**PROTOCOL TITLE** *The impact of deep versus standard muscle relaxation on intra-operative safety during laparoscopic surgery: a multicenter strategy study – EURO RELAX STUDY*

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## LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

| | |
|---|---|
| **ABR** | General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier) |
| **AE** | Adverse Event |
| **AR** | Adverse Reaction |
| **ASA** | ASA Physical Status Classification System |
| **BAC** | Blinded Adjudication Committee |
| **CA** | Competent Authority |
| **CCMO** | Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek |
| **CV** | Curriculum Vitae |
| **DSMB** | Data Safety Monitoring Board |
| **GCP** | Good Clinical Practice |
| **GDPR** | General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG) |
| **iAEs** | Intra-operative Adverse Events |
| **IC** | Informed Consent |
| **METC** | Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC) |
| **NMB** | Neuromuscular block |
| **PTC** | Post Tetanic Count |
| **(S)AE** | (Serious) Adverse Event |
| **Sponsor** | The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party. |
| **TIVA** | Total intravenous anesthesia |
| **TOF** | Train of Four |
| **UAVG** | Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG |
| **NRS** | Numeric Rating Scale |
| **WMO** | Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen |

**SUMMARY**

**Rationale:** Muscle relaxants are routinely applied during anesthesia to facilitate endotracheal intubation and to improve surgical working conditions. Several investigations have shown that a deep neuromuscular block (NMB) improves the surgical working conditions over a standard NMB and effectively precludes sudden deterioration of the surgical field. However, whether the improvement of surgical working conditions translates into less intra- and postoperative complications remains uncertain. Small prospective or retrospective studies shown an decrease of the incidence of intraoperative adverse events and postoperative complications after a deep NMB. There is a need to confirm these outcome data prospectively, in a large number of patients and clinics and during a variety of surgical procedures.

**Objective**: To study the effect of deep neuromuscular block as compared to standard neuromuscular block on intra-operative adverse events during laparoscopic surgery.

**Study design:** Multi center, randomized controlled clinical trial

**Study population:** 922 patients planned for elective laparoscopic abdominal surgery.

**Intervention**: Patients will be randomized between a deep NMB (group 1; aimed at PTC 1-2) and standard care (group 2; standard care NMB).

**Main study parameters/endpoints:** Primary endpoint is the difference in incidence of intra-operative adverse events during laparoscopic surgery graded on the CLASSIC scale (*ie.* CLASSIC grade ≥ 2) between both groups

Secondary endpoints include the surgical working conditions, 30 day post-operative complications and quality of recovery.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** The aim of this study is to compare two targets of neuromuscular block that are currently interchangeably used (both deep and standard NMB are routine practice at the LUMC). Additionally, all other anesthesia and surgery related procedures (*eg.* medication and monitoring) follow routine practice. We therefore anticipate no additional risks from study related procedures. Before surgery a Quality of Recovery and Short Form Health Survey will be obtained.After surgery the QoR-40 will be repeated twice, and the SF-36 will be obtained at 30 days after surgery.

## 1. INTRODUCTION AND RATIONALE

Muscle relaxants (*ie.* neuromuscular blocking agents; NMBAs) are routinely applied during anesthesia to facilitate endotracheal intubation and to improve surgical working conditions. However, as NMBAs have relatively long half lifes, the dosing of these agents is often restricted in clinical practice. Incomplete recovery of neuromuscular block (NMB) is associated with postoperative adverse events and should therefore be avoided at all costs. Hence, in standard clinical practice, NMB is often instituted only at the induction of anesthesia and hereafter allowed to recover spontaneously to limit the chance of residual NMB. Surgical procedures however have evolved to become increasingly complex. For instance, robotic surgery and increasingly complex laparoscopic surgery are now routinely performed. These types of surgery demand optimal working conditions to be successful and the standard use of NMBAs in these procedures may not be sufficient. Indeed, several investigations have shown that a deep neuromuscular block (*ie.* Post-tetanic-count of 1-2 twitches; PTC 1-2) during these procedures 1-2 twitches) improves the surgical working conditions over a standard NMB (*ie.* Train-of-four count > 0 twitches; TOF 1-3) and effectively precludes sudden deterioration of the surgical field.[1-8] Additionally, deep NMB has become feasible due to the availability of the selective reversal agent sugammadex. Sugammadex ensures quick and safe recovery of any depth of NMB and prevents residual NMB.[9] However, whether the use of a deep NMB translates into less intra- and postoperative complications remains uncertain. A recent retrospective analysis of neuromuscular management during laparoscopic retroperitoneal surgery showed a reduced rate of unplanned 30 day readmissions when a deep NMB over a moderate NMB was applied (3.8% vs. 12.7%).[10] In addition, a pooled analysis of 4 randomized controlled trials comparing different levels of intra-abdominal pressure and neuromuscular blockade during laparoscopic donor nephrectomy, showed a significant reduction in the incidence of intra-operative surgical complications from 12.6% with moderate NMB to 4.8% with deep NMB. [11-14]These previous observations were made in small prospective or retrospective studies. There is a need to confirm these outcome data prospectively, in a larger prospective trial for a variety of surgical procedures. We therefore propose a multi-center, randomized controlled trial, to study the effect of a deep NMB (PTC 1-2 twitches) versus standard NMB (single induction dose rocuronium) in a variety of laparoscopic surgical procedures on the incidence of intraoperative adverse events and postoperative outcome data.

