***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; 33:363–374. 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).



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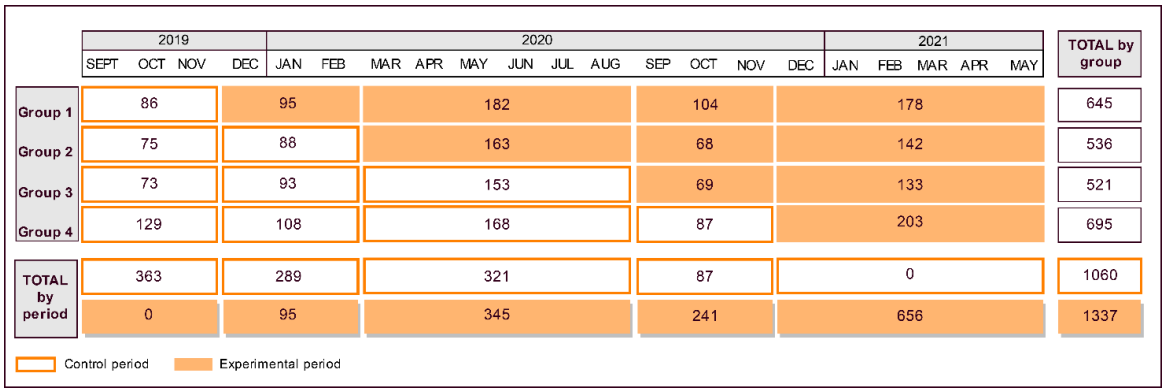
**2) Figure S1. Diagram of the ERAS Colon-rectum Piemonte study, showing number of patients recruited in each group of clusters and study period. * Three months' extension due to COVID-19 pandemic.**

