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CHAPTER 6

An individualized versus a conventional pneumoperitoneum pressure strategy during colorectal laparoscopic surgery: rationale and study protocol for a multicentre randomised clinical study

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BACKGROUND

Compared to open surgery, laparoscopic surgery generally results in better outcomes.(1,2) Compared to open abdominal surgery, a laparoscopic approach during abdominal surgery is associated with less blood loss and fewer needs for blood transfusions,(3,4) faster recovery of bowel function and oral intake resumption,(5,6) less analgesics requirements,(6,7) and shorter length of hospital stay (LOS).(3–8) Patient reported outcomes (PROs) are new tools for testing quality of recovery in the postoperative seeting and Post operative quality of recovery scale (PQRS) has been successfully tested in previous studies.

A high intraoperative intra–abdominal pressures (IAPs) is clearly associated with perioperative morbidity.(9–14) While guidelines for laparoscopic abdominal surgery recommend the lowest possible IAP at which the surgeon has adequate workspace rather than using a predetermined level,(15,16) it remains common practice to use a standard IAP level throughout the surgical procedure, usually between 12 and 15 mm Hg and sometimes even higher depending on surgical indication.(17) Interestingly, while the surgical condition depends mainly on the intra–abdominal volume (IAV) and the workspace obtained at a given IAP, the focus during pneumoperitoneum insufflation remains with the applied IAP.(18)

Several factors improve the relation between IAP and the obtained surgical workspace, including patient positioning,(19) use of neuromuscular blockade,(20,21) and pre–stretching of the abdominal wall.(22) The preceding 'Individualized Pneumoperitoneum Pressure in Colorectal Laparoscopic Surgery' (IPPCoILapSe) I study shows that combining all these factors with individualized IAP titration resulted in an acceptable working space at 8 mmHg IAP in 61 out of 78 patients (78%).(23) The here presented 'IPPCollapse II' study tests the hypothesis that this individualized pneumoperitoneum pressure strategy improves PQRS when compared to a conventional strategy that uses a fixed pneumoperitoneum pressure approach in patients undergoing scheduled colorectal laparoscopic surgical intervention.

METHODS/DESIGN

Study reporting

This report follows the 'Standard Protocol Items: Recommendations for Interventional Trials and Patient–Reported Outcomes' (SPIRIT–PRO) guidelines. (24,25) Online IPPCollapse II SPIRIT checklist.

Study design

The IPPCollapse II study is a multicentre two–arm parallel–group single–blinded randomized clinical study (Figure 1).

Study setting

The IPPCollapse II study runs in the operating room and surgical wards of four academic hospitals in Spain (OnlineTable 1).

Study population

Patients are eligible for participation if (a) scheduled for laparoscopic colorectal surgery; (b) aged > 18 years; (c) have an American Society of Anaesthesiologists (ASA) physical status I to III; and (d) have no cognitive deficits. Exclusion criteria are: (a) no written informed consent; (b) emergency or unplanned surgery; (c) pregnancy or breastfeeding; (d) immunologic or neuromuscular diseases; (e) advanced stage of cardiopulmonary, renal or hepatic disease; and (f) allergy to or contraindications for rocuronium or sugammadex.

Randomization and blinding

Patients are randomized in a 1:1 ratio to an individualized pneumoperitoneum pressure strategy (the intervention group) or a standard pneumoperitoneum pressure strategy (the control group). Local investigators perform randomisation using a web–based automated randomization system (Biostatistics Unit of the Health Research Institute la Fe, Valencia, Spain).

Randomisation is performed with random block sizes and is stratified per centre. While attending anaesthesiologists are aware of the assigned pneumoperitoneum pressure strategy, patients and attending surgeons remain unaware of the assigned pneumoperitoneum pressure strategy at all times. PQRS is a patient reported outcome where the care provider has little room for causing bias even unwillingly. Patient is actually blinded to the treatment arm. Pneumoperitoneum insufflator screen is covered

by a surgical drap. Study team member, who are not blinded to randomization, perform postoperative PQRS measurements.

Standard pneumoperitoneum pressure strategy

The standard strategy consists of the following elements, to be performed in the same order in all patients in the control group: (a) patients are placed in a position according to the surgeon's preference within a predefined range of Trendelemburg (0–30°); (b) patients receive moderate neuromuscular blockade with rocuronium, cisatracurium or atracurium throughout surgery to maintain a train–of–four (TOF) between 2 and 4; and (c) IAP is set at 12 mm Hg throughout surgery. At any time, surgeons can request for an IAP increase if workspace becomes 'inadequate'; in that case IAP is increased in steps of 1 mm Hg during 1–minute intervals to a maximum of 15 mm Hg, but not higher than the level at which the surgical workspace returns to become 'adequate'. Surgeons will be warned if the IAP reaches the predefined upper limit. Neuromuscular blockade pharmacological reversion is achieved with neostigmine (2.5 mg or 30–50 $\mu g \cdot kg^{-1}$), according to usual care.

