**Development of a Model Care Pathway for Adults
 undergoing Colorectal Cancer Surgery: evidence-based key
 interventions and indicators**

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Keywords:	structured reviews, clinical guidelines
Abstract:	<p>Rationale, aims and objectives</p> <p>During the last decades, perioperative care for patients with colorectal cancer has shifted towards more standardized care, the so-called 'enhanced recovery after surgery' (ERAS). Those programs aim to optimize interventions in perioperative care in order to decrease the rate of postoperative complications, improve patients' recovery, and shorten hospital stay. The purpose of this literature review is to identify, summarize and operationalize the clinical content of both key interventions and clinical indicators in order to develop an evidence-based model pathway for surgical patients with colorectal cancer.</p> <p>Methods</p> <p>A systematic search in three databases was conducted to identify key interventions (KI) and indicators to measure the effect of implementation of the care pathway. The KI's from the ERAS protocol were listed and used as framework to identify and match the KI used in the included studies. The Clinical Pathway Compass was used to categorize the indicators.</p> <p>Results</p> <p>Fifteen studies were included. The number of KI used in the study</p>

	<p>protocols ranged from 9 – 20. In total, 33 KI’s were identified. Little information was available concerning the implementation of and compliance to the protocol. Length of stay (LOS) and complication rate are the most common used indicators (used in 15/15 and 14/15 of the studies), followed by 21 other measures. All but 1 of the included studies reported a reduction in LOS.</p> <p>Conclusion</p> <p>There is considerable variation in both the number of key interventions and indicators as well as the operationalization of key interventions, for surgical patients with colorectal cancer documented in literature. Therefore, we summarized the input from the different studies and developed an evidence-based model pathway, which can serve as basis for a local / regional care pathway team to build their own pathway.</p>

Descriptive title: Development of a Model Care Pathway for Adults undergoing Colorectal Cancer Surgery: evidence-based key interventions and indicators

Running title: Model Care Pathway for Colorectal Cancer Surgery

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Descriptive title: Development of a Model Care Pathway for Adults undergoing colorectal cancer surgery: evidence-based key interventions and indicators

Short title: Model Care Pathway for colorectal cancer surgery

Abstract

Rationale, aims and objectives

During the last decades, perioperative care for patients with colorectal cancer has shifted towards more standardized care, the so-called 'enhanced recovery after surgery' (ERAS). Those programs aim to optimize interventions in perioperative care in order to decrease the rate of postoperative complications, improve patients' recovery, and shorten hospital stay. The purpose of this literature review is to identify, summarize and operationalize the clinical content of both key interventions and clinical indicators in order to develop an evidence-based model pathway for surgical patients with colorectal cancer.

Methods

A systematic search in three databases was conducted to identify key interventions (KI) and indicators to measure the effect of implementation of the care pathway. The KI's from the ERAS protocol were listed and used as framework to identify and match the KI used in the included studies. The Clinical Pathway Compass was used to categorize the indicators.

Results

Fifteen studies were included. The number of KI used in the study protocols ranged

from 9 – 20. In total, 33 KI's were identified. Little information was available concerning the implementation of and compliance to the protocol. Length of stay (LOS) and complication rate are the most common used indicators (used in 15/15 and 14/15 of the studies), followed by 21 other measures. All but 1 of the included studies reported a reduction in LOS.

Conclusion

There is considerable variation in both the number of key interventions and indicators as well as the operationalization of key interventions, for surgical patients with colorectal cancer documented in literature. Therefore, we summarized the input from the different studies and developed an evidence-based model pathway, which can serve as basis for a local / regional care pathway team to build their own pathway.

Introduction

During the last decades, perioperative care for patients with colorectal cancer has shifted towards more standardized care, the so-called 'enhanced recovery after surgery' (ERAS) documented in the ERAS-society protocol (1). These programs aim to optimize interventions in the perioperative care in order to decrease the rate of postoperative complications, improve patients' recovery, and shorten length of stay (LOS) (2,3). Recent guidelines strongly recommend the use of the ERAS program (4). The key interventions (or 'care elements' in ERAS terminology) of structured care methodologies like ERAS protocol in colorectal surgery, are based on the best evidence available. They include patient education and preparation, preservation of gut function, minimization of pain and discomfort and promotion of patient autonomy

(1,5). The most common interventions in pre- and postoperative care are nutritional management, pain management, and early mobilization (5,6,7). Other interventions are fluid restriction, the use of thoracic epidurals, and preemptive analgesia (6,7). The ERAS protocol is defined as 'a multimodal pathway'. This means that the protocol consists of multiple interventions working interactively to achieve early recovery for patients with major surgery, including colorectal cancer surgery. The interventions in the protocol are divided in three distinct phases of the care process: preoperative, intraoperative, and postoperative care (1,6).

Despite growing evidence for the benefit of implementing such standardized programs, adherence remains difficult in daily practice (2,5,8,10). One method to successfully implement and follow-up structured care methodologies in daily practice, is the development and implementation of a clinical pathway, also known as care pathway. A systematic review, published in *Annals of Surgery* 2014 defines care pathways as one of the proven interventions to reduce adverse events in surgery (11). A recent meta-analysis by Song et al. on the effects of clinical pathways for patients with gastro-intestinal cancer, shows a reduction in expenditure and higher patient satisfaction, and a significant reduction in average length of stay (12).

The European Pathway Association uses 'care pathway' as terminology. Their definition of a care pathway is: "a complex intervention for the mutual decision making and organization of care processes for a well-defined group of patients during a well-defined period". The aim of a care pathway is to enhance the quality of care across the continuum by improving risk-adjusted patient outcomes, promoting patient safety, increasing patient satisfaction and optimizing the use of resources (13).

A complex intervention is defined as a health service intervention, built up from a number of components, which may act both independently and interdependently

(14). For the development and implementation of care pathways, these components are: 1) integration of a set of evidence based key interventions, 2) objective feedback on the current care process, and 3) systematic approach to change / improve current care process.

The purpose of this literature review is to identify, summarize and operationalize the clinical content of both key interventions and clinical indicators in order to develop an evidence-based model pathway for surgical patients with colorectal cancer (component 1 of the complex intervention). Therefore, evidence-based key interventions for a care pathway for surgical patients with colorectal cancer in pre-, intra-, and postoperative care (30 day follow-up) were listed and indicators measuring the effect of the care pathway were identified.