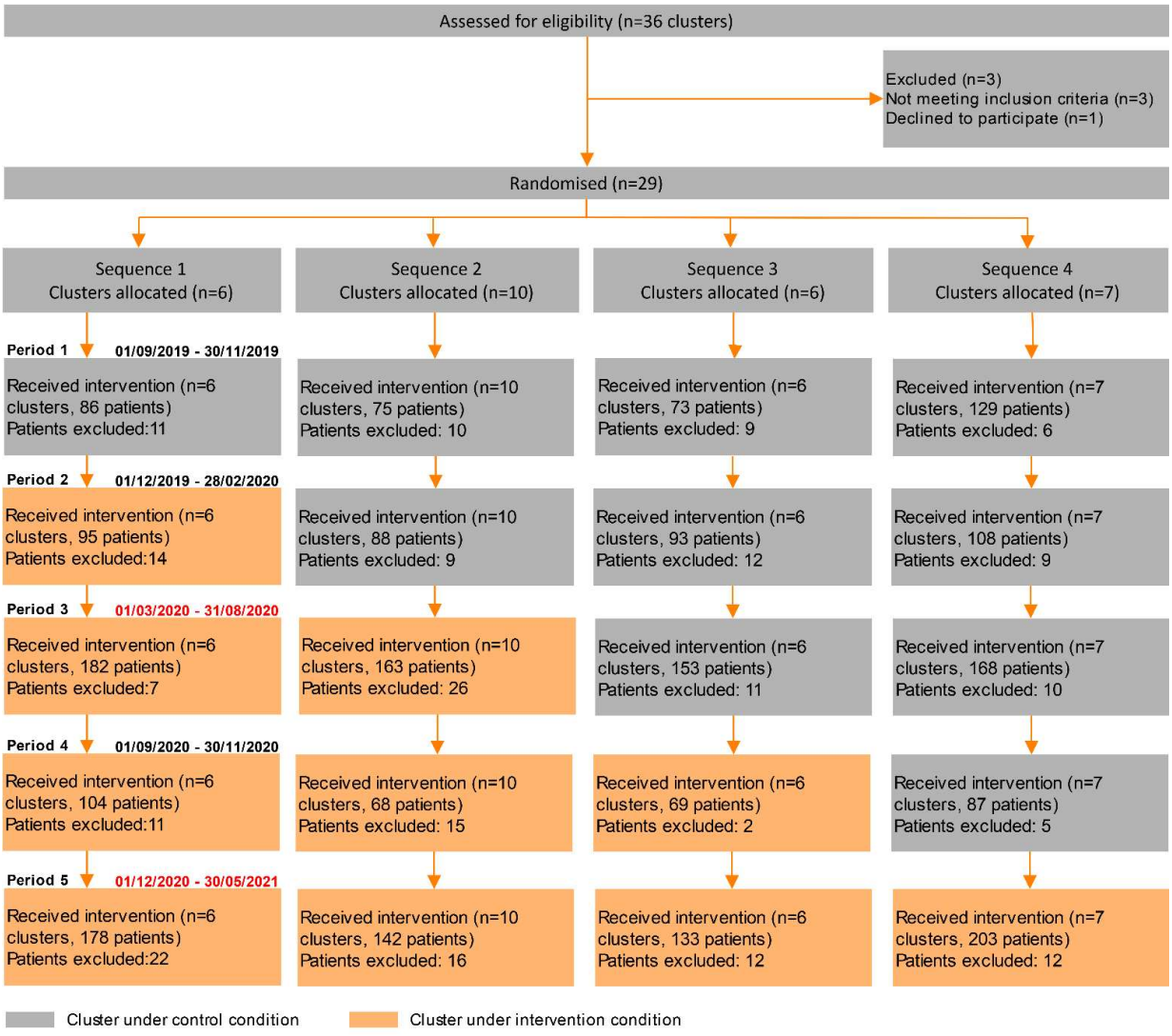


**3) Table S1. Description of Enhanced recovery after surgery (ERAS) items and related compliance indicators, by phase of care, and discharge criteria.**

| 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<br>2. Resumption of bowel function<br>3. Pain control with oral analgesics<br>4. Motor and personal hygiene self-sufficiency<br>5. No clinical/laboratory evidence of postoperative complications<br>Hospital discharge also requires the patient's consent. | | |

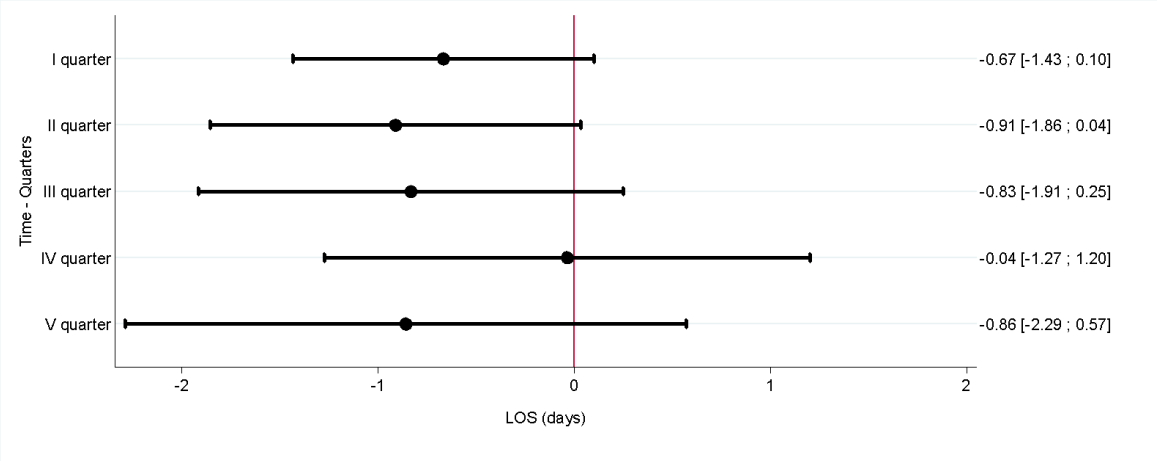
**4) Figure S2. Study flow-chart by allocation sequence and study period.**



