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Implementation of an enhanced recovery after surgery protocol for colorectal cancer in a regional hospital network supported by audit and feedback: a stepped wedge, cluster randomised trial

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ABSTRACT

Background Enhanced recovery after surgery (ERAS) protocols are known to potentially improve the management and outcomes of patients undergoing colorectal surgery, with limited evidence of their implementation in hospital networks and in a large population. We aimed to assess the impact of the implementation of an ERAS protocol in colorectal cancer surgery in the entire region of Piemonte, Italy, supported by an audit and feedback (A&F) intervention.

Methods A large, stepped wedge, cluster randomised trial enrolled patients scheduled for elective surgery at 29 general surgery units (clusters). At baseline (first 3 months), standard care was continued in all units. Thereafter, four groups of clusters began to adopt the ERAS protocol successively. By the end of the study, each cluster had a period in which standard care was maintained (control) and a period in which the protocol was applied (experimental). ERAS implementation was supported by initial training and A&F initiatives. The primary endpoint was length of stay (LOS) without outliers (>94th percentile), and the secondary endpoints were outliers for LOS, postoperative medical and surgical complications, quality of recovery and compliance with ERAS items.

Results Of 2626 randomised patients, 2397 were included in the LOS analysis (1060 in the control period and 1337 in the experimental period). The mean LOS without outliers was 8.5 days during the control period (SD 3.9) and 7.5 (SD 3.5) during the experimental one. The adjusted difference between the two periods was a reduction of −0.58 days (95% CI −1.07, −0.09; p=0.021). The compliance with ERAS items increased from 52.4% to 67.3% (estimated absolute difference +13%; 95% CI 11.4%, 14.7%). No difference in the occurrence of complications was evidenced (OR 1.22; 95% CI 0.89, 1.68).

Conclusion Implementation of the ERAS protocol for colorectal cancer, supported by A&F approach, led to a substantial improvement in compliance and a reduction in LOS, without meaningful effects on complications.

Trial registration number NCT04037787.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Enhanced recovery after surgery (ERAS) protocols are expected to improve the management and outcomes of colorectal surgery patients, but the effectiveness of their implementation, supported by an audit and feedback (A&F) strategy, in a large regional hospital network remains unproven.

⇒ A&F strategies were proven to be effective in improving quality of care and are considered a key component of the ERAS protocols.

INTRODUCTION

Enhanced recovery after surgery (ERAS) protocols are multimodal perioperative care pathways developed for several surgical procedures to achieve early recovery after surgery by preserving preoperative organ function and reducing physical stress responses. The key elements of the ERAS protocols include preoperative counselling and nutritional

WHAT THIS STUDY ADDS

⇒ A regional implementation of the ERAS protocol in elective colorectal cancer surgery with the support of an A&F strategy markedly increased the compliance with most items and slightly reduced the length of stay, without meaningful effects on complications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The A&F approach can be employed as an effective strategy to engage clinicians and centres and may overcome resistance to the cultural and organisational changes required by the ERAS implementation.

assessment, avoidance of preoperative fasting and bowel preparation, standardised opioid-sparing analgesic and anaesthetic regimens, and early refeeding and mobilisation. Such multimodal stress-minimising approach has been shown to reduce the rates of morbidity, improve recovery and shorten length of stay (LOS) after major colorectal surgery.[1] Despite the strong background theory and the available evidence supporting the potential improvements in colorectal cancer surgery,[1–4] the ERAS protocols still pose a challenge to traditional surgical doctrine.

After the fourth updated version of the ERAS protocol in colorectal cancer,[1] only three selected hospitals, particularly open to change, have adopted this approach in routine care in Piemonte, an Italian region of around 4.2 million inhabitants.[5] The Piemonte region has a large network of medium-small public-funded hospitals treating colorectal cancer, referring to the Piemonte e Valle d'Aosta Cancer Network (http://www.reteoncologica.it/). Initiatives to improve the quality of cancer care within the network were mainly based on the adaptation and implementation of regional clinical guidelines (https://next.cpo.it/it/publications) and their monitoring with administrative data.[6] The slow, spontaneous diffusion of the ERAS protocol within the hospital network has had a limited impact on the overall quality of perioperative care at the regional level and may have increased heterogeneity between centres and inequalities between patients. In addition to the usual barriers to implementing new organisational models, the limited evidence from properly designed randomised trials[2 7 8] and the lack of structured local audit and feedback (A&F) strategies may have limited the dissemination of the ERAS protocol.[9]

The ERAS Protocol Implementation in Piemonte Region for Colorectal Cancer Surgery (ERAS Colon-Rectum Piemonte study)[10] was conducted to promote a systematic adoption of the protocol throughout the entire regional hospital network, with the goal of enhancing quality of care through an equitable and pragmatic approach. The study, registered with ClinicalTrials.gov (NCT04037787), is part of a larger project that evaluates the effectiveness of A&F interventions in different settings and health services (EASY-NET), a network project funded by the Italian Ministry of Health and the participating regions.

The aim of this study was to assess the impact of introducing an ERAS protocol, supported by an A&F intervention,[11] on LOS and other clinical outcomes in a large population undergoing elective surgery for colorectal cancer, using a stepped wedge, cluster randomised trial (SW-RCT) design[12] and involving the entire hospital regional network.

METHODS

The article was written according to the Consolidated Standards of Reporting Trials (CONSORT) statement for SW-CRT[13–15] and the Reporting on ERAS Compliance, Outcomes and Elements Research (RECOvER) checklist[16] (online supplemental annex). The study protocol has been previously published.[10]

Design and participants

The ERAS Colon-Rectum Piemonte study is a pragmatic SW-RCT conducted among patients with colorectal cancer at 29 general surgery departments located in public hospitals in the Piemonte region.

Given all the available evidence on the ERAS protocol, with a favourable balance of benefits and risks (for both patients and staff), the SW-CRT was considered an appropriate design to allow sufficient time for training all the regional hospital teams, to send them periodic feedback while the study was ongoing and to achieve roll-out of ERAS across the entire hospital network at the end of the trial.[12]

All regional general surgery units that performed at least 30 elective surgical procedures for colorectal cancer in 2018 were invited to participate. The surgical units formed the study clusters, which sequentially adopted the ERAS protocol, by group of units.

All consecutive patients with colorectal cancer scheduled for elective surgery between 1 September 2019 and 31 May 2021 were included, with very few exclusions (eg, emergency admissions and patients with an American Society of Anesthesiologists (ASA) score of 5). All participants provided written informed consent and data were collected by the hospital staff on paper case report forms.

The recruitment period, originally set at 15 months, was later extended to 21 months to compensate for the negative impact of the COVID-19 pandemic on hospital activity. The third step was completed in August 2021 instead of May 2021 to allow for more time to organise the web-based training (previously scheduled in person) and to ask centres to start implementing ERAS during a remission of the COVID-19 pandemic in September 2021. The last step was extended due to concerns that the COVID-19 pandemic would be a

barrier to the centres' ability to change clinical practice and improve quality of care.

During the first 3 months of the study (baseline), standard treatment was continued in all groups. Thereafter, the four groups started adopting the ERAS protocol every 3 months, until all groups had a 'control' period of standard treatment and an 'experimental' period of application of the ERAS protocol, as described in online supplemental figure S1.

Randomisation

Surgical units were stratified by volume of colorectal procedures performed in 2018 and then randomly divided into four groups with a similar number of procedures. The randomisation procedure was carried out by the clinical epidemiology unit after the surgical units had been anonymised. The allocation was concealed to centres until 2 months before the start of the experimental period to allow sufficient lead time to train the local ERAS team and organise the trial activities.

Due to the nature of the intervention, it was not possible to blind participants, carers and researchers to group allocation.

Procedure

Each centre identified an 'ERAS team', including at least a surgeon, an anaesthetist, a nurse and a dietitian, to support local implementation of the protocol and to serve as a reference for data collection. These local teams received a 1-day interactive course on the principles of ERAS as well as organisational aspects and practical experience. All four editions of the training were delivered by a team of experts with consolidated experience in teaching and working with the ERAS protocol, with the last two editions delivered online due to COVID-19 restrictions.

The ERAS protocol to be implemented at the regional level was adapted from the ERAS Society guidelines for colorectal surgery.[1 17] The ERAS items are described in online supplemental table S1, together with related indicators and discharge criteria.

A newsletter was sent to all local ERAS teams every 2 months to maintain commitment and motivation for the overall project and to share information on the progress of the study. To monitor the completeness of study enrolment at each centre, a graph was constantly updated on the study website comparing the number of patients actually enrolled with the expected number in the same calendar period of the previous year. According to the A&F intervention, once the experimental period had started, the hospital teams were given access to a feedback section of the study website to assess their progress in implementing the protocol, so that critical issues could be immediately identified and corrective actions addressed. The feedback indicators were also discussed with each group of centres in meetings, mostly online, a few months after the introduction of ERAS, together with the experts previously involved in the training and the study coordination/data management team.

Details on the intervention are reported in the Template for Intervention Description and Replication checklist[18] in the online supplemental materials.

Outcomes

The primary endpoint was LOS, which was calculated after excluding outliers (LOS >94th percentile).

The secondary endpoints were the percentages of LOS outliers; of postoperative complications, defined according to the Clavien-Dindo classification[19]; and of admissions 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 the presence of at least one complication, total and major complications (Clavien-Dindo III–IV) or death. All the outcomes before discharge were collected with the case report form. Outcomes at 30 days after discharge were collected from regional administrative data.

The quality of postoperative recovery was measured with the validated Italian version of the Quality of Recovery-15 (QoR-15) questionnaire,[20 21] filled in by patients 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 (VAS) for well-being, where 0 indicates the worst health status and 10 the best. Other secondary outcomes, including patients' and professionals' interviews, and an analysis of healthcare costs will be presented in another article.

Difference in compliance with ERAS items between the two study periods was measured overall, by phase of care and by single items.

Statistical analysis

Considering available literature and local data, the study was planned with a statistical power of 0.98 and with an alpha error of 0.05 (two-sided) to detect a reduction of 1 day of mean LOS without outliers (from 9.0 to 8.0, SD=3.7). Details on the sample size calculation were extensively reported in the study protocol publication[10] and are summarised in the online supplemental materials.

Compliance with ERAS

Compliance with ERAS items during the two study periods was measured as the mean percentage of adherence with a list of indicators (online supplemental table S1), overall and for groups of items classified by phase of care (preoperative, intraoperative and postoperative). Multilevel linear models were used to estimate the difference in average compliance levels between the two study periods, overall and by

phase of care, adjusting for patient characteristics and time period, and considering surgical units as random effects. Patient covariates included in the models were sex, age, Charlson Comorbidity Index (0 or 1), body mass index (BMI) class (<18.5, 18.5–24.9, 25–29.9, ≥30) and ASA score (1–2 or 3–4). The same set of covariates was used for adjusting Poisson models used to estimate the difference in compliance between the two study periods for each individual ERAS indicator (dichotomous).

Primary endpoint

LOS without outliers was described as median, mean and SD. The difference between the two study periods was estimated using a multilevel linear model adjusted for patient characteristics and time period and accounting for surgical units as random effects. In addition to the covariates included in the analysis of compliance, the cancer site (colon, rectum), the creation of a stoma and the type of surgical access, classified as open or minimally invasive (laparoscopic or robot-assisted), were also included.

Secondary endpoints

The percentages of outliers for LOS, postoperative complications (total, surgical and medical), incidence of transfusions, access to ICU after surgery, 30-day mortality after surgery, and ED admissions, readmissions and reinterventions were all analysed as dichotomous variables using random-effects logistic regression models, with the same set of covariates included in the model for the LOS analysis, except for BMI, cancer site and ASA score.

For the QoR assessment, only questionnaires with all 15 items completed within 1–4 days after surgery were included. The mean total scores and the mean scores for the physical and psychological subscales were reported. The effect of ERAS on the QoR scales and well-being VAS was estimated using multilevel linear models, with centres serving as random effects and adjusting for the same set of covariates used for the other secondary outcomes.

Subgroup and sensitivity analyses

For the primary endpoint, planned subgroup analyses were conducted by patient characteristics (sex, age, education, tumour location, Charlson Comorbidity Index, ASA score, surgical approach) and by centre characteristics (level of compliance with the ERAS protocol during the control period, increase in compliance with the ERAS protocol after its adoption, completeness of enrolment, volume of interventions). Enrolment completeness was assessed using the regional hospital discharge record database. To assess the achievement curve, we also analysed the change in LOS according to the time (in quarters) elapsed since the introduction of ERAS.

To account for the learning phase in each centre, the impact of the intervention on LOS was also analysed excluding the first month of each implementation period of the ERAS protocol.

Subgroup analyses were also conducted for compliance, using the same analytical approach as for LOS, to identify facilitators and barriers to the intervention. Finally, the association between the level of compliance with the ERAS protocol (10% increase) and the clinical outcomes was analysed, overall and by study period. To control for a possible reverse-causation effect between compliance with the protocol (especially for postoperative items) and patient-level outcomes, LOS was analysed with centre mean compliance with the protocol as a fixed effect.

Statistical analyses were performed using SAS V.9.4.

RESULTS

Of the 36 public general surgery facilities treating patients with colorectal cancer in the Piemonte region in 2018, 3 were excluded because they had already implemented the ERAS protocol, 3 because they had a low case load and 1 declined to participate. Six centres had a case load slightly below 30 cases in 2018, but they asked to be included in light of an expected increase in activity during the study period. The final number of participating centres was therefore 29.

As described in the flow chart of the study (figure 1), 2626 patients were included (a more detailed flow chart can be found in online supplemental figure S2).

The personal and clinical characteristics of the participants are shown in table 1. Overall, the mean age was 72 years (SD 10.9), 43% were women, about 70% of cases had colon cancer and 50% had a Charlson Comorbidity Index ≥1. No evident unbalances were observed between the two study periods.

Table 2 shows the impact of the implementation of ERAS on the outcomes of the study.

Primary endpoint

The mean LOS without outliers (defined as LOS >20 days, corresponding to the 94th percentile of the LOS distribution) was 8.5 days during the control period (SD 3.9) and 7.5 (3.5) during the experimental period, with a raw reduction of 1 day (table 2). After excluding six patients with missing data on the covariates, the estimated adjusted difference between the two periods was a reduction of −0.58 days (95% CI −1.07, −0.09; p=0.021).

The planned subgroup analyses, depicted in figure 2, revealed only moderate differences in LOS reduction by patients' and centres' characteristics. A tendency towards larger effects on LOS reduction was observed in centres that had a lower compliance with ERAS at baseline (−0.78 days; 95% CI −1.31, −0.26; p value for interaction=0.056) and in centres with ≥80% completeness of enrolment (−0.68 days; 95% CI −1.18, −0.18; p value for interaction=0.058).

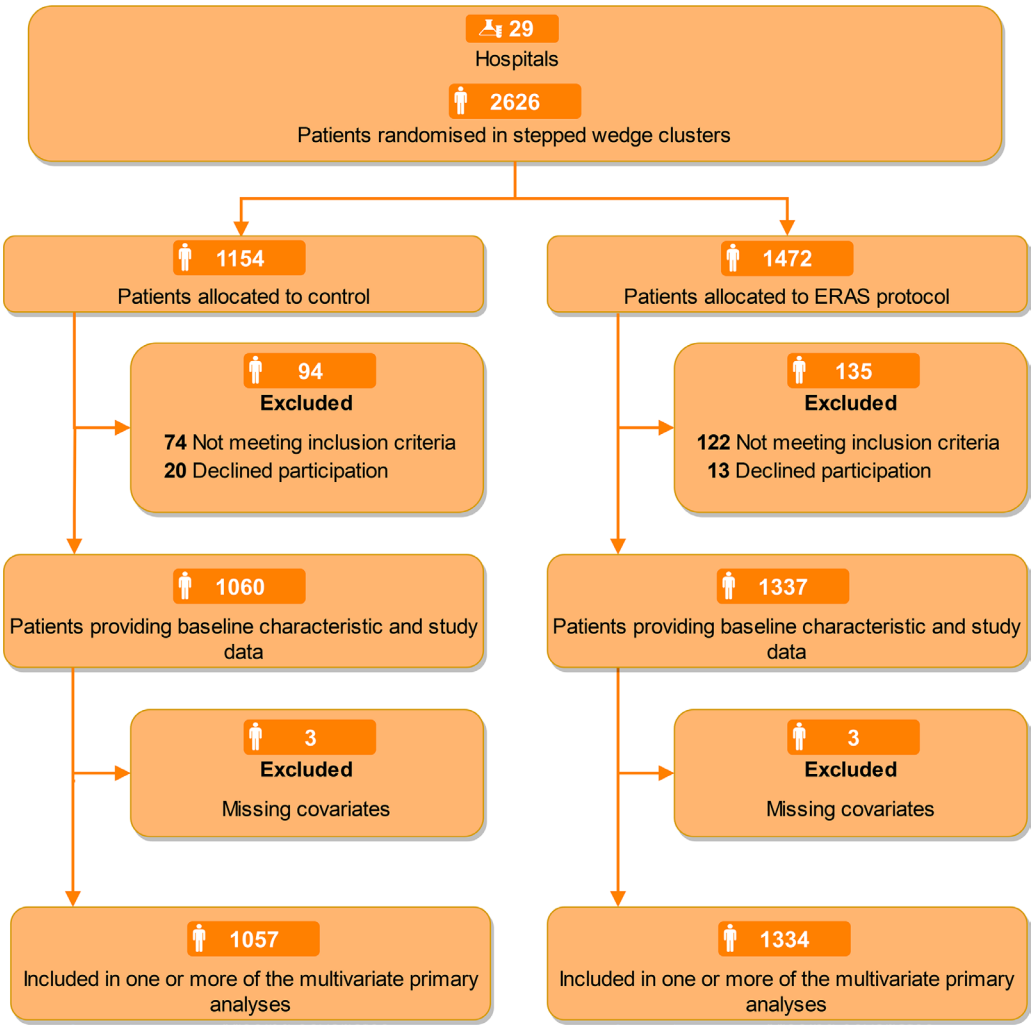

Figure 1 ERAS Colon-Rectum Piemonte study flow. ERAS, enhanced recovery after surgery.