Individualized pneumoperitoneum pressure strategy

The multifaceted individualized pneumoperitoneum strategy consists of the following elements, that will be performed in the same order in all patients in the intervention group: (1) patient position is modified to increase the anteroposterior intra–abdominal space by correcting lumbar lordosis (2) patients receive deep neuromuscular blockade throughout surgery to maintain a (TOF) of 0 and a Post–Tetanic Count (PTC) between 1 and 5; (3) the abdominal wall and muscles are pre–stretched by maintaining an IAP of 15 mm Hg for 5 minutes during the first CO_2 gas insufflation and insertion of trocars (to achieve this the CO_2 gas insufflator will be initially set at 15 mm Hg with a flow rate of 3 $L \cdot min^{-1}$); and (4) individualized IAP titration when the patient is placed in the surgical position (0–30º Trendelenburg); for this, the flow rate is increased to 30 $L \cdot min^{-1}$ and IAP is decreased from 15 to 12 mmHg, and thereafter stepwise to 11, 10, 9 and finally 8 mm Hg as long as the attending surgeon keeps 'adequate' workspace. As in the standard pneumoperitoneum pressure group surgeons can request an IAP increase up to 15 mm Hg which will be performed likewise. Of note, the pressure increment is available in both groups with the same methodology, a previous feasibility study showed that pressure increase is seldom needed (17 out of 78 need limited increase during pelvic dissection). (23)

Neuromuscular blockade pharmacological reversion at the end of surgery, before tracheal extubation, is achieved with sugammadex 4 $mg \cdot kg^{-1}$.

For clarity, the elements of the two groups strategies compared are summarized in Table 1.

Standard care

Perioperative management other than the pneumoperitoneum strategy is suggested to follow the Spanish Enhanced Recovery Pathway recommendations (detailed in onlineTable 2) (26). Continuous intraoperative neuromuscular monitoring with acceleromyography (TOF–Watch–SX™, Organon–Teknika, Oss, The Netherlands) is used. At the end of surgery neuromuscular blockade will be fully reversed to a TOF ratio (TOFr) of at least 0.9 before tracheal extubation. An electronic CO_2 insufflator (Endoflator™, Karl Storz, Tuttlingen, Germany) will be used for gas insufflation into the abdominal cavity through a paraumbilical–placed laparoscopic trocar/Veress needle.

Patients in both groups will be ventilated in a volume controlled ventilation mode, using a tidal volume of 8 ml/kg predicted ideal body weight, with a 20% inspiratory pause time, and positive end–expiratory pressure set at 5 or 10 mm Hg, in patients with a body mass index (BMI) < 30 or ≥ 30 $kg \cdot m^{-2}$, respectively. Oxygen inspiratory fraction is 0.8 throughout surgery. Respiratory rate is set at 12 to 15 per minute to maintain normal end–tidal CO_2 values (27).

Primary outcome

The primary outcome is the Post–operative Quality of Recovery Scale (PQRS) at postoperative day 1 (POD1) (see below for details).

Secondary outcomes

Secondary outcomes include PQRS at 15 minutes (T15) and at 40 minutes (T40) after arrival in the Post Anaesthesia Care Unit (PACU), and in the surgical wards during the morning at postoperative day 3 (POD3). Other secondary clinical outcomes include daily postoperative complications until hospital discharge, and at postoperative day 28, hospital length of stay and secondary process–related outcomes that include the highest IAP level and intra–abdominal volume (IAV) at which surgery could be performed, hepatic perfusion during pneumoperitoneum, and the ventilatory parameters plateau pressure and driving pressure.

Occurrences of diaphragm and abdominal wall contractions or spontaneous breathing efforts and coughing during surgery are collected and compared between the two study groups.

Substudies

The IPPCollapse II study has three substudies (please see Protocol supplementary content for additional details):

1. Levels of biomarkers (neutrophil–lymphocyte ratio, C–reactive protein, Interleukin 6, and procalcitonin) are measured in peripheral venous blood samples obtained before surgery and at POD1 and POD 3 and compared between the two study groups. For this substudy, blood samples are obtained in all participating centres.
2. Untargeted metabolomics analysis is performed of peripheral venous blood samples and peritoneal tissue, both obtained after initial insufflation of pneumoperitoneum and at the end of the procedure. This substudy includes the first 10 patients in the Hospital Universitari i Politecnic La Fe, Valencia, Spain.
3. Plasma disappearance rate of indocyanine green (PDR_{ICG}) after intravenous ICG injection, to evaluate hepatic perfusion during pneumoperitoneum as a marker of liver function. (28) This substudy runs only at the University Hospital Gregorio Marañon, Madrid, Spain.

Post–operative Quality of Recovery Scale

PQRS is a validated multi–dimensional Patient–Reported Outcomes (PROs)–tool,(29–31) designed to assess patients' recovery to baseline status in the postoperative period (www.postopqrs.com). In every patient a baseline measurement of PQRS is performed prior to surgery. After surgery, the measurement of PQRS is repeated at 15 minutes (T15) and at 40 minutes (T40) after arrival in the Post Anaesthesia Care Unit (PACU), as well as in the ward in the morning of postoperative day 1 (POD1) and 3 (POD3). PQRS is a verbal survey tool that depicts recovery in the following 5 domains: physiologic, nociceptive, emotive, functional, cognitive, and also collects overall patient perspective. Each of these domains is assessed with multiple items on an ordinal scale and compared with baseline to evaluate recovery (see Table 2 for details). Recovery is a dichotomized outcome defined by a return to at least baseline values or better at each of the postoperative measurement time points. Overall recovery requires recovery in all domains being assessed, and failure in any domain results in failure of overall recovery.