## 2. OBJECTIVES

**Primary Objectives**:
To study the effect of deep neuromuscular block compared to standard neuromuscular block on intra-operative adverse events during laparoscopic surgery using the CLASSIC score system; see Table 2.

**Secondary Objectives:**
To study the effect of deep neuromuscular block as compared to standard neuromuscular block on:

- Surgical working conditions (using the validated Leiden surgical rating scale: L-SRS, Table 3)
- 30-day post-operative complications (using the Clavien-Dindo classification, Table 6)
- 30-day post-operative complications according to the Comprehensive Complication Index (https://www.assessurgery.com/)
- 30-day unplanned readmission rates
- Quality of recovery at post-operative day 1, 2 and 30 after laparoscopic surgery.
    - Quality-of-recovery (QoR-40 questionnaire at postoperative day 1 and 2 (Appendix 1)
    - Quality-of-life at postoperative day 30 (SF36 questionnaire, Appendix 2)

**Primary hypothesis:**
Deep neuromuscular blockade reduces the incidence of intra-operative adverse events as measured by the CLASSIC score during laparoscopic surgery as compared to standard neuromuscular blockade.

**Secondary hypotheses:**
Deep neuromuscular blockade improves surgical working conditions and the early quality of recovery and reduces 30-day post-operative complications and unplanned readmissions after laparoscopic surgery, as compared to standard neuromuscular blockade.

## 3. STUDY DESIGN

The EURO Relax is a multi-center, randomized controlled trial in patients undergoing laparoscopic abdominal surgery. Patients undergoing elective laparoscopic surgery in different fields of abdominal surgery will be randomized 1:1 in blocks of 2 and 4 to the deep or standard neuromuscular block group. Randomization will be stratified per center and BUPA category (MAJOR, MAJOR PLUS or COMPLEX MAJOR; for examples see table 1).

Patient inclusion will occur competitively in each center. Due to differences in inclusion rate, final inclusion could differ slightly in comparison with the proposed inclusion number per center.

