RECOvER checklist

	Item	Recommendation	Page
Title			
Title	1	Implementation of the ERAS protocol for colorectal cancer surgery within a regional hospital network supported by an audit and feedback approach. The ERAS Piemonte - colorectal study. A stepped wedge cluster randomised trial	1
Introduction			
Background	2	The Enhanced Recovery After Surgery (ERAS) protocol is a multimodal perioperative care pathway that aims to achieve early recovery after surgery by preserving preoperative organ function and reducing physical stress responses caused by injury. Despite the numerous publications supporting the potential improvements in colorectal cancer surgery, the ERAS protocol still poses a challenge to traditional surgical doctrine. The ERAS Protocol Implementation in Piemonte Region for Colorectal Cancer Surgery (ERAS Colon-Rectum Piemonte) was conducted to promote systematic adoption of ERAS throughout the entire regional hospital network. The aim of the study was to assess the true impact of the protocol on a large, unselected population undergoing elective surgery for colorectal cancer using a stepped-wedge cluster randomised design, supported by an A&F intervention.	2
Guidelines	3	Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations: 2018. World Journal of Surgery [Internet]. 2018 Nov 13;43(3):659–95. Available from: https://link.springer.com/article/10.1007/s00268-018-4844-y. Braga M , Scatizzi M, Borghi F, Missana G, Radrizzani D, Gemma M, Perioperative Italian Society. Identification of core items in the enhanced recovery pathway. Clin Nutr ESPEN2018 Jun;25:139-144.	Ref
Outcomes	4	The primary outcome was length of stay (LOS), which was calculated after excluding outliers, i.e. patients whose LOS exceeded the 94th percentile of the distribution. Secondary outcomes were incidence of postoperative complications defined according to the Clavien-Dindo classification,15 admission to the intensive care unit, transfusions and reinterventions during the postoperative hospital stay. Other clinical outcomes assessed within 30 days of discharge were any readmission to the emergency department (ED), readmission to hospital and reintervention.	4
Methods			
IRB approval	5	The study protocol was approved by the Ethics Committee of the promoting centre, Hospital of Cuneo (N.8-18 of 06/06/2018) and subsequently by all participating units. In addition, all participants gave informed consent before participating in the study.	10
Study design	6	Multi-center stepped wedge cluster randomised trial.	2

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Setting	7	This paper outlines the results of the ERAS-colorectal Piemonte study, conducted to adopt the ERAS protocol for colorectal surgery in Piedmont (a region of Northwest of Italy with 4.2 million population), through a structured A&F strategy and a stepped wedge cluster randomised controlled trial (SW-CRT). Inpatient units of general surgery represented the study clusters, progressively adopting the ERAS protocol by groups of units.	2
Timing	8	During the first 3-months of the study (baseline period), all the units were asked to continue their usual care. Thereafter, in each quarter, a group of clusters started the adoption of the ERAS protocol. At the end of the study, each cluster contributed both to control and experimental periods. The total duration of the study was increased from 15 to 21 months (from September 2019 to May 2021) to counterbalance the reduced hospital activity during the COVID-19 pandemic.	3
Participants	9	All consecutive colorectal cancer patients who were scheduled for elective surgery between 1 September 2019 and 31 May 2021 and who met the inclusion criteria were informed about the study at the preoperative visit. Only patients admitted via the emergency department who required urgent surgical intervention and patients with very high complexity or clinical severity (e.g. patients with ASA score V) were excluded. All participants provided written informed consent for data use.	3
Enhanced recovery protocol	10	During the first 3 months of the study period (baseline), standard treatment was continued in all groups. Thereafter, a first group of clusters started adopting the ERAS protocol, while all others maintained the standard treatment. This process continued until all groups had started the intervention. At the end of the study, each cluster had a period in which standard care was maintained ("control period") and a period in which the protocol was applied ("experimental period"), with a cross-over-like design but with a single transition (from control to experimental).	3
	11	See Supplementary: Table S1 lists ERAS protocol items for colorectal cancer surgery and the continuum of care detailing the enhanced recovery protocol including the following elements from (a) to (p).	Supp
		(a) Preadmission patient education regarding the protocol	
		(b) Preadmission screening and optimization as indicated for nutritional deficiency, frailty, anaemia, HbA1c, tobacco cessation, and ethanol use	
		(c) Fasting and carbohydrate loading guidelines	
		(d) Preemptive analgesia (dose, route, timing)	
		(e) Antiemetic prophylaxis (dose, route, timing)	
		(f) Intraoperative fluid management strategy	

