M, et al. Enhanced recovery after surgery protocols - compliance and variations in practice during routine colorectal surgery. Colorectal Dis. 2012;14(9):1045-51.
6. Cheng-Le Z, Xing-Zhao YX-D, Z., Bi-Cheng C, et al. Enhanced recovery after surgery programs versus traditional care for colorectal surgery: A meta-analysis of randomized controlled trials. Dis Colon Rectum. 2013;56:667-78.
7. Wind J, Polle SW, Fung Kon Jin PH, et al. Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg. 2006;93(7):800-9.
8. Walter CJ, Collin J, Dumville JC, et al. Enhanced recovery in colorectal resections: a systematic review and meta-analysis. Colorectal Dis. 2009 May;11(4):344-53.
9. Spanjersberg Willem R, Reurings J, Keus F, et al. Fast track surgery versus conventional recovery strategies for colorectal surgery. Cochrane Database of Systematic Reviews. 2011 (2).
10. Eskicioglu C, Forbes SS, Aarts M-A, et al. Enhanced Recovery after Surgery (ERAS) programs for patients having colorectal surgery: a meta-analysis of randomized trials. J Gastrointest Surg. 2009 Dec;13(12):2321-9.
11. Gouvas N, Tan E, Windsor A, et al. Fast-track vs standard care in colorectal surgery: a meta-analysis update. Int J Colorectal Dis. 2009 Oct;24(10):1119-31.
12. Varadhan KK, Neal KR, Dejong CH, et al. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr. 2010;29(4):434-40.
13. Adamina M, Kehlet H, Tomlinson GA, et al. Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. Surgery. 2011;149(6):830-40.
14. Lv L, Shao Y-f, Zhou Y-b. The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. Int J Colorectal Dis. 2012;27:1549–54.
15. Rawlinson A, Kang P, Evans J, et al. A systematic review of enhanced recovery protocols in colorectal surgery. Ann R Coll Surg Engl. 2011;93(8):583-8.
16. van Bree SH, Vlug MS, Bemelman WA, et al. Faster recovery of gastrointestinal transit after laparoscopy and fast-track care in patients undergoing colonic surgery. Gastroenterology. 2011 Sep;141(3):872-80.e1-4.
17. Delaney CP, Zutshi M, Senagore AJ, et al. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. Dis Colon Rectum. 2003 Jul;46(7):851-9.
18. Khoo CK, Vickery CJ, Forsyth N, et al. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. Ann Surg. 2007 Jun;245(6):867-72.
19. Muller S, Zalunardo MP, Hubner M, et al.A fast-track program reduces complications and length of hospital stay after open colonic surgery. Gastroenterology. 2009 Mar;136(3):842-7.

20. Serclova Z, Dytrych P, Marvan J, et al. Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456). Clin Nutr. 2009 Dec;28(6):618-24.
21. Vlug MS, Wind J, Hollmann MW, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg. 2011 Dec;254(6):868-75.
22. Lee TG, Kang SB, Kim DW, et al. Comparison of early mobilization and diet rehabilitation program with conventional care after laparoscopic colon surgery: a prospective randomized controlled trial. Dis Colon Rectum. 2011 Jan;54(1):21-8.
23. Siontis KC, Hernandez-Boussard T, Ioannidis JP. Overlapping meta-analyses on the same topic: survey of published studies. BMJ. 2013;347:f4501.
24. Woodman J, Thomas J, Dickson K. How explicable are differences between reviews that appear to address a similar research question? A review of reviews of physical activity interventions. Systematic reviews. 2012;1:37.
25. Chambers D, Wilson P, Thompson C, et al. Maximizing the impact of systematic reviews in healthcare decision-making: a systematic scoping review of knowledge translation resources. Milbank Q. 2011;89(1):131-56.
26. Lavis JN. How can we support the use of systematic reviews in policymaking? PLoS Medicine. 2009;6(11):e1000141.
27. Chambers D, Wilson P. A framework for production of systematic review based briefings to support evidence-informed decision-making. Systematic reviews. 2012;1:32.
28. Khangura S, Konnyu K, Cushman R, et al. Evidence summaries: the evolution of a rapid review approach. Systematic reviews. 2012;1:10.
29. Noyes J, Gough D, Lewin S, et al. A research and development agenda for systematic reviews that ask complex questions about complex interventions. J Clin Epidemiol. 2013 Nov;66(11):1262-70.
30. Greco M, Capretti G, Beretta L, et al. Enhanced Recovery Program in Colorectal Surgery: A Meta-analysis of Randomized Controlled Trials. World J Surg. 2013 Dec 25.
31. Gianotti L, Beretta S, Luperto M, et al. am required to achieve the target? Int J Colorectal Dis. 2013 Dec 13.
32. Booth A, Clarke M, Dooley G, et al. PROSPERO at one year: an evaluation of its utility. Systematic reviews. 2013;2:4.
33. Anderson AD, McNaught CE, MacFie J, et al. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. Br J Surg. 2003 Dec;90(12):1497-504.
34. Gatt M, Anderson AD, Reddy BS, et al. Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. Br J Surg. 2005 Nov;92(11):1354-62.
35. Ionescu D, Iancu C, Ion D, et al. Implementing fast-track protocol for colorectal surgery: a prospective randomized clinical trial. World J Surg. 2009 Nov;33(11):2433-8.
36. Garcia-Botello S, Canovas de Lucas R, Tornero C, et al. Implementation of a perioperative multimodal rehabilitation protocol in elective colorectal surgery. A prospective randomised controlled study. Cir Esp. 2011 Mar;89(3):159-66.
37. Ren L, Zhu D, Wei Y, et al. Enhanced Recovery After Surgery (ERAS) program attenuates stress and accelerates recovery in patients after radical resection for colorectal cancer: a prospective randomized controlled trial. World J Surg. 2012 Feb;36(2):407-14.
38. Wang G, Jiang Z, Zhao K, et al. Immunologic response after laparoscopic colon cancer operation within an enhanced recovery program. J Gastrointest Surg. 2012 Jul;16(7):1379-88.
39. Wang Q, Suo J, Jiang J, et al. Effectiveness of fast-track rehabilitation vs conventional care in laparoscopic colorectal resection for elderly patients: a randomized trial. Colorectal Dis. 2012 Aug;14(8):1009-13.
40. Yang D, He W, Zhang S, et al. Fast-track surgery improves postoperative clinical recovery and immunity after elective surgery for colorectal carcinoma: randomized controlled clinical trial. World J Surg. 2012 Aug;36(8):1874-80.