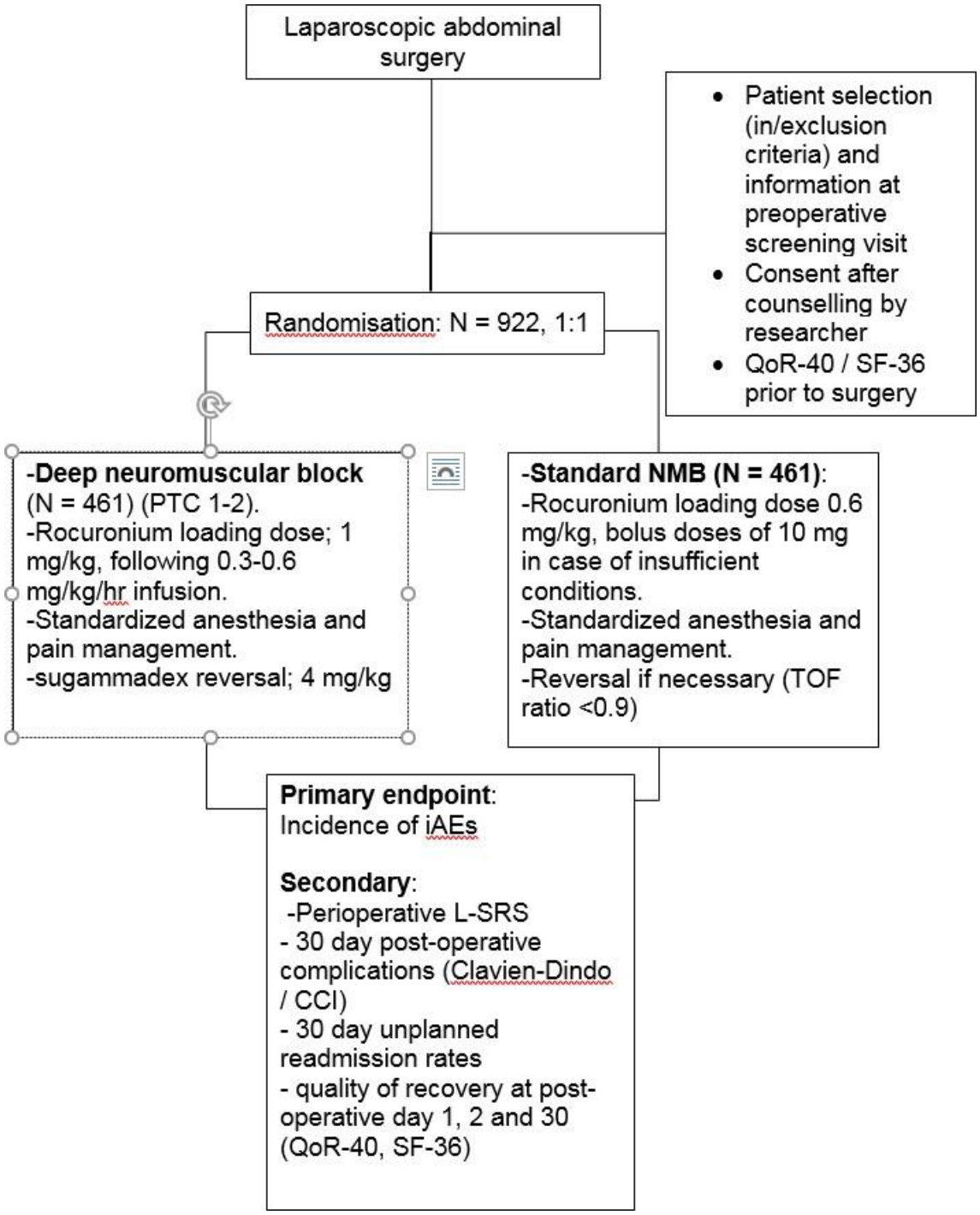


**Figure 1**. Inclusion flowchart EURO Relax study. *QoR: quality of recovery; iAE: intraoperative adverse event; L-SRS: Leiden Surgical Rating Scale; CCI: composite complication index.*

## 4. STUDY POPULATION

### 4.1 Population (base)

922 ASA class 1-3, aged > 18 years, scheduled for elective laparoscopic abdominal surgery (such as, but not restricted to upper gastrointestinal tract-, lower gastrointestinal tract-, urological- and gynecological surgery)

### 4.2 Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

- Patients scheduled for elective laparoscopic abdominal procedure with a complexity according to the BUPA classification for case complexity: 'MAJOR', 'MAJOR PLUS' or 'COMPLEX MAJOR'. Several examples of eligible procedures are stated in Table 1. Procedures not listed in Table 1 that are of listed in https://codes.bupa.co.uk/procedures as a Surgeon's Category ≥ 'Major 3', can be enrolled to the trial. The BUPA class of the specific procedure is listed under BUPA hospital category.
- ASA class I-III
- ≥ 18 years of age
- Ability to give oral and written informed consent

**Table 1. E**xamples of cases with BUPA classification for case complexity major, major plus or complex major used for the Classic validation study. *(with permission of dr. Salome Dell-Kuster (principle investigator of the CLASSIC validation study; NCT03009929).*

| | |
|---|---|
| • BUPA MAJOR: | -cholecystectomy |
| • BUPA MAJOR PLUS: | -colorectal resection<br>-nephrectomy<br>-hysterectomy<br>-adrenalectomy (uni)<br>-right colectomy<br>-partial nephrectomy<br>-gastric sleeve<br>-gastric bypass<br>-donor nephrectomy<br>-left colectomy<br>-sigmoidectomy<br>-laparoscopic partial stomach resection<br>-myomectomy |

| | |
|---|---|
| • BUPA COMPLEX MAJOR: | -low anterior resection<br>-partial hepatectomy<br>-prostatectomy<br>-hemi hepatectomy<br>-esophagostomy<br>-laparoscopic pyeloplasty<br>-laparoscopic stomach resection<br>-total cystectomy |

### 4.3 Exclusion criteria

- Low or intermediate complexity laparoscopic procedures (BUPA 'SIMPLE' or 'INTER')
- Known or suspected neuromuscular disorders impairing neuromuscular function
- Allergies to muscle relaxants, anesthetics or narcotics mentioned in paragraph 8.3
- A (family) history of malignant hyperthermia
- Women who are or may be pregnant or are currently breast feeding
- Chronic use of any type of opioid or psychotropic drug for the treatment of chronic pain
- Use of NSAID's shorter than 5 days before surgery for the treatment of chronic pain
- Indication for rapid sequence induction
- Contra-indication for sugammadex use (e.g. known sugammadex allergy or GFR<30 ml/min)

### 4.4 Sample size calculation

Preliminary data of the CLASSIC validation study as confidentially provided by dr. S. Dell-Kuster (principle investigator; NCT03009929) confirm that the incidence of GRADE ≥ 2 iAEs (Table 2) is 20% for BUPA categories (unpublished data).

