Clinical trial protocol

Prof Colin Royse

Study Title:	***A randomized trial of deep neuromuscular blockade reversed with sugammadex versus moderate neuromuscular block reversed with neostigmine, on postoperative quality of recovery***
Institution Name	**The University of Melbourne**
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Section #2- Core Protocol	
2.1 Objectives & Hypotheses	**Objectives** 1. To identify whether the rate/quality of recovery is affected by deep neuromuscular block (DNB) and reversal with sugammadex versus light/moderate neuromuscular block reversed with neostigmine in patients undergoing operative gynecological or abdominal laparoscopic surgery of at least 1-hour duration. **Hypothesis** 1. The technique of deep neuromuscular block and reversal with sugammadex will result in improved quality of recovery, including cognition, compared to the current standard of care technique using light/moderate neuromuscular block reversed with neostigmine in patients undergoing operative gynecological or abdominal laparoscopic surgery of at least 1-hour duration.
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	**Importance and assessment of quality of recovery** Recovery following general anesthesia is a complex issue confounded by the type of surgery, inflammation, different anesthetic drugs and techniques, patient co-morbidities, and differing patient and clinician perceptions of what constitutes good recovery. Recovery is not a single entity but rather covers many aspects or domains such as physiological recovery, pain and nausea, emotion and mood, return to normal life or work activities, and cognitive function. It is an entity that is difficult to quantify, which then makes it difficult to study in a systematic manner. For anesthesiologists, poor recovery is often relayed by the surgeon days or weeks after the event, and it is usually categorized as an adverse outcome. Research tools such as the Aldrete (1) or the QoR (2, 3) scales, focus on early physiological recovery, or the immediate perioperative period. These recovery scores are not sensitive enough to measure the rate of recovery (change over time), and have not been designed for repeated measures. They are also inadequate to identify poor cognitive recovery. In 2007, an international group of anesthesiologists and neuropsychologists formed an advisory board to create a new quality of recovery scale. The aim was to produce a tool that was simple to perform, but sensitive enough to detect change in multiple domains of recovery over time. The initial validation experiment included over 700 patients, and this work has been published in *Anesthesiology*. It is called the Postoperative Quality Recovery Scale (PostopQRS)(4). Six domains of recovery are identified: physiological, nociceptive (pain and nausea) emotive (anxiety and depression), functional recovery (return of activities of daily living), cognitive recovery, and an overall patient perspective domain including satisfaction. The scale is completed prior to surgery to provide baseline values, and then repeated at user-defined intervals. From some of the subsequent discriminant validation studies, time points have included early and late measures such as 15 minutes, 40 minutes, 1 and 3 days, and 3 months after the completion of anesthesia (typically defined as after the last surgical stimulation). Recovery is broadly defined as return to baseline values or better, except for the cognitive domain where a tolerance factor is included to allow for normal performance variability, such that patients are allowed to perform

a little worse than baseline as still be scored as recovered (5). Because repeated tests tend to have a learning effect, the cognitive domain uses parallel forms, and only a small learning has been shown (5).

One of the most important benefits of the PostopQRS scale is that it enables recovery to be quantified and measured. This makes it possible to compare different interventions with the express purpose of developing clinical interventions to improve quality of recovery. The PostopQRS offers a tool to provide the recovery process to be examined. There are no other tools in existence that provide a comprehensive, sensitive assessment of the multiple aspects or domains of recovery, and is yet relatively simple to perform. Validation studies have been performed and show good discriminative ability (5-8). Ease of use is facilitated by using a web based data entry system and the ability to use the telephone to conduct surveys after discharge form hospital. Telephone survey has been shown to be equivalent to face to face interviews using the PostopQRS (5). Further, the PostopQRS allows users to drill down to identify which recovery domain is affected for individuals in real time as well as for group audit.

Quality of recovery after operative laparoscopy

The majority of the literature compares different operative techniques with outcome measures aimed at specific complications or length of stay. Few studies include quality of recovery or quality of life measures as secondary endpoints (9-12). However, for potential benefits relating to the use of sugammadex, there are a few studies primarily centered around deep neuromuscular block (DNB) facilitating low intraabdominal inflation pressures. Most outcomes relate to operative conditions with little data on patient centered outcomes especially after discharge. The inclusion of sugammadex is to permit the use of DNB, and most comparative groups (of moderate block) are reversed with neostigmine.