**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 |



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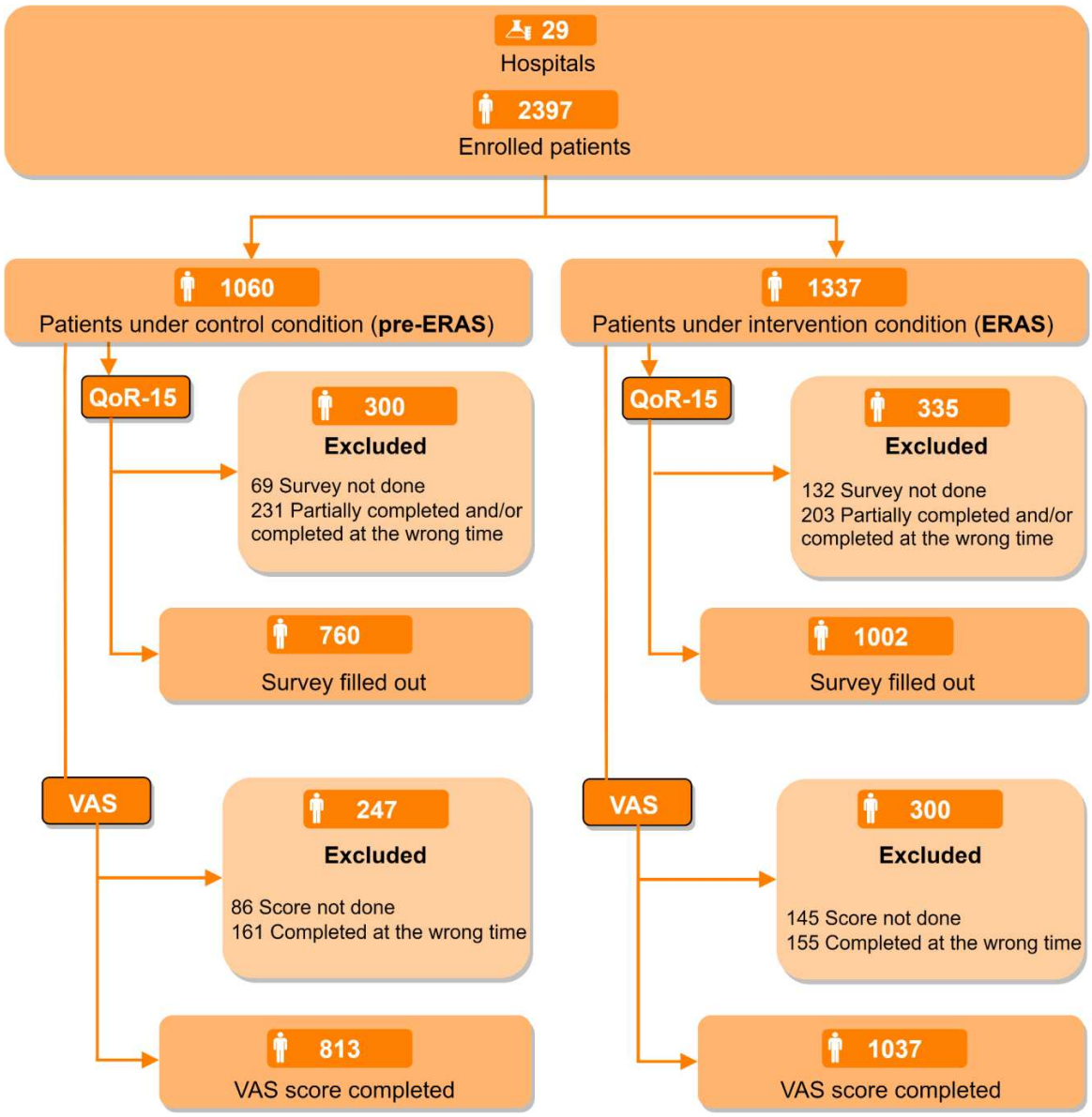
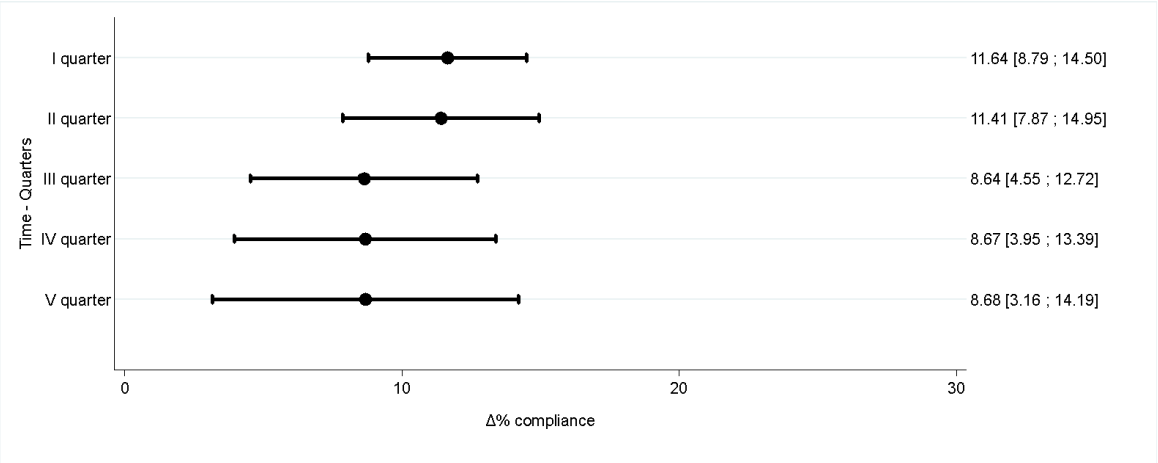
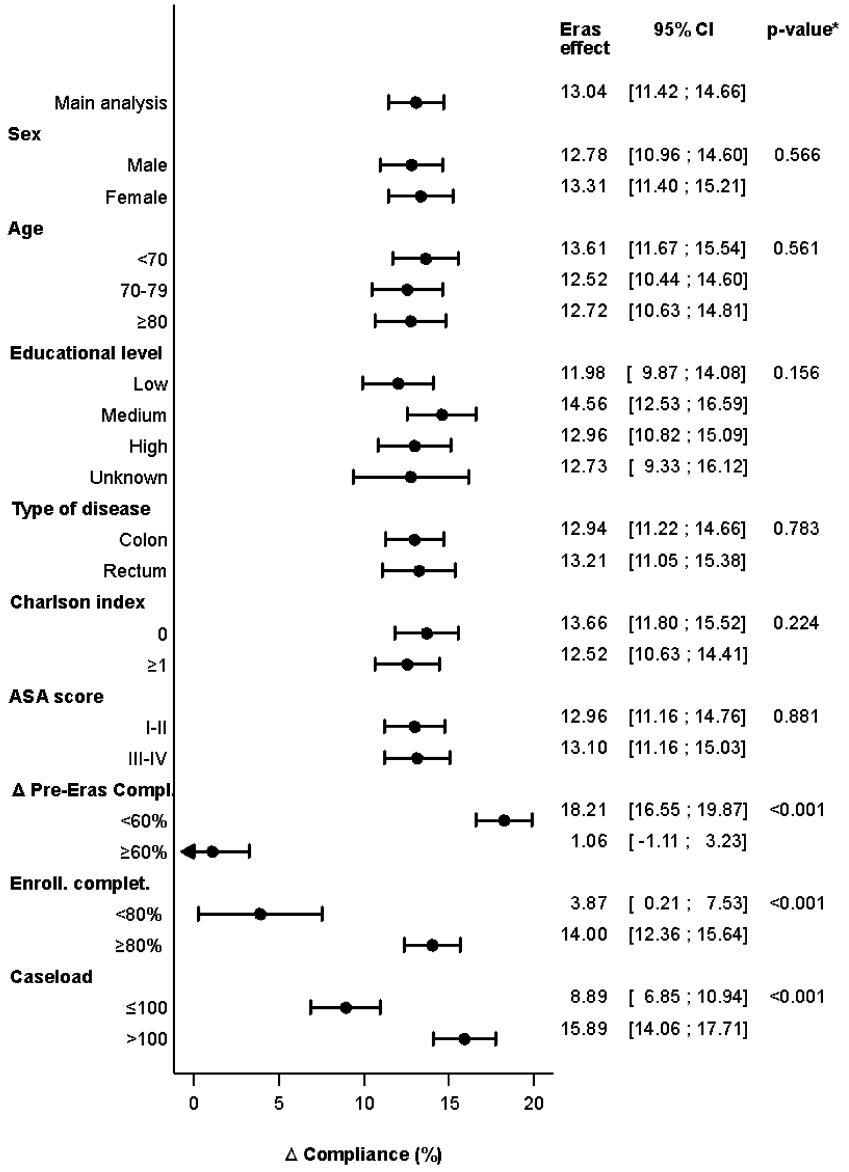
**8) Figure S4. ERAS Colon-Rectum Piemonte study flow for Quality of recovery (QoR) and Visual Analogue Scale (VAS) analyses.**



**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.

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**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.

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**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.