**Table 2.** Adapted version of the *CLASSIC* classification for intra-operative adverse events *(with permission of dr. Salome Dell-Kuster (principle investigator of the CLASSIC validation study; NCT03009929).*

| | |
|---|---|
| **Grade 0** | No deviation from the ideal intraoperative course |
| **Grade 1** | Any deviation from the ideal intraoperative course without the need for any additional treatment or intervention; patient asymptomatic or mild symptoms |
| **Grade 2** | Any deviation from the ideal intraoperative course with the need for any additional minor treatment or intervention; patient with moderate symptoms, not life- threatening and not leading to permanent disability |
| **Grade 3** | Any deviation from the ideal intraoperative course with the need for any additional moderate treatment or intervention; patient with severe symptoms, potentially life- threatening and/or potentially leading to permanent disability |
| **Grade 4** | Any deviation from the ideal intraoperative course with the need for any additional major treatment or intervention; patient with life-threatening symptoms and/or leading to permanent disability |
| **Grade 5** | Any deviation from the ideal intraoperative course with intraoperative death of the patient |

The following events are not defined as intraoperative complications: sequelae, failures of cure, events related to the underlying disease, wrong-site or wrong-patient surgery or errors in indication

- To date, the minimal clinically important difference (MCID) for intra-operative adverse events according to the CLASSIC classification has not been published. We consider a relative reduction in intra-operative adverse events, CLASSIC grade ≥ 2, of 40% a clinically relevant difference. As de-

scribed above the reported average rate of grade 2 intra-operative Adverse Events (iAEs) is 20%.

- With an alpha of 5% and beta of 90%, 439 patients are required in each arm of the study (in total 878 patients).
    - Assuming a 5% rate of drop-out a total of 922 patients should be randomized 1:1 in this study. Reasons for drop-out are:
        - conversion to open surgery within the first 20 minutes of the procedure due to unforeseen adhesions, tumor progression, (peritoneal) metastases or other diagnosis
        - pre-incision alteration of surgical plan to laparotomy instead of laparoscopy after patient randomization to deep NMB or standard-of-care group
        - patient safety concerns at induction of anesthesia, *e.g.* anaphylaxis at induction of anesthesia or unanticipated difficult airway
    - Patients with a conversion to deep NMB due to intra-operative adverse events will not be excluded.

### 4.5 Pre-study requirements

There are no specific study requirements.

## 5. TREATMENT OF SUBJECTS

There are no specific study-related pre-study requirements. On the day of surgery, patients will be randomized between the two treatment groups. Anesthesia and postoperative care follow routine local protocol, apart from neuromuscular management. Neuromuscular management during surgery depends on the treatment allocation; patients will be randomized between one of the following groups:

Group 1 (experimental): Deep neuromuscular block.

- Muscle relaxation with rocuronium (Esmeron, MSD BV), target depth: post-tetanic-count of 1-2 twitches from start of surgery until the end
- Induction dose rocuronium: 0.6 – 1.0 mg/kg, aimed at PTC 1-2 at surgery start
- Maintenance: continuous infusion of rocuronium at 0.2-0.6 mg/kg/hr, titrated to maintain PTC 1-2
- Reversal of NMB with sugammadex 4 mg/kg at the end of surgery

Group 2 (comparator): standard care

- Muscle relaxation with rocuronium (Esmeron, MSD BV), target depth: train-of-four count of > 0 twitches from start of surgery until the end.
- Induction dose rocuronium: 0.3-0.6 mg/kg, aimed at a TOF count of > 0 twitches at surgery start
- Repeated doses of rocuronium 10 mg on request by the surgeon only
- Reversal of NMB with sugammadex 2 mg/kg at the end of surgery, when TOF ratio < 0.9 at surgery end.

### 5.1 Investigational treatment

Not applicable.

### 5.2 Use of co-intervention

Not applicable

### 5.3 Escape medication

Not applicable

## 6. INVESTIGATIONAL PRODUCT

Not applicable.

## 7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

## 8. METHODS

### 8.1 Study parameters/endpoints

**Main study parameter/endpoint**

Incidence of intra-operative adverse events during laparoscopic surgery (CLASSIC grade ≥ 2, Table 2) in both groups

### 8.1.1 Secondary study parameters/endpoints

To study the effect of deep neuromuscular block as compared to standard neuromuscular block on:

- Surgical working conditions (L-SRS, Table 3)
- 30-day post-operative complications (Clavien-Dindo, Table 6)
- 30-day post-operative complications according to the Comprehensive Complication Index
- 30-day unplanned readmission rates
- Quality of recovery at post-operative day 1, 2 and 30 after laparoscopic surgery.
    - Quality-of-recovery (QoR-40 at postoperative day 1 and 2; Aldrete score (Table 5) at the PACU)
    - Quality-of-life at postoperative day 30 (SF36, Appendix 2)