Definitions

IAP will be recorded as read from the gas insufflator device. In the intervention group the 'individualized IAP' is defined as the highest IAP needed to obtain and maintain an adequate workspace until completion of surgery. IAV is calculated by linear interpolation from patient's IAP–IAV curve obtained during initial pneumoperitoneum insufflation matching to IAP at which surgery is performed.

'Adequate' workspace is defined as the intra–abdominal workspace sufficient to perform the surgical procedure with no need for corrective manoeuvres (i.e., IAP increase) as judged by the attending surgeon who remains blinded for the actual IAP. Consequently, 'inadequate' workspace is defined as the intra–abdominal workspace insufficient to perform the surgical procedure with the need for corrective manoeuvres (i.e., IAP increase).

Definitions of the various postoperative complications recorded are according to the current European standards for perioperative outcomes (Table 3). (32) Severity of postoperative complications is evaluated using Clavien–Dindo grading (Table 4).(33)

Respiratory system driving pressure (ΔP_{rs}) is calculated by subtracting PEEP from Pplat. (34)

Perioperative safety issues are recorded during the surgery and are related to involuntary patient movements, and defined as diaphragm or abdominal wall contractions, or spontaneous breathing efforts or coughing during anaesthesia.

Hospital length of stay is defined as hospital discharge date minus hospital admission date.

Data to be collected

Before anaesthesia: demographic data including age (years), gender, body height (cm) and body weight (kg), BMI ($kg.m^{-2}$), ASA physical status score; comorbidities; number of previous abdominal surgeries and number of previous laparoscopic surgeries; PQRS.

During anaesthesia: levels of IAPs at which surgery is performed (mmHg) in both groups; proportion of patients that needed a pressure increment to achieve acceptable surgical workspace; IAV at start of pneumoperitoneum (litres); coughing and spontaneous movements (yes/no); type of surgery and oncologic status; duration of surgery (minutes), duration of anaesthesia (minutes); proportion of patient that needed conversion from laparoscopic to open surgery and the reason for it (only if applicable); ventilation data including PEEP (cm H_2O), plateau pressure (cm H_2O), respiratory driving pressure ($\Delta P_{rs,}$) (cm H_2O) before pneumoperitoneum generation and during initial IAP titration until a stable level of IAP is reached in both groups; type and dose of neuromuscular blocking agent (mg); type and dose of neuromuscular blocking reversal agent (mg); total opioid requirement during the first 24 hours if used (mg); and plasma disappearance rate of indocyanine green (PDR_{ICG}) in the stable pneumoperitoneum phase.

Directly after anaesthesia, in the PACU: PQRS at 15 and 40 minutes after PACU admission and on Postoperative day 1 and 3: PQRS in the morning and peripheral venous blood samples are obtained for determination levels of biomarkers.

All postoperative days till hospital discharge and at day 28: occurrence of postoperative complications and location.

Analysis plan

The statistical analysis plan (SAP) is specified before enrolment of the first patient. In the absence of studies assessing differences in recovery, based on intraoperative IAP management during laparoscopic colorectal surgery, we performedthe sample size calculation assuming an odds ratio of 2.65 (equivalent to a difference of 0.5 units in the logit scale) between groups in the physiologic PQRS recovery scale, it was estimated that a sample size of 170 patients is required to achieve 80% power at a significance level of alpha = 0.05. All reasons for dropouts, expected to be as low as 10%, will be collected and reported. Conversion to open surgery was the main reason for drop out in previous study. We will recruit a total of 190 patients to compensate for potential losses.

All analysis will be performed with R software (R Foundation for Statistical Computing, Vienna, Austria). Data will be expressed as the mean (SD) or median [IQR] for continuous variables depending on their distribution (normality will be checked with Shapiro–Wilks test), and by counts and proportions for categorical variables. The 95% confidence intervals will be calculated for each of the estimated percentiles. Statistical significance level will be set at $P < 0.05$.

The analysis of the primary endpoint follows the intention–to–treat principle. The difference between the PQRS score between groups, primary outcome on POD1, will be assessed by mixed ordinal logistic regression introducing the patient as random factor, and age, weight, BMI and sex as covariables.

The differences in Clavien–Dindo grading of postoperative complications will be assessed by ordinal regression.

For IAV calculation the relationship between IAP and the insufflated volume of CO_2 will be determined for each patient during initial pneumoperitoneum insufflation. The relationship between IAP and IAV was analysed by linear interpolation from the individual IAP/IAV curves to determine the actual IAV at which surgery is performed. The IAP before CO_2 gas insufflation was considered the basal IAP or intra–abdominal pressure

at volume zero, and was estimated by fitting multiadaptive linear regression splines to intraabdominal volume and pressure relationship.

Differences in continuous variables between groups (IAP, IAV, LOS, inflammatory biomarkers) will be assessed by linear regression or with Mann–Whitney U test (if normal distribution assumption rejected by Shapiro-Wilks test).

Differences in ΔP_{rs} between groups will be assessed by linear regression. A multivariable model introducing BMI, previous laparoscopic surgery and age, will be fitted for predictive purposes.

Differences in the plasma disappearance rate of ICG are assessed by beta regression.