It has been shown that more patients can be operated on with low intraabdominal pressure with DNB, and that operative conditions are rated as better in more patients with DNB (13, 14), though it is not absolute and there are frequent crossovers. That is, there are patients with moderate block and low pressure, and equally patients with DNB requiring high inflation pressures. The very few data on patient centered outcomes show reduced pain and nausea after DNB (13, 15-17), but lack of evidence of benefit for other recovery outcomes. This paucity of data has been stressed by review articles and editorials that DNB is associated with a modest effect on improving operating conditions but very little data to identify recovery benefits (13, 18)

Sugammadex is an effective drug to reduce deep neuromuscular blockade

There is no clinical question that sugammadex is highly effective in reversing neuromuscular blockade with rocuronium or vecuronium. This has been the subject of a Cochrane review which included 18 randomized trials, showing that sugammadex can reverse blockade with rocuronium or vecuronium independent on the depth of block, and superiority to neostigmine (19). This aspect of sugammadex does not require further study. This translates to a low incidence of residual blockade in the PACU compared to neostigmine reversal. The "safety" benefit to using sugammadex has been proven, but this does not necessarily translate into better outcomes. Sugammadex, however, is an enabling drug to facilitate deep neuromuscular blockade, allowing the anesthesiologist to continue that block until the end of surgery and reliably reverse the block. This is just not possible with neostigmine reversal, as one must wait until a train of four count of at least 2 twitches (or TOF ratio > 0.7) to safely reverse the block with neostigmine.

Sugammadex is not a single intervention

The role of sugammadex as a single intervention can only be applied when reversing neuromuscular block, when the block is moderate and a TOF 0.7 is achieved, with the outcome restricted to reversal of blockade.

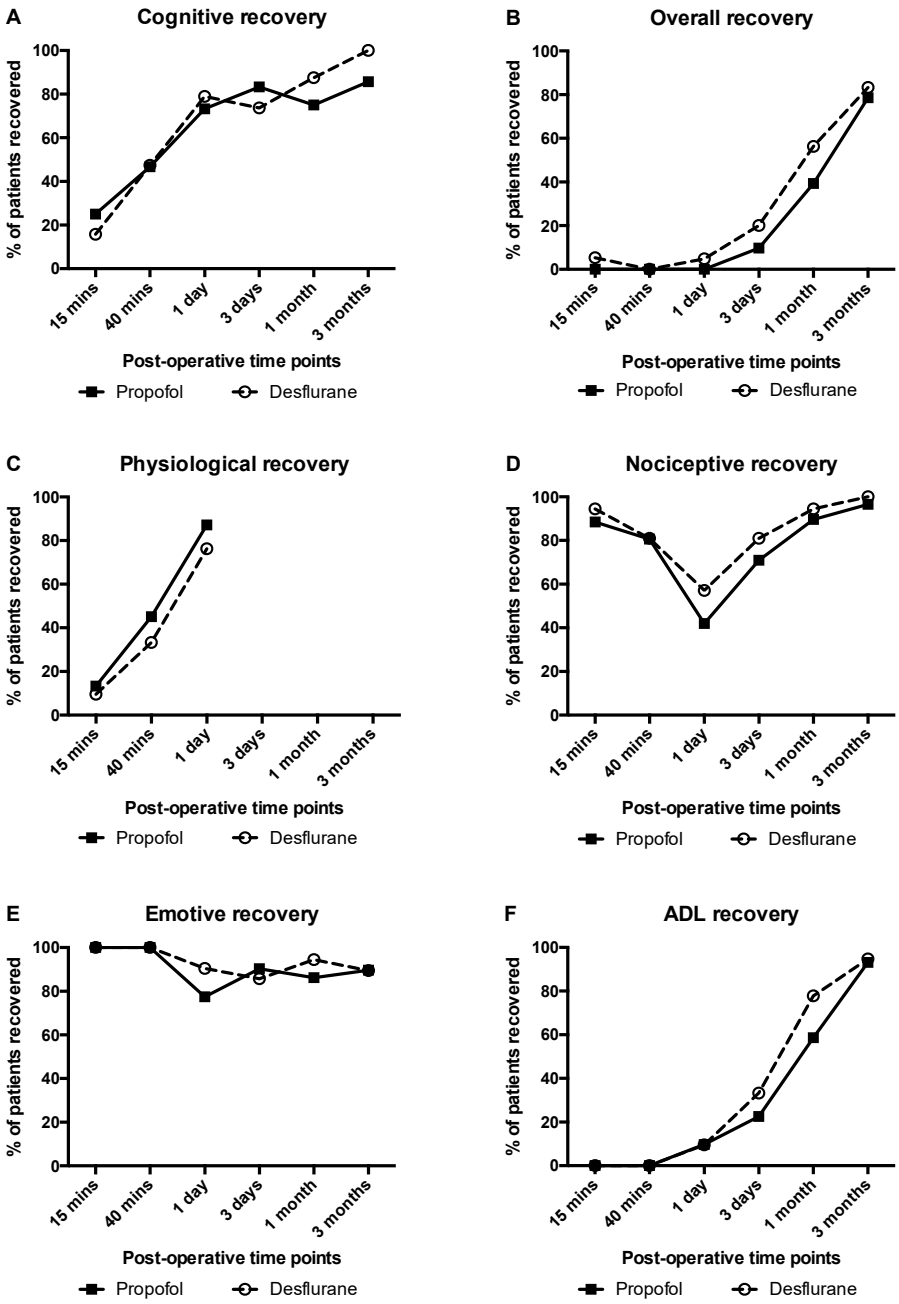
When sugammadex is used as a tool to facilitate deep muscular block, the intervention is principally the DNB rather than sugammadex. In any randomized trial comparing sugammadex with neostigmine for reversal of DNB, the extra time that anesthesia is continued in the neostigmine group will be a confounder on post-operative outcomes. In a study comparing sugammadex vs. neostigmine to reverse DNB, the anesthetic time in the neostigmine group was almost double that of the sugammadex group (47 vs 95 min) (20). This markedly increased anesthetic duration was due to the time taken for the TOF ratio to exceed 0.9 and facilitate safe extubation. It is therefore not possible to examine the issue of deep neuromuscular block and unbundle sugammadex from the anesthetic technique required.