Methods

Literature Search

We conducted a systematic literature search in the three electronic databases (Medline, Embase and Cinahl) from 2006 (the end date of a previous systematic review on care pathways for patients with colorectal cancer surgery (5)) up to February 2014. The following terms were used: 'clinical pathway' combined with 'colorectal'; 'cancer', 'surgery', 'preoperative', 'perioperative', 'postoperative', 'fast track', 'enhanced recovery program'. All synonyms for these terms were included in the search. From this search, we included papers written in English, Dutch or German. In addition, the reference lists from published original and review articles were searched manually to identify other possible eligible studies.

Study Selection

Inclusion criteria were: 1) papers including adults undergoing elective colorectal surgery; 2) studies concerning the implementation and use of clinical/critical/care pathways in an inpatient setting; 3) retro- or prospective comparison with a control group (conventional/usual care); 4) studies reporting at least one of the following clinical relevant outcome measures: length of hospital stay, complication rates, re-admission rates or mortality; and 5) published in a peer-reviewed journal between January 2006 and February 2014, as the model pathway was used in a study which started in October 2014. Studies not meeting all 5 criteria were excluded.

Data extraction

Two independent reviewers read all abstracts and made a selection of eligible studies. In case of disagreement, consensus was obtained on the articles that could be included for full-text analysis. All full-text articles were read by one reviewer to decide whether the article fulfilled the inclusion criteria. In case of any doubt the second reviewer was consulted and consensus was reached. A specifically developed data extraction sheet was used to gather data on study source, study design, level of evidence, sample size, pre-, intra- and postoperative interventions, and the studies' different outcome parameters and results. The content of the clinical pathway was divided into preoperative, intraoperative, and postoperative key interventions in accordance with the ERAS-protocol (1,6). The ERAS protocol was used as framework for the data extraction of clinical content. We listed the 22 key interventions of the ERAS protocol and compared the key interventions used in the included studies with this list. Any additional interventions not listed in the ERAS protocol, were added to the list.

For the clinical indicators, we used the Leuven Clinical Pathway Compass as framework (15). This compass consists of five domains in which indicators can be subdivided: clinical (e.g. complication rate, mortality), financial (e.g. LOS), process (e.g. time between diagnosis and surgery), service (e.g. patient satisfaction), and team indicators (e.g. job satisfaction, team effectivity). The compass serves as a conceptual framework specifically developed to measure the effect of care pathways and to follow-up a patient population (15).

Statistical Analysis

Descriptive statistics were used to summarize our results. Categorical data were presented by their observed frequencies and percentages.

Results

Literature Search

One hundred eighty potentially relevant studies were retrieved from the search in the electronic databases, and 2 extra studies were found by manual search and cross referencing. Sixty one papers met all the mentioned inclusion criteria, of which, 3 were unavailable/irretrievable, 10 compared open vs laparoscopic technique, regardless of fast track and 7 were non-comparative studies. Papers commenting on other studies, sharing the same population or protocol/pathway, reporting the effect of one single intervention (e.g. early mobilization) were also excluded. Ultimately, 15 studies were included in the analysis (Figure 1).

<< figure 1 >>

The study methodologies were very heterogeneous: 4 papers were prospective comparative studies (16,17,18,19), 5 were RCT's (20,21,22,23,24), 3 were pre-posttest designs (3,25,26), and 3 were observational studies (8,9,27). Three were multicenter studies (8, 17,25).

We rated the studies according to the levels of evidence from the Oxford Centre of Evidence Based Medicine (28). See Annex 1 for the study characteristics.

Key interventions

Many studies named the interventions or protocols differently. The most common names were ERAS (Enhanced Recovery After Surgery), ERP (Enhanced Recovery Protocol) or 'Fast Track'. Moreover, the content of the protocols differed. The number of key interventions (or care elements) that are listed in the included studies range from 9 interventions (25) to 20 interventions (27). In comparison, the ERAS protocol contains 22 care elements. The reported interventions and their usage are summarized in Table 1. The description or operationalisation of the specific interventions differs between the studies. For example the key intervention "No prolonged fasting" is described as "Fluids up till 3h before surgery" (21), but also as "Clear fluids until 2h before initiation of anesthesia and 6h for solid food" (24). A more detailed overview of the different descriptions of the key interventions is provided in Annex 2.

We identified a number of interventions used in the included studies that are not included in the ERAS protocol. In total, 33 key interventions were listed, of which 11 were not included in the ERAS protocol.

<<table 1 >>

Clinical indicators

The indicators that were used in the included studies were identified and allocated to the domains of the Clinical Pathway Compass. Clinical and financial indicators are used in all 15 studies. Two of the studies used process indicators, two studies used a service indicator. Indicators in the team-domain were not used.

The most common used (outcome) indicators are LOS (15/15) and complication rate (14/15). Table 2 presents the individual indicators used to measure the effect of using ERAS/fast track, and the observed effect. All but 1 study report reduction in LOS. Other outcome indicators, e.g. complication rate, mortality, readmission rate, show no effect. In none of the studies a negative effect is reported. This implies that LOS can be reduced without compromising the quality of care.

<< table 2 >>

Discussion

Since the publication of the report “To Err is Human” in 2000 (Institute of Medicine - IOM), attention to quality of care is increasing (29) . In order to provide high quality care, overuse and particularly underuse of evidence based activities should be eliminated (30,31). Care pathways, also known as critical pathways or clinical pathways, are used worldwide as one of the tools to structure or design care processes around patients’ needs and, by doing so, to improve the quality of

delivered care (32). However, to the best of our knowledge, there is no evidence-based model (clinical) pathway available yet.

ERAS or fast track pathways are strongly suggested in current clinical guidelines (4). Nevertheless, most of the included studies incorporated only a limited number of key interventions from the original ERAS protocol. Even routine interventions, such as thromboprophylaxis and antibiotic prophylaxis, are only mentioned in 1 study protocol (27). ERAS is a multimodal pathway, suggesting that the different elements are applied together. Alcantara-Moral et al. found that the more interventions from the protocol are applied, the shorter the LOS, with similar morbidity and without any increase in readmissions or reinterventions (8). We believe that in this matter 'more is better'. An enhanced recovery protocol is a complex intervention, built up from a number of components, which may act both independently and interdependently (14). Not applying the suggested, evidence-based key interventions could mean that patients do not receive optimal care, and in fact are *undertreated*.