The occurrence of cough or spontaneous movements during anaesthesia are assessed by logistic regression.

The relationship between IAP and IAV will analysed by linear interpolation from the individual IAP/IAV curves. The IAP before CO_2 gas insufflation (IAP at volume zero) will be estimated by fitting multi–adaptive linear regression splines to intra-abdominal volume and pressure relationship. If a variable has a frequency of missing data > 5% data will be imputed by the multiple imputation method.

As there is no ethically unacceptable risk related to the primary outcome analyzed there will be no planned interim analysis.

Adverse events

The investigator record in the CRF any adverse event (AE, serious, SAE or non-serious, nSAE) that occurs in a patient in the clinical trial, related to the study medication or not, (including the observational period, and before and after treatment). The AE will be followed up by the investigator and documented in the CRF up to 28 days after the end of the treatment period. All AEs (except those identified as not requiring immediate notification by the study protocol) will be notified within 24 hours to the Steering committee of the investigator becoming aware of the SAE.

Auditing

Site may be subject to audits, IEC/IRB review, and regulatory inspection(s). Local investigators will provide direct access to the source data documents (See Additional file 4 content for full detail).

Ethics and dissemination

The study will be carried out according to a protocol reviewed and approved at a national level by the Institutional Review Board (IRB) of Hospital Universitari I Politécnic la Fe, Valencia, Spain, and Agencia Española del Medicamento y Productos sanitarios (AEMPS). The study has been registered at clinicaltrials.gov (identifier: NCT02773173, May 16, 2016) and EudraCT (2016–001693–15), and is conducted in accordance with the Declaration of Helsinki on ethical principles for medical research in human subjects, adopted by the General Assembly of the World Medical Association (1996). Data management, monitoring and reporting of the study is performed in accordance with the International Conference on Harmonization – Good Clinical Practice guidelines (ICH) (CPMP/ICH/135/95) and the regulatory requirements for participating institutions by Spanish Clinical Research Network (SCReN). Investigators collect a written informed consent form in compliance with the GCP recommendations to the patient or his/her legal representative if his/her clinical conditions do not allow him to review and approve it. Investigators provide a copy of the signed informed consent form to each subject and keep a copy in the subject's study file. This study protocol is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and Patient–Reported Outcomes (SPIRIT–PRO) guidelines (24)(25).

The results of the study will be communicated through the portal of European Medicine Agency and will be sent for publication in a peer–reviewed medical journal. Authorship will be based on International committee of medical journal editors (ICMJE) criteria. No professional writer will be involved. After publication of the primary results, upon request, the pooled dataset will be available for all members of the IPPCoILapSe II study group for secondary analysis, after judgment and approval of scientific quality and validity of the proposed analysis by the Steering Committee. Access to source data will be made available through national or international anonymized datasets upon request and after agreement of the IPPCoILapSe II steering committee.

DISCUSSION

This study is the first randomized clinical study that tests the hypothesis that an individualized pneumoperitoneum pressure strategy focusing on using the lowest possible IAP, compared to a conventional pneumoperitoneum pressure strategy, improves recovery after laparoscopic colorectal surgery. This study uses PQRS as well as the occurrence of postoperative complications until postoperative day 28, and hospital length of stay. Furthermore, we assess process–related outcomes like IAP and IAV during pneumoperitoneum, and associated ventilator parameters. A strong

multidisciplinary commitment between members of the perioperative team, consisting of surgeons and anesthesiologists, makes this complex study feasible.

The IPPColLapSe II study has several strengths. Its prospective design will allow high accuracy of data to be collected, and its sample size allows us to draw valid conclusions. Selection of patient–reported outcomes as the primary outcome of this study facilitate the translation into clinical practice. To the best of our knowledge this is the first multicentre randomized clinical study evaluating the clinical effect of a tailored IAP management. Surgeon will remain blinded for the IAP allowing us to titrate the IAP to the lowest possible level, i.e., the level at which surgeons have adequate working space. Furthermore, we aim to describe the relationship between IAP and actual IAV at which surgery is performed. This could lead, on one hand, to gather evidence towards establishing a volume threshold (e.g. actual workspace) for colorectal laparoscopic to replace the standard pressure threshold, and on the other, to describe the abdominal pressure–volume relationship in a first attempt to achieve something similar to our understanding of lung dynamics during ventilation. Additionally, we link directly the respiratory system and abdomen by assessing IAP and respiratory driving pressure relationship. This could lead to make a step further as far as protective ventilation in the operating room in concerned.

The here proposed study differs from previous studies on this topic. Most studies so far evaluated the individual components of the multifaceted strategy and are largely focused on surgical conditions and not patient–centred outcomes. Besides they just find minor gains from abdominal pre-stretching, or patient positioning optimization and offer inconclusive results or marginally positive effect for the level of neuromuscular blockade. (35–45) Two studies find useful IAP titration in decreasing conventional IAP management, but do not focus on clinical outcomes (46,47).