Outcomes and confounders when assessing post-operative quality of recovery
There are a few data assessing the impact of anesthetic drugs rather than surgical techniques or different operations on the post-operative quality recovery. It is very likely that different anesthetic drugs may independently contribute to changes in post-operative quality of recovery, over and above the use of deep neuromuscular block for laparoscopic surgery.

The two most commonly used anesthetic drugs are propofol and sevoflurane. Both are relatively short acting drugs, but have a wide variation of offset, particularly with more prolonged anesthesia, and patient factors such as morbid obesity (21-23). Desflurane is a volatile agent which is very short acting, and more importantly has highly predictable offset, which is independent of patient factors such as obesity (21) or of operation duration. In patients receiving moderate neuromuscular block and reversal with neostigmine, the use of desflurane lead to earlier response to command and return of airway reflexed compared to sevoflurane (24).

Our research group is currently conducting research into different anesthetic techniques. Previously, we studied effect of desflurane vs. propofol in patients undergoing cardiac surgery, and showed less cognitive dysfunction one week after surgery but not at three months after surgery with desflurane (25). We have recently concluded but not published a pilot study investigating propofol sedation vs. desflurane general anesthesia to supplement spinal anesthesia for total hip replacement. The participant numbers are too small for meaningful statistical analysis, but there is a trend towards improved recovery and better cognitive recovery in the desflurane group (absolute difference 15% and OR 2.3). What is interesting, though, is that the early differences were negligible, and the trend occurred at 1 month and 3 months after surgery.

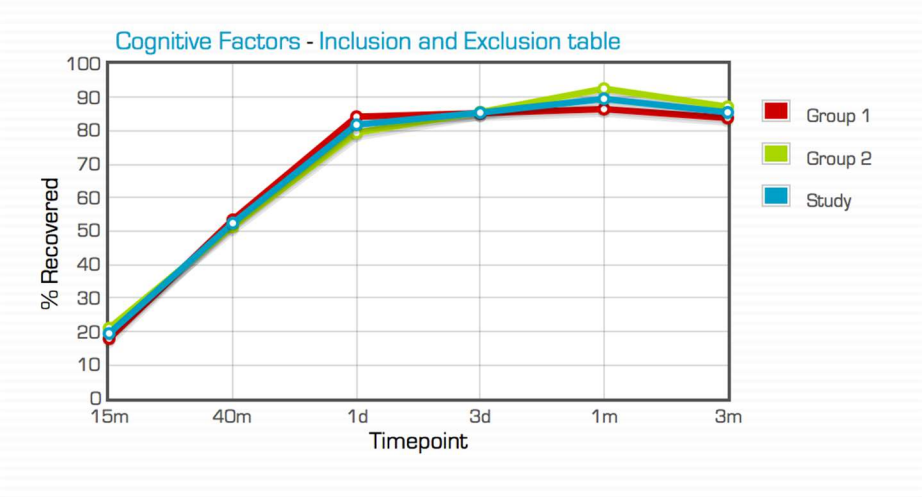
The recovery graphs for the PostopQRS are shown below. The Y axis is the proportion of patients recovered for each domain, and the X axis shown the time points where the PostopQRS was conducted.