For minimally invasive surgery, where the initial LOS was already at the target level of 8 days, the adoption of ERAS had a smaller impact on LOS (−0.49 days; 95% CI −1.00, 0.02), while for open surgery, with an initial LOS of 10 days, the reduction was more pronounced (−1.03 days; 95% CI −1.83, −0.22; p value for interaction=0.162).

Online supplemental figure S3 describes the change in LOS according to time elapsed since the introduction of ERAS (in quarters), showing a stable effect over time.

After excluding data collected in the first month of the roll-out period of the ERAS protocol, the results did not change (LOS reduction −0.61; 95% CI −1.15, −0.07).

Secondary endpoints

No differences were observed in the frequency of outliers in LOS, complications, need for transfusion, access to intensive care in the postoperative period and in-hospital mortality (table 2).

The incidence of postoperative complications is described in online supplemental table S2 by study period. The occurrence of complications did not differ either overall (OR 1.22; 95% CI 0.89, 1.68; p=0.211) or by type (surgical, medical) or severity (Clavien-Dindo I–II, III–IV).

Outcomes at 30 days after discharge did not differ between the two study periods.

Patients included in the QoR (1762, 73.5%) and VAS (1850, 77.2%) analyses are described in online supplemental figure S4. The mean QoR score was 7.12 and 7.46 in the control and ERAS periods, with a small improvement of 0.24 points (95% CI 0.01, 0.47; p=0.039). This improvement was mainly due to a difference in the physical scale. There was also a small improvement between the two study periods in the VAS score for general well-being (0.31; 95% CI 0.05, 0.57; p=0.021).

Compliance with ERAS protocol

Overall, the level of compliance with the ERAS protocol changed from 52.4% during the control period to 67.3% during the experimental period, with an adjusted absolute difference of +13% (95% CI 11.4%, 14.7%; p=0.0001) (table 3A). Compliance

Table 1 Personal and clinical characteristics of the participants

	Control period (n=1060)		ERAS period (n=1337)		Total (N=2397)	
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**
Sex						
Male	603	56.9	762	57.0	1365	56.9
Female	457	43.1	575	43.0	1032	43.1
Age classes						
<70	414	39.1	504	37.7	918	38.3
70–79	317	29.9	431	32.2	748	31.2
≥80	329	31.0	402	30.1	731	30.5
Education						
Low	303	28.6	386	28.9	689	28.7
Medium	369	34.8	440	32.9	809	33.8
High	282	26.6	407	30.4	689	28.7
Missing	106	10.0	104	7.8	210	8.8
Marital status						
Not married	301	28.4	387	28.9	688	28.7
Married	712	67.2	884	66.1	1596	66.6
Missing	47	4.4	66	4.9	113	4.7
Charlson Comorbidity Index						
0	526	49.6	671	50.2	1197	49.9
≥1	533	50.3	665	49.7	1198	50.0
Missing	1	0.1	1	0.1	2	0.1
ASA class						
1–2	607	57.3	740	55.3	1347	56.2
3–4	452	42.6	595	44.5	1047	43.7
Missing	1	0.1	2	0.1	3	0.1
BMI class						
<18.5	40	3.8	36	2.7	76	3.2
18.5–24.9	509	48.0	542	40.5	1051	43.8
25–29.9	365	34.4	534	39.9	899	37.5
≥30	144	13.6	224	16.8	368	15.4
Missing	2	0.2	1	0.1	3	0.1
Cancer location						
Colon	743	70.1	949	71.0	1692	70.6
Rectum	317	29.9	388	29.0	705	29.4
Neoadjuvant therapy						
Not executed	906	85.5	1103	82.5	2009	83.8
Executed	153	14.4	233	17.4	386	16.1
Missing	1	0.1	1	0.1	2	0.1
Type of procedure						
Right colectomy	420	39.6	510	38.1	930	38.8
Left colectomy	182	17.2	254	19.0	436	18.2
Transverse colectomy	38	3.6	73	5.5	111	4.6
Partial mesorectal excision	104	9.8	91	6.8	195	8.1
Total mesorectal excision	175	16.5	242	18.1	417	17.4
Miles' resection	52	4.9	65	4.9	117	4.9
Others	89	8.4	99	7.4	188	7.8
Missing	–	–	3	0.2	3	0.1
Stoma						
Absent	806	76.0	1010	75.5	1816	75.8
Present	251	23.7	326	24.4	577	24.1
Missing	3	0.3	1	0.1	4	0.2
Type of surgery						
Laparotomy	741	69.9	906	67.8	1647	68.7

Continued

Table 1 Continued

Characteristics	Control period (n=1060)		ERAS period (n=1337)		Total (N=2397)	
	n	%	n	%	n	%
Laparoscopy	222	20.9	237	17.7	459	19.1
Robotic	96	9.1	193	14.4	289	12.1
Missing	1	0.1	1	0.1	2	0.1

ASA, American Society of Anesthesiologists; BMI, body mass index; ERAS, enhanced recovery after surgery.

was lowest for postoperative items (35.4% and 52.5% in the control and experimental periods). The largest absolute difference between the two periods was recorded for preoperative items (+18.2%; 95% CI 16.5%, 20.0%; p=0.0001). Intraoperative items also appeared to be frequently used during the control period (67.8%) and showed a small increase in compliance (+5.4%; 95% CI 2.4%, 8.3%; p<0.001). Table 3B shows the adjusted implementation effect (risk ratio) on compliance for each individual ERAS indicator, grouped by phase of care. Online supplemental figure S5 describes the change in compliance according to the time elapsed since the introduction of ERAS (in quarters). Compared with the baseline period, the increase in compliance was larger in the first two quarters after starting the experimental period (around 11%) but remained stable afterwards (around 8.5% in all the following quarters). The results of the subgroup analyses are shown in online supplemental figure S6. Patients' characteristics did not impact the change in ERAS compliance, but low compliance with the ERAS items prior to initiation of the study, high completeness of patient inclusion in the study and high volume of surgical activity were relevant facilitating factors.

Online supplemental table S3 shows the impact of compliance with ERAS items overall and stratified by study period on study outcomes. A 10% increase in overall compliance was associated with a reduction in LOS (−0.65 days; 95% CI −0.76, −0.54) and in most clinical outcomes, with a stronger effect during the ERAS period, when an integrated implementation of all items was supported by the A&F approach. After adjustment for mean centre-level compliance,

Table 2 Effect of ERAS implementation on study outcomes

Study outcomes	Control period (n=1060)		ERAS period (n=1337)		Effect measure		
Primary endpoint	**n**	**Mean (median; SD)**	**n**	**Mean (median; SD)**	**Mean difference**	**95% CI**	**P value**
LOS	979	8.55 (7; 3.87)	1264	7.5 (7; 3.49)	−0.58	−1.07, −0.09	0.021
Secondary endpoints	**n/total**	**%**	**n/total**	**%**	**OR**	**95% CI**	**P value**
LOS outliers	81/1060	7.64	73/1337	5.46	1.02	0.58, 1.80	0.944
Complications							
Total	285/1058	26.9	364/1336	27.2	1.22	0.88, 1.68	0.218
Medical	148/1058	14.0	182/1336	13.6	1.20	0.79, 1.84	0.380
Only minor medical	125/1058	11.8	133/1336	10.0	0.94	0.59, 1.49	0.770
Major medical	22/1058	2.1	44/1336	3.3	2.13	0.98, 4.62	0.055
Surgical	194/1058	18.3	257/1336	19.2	1.32	0.94, 1.85	0.109
Only minor surgical	112/1058	10.6	151/1336	11.3	1.43	0.94, 2.19	0.093
Major surgical	84/1058	7.9	108/1336	8.1	1.12	0.68, 1.85	0.636
Transfusions	107/1058	10.1	120/1336	9.0	0.71	0.45, 1.12	0.136
ICU access	144/1058	13.6	191/1336	14.3	0.97	0.61, 1.54	0.906
Inpatient mortality	16/1060	1.51	21/1337	1.57	1.63	0.61, 4.38	0.316
30-day ED admissions	61/1044	5.84	76/1316	5.78	1.51	0.88, 2.60	0.131
30-day hospital readmissions	98/1044	9.39	105/1316	7.98	1.16	0.74, 1.81	0.511
30-day reinterventions	78/1044	7.47	95/1316	7.22	1.47	0.89, 2.44	0.131
	n	**Mean (median; SD)**	**n**	**Mean (median; SD)**	**Mean difference**	**95% CI**	**P value**
Mean QoR score	760	7.12 (7.2; 1.52)	1002	7.46 (7.6; 1.37)	0.24	0.01, 0.47	0.039
Mean QoR score - physical scale	760	7.14 (7.3; 1.64)	1002	7.56 (7.80; 1.50)	0.33	0.08, 0.57	0.011
Mean QoR score - mental scale	760	7.08 (7.60; 2.00)	1002	7.26 (7.80; 1.97)	0.08	−0.24, 0.40	0.622
Well-being Visual Analogue Scale score	813	6.72 (7; 1.72)	1037	7.14 (7; 1.6)	0.31	0.05, 0.57	0.021

ED, emergency department; ERAS, enhanced recovery after surgery; ICU, intensive care unit; LOS, length of stay; QoR, Quality of Recovery.

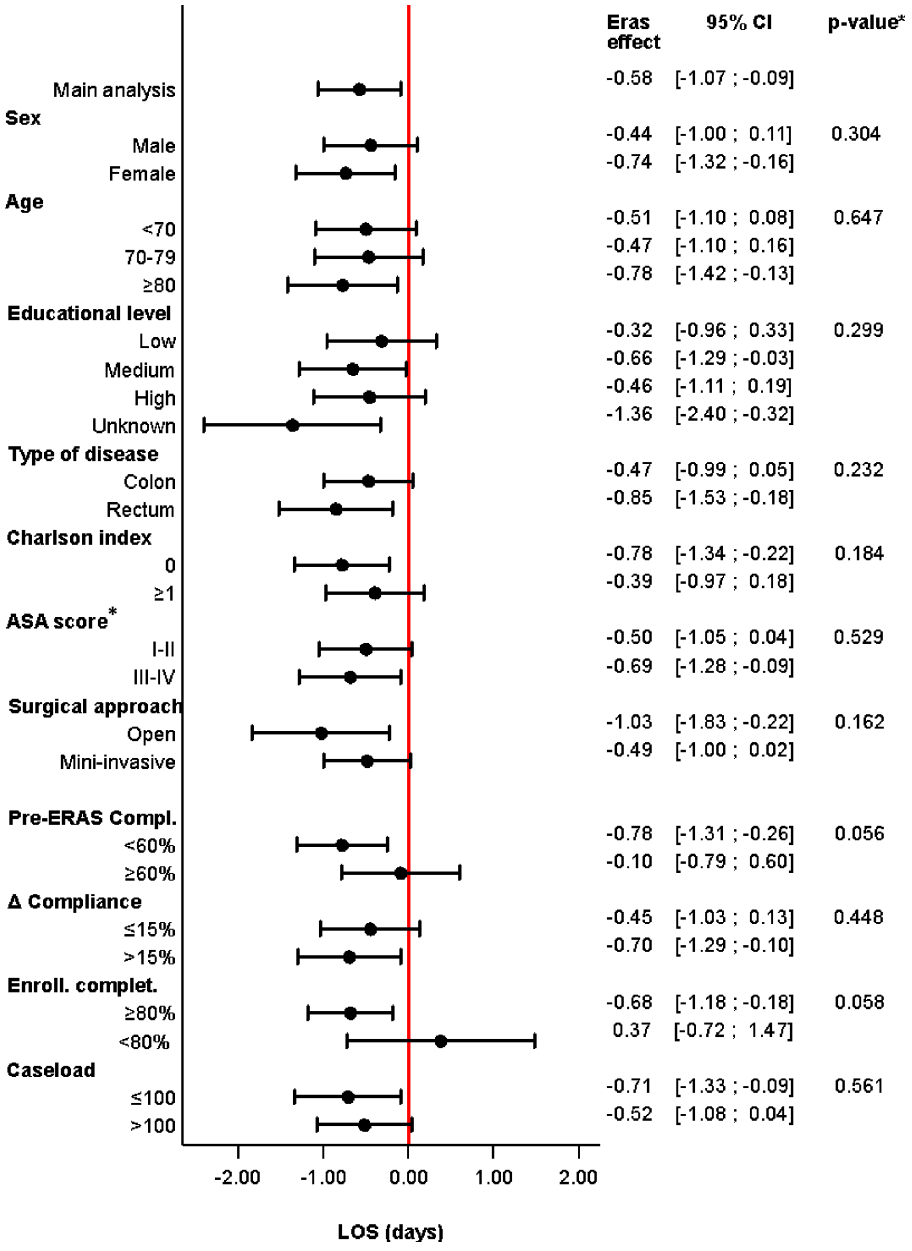

Figure 2 Estimated difference in LOS (primary outcome) between the two study periods and related subgroups analyses: patients' and structure characteristics. ASA, American Society of Anesthesiologists; ERAS, enhanced recovery after surgery; LOS, length of stay.

*** Interaction p value.**

the estimated LOS reduction was −0.30 days (95% CI −0.50, −0.10) (data not shown).

DISCUSSION

Key findings

In this large, pragmatic SW-RCT of patients surgically treated for colorectal cancer, implementation of the ERAS protocol supported by an A&F intervention across the network of regional hospitals in Piemonte reduced the mean LOS by 0.6 days during the experimental period compared with the control period. The subgroup analyses showed greater improvements in hospitals where the opportunity to improve compliance with the ERAS protocol was greater. The application of the ERAS programme did not lead to any meaningful impact on postoperative complications, either during hospitalisation or 30 days after discharge.