From our knowledge, only one study so far focused on quality of recovery, using the QoR–40, a 40–item questionnaire on quality of recovery from anaesthesia (36). This study, comparing surgery at low IAP (6 mm Hg) versus standard IAP (12 mm Hg) during laparoscopic donor nephrectomy under deep neuromuscular blockade, found no differences in QoR–40. Of note, in this study surgeons were not blinded for the IAP and in 25% of patients surgery had to be converted to the standard pressure, probably due to surgeon's learning curve. We recently performed the IPPColLapSe I study in which we evaluated feasibility of the intervention that is to be tested in the present study (23). The intervention was found to be safe, highly feasible and resulted in an acceptable

working space at low IAP in most patients. We did not look at patient outcomes in the preceding study.

PQRS has been successfully tested in previous studies to evaluate differences in recovery.(48-51) We acknowledge that finding differences in patient reported outcomes by PQRS modifying a single strategy in a high quality environment could be difficult (52–54). In order to evaluate minor differences in recovery mainly in laboratory data we perform three substudies. Levels of biomarkers (neutrophil–lymphocyte ratio, C–reactive protein, Interleukin 6, and procalcitonin) in the postoperative recovery period are linked to immunosuppression and postoperative complications.(55,56) Metabolomics untargeted intraoperative analysis of blood samples and peritoneum biopsies allow us to depicted differences between groups in the intraoperative and generate hypothesis for new studies. Plasma disappearance rate of indocyanine green (PDR_{ICG}) has been used successfully to evaluate hepatic perfusion in critically ill patients with intra-abdominal hypertension (28) and could draw differences in hepatic perfusion during pneumoperitoneum in this study.

This study has limitations. We exclude ASA IV patients that could benefit more from working with low IAP: Since we test a multifaceted strategy it will remain uncertain which part of the strategy will have the largest impact. In fact, it could be that not all parts have the same magnitude of effect, and it could even be that some parts have no effect at all. Of note, reversal of neuromuscular blockade with sugammadex instead of neostigmine could improve PQRS recovery at T40 although not at POD1 or POD3. Surgeons, blinded for the actual IAP, will evaluate surgical conditions in a practical dichotomous manner as adequate or not, depending on whether any corrective action is needed. This way of measurement might difficult comparisons with other studies, as those using the Leiden–Surgical Rating Scale. The investigators performing PQRS evaluation are not blinded for the intervention, creating a risk of detection bias. Nevertheless, this risk is somewhat attenuated by the fact that as with PRO by design, the ultimate outcome assessor is the patient which is kept blind to the intervention. We calculated the sample size of our study on PQRS differences thus our sample could be underpowered for some secondary outcome that can potentially require a larger sample. In conclusion IPPColLapSe II study is designed to test if an individualized pneumoperitoneum pressure and optimized management versus conventional care affects outcome of patients undergoing colorectal laparoscopic surgery using relevant patient-centred outcomes.

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	STUDY PERIOD							
	ENROLMENT	ALLOCATION	POST ALLOCATION					CLOSE OUT
Timepoints	Preanaesthetic visit	Prior to surgery	Intraoperative evaluation	Postoperative evaluation	POD1 evaluation	POD 3 evaluation	Hospital Discharge evaluation	POD28
ENROLMENT:								
Informed consent	+							
Eligibility screen	+							
Inclusion /exclusion criteria	+							
Demographic data	+							
Comorbidities	+							
Allocation		+						
ASSESSMENTS:								
PQRS baseline		+						
PQRS T15/T40				+				
PQRS POD 1					+			
PQRS POD 3						+		
Blood sample					+	+		
Abdominal compliance data			+					
Airway pressures			+					
PDRicg (HUGMarañon)			+					
Metabolomics sampling (HUiPlaFe)			+					
Pain evaluation VAS					+			
Complications Clavier-Dindo							+	+
Adverse events							+	+

PQRS: Postoperative Quality Recovery Scale. POD: Postoperative Day. VAS: Visual Analogic Scale. PDRicg: Plasma disappearance rate indocyanin green. PACU Post Anaesthesia Care Unit T15. 15 minutes in PACU. T40. 40 minutes in PACU. HUGMarañon. University Hospital Gregorio Marañon. HUiPlaFe. University and Polytechnic Hospital la Fe.

Figure 1. Study time–points.