We advise caution in interpreting the effect of the key interventions. First of all, although we present an overview of the key interventions used in these pathways, we did not consider the evidence for the rationale behind each specific key intervention. Most of the ERAS care elements are used in studies that provide moderate evidence (level II + level III studies). Exceptions are Antibiotic prophylaxis and Thromboprophylaxis, and Maintenance of normothermia, which are used in lower level studies. From the 11 additional key interventions we identified, Type of incision and Laparoscopic access are also used in studies that provide moderate evidence. The other 9 interventions are used in studies that support weak evidence. However,

this does not mean that routine interventions, such as administering antibiotic prophylaxis, or weighing the patient, are to be excluded from the care pathway. There might be other evidence, based on guidelines and studies for these interventions (e.g. guidelines on antibiotic prophylaxis), or clinical expertise (e.g. monitoring body weight as important indicator) supporting the application of the interventions. We listed the interventions in our overview, including references and description, so that teams can consider the appropriateness of including this intervention in their local care pathway.

Secondly, the level of compliance to the protocols is unknown. Polle et al. evaluated compliance to the ERAS interventions and found that patients received on average 7.4 out of 13 key interventions (3). Alcantara-Moral et al. report a slightly higher compliance: 8.4 out of 13 interventions (8). This means it is difficult or even impossible to determine the level of implementation fidelity and spread, for both the complete protocols, and the individual key interventions. It is therefore impossible to conclude which intervention is contributing to what effect.

The indicators used in the included studies, suggest that there is primarily attention to clinical and financial outcomes. LOS is predominantly used, followed by complication rate. The other domains receive little (process and service) or no (team) attention. This is in line with a previous review by Lemmens et al. (33). The process domain should deserve more attention, especially 'compliance to protocol'. The service domain, with indicators e.g. patient satisfaction, patient experience, is an important domain to include in studies concerning a patient centered concept such as care pathways. The team domain is completely overlooked. We think this is an omission, because it is people that make care pathways work. Deneckere et al. showed that

teams working with care pathways have better team performance (teamwork, higher level of organized care, and lower burnout risk) than teams not working with pathways (34).

The indicators that are used in the included studies, show a wide variety in topics. It could be useful to develop an international set of common indicators, so that teams can compare their results internationally.

Strength and limitations

This review comes with its strengths and limitations. We made a strict selection of eligible studies, only peer-reviewed, comparative studies on care pathways were retained, which strengthens this review. On the other hand, there are two limitations. First of all, we only found positive results, which raises questions about publication bias. Second, the included studies use different methodologies, and some of the studies with a stronger design have a small population.

Conclusion

We have observed considerable variation in both the number of key interventions and indicators as well as the operationalization of the key interventions, for surgical patients with colorectal cancer documented in the literature. Therefore, we summarized the input from the different studies and developed an evidence-based model pathway, which can serve as a basis for a local / regional care pathway team to build their own pathway.

Next to the model pathway we present input for current and future indicator selection for monitoring and follow-up of surgical patients with colorectal cancer.

Compliance to care pathways or protocols can be difficult, but has to be strived for, in order to deliver the best possible care for patients. Different type of indicators, e.g. clinical (complication rate, time to first bowel movement, mobilization), financial (LOS), and process (compliance) should be monitored to gain insight in performance of the team.

<< Annex 1&2 >>

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Conflict of interest

Research made possible by an unconditional educational grant by Baxter SA. Baxter SA had no influence on the review.

Contributions

I.J. performed the literature search, I.J. and R.v.Z. selected the studies. R.v.Z. and E.C. summarized the studies and prepared the draft. K.V. and A.d.B.v.O. supervised the review and commented on the draft. M.P. and W.S. commented on the final draft.

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Figure Legends

Figure 1. Systematic review flow diagram

Table 1. Key interventions for patients undergoing colorectal cancer surgery

Legend: Gen=General;Pre=Preoperative;Intra=Intraoperative;Post=Postoperative

Table 2. Indicators per domain of Clinical Pathway Compass, and effect per indicator

Legend: Indicators used to evaluate the effect of clinical pathway/ERAS protocol.

Number of studies=number of included papers that describe the specific indicator.

Positive effect, No effect, Negative effect=proportion of papers that describe the specific indicator, that show improvement, no difference, or deterioration in outcome.

References by first author between brackets.

LOS=Length Of Stay;HDU=High Dependency Unit;ICU=Intensive Care Unit

*study reported improvement for laparoscopic group, and no difference for open group

Annex 1. Characteristics of included studies

Legend: D=days;KI=number of key interventions used in study;ns=not significant

Annex 2. Components Care Pathway for surgical patients with colorectal cancer

Legend: Day 0 = day of surgery, day 1 = 1st postoperative day, et cetera. Blue = add on to ERAS protocol

Table 1. Key interventions for patients undergoing colorectal cancer surgery

Phase	Intervention	Eras element	Used	Reference by first author
Gen	Dedicated ward	N	2/15	Christensen; Khoo
Gen	Dedicated team	N	2/15	Christensen; Feo
Gen	OR scheduling (Tu or Wed, 1 st on program)	N	1/15	Christensen
Pre	Fluid and carbohydrate loading	Y	10/15	Alcantara-Moral; Gouvas; Huibers; Ionescu; Khoo; King Polle; Ren; Wang (2012); Wang (2011)
Pre	No/selective bowel preparation	Y	9/15	Alcantara-Moral; Christensen; Huibers; Ionescu; Moronczyk; Ren; Schwarzbach; Wang (2012); Wang (2011)
Pre	Preadmissions counseling	Y	8/15	Christensen; Gouvas; Huibers; Ionescu; King Moronczyk; Polle; Wang (2011)
Pre	No prolonged fasting	Y	6/15	Gouvas; Huibers; Khoo; Polle; Wang (2012); Wang (2011)
Pre	No premedication	Y	4/15	Alcantara-Moral; Christensen; Polle; Wang (2011)
Pre	Antibiotic prophylaxis	Y	1/15	Huibers
Pre	Thromboprophylaxis	Y	1/15	Huibers
Intra	Mid-thoracic epidural anesthesia/analgesia	Y	12/15	Alcantara-Moral; Christensen; Gouvas; Huibers; Ionescu; Khoo; King; Polle; Ren; Schwarzbach; Wang (2012); Wang (2011)
Intra	Avoidance of salt and water overload	Y	8/15	Alcantara-Moral; Christensen; Gouvas; Khoo; King; Polle; Schwarzbach; Wang (2011)
Intra	Short acting anesthetic agents	Y	7/15	Christensen; Feo; Khoo; King; Polle; Wang (2012); Wang (2011)
Intra	No drains	Y	7/15	Alcantara-Moral; Khoo; Moronczyk; Polle; Ren; Wang (2012); Wang (2011)
Intra	Laparoscopic technique	N	5/15	Gouvas; Huibers; Lloyd; Polle; Wang (2012)
Intra	Maintenance of normothermia (bodywarmer/warm IV fluids)	Y	4/15	Alcantara-Moral; Gouvas; Huibers; Polle
Intra	Incision	N	4/15	Christensen; King; Polle; Wang (2011)
Intra	Wound infiltration	N	3/15	Moronczyk; Polle; Wang (2011)
Intra	Preemptive analgesia	N	2/15	Christensen; Huibers
Intra	Standard ASA monitors	N	1/15	Feo
Post	Early mobilization	Y	15/15	Alcantara-Moral; Christensen; Feo; Gouvas; Huibers; Ionescu; Khoo; King; Lloyd; Moronczyk; Polle; Ren; Schwarzbach; Wang (2012); Wang (2011)