The A&F initiative supporting ERAS implementation determined a relevant change in clinical practice, with an absolute increase in compliance with the ERAS protocol of around 13%, an impact much larger than the average effect (median 4.3% improvement) estimated by a previous systematic review.[22]

Comparison with existing literature

The decrease in LOS observed in our study is consistent with, but smaller than, that estimated by a

Table 3 Compliance with ERAS items in the two study periods and the adjusted effect: (A) difference in compliance (%) overall and by phase of care and (B) risk ratio on compliance for each single ERAS indicator

(A) Overall and by phase of care	Control period (%)	ERAS period (%)	Delta % compliance	95% CI	P value
All items	52.4	67.3	13.04	11.42, 14.66	<0.0001
Preoperative items	61.2	80.5	18.21	16.46, 19.96	<0.0001
Intraoperative items	67.8	70.7	5.35	2.38, 8.31	0.001
Postoperative items and follow-up	35.4	52.5	12.18	9.49, 14.87	<0.0001
(B) Single indicators	**Control period (%)**	**ERAS period (%)**	**Risk ratio**	**95% CI**	**P value**
Preoperative items					
Anaesthesiological visit time	32.4	29.4	0.84	0.60, 1.19	0.332
Preadmission counselling	32.7	85.6	2.89	1.43, 5.83	0.003
Nutritional risk assessment	41.0	91.0	2.30	1.32, 4.01	0.003
Anaemia correction	41.0	43.6	0.94	0.62, 1.41	0.757
No bowel preparation - colon	88.8	90.2	1.03	0.90, 1.17	0.707
No premedication	96.9	97.1	0.98	0.93, 1.04	0.532
Thromboembolism prophylaxis	90.9	95.4	1.11	0.94, 1.30	0.219
Antibiotics prophylaxis	80.6	76.5	0.98	0.85, 1.12	0.763
No prolonged fasting	74.6	89.2	1.23	0.89, 1.71	0.209
Carbohydrate loading	30.2	87.1	2.89	1.45, 5.75	0.003
Intraoperative items					
Mini-invasive surgery	69.3	72.9	1.04	0.89, 1.22	0.629
No surgical drainage - colon	42.8	49.4	1.25	0.91, 1.72	0.176
Epidural anaesthesia in laparotomy	42.8	44.3	1.08	0.71, 1.65	0.702
Prevention of hypothermia	72.8	72.3	0.94	0.72, 1.23	0.677
Fluid normovolaemia intraoperatively	55.1	60.2	1.02	0.74, 1.42	0.882
Postoperative nausea and vomiting prevention	90.2	91.8	0.97	0.89, 1.06	0.544
Postoperative items					
Fluid normovolaemia postoperatively	58.0	77.3	1.38	0.92, 2.07	0.121
Early removal of intravenous therapy	21.2	39.5	1.91	0.85, 4.30	0.116
Early rehydration	22.5	41.9	1.90	0.84, 4.28	0.122
Early refeeding	21.5	42.8	2.11	0.99, 4.50	0.054
No nasogastric tubes	59.6	75.5	1.44	1.00, 2.08	0.053
Early removal of urinary catheter	43.1	55.3	1.34	1.05, 1.71	0.020
Early mobilisation - day 1 media	14.1	22.5	2.43	1.44, 4.12	0.001
Minimised opioid use	55.1	75.9	1.42	1.00, 2.02	0.051
Early follow-up	26.8	47.3	2.12	1.38, 3.25	0.001

ERAS, enhanced recovery after surgery.

meta-analysis of randomised controlled trials for elective colorectal surgery, reporting a mean LOS of 5.8 and 8 days in the ERAS and control groups, respectively.[2] Similar effects on LOS were reported by meta-analyses of randomised trials including colorectal surgery and other types of interventions.[3 4] A reduction in median LOS associated with the adoption of the ERAS programme in colorectal cancer surgery was also reported by cohort studies conducted within hospital networks,[23 24] despite a reduced impact when the results were adjusted for the background time trend reduction of LOS.[25] Analyses of data from the international multicentre ERAS registry for elective colorectal cancer resection reported a median overall LOS of 6 days (IQR 4–8).[26]

The absence of a meaningful impact of our study on postoperative complications is in contrast to previous experiences,[2–4] but in line with some recent systematic reviews of randomised controlled trials assessing specific ERAS items, as prehabilitation[27] and early mobilisation interventions.[28]

According to a Cochrane systematic review of the efficacy of A&F[22] in modifying healthcare behaviours, the global change in compliance observed in the present study can be considered a relevant result. Specific comparisons with previous experiences of ERAS implementation are not easy because it is not clear whether and how explicit A&F interventions were adopted.[9] Consistent with the findings of Nelson *et al*,[29] the greatest increase in compliance was for preoperative items (+18.2%), which included practices not commonly found outside ERAS, such as counselling, nutritional risk assessment and introduction of a carbohydrate load.

Interpretation

Although the adjusted effect on LOS in our study (−0.6 days) was smaller than planned in the study protocol (−1 day, from 9 to 8), it should be noted that the mean LOS in the baseline period of the study was already reduced to 8.5 days, which left little room for further improvement. The reduction in LOS from 2018 to the end of 2019 may be partly the result of a long-term trend and partly an indirect effect of the centres' involvement in writing the study protocol.

The decrease in LOS was achieved in the first period of implementation of the ERAS protocol, that is, up to 6 months, and thereafter LOS remained stable. This result seems to contradict the notion of a learning curve.[30 31] However, a major influence on this result is probably the COVID-19 pandemic, which affected the organisation of the hospital and the implementation of the study. In the fourth quarter of the implementation of ERAS, corresponding to the peak of the pandemic in the Piemonte region (March–May and October–December 2020), no decrease in LOS was observed compared with baseline, likely due to organisational stress for COVID-19 management.

In general, the COVID-19 pandemic had a strong impact on the study's ability to change clinical practice and improve the quality of care. As reported by the healthcare staff in the feedback meetings, it affected the full implementation of the ERAS protocol and weakened the adoption of the A&F approach in several ways. ERAS implementation requires close collaboration between different health professionals,[1] with nurses and anaesthetists playing a key role, both of whom were heavily involved in pandemic management. In addition, ERAS benefits from strong patient[32 33] and caregiver[34] involvement, which was drastically reduced by social distancing measures. Similarly, A&F requires discussion of results in meetings with all stakeholders, but due to the pandemic, only one meeting was held per group of centres, and for two groups only via web conference. To limit the negative impact of COVID-19, the study duration was extended by three additional months in both the third and fifth steps. As this extension affected the middle and last period of the study, the variation in the final study sample size and the imbalance between the two groups were negligible.

Strengths and weaknesses

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, the implementation of the programme within the entire regional hospital network, and the 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. The research framework allowed a full adoption of ERAS across the entire regional network, reducing heterogeneity in patient care and consequently inequalities.

The subgroup analyses on compliance with ERAS items found that some centre characteristics resulted as facilitating factors. Other factors perceived as facilitators of such positive results were the substantial methodological and organisational support, the leading role of referral centres experienced in delivering ERAS and the presence of the PeriOperative Italian Society offering specific expertise. In addition, the intervention has benefited from the presence of a regional oncology network and the strong commitment of the regional healthcare authority.

Our study differs from most previous studies, mainly monocentric and with small sample sizes, in which individual patients were randomised within the same ward, with a high risk of bias. This is because implementing the ERAS protocol requires cultural and organisational changes that cannot be achieved with an 'on/off' intervention at the patient level. In addition, the stepped wedge design allowed us to account for time trend effects, a bias that typically occurs in studies comparing outcomes between pre-implementation and postimplementation periods.[25 29]

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 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. 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.

In our opinion, the A&F approach was useful in engaging clinicians and centres and in overcoming resistance to the cultural and organisational changes required by the ERAS implementation, but a formal analysis of the data collected by surveying local ERAS teams was not included in the present paper.

Because the study was conducted in a region with a public health system, the results may have limited generalisability 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.

CONCLUSIONS

A regional implementation programme supported by an A&F approach led to a successful adoption of the ERAS protocol for colorectal cancer surgery across an entire hospital network, with significant improvement in compliance and reduction in LOS. However, the overall suboptimal compliance achieved after the

introduction of the ERAS protocol may have precluded a significant impact on clinical outcomes and represents an area for further quality improvement. The A&F approach has been a useful and effective strategy for engaging clinicians and centres and overcoming resistance to cultural and organisational change required to implement the ERAS protocol for colorectal cancer surgery in the entire regional hospital network.

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Competing interests None declared.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Anonymised data can be made available upon reasonable request, with appropriate human research ethics approvals and data transfer agreements in place.

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Consort check list

		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	1
Introduction			
Background and objectives	#2a	Scientific background and explanation of rationale	2
Background and objectives	#2b	Specific objectives or hypothesis	2
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	2
Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	3
Participants	#4a	Eligibility criteria for participants	3
Participants	#4b	Settings and locations where the data were collected	3
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Refer to TIDieR checklist
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	4
Sample size	#7a	How sample size was determined.	4 and supplementary material
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	na
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	4
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)	4
Randomization - Allocation	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers),	4

concealment mechanism		describing any steps taken to conceal the sequence until interventions were assigned	
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	4
Blinding	#11b	If relevant, description of the similarity of interventions	4
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	4
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	5
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	5
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	Figure 1
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	3 and figure S1
Recruitment	#14b	Why the trial ended or was stopped	na
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6 and figure 1
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	7,8
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 2
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8 and Figure 3
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	na

Discussion			
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	7
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	7
Registration	#23	Registration number and name of trial registry	2
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	8
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	8
Registration	#23	Registration number and name of trial registry	2
Protocol	#24	Where the full trial protocol can be accessed, if available	Here: https://bmjopen.bmj.com/content/11/6/e047491
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	10

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

	Item	Recommendation	Page
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	

	Item	Recommendation	Page
		(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

	Item	Recommendation	Page
		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

	Item	Recommendation	Page
		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

Supplementary Contents

Implementation of an enhanced recovery after surgery protocol for colorectal cancer in a regional hospital network supported by audit and feedback: a stepped wedge cluster randomised trial.

Summary

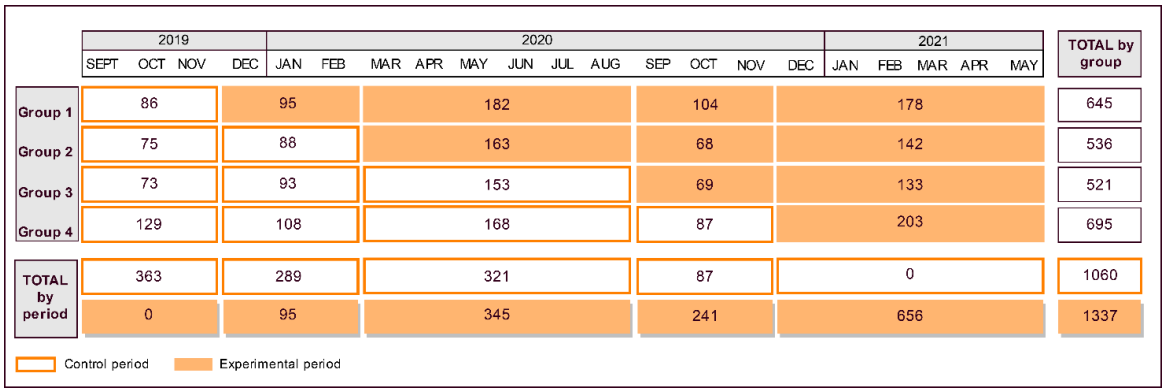
Pagano E, *et al. BMJ Qual Saf* 2024;0:1–12. doi: 10.1136/bmjqs-2023-016594

1) Sample size calculation

The sample size was determined using available data on regional colorectal cancer procedures performed in 2018. With an expected total number of 2240 patients over 15 months (approximately 1120 cases in the control period and 1120 in the experimental period), the statistical power of the study was calculated assuming a reduction in mean LOS (calculated after excluding LOS of 22 days, corresponding to the 94th percentile) of at least 1 day (from 9.0 to 8.0, with a standard deviation of 3.7), corresponding to an effect size of approximately 0.27. With an alpha error of 0.05 (with two tails), a within-cluster correlation coefficient (ICC) of 0.20, an average cluster size in each step of 16, with 7 clusters per step and 4 steps (excluding the baseline), the total number of expected cases (2240) had a statistical power of 0.98. It was estimated that the study also had a statistical power of 0.84 to detect absolute differences of at least 10% in secondary outcomes measurable as percentages, such as the occurrence of complications or re-interventions, with an alpha error of 0.05 (two tails).

Pagano E, *et al. BMJ Qual Saf* 2024;0:1–12. doi: 10.1136/bmjqs-2023-016594

2) Figure S1. Diagram of the ERAS Colon-rectum Piemonte study, showing number of patients recruited in each group of clusters and study period. * Three months' extension due to COVID-19 pandemic.

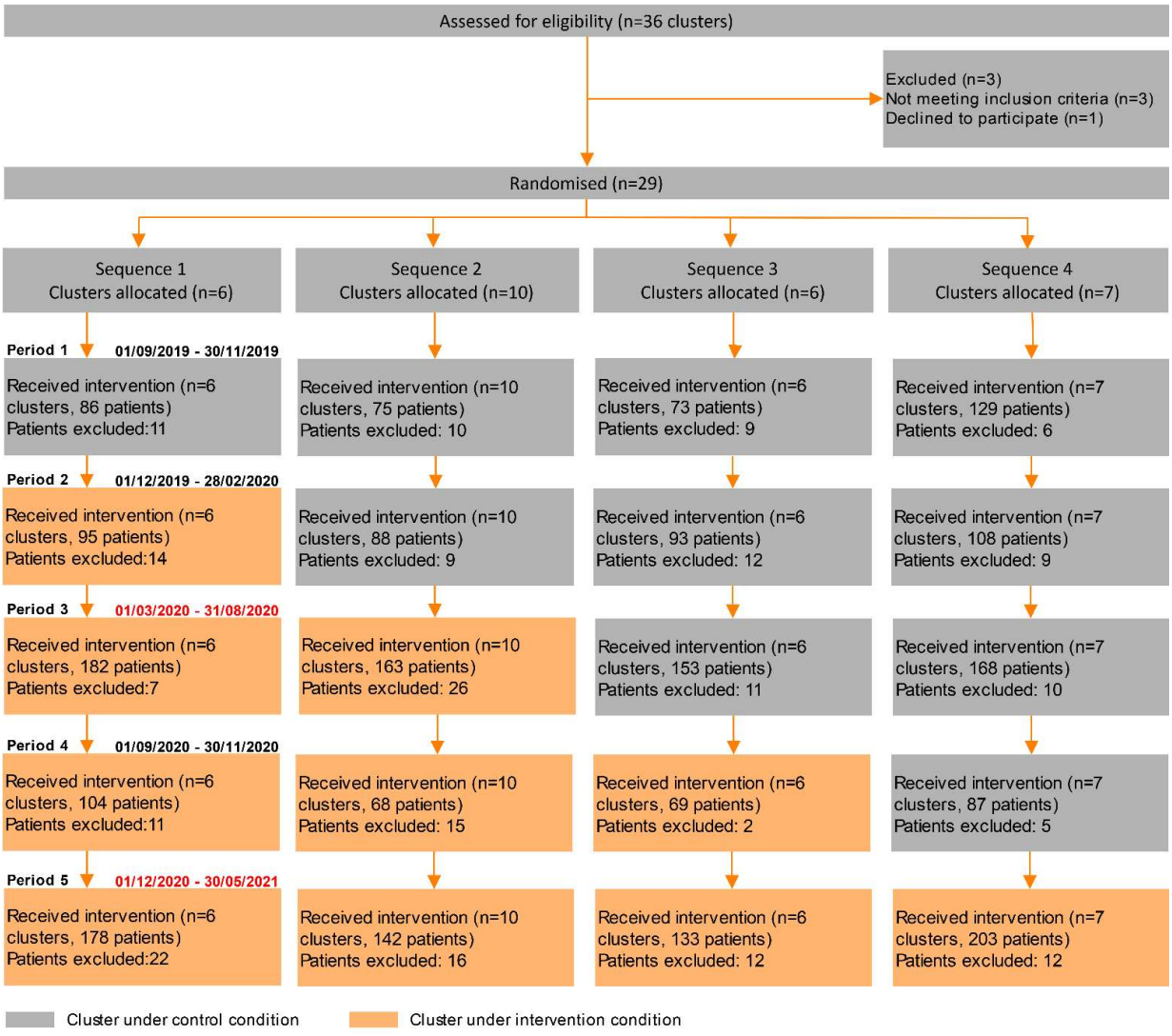


3) Table S1. Description of Enhanced recovery after surgery (ERAS) items and related compliance indicators, by phase of care, and discharge criteria.