Table 1: Overview of systematic reviews of ERAS for colorectal surgery

Review	Minimum definition of ERAS intervention	Search cut-off date	Included RCTs
Wind 2006(7)	At least four elements required	December 2005	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34)
Eskicioglu 2009(10)	Not stated	May 2008	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18)
Gouvas 2009(11)	At least four elements required	July 2008	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18)
Walter 2009(8)	At least five elements required (pre-, peri- and post-operative)	January 2007	Anderson 2003(33); Gatt 2005(34)
Varadhan 2010(12)	At least four elements required (pre-, peri- and post-operative)	November 2009	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20)
Adamina 2011(13)	Documented compliance with at least four of five key elements	June 2010	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20)
Rawlinson 2011(15)	At least four elements required (pre-, peri- and post-operative)	February 2011	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20)
Spanjersberg 2011(9)	At least seven elements required	Unclear (January 2011?)	Anderson 2003(33); Gatt 2005(34); Khoo 2007(18); Serclova 2009(20)
Lv 2012(14)	Not stated	April 2012	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20); Vlug 2011(21)
Zhuang 2013.(6)	At least seven elements required	July 2012	Anderson 2003(33); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20); Ionescu 2009(35); Vlug 2011(21)Garcia-Botello 2011(36); Bree 2011(16); Ren 2012(37); G Wang 2012(38); Q Wang 2012(39); Yang 2012(40)

Table 2: Risk of bias in included systematic reviews

Review	Adequate search	Risk of bias assessed	Quality score accounted for in	Study details reported and	Statistical heterogeneity investigate	Gaps in research identifie	Conclusions justified

			analysis	differences accounted for	d	d	
Wind 2006(7)	✓	✓	✓	✓	✓	✓	✓
Eskicioglu 2009(10)	✓	✓	X	✓	✓	✓	✓
Gouvas 2009(11)	✓	✓	X	✓	✓	✓	✓
Walter 2009(8)	✓	✓	✓	✓	✓	✓	✓
Varadhan 2010(12)	✓	✓	X	✓	✓	✓	✓
Adamina 2011(13)	✓	✓	UC	✓	UC	✓	✓
Rawlinson 2011(15)	✓	X	X	✓	UC	X	UC
Spanjersberg 2011(9)	✓	✓	✓	✓	✓	✓	✓
Lv 2012(14)	✓	✓	X	X	✓	✓	✓
Zhuang 2013.(6)	✓	✓	✓	✓	✓	✓	✓

UC, unclear

Table 3: Cross-citation among included systematic reviews

Review	Reviews cited	Cited by subsequent reviews
Wind 2006(7)	NA	Eskicioglu 2009(10); Gouvas 2009(11); Walter 2009(8); Varadhan 2010(12); Adamina 2011(13); Rawlinson 2011(15); Spanjersberg 2011(9); Zhuang 2013.(6)
Eskicioglu 2009(10)	Wind 2006(7)	Varadhan 2010(12); Rawlinson 2011(15); Zhuang 2013.(6)
Gouvas 2009(11)	Wind 2006(7)	Varadhan 2010(12); Adamina 2011(13); Rawlinson 2011(15); Spanjersberg 2011(9); Lv 2012(14); Zhuang 2013.(6)
Walter 2009(8)	Wind 2006(7)	Varadhan 2010(12); Spanjersberg 2011(9); Lv 2012(14); Zhuang 2013.(6)
Varadhan 2010(12)	Wind 2006(7); Eskicioglu 2009(10); Gouvas 2009(11); Walter 2009(8)	Rawlinson 2011(15); Spanjersberg 2011(9); Lv 2012(14); Zhuang 2013.(6)
Adamina 2011(13)	Wind 2006(7); Gouvas 2009(11)	Zhuang 2013.(6)
Rawlinson 2011(15)	Wind 2006(7); Eskicioglu 2009(10); Gouvas 2009(11); Varadhan 2010(12)	Not cited
Spanjersberg 2011(9)	Wind 2006(7); Gouvas 2009(11); Walter 2009(8); Varadhan 2010(12)	Lv 2012(14); Zhuang 2013.(6)
Lv 2012(14)	Gouvas 2009(11); Walter 2009(8); Varadhan 2010(12); Spanjersberg 2011(9)	Not cited
Zhuang 2013.(6)	Wind 2006(7); Eskicioglu 2009(10); Gouvas 2009(11); Walter 2009(8); Varadhan 2010(12); Adamina 2011(13); Spanjersberg 2011(9)	NA

NA, not applicable

Table 4: Summary of meta-analyses for length of stay

Review	Definition of primary length of stay	Meta-analysis model	Pooled effect estimate for primary length of stay	Pooled effect estimate for total length of stay
Wind 2006(7)	Days in hospital after surgery	Random	WMD -1.89 (-3.61 to -0.18) I^2 = 63.4%	Not calculated
Eskicioglu 2009(10)	Days in hospital after surgery	NA	Not calculated (authors stated pooling was not feasible)	
Gouvas 2009(11)	Days in hospital after surgery	Random	WMD -1.88 (-3.35 to -0.41) I^2 = 45%	WMD -1.73 (-3.50 to 0.04) I^2 = 0%
Walter 2009(8)	Days in hospital during index admission	Fixed	WMD -3.64 (-4.98 to -2.29) I^2 = 0%	WMD -3.75 (-5.11 to -2.40) I^2 = 0%
Varadhan 2010(12)	Not explicitly defined but appears to be days in hospital after surgery	Random	WMD -2.51 (-3.54 to -1.47) I^2 = 55%	Not calculated
Adamina 2011(13)	Length of stay outcome not explicitly defined	Bayesian	Mean difference for 'length of stay' -2.5 (95% CrI -3.92 to -1.11) I^2 not reported	
Rawlinson 2011(15)	Not defined	NA	Not calculated (authors cited findings from Gouvas and Varadhan)	
Spanjersberg 2011(9)	Not explicitly defined but appears to be days in hospital after surgery	Fixed	WMD -2.94 (-3.69 to -2.19) I^2 = 0%	Not calculated
Lv 2012(14)	Days in hospital during index admission	Random	WMD -1.88 (-2.91 to -0.86) I^2 = 75%	Not calculated
Zhuang 2013.(6)	Days in hospital after surgery	Random	WMD -2.44 (-3.06 to -1.83) I^2 = 88%	WMD -2.39 (-3.70 to -1.09) I^2 = 85%

NA, not applicable

~~Effect of enhanced recovery programmes on length of hospital stay in colorectal surgery: a~~An overview and methodological assessment of systematic reviews and meta-analyses of enhanced recovery programmes in colorectal surgery

Duncan Chambers, Fiona Paton, Paul Wilson, Alison Eastwood, Dawn Craig, Dave Fox, David Jayne, Erika McGinnes

Centre for Reviews and Dissemination, University of York D Chambers, F Paton, P Wilson, A Eastwood, D Craig, D Fox

Leeds Teaching Hospitals NHS Trust, Leeds D Jayne, E McGinnes

Corresponding author: Duncan Chambers (duncan.chambers@york.ac.uk)

Disclaimer:

This report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and do not necessarily reflect those of the NIHR Health Services and Delivery Research programme or the Department of Health.