Post	Early oral nutrition	Y	14/15	Alcantara-Moral; Christensen; Feo; Gouvas; Huibers; Ionescu; Khoo; King; Lloyd; Moronczyk; Polle; Ren; Schwarzbach; Wang (2011)
Post	Mid-thoracic epidural anesthesia/analgesia	Y	13/15	Alcantara-Moral; Christensen; Feo; Gouvas; Huibers; Ionescu; Khoo; King; Moronczyk; Polle; Schwarzbach; Wang (2012); Wang (2011)
Post	No nasogastric tubes	Y	13/15	Alcantara-Moral; Feo; Gouvas; Huibers; Ionescu; Khoo; King; Lloyd; Moronczyk; Polle; Ren; Schwarzbach; Wang (2011)
Post	Non-opioid oral analgesia/NSAIDs	Y	13/15	Alcantara-Moral; Christensen; Gouvas; Huibers; Ionescu; Khoo; King; Lloyd; Moronczyk; Polle; Ren; Schwarzbach;
Post	Audit of compliance and outcomes	Y	12/15	Feo; Gouvas; Huibers; Ionescu; King; Lloyd; Moronczyk; Polle; Ren; Schwarzbach; Wang (2012); Wang (2011)
Post	Early removal of catheter	Y	11/15	Christensen; Gouvas; Huibers; Ionescu; Khoo; King; Lloyd; Moronczyk; Schwarzbach; Wang (2012); Wang (2011)
Post	Prevention of nausea and vomiting	Y	10/15	Alcantara-Moral; Christensen; Huibers; Ionescu; Khoo; Lloyd; Polle; Ren; Wang (2012); Wang (2011)
Post	Avoidance of salt and water overload	Y	9/15	Christensen; Huibers; Khoo; Lloyd; Moronczyk; Polle; Ren; Schwarzbach; Wang (2011)
Post	Stimulation of gut motility	Y	6/15	Alcantara-Moral; Christensen; Huibers; Khoo; Ren; Schwarzbach
Post	Respiratory training	N	1/15	Schwarzbach
Post	Routine monitoring at Medium Care Unit	N	1/15	Schwarzbach
Post	Body weight	N	1/15	Christensen

Gen=General;Pre=Preoperative;Intra=Intraoperative;Post=Postoperative

Table 2. Indicators per domain of Clinical Pathway Compass, and effect per indicator

Indicators used to evaluate the effect of clinical pathway/ERAS protocol.

Number of studies=number of included papers that describe the specific indicator.

Positive effect, No effect, Negative effect=proportion of papers that describe the specific indicator, that show improvement, no difference, or deterioration in outcome.

References by first author between brackets.

Clinical domain	# of studies	Positive effect	No effect	Negative effect
Complication rate	14/15	7% (Gouvas)	93% (Alcantara-Moral; Christensen; Feo; Huibers; Ionescu; Khoo; King; Lloyd; Moronczyk; Polle; Ren; Schwarzbach; Wang (2012); Wang (2011))	
Readmission rate (<30d)	11/15		100% (Alcantara-Moral; Christensen; Gouvas; Huibers; Ionescu; King; Lloyd; Moronczyk; Polle; Schwarzbach; Wang (2011))	
Time to passage of stool	9/15	56% (Gouvas; Huibers; Ionescu; Khoo; Ren)	44% (Feo; Lloyd; Moronczyk; Schwarzbach)	
Time to solid diet	7/15	86% (Ionescu; Moronczyk; Schwarzbach; Wang (2012))	14% (Lloyd)	
Mortality	6/15		100% (Gouvas; Huibers; King; Moronczyk; Polle; Schwarzbach)	
Reoperations / reinterventions	6/15	17% (Moronczyk)	83% (Alcantara-Moral; Huibers; King; Polle; Schwarzbach)	
Time to passage of flatus	4/15	75% (Ren; Wang (2012); Wang (2011))	25% (Feo)	
Time to independent mobility	5/15	100% (Ionescu; Khoo; Schwarzbach; Wang (2012) Wang (2011))		
Postoperative pain	3/15	100% (Gouvas; Ionescu; Lloyd*)	33% (Lloyd*)	
Vomiting	3/15		100% (Feo; Ionescu; Moronczyk)	
Time to remove catheter	3/15	67% (Moronczyk; Wang (2012))	33% (Schwarzbach)	
Time to semi-liquid diet	2/15	100% (Ionescu; Wang (2012))		
Time to remove drain	1/15	100% (Moronczyk)		
Use of NG tubes	1/15		100% (Feo)	
Use of Central Venous Catheter	1/15		100% (Schwarzbach)	
Use of epidural	1/15	100% (Schwarzbach)		

catheter				
Use of drains	1/15	100% (Wang (2012))		
Nutrition and metabolism index	1/15	100% (Ren)		
Stress index	1/15	100% (Ren)		
Fincanial domain				
(Postoperative) length of stay	15/15	93% Alcantara-Moral; Christensen; Feo; Gouvas; Huibers; Ionescu; Khoo; King; Lloyd; Moronczyk; Polle; Ren; Wang (2012); Wang (2011)	7% (Schwarzbach)	
Cost	2/15	100% (King; Ren)		
LOS in HDU/ICU	1/15	100% (Ionescu)		
Process domain				
Compliance to protocol	2/15	100% (Alcatara-Moral; Polle)		
Service domain				
Quality of life	1/15		100% (King)	
Patient satisfaction	1/15		100% (Polle)	
Team domain				
-	-	-		