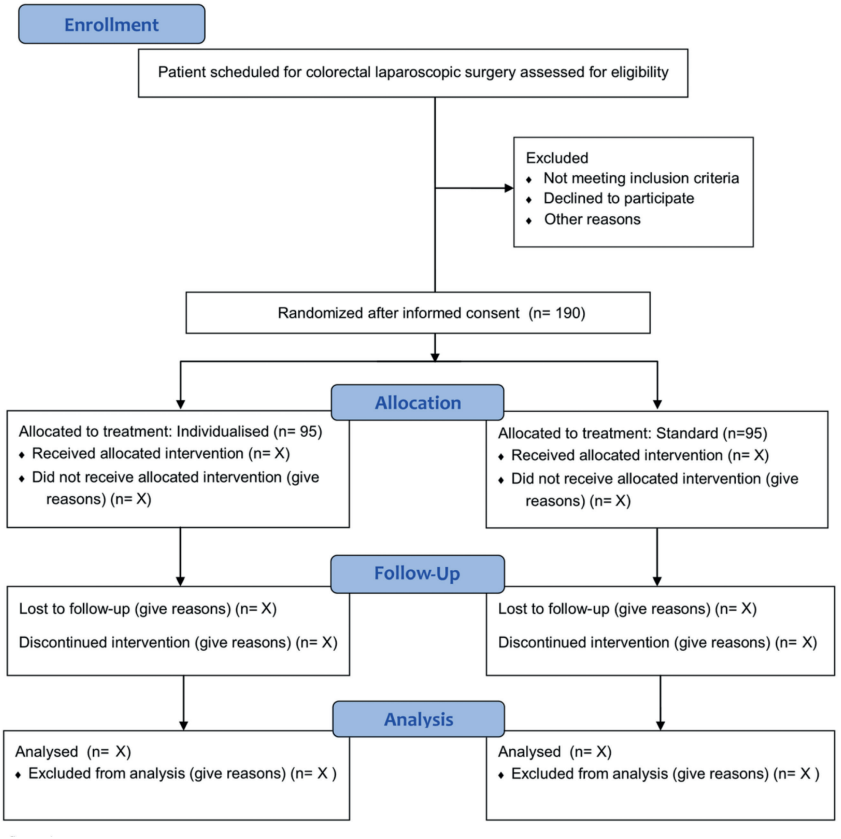

Figure 2. IPPCollapse II flowchart.

Table 1. Collaborating centres in the IPPCOLLAPSE II study, and expected number of patients recruited

Hospital	Number of patients expected to be recruited (n)
Hospital Universitari I Politecnic la Fe, *Valencia*, Spain	100
Hospital General Universitario, *Castellon*, Spain	30
Hospital General Universitario Gregorio Marañon, *Madrid*, Spain	30
Hospital Universitario Virgen Macarena, *Sevilla*, Spain	30

Table 2. Postoperative Quality of Recovery Scale (PQRS).

Domain	Variable	Score	Baseline	T15	T40	POD1	POD3
Physiologic	Blood pressure	1-3	+	+	+	+	+
Physiologic	Heart rate	1-3	+	+	+	+	+
Physiologic	Temperature	1-3	+	+	+	+	+
Physiologic	Respiration	1-3	+	+	+	+	+
Physiologic	SpO2	1-3	+	+	+	+	+
Physiologic	Airway	1-3	+	+	+	+	+
Physiologic	Agitation	1-3	+	+	+	+	+
Physiologic	Consciousness	1-3	+	+	+	+	+
Physiologic	Activity on command	1-3	+	+	+	+	+
Nociceptive	Pain	1-5 Likert	+	+	+	+	+
Nociceptive	PONV	1-5 Likert	+	+	+	+	+
Emotional	Sadness/Depression	1-5 Likert	+	+	+	+	+
Emotional	Anxiety/Nervousness	1-5 Likert	+	+	+	+	+
Functional	Stand	1-3	+	-	-	+	+
Functional	Walk	1-3	+	-	-	+	+
Functional	Eat/drink	1-3	+	-	-	+	+
Functional	Get dressed	1-3	+	-	-	+	+
Cognitive	Name, city and DOB	TF 0	+	-	-	+	+
Cognitive	Numbers forward	TF 2	+	-	-	+	+
Cognitive	Numbers backwards	TF 1	+	-	-	+	+
Cognitive	Word task: list	TF 3	+	-	-	+	+
Cognitive	Executive memory	TF 3	+	-	-	+	+

Online scale to assess multiple domains of post-operative recovery over time. Timeline: **T15** - 15 minutes in PACU; **T 40**- 40 minutes in PACU; **POD1**- Postoperative day 1; **POD3** - postoperative day 3. **PONV**: Postoperative Nausea and Vomiting. **DOB**: Date of birth. **Scoring**: Physiologic 1-3; Nociceptive/emotional: 1–5 Likert rating scale using a faces pictorial display; Functional: Scored as 3: easily, 2: difficulty, and 1: not at all; Cognitive: Performance variability tolerance factor (TF) is applied. Participants not included in subsequent analysis if baseline scores are equal to or less than the tolerance factor.

Table 3. Classification of post-operative complications

1. Acute kidney damage.
2. Acute respiratory distress syndrome (ARDS)
3. Suture dehiscence
4. Arrhythmia
5. Cardiac arrest
6. Cardiogenic pulmonary edema
7. Deep vein thrombosis
8. Postoperative delirium
9. Gastrointestinal bleeding
10. Infection
11. Bacteremia
12. Myocardial infarction.
13. Myocardial injury after non-cardiac surgery
14. Pneumonia
15. Paralytic ileus
16. Post-operative hemorrhage
17. Pulmonary embolism
18. Cerebrovascular accident
19. Infection of surgical wound (superficial)
20. Infection of surgical wound (deep)
21. Infection of surgical (organ) wound
22. Urinary tract infection
Postoperative pulmonary complications:
1. Respiratory infection
2. Respiratory failure
3. Pleural effusion
4. Atelectasis
5. Pneumothorax
6. Bronchospasm
7. Pneumonia due to aspiration

Postoperative complications recorded according to the current European standards for perioperative outcomes

Table 4. Severity grade by Clavien-Dindo definition.