ERAS protocol item	Definition of compliance to the specific item	Indicator label
Preoperative		
Assure enough time for preoperative optimization or "prehabilitation". The preoperative assessment should be schedule well in advance before surgery.	Visit performed at least 14 days before surgery	Anaesthesiologic visit time
Patients should routinely receive dedicated preoperative counselling, supported by the available informative leaflet for patients	Counselling provided	Counselling
Preoperative routine nutritional assessment offers the opportunity to correct malnutrition and should be offered	Nutritional risk assessed with Malnutrition Universal Screening Tool (MUST) score or during a nutritional visit	Nutritional risk assessment
Screening and treatment of iron deficiency anaemia before surgery	Correction of iron deficiency anaemia for patients with haemoglobin value <=12 g/dl	Anaemia correction
Mechanical bowel preparation has no clear clinical advantage in colon surgery and should not be used routinely.	Avoid mechanical bowel preparation for colon surgery	No mechanical bowel preparation (colon)
Long-acting sedative medication before surgery should be avoided.	Avoid any long-acting sedative medications is required for compliance to the item	No premedication
Prophylaxis for deep vein thrombosis (DVT) to be prescribed according to local guidelines	Prophylaxis with either heparin or stockings	Thromboprophylaxis
Antibiotics prophylaxis according to local guidelines	Antibiotic prophylaxis administered for less than 24 hours	Antibiotics prophylaxis
Patients should be allowed to eat up until 6 hours before initiation of anaesthesia	Last food intake between 6 and 18 hours before surgery	No prolonged fasting
Maltodextrins drinks reduce hunger, thirst, anxiety, postoperative resistance to insulin and help maintain anabolic state	Maltodextrins administered before surgery	Carbohydrate loading
Intraoperative		
Minimally invasive approach for colorectal surgery has better short-term postoperative outcomes and reduces postoperative stress response	Laparotomic approach or conversion from MIS to open surgery is considered as not compliant	Minimally invasive (MIS) surgery
Peritoneal drains show no effect on clinical outcome and should not be used routinely	The use of abdominal drain in colonic surgery is assessed as a not compliant	No surgical drainage (colon)
The epidural analgesia in laparotomic approach is the best technique for ensuring an opioid sparing analgesia	Epidural analgesia in laparotomic approach	Epidural anaesthesia in laparotomic
Reliable temperature monitoring and methods to actively warm patients should be employed	Both maintenance of normothermia and	Prevention of hypothermia

ERAS protocol item	**Definition of compliance to the specific item**	**Indicator label**
	prewarming are required for compliance to the item	
Perioperative near-zero fluid balance should be the target of fluid therapy	Total fluid volume <=4ml/Kg/h during surgery	Fluid normovolemia
A multimodal approach to Postoperative Nausea and Vomiting (PONV) prophylaxis should be considered	PONV prophylaxis administered	Prevention of nausea and vomiting (PONV)
Postoperative items and Follow up		
Net ‘‘near-zero’’ fluid and electrolyte balance should be maintained	Total fluid volume <= 2ml/Kg/h in postoperative period	Fluid normovolemia
Maintain the hydro-electrolytic balance by favouring oral fluid intake	Removal of i.v. within day 1 after surgery is required for compliance to the item	Early removal of i.v.
Patients should be encouraged to drink when they are awake and free of nausea	Oral diet restarted on the day of surgery	Early rehydration
Most patients can and should be offered food from the day of surgery	Re-feeding within day 1 after surgery	Early re-feeding
Postoperative NasoGastric Tube (NGT) should not be used routinely	Removal of NGT whitin day 1 after surgery is required for compliance to the item	No nasogastric tubes (NGT)
Patients at low risk should have routine removal of urin catheter on the first day after surgery	Removal of urin catheter whitin day 1 after surgery	Early removal of urin catheter
Prolonged immobilisation is associated with a variety of adverse effects and patients should therefore be mobilised	At least 2 hours of mobilization on day 1 after surgery	Early mobilization
Avoid opioids and apply multimodal analgesia in combination with spinal/epidural analgesia or transversus abdominis plane (TAP) blocks when indicated	Usage of routinary opioids is considered as not compliant	Minimized opioid use
Follow-up after discharge should be offered to all patients	Follow up, by hospital visit or by phone contact, within 3 days after discharge	Early follow-up
Discharge criteria		
1. Adequate oral nutrition 2. Resumption of bowel function 3. Pain control with oral analgesics 4. Motor and personal hygiene self-sufficiency 5. No clinical/laboratory evidence of postoperative complications Hospital discharge also requires the patient's consent.		

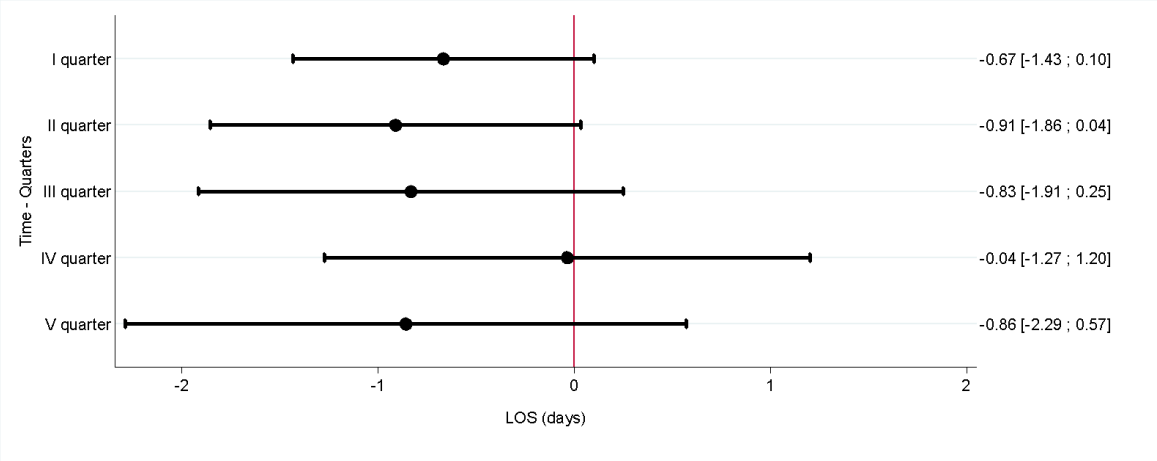
4) Figure S2. Study flow-chart by allocation sequence and study period.



5) Table S2. Postsurgical complication, by study period.

	Control period				ERAS period			
	Total		Clavien-Dindo III-IV		Total		Clavien-Dindo III-IV	
Surgical complications	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Postoperative ileus	52	4.91	4	0.38	95	7.11	7	0.52
Anastomotic leakage	45	4.25	38	3.58	67	5.01	52	3.89
Bleeding	47	4.44	12	1.13	52	3.89	20	1.5
Wound dehiscence	30	2.84	6	0.57	25	1.87	11	0.82
Wound infection	25	2.36	5	0.47	29	2.17	3	0.22
Abdominal abscess	12	1.13	7	0.66	15	1.12	9	0.67
Intestinal perforation/obstruction	9	0.85	6	0.57	13	0.97	11	0.82
Intestinal ischemia	4	0.38	4	0.38	6	0.45	6	0.45
Bladder injuries	4	0.38	2	0.19	3	0.22	0	0
Ureteral injuries	4	0.38	4	0.38	2	0.15	2	0.15
Other surgical complications	10	0.95	7	0.66	5	0.37	3	0.22
Medical complications								
Pneumonia	36	3.4	6	0.57	39	2.92	10	0.75
Urinary retention	22	2.08	1	0.09	33	2.47	3	0.22
Acute renal failure	14	1.32	2	0.19	17	1.27	5	0.37
Sepsis	12	1.13	7	0.66	19	1.42	15	1.12
Arrhythmia	16	1.51	0	0	14	1.05	2	0.15
Fever	21	1.98	1	0.09	3	0.22	0	0
Psychic alterations	7	0.66	0	0	14	1.05	0	0
Respiratory failure	6	0.57	3	0.28	13	0.97	8	0.6
COVID infection	3	0.28	0	0	15	1.12	5	0.37
Diarrhea	8	0.76	0	0	8	0.6	1	0.07
Urinary infection	4	0.38	0	0	9	0.67	2	0.15
Pleural effusion	4	0.38	0	0	7	0.52	3	0.22
Complications related to spinal/epidural anesthesia	5	0.47	0	0	5	0.37	0	0
Other medical complications	26	2.46	5	0.47	35	2.62	3	0.22

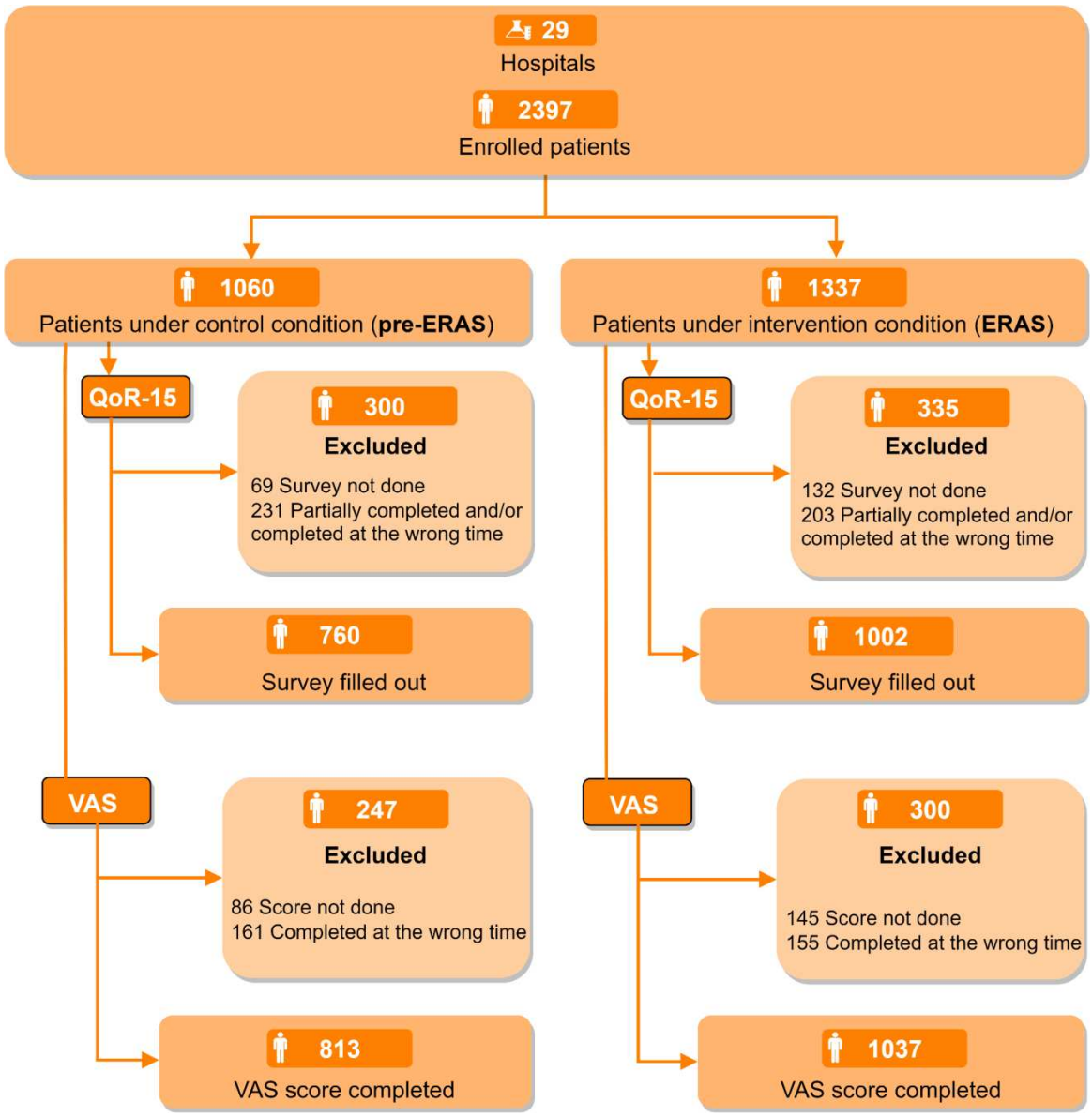
6) Figure S3. Adjusted difference in Length of Stay (LOS) between each quarter since ERAS implementation and the baseline period (September-November 2019).



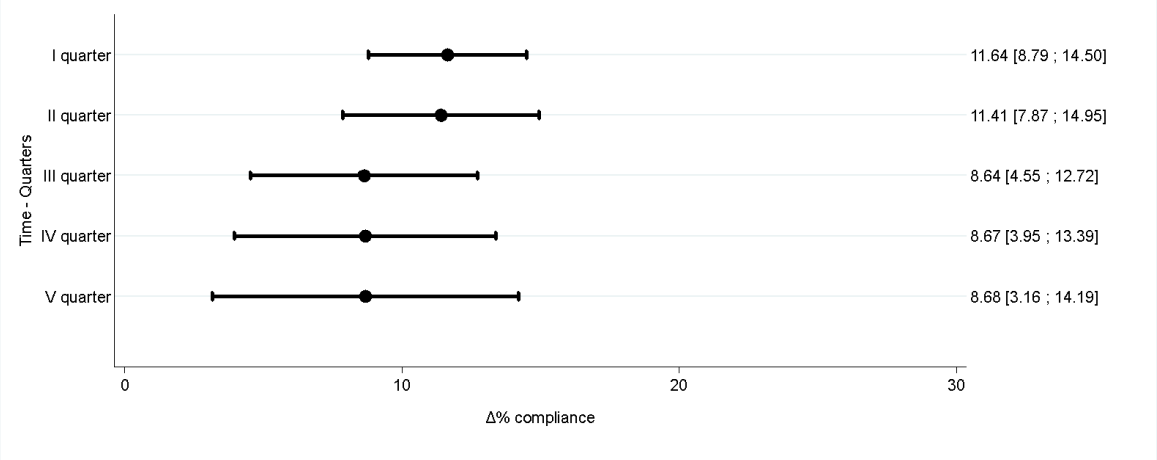
7) Table S3. Effect of compliance to ERAS items (per 10% increase), overall and by phase of care (preoperative, intraoperative and postoperative), on the study outcomes.

Study outcomes	All patients				Control period				ERAS period			
	Difference (Days)	95%CI		p-value	Difference (Days)	95%CI		p-value	Difference (Days)	95%CI		p-value
LOS	-0.65	-0.76	-0.54	<.0001	-0.63	-0.85	-0.41	<.0001	-0.81	-0.98	-0.64	<.0001
	OR	95%CI		p-value	OR	95%CI		p-value	OR	95%CI		p-value
Complications:												
total	0.86	0.80	0.93	0.000	0.89	0.78	1.01	0.070	0.71	0.64	0.80	<.0001
medical	0.94	0.85	1.04	0.221	1.02	0.86	1.21	0.835	0.81	0.70	0.93	0.003
surgical	0.86	0.79	0.93	0.000	0.82	0.71	0.94	0.006	0.72	0.63	0.81	<.0001
Transfusion	0.86	0.77	0.96	0.006	0.80	0.67	0.95	0.011	0.89	0.75	1.05	0.173
Inpatient mortality	0.74	0.58	0.94	0.014	0.79	0.52	1.19	0.253	0.54	0.38	0.78	0.001
Intensive Care Unit (ICU) access	0.72	0.64	0.80	<.0001	0.70	0.57	0.86	0.001	0.57	0.48	0.68	<.0001
30-days ED admissions	0.97	0.86	1.10	0.648	1.01	0.84	1.21	0.948	0.89	0.73	1.08	0.226
30 days hospital re-admissions	0.97	0.87	1.07	0.498	1.05	0.90	1.22	0.566	0.90	0.76	1.06	0.199
30 days re-interventions	0.90	0.81	1.01	0.077	0.95	0.80	1.14	0.594	0.79	0.66	0.95	0.010

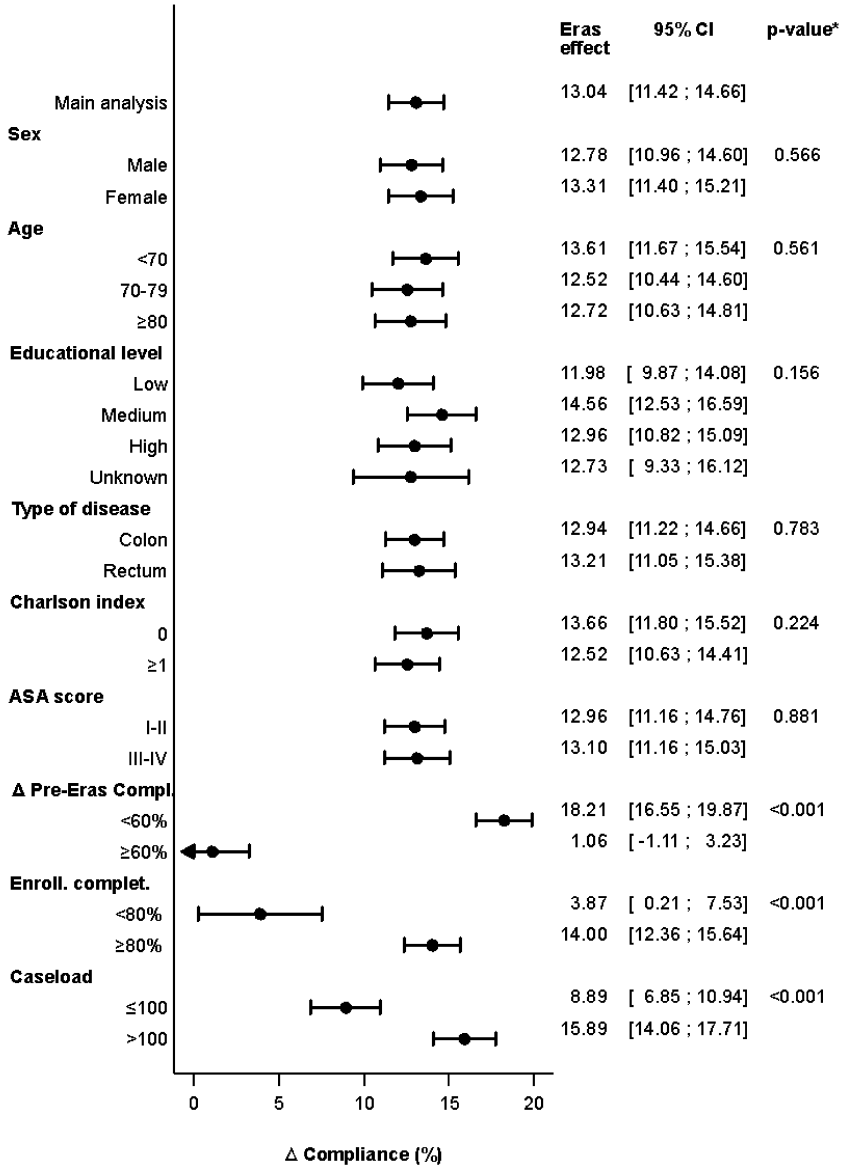
8) Figure S4. ERAS Colon-Rectum Piemonte study flow for Quality of recovery (QoR) and Visual Analogue Scale (VAS) analyses.