LOS=Length Of Stay;HDU=High Dependency Unit;ICU=Intensive Care Unit

*study reported improvement for laparoscopic group, and no difference for open group

Figure 1. Systematic review flow diagram

Annex 1. Characteristics of included studies

Author, year	Study type	Level of evidence	Population, Intervention (control)	Main outcome measures	Results	Nr KI
Alcantara-Moral, 2014	Observational, cross-sectional, multicenter	4	Coloncancer N= 190 (173)	LOS Morbidity Readmission rate	5.2 vs 6.2 d (p<0.05) 31.1 vs 24.3% (ns) 3 vs 5% (ns)	13
Christensen, 2011	Retrospective observational	4	Maligne, benigne, open elective colorectal resections N=131 (39)	LOS Complication rates Readmissions	3 vs 7 d (p<0.0001) No differences 15% vs 16% (ns)	19
Feo, 2009	Controlled trial	3	Colorectal resections, elective N=50 (50)	Complication rate Morbidity LOS	28 vs 26% (ns) 22 vs 32% (ns) 5 vs 7 d (p<0.001)	9
Gouvas, 2012	Multicenter, comparative, prospective	3	Open en lap. Sphincter preserving rectal resection N= 156 in 4 groups: Open Fasttrack (36), Lap Fasttrack (42), Open Usual care (45), Lap Usual care (33)	Mortality Major morbidity / complications Readmission LOS	Lap: 2.4 vs 0 (ns) 21.4 vs 51.5 (p=0.007) ns 4 vs 8 d (p<0.001) Open: 2.8 vs 0 (ns) 38.9 vs 55.6 (p=0.007) ns 7 vs 8 d (p=0.001)	14
Huibers, 2012	Retrospective comparative	4	Laparoscopic TME, Rectal cancer N=43 (33)	Postoperative LOS Complications Readmission (<30d) Mortality (<30d)	7 vs 10 d (p=0.04) ns 11.6 vs 18.2% (ns) 0 vs 0	20
Ionescu, 2009	Randomised Controlled Trial	2	Colorectal cancer, open N=48 (48)	PONV LOS in HDU/ICU LOS Readmissions Complications	34.7 vs 42.8% (p=0.538) 0.9 vs 1.8 d (p=0.001) 6.4 vs 9.2 d (p=0.001) No difference No difference	12
Khoo, 2007	Randomised Controlled Trial	3	Colorectal resections, elective N=35 (35)	Postop LOS	5 vs 7 d (p<0.001)	13
King, 2006	Prospective	3	Colorectal resections	Postop LOS	5.8 vs 10.7 d (p<0.001)	15

	comparative		N=60 (86)	Readmissions <30d Major complications Mortality <30d	12 vs 9% (ns) 18 vs 28% (ns) 3 vs 7% (ns)	
Lloyd, 2010	Interrupted Time Series	4	Open or laparoscopic colorectal resection Open: N=25 (22) Laparoscopic: N=55 (15)	Postop LOS Complication rate	Lap: 6 vs 9.5 d (p=0.01) Ns Open: 7.5 vs 12 d (p=0.04) ns	8
Moronczyk, 2011	Prospective comparative	4	Colon resection N=15 (18)	Complication rate Mortality Reoperation rate Re-hospitalization LOS	40 vs 22.2% (ns) 6.7 vs 22.2% (ns) 0 vs 11.1% 0 vs 0 8 vs 10.5 d (p<0.05)	12
Polle, 2007	Retrospectively controlled comparative	4	Elective colorectal resection N=55 (52)	Complication rate Reoperation rate LOS Readmission <30d Mortality <30d	27.3 vs 30.8% (ns) 12.7 vs 9.6% (ns) 4 vs 6 d (p= 0.002) 10.9 vs 5.8% (ns) 0 vs 0	19
Ren, 2012	Randomised Controlled Trial	2	Elective colorectal resection N= 299 (298)	Postop LOS Complications	5.7 vs 6.6 d (p<0.001) Ns	16
Schwarzbach, 2011	Interrupted Time Series	4	Colon resections N= 78 (133)	LOS Morbidity Mortality Readmission rate	9 vs 9 d (p=0.84) 28.2 vs 32.3% (p=0.53) 1.3 vs 2.2% (p=1) 2.6 vs 3.8 (p=1)	14
Wang, 2012	Randomised Controlled Trial	2	Lap. Colon resections N=49 (50)	Postop LOS Complication rate	4 vs 5 d (p<0.01) 12 vs 20% (ns)	13
Wang, 2011	Randomised Controlled Trial	2	Colorectal cancer N=104 (106)	Morbidity <30 days Postop LOS Readmission rate	14 vs 28 patients (p=0.016) 5 vs 7 d (p<0.01) 4 vs 9% (ns)	19

D=days;KI=number of key interventions used in study;ns=not significant

Annex 2. Components Care Pathway for surgical patients with colorectal cancer

Day 0 = day of surgery, day 1 = 1st postoperative day, et cetera. Blue = add on to ERAS protocol