### 8.1.2 Other study parameters

- Patient age, gender, length and weight, ASA class, underlying disease(s), planned procedure, blood pressure and heart rate, center of admission
- Pre-operative NRS, QoR-40 and SF 36
- Per operative the following variables will be noted, after installation of the pneumoperitoneum at 15 minute intervals until the end of the surgery. At these moments the L-SRS is also scored:
    - Heart rate (/min), blood pressure in mmHg
    - Intra-abdominal pressure in mmHg and total insufflations volume (in Liters)
    - Depth of anesthesia: Bispectral Index and end-tidal sevoflurane
    - Depth of NMB (TOF count and/or PTC)
    - Duration of surgery and anesthesia
    - Time of extubation
    - Cumulative drug dosages (propofol, opioids, muscle relaxant, reversal agent, inotropics, NSAIDS's or metamizol)
    - Core temperature in degrees Celsius
    - Surgical satisfaction with the anesthesia: 'very dissatisfied', 'dissatisfied', 'satisfied' tot 'very satisfied'.
- Postoperative recovery scores:
    - Time to discharge readiness (Aldrete score≥9 and NRS<5)
    - Heart rate (/min), blood pressure in mmHg
    - peripheral oxygen saturation, respiratory rate (/min), use of supplemental $O_2$ (in liters/minute)
    - NRS and administration of analgesic medication
    - Ramsay sedation scale and Aldrete score
    - Nausea or vomiting

- Length of admission at the PACU and/or ICU (if applicable) and duration of hospital admission
    - Pain scores (numeric rating scale; NRS 0 no pain – 10 worst pain imaginable) at movement (and rest) three times daily until discharge or to a maximum of 72 hours will be extracted from the patient clinical charts.
    - Medication use (three times daily until discharge or to a maximum of 72 hours) will be extracted from the patient clinical charts.
        - Cumulative opiate use
        - Cumulative use of other analgesics and anti-emetics

### 8.2 Randomization, blinding and treatment allocation

Patient will be randomized between group 1 (deep NMB) or group 2 (standard care) just prior to surgery by an independent research nurse. Randomization will be performed using a dedicated, password protected website. The randomization sequence is generated by a dedicated computer randomization software; Castor (Castor EDC, CIWIT B.V., www.castoredc.com), stratified per center and BUPA category (MAJOR, MAJOR PLUS or COMPLEX MAJOR). To ensure a balanced distribution block, randomization will be used with 2 and 4 cases per block.

Blinding:

During every procedure, an unblinded researcher will be present to ensure adherence to the study protocol. Specifically, he or she will be responsible for maintaining the desired level of NMB. The researcher will not be involved in scoring of the Classic events (primary outcome). Classic scorings will be done by the attending anesthesiologist and surgeon who will be blinded.
To avoid deblinding of the surgical team in the standard NMB group (by noting the absence of a rocuronium perfusion), a syringe pump with NaCl 0.9% will substitute the rocuronium infusion. Postoperative care nurses and the investigator assessing postoperative endpoints are blinded to group allocation. Additionally, data analysis will be performed by blinded researchers.

### 8.3 Study procedures

**Informed consent procedure**

Patients will be screened for eligibility on the routine preoperative visit at the anesthesia outpatient department. Should a patient be eligible, than he or she will be contacted by one of the researchers by phone to receive oral and written information about the study. This contact will take place at least 2 weeks prior to the surgical procedure. If the patient is willing to participate, written consent will be obtained

**Preoperative procedures**

After informed consent has been obtained, baseline QoR-40 and SF36 questionnaires will be taken prior to surgery and randomization.

**Perioperative procedures**

**Anesthesia procedures:** Anesthesia procedures will follow local protocol on all aspects, except for

the neuromuscular block. Standard anesthesia iv access and standard monitoring according to local institutional protocol will be applied. General anesthesia will be induced and maintained with propofol or sevoflurane or desflurane. Intraoperative antinociceptive treatment will be with sufentanil, fentanyl or remifentanil. The choice regarding the type of hypnotic and opioid is upon the discretion of the attending anesthesiologist and is not influenced by this study. Hypnotic depth of all patients will be routinely monitored with bispectral index monitoring (BIS module, Philips, Eindhoven, The Netherlands) or entropy assessment to assess the level of hypnosis. The target level of the BIS is 50 +/- 5 during the procedure, and propofol dosage or end-tidal sevoflurane/desflurane will be steered to maintain the target BIS level to avoid under- or overdosing of the hypnotic agent.

Postoperative pain relief will be ensured with morphine, or equivalent (*eg.* Piritramide or methadone), and NSAIDs (*eg.* Diclofenac 50 - 75 mg) or metamizole 1g, and acetaminophen 1g. Lidocaine iv, magnesium, β-blocking agents, and/or loco-regional infiltration / techniques are not allowed.

**Ventilation:** will be adjusted to maintain end-tidal pCO2 of 4.5 to 5.5 kPa.

**Postoperative pain relief.** Pain relief at the PACU is left to at discretion of the attending anesthesiologists. All analgesics that are administered will be recorded in the e-CRF

**Neuromuscular management**

All patients will receive neuromuscular monitoring according to international guidelines for neuromuscular monitoring in research.[15] Neuromuscular monitoring will exclusively be applied at the m. adductor pollicis of one of the free moving thumbs  The following devices are allowed in this study: TOF-scan, Idmed, France, CE 0459 TOF-Watch, Organon, Ireland, CE 0543; or electromyography; GE NMT, GE-healthcare, Finland, CE 0537 .