9) Figure S5. Adjusted difference in compliance to ERAS items between each quarter since ERAS implementation and the baseline period (September-November 2019).



10) Figure S6. Estimated difference in compliance to ERAS items between the two study periods and related subgroups analyses by patients' characteristics and structure characteristics.



11) TIDieR check list

Implementation of Enhanced Recovery After Surgery (ERAS) protocol supported by audit and feedback (A&F) intervention across an entire regional hospital network.

TIDieR

Implementation of Enhanced Recovery After Surgery (ERAS) protocol supported by audit and feedback (A&F) intervention across an entire regional hospital network.

Why:

The Enhanced Recovery After Surgery (ERAS) protocol is a multimodal perioperative care pathway aimed at reducing surgical stress and favouring early recovery after surgery. Despite the numerous publications supporting the potential improvements in colorectal cancer surgery, in 2019 only a few selected hospitals in the Piedmont region that are particularly open to change have adopted this approach in routine care. In order to implement the routine and long-term adoption of the ERAS protocol throughout the entire region, the A&F strategy was adopted. The aim was to overcome the usual barriers to implementing new organisational models with a structured A&F strategy and to contribute with a pragmatic cluster randomised trial to the relatively weak evidence from previous trials that compared patients within the same department.

What (material):

According to the cluster stepped wedge design, the interventions were delivered to all centers at different times with a mixture of different materials:

Each centre received copies of the ERAS perioperative protocol (both electronic and printed copies), which were discussed in detail at dedicated training days. On the training days, the theoretical part was presented by experts using visual material (PowerPoint slides) to explain the rationale behind the elements and indicators of the protocol. Part of the training was conducted interactively, in smal groups, presenting and discussing case studies. The centres also received materials to support the local implementation of ERAS (information sheet for patients, checklist to support source data collection and supporting documentation). Details and materials on the training programme and the material provided to the centres can be accessed here: https://new.epiclin.it/it/eras_colonretto/documents (access credential required on request to the corresponding author).

Feedback was structured through a dedicated website (https://new.epiclin.it /en/eras_colonretto/) where centres had access to a "monitoring" section and a "feedback" section. Feedback was also provided via newsletters and scheduled online feedback sessions. Copies of the newsletters and feedback meeting materials can be found on Epiclin website at: https://new.epiclin.it/it/eras_colonretto/ (access credential required on request to the corresponding author).

What (procedures):

Due to the cluster design, the procedures used in the interventions were activated several times during the study period, depending on the centres' activation calendar:

Prior to the start of the ERAS period, the centres were asked to identify a "ERAS team" that would participate in the one-day interactive training and be responsible for disseminating the information in their local organisation, train local personnel and act as a "ERAS champion" to support and facilitate practice change. The training included theory around the principles of ERAS, organisational aspects and practical experiences with case studies. After the training sessions and during the experimental period, the local ERAS team had the opportunity to contact the expert trainers to discuss specific barriers and receive ad hoc support.

After the start of the experimental period, the ERAS teams and local healthcare professionals involved in the patients' care had the opportunity to use the online feedback section on Epiclin to review their progress in applying the protocol. The feedback section on the Epiclin website can be accessed here:

Implementation of Enhanced Recovery After Surgery (ERAS) protocol supported by audit and feedback (A&F) intervention across an entire regional hospital network.

https://new.epiclin.it/it/eras_colonretto/feedback (access authorisation required upon request to the corresponding author).

A few months after the start of the experimental period, the feedback indicators were discussed with each group of hospitals during online meetings. Moreover, the same group of experts who conducted the training programme was also involved in discussing and commenting on the indicators.

After the start of the experimental period and regularly throughout the study, newsletters were sent to all local ERAS teams to maintain commitment and motivation for the overall project and to provide information on the progress of the study and relevant news.

Who provided:

Activating the ERAS protocol across a region with an A&F strategy required a variety of actors and providers, so that interventions could work at different levels:

Regional stakeholders, local health authorities and the Regional Cancer Network were involved in the project from the planning phase. They have publicly given their full support to the initiative and recognised the potential to improve clinical practice across the region.

ERAS protocol and the training were designed and delivered by recognised experts in the field, supported by a scientific society (ERAS Periorative Italian Society - POIS)

Training and feedback was provided and delivered to the entire multidisciplinary healthcare team caring for patients undergoing colorectal cancer surgery (nurses, surgeons, dieticians, anaesthetists, hospital managers and directors, and local clinical protocol writers). The staff involved had backgrounds in oncologic surgery, colorectal surgery, intraoperative care and postoperative care.

The online monitoring and feedback website was designed at coordinating centre (the Clinical Epidemiology unit at regional main hospital) with the help of a multidisciplinary team of statisticians, data managers, epidemiologists and health economists, all trained in A&F strategy. Software developers operating at the coordinating centre were responsable for the Epiclin website, including sofware development and technical support.

How (mode of delivery; individual or group):

The interventions were given different modalities and characteristics:

The ERAS protocol and the accompanying documents were distributed in printed form during the training sessions and by email. They were also available for download on the Epiclin website.

The one-day interactive training and feedback meeting were conducted at group of cluster level as a combination of face-to-face meetings and online meetings (two edition of the training meetings and all editions of the feedback meetings were delivered online because of the pandemic constraints in place). Both format included an interactive discussion session.

In the feedback section of the Epiclin website, a bar graph for each indicator showed the performance of each centre before and after the implementation of the ERAS protocol, as well as in comparison to the control group and the other participating centres. Radar graphs showed performance at regional level. All graphs were automatically updated each time data were recorded in the electronic case report form, so the gap between data collection and feedback was very small.

Newsletters were sent electronically to the email addresses of all ERAS team members, local healthcare professional involved in perioperative care and hospital managers.

Implementation of Enhanced Recovery After Surgery (ERAS) protocol supported by audit and feedback (A&F) intervention across an entire regional hospital network.

Where:

The implementation of the ERAS protocol took place in almost every general surgery unit of the Piedmont hospital network with a minumum annual caseload of at least 30 elective surgical procedures for colorectal cancer (29 centres were included after assessment of inclusion criteria and willingness to participate, out of 36 centres assessed).

Training meetings delivered face-to-face were held in Turin, the largerst city of the Piedmont region, with a central location to allow members to easily travel from the different areas.

When and how much:

The interventions took place at different times and with different frequency:

Training on ERAS protocol was organised in four editions: one training day for each group of clusters, held 6/8 weeks before the start of the experimental period (with the last two editions delivered online due to COVID restrictions). The number of participants was: first edition: 40; second edition: 52; third edition: 33; forth edition: 44. The breakdown of occupations included: nurses, surgeons, anaesthetists, nutritionist, dieticians, health managment managers, regional delegates, oncology network directors.

Feedback sessions were held 4 times: one meeting for each group of clusters.

N°8 newsletter were produced and distributed during the study period.

The online feedback was conducted through a platform that was accessible 24/7 with a personal access credential. The feedback section on the Epiclin website can be accessed here: https://new.epiclin.it/it/eras_colonretto/feedback (access authorisation required upon request to the corresponding author).

Tailoring:

Not applicable

Modification:

During the first feedback meeting, participants reported that the pandemic had a strong impact on their ability to deliver routine care, to change clinical practice, to implement the ERAS protocol and on the ability to respond to the feedback received.
For these reasons, the study recruitment period, originally set at 15 months, was later extended to 21 months to compensate for the negative impact of the COVID -19 pandemic. The extension of two study periods did not alter the balanco of the population treated according to standard and experimental stategies.
In addition, due to the pandemic, two editions of the training sessions and all editions of the feedback sessions were held online, although it was originally planned to hold all sessions in person.

How well (planned):

Adherence to ERAS protocol was assessed comparing the control period (where the adherence to the ERAS items was 52%) and the intervention period (with an adherence to the ERAS items of 67.3%). The Increment of adherence was +13% (IC 95% 11.4-14.7), a relevant result, considering the results reported in the literature on A&F (showing a median improvement of +4%).
Facilitating factors include the degree of compliance with the ERAS items prior to initiation of the study, completeness of patient inclusion in the study and volume of surgical activity (according to subgroup analyses). The presence of a Regional Oncology Network, a scientific society that support the implementation of ERAS (POIS society), referral centres already using the ERAS protocol, supportive evidence in the literature and a strong coordination of all study phases may also have acted as facilitating factors.

Implementation of Enhanced Recovery After Surgery (ERAS) protocol supported by audit and feedback (A&F) intervention across an entire regional hospital network.

How well (actual): One obstacle to the application of the ERAS protocol and to the optimal impact of the feedback strategy may be the relative novelty of the initiative. In some of the smaller centres it was unusual to participate in research projects or audit initiatives, as there was no frequent regional or national audit programme in the italian NHS. As a result, there was a lack of local dedicated resources for these initiatives and the experience of the staff involved was limited.
Another major obstacle to implementation was the COVID pandemic that started in March 2020, a few months after the start of the study.

Titolo	**Studio controllato randomizzato a cluster - stepped wedge - sull' implementazione del protocollo ERAS (Enhanced Recovery After Surgery) nella gestione perioperatoria di pazienti con neoplasia del colon-retto sottoposti a resezione in Piemonte. Uno studio del progetto EASY-NET**
Titolo breve	**ERAS in chirurgia colo-rettale**
Versione	2.0 - Gennaio 2020
Promotore	ASO Santa Croce e Carle di Cuneo SC Chirurgia Generale e Oncologica
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Background	Il protocollo ERAS (Enhanced Recovery After Surgery, recupero accelerato dopo chirurgia) è un percorso multimodale volto ad attenuare lo stress chirurgico, cercando di mantenere l'omeostasi corporea al fine di consentire una rapida ripresa post operatoria del paziente sottoposto a chirurgia maggiore (1-2). I principali obiettivi di ERAS sono: • ottimizzare la gestione perioperatoria utilizzando procedure basate sull'evidenza scientifica • favorire un migliore recupero dell'autonomia del paziente nel post operatorio • favorire una diminuzione dei tempi di ricovero • aumentare il livello di soddisfazione dei pazienti in merito alle cure ricevute • ridurre l'incidenza di complicanze, riammissioni ospedaliere e costi (3-5). Questo percorso, nato in chirurgia colo-rettale intorno alla seconda metà degli anni Novanta, ha dimostrato i suoi vantaggi sia in termini di riduzione delle degenze post operatorie ma soprattutto in termini di riduzione delle complicanze, rispetto ad una gestione perioperatoria tradizionale (6-7). L'ERAS Society ha promosso lo sviluppo di tale percorso grazie alla stesura di linee guida per la chirurgia colo-rettale ed ha inoltre consentito la sua diffusione anche al di fuori di tale ambito chirurgico, creando protocolli adattati alle diverse discipline chirurgiche (8-11) tra queste la chirurgia ginecologica. La strategia ERAS prevede un'ottimizzazione dello stato preoperatorio del paziente sia dal punto di vista fisico, psichico che nutrizionale, incentivando la sospensione del fumo e l'attività fisica. Viene inoltre limitato il digiuno preoperatorio e vengono somministrate maltodestrine circa 3 ore prima della chirurgia. La preparazione intestinale con lassativi viene limitata a casi selezionati, quali la chirurgia del retto medio-inferiore in cui è previsto il confezionamento di una stomia di protezione. Il protocollo prevede inoltre la profilassi del tromboembolismo, la profilassi antibiotica, la prevenzione dell'ipotermia intraoperatoria, l'euvolemia perioperatoria, il privilegiare tecniche chirurgiche mininvasive, la prevenzione della nausea e del vomito postoperatorio, un uso molto limitato del sondino nasogastrico e dei drenaggi chirurgici, la rimozione precoce del catetere urinario e delle infusioni endovenose, un'analgesia multimodale per ridurre al minimo il consumo di oppiacei, la mobilizzazione e la rialimentazione precoce nel post-operatorio, per favorire una rapida ripresa delle funzioni gastro-intestinali (4,6,7, 20). Una recente metanalisi condotta su studi randomizzati conferma che l'implementazione del protocollo ERAS in chirurgia colo-rettale consente una significativa riduzione delle complicazioni post operatorie, specialmente di quelle non chirurgiche, rispetto ad una gestione perioperatoria tradizionale. La stessa metanalisi conferma che l'implementazione di un percorso ERAS permette un significativo abbattimento delle degenze post operatorie, senza incrementare il tasso di riammissioni ospedaliere (12). Studi condotti in Alberta a seguito della diffusione nazionale del percorso ERAS in chirurgia colo-rettale hanno dimostrato una significativa riduzione anche dei costi sanitari con un ritorno dell'investimento di 3.8 (cioè, ogni dollaro canadese investito ha consentito un introito di 3.8 dollari canadesi)

	(13). Di fronte a tali evidenze il protocollo ERAS in chirurgia colo-rettale dovrebbe essere adottato in ogni centro chirurgico ma la penetranza del percorso rimane tuttora piuttosto bassa. La ragione di questo risiede nella difficoltà derivante dalla introduzione routinaria di tale percorso. Seppure sarebbe auspicabile ottenere un protocollo più snello e facile da introdurre, non esistono evidenze che ci consentano di poter applicare solo alcuni items del percorso, evitandone altri. Indubbiamente, alcuni elementi hanno un valore determinante su altri. Infatti, dall'analisi dei dati raccolti nel registro ERAS internazionale e nel registro italiano della POIS (Peri-Operative Italian Society, ERAS Italian Chapter), si evince un ruolo determinate della laparoscopia nella ripresa post-operatoria del paziente anche all'interno di un percorso ERAS (14-15). Gli stessi registri dimostrano inoltre come la chirurgia resettiva del retto, specialmente se associata al confezionamento di una stomia di protezione, sia un fattore rallentante la ripresa del paziente anche nell'ambito di un corretto percorso ERAS. Per ovviare alle difficoltà nella implementazione di un percorso così complesso si è ritenuto essenziale una politica Regionale di sensibilizzazione e di formazione dei diversi centri chirurgici. Un programma formale per l'implementazione del protocollo ERAS richiede tre elementi (13-15): i) un protocollo operativo ERAS aggiornato e condiviso ii) un team che lavora per la formazione degli operatori e per aumentare la compliance al protocollo iii) un sistema di audit (database) per verificare la compliance al protocollo e per monitorare gli outcome clinici. In Italia la diffusione della strategia ERAS è l'obiettivo POIS (http://perioperativeitaliansociety.org) la cui mission è promuovere la mini-invasività del percorso chirurgico e migliorare la qualità di vita del paziente nel periodo perioperatorio. La Società ha attivato un network di oltre 70 ospedali italiani e ha messo a punto un database per la chirurgia colo-rettale che ha permesso la recente pubblicazione di studi multicentrici (15-17). Nell'ambito della chirurgia colo-rettale il protocollo ERAS-POIS stilato sarà il riferimento dello studio in oggetto (allegato n.1). L'ipotesi di sperimentare l'applicazione del protocollo ERAS per alcuni interventi selezionati (in particolare per la chirurgia colo-rettale e per gli interventi di isterectomia) e di valutarne l'impatto in termini di miglioramento di efficienza e di sicurezza è stata considerata una priorità regionale, tale da includerla nel più generale progetto di rete sulla valutazione di efficacia degli interventi di audit and feedback (Progetto di rete - Ricerca Sanitaria Finalizzata 2016). In questo progetto di rete (NET-2016-02364191), che coinvolge a livello nazionale 7 regioni con il coordinamento della Regione Lazio, la Regione Piemonte è responsabile del Work Package 3 (WP3) che prevede l'impiego di un disegno controllato e randomizzato a cluster per stimare l'effetto sull'intero sistema ospedaliero di interventi di miglioramento della qualità dell'assistenza in ambito oncologico, con un approccio di audit and feedback intensivo basato su dati raccolti in database dedicati, gestito centralmente, rispetto ad approcci tradizionali di audit basati su iniziative locali o con indicatori centrali che utilizzano solo dati correnti.
Ipotesi	Questo studio è stato progettato sulla base di due ipotesi principali: a) il protocollo ERAS ha una elevata probabilità, sulla base delle evidenze