Acknowledgements: This project was funded as part of a programme of research funded by the NIHR Health Services and Delivery Research programme (Project ref: 11/1026/04).

Abstract

Objectives: To identify and critically assess the extent to which systematic reviews of enhanced recovery programmes for patients undergoing colorectal surgery differ in their methodology and reported estimates of ~~the~~ effect.

Design: Review of published systematic reviews. We searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) Database from 1990 to March 2013. Systematic reviews of enhanced recovery programmes for patients undergoing colorectal surgery were eligible for inclusion.

Primary and secondary outcome measures: The primary outcome was length of hospital stay. We assessed changes in pooled estimates of treatment effect over time and how these might have been influenced by decisions taken by researchers as well as by the availability of new trials. The quality of systematic reviews was assessed using the CRD DARE critical appraisal process.

Results: Ten systematic reviews were included. Systematic reviews of RCTs have consistently shown a reduction in length of hospital stay with enhanced recovery compared with traditional care. The estimated effect tended to increase from 2006 to 2010 as more trials were published but has not altered significantly in the most recent review, despite the inclusion of several unique trials. The best estimate appears to be an average reduction of around 2.5 days in primary post-operative length of stay. Differences between reviews reflected differences in interpretation of inclusion criteria, searching and analytical methods or software.

Conclusions: Systematic reviews of enhanced recovery programmes show a high level of research waste, with multiple reviews covering identical or very similar groups of trials. Where multiple reviews exist on a topic, interpretation may require careful attention to apparently minor differences between reviews. Researchers can help readers by acknowledging existing reviews and through clear reporting of key decisions, especially on inclusion/exclusion and on statistical pooling.

Word count: 298

Strengths and limitations

- Systematic reviews of randomised trials have consistently shown that enhanced recovery programmes reduce length of hospital stay for patients undergoing colorectal surgery, compared with usual care. The strength of this study is that we have looked in some detail at the available reviews to identify differences between them and possible explanations, such as differences in intervention and outcome definitions and handling of missing data from included trials in meta-analyses.

- We found a high level of research waste, with multiple reviews covering identical or very similar groups of trials. Differences in pooled effect estimates across reviews reflected differences in interpretation of inclusion criteria, searching and analytical methods or software.

- Where multiple reviews exist on a topic, interpretation may require careful attention to apparently minor differences between reviews. Researchers can help readers by acknowledging existing reviews and through clear reporting of key decisions, especially on inclusion/exclusion and on statistical pooling.

- We identified limitations in reporting as one of the main barriers to understanding differences between reviews. These reporting issues often limited our ability to comment on whether decisions taken by review authors appear to be right' or 'wrong'.

Introduction

Reduction in length of stay in secondary care hospital settings provides a key potential opportunity to improve productivity in healthcare systems. There has been growing interest over recent years in the use of enhanced recovery programmes (also known as ERAS, fast track, multimodal, rapid or accelerated recovery programmes). The approach was pioneered in Denmark in the late 1990s for patients undergoing colorectal surgery and is now spreading to other surgical pathways such as musculoskeletal, urology and gynaecology.

The underlying aim of enhanced recovery programmes is to ensure that patients are in optimal condition for treatment (to minimise the risk of surgery being postponed or cancelled because of the patient's condition), receive innovative care during surgery and experience optimal post-surgical rehabilitation.(1) Programmes differ widely but share common elements such as patient education and involvement in preoperative planning processes, preoperative oral carbohydrates, improved anaesthetic and postoperative analgesic techniques to reduce the physical stress of the operation, early oral feeding and mobilisation.(2, 3) Enhanced recovery programmes have been delivered in the UK NHS since the early 2000s. Implementation has to date been variable despite the support of the Department of Health and more recently the Royal Colleges. It is likely that this variation reflects both the complexity of enhanced recovery programmes themselves and issues around implementing change in fundamental surgical procedures at a time when the NHS is facing severe funding constraints.

There are a substantial number of systematic reviews and economic evaluations that examine the effectiveness and cost-effectiveness of enhanced recovery programmes. We have used this evidence as the basis of a comprehensive rapid evidence synthesis relating to the effectiveness, cost effectiveness, implementation, delivery and impact of enhanced recovery programmes with particular reference to secondary care hospital settings in the NHS (Paton et al., in preparation). During the course of this project we became aware of significant methodological differences between systematic reviews of enhanced recovery programmes in colorectal surgery (by far the largest body of evidence for any surgical speciality). Reviews published at around the same time varied in the trials they included and in their estimates (derived by meta-analysis) of the reduction in length of stay associated with enhanced recovery programmes.

The objective of this study, therefore, is to provide a critical overview of the methodology of the available systematic reviews and their contribution to the development of the evidence base available to decision-makers. In particular, we will examine how numerical estimates of the benefit of enhanced recovery on length of hospital stay have changed over time and how these might have been influenced by decisions taken by systematic reviewers as well as by the availability of new trials.

Methods

Literature searches

This study was carried out following a rapid synthesis of evidence relating to enhanced recovery programmes in all types of surgery (Paton et al., in preparation). To identify systematic reviews, we searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) Database from 1990 to March 2013. See Appendix 1 for search strategies. The PROSPERO database was searched to identify any ongoing systematic reviews. Systematic reviews evaluating enhanced recovery programmes in patients undergoing any type of elective surgery in a hospital setting in the UK NHS or a comparable healthcare system were eligible for inclusion in the rapid evidence synthesis. Review authors' definitions of enhanced recovery programmes were accepted. Outcomes of interest were any measure of clinical outcomes, patient experience or resource use. Reviews had to compare enhanced recovery with usual/standard care without a structured multimodal enhanced recovery pathway. For this methodological study, only systematic reviews of enhanced recovery programmes for colorectal surgery were considered.

Study selection

We stored the literature search results in a reference management database (EndNote X6). Two researchers independently screened all titles and abstracts obtained through the searches for potentially relevant articles. Full manuscripts of potentially relevant articles were ordered and two researchers independently assessed the relevance of each article using the criteria stated above. Disagreements between researchers were resolved by discussion or by recourse to a third researcher where necessary.