All monitors will be applied in accordance with the guidelines of the manufacturer, including any baseline and calibration procedures; these will take place after the patient has been put under general anesthesia, but before the administration of any NMBA. Baseline TOF ratio will be noted in the CRF.  All monitor types can be used interchangeably in practice of this study. Patients may only be extubated when the TOF ratio is at least 0.9.

**Surgical procedures:** All laparoscopic procedures will exclusively be performed at standard insufflation pressures (IAP 12 mmHg). After insufflation, intra- abdominal volume will be recorded. This provides an indirect measure of abdominal wall compliance and workspace.

## Intra operative scoring procedures

**Intra operative adverse events**

Intra operative adverse events will be scored using the CLASSIC score (see table 2). This score has recently been developed and validated in a Delphi study (NCT03009929). Scoring of the CLASSIC scale

will be done by the blinded surgeon and blinded attending anesthesiologist (based on consensus) at the end of every procedure. Notably, the unblinded researcher on the OR is NOT involved in the scoring. CLASSIC classification is only applicable for events that have occurred *during* the procedure, any adverse event at PACU and beyond will be scored using Clavien Dindo scale (see table 6).

All surgeons will be trained prior to inclusion to objectively score CLASSIC grades consistently over the different centers. This will be done by a group of investigators that will form a blinded adjudication committee (BAC) that will review each case based on the operative report. The first two to three cases in each center will be attended by the BAC to evaluate whether the surgeons are able to score reliably after the initial training phase. Furthermore, interim evaluation of consistent reporting of the primary outcome will be performed by the BAC after N=10, N=20, N=50, and N=100 cases to check for discrepancies. Further training of surgeons after interim evaluation moments may be warranted

**Intraoperative surgical conditions**

Surgical working conditions will be scored by the blinded surgeon at 15 minutes intervals during the procedure, using the validated Leiden surgical rating scale (see table 3)[16].

Surgeons involved in the study will be trained in L-SRS scoring prior to study start by the local sub-PI

**Table 3.** *L-SRS* classification in laparoscopic surgery[6, 17].

| | |
|---|---|
| 1 | **Extremely poor conditions:** The surgeon is unable to work due to coughing or due to the inability to obtain a visible laparoscopic field because of inadequate muscle relaxation. Additional muscle relaxants are given. |
| 2 | **Poor conditions:** There is a visible laparoscopic field but the surgeon is severely hampered by inadequate muscle relaxation with continuous muscle contractions and/or movements with the hazard of tissue damage. Additional muscle relaxants are given. |
| 3 | **Acceptable conditions**: There is a wide visible laparoscopic field but muscle contractions and/or movements occur regularly causing some interference with the surgeon's work. There is the need for additional muscle relaxants to prevent deterioration. |
| 4 | **Good conditions:** There is a wide laparoscopic working field with sporadic muscle contractions and/or movements. There is no immediate need for additional muscle relaxants unless there is the fear for deterioration. |
| 5 | **Optimal conditions:** There is a wide visible laparoscopic working field without any movement or contractions. There is no need for additional muscle relaxants. |

In case of suboptimal surgical working conditions (deterioration of the L-SRS) or an adverse event CLASSIC ≥ 2, the following measures may be taken (and will be recorded):

1. Administration of rocuronium: 10 mg (repeated on request)
2. Administration of propofol 20-50 mg

3. Additional bolus of opioids (remifentanil, sufentanil, fentanyl)
4. Increasing the intra-abdominal pressure (with a maximum of 16 mmHg)

**Immediate postoperative measurements**

These postoperative measurements will be recorded by an independent and blinded nurse/researcher at the post anesthesia care unit (PACU). The measurements include:

*At 15 minutes intervals*

Oxygen saturation and use of any supplemental oxygen

Hart rate and blood pressure

Pain: using numeric rating scale (NRS: 0 no pain to 10 worst pain imaginable)

Sedation scores: using ramsey sedation score (see table 4)

*Other variables recorded:*

Medication use, including analgesic consumption

Time until discharge readiness: Aldrete score ≥9 (see table 5) and NRS <5

Adverse events at the PACU and beyond will be recorded using the Clavien Dindo scale (see table 6). These events will be scored by a blinded researcher.