	disponibili, di introdurre nella pratica clinica procedure con un bilancio favorevole tra benefici e rischi (sia per i pazienti, sia per il personale); b) che la semplice diffusione del protocollo in ospedali selezionati e favorevolmente predisposti al cambiamento avrebbe un impatto limitato sulla qualità complessiva degli interventi su scala regionale, con conseguente accentuazione dell'eterogeneità delle prestazioni tra centri e di riduzione dell'equità tra i pazienti. Tenuto conto delle evidenze disponibili e delle opportunità fornite dal contesto regionale, l'Assessorato alla Sanità della Regione Piemonte ha considerato l'implementazione del protocollo ERAS in tutti gli ospedali regionali, nell'ambito di un progetto di ricerca, un obiettivo ad elevata priorità. Sulla base di queste premesse è stato disegnato un progetto di ricerca/intervento che dovrebbe, in un arco di tempo di circa 2 anni, favorire una corretta conoscenza ed adozione sistematica del protocollo ERAS su scala regionale da parte di tutti i centri che eseguono interventi chirurgici di resezione colo-rettale per neoplasia. Per poter stimare in modo accurato l'impatto reale del protocollo è stato disegnato uno studio randomizzato a cluster (dove i cluster sono rappresentati dai reparti di chirurgia generale degli ospedali regionali) con adozione progressiva del protocollo da parte di gruppi di reparti secondo un calendario determinato in modo random (definito "stepped wedge") che al termine dello studio avrà coinvolto tutti i cluster. Al termine dello studio ogni cluster avrà un periodo di attività con procedure abituali ("periodo di controllo") ed uno successivo all'introduzione del protocollo ("periodo sperimentale") analogamente ai disegni con cross-over, ma con una sola transizione (da controllo a sperimentale). Ipotizziamo che l'adozione del protocollo determini una riduzione della durata della degenza, delle complicanze, dei costi sanitari e migliori il recupero funzionale e la soddisfazione delle pazienti.

Obiettivo principale	Ridurre la durata della degenza totale nel periodo sperimentale rispetto al periodo di controllo attraverso l'implementazione del protocollo perioperatorio standardizzato ERAS per la gestione dei pazienti candidati a intervento resettivo colo-rettale per neoplasia (protocollo ERAS-POIS)
Obiettivi secondari	Verificare che nel passaggio da periodo di controllo a periodo sperimentale si riduca la frequenza di: • complicanze post chirurgiche • trasferimenti in terapia intensiva • degenze di durata superiore alla soglia • reinterventi • accessi in PS • riammissioni in ospedale Valutare la compliance al protocollo ERAS, complessivamente e per i singoli aspetti/procedure. Comparare tra i due periodi: • l'utilizzo della tecnica laparoscopica. • la qualità del recupero post-operatorio • la soddisfazione percepita dai pazienti • l'impatto economico Nel periodo sperimentale analizzare: • i fattori organizzativi e strutturali dei reparti associati alla compliance al protocollo ERAS • la relazione tra compliance al protocollo ERAS e outcome dei pazienti • la soddisfazione degli operatori
Disegno dello studio	Studio multicentrico controllato randomizzato a cluster, con disegno *stepped wedge*, di confronto tra la gestione perioperatoria standard e quella secondo il protocollo ERAS.
Criteri di inclusione	Tutti i reparti di chirurgia generale degli ospedali regionali che eseguono interventi di chirurgia colo-rettale per neoplasia per via laparoscopica o laparotomica. Tutti i pazienti che durante lo studio vengono ricoverati per intervento chirurgico elettivo di resezione colo-rettale per patologia maligna con o senza confezionamento di stomia di protezione

Criteri di esclusione	Reparti con una casistica inferiore a 30 interventi all'anno di chirurgia resettiva colo-rettale. Pazienti sottoposti a intervento in regime di urgenza. Particolari condizioni di complessità o gravità clinica, da documentare al momento del ricovero, che rappresentino controindicazioni all'applicazione del protocollo ERAS (es. pazienti con ASA score V). I pazienti con disagio socio-assistenziale, da documentare al momento del ricovero, che non permettano un adeguato standard di autonomia personale o di assistenza domiciliare post operatoria (condizioni di demenza grave, disfunzione fisica, stato di indigenza) saranno inclusi e gestiti secondo quanto previsto dallo studio, salvo la decisione della dimissione che dovrà essere valutata in relazione ai problemi specifici (informazioni previste nel database).
Metodi di stratificazione e randomizzazione dei centri	In base ad una scelta di tipo programmatorio regionale sono inclusi nello studio tutti i centri accreditati ad effettuare chirurgia colo-rettale per patologia neoplastica nella Regione Piemonte che soddisfino i criteri di inclusione specifici dello studio. Prima dell'inizio dello studio tutti i reparti saranno contattati dal gruppo di coordinamento per valutare il livello di conoscenza del protocollo ERAS per la chirurgia colo-rettale, la predisposizione ad adottarlo (con registrazione delle principali barriere esistenti) o l'eventuale adozione già avvenuta precedentemente. I centri che risultassero avere già adottato pienamente il protocollo prima dell'inizio dello studio saranno esclusi dalla randomizzazione e inclusi in un gruppo osservazionale. Tutti gli altri centri saranno ordinati in base al volume di interventi colo-rettali programmati nel corso del 2017 e suddivisi in 4 strati (con un numero uguale di reparti per strato). Saranno quindi estratti in modo random gruppi di 4 centri (uno per strato) e i gruppi così formati saranno ordinati secondo una sequenza random di periodo di attivazione del protocollo. In questo modo si garantisce una numerosità degli interventi ed una composizione omogenea dei gruppi per ciascun periodo di attivazione. Tutte le procedure di randomizzazione saranno eseguite dopo aver anonimizzato i centri. La data di attivazione del protocollo e dell'evento formativo sarà infine comunicata a ciascun centro con un preavviso di circa 3 mesi (tempo minimo necessario per consentire la formazione del personale e la predisposizione degli aspetti organizzativi locali). Tutte le procedure di randomizzazione saranno eseguite centralmente dalla SSD Epidemiologia Clinica e Valutativa del CPO – Piemonte.
Gestione peri-operatoria standard	Prima dell'attivazione del protocollo ciascun centro continuerà a gestire il perioperatorio dei pazienti secondo i protocolli abituali, possibilmente senza introdurre variazioni.
Gestione sperimentale (ERAS)	Per ciascun gruppo di circa 4-6 centri nel trimestre precedente la data di attivazione del protocollo verrà effettuata un'approfondita formazione in merito ai principi ERAS e al nuovo protocollo ERAS-POIS (allegato n.1). La formazione si articolerà in un corso della durata di una giornata gestito da esperti formatori POIS. Ciascun centro aderente dovrà identificare, oltre al direttore della struttura e al coordinatore infermieristico, un professionista di riferimento per ciascuna figura professionale coinvolta nel progetto (chirurgo-anestesista-infermiere-dietologo/dietista, medico di direzione sanitaria). Il "TEAM ERAS" regionale parteciperà alla formazione e si renderà successivamente disponibile per

	approfondimenti e fornire supporto all'implementazione locale del protocollo e alla formazione.
Endpoint	Primario: • durata media della degenza, calcolata escludendo le durate superiori ad una soglia predefinita di 22 giorni (corrispondente al 94° percentile della distribuzione delle durante di degenza nel 2018). Secondari: • incidenza di complicanze post chirurgiche nel post-operatorio, definite secondo la classificazione Clavien-Dindo • trasferimenti in terapia intensiva nel post-operatorio • percentuale di degenze di durata superiore alla soglia (>=12 giorni) • percentuale di reinterventi (entro lo stesso ricovero o comunque nei 30 giorni successivi all'intervento) • percentuale di accessi in PS entro 30 giorni dall'intervento (indipendentemente dal motivo e dall'eventuale ricovero) • percentuale di riammissioni in ospedale entro 30 giorni dall'intervento (indipendentemente dal motivo) • percentuale di interventi eseguiti con tecnica laparoscopica • score di qualità del recupero post-operatorio (misurato con il questionario QoR-15 [18] a circa 24 ore dall'intervento • score di soddisfazione percepita dei pazienti misurato con il questionario SSQ-8 [19] tramite intervista telefonica a due settimane dalla dimissione (solo per un campione di pazienti o in alternativa loro caregivers che accettino di essere intervistati) • valutazione della soddisfazione degli operatori, rilevata in modo qualitativo attraverso focus group, al termine della sperimentazione • costi medi assistenziali, calcolati dal pre-ricovero fino a 30 giorni dopo l'intervento.
Metodi e strumenti di raccolta dei dati e di feedback	Prima dell'avvio dello studio tutti i centri saranno abilitati ad inserire i dati dei pazienti sottoposti a chirurgia colo-rettale inclusi nello studio in un'area dedicata su una piattaforma elettronica (sviluppata e gestita dalla SSD Epidemiologia Clinica e Valutativa - CPO della CSS di Torino). Nel database saranno registrati in modo prospettico e dopo anonimizzazione reversibile i dati relativi alla gestione del peri-operatorio di tutti i pazienti sottoposti a interventi programmati chirurgia colo-rettale per neoplasie che avranno accettato di rendere disponibili i loro dati ai fini dello studio sottoscrivendo un modulo ci consenso, dopo aver ricevuto adeguata informazione scritta ed orale nel periodo del pre-ricovero. La scheda raccolta dati (Case Report Form – CRF) è riportata nell'allegato 2. I componenti del TEAM ERAS di ciascun centro avranno accesso a tale piattaforma attraverso ID e password individuali e potranno visualizzare e modificare soltanto i dati relativi ai propri pazienti. Il database sarà sviluppato rispettando tutti i requisiti di sicurezza previsti dalla GDPR (regolamento EU 2016/679) in vigore dal 25/5/2018 e successive modificazioni Pertanto, dopo l'avvio dello studio (che avverrà contemporaneamente in tutti i centri), ciascun centro registrerà sulla piattaforma web i dati relativi alla gestione standard dei propri pazienti candidati ad intervento di chirurgia colo-rettale. Successivamente, in base al calendario di attivazione del protocollo ERAS in ciascun centro, il team abilitato del reparto avrà anche accesso alla sezione di monitoring dell'area nella quale saranno disponibili, con aggiornamento contemporaneo al caricamento dei dati, grafici con i principali endpoint dello studio, informativi sull'andamento generale del protocollo a

	livello regionale e del centro specifico. Questa forma di feedback, centrata su indicatori di processo (aderenza della pratica clinica alle procedure previste nel protocollo ERAS) e di esito (durata della degenza, endpoint secondari) dovrebbe consentire a ciascun reparto l'identificazione puntuale e tempestiva delle criticità per poter indirizzare gli eventuali interventi correttivi. Il recupero post-operatorio sarà misurato a circa 24 ore dall'intervento attraverso il questionario QoR-15 (disponibile e validato in lingua inglese). La versione in italiano è stata ottenuta attraverso un processo di traduzione e retro traduzione ("forward/backward translation") e successiva validazione su un primo campione di pazienti (allegato n.3). A tal fine verrà somministrato ai pazienti anche una visual analog scale (VAS), con scala compresa tra "recupero scadente" e "recupero eccellente", come misura sintetica della qualità del di recupero. La soddisfazione percepita dai pazienti sarà misurata attraverso il questionario SSQ-8, somministrato telefonicamente ad un campione di pazienti o in alternativa loro caregivers dopo due settimane dalla dimissione, da personale esperto nella somministrazione di questionari a contenuto sanitario. Poichè il questionario, validato e disponibile in lingua inglese, non è disponibile in lingua italiana, la versione italiana è stata ottenuta attraverso un processo di traduzione e retro traduzione ("forward/backward translation") e successiva validazione su un primo campione di pazienti, attraverso la correlazione con complicanze, reinterventi, accessi in PS e riammissioni (allegato n.4). La valutazione della soddisfazione degli operatori sarà effettuata attraverso questionari e, in modo qualitativo, attraverso la conduzione di focus group, nella fase conclusiva della sperimentazione, coinvolgendo separatamente i diversi gruppi di professionisti (infermieri, chirurghi, anestesisti). I focus group saranno condotti da personale esperto. I costi assistenziali saranno valutati includendo le seguenti categorie di risorse: visite pre-intervento, giornate di degenza (incluse giornate in terapia intensiva), tipologia di intervento, trattamento delle complicanze, reinterventi, accessi in PS, nuovi ricoveri. Per la valutazione dei fattori organizzativi e strutturali dei reparti associati alla compliance al protocollo ERAS si intende somministrare ai centri partecipanti un breve questionario, in concomitanza dello svolgimento dei corsi di formazione, al fine di raccogliere alcune informazioni di contesto (dimensioni del reparto, organizzazione, conoscenza e predisposizione verso il protocollo ERAS, criticità).
Considerazioni statistiche su numerosità e potenza dello studio	Tenuto conto che nel 2018 gli ospedali che hanno eseguito almeno 30 interventi programmati per tumori del colon-retto sono stati 32 e che almeno 4 ospedali hanno già implementato il protocollo ERAS, il totale degli ospedali inclusi nella sperimentazione sono 28, con una media di circa 64 interventi/anno (16 per ospedale a trimestre e 1790 interventi totali attesi in regione in 12 mesi). Con un calendario di attivazione che prevede un gruppo di 7 ospedali ogni trimestre, sono necessari 4 periodi (15 mesi in totale) per completare l'implementazione su tutti i centri in regione. Lo schema della tabella seguente riporta una possibile sequenza di attivazione dei cluster nel corso dello studio con la numerosità dei centri e dei pazienti per il periodo di controllo e sperimentale. Con questa ipotesi di numerosità totale attesa in 15 mesi (n=2240, di cui circa 1120 interventi nel periodo di controllo e 1120 nel periodo sperimentale) e di disegno è stata calcolata la potenza statistica dello studio sia per l'endpoint principale (durata della degenza), sia per gli endpoint dicotomici.

	Per il calcolo della potenza statistica dello studio è stato applicato il metodo di Hemming e Girling utilizzando il software STATA (v. 13). La potenza è stata calcolata ipotizzando che l'applicazione del protocollo comporti una riduzione della durata media della degenza (calcolata dopo aver escluso le degenze >22 giorni, corrispondenti al 94° percentile) di almeno 1 giorno (da 9.0 a 8.0) per essere definito efficace, che in relazione alla deviazione standard (3.7) rappresenta un effect size di circa 0.26. I parametri utilizzati per il calcolo sono: Degenza media (standard): 9.0 giorni (DS: 3.7) Degenza media (sperimentale): <= 8.0 giorni (DS 3.7) Errore alfa (due code): 0.05 Coefficiente di correlazione entro cluster (ICC): 0.20 Numerosità media dei cluster: 16 Numero di cluster randomizzati per step: 7 Numero di step (escluso il baseline): 4 Numerosità totale dello studio: 2240 Potenza statistica: 0.98 È stata anche calcolata la potenza statistica dello studio per evidenziare come statisticamente significative differenze assolute di almeno 10% degli endpoint secondari misurabili come percentuali (es. aderenza al protocollo ERAS, complicanze, reinterventi, ecc…). Assumendo un valore di riferimento pari a 0.5 (valore più sfavorevole da un punto di vista statistico), e mantenendo tutti i parametri precedenti, lo studio ha una potenza di 0.84.

mesi	0	3	6	9	12	Totale
Step 4	112	112	112	112	112	
Step 3	112	112	112	112	112	
Step 2	112	112	112	112	112	
Step 1	112	112	112	112	112	
Numerosità per periodo:						
• pazienti (di controllo)	448	336	224	112	0	1120
• pazienti (sperimentali)	0	112	224	336	448	1120

Analisi Statistiche	Le degenze medie (calcolate escludendo le durate maggiori della soglia) saranno confrontate tra i periodi con e senza implementazione del protocollo ERAS usando modelli di regressione lineare ad effetti casuali. Nel modello, la degenza verrà trattata come variabile dipendente mentre tra le indipendenti una variabile dicotomica indicherà per ciascun centro l'implementazione del protocollo nel periodo di riferimento della degenza. L'effetto dell'implementazione del protocollo ERAS sulla degenza media verrà aggiustato includendo nel modello le variabili tempo (identificato dagli step previsti), la sede del tumore (colon, retto) e la tecnica chirurgica (LPT, LPS). Il centro verrà incluso nel modello come effetto casuale. Per gli endpoint dicotomici misurati come proporzioni (es. durate di degenza superiori alla soglia, complicanze, riammissioni in ospedale) si stimerà l'effetto dell'implementazione del protocollo ERAS con modelli di regressione logistica ad effetti casuali, utilizzando un indicatore dell'evento (0, 1) come variabile dipendente e includendo nel modello lo stesso set di covariate utilizzato per l'analisi della durata di degenza.