Quality assessment

Quality assessment of systematic reviews was based on the CRD critical appraisal processes for DARE (http://www.crd.york.ac.uk/crdweb/HomePage.asp). Specific aspects assessed were adequacy of the search; assessment of quality/risk of bias of included studies; quality assessment results taken into account in the analysis; study details reported and differences between studies accounted for; investigation of statistical heterogeneity; were gaps in research identified; and were the review conclusions justified. The quality assessment was performed by one researcher and checked by a second. Discrepancies were resolved by discussion or by recourse to a third researcher.

Data extraction and analysis

Clinical effectiveness data for the rapid evidence synthesis were extracted into review software (EPPI Reviewer 4.0). An analysis plan for this methodological study was prepared in advance and additional methodological information was extracted into a Microsoft Excel spreadsheet. Data were extracted by one researcher and checked by another; discrepancies were resolved by consensus or where necessary by recourse to a third researcher.

Data extracted from the reviews included the systematic review inclusion criteria (particularly the definition of an ERAS programme); RCTs included (number and list); length of stay mean difference (MD) estimates and 95% confidence intervals (CIs) for each RCT as reported in the review; meta-analysis methods (e.g. type of model used); method used to handle missing means/SDs; definition of primary and total length of stay; pooled estimates of weighted MD (WMD) in length of stay between ERAS and control groups; and source of funding.

Extracted data were examined and tabulated to identify differences between reviews that may have influenced their conclusions and quantitative estimates of the effectiveness of enhanced recovery programmes compared with usual care. We focused on the outcome of length of primary hospital stay (and total length of stay including readmissions, where reported) because reduction of length of stay is a key objective of enhanced recovery programmes and because length of stay was a primary outcome of most included systematic reviews. Only length of stay data from randomised controlled trials (RCTs) were included in this analysis.

Results

The report by Paton et al. included 11 systematic reviews of ERAS programmes for colorectal surgery. One review(4) focused on quality of life and patient satisfaction and another on compliance and variations in practice(5), leaving nine reviews that reported length of stay, of which seven reported a pooled effect estimate (weighted mean difference (WMD) in days). The review by Zhuang et al.,(6) which was published too late to be fully discussed by Paton et al., is also included in this report, giving a total of ten systematic reviews that met the inclusion criteria for this methodological study (Table 1).

Most of the included reviews were reasonably well conducted and reported (Table 2). The reviews by Wind et al., (7) Walter et al. (8), Spanjersberg et al. (9) and Zhuang et al. (6) met all seven quality criteria and were considered at low risk of bias. Three other reviews met six criteria but all failed to take study quality into account in their synthesis.(10-12) Adamina et al. (13) and Lv et al. (14) failed to meet two of the criteria, while the paper by Rawlinson et al. (15) only clearly met two criteria and was considered potentially at high risk of bias.

Chronological development of the evidence base

Four systematic reviews were published in the years 2006–2009. At this stage only a few randomised trials were available. Wind et al. Wind 2006(7) included three trials; Eskicioglu et al. and Gouvas et al. four trials; and Walter et al. included just two trials (Table 1).

Four further reviews were published in 2010 and 2011. These all considered the same six trials, although one review chose to exclude two of these from its main analysis because the intervention did not meet the review definition of an ERAS programme. (9)

A systematic review by Lv et al. published in 2012 added one more trial, bringing the total to seven. However, just a year later Zhuang et al. published a systematic review with 13 included trials, among them four recent trials by Chinese investigators. With one exception,(16) the trials included in this review were identified and discussed by Paton et al. in our review of trials not included in the then-available systematic reviews.

The included reviews varied somewhat in the extent to which they cited previously published reviews of the field. However, in general reviews tended to cite most of the earlier reviews that would have been available at the time of writing. The first systematic review, by Wind et

al., was cited by eight of the nine subsequent reviews. Gouvas et al.'s review was cited by six of seven subsequent reviews and Varadhan et al. by four out of five (Table 3). The main exception was the paper by Rawlinson et al.,(15) which was not cited by three later reviews. Adamina et al. differed from other researchers in their use of Bayesian methodology and their work was only cited by one of the four later reviews. Zhuang et al. cited all the previous systematic reviews except that of Lv et al., which may have been published too late to be included.

Methodological differences between systematic reviews

The four early systematic reviews of ERAS for colorectal surgery showed a number of methodological differences. Although inclusion criteria appeared similar, Walter et al. excluded two trials that were included in the reviews by Eskicioglu et al. and Gouvas et al. In one case(17) this was reported to be because the trial included some patients who had undergone small bowel surgery; the reason for the other exclusion(18) was not reported. Walter et al. also differed from the other reviews in its definition of outcomes: length of stay was measured as total days of admission in this review and as days spent in hospital after surgery in the other reviews published in the same period.

In terms of data synthesis, Eskicioglu et al. was the only one of the four early reviews that did not perform a meta-analysis, on the grounds that data in the right form (means and standard deviations) were not available. The remaining three reviews elected to pool. Gouvas et al. and Wind et al. used random-effects models for their main meta-analysis, while Walter et al. used a fixed-effect model. Both Wind et al. and Walter et al. justified their choice on the basis of a random-effects model being more appropriate in the presence of some heterogeneity but neither stated a level of heterogeneity above which a random-effects model should be used. Wind et al. stated that trials without means and standard deviations were omitted from the analysis, while Gouvas et al. estimated from reported medians and ranges where necessary. Walter et al. did not report on this point.

Pooled estimates (WMD) of the effect of ERAS on primary length of stay varied substantially, being considerably higher and with a wider confidence interval in Walter et al. compared with the other reviews (Figure 1 and Table 4). Wind et al. and Gouvas et al. provided almost identical WMDs, the only effect of an additional trial in Gouvas et al. being to slightly narrow the 95% confidence interval. Walter et al. reported no statistical heterogeneity while the other two reviews found some evidence of heterogeneity.

Overall, these reviews suggested considerable uncertainty about the magnitude of the effect of ERAS programmes in reducing length of hospital stay. Based on 95% confidence intervals, the effect could plausibly range from less than 0.5 days to almost 5 days.

The next group of systematic reviews to be published(9, 12, 13, 15) included up to six RCTs (additional RCTs by Muller et al. (19) and Serclova et al. (20) were now available). Spanjersberg et al. differed from other authors in treating length of stay as a secondary outcome of the review and more significantly by excluding two trials that were included in most other systematic reviews. The authors stated that Muller et al. and Delaney et al. (17) failed to meet the inclusion criterion of including at least seven elements in the ERAS intervention.

None of these reviews provided clear definitions of outcomes but Varadhan et al. and Spanjersberg et al. appeared to measure days in hospital after surgery (i.e., primary length of stay). Adamina et al. reported their outcome as length of hospital stay without definition or distinguishing between primary and total length of stay. The reviews also differed in their reported treatment of studies with missing data (mean/standard deviation): Varadhan et al. obtained data from original authors, Spanjersberg et al. calculated from median and range and Adamina et al. did not report their methods. Adamina et al. were the only authors who used Bayesian methods for meta-analysis, although few details were reported. (13) Rawlinson et al. (15) did not report an original meta-analysis but instead discussed the findings of Gouvas et al. and Varadhan et al.