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetic, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anaesthesia
- IIIb	Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	Single organ dysfunction (including dialysis)
- IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patients suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding,but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit CNS: Central Nervous system

APPENDIX TO CHAPTER 6

Published as online supplement and as a correction to the original protocol

SPIRIT checklist for IPPCollapse II study

		Reporting Item	Page
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,35
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-21
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	11-12
Objectives	#7	Specific objectives or hypotheses	6-8

		Reporting Item	Page
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8, table 1
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8-14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8-14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12

		Reporting Item	Page
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-19
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16-19
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	18-21

		Reporting Item	Page
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18-21
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18-21
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18-21
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-19
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19-20

		Reporting Item	Page
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-21
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18-21
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20-21
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	18-21
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18-21
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	18-21
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18-21
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18-21

		Reporting Item	Page
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18-21
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a just in spanish
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	14-16

Enhanced Recovery Pathways Spanish guidelines summary RICA (Intensive recovery in abdominal surgery)		
TIME	**PROTOCOL**	**PROFESSIONAL**
Before hospitalization	Preoperatory evaluation, nutritional optimization, cardiologic test if it is indicated.	Surgeon + Anaesthesiologist
Immediate preoperative (without previous hospitalization)	Thromboembolic prophylaxis (12 h before surgery). Preoperative solid fast 6 hours and clear liquid fast 2 hours. In colon surgery is not indicated bowel mechanical preparation (reserve to rectum surgery)	Surgeon + Anaesthesiologist + Nurse
Perioperative	**Previous surgery** Cleaning enema at 7 am (colorectal surgery) Compression tights or intermittent pneumatics socks for thromboembolic prophylaxis. Carbohydrate 12,5% maltodextrins drinks 250cc 2 hours before surgery. Antibiotic prophylaxis 1 hour before incision. **Intraoperative** Insertion epidural catheter in laparotomy surgery Anaesthesia induction Oxygenation FiO2 60-80% Active warming with air convection blanket Goal directed fluid therapy Balanced solution (laparoscopy 3,5ml/Kg/h) Minimal invasive surgery (when it is possible) Avoid nasogastric tube Nauseas and vomits prophylaxis using Apfel scale. Local anaesthesia in laparoscopic access vs Abdominal Transverse Block. Bladder catheter **Immediate postoperative** Maintenance active warming. FiO2 50% at least 2 hours. Restrictive fluid therapy Oral tolerance 6 hours after surgery Early mobilization Thromboembolic prophylaxis with Enoxaparin 40mg at 10pm. Reduce as minimal opioid administration	Surgeon + Anaesthesiologist + Nurse
POD1	Diet depends on tolerance Active mobilisation (sitting) Intravenous analgesia Consider withdraw bladder catheter Consider withdraw abdominal drains. Nutritional supplements	Nurse + Surgeon + Anaesthesiologist
POD2	Normal diet Active mobilisation (start ambulation) Thromboembolic prophylaxis	Nurse + Surgeon + Anaesthesiologist
Postoperative until hospital discharge	Normal diet Oral analgesia Active mobilisation Thromboembolic prophylaxis	Nurse + Surgeon + Anaesthesiologist
Home	Thromboembolic prophylaxis until POD28 Phone contact Ambulatory support	

ADDITIONAL PROTOCOL DETAILS

1. Sample processing, preparation and analysis. Protocol for substudies of IPPCollapse–II.

Sample processing

Blood samples for the level of biomarkers are collected according to usual clinical practice in each collaborating centre and analysed by its respective reference laboratory.

Blood samples for metabolomics analysis are collected prior to anesthesia induction, immediately after pneumoperitoneum generation and at the end of the laparoscopic procedure. Samples consisting of 5 ml of blood are extracted from a peripheral venous access in a heparin anticoagulant tube, and identified with the patient's identification number and sample number. Samples are kept at 4ºC before being transferred to the metabolomics unit within the hospital within 2 hours. The samples are centrifuged for 10 minutes at 1300 rpm and 4ºC. After centrifugation, 400uL plasma is aliquoted and stored at –80º C.

Peritoneal tissue samples for metabolomics analysis are collected following the same methodology at baseline after pneumoperitoneum generation and at the end of the laparoscopic procedure. Samples are identified with the patient's identification number and sample number and kept in liquid nitrogen tank located in the surgical unit until analysis.

Sample preparation

For the procedure of the plasma samples, once thawed, the proteins will be precipitated by using three volumes of organic solvent, centrifugation (3500 rpm), collecting the supernatant and transferring it to a chromatographic vial for analysis.

The treatment of the tissue samples will be carried out by homogenization with methanol in Precellys homogenizer at 4 ° C using two cycles of 25s at a speed of 6500rpm with intervals of 10 s. After centrifugation of the extract, the supernatant will be concentrated and redissolved in the ideal solution for subsequent chromatographic analysis.

LC-QToF Analysis

The metabolomics analysis will be carried out by means of a chromatographic separation using the UPLC (ultra performance liquid chromatography) chromatographic system available in the Analytical Unit and a Acquity UPLC HSS T3 type chromatographic column (100 x 2.1 mm, 1.8 µm) from Waters (Wexford, Ireland) or similar. The detection

will be carried out by means of a mass spectrometer with time of flight analyser, 6550 QTOF Agilent, available in the Analytical Unit and ideal for "untargeted" approaches. The data in TOF MS full scan mode will be recorded from 50 to 1000 m / z (mass / load ratio) with a scan time of 0.1 s. A LockSpray interface will be used to maintain mass accuracy during the analysis.

The treatment of the samples, as well as the acquisition of data will be carried out under BPL regulations (good laboratory practices), which guarantees the quality and traceability of the results obtained.