Pagano E, *et al. BMJ Qual Saf* 2024;0:1–12. doi: 10.1136/bmjqs-2023-016594

	Le analisi principali saranno stratificate per caratteristiche dei centri (classificati per volume di attività, per grado di aderenza al protocollo ERAS al baseline e per altre caratteristiche strutturali) e dei pazienti (classi di età, diagnosi, tecnica chirurgica utilizzata). Dall'analisi principale saranno esclusi a posteriori i centri con elevata aderenza al protocollo ERAS al baseline. Per ridurre il rischio di bias dovuto ad una inclusione selezionata di pazienti nello studio da parte dei centri (selection bias, valutato in base alla percentuale di casi inseriti sul totale delle schede di dimissione dello stesso periodo di arruolamento), si stratificheranno le analisi per completezza dell'arruolamento (con possibilità di esclusione dei centri con maggiore incompletezza). Per tenere conto del periodo di adattamento in ciascun centro è prevista un'analisi di sensibilità che escluderà dal confronto il primo mese di ogni periodo di attivazione del protocollo ERAS. L'impatto del protocollo ERAS sarà anche analizzato in funzione del tempo trascorso dalla sua introduzione per valutare la curva di raggiungimento di un livello accettabile ed ottimale di applicazione. Come analisi secondaria si valuterà l'endpoint principale dello studio sull'intera casistica regionale rilevabile attraverso le schede di dimissione ospedaliera della regione Piemonte, selezionando i pazienti con i criteri di inclusione dello studio. Inoltre, si prevede di valutare l'andamento nel tempo della durata media della degenza rilevabile attraverso le schede di dimissione ospedaliera nei 5 anni precedenti l'attivazione del protocollo ERAS e nell'anno successivo, attraverso un disegno a serie temporali interrotte.
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Allegato 1 - Protocollo ERAS per la gestione perioperatoria dei pazienti sottoposti a resezione colo-rettale per neoplasia.

Criteri di inclusione

- Il protocollo ERAS trova applicazione per tutti i pazienti candidati a chirurgia resettiva colo-rettale per patologia maligna, sia con approccio open che laparoscopico.

Criteri di esclusione

- ASA V.
- Interventi di resezione colo rettale eseguiti per patologia benigna.
- Procedure chirurgiche eseguite in regime di urgenza.

Valutazione e informazione pre-operatoria

- Valutazione anestesiologica
Visita anestesiologica da eseguire almeno 2 settimane prima dell' intervento chirurgico per stabilizzazione delle eventuali condizioni cliniche: malattie cardiologiche, anemia, BPCO, diabete, stati di carenze nutrizionale. Iinvitare inoltre con adeguato supporto l'astensione dal fumo e alcol. Qualora il paziente presenti un'anamnesi positiva per patologia respiratoria severa (BPCO, asma, sindrome delle apnee notturne), con un quadro clinico non compensato, è indicato richiedere una valutazione clinico-strumentale della funzionalità respiratoria, volta all'identificazione dei soggetti che potrebbero beneficiare di un trattamento fisioterapico pre- e/o postoperatorio.

- Counseling preoperatorio
Dovrà prevedere un momento di incontro tra il paziente e il team multidisciplinare (chirurgo, anestesista e infermiere). Lo scopo è quello di favorire la compliance al protocollo, condividendo con il paziente gli obiettivi e motivandolo ad aderire al percorso delineato. A tal fine risulta utile il coinvolgimento dei familiari che parteciperanno al colloquio preoperatorio e assisteranno il paziente sia durante la degenza che una volta rientrato al domicilio. E' opportuno che il counseling avvenga con sufficiente anticipo (indicativamente almeno 2 settimane) rispetto alla data prevista del ricovero. E' consigliabile che l'incontro si svolga in ambito multidisciplinare, con la partecipazione, se possibile, contemporanea di tutti i professionisti coinvolti. Ciò consente di condividere i contenuti di educazione sanitaria ed informazione che il paziente deve ricevere, per evitare ripetizioni e finalizzare in maniera ottimale il colloquio. Anestesista e chirurgo informano il paziente sulle procedure di relativa competenza e ottengono il consenso informato. L'infermiere ha il compito di:

- effettuare la valutazione dei bisogni del paziente, incluso il rischio nutrizionale, e dei familiari;
- informare il paziente sull'organizzazione del reparto, sul personale operante e sui presidi necessari;
- informare il paziente sulla preparazione (eventuale preparazione intestinale, alimentazione, programma motorio) e sulla gestione del dolore e di eventuale nausea/vomito postoperatori.

E' consigliabile che l'informazione verbale sia integrata con la consegna del materiale informativo appositamente predisposto (opuscolo informativo in allegato n.5).

-Valutazione dello stato nutrizionale e prescrizioni dietetiche

- Deve essere eseguita una valutazione preoperatoria del rischio nutrizionale utilizzando il Malnutrition Universal Screening Tool (allegato n.6).
- Nei pazienti con score MUST ≥ 1 è indicata valutazione specialistica del Servizio di Dietetica e Nutrizione Clinica per la valutazione dello stato nutrizionale e per la terapia dietetica, compresa l'immunonutrizione.
- Per la diagnosi di malnutrizione utilizzare i criteri GLIM individuati nel documento di consenso dell'ESPEN 2018 (allegato n.7).
- In tutti i pazienti malnutriti è indicata la somministrazione preoperatoria di immunonutrizione per 5-7 giorni prima dell'intervento. Il trattamento immunonutrizionale preoperatorio consiste nella somministrazione di n°2 briks per circa 450-500ml di supplemento nutrizionale orale arricchito di immunonutrienti (arginina, acidi grassi w-3 e RNA).
- Nei pazienti malnutriti è necessario che la valutazione nutrizionale avvenga almeno 10 giorni prima dell'intervento; in caso di malnutrizione severa può essere necessario posticipare l'intervento chirurgico.
- Per valutare la compliance dei pazienti all'immunonutrizione utilizzare scheda per il monitoraggio dell'assunzione del supplemento nutrizionale preoperatorio (allegato n.8).
- Nessuna restrizione alimentare fino a 6 ore prima dell'intervento; possibilità di assumere liquidi chiari fino a 2 ore prima dell'intervento.
- Carico glucidico: somministrazione di bevanda a base di maltodestrine e priva di lipidi, lattosio, fibre e glutine. Dose: 800 cc la sera precedente l'intervento e 400 cc 2-3 ore prima dell'intervento, poi digiuno. La bevanda va assunta possibilmente fresca. L'assunzione della bevanda a base di maltodestrine non è controindicata nel paziente diabetico, ma in caso di quadro clinico non compensato è opportuna la valutazione da parte dello specialista.
- L'assunzione di liquidi chiari, incluse maltodestrine, nelle 2-3 ore prima dell'intervento è controindicata nei pazienti con rallentato svuotamento gastrico o nei quali sia prevista una difficile gestione delle vie aeree.
- La somministrazione della bevanda a base di maltodestrine nella dose di 800 cc il giorno precedente l'intervento, non sarà effettuata nei pazienti sottoposti ad immunonutrizione preoperatoria, in quanto questi pazienti continueranno l'assunzione del supplemento nutrizionale orale arricchito di immunonutrienti.

-Preparazione colica:

Nessuna preparazione di principio. Rectal washing la sera precedente l'intervento per i pazienti candidati a colectomia sinistra e resezione anteriore del retto alta. I pazienti candidati a resezione anteriore del retto bassa o ultra-bassa, nel caso in cui sia prevista la stomia di protezione, eseguono una preparazione colica standard per os secondo le abitudini del team. In caso di restrizioni alimentari adeguare gli apporti ai fabbisogni con integratori orali calorici/proteici/salini privi di fibre.

-Profilassi antitrombotica secondo le linee guida o la pratica clinica corrente dell'azienda.

-Profilassi antibiotica secondo le linee guida o la pratica clinica corrente dell'azienda.

-Prevenzione dell'anemia:

Prima dell'intervento chirurgico è opportuno tentare di correggere l'anemia secondo le linee guida o la pratica clinica corrente dell'azienda. I preparati di ferro per via endovenosa sono da preferirsi al ferro orale per ripristinare più rapidamente le

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concentrazioni di emoglobina sia nell'anemia da carenza di ferro che nell'anemia da malattia cronica. La trasfusione di sangue dovrebbe essere evitata, se possibile.

Protocollo anestesiologico

- Nessuna preanestesia di principio, evitando in particolare la somministrazione di benzodiazepine long acting.
- Nella chirurgia laparotomica il protocollo prevede il posizionamento di catetere epidurale (indicativamente a livello toracico) prima dell'induzione dell'anestesia generale. Somministrare dose test di verifica e bolo iniziale di anestetico locale.
- In chirurgia laparoscopica il posizionamento del catetere epidurale è a discrezione dell'anestesista.
- Anestesia generale inalatoria o TIVA (+ eventuale anestesia locoregionale epidurale), induzione e mantenimento con farmaci short-acting (propofol, remifentanil) e curarizzazione. Quando possibile si raccomanda l'utilizzo di monitoraggi per misurare la profondità dell'anestesia e la curarizzazione, come si raccomanda l'utilizzo di antagonisti reversal dei curari al termine dell'anestesia.
- Intubazione oro-tracheale ventilazione IPPV o Pressure support, ove necessario, con aria/O2 (35/65%).
- Idratazione intraoperatoria restrittiva, 4 ml/kg/h di soluzioni cristalloidi. Mantenere una diuresi intraoperatoria di almeno 0.5 ml/kg/h. Utilizzare la Goal Directed Fluid Therapy (GDFT) nei pazienti ad alto rischio.
- Si raccomanda l'utilizzo di vasocostrittori nei pazienti normovolemici ipotesi in trattamento con analgesia peridurale.
- Prevenzione dell'ipotermia e costante monitoraggio della temperatura corporea.
- Profilassi emesi selettiva:
    - Apfel score 1-2, profilassi con 2 farmaci di prima linea;
    - Apfel score ≥ 3, profilassi con 2-3 farmaci antiemetici.
- Nel caso il catetere epidurale non sia stato posizionato si prevede una analgesia multimodale preferendo strategie analgesiche opioid-sparing.
- Posizionamento catetere vescicale.
- Posizionamento sondino naso-gastrico.

Tecnica chirurgica

- Resezione colica o colorettale secondo tecnica standard, open o laparoscopica. L'approccio laparoscopico è preferibile dove vi sia adeguata esperienza da parte degli operatori e sia tecnicamente applicabile al paziente candidato alla procedura in oggetto.
- La tecnica chirurgica deve preservare gli standard oncologici raccomandati per le patologie neoplastiche (legatura all'origine dei vasi, adeguato margine libero da malattia prossimale e distale, negatività del margine radiale mesorettale (CRM), nella chirurgia del retto con TME, numero di linfonodi adeguati per una corretta stadiazione patologica).
- Uso di incisioni chirurgiche di preferenza trasversali. In chirurgia laparoscopica, la minilaparotomia per l'estrazione del pezzo operatorio viene realizzata di preferenza in sede sovrapubica (incisione di Pfannenstiel).
- Astensione dall'uso routinario dei drenaggi salvo anastomosi extraperitoneale, anche con stomia di protezione:
    - Il posizionamento del drenaggio potrebbe essere opportuno nei casi di aumentato rischio di sanguinamento o di aumentato rischio di deiscenza (per contaminazione intraoperatoria, inadeguata vascolarizzazione, livello

dell'anastomosi, positività della prova pneumatica, motivi tecnici legati alla sutura, comorbidità del paziente, etc).

- Infiltrazione delle ferite con anestetico locale (levobupivacaina 0.5 % + fisiologica qb) al termine dell'intervento se non è stato posizionato un caterere peridurale.

Gestione postoperatoria

- Rimozione del SNG al risveglio. L'indicazione all'eventuale riposizionamento nel postoperatorio è la persistenza del vomito malgrado adeguata terapia farmacologica multimodale (vedi paragrafo "Terapia antiemetica").

- Monitoraggio nell'immediato postoperatorio:
  - recupero delle capacità cognitive;
  - dopo intervento laparoscopico monitoraggio continuo della saturazione in respiro spontaneo per 1 ora;
  - mantenimento di ossigenoterapia a bassi flussi (2 l/min) opzionale sino al mattino seguente;
  - valutazione del dolore;
  - controllo temperatura ascellare (tempo 0/3/6 h).

- Alimentazione precoce e terapia infusionale:
  - infusione di liquidi post-operatoria di circa 1-2 ml/kg/ora in prima giornata;
  - rimozione delle infusioni endovenose entro la prima giornata post-operatoria. Se l'alimentazione orale precoce (vedi schema seguente) non è realizzabile va mantenuta la terapia infusionale da modificare comunque secondo l'assunzione orale di liquidi;
  - due ore dopo il risveglio dall'anestesia reintroduzione della dieta idrica;
  - la sera dell'intervento (almeno 6 ore dopo il risveglio): liquidi o dieta leggera in funzione dell'orario di fine della procedura chirurgica. Per i pazienti operati nel pomeriggio è ammesso che il primo pasto sia la colazione del mattino successivo;
  - dalla prima giornata bere idealmente sino ad un massimo di 2 litri di liquidi incrementando l'alimentazione per os (i pasti vengono consumati seduti a tavola);
  - uso di integratori orali calorico-proteici liquidi o cremosi: suggerito fino al raggiungimento dei fabbisogni calorici e proteici; per i pazienti malnutriti è indicata la somministrazione di immunonutrizione per 5 giorni post intervento;
  - procinetici (opzionale): valutare la somministrazione dall'immediato postoperatorio fino all'avvenuta canalizzazione.
  - E' utile che il paziente tenga un diario in cui registrare l'assunzione di bevande e alimenti post-intervento (allegato n.9).

- Mobilizzazione precoce:
  - il giorno dell'intervento: dopo 4 ore dal risveglio mobilizzare (seduto) con obiettivo di stare per 2 ore seduto;
  - 1^ giornata: obiettivo per il paziente è restare fuori dal letto almeno 8 h e camminare;
  - 2^ giornata: attività normale, non inferiore a quanto descritto per la 1^ giornata.

  Si raccomanda di utilizzare locali e poltrone adeguati per favorire la permanenza fuori dal letto. E' utile che il paziente tenga un diario in cui

registrare il tempo trascorso fuori dal letto ed eventualmente, fornendogli i riferimenti opportuni, la distanza percorsa camminando (esempio in allegato n.9).

- Rimozione precoce del catetere vescicale. Il catetere vescicale va rimosso all'inizio della 1^ giornata post operatoria. Il catetere va mantenuto in sede nei seguenti casi:
    - Diuresi < 500 ml/24 h;
    - Resezione anteriore con anastomosi extraperitoneale (rimozione in 2^ giornata).

- Analgesia:
    - Nei pazienti con catetere epidurale funzionante con infusione continua (di regola fino alla 2^ giornata) l'analgesia va integrata se necessario con paracetamolo 1 g ev (max 4g/die) e, dopo rimozione del catetere epidurale, con FANS al bisogno.
    - Se il catetere epidurale non è stato posizionato si prescrivono FANS + paracetamolo ed eventualmente oppioidi minori.
    - Si sconsiglia l'uso di oppioidi maggiori che presentando effetti collaterali dose dipendente potrebbero ritardare una precoce ri-alimentazione ed aumentare le probabilità di ileo post-operatorio.

- Terapia antiemetica.
    - L'obiettivo è di non sospendere l'assunzione di liquidi e l'alimentazione per os. E' pertanto necessario un controllo ottimale dei sintomi (nausea e vomito) con terapia farmacologica multimodale (ad esempio cortisonico, ondansetron). Nei soggetti con rischio elevato di PONV (valutato in base all'Apfel score) la terapia antiemetica va prescritta di principio.