Compared with the earlier reviews, this group of systematic reviews reported a substantially narrower range of effect estimates, all suggesting a reduction of 2.5 to 3 days in primary hospital stay associated with ERAS programmes (Table 1). The range of 95% confidence intervals was also narrower (approximately 1.1 to 3.9 days).

The 2012 review by Lv et al. added one additional RCT for a total of seven trials. (14) The new trial(21) compared ERAS with traditional care in patients undergoing both laparoscopic and open surgery and so was treated as two trials in the meta-analysis. The trial showed a 1 day reduction in length of stay in the laparoscopic setting but there was no difference in patients undergoing open surgery. Lv et al. also differed from most of the earlier reviews in defining length of stay as length of the index admission (rather than days in hospital after surgery). It is unclear whether this explains the discrepancy but Lv et al. reported a smaller reduction in length of stay compared with the reviews immediately preceding it (-1.88 days,

95% CI -2.91 to -0.86). However, this estimate was still compatible with a 'true' reduction of around 2 to 3 days in primary length of stay.

The most recent systematic review that we are aware of was published in May 2013, too late to be considered in detail in the full report.(6) It is more comprehensive than the previous reviews, with 13 included trials (two with both open and laparoscopic arms) and 1910 participants. All except one(22) of the RCTs included in our report were also in this systematic review. However, Zhuang et al. also included one trial that we excluded.(16) In fact this publication is a single-centre report of results from the LAFA trial that was reported in full by Vlug et al.(21) so it is likely that there was double-counting of these patients in Zhuang et al.'s meta-analyses. However, this publication was not included in the meta-analysis of length of stay outcomes.

Some of the trials included for the first time in Zhuang et al.'s review, particularly that of Ionescu et al. (2009), were available to earlier systematic reviewers. Of the reviews published in 2010 or later, Varadhan et al. did not give references for any excluded studies. Adamina et al. gave references for excluded studies but did not list Ionescu et al., suggesting that their search did not locate this trial. Rawlinson et al. did not list excluded studies, while the Cochrane review by Spanjersberg et al. did not list Ionescu et al. among the excluded studies. Lv et al. excluded 26 out of 33 studies examined in full text but did not report any details.

There was a discrepancy between Zhuang et al. and Lv et al. in their data extraction of the trial by Vlug et al. There were also minor data extraction discrepancies between these reviews for two other trials but as they were in opposite directions in the two cases this is unlikely to have had a major impact on the overall meta-analysis results.

Like most included reviews, Zhuang et al. defined length of stay as time in hospital after surgery. The pooled estimate of a 2.44 day reduction in primary length of stay (95% CI 1.83 to 3.06) for ERAS relative to traditional care was very similar to those reported by Varadhan et al. (12) and Adamina et al. (13)

Discussion

Main findings

Systematic reviews of randomised trials have consistently shown a reduction in length of hospital stay with ERAS compared with traditional care. The estimated effect tended to increase over time from 2006 to 2010 as more trials were published but has not altered significantly in the most recent review, despite the inclusion of several unique trials. The best estimate appears to be an average reduction of around 2.5 days in primary post-operative length of hospital stay. However, there is considerable heterogeneity in most pooled estimates and the complexity of ERAS as an intervention means that the benefits achieved in routine practice may differ from those reported in clinical trials. These issues are discussed in the full project report (Paton et al., in preparation).

The published systematic reviews show a high level of redundancy, with multiple reviews covering identical or very similar groups of trials. Differences in pooled effect estimates across reviews reflect differences in interpretation of inclusion criteria, searching and analytical methods or software. A few data extraction discrepancies were observed but these are unlikely to have significantly affected review conclusions.

Findings in relation to previous studies

The existence of multiple systematic reviews covering the same topic was investigated by Siontis et al.(23) They found that of 73 systematic reviews (with meta-analysis) published in 2010, 49 (67%) had at least one other published meta-analysis on the same topic. A particularly striking example was the existence of 11 meta-analyses of statins to prevent atrial fibrillation after cardiac surgery; all except the first of these showed a large positive effect of the intervention. Our findings reinforce those of Siontis et al., although even where reviews included exactly the same trials their pooled estimates of effect were not necessarily identical. Enhanced recovery differs from an intervention like statins after cardiac surgery, being more complex and changing over time as more elements are incorporated into routine practice. This would tend to favour increased variation between reviews along the lines we observed.

A slightly different approach to investigating overlap between systematic reviews was taken by Woodman et al., who looked at the differences between eight reviews of community interventions to promote physical activity.(24) Across the eight reviews there were 28

included studies, of which 22 (79%) were only included in one review. There was little cross-citation between reviews. For most reviews, Woodman et al. could explain why primary data were not included, which was usually due to the reviews having a relatively narrow scope. Despite these issues, the review conclusions were similar. Comparing our results with those of Woodman et al., the enhanced recovery reviews had a higher degree of overlap although they differed with respect to inclusion of non-randomised studies (not discussed in this paper). The differences between the enhanced recovery and physical activity reviews probably reflect the fact that enhanced recovery, although a complex intervention, is more narrowly defined than interventions to increase physical activity

Implications

The findings of this study have implications for systematic reviewers, readers of systematic reviews and producers of systematic review-based evidence products. Systematic reviewers can help readers compare their reviews with other similar studies by clear reporting of key decisions, especially on inclusion/exclusion and on statistical pooling. Most of the reviews of enhanced recovery programmes performed a meta-analysis to calculate a WMD in length of stay between enhanced recovery and usual care groups. Calculating the WMD requires the means and standard deviations (SDs) of length of stay in each group in the included trials, but trials often report a different measure such as median and range (or interquartile range). Systematic reviews can deal with this situation in different ways, for example by using formulae to estimate the mean and SD, contacting the trial authors or omitting trials from any meta-analysis if mean and SD are not reported. The enhanced recovery reviews adopted all of these approaches but did not report which data were estimated rather than derived directly from trial reports. Improved reporting in this area would improve transparency and help readers to understand discrepancies between apparently similar meta-analyses. Length of stay outcomes were not always clearly defined or reported and differences between reviews may in part stem from the fact that they were measuring an outcome in different ways.

Readers of systematic reviews need to be aware of the existence of multiple systematic reviews for a high percentage of topics. This means they should not rely uncritically on the first review they find and underlines the importance of services that critically appraise systematic reviews and those that provide overviews of reviews across a topic area.(25, 26) As an aid to transparency, authors of new systematic reviews should also acknowledge the existence of any systematic reviews addressing the same or a similar question.