General	
Dedicated ward	Patients admitted on 1 ward (Christensen; Khoo)
Dedicated team	Fast track team: surgeons, nurses, anesthetists (Christensen) and pain management, physical therapy, social work (Feo)
OR scheduling	Patients first on operating program and scheduled for surgery on Tuesdays or Wednesdays to avoid discharge on weekends (Christensen)
Pre-operative care	
Preadmission counseling	<p>ERAS: <i>patients should routinely receive dedicated preoperative counseling (Gustafsson)</i></p> <p>Information on the consecutive steps of postoperative care (Ionescu; Moronczyk; Wang (2011)) and expected length of stay (Christensen); Pre-operative assessment with written information (King); Written and oral information on Fast Track, informed consent (Huibers; Polle); Guided tour on surgical ward (Polle); Written and oral information, explanation epidural pump (Gouvas)</p>
Fluid and carbohydrate loading	<p>ERAS: <i>Preoperative oral carbohydrate treatment (400ml of 12.5% drink of mainly maltodextrins) should be used routinely (Gustafsson)</i></p> <p>Liquid protein/calorie supplement from admission, 3 drinks (Khoo; King); Last carbohydrate loaded drink 2h before surgery (Polle); 400ml nutritional supplements before midnight or 6h before surgery, 200ml 2h before surgery (Ren); 100g of glucose in 1000ml of water (glucose injection 10%) orally administered at 10pm on the evening before surgery, a further 50g of carbohydrate in 500ml of water given 3-4h before surgery (Wang (2012)); Oral nutrition with high-calorie carbohydrate drinks until 2h prior to surgery (Gouvas); 4 packages of carbohydrate drinks on day -1 (Wang (2011)); 2 packages of carbohydrate drinks 2h before surgery (Huibers; Wang (2011)); Carbohydrate fluids load 3h before surgery (Alcantara-Moral; Ionescu)</p>
No prolonged fasting	<p>ERAS: <i>Patients should be screened for nutritional status and, if deemed to be at risk of under-nutrition, given active nutritional support. Clear fluids should be allowed up to 2h and solids up to 6h prior to induction of anesthesia (Gustafsson)</i></p> <p>Fluids up to 3h before surgery (Khoo); Last meal 6h before surgery (Polle; Wang (2011)); Clear fluids until 2h before initiation of anesthesia and 6h for solid food (Wang (2012)); Oral nutrition with high-calorie carbohydrate drinks until 2h prior to surgery (Gouvas); Normal diet until midnight, fluid intake until 2h before surgery (Huibers)</p>

No / selective bowel preparation ERAS: <i>Mechanic Bowel Preparation should not be used routinely in colonic surgery (Gustafsson)</i> No bowel preparation (Alcantara-Moral; Christensen; Ionescu; Ren; Wang (2012); Wang (2011)); No mechanical preoperative bowel preparation (only a small enema allowed) (Moronczyk); Two enemas the evening before surgery (Huibers); Only in the cases of planned intraoperative colonoscopy (Schwarzbach)
Antibiotic prophylaxis ERAS: <i>Routine prophylaxis with intravenous antibiotics should be given 30–60 min before initiating colorectal surgery. Additional doses should be given during prolonged procedures according to the half-life of the drug used (Gustafsson)</i> Cefazoline (1000mg) and metronidazole (500mg) IV 30m before first incision, repeated after 3.5h (Huibers)
Thromboprophylaxis ERAS: <i>Patients should wear well-fitting compression stockings, have intermittent pneumatic compression, and receive pharmacological prophylaxis with LMWH. Extended prophylaxis for 28 days should be given to patients with colorectal cancer (Gustafsson)</i> 0.3ml fraxiparine from day -1 until discharge (Huibers)
No premedication ERAS: <i>Patients should not routinely receive long- or short-acting sedative medication before surgery because it delays immediate postoperative recovery. If necessary, short-acting intravenous drugs can be titrated carefully by the anesthetist to facilitate the safe administration of epidural or spinal analgesia because these do not significantly affect recovery (Gustafsson)</i> No premedication (Alcantara-Moral; Christensen; Polle; Wang (2011)); Lorazepam 1mg evening before surgery if necessary (Polle); Haloperidol (1.5 mg) intraoperatively (Huibers)

Intra-operative care
Pre-emptive analgesia Epidural pain relief by 0.5% ropivacaine Preoperatively (Christensen); 4x1000mg paracetamol from day -1 until discharge (Huibers)
Short acting anesthetic agents ERAS: <i>A standard anesthetic protocol allowing rapid awakening should be given (Gustafsson)</i> Propofol or remifentanil (Christensen); Propofol, 1,5-2,5mg/kg or 2-4 mg/kg thiopental or fentanyl 2-3µg/kg and vecuronium 0.1±0.02 mg/Kg (Feo); Propofol (King); Remifentanil 1µg/kg/min, Propofol 2-4mg/kg/h, Cisatracium 0.15mg/kg (Wang (2012); Wang (2011))
Midthoracic epidural anesthesia / analgesia ERAS: <i>Mid-thoracic epidural blocks using local anesthetics and low-dose opioids should be considered for open surgery. In laparoscopic surgery, spinal analgesia or morphine PCA is an alternative to epidural anesthesia. If intravenous opioids are to be used the dose should be titrated to minimize the risk of unwanted effects (Gustafsson)</i> Epidural catheter placed between T6 and T9 thoracic vertebrae for right-sided colonic resections, and between T8 and T11 thoracic vertebrae for left-sided resections, by 0.2% ropivacaine containing 50µg morphine per ml (Christensen); Between T10 and T12 (Feo; Ionescu); Between T8-T9, bupivacaine 0.5% <= 10ml, diamorphine 2.5mg in bupivacaine 0.25% at wound closure (King); Placement of thoracic epidural catheter (T6-T10, depending on the surgical

resection); test-dose (bupivacaine 0.25% with adrenaline 1:200,000), top-up dose (bupivacaine 0.25% (± 10 ml) with sufentanil 25 μ g, (Polle); Continuous epidural anesthesia combined with general endotracheal anesthesia (Ren); Placed between T6 and T12 (Wang (2012)); Placed between T10 and T12 (Wang (2011)) Test: lidocaine 2% 3ml with epinephrine, bupivacaine 0.5% (6+6)ml (Wang (2012); Wang (2011)); Placement of epidural catheter unless contraindicated (Alcantara-Moral; Gouvas); Between T9 and T11, levobupivacaine and sufentanil (15); Epidural catheter placement (Schwarzbach)

No drains

ERAS: Routine drainage is discouraged because it is an unsupported intervention that probably impairs mobilization (Gustafsson)

No drains (Alcantara-Moral; King; Moronczyk; Polle; Wang (2012); Wang (2011)); According to circumstances (Ren)

Avoidance of salt and water overload

ERAS: Balanced crystalloids should be preferred to 0.9 % saline. In open surgery, patients should receive intraoperative fluids (colloids and crystalloids) guided by flow measurements to optimize cardiac output. Flow measurement should also be considered if: the patient is at high risk with comorbidities; if blood loss is >7 ml/kg; or in prolonged procedures. Vasopressors should be considered for intra- and postoperative management of epidural-induced hypotension provided the patient is normovolaemic (Gustafsson)