**Table 4.** Ramsay sedation score.[18, 19]

| Score | Response |
|---|---|
| 1 | Awake and anxious, agitated, or restless |
| 2 | Awake, cooperative, accepting ventilation, oriented, or tranquil |
| 3 | Awake, responds only to commands |
| 4 | Asleep, brisk response to light, glabella tap, or loud noise |
| 5 | Asleep, sluggish response to light, glabella tap, or loud noise |
| 6 | Asleep, no response to light, glabella tap, or loud noise |

**Table 5.** Aldrete score[20]

| Activity | Respiration | Circulation | Consciousness | Oxygen Saturation |
|---|---|---|---|---|
| 2: Moves all extremities voluntarily/ on command | 2: Breaths deeply and coughs freely. | 2: BP + 20 mmHg of preanesthetic level | 2: Fully awake | 2: $SpO^2$ > 92% on room air |
| 1: Moves 2 extremities | 1: Dyspnoeic, shallow or limited breathing | 1: BP + 20-50 mmHg of preanesthetic level | 1: Arousable on calling | 1: Supplemental $O^2$ required to maintain$SpO^2$ >90% |

| | | | | |
|---|---|---|---|---|
| 0: Unable to move extremities | 0: Apnoeic | 0: BP +50 mmHg of preanesthetic level | 0: Not responding | 0: $SpO^2$ <90% with $O^2$ supplementation |

**Table 6.** Clavien-Dindo Classification.[21]

| | |
|---|---|
| **Grade I** | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological intervention. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, 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 IVa Single organ dysfunction (incl. dialysis) IVb Multi organ dysfunction |
| **Grade V** | Death of a patient |
| **Suffix 'd'** | If the patient suffers from a complication at the time of discharge, the suffix 'd' (for 'disability') is added to the respective grade of complication. |

‡ brain haemorrhage, ischaemic stroke, subarachnoidal bleeding, but excluding transient ischaemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit

**Other postoperative measurements**

Pain scores (NRS) at movement (and rest) three times daily at the ward until discharge or to a maximum of 72 hours, which will be extracted from the patient clinical charts.

Adverse events on the ward will be evaluated daily at hospitalization until discharge by a blinded researcher using the Clavien Dindo scale.

The quality of recovery score (QOR-40 questionnaire, appendix 1)[22] are filled in by the patient at day 1 and 2 after surgery.

30 days after surgery, a blinded researcher will evaluate any unplanned readmissions. In addition, patients will be contacted whether or not they have been readmitted in this period in any other hospital.

Also the SF36[23] questionnaire will be taken during this contact.

Additionally, the Comprehensive Complication Index (https://www.assessurgery.com/) will be used to grade postoperative complications [24]

### 8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons such as anaphylaxis or unanticipated difficult airway at induction of anesthesia.

#### 8.4.1 Specific criteria for withdrawal

Not applicable in this study

### 8.5 Replacement of individual subjects after withdrawal

Patients who are not randomized (the surgery is cancelled due to logistic or patient factors) are replaced by new subjects. Patients that underwent surgery will not be replaced.

### 8.6 Follow-up of subjects withdrawn from treatment

Patients who are withdrawn (conversion to deep NMB) by their physician will be subjected to follow up according to the intention to treat principle. When a patient withdraws their consent they will not be subjected to follow–up.

Patient that met the drop-out criteria stated in paragraph 4.4 will not reach the studies primary outcome.

### 8.7 Premature termination of the study

In case the study is ended prematurely, the investigator will notify the accredited IRB or METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications or abstracts of the study, to the accredited METC.

# 9. SAFETY REPORTING

## 9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

## 9.2 AEs, SAEs and SUSARs

### 9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded, only if judged to be substantial deviating from expected standard

clinical course. This includes severe adverse events that influence

postoperative recovery or clinical outcome.

### 9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. Subjects will be followed up for AEs and SAEs until the final study procedures or 7 days after discontinuation of the study. All reports will be digitally filed in the electronic clinical research form; Castor ((Castor EDC, CIWIT B.V., www.castoredc.com ).

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited. METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report.

All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

#### 9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable as in this study there is no investigational medicinal product.

### 9.3 Annual safety report

Not applicable as in this study there is no investigational medicinal product.

### 9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

### 9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

In this strategy study, which compares two standard-of-care rocuronium dosage regimens, there are no additional risks for the patients. We therefore see no need for a DSMB in this low risk study.

# 10. STATISTICAL ANALYSIS

## 10.1 Primary study parameter

Data will be analyzed comparing the incidence of adverse events during laparoscopic surgery, following the Classic criteria using $\chi 2$ test with $p < 0.05$ considered significant. Data analysis will be performed using R Studio, Boston, MA, USA.

## 10.2 Secondary study parameters

Continuous normally distributed variables will be expressed by their mean and standard deviation or when not normally distributed as medians and their interquartile ranges. Categorical variables will be expressed as n (%). To test groups Student's t test will be used, if continuous data are not normally distributed the Mann-Whitney U test will be used. Categorical variables will be compared with the Chi-square test or Fisher's exact tests. P-values < 0.05 will be considered significant for the primary outcome. A cut off p-value of < 0.01 will be applied for secondary outcomes.
Data analysis will be performed using R Studio, Boston, MA, USA..