The use of systematic reviews to produce rapid evidence summaries to inform decision-making is an area where methodology is still developing, although some methodological frameworks have been published.(27, 28) Assessment of the quality and reliability of systematic reviews is an important part of this process but the present study suggests that conventional approaches to critical appraisal are not sufficient and careful attention should be paid to apparently minor differences between reviews. This may require increased extraction of methodological data even though the results may not be included in published evidence summaries aimed at decision-makers.

Strengths and limitations

The strength of this study is that we have looked in some detail at reviews of a complex clinical intervention to identify differences between them and possible explanations, such as differences in intervention and outcome definitions and handling of missing data from included trials in meta-analyses. We have identified limitations in reporting as one of the main barriers to understanding differences between reviews of the same topic. These reporting issues have often limited our ability to comment on whether decisions taken by review authors appear to be 'right' or 'wrong'. The discrepancies between reviews identified in this study sometimes arose from decisions where both options could be considered reasonable, for example whether or not to exclude the trial by Delaney et al.(17) because a small number of patients undergoing small bowel surgery were included.

This study only considered length of stay outcomes. Length of stay was selected as the primary outcome because of its importance for the health service at a time of acute financial pressure and because it was an outcome considered in all the included systematic reviews. Other important outcomes, including morbidity and mortality, are discussed in the full report (Paton et al., in preparation).

Unanswered questions/further research

The current study suggests a need for further, more in-depth research into methods of quality assessment of systematic reviews; to make the best use of a cumulative evidence base for decision-making; and to identify methodological issues and decision points that may influence the eventual conclusions of a review. These issues are particularly important for researchers seeking to help decision-makers interpret and use systematic reviews. Enhanced recovery is a complex intervention with multiple components and its successful implementation is likely to be influenced by numerous background factors. Given this

background, researchers and clinicians carrying out new systematic reviews should ensure that their chosen method of synthesis is appropriate for exploring intervention complexity. The recently published research agenda for reviews of complex interventions(29) provides timely guidance in this regard. Ideally, systematic reviews of emerging complex interventions (for example, interventions to support integration of health and social care) should use standardised methods and outcome definitions and be regularly updated, although this may be difficult to achieve in practice.

Systematic reviews of enhanced recovery programmes in colorectal surgery continue to be published and we are aware of at least two publications since our search was completed.(30, 31) The authors of one of these reviews refer to their paper as 'a substantial update from previous meta-analyses'(30) but in fact the included trials and overall findings are almost identical to those of Zhuang et al.(6) This is not the fault of the authors but represents an avoidable waste of research resources. Systematic reviews are now increasingly being registered prospectively at the outset on databases such as PROSPERO(32) and it will be interesting to see whether the production of overlapping reviews decreases over time.

Word count (main text): 3973

Contributors: All authors contributed to the design of this methodological study and commented on the analysis plan and/or draft manuscript. PW took overall responsibility for the rapid evidence synthesis and is guarantor. D Chambers and FP extracted additional methodological data. D Chambers wrote the first draft of the paper. All authors have seen and approved the final version.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. Enhanced Recovery Partnership Programme. Delivering enhanced recovery – Helping patients to get better sooner after surgery. London: Department of Health, 2010 March 31st.
2. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg. 2002 Jun;183(6):630-41.
3. Sturm L, Cameron AL. Brief review: Fast-track surgery and enhanced recovery after surgery (ERAS) programs. Melbourne: Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S), 2009 Contract No.: 3.
4. Khan S, Wilson T, Ahmed J, Owais A, MacFie J. Quality of life and patient satisfaction with enhanced recovery protocols. Colorectal Dis. 2010;12(12):1175-82.
5. Ahmed J, Khan S, Lim M, Chandrasekaran TV, MacFie J. Enhanced recovery after surgery protocols - compliance and variations in practice during routine colorectal surgery. Colorectal Dis. 2012;14(9):1045-51.
6. Cheng-Le Z, Xing-Zhao YX-D, Z., Bi-Cheng C, Zhen Y. Enhanced recovery after surgery programs versus traditional care for colorectal surgery: A meta-analysis of randomized controlled trials. Dis Colon Rectum. 2013;56:667-78.
7. Wind J, Polle SW, Fung Kon Jin PH, Dejong CH, Meyenfeldt MF, Ubbink DT, et al. Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg. 2006;93(7):800-9.
8. Walter CJ, Collin J, Dumville JC, Drew PJ, Monson JR. Enhanced recovery in colorectal resections: a systematic review and meta-analysis. Colorectal Dis. 2009 May;11(4):344-53.
9. Spanjersberg Willem R, Reurings J, Keus F, van Laarhoven Cornelis JHM. Fast track surgery versus conventional recovery strategies for colorectal surgery. Cochrane Database of Systematic Reviews. 2011 (2).
10. Eskicioglu C, Forbes SS, Aarts M-A, Okrainec A, McLeod RS. Enhanced Recovery after Surgery (ERAS) programs for patients having colorectal surgery: a meta-analysis of randomized trials. J Gastrointest Surg. 2009 Dec;13(12):2321-9.
11. Gouvas N, Tan E, Windsor A, Xynos E, Tekkis PP. Fast-track vs standard care in colorectal surgery: a meta-analysis update. Int J Colorectal Dis. 2009 Oct;24(10):1119-31.
12. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr. 2010;29(4):434-40.
13. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ, Delaney CP. Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. Surgery. 2011;149(6):830-40.
14. Lv L, Shao Y-f, Zhou Y-b. The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. Int J Colorectal Dis. 2012;27:1549–54.
15. Rawlinson A, Kang P, Evans J, Khanna A. A systematic review of enhanced recovery protocols in colorectal surgery. Ann R Coll Surg Engl. 2011;93(8):583-8.
16. van Bree SH, Vlug MS, Bemelman WA, Hollmann MW, Ubbink DT, Zwinderman AH, et al. Faster recovery of gastrointestinal transit after laparoscopy and fast-track care in patients undergoing colonic surgery. Gastroenterology. 2011 Sep;141(3):872-80.e1-4.
17. Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. Dis Colon Rectum. 2003 Jul;46(7):851-9.
18. Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. Ann Surg. 2007 Jun;245(6):867-72.

19. Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N, Zurich Fast Track Study G. A fast-track program reduces complications and length of hospital stay after open colonic surgery. Gastroenterology. 2009 Mar;136(3):842-7.
20. Serclova Z, Dytrych P, Marvan J, Nova K, Hankeova Z, Ryska O, et al. Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456). Clin Nutr. 2009 Dec;28(6):618-24.
21. Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg. 2011 Dec;254(6):868-75.
22. Lee TG, Kang SB, Kim DW, Hong S, Heo SC, Park KJ. Comparison of early mobilization and diet rehabilitation program with conventional care after laparoscopic colon surgery: a prospective randomized controlled trial. Dis Colon Rectum. 2011 Jan;54(1):21-8.
23. Siontis KC, Hernandez-Boussard T, Ioannidis JP. Overlapping meta-analyses on the same topic: survey of published studies. BMJ. 2013;347:f4501.
24. Woodman J, Thomas J, Dickson K. How explicable are differences between reviews that appear to address a similar research question? A review of reviews of physical activity interventions. Systematic reviews. 2012;1:37.
25. Chambers D, Wilson P, Thompson C, Hanbury A, Farley K, Light K. Maximizing the impact of systematic reviews in healthcare decision-making: a systematic scoping review of knowledge translation resources. Milbank Q. 2011;89(1):131-56.
26. Lavis JN. How can we support the use of systematic reviews in policymaking? PLoS Medicine. 2009;6(11):e1000141.
27. Chambers D, Wilson P. A framework for production of systematic review based briefings to support evidence-informed decision-making. Systematic reviews. 2012;1:32.
28. Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence summaries: the evolution of a rapid review approach. Systematic reviews. 2012;1:10.
29. Noyes J, Gough D, Lewin S, Mayhew A, Michie S, Pantoja T, et al. A research and development agenda for systematic reviews that ask complex questions about complex interventions. J Clin Epidemiol. 2013 Nov;66(11):1262-70.
30. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced Recovery Program in Colorectal Surgery: A Meta-analysis of Randomized Controlled Trials. World J Surg. 2013 Dec 25.
31. Gianotti L, Beretta S, Luperto M, Bernasconi D, Valsecchi MG, Braga M. Enhanced recovery strategies in colorectal surgery: is the compliance with the whole program required to achieve the target? Int J Colorectal Dis. 2013 Dec 13.
32. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, et al. PROSPERO at one year: an evaluation of its utility. Systematic reviews. 2013;2:4.
33. Anderson AD, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. Br J Surg. 2003 Dec;90(12):1497-504.
34. Gatt M, Anderson AD, Reddy BS, Hayward-Sampson P, Tring IC, MacFie J. Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. Br J Surg. 2005 Nov;92(11):1354-62.
35. Ionescu D, Iancu C, Ion D, Al-Hajjar N, Margarit S, Mocan L, et al. Implementing fast-track protocol for colorectal surgery: a prospective randomized clinical trial. World J Surg. 2009 Nov;33(11):2433-8.
36. Garcia-Botello S, Canovas de Lucas R, Tornero C, Escamilla B, Espi-Macias A, Esclapez-Valero P, et al. Implementation of a perioperative multimodal rehabilitation protocol in elective colorectal surgery. A prospective randomised controlled study. Cir Esp. 2011 Mar;89(3):159-66.
37. Ren L, Zhu D, Wei Y, Pan X, Liang L, Xu J, et al. Enhanced Recovery After Surgery (ERAS) program attenuates stress and accelerates recovery in patients after radical resection for colorectal cancer: a prospective randomized controlled trial. World J Surg. 2012 Feb;36(2):407-14.

38. Wang G, Jiang Z, Zhao K, Li G, Liu F, Pan H, et al. Immunologic response after laparoscopic colon cancer operation within an enhanced recovery program. J Gastrointest Surg. 2012 Jul;16(7):1379-88.
39. Wang Q, Suo J, Jiang J, Wang C, Zhao YQ, Cao X. Effectiveness of fast-track rehabilitation vs conventional care in laparoscopic colorectal resection for elderly patients: a randomized trial. Colorectal Dis. 2012 Aug;14(8):1009-13.
40. Yang D, He W, Zhang S, Chen H, Zhang C, He Y. Fast-track surgery improves postoperative clinical recovery and immunity after elective surgery for colorectal carcinoma: randomized controlled clinical trial. World J Surg. 2012 Aug;36(8):1874-80.

Table 1: Overview of systematic reviews of ERAS for colorectal surgery

Review	Minimum definition of ERAS intervention	Search cut-off date	Included RCTs
Wind 2006(7)	At least four elements required	December 2005	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34)
Eskicioglu 2009(10)	Not stated	May 2008	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18)
Gouvas 2009(11)	At least four elements required	July 2008	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18)
Walter 2009(8)	At least five elements required (pre-, peri- and post-operative)	January 2007	Anderson 2003(33); Gatt 2005(34)
Varadhan 2010(12)	At least four elements required (pre-, peri- and post-operative)	November 2009	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20)
Adamina 2011(13)	Documented compliance with at least four of five key elements	June 2010	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20)
Rawlinson 2011(15)	At least four elements required (pre-, peri- and post-operative)	February 2011	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20)
Spanjersberg 2011(9)	At least seven elements required	Unclear (January 2011?)	Anderson 2003(33); Gatt 2005(34); Khoo 2007(18); Serclova 2009(20)
Lv 2012(14)	Not stated	April 2012	Anderson 2003(33); Delaney 2003(17); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20); Vlug 2011(21)
Zhuang 2013.(6)	At least seven elements required	July 2012	Anderson 2003(33); Gatt 2005(34); Khoo 2007(18); Muller 2009(19); Serclova 2009(20); Ionescu 2009(35); Vlug 2011(21)Garcia-Botello 2011(36); Bree 2011(16); Ren 2012(37); G Wang 2012(38); Q Wang 2012(39); Yang 2012(40)

Table 2: Risk of bias in included systematic reviews

Review	Adequate search	Risk of bias assessed	Quality score accounted for in analysis	Study details reported and differences accounted for	Statistical heterogeneity investigated	Gaps in research identified	Conclusions justified
Wind 2006(7)	✓	✓	✓	✓	✓	✓	✓
Eskicioglu 2009(10)	✓	✓	X	✓	✓	✓	✓
Gouvas 2009(11)	✓	✓	X	✓	✓	✓	✓
Walter 2009(8)	✓	✓	✓	✓	✓	✓	✓
Varadhan 2010(12)	✓	✓	X	✓	✓	✓	✓
Adamina 2011(13)	✓	✓	UC	✓	UC	✓	✓
Rawlinson 2011(15)	✓	X	X	✓	UC	X	UC
Spanjersberg 2011(9)	✓	✓	✓	✓	✓	✓	✓
Lv 2012(14)	✓	✓	X	X	✓	✓	✓
Zhuang 2013.(6)	✓	✓	✓	✓	✓	✓	✓