Intraoperative fluids restricted to 1500ml unless bleeding in excess of 500ml (Khoo); 2000ml crystalloid intraoperatively (King); Restricted per-operative fluid infusion regime (Ringers lactate 20ml $\times$ kg $^{-1}$ in the 1st h followed by RL 6ml $\times$ kg $^{-1}$ $\times$ h $^{-1}$) (Polle); Restrictive protocol (4ml/kg/h) (Ren); Fluid restriction 10ml/kg/h; Limited intravenous administration of colloids (Gouvas); Restrictive fluid therapy (Alcantara-Moral); Goal of perioperative fluid management: achieve normovolemia (Schwarzbach)

Maintenance of normothermia

ERAS: Intraoperative maintenance of normothermia with a suitable warming device and warmed intravenous fluids should be used routinely to keep body temperature $>36^{\circ}\text{C}$. Temperature monitoring is essential to titrate warming devices and to avoid hyperpyrexia (Gustafsson)

Forced body heating (Bair hugger system/warmer coat and warmed IV fluids) (Polle; Ren); Active warming of patient (Alcantara-Moral; Gouvas); Using warm blankets (Huibers)

Incision

Right-sided horizontal incision was used for right colectomy and transverse resection, and a curved incision in the left iliac fossa was used for left hemicolectomy and sigmoid resection (Christensen); Transverse / curved incision for open surgery (King); Minimal invasive incisions (Polle); Minimal-access surgery or transverse curved incision used included right-sided hemicolectomy through a right horizontal incision above the umbilicus, sigmoid resection through a curved incision in the left iliac fossa (Wang (2011))

Laparoscopic technique

Based on clinical assessment of the most appropriate method (Lloyd); Laparoscopic in all patients (Huibers; Wang (2012)); Low anterior rectal resection through a mini-laparotomy in the subumbilicus which was extended toward the curvature if necessary (Wang (2012))

Wound infiltration

Infiltration of surgical wounds with bupivacaine (Moronczyk; Polle; Wang (2011))

Standard ASA monitors

EKG, blood pressure, pulse oximetry (Feo)

Post-operative care
<p>Mid-thoracic epidural anesthesia / analgesia</p> <p>ERAS: Thoracic Epidural Analgesia (TEA) using low-dose local anesthetic and opioids should be used in open surgery. For breakthrough pain, titration to minimize the dose of opioids may be used. In laparoscopic surgery, an alternative to TEA is a carefully administered spinal analgesia with a low-dose, long-acting opioid (Gustafsson)</p> <p>Epidural catheter placed between T6 and T9 thoracic vertebrae for right-sided colonic resections, and between T8 and T11 thoracic vertebrae for left-sided resections, by 0.2% ropivacaine containing 50 µg morphine per milliliter. Second postoperative day: removal of epidural catheter (Christensen)</p> <p>Between T10 and T12, 30 minutes before end of surgery bolus of ropivacaine 0.75% 10 ml, infusion of ropivacaine 2% 5-10 ml/h, for 48 hrs (Feo); Thoracic epidural, bupivacaine 0.167% and diamorphine, for 48 hrs (Khoo); Continuous epidural analgesia (2 days) 5 mg diamorphine in 60 ml bupivacaine 0.125% at 0–10 ml/h (King); Epidural (bupivacaine with fentanyl (Moronczyk); Continuous infusion (bupivacaine 0.125% with fentanyl 2.5 µg x ml⁻¹) until day 2 postoperatively (Polle); Continuous epidural anesthesia combined with general endotracheal anesthesia (Ren); Bupivacaine 0.125% with fentanyl 2.5µm⁻¹ (Wang (2012); Wang (2011)); Day 1 epidural analgesia with continuous infusion of local anesthetics (epidural-PCA) (Gouvas); Remove epidural catheter if pain score (VAS) < 4 (Huibers); Bupivacaine 0.125% + fentanyl 2 µg/ml via epidural catheter (Ionescu); Epidural catheter placement (Schwarzbach)</p>
<p>No nasogastric tubes</p> <p>ERAS: Postoperative nasogastric tubes should not be used routinely. Nasogastric tubes inserted during surgery should be removed before reversal of anesthesia (Gustafsson)</p> <p>No NG tube (Alcantara-Moral; Feo; Huibers; King; Moronczyk; Ren); Removal in recovery room (Khoo); remove before leaving Operating Theatre (Lloyd; Schwarzbach); Removal of NG tube before extubation (Gouvas; Polle); no NG tube unless severe PONV (Ionescu; Wang (2011))</p>
<p>Prevention of nausea and vomiting</p> <p>ERAS: A multimodal approach to PONV prophylaxis should be adopted in all patients with ≥2 risk factors undergoing major colorectal surgery. If PONV is present, treatment should be given using a multimodal approach (Gustafsson)</p> <p>Treatment of nausea (Christensen); regular Domperidone, magnesium hydroxide 8% (Khoo); Ondansetron (4 mg) (King; Polle; Wang (2012); Wang (2011)); Combination of dexamethasone and tropisetron (Ren); Dexamethasone (5mg) and ondansetrone (4mg) preoperatively (Huibers); Metoclopramide IV 10mg every 8h, ondansetrone only for severe PONV (Ionescu); Using prokinetics (Alcantara-Moral)</p>
<p>Avoidance of salt and water overload</p> <p>ERAS: The enteral route for fluid postoperatively should be used as early as possible, and intravenous fluids should be discontinued as soon as is practicable (Gustafsson)</p> <p>Free oral fluids immediately after the operation, discontinue IV fluids when patient is able to tolerate 200 ml of water over 30 minutes (Khoo); Day 0: 1 liter oral intake, 2 protein drinks, day 1: 4 protein drinks (Christensen); 1 high protein/high calorie drink on day 0, 3 high protein/high calorie drinks per day thereafter, Free fluids from day 0 (King; Lloyd); Oral fluid from day 0, limiting IV fluid in favor of oral (Moronczyk); First oral drinks at 2 h post-surgery + IV infusion of RL 1.5 liters x day⁻¹, day 1 oral intake >2l (including 4 units CHL drinks), stop IV fluid administration (leave cannula) (Polle; Wang (2011)); Restrictive protocol, 1500ml/day, 500 ml water starting at 6 h after surgery on day 0 and 500ml nutritional supplements and 1000ml water daily post-operatively (Ren); Day 0, oral fluid intake directly encouraged, IV fluid restricted to 1 liter per 24h (Huibers); High-calorie drinks a few hours after surgery</p>