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		(g) Types, doses, and routes of anaesthetics administered	
		(h) Patient warming strategy	
		(i) Management of postoperative fluids	
		(j) Postoperative analgesia and anti-emetic plans	
		(k) Plan for opioid minimization	
		(l) Drain and line management	
		(m) Early mobilisation strategy	
		(n) Postoperative diet and bowel regimen management	
		(o) Criteria for discharge	
		(p) Tracking of post-discharge outcomes	
Enhanced recovery auditing	12	Data were locally collected by the ERAS teams and the Case Report Forms (CRF) periodically sent to the coordinating centre that checked and entered the data into a database (https://new.epiclin.it/it/eras_isterectomia/). Compliance with ERAS items during the two study periods was measured as the mean percentage of compliance with a list of indicators (see Table S1, together with the rationale and calculation methods). Mean compliance was calculated overall and for groups of items differentiated by phase of care (preoperative, intraoperative and postoperative).	3
Outcomes	13	(a) The primary outcome was length of stay (LOS), which was calculated after excluding outliers, i.e., patients whose LOS exceeded the 94th percentile of the distribution. As the protocol ERAS identifies key elements to consider patients fit for discharge, but discharge could be delayed due to organisational issues, this information was collected and LOS at fit for discharge (LOS-FFD) was analysed as a secondary outcome. To account for outliers in the LOS and LOS-FFD distribution, the percentage of admissions with LOS and LOS-FFD outliers was included as a secondary outcome. Secondary outcomes were incidence of postoperative complications defined according to the Clavien-Dindo classification, admission to the intensive care unit, transfusions and reinterventions during the postoperative hospital stay. Other clinical outcomes assessed within 30 days of discharge were any readmission to the emergency department (ED), readmission to hospital and reintervention. Postoperative complications were analysed as presence of at least one complication, total and major complications (Clavien-Dindo III-IV) or death. Postoperative quality of recovery was measured with the validated Italian version of the QoR-15 questionnaire,16-17 which was presented approximately 48 hours after surgery. The QoR-15 is an instrument based on 15 items with a scale of 0-10 and a visual analogue scale for well-being (VAS), where 0 indicates the worst health status and 10 the best. Other secondary	4

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		outcomes were patient satisfaction, health care costs and professional satisfaction, which were not analysed in this article.	
		(b) Clinical and quality of life outcomes	
PROs	14	Stark PA, Myles PS, Burke JA. Development and Psychometric Evaluation of a Postoperative Quality of Recovery Score. Anesthesiology. 2013 Jun;118(6):1332–40. Rosato R, Palazzo V, Borghi F, Camanni M, Puppo A, Elena Maria Delpiano, et al. Factor structure of post-operative quality of recovery questionnaire (QoR-15): An Italian adaptation and validation. 2022 Jan 1;13:1096579–9.	Ref
Results			
Patient population	15	See Figure 1	
		(a) See Table 1	
		(b)Variable: CCI index (missing data for n. 2 participants) Variable: BMI (missing data for n. 3 participants) Variable: ASA score (missing data for n. 3 participants) Variable: Presence of stomia (missing data for n. 4 participants)	Table 1
Enhanced recovery compliance	16	See Supplementary Figure S5: Adjusted difference in compliance to ERAS items between each quarter since ERAS implementation and the baseline period (September-November 2019)	
Correlations	17	See Table 2: Effect of ERAS implementation on study outcomes (linear regression as primary outcome is LOS).	
Discussion			
Context	18	In this large, pragmatic, stepped-wedge cluster randomised trial of patients treated surgically for colorectal cancer, implementation of the ERAS protocol supported by an A&F intervention across the network of regional hospitals in Piemonte reduced mean LOS by 0.6 days during the experimental period compared with the control period. The most original features of our study, which to our knowledge is the largest ERAS randomised trial to date, are the cluster randomisation design and its pragmatic approach, with the implementation of the programme within the entire regional hospital network, with a high level of engagement and involvement of most eligible patients. Participating centres also included those usually excluded from research projects and unlikely to adopt the ERAS and A&F approach on their own.	8
Limitations	19	As the ERAS protocol circulated within the regional hospital network as part of the ERAS Colon-rectum Piemonte study protocol, group contamination cannot be excluded. The groups waiting to implement ERAS may have anticipated	8

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		some changes during the standard period, reducing the potential difference between the two periods in terms of adherence to ERAS items and impact on clinical outcomes. In addition, the suboptimal level of compliance achieved during the ERAS period (67%), at least in part attributable to the COVID-19 pandemic, may have compromised the ability to achieve relevant effects on secondary outcomes. Because the study was conducted in a Region with a public health system, the results may have limited generalizability to other countries with different health systems. A final issue is the recognition that it is difficult to monitor detailed quality of care measures after the study is completed using only currently available data.	
Other information			
Funding	20	This work was supported by the Italian Ministry of Health and the Regione Piemonte as part of the Easy-Net Project, grant number NET-2016-02364191.	10