Longitudinal data (heart rate, blood pressure, L-SRS, BIS levels compared to the depth of NMB at the given moment) will be analyzed using linear mixed models. NONMEM (ICON Development Solutions, Ellicott, MD, USA), will be used for statistical analysis.

## 10.3 Other study parameters

Demographic data, pre-operative NRS scores, perioperative administered cumulative drugs dosage and length of admission (at PACU, ICU and/or ward) will be reported.
Continuous normally distributed variables will be expressed by their mean and standard deviation or when not normally distributed as medians and their interquartile ranges. Categorical variables will be expressed as n (%). To test groups Student's t test will be used, if continuous data are not normally distributed the Mann-Whitney U test will be used. Categorical variables will be compared with the Chi-square test or Fisher's exact tests. P-values < 0.05 will be considered significant.
Data analysis will be performed using R Studio, Boston, MA, USA..

## 10.4 Interim analysis

No planned interim analysis will be performed.

# 11. ETHICAL CONSIDERATIONS

## 11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki as stated in the current version of Fortaleza, Brazil, 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO).

## 11.2 Recruitment and consent

Only adults who are not incapacitated are recruited after initial screening at the preoperative screening visit. All possible study candidates will receive a copy of the patent information sheet and a copy of the consent form, at a considerable time before surgery. Patient consent will be obtained, in person, before surgery by one of the researchers.

## 11.3 Benefits and risks assessment, group relatedness

Not applicable

## 11.4 Compensation for injury

In this study two common practices are compared that are deemed safe. Hence there are no potential issues of concern and insurance according to Article 7 WMO is not required in this study.

## 11.5 Incentives

Not applicable

## 12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

### 12.1 Handling and storage of data and documents

The principle investigators have responsibility with regard to the data at every site. MW and MvV hold final responsibility with regard to the pooled data. Castor will be used to minimize errors and to ensure traceability. An independent statistician will provide assistance for data-analysis of the blinded data.

All patients will be addressed to with a random patient identification code. Patient identifying data will be omitted. The codebook will be stored digitally and in paper and will be safeguarded by the investigator. The paper version will be stored behind a lock and the digital form will be encrypted. Source data will be stored at the specific study site where it originated and will be safeguarded by the local investigator. Data sent to the investigator will only contain this code and will not contain patient identifying data. Other involved parties (monitor, Inspectie Gezondheidszorg en Jeugd) could be granted access to patient data, also patient identifying data, to review if the research is being executed safely. These involved parties will handle the patient identifying data in a confidential manner. The sponsor, local researchers and project leader are responsible for data processing. When a subject withdraws consent, data collected until that moment will be used. All data will be stored for the length of the study and for 15 years afterwards, for further publication. All handling of personal data will comply with the Dutch Act on Implementation of the General Data Protection Regulation.

The Functionaris Gegevensbescherming from the LUMC has been informed about the data handling in the EURO-Relax-trial. When subjects have questions or complaints about data handling they can contact the Functionaris Gegevensbescherming (contact information is mentioned in the patient information letter). Additionally, the Functionaris Gegevensbescherming will assess if our data are handled in compliance with the law.

Data needed to assess primary- and secondary objectives will be collected (see paragraph 8.1.1, 8.1.2 and 8.1.3)

### 12.2 Monitoring and Quality Assurance

On-site monitoring will comprise controlling presence and completeness of the research dossier and the informed consent forms, source data checks will be performed as described in the monitoring plan. Every participating centre will be visited at least once every year. The monitor of this study in the LUMC is selected out of the monitoring pool of the LUMC. The other study sites will be monitored by a trained monitor not involved in the study. The details of monitoring will be described in the monitoring plan.

### 12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

### 12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

### 12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

### 12.6 Public disclosure and publication policy

The study protocol and analysis plan will be published before start of the study on clinicaltrial.gov (trialnumber: tbd). The results of the study will find their way into (inter–) national scientific journals

and guidelines. We will submit analyses to scientific journals in the field of anaesthesiology. The results of this study will be disclosed unreservedly according to the Central Committee on Research Involving Human Subjects (CCMO) statement on publication policy (http://www.ccmo.nl/attachments/files/ccmo-statement-publicatiebeleid-3-02-en.pdf).

Material for public dissemination will be submitted to the sponsor for review prior to submission for publication.

## 13. STRUCTURED RISK ANALYSIS

### 13.1 Potential issues of concern

In this study two common practices are compared that are deemed safe. Hence there are no potential issues of concern.

### 13.2 Synthesis

The aim of our this is to compare two common anesthesia practices. The patient population is able to provide consent and without an increased risk for any unwanted effects stated below. The types of surgery in this study are not associated with a high risk of complications. Hence, there will be no additional risks to the patient that participate in this study.

## 14. Appendixes

QOR-40 questionnaire, appendix 1

SF36 questionnaire, appendix 2

## 15. References


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