Data analysis
The metabolomics comparative analysis between the different samples (data matrices) will require a processing of the data before its analysis, normally an alignment and a normalization. A chemometric approach will be applied, based on PACA and PLSDA models, for the selection of informative and discriminant variables (metabolites) that facilitate the marker selection process. Once the list of possible markers is configured, an unsupervised hierarchical analysis will be carried out in order to check their discriminatory capacity and subsequently they will be identified by consulting databases (HMDB, KEGG), MS / MS spectra and / or injection. of standards.

2. Details on study logistics and data management
Study organization
The principle investigator (Diaz-Cambronero) and the two investigators involved in the initial design of IPPColLapSe II study (Mazzinari and Errando) form the Steering Committee. Local main investigators are responsible for identifying and recruiting participating patients in each centre. They will assist and train local investigators and oversee conduct of the study, including administrative management, record keeping and data management. Local investigators at individual participating centres will provide scientific and structural leadership, ensuring local ethical and regulatory approvals are obtained before patient inclusion starts. The sponsor guarantees the quality and security of the data collected.

Prior to the start of the study, the teams in each centre will receive a training session on how to capture data in the electronic Case Report Form (eCRF). All team members will be provided with a manual of operations with instructions on how to accurately fill the forms and the screening log.

Data management

Data will be collected from the patient paper/electronic medical chart and recorded on paper CRF and successively transcribed into an electronic CRF (eCRF) at a later time point. Local investigators transcribe the collected data directly onto an anonymized internet–based eCRF (http://remote.iislafe.san.gva.es/ippcollapse/). Access to the data–entry system is protected by a personalized username and password. To optimize the quality of the data, the implemented eCRF automatically cross–check the entries and check for abnormal or erroneous values in data.

The data will be kept on a central secured server located at the Hospital Universitari i Politecnic la Fe, Valencia, Spain. Personal information will be protected as dictated by the Spanish Personal Data Protection Law (Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal).

Data monitoring

Data managing, monitoring, and study reports will be done by independent monitors from the Spanish Clinical Research Network (SCReN; https://www.scren.es) as per the ICH-GCP Guidelines (CPMP/ICH/135/95). Monitoring activities will be conducted to ensure the protection of the rights and well–being of the participants in the clinical trial, to ensure that the data recorded are precise, complete and verifiable from the source documentation and that the conduct of the trial is done in accordance with the current approved version of the protocol and modifications in effect, with the GCPs, SOPs and any other applicable regulations. Sponsor's monitors will guarantee that all parts involved in the trial receive training in the specific protocol procedures, that adverse events and follow–up are adequately reported, that the CRFs are completed on time, and that any major deviations from the protocol are identified and reported without delay. The frequency and proportion of parameter verifications will be performed at each centre in accordance with what is established in the Monitoring Plan. All monitoring activities, including initiation, follow–up and close out visits will be documented in accordance with the Sponsor's procedures.

CORRECTION TO THE ORIGINAL PROTOCOL.

Published in Trials 2020; 21:70

After the publication of the original article [1], the authors have notified us that there are changes in the primary outcome and the statistical analysis plan of the study. These changes were made after the recruitment of participants and after approval by the

Institutional Review Board, and registration at clinicaltrials.gov (study identifier), but before cleaning and closing of the database.

The Postoperative Quality of Recovery Scale (PQRS), an outcome used in the IPPCollapse II study, is a five–dimensional ordinal scale designed to estimate patients' recovery in the postoperative period [2]. Each patient is scored at predefined time points and is classified as either 'recovered' if the score reaches at least the predetermined baseline score or 'not recovered' if otherwise. The five dimensions are then combined in an 'overall score' – a patient is classified as 'overall recovered' if 'recovered' in *every* domain and as 'overall not recovered' if 'not recovered' in *any* of the five domains.

Outcome variables that are repeatedly assessed over time in the same study patients are to be treated as 'repeated measures' or 'longitudinal data' [3]. Common statistical techniques applied on cross-sectional data assume independence between observations [4]. This crucial assumption is not fulfilled by 'repeated measures' or 'longitudinal data'. Ignoring this correlation can lead to biased estimates, invalid P values and confidence intervals, as well as loss of statistical power [5,6].

We incorrectly detailed how the PQRS score was to be analysed. We suggested to treat the scores at the four different time points as individual outcomes. From hindsight we feel that this approach does not consider the conceptual underlying model (i.e., between patients' variability) and the temporal design. Furthermore we also imperfectly reported our primary outcome since we did not specified which domain of the scale was analyzed as primary endpoint although we did report which one we used (i.e. physiologic score) in the sample size calculation. We therefore changed the primary and secondary outcomes as follows:

1. The primary outcome of the IPPCollapse II study is the recovery of the 'physiologic' component of the PQRS score over the assessed time points;
2. The other domains, i.e., the 'nociceptive', 'emotional', 'cognitive', and 'functional' components, as well as the 'overall score' are used as secondary outcomes;
3. Association between group assignment and recovery of PQRS score in each domain is assessed by a mixed logistic regression, introducing patients as random factors, and age, weight, BMI and sex as covariables;
4. The originally reported analysis (i.e. ordinal regression) is still carried out, however only as a sensitivity analysis.

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