UC, unclear

Table 3: Cross-citation among included systematic reviews

Review	Reviews cited	Cited by subsequent reviews
Wind 2006(7)	NA	Eskicioglu 2009(10); Gouvas 2009(11); Walter 2009(8); Varadhan 2010(12); Adamina 2011(13); Rawlinson 2011(15); Spanjersberg 2011(9); Zhuang 2013.(6)
Eskicioglu 2009(10)	Wind 2006(7)	Varadhan 2010(12); Rawlinson 2011(15); Zhuang 2013.(6)
Gouvas 2009(11)	Wind 2006(7)	Varadhan 2010(12); Adamina 2011(13); Rawlinson 2011(15); Spanjersberg 2011(9); Lv 2012(14); Zhuang 2013.(6)
Walter 2009(8)	Wind 2006(7)	Varadhan 2010(12); Spanjersberg 2011(9); Lv 2012(14); Zhuang 2013.(6)
Varadhan 2010(12)	Wind 2006(7); Eskicioglu 2009(10); Gouvas 2009(11); Walter 2009(8)	Rawlinson 2011(15); Spanjersberg 2011(9); Lv 2012(14); Zhuang 2013.(6)
Adamina 2011(13)	Wind 2006(7); Gouvas 2009(11)	Zhuang 2013.(6)
Rawlinson 2011(15)	Wind 2006(7); Eskicioglu 2009(10); Gouvas 2009(11); Varadhan 2010(12)	Not cited
Spanjersberg 2011(9)	Wind 2006(7); Gouvas 2009(11); Walter 2009(8); Varadhan 2010(12)	Lv 2012(14); Zhuang 2013.(6)
Lv 2012(14)	Gouvas 2009(11); Walter 2009(8); Varadhan 2010(12); Spanjersberg 2011(9)	Not cited
Zhuang 2013.(6)	Wind 2006(7); Eskicioglu 2009(10); Gouvas 2009(11); Walter 2009(8); Varadhan 2010(12); Adamina 2011(13); Spanjersberg 2011(9)	NA

NA, not applicable

Table 4: Summary of meta-analyses for length of stay

Review	Definition of primary length of stay	Meta-analysis model	Pooled effect estimate for primary length of stay	Pooled effect estimate for total length of stay
Wind 2006(7)	Days in hospital after surgery	Random	WMD -1.89 (-3.61 to -0.18) I^2 = 63.4%	Not calculated
Eskicioglu 2009(10)	Days in hospital after surgery	NA	Not calculated (authors stated pooling was not feasible)	
Gouvas 2009(11)	Days in hospital after surgery	Random	WMD -1.88 (-3.35 to -0.41) I^2 = 45%	WMD -1.73 (-3.50 to 0.04) I^2 = 0%
Walter 2009(8)	Days in hospital during index admission	Fixed	WMD -3.64 (-4.98 to -2.29) I^2 = 0%	WMD -3.75 (-5.11 to -2.40) I^2 = 0%
Varadhan 2010(12)	Not explicitly defined but appears to be days in hospital after surgery	Random	WMD -2.51 (-3.54 to -1.47) I^2 = 55%	Not calculated
Adamina 2011(13)	Length of stay outcome not explicitly defined	Bayesian	Mean difference for 'length of stay' -2.5 (95% CrI -3.92 to -1.11) I^2 not reported	
Rawlinson 2011(15)	Not defined	NA	Not calculated (authors cited findings from Gouvas and Varadhan)	
Spanjersberg 2011(9)	Not explicitly defined but appears to be days in hospital after surgery	Fixed	WMD -2.94 (-3.69 to -2.19) I^2 = 0%	Not calculated
Lv 2012(14)	Days in hospital during index admission	Random	WMD -1.88 (-2.91 to -0.86) I^2 = 75%	Not calculated
Zhuang 2013.(6)	Days in hospital after surgery	Random	WMD -2.44 (-3.06 to -1.83) I^2 = 88%	WMD -2.39 (-3.70 to -1.09) I^2 = 85%

NA, not applicable

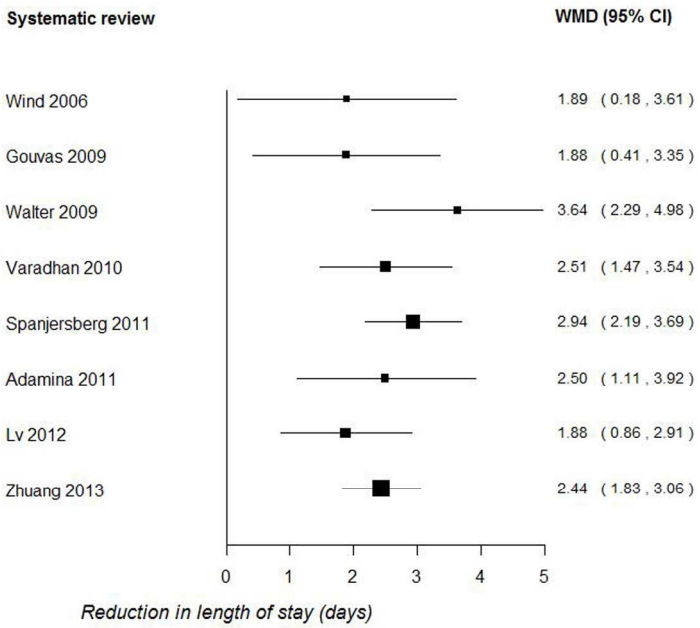
Figure 1: Summary of pooled results for primary length of stay

Appendix 1: Search strategy for systematic reviews

#1 ERAS:ti,ab
#2 ((enhanced or early or accelerated or fast track or fast-track or rapid) near/1 (recover* or rehabilitat* or convalesc* or mobil* or ambulat* or walk* or feed* or nutrition* or eat*) near/3 (surger* or program* or protocol* or pathway*)):ti,ab
#3 ((multimodal or optimised or optimized) near/1 (recover* or rehabilitat* or convalesc*)):ti,ab
#4 #1 or #2 or #3
#5 MeSH descriptor: [Receptors, Endothelin] explode all trees
#6 #4 not #5

Appendix 1: Search strategy for systematic reviews

#1 ERAS:ti,ab
#2 ((enhanced or early or accelerated or fast track or fast-track or rapid) near/1 (recover* or rehabilitat* or convalesc* or mobil* or ambulat* or walk* or feed* or nutrition* or eat*) near/3 (surger* or program* or protocol* or pathway*)):ti,ab
#3 ((multimodal or optimised or optimized) near/1 (recover* or rehabilitat* or convalesc*)):ti,ab
#4 #1 or #2 or #3
#5 MeSH descriptor: [Receptors, Endothelin] explode all trees
#6 #4 not #5



Summary of pooled results for primary length of stay
245x202mm (300 x 300 DPI)