Rilevazione giornaliera dei criteri " fit for discharge"

1. Alimentazione orale tollerata.
2. Ripresa funzione intestinale.
3. Controllo del dolore con analgesici per os.
4. Autonomia motoria e nelle cure igieniche personali.
5. Non evidenza clinica / laboratoristica di complicanze postoperatorie
6. Consenso del paziente alla dimissione.

Controlli post-dimissione

- Contatto telefonico con il paziente 2-3 giorni post-dimissione.
- Visita postchirurgica nei 30-40 gg successivi all'intervento.

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Allegato 2 - Scheda raccolta dati (Case Report Form – CRF).

File pdf allegato

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Allegato 3 - Questionario QoR-15 per valutare la qualità del recupero post-operatorio.

File pdf Allegato

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Allegato 4: Questionario SSQ-8 per valutare la soddisfazione dei pazienti dopo la dimissione - Versione in italiano ottenuta attraverso un processo di traduzione e retro traduzione ("forward/backward translation"), da sottoporre a validazione su un primo campione di pazienti.

Studio ERAS
Chirurgia colorettale
Questionario per valutare la soddisfazione dopo un intervento chirurgico

Istruzioni: di seguito sono elencate alcune domande relative al grado di soddisfazione per l'intervento chirurgico al quale si è sottoposto/a recentemente. Per piacere, indichi quale delle risposte esprime meglio la sua esperienza. Tutte le risposte sono strettamente confidenziali e coperte dal regolamento EU 269/2016.

1. Quanto è soddisfatto/a di come è stato controllato il suo dolore dopo l'intervento mentre era in ospedale?
   ☐ molto soddisfatto/a ☐ soddisfatto/a ☐ parzialmente soddisfatto/a ☐ insoddisfatto/a ☐ molto insoddisfatto/a

2. Quanto è soddisfatto/a di come è stato controllato il suo dolore una volta tornata a casa dopo l'intervento?
   ☐ molto soddisfatto/a ☐ soddisfatto/a ☐ parzialmente soddisfatto/a ☐ insoddisfatto/a ☐ molto insoddisfatto/a

3. Quanto è soddisfatto/a del tempo che ha impiegato per riprendere le sue attività quotidiane, per esempio svolgere lavori domestici o attività sociali fuori casa?
   ☐ molto soddisfatto/a ☐ soddisfatto/a ☐ parzialmente soddisfatto/a ☐ insoddisfatto/a ☐ molto insoddisfatto/a

4. Se lavora (altrimenti saltare la domanda), quanto è soddisfatto/a del tempo che ha impiegato per tornare al suo lavoro?
   ☐ molto soddisfatto/a ☐ soddisfatto/a ☐ parzialmente soddisfatto/a ☐ insoddisfatto/a ☐ molto insoddisfatto/a

5. Quanto è soddisfatto/a del tempo che ha impiegato per riprendere la sua normale attività fisica?
   ☐ molto soddisfatto/a ☐ soddisfatto/a ☐ parzialmente soddisfatto/a ☐ insoddisfatto/a ☐ molto insoddisfatto/a

6. Quanto è soddisfatto/a dell'assistenza ricevuta?
   ☐ molto soddisfatto/a ☐ soddisfatto/a ☐ parzialmente soddisfatto/a ☐ insoddisfatto/a ☐ molto insoddisfatto/a

7. Quanto è soddisfatto/a delle informazioni ricevute dal personale sanitario (medico o infermieristico) sul suo intervento?
   ☐ molto soddisfatto/a ☐ soddisfatto/a ☐ parzialmente soddisfatto/a ☐ insoddisfatto/a ☐ molto insoddisfatto/a

8. Consiglierebbe ad altre persone con lo stesso problema di farsi operare nello stesso ospedale?
   ☐ sì ☐ forse ☐ non so ☐ non credo ☐ no

Allegato 5 - Opuscolo informativo per i pazienti.

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Allegato 6 - MUST score

'Malnutrition Universal Screening Tool'

(Strumento di screening universale della malnutrizione)

BAPEN www.bapen.org.uk

MAG Malnutrition Advisory Group A Standing Committee of BAPEN

Numero di registrazione della BAPEN 1023927 www.bapen.org.uk

'MUST'

Il 'MUST' è uno strumento di screening in cinque fasi per identificare **adulti** malnutriti, a rischio di malnutrizione (sottonutrizione) od obesi. Include anche linee guida gestionali che possono essere utilizzate per sviluppare un programma terapeutico.

È adatto all'uso in ospedale, comunità e altre strutture assistenziali e può essere utilizzato da tutti gli operatori sanitari.

Questa guida contiene:

- Un diagramma di flusso che illustra le 5 fasi da seguire per lo screening e la gestione
- Il grafico IMC
- Tabelle del calo di peso
- Misure alternative quando non è possibile ottenere l'IMC misurando peso e altezza.

Le 5 fasi del 'MUST'

Fase 1

Misurare altezza e peso per ottenere un punteggio di IMC usando il grafico fornito. *Se è impossibile ottenere l'altezza e il peso, usare le procedure alternative illustrate in questa guida.*

Fase 2

Annotare il calo di peso percentuale non programmato e assegnarvi un punteggio usando le tabelle fornite.

Fase 3

Stabilire l'effetto di malattie acute e assegnarvi un punteggio.

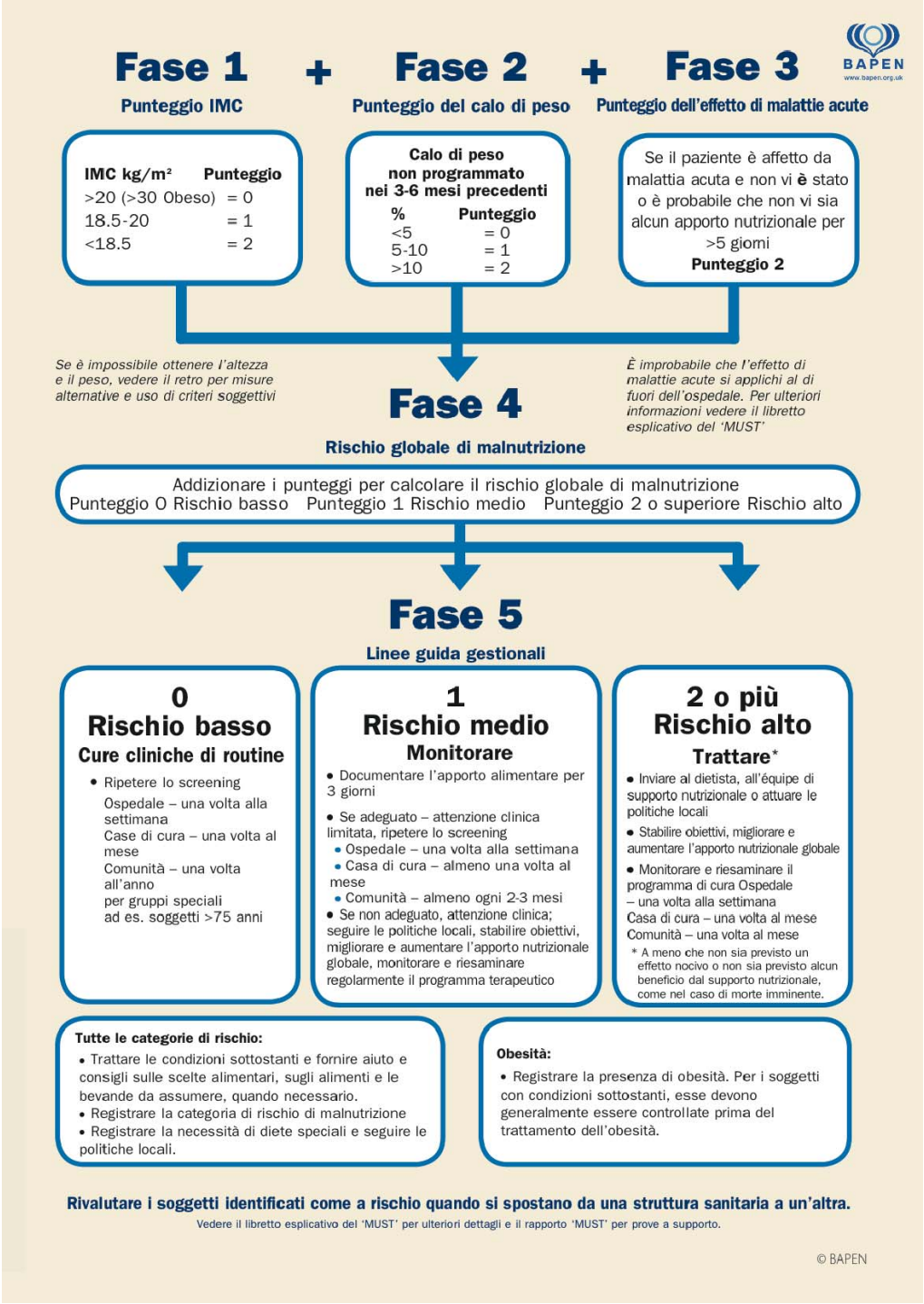
Fase 4

Addizionare i punteggi dei passaggi 1, 2 e 3 per ottenere il rischio globale di malnutrizione.

Fase 5

Usare le linee guida gestionali e/o le politiche locali per sviluppare un programma terapeutico.

Fare riferimento al libretto esplicativo del 'MUST' per maggiori informazioni qualora peso e altezza non possano essere misurati e nei casi in cui si effettui lo screening di gruppi di pazienti per i quali è necessaria una cautela particolare nell'interpretazione dei dati (ad es. soggetti con disturbi dei liquidi, ingessature, amputazioni, malattie critiche e donne in gravidanza o allattamento). Questo libretto può anche essere utilizzato per la formazione. Vedere il rapporto 'MUST' per prove a supporto. Si osservi che il 'MUST' non è stato progettato per rilevare carenze o apporti eccessivi di vitamine e minerali ed è adatto all'uso **solo negli adulti.**



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Misure alternative e considerazioni

Fase 1: IMC (Indice di massa corporea)

Se non è possibile misurare l'altezza

- Usare un'altezza documentata recentemente o autoriferita (se affidabile e realistica).
- Se il soggetto non conosce o non è in grado di riferire la propria altezza, usare una delle misure alternative per stimarla (ulna, altezza al ginocchio o semiampiezza delle braccia).

Fase 2: Calo recente di peso non programmato

Se un calo di peso recente non può essere calcolato, usare il calo di peso autoriferito (se affidabile e realistico).

Criteri soggettivi

Se non è possibile ottenere altezza, peso o IMC, i seguenti criteri a essi correlati possono facilitare un giudizio clinico sulla categoria di rischio nutrizionale del soggetto. Si osservi che questi criteri devono essere usati collettivamente e non separatamente come alternative alle fasi 1 e 2 del 'MUST' e non sono ideati per assegnare un punteggio. La circonferenza media del braccio (MUAC) può essere usata per stimare la categoria di IMC a supporto dell'impressione globale del rischio nutrizionale del soggetto.

1. IMC

- Impressione clinica – magro, peso accettabile, sovrappeso. Si possono anche notare deperimento evidente (molto magro) e obesità (molto sovrappeso).

2. Calo di peso non programmato

- Gli indumenti e/o i gioielli sono diventati molto larghi (calo di peso).
- Precedenti di diminuzione dell'assunzione di cibo, riduzione dell'appetito o problemi di deglutizione per 3-6 mesi e malattie sottostanti o disabilità psicosociali/fisiche che potrebbero causare un calo di peso.

3. Effetto di malattie acute

- Malattia acuta e nessun apporto nutrizionale o probabilità di nessun apporto per più di 5 giorni.

Maggiori dettagli sulle misure alternative, su circostanze speciali e criteri soggettivi si possono trovare nel libretto *esplicativo del 'MUST'*. È possibile scaricarne una copia dal sito www.bapen.org.uk o acquistarla dagli uffici della BAPEN. Le prove complete a supporto del 'MUST' sono incluse nel *rapporto 'MUST'*, che può anche essere acquistato presso gli uffici della BAPEN.

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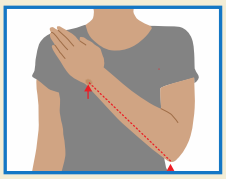
Il 'MUST' è supportato dalla British Dietetic Association (Associazione britannica di dietetica), dal Royal College of Nursing (Collegio reale degli infermieri) e dalla Registered Nursing Home Association (Associazione registrata delle case di cura).

Misure alternative: istruzioni e tabelle

Se non è possibile ottenere l'altezza, usare la lunghezza dell'avambraccio (ulna) per calcolarla usando le tabelle seguenti.
(Vedere il libretto esplicativo del 'MUST' per dettagli sulle altre misure alternative (altezza al ginocchio e semiampiezza delle braccia) che possono essere utilizzate per stimare l'altezza).

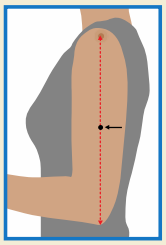
Stima dell'altezza dalla lunghezza dell'ulna



Misurare tra il punto del gomito (processo olecranico) e il punto centrale dell'osso sporgente del polso (processo stiloideo) (se possibile sul lato sinistro).

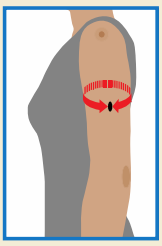
Altezza (m)	Uomini (<65 anni)	1.94	1.93	1.91	1.89	1.87	1.85	1.84	1.82	1.80	1.78	1.76	1.75	1.73	1.71
	Uomini (≥65 anni)	1.87	1.86	1.84	1.82	1.81	1.79	1.78	1.76	1.75	1.73	1.71	1.70	1.68	1.67
	Lunghezza dell'ulna (cm)	32.0	31.5	31.0	30.5	30.0	29.5	29.0	28.5	28.0	27.5	27.0	26.5	26.0	25.5
Altezza (m)	Donne (<65 anni)	1.84	1.83	1.81	1.80	1.79	1.77	1.76	1.75	1.73	1.72	1.70	1.69	1.68	1.66
	Donne (≥65 anni)	1.84	1.83	1.81	1.79	1.78	1.76	1.75	1.73	1.71	1.70	1.68	1.66	1.65	1.63
Altezza (m)	Uomini (<65 anni)	1.69	1.67	1.66	1.64	1.62	1.60	1.58	1.57	1.55	1.53	1.51	1.49	1.48	1.46
	Uomini (≥65 anni)	1.65	1.63	1.62	1.60	1.59	1.57	1.56	1.54	1.52	1.51	1.49	1.48	1.46	1.45
	Lunghezza dell'ulna (cm)	25.0	24.5	24.0	23.5	23.0	22.5	22.0	21.5	21.0	20.5	20.0	19.5	19.0	18.5
Altezza (m)	Donne (<65 anni)	1.65	1.63	1.62	1.61	1.59	1.58	1.56	1.55	1.54	1.52	1.51	1.50	1.48	1.47
	Donne (≥65 anni)	1.61	1.60	1.58	1.56	1.55	1.53	1.52	1.50	1.48	1.47	1.45	1.44	1.42	1.40

Stima della categoria di IMC in base alla circonferenza media del braccio (MUAC)



Il braccio sinistro del soggetto deve essere piegato al gomito con un angolo di 90 gradi, con il braccio parallelo al lato del corpo. Misurare la distanza tra la protrusione ossea sulla spalla (acromion) e il punto del gomito (processo olecranico). Segnare il punto centrale.

Chiedere al soggetto di lasciare il braccio pendere e misurarne la circonferenza nel punto centrale, assicurandosi che il metro a nastro sia aderente ma non stretto.



Se la MUAC è <23,5 cm, è probabile che l'IMC sia <20 kg/m².
Se la MUAC è >32,0 cm, è probabile che l'IMC sia >30 kg/m².

L'uso della MUAC fornisce un'indicazione generale dell'IMC e non è destinato a generare un punteggio vero e proprio da usare con il 'MUST'. Per ulteriori informazioni sull'uso della MUAC fare riferimento al libretto *esplicativo del 'MUST'*.

Allegato 7 - Documento di consenso dell'ESPEN 2018

File allegato .pdf

Allegato 8: Esempio di scheda per il monitoraggio dell'assunzione del supplemento nutrizionale preoperatorio

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Pagano E, *et al. BMJ Qual Saf* 2024;0:1–12. doi: 10.1136/bmjqs-2023-016594

Allegato 9: Esempio di diario del paziente per il monitoraggio della mobilizzazione e della assunzione di bevande ed alimenti post-intervento

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Pagano E, *et al. BMJ Qual Saf* 2024;0:1–12. doi: 10.1136/bmjqs-2023-016594