(Gouvas); Goal of perioperative fluid management: achieve normovolemia, remove venous canula as soon as patient is able to drink (Schwarzbach)
<p>Early removal of catheter</p> <p>ERAS: Routine transurethral bladder drainage for 1–2 days is recommended. The bladder catheter can be removed regardless of the usage or duration of Thoracic Epidural Analgesia (Gustafsson)</p> <p>Day 1 (colon), day 3 (rectum) (Christensen; Feo; Khoo); Day 1 (laparoscopic), day 2 (open) (Lloyd); Early removal (Moronczyk); Suprapubic urine catheter, close and remove when residue <50ml (Polle); Use for the duration of thoracic epidural analgesia and early removal (Ren); Usually within 24h (Wang (2012); Ionescu; Wang (2011)); Removal if urine output >40 ml/h (Gouvas); Removal on day 2 (Huibers); Directly after operation (Schwarzbach)</p>
<p>Early oral nutrition</p> <p>ERAS: Patients should be encouraged to take normal food as soon as possible after surgery. Oral nutritional supplements can be used to supplement total intake (Gustafsson)</p> <p>From day 2: normal diet (Christensen); Liquid diet day 1, soft diet day 2 and regular diet as tolerated (Feo); Normal diet allowed immediately after surgery (Khoo); Normal diet offered and encouraged from day 1 (King); Day 1 light diet, day 2 regular diet (Lloyd); Introduction of diet on day 1 (Moronczyk); First semi-solid food intake in the evening, from day 1 offer solid food (Polle); Clear liquid diet after the first postoperative flatus (Ren); Day 1 solid diet (Gouvas); Day 0 liquid diet in the evening, day 1 restart normal diet at noon (Huibers); Day 0 fluids if tolerated, day 1 semi-solid food, day 2 solid food, regular diet (Ionescu); Day 1 semi-solid food, day 2 normal diet (Wang (2012)); Oral diet within 12h (Alcantara-Moral); Yoghurt on the evening day 0 and normal diet from day 1 (Schwarzbach)</p>
<p>Non-opioid oral analgesia / NSAIDs</p> <p>ERAS: In connection with TEA withdrawal, NSAIDs and Paracetamol should be used (Gustafsson)</p> <p>Paracetamol or NSAIDs, nicomorphine as rescue medication (Christensen); Paracetamol (1000mg) and ibuprofen (400mg) 4xd (Khoo); Paracetamol 1g 4 hourly from day 1, Ibuprofen 400mg 8 hourly +200mg PRN (max 1.2g/d) once epidural stopped, morphine as rescue medication (King); From day 1 tramadol and NSAID (Lloyd); Analgesia complemented with parenteral, and then oral NSAIDs, paracetamol or tramadol, opioid as needed (Moronczyk); paracetamol 4x 1 g x d⁻¹, from day 2 add NSAID (Polle); Patient-controlled analgesia and oral NSAIDs (Ren); Analgesia with NSAIDs or paracetamol intramuscularly (Gouvas); diclofenac 50mg 3xd from day 2 (Huibers; Wang (2011)); Ketorolac IV 60mg/8h the first 48h and orally after, and paracetamol 1g/8h orally (or intravenously if PONV) (Ionescu); No opioids (Alcantara-Moral); Additional standardized oral analgesic scheme: ibuprofen 400mg 2x day, metamizol 1g 3x day and, only if required, oxycodone/naloxone 10/5mg 2x day (Schwarzbach)</p>
<p>Early mobilization</p> <p>ERAS: Prolonged immobilization, increases the risk of pneumonia, insulin resistance, and muscle weakness. Patients should therefore be mobilized (Gustafsson)</p> <p>Day 0: out of bed for >2h, day 1: out of bed for >8h (Christensen, King); Resume physical activities day 1 (Feo; Khoo); 4 x 60m walks from day 1 (King); Mobilize bed-chair evening of surgery, walk 100m by the end of day 1, more than 100m the following day (Lloyd); Attempt at bedside rehabilitation at day 0, rehabilitation from day 1 (Moronczyk); Mobilization in the evening (>2h out of bed); day 1 expand mobilization (>6h out of bed), day 2 expand mobilization (>8h out of bed) (Polle; Wang (2011)); Out of bed for 2h on day 1 and 4–6h each day thereafter (Ren); Encourage patients to ambulate early (Wang (2012)); Mandatory 1h mobilization out of bed on day 0, 4h mobilization out of bed on day 1, fully mobilized on day 2 (Gouvas); Day 1 2–3h of mobilization, day 2 stimulate to fully mobilize (Huibers); Day 0 mobilized in bed (turning, sitting in bed), day 1 mobilized out of bed (Ionescu); Mobilization</p>

at 24h (Alcantara-Moral); Ambulation scheduled to start on the evening of day 0 (Schwarzbach)
Stimulation of gut motility <i>ERAS: Chewing gum can be recommended, whereas oral administration of magnesium and alvimopan (when using opioid based analgesia) can be included (Gustafsson)</i> Prokinetics (Alcantara-Moral; Christensen); Infusion of raw rhubarb 10g 5x day after surgery, injection of neostigmine 0.5 mg at each Zusanli acupoint daily after surgery (Ren); Start magnesium oxide on day 1 (Huibers); Postoperative bowel activity was stimulated by oral laxatives (magnesium oxide) and enemata if needed (Schwarzbach)
Audit of compliance and outcomes <i>ERAS: A systematic audit is essential to determine clinical outcome and measure compliance to establish successful implementation of the care protocol. The system should also report patient experience and functional recovery, but validated tools are required for this aspect (Gustafsson)</i> Evaluating discharge criteria; discharge if fulfilled (Feo; Gouvas; Huibers; Ionescu; Khoo; Lloyd; Moronczyk; Polle; Ren; Schwarzbach; Wang (2012); Wang (2011))
Routine monitoring at Medium Care Unit Routine postoperative monitoring of patients at the intermediate care unit was done when deemed necessary by the surgeon and/or anesthesiologist (Schwarzbach)
Respiratory training Every patient was instructed to perform respiratory training with an incentive spirometer (Schwarzbach)
Body weight At discharge (Christensen)