Our data cannot explain why there were differences late rather than early. However, the cognitive domain is very sensitive to pain, analgesics and inflammation, and it is possible that modest but clinically important differences could be masked early after surgery by these factors, and only become evident after the inflammation and requirement for analgesia ceases. There were no intermediate time points between 3 days and 1 month, so we cannot be sure when this possible effect is starting.

We are conducting a blinded study for sevoflurane vs. desflurane for knee arthroscopy and measuring recovery using the PostopQRS. However, we performed a blinded interim analysis, which shows group separation of around 10% in recovery

and cognitive domain at the 1-month time point, but not at earlier or later time points. The cognitive domain is shown below:



Further, it is possible that other components of the anesthetic technique such as analgesia could also be a confounder in recovery.

The importance of the anesthetic confounders, is that is not possible to unbundle sugammadex from the anesthetic and still provide deep block, due to the much longer anesthesia time if neostigmine is used.

The concept of anesthetic bundles of technique

This introduces the concept of bundling agents together which have similar offset properties, and comparing that to real-world practice of light/moderate block, reversal with neostigmine and typically using sevoflurane as the maintenance anesthetic. The group receiving short acting drugs should have much less variance between effective block reversal and emergence, whilst at the same time facilitate optimal operating conditions. The coupling of agents should provide the greatest group separation for the use of sugammadex and potentially for postoperative quality outcomes.

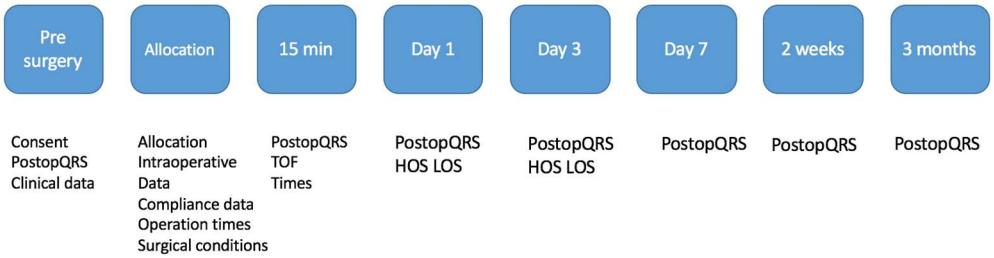
In this study, we wish to primarily investigate the effect of the role of DNB, and to reduce the potential for confounding from different anesthetic techniques, we will standardize the anesthetic to use the shortest acting anesthetic bundle, and use desflurane coupled with short acting opiates and multimodal analgesia in patients undergoing operative gynecological or abdominal laparoscopic surgery of at least 1-hour duration.

The research team

The team will be managed by Prof Colin Royse at the University of Melbourne. Colin is one of the founders of the PostopQRS and is the co-director of the group. We aim to recruit centers with high volume of operative gynecological or abdominal laparoscopic surgery. The University of Melbourne department is co-located with the Royal Melbourne Hospital and the Royal Women's Hospital, and connected to our specialist cancer hospital the Peter MacCallum Cancer Center. We also have access to a private hospital (Northpark Private Hospital) which has a high volume of gynecological surgery. These centers will be the initial target hospitals with potential to expand the number of hospitals once the trial is underway. The team statistician is

	Dr. Sandy Clarke, Statistical Consulting Centre, Department of Mathematics, The University of Melbourne. **Clinical significance** Quality of recovery is an emerging field within anesthesia of great importance. Although large outcome studies are very important in anesthesia, there is a changing focus from "mortality and morbidity studies", to quality of recovery. The reason is that the frequency of mortality is now very low with the result that few interventions will further reduce mortality and in any event very large numbers will be required to demonstrate any improvements in surgery and anesthesia with mortality as an outcome. However early data on the PostopQRS as well as clinical reports indicate that the quality of recovery is often poor in many patients, and yet these are not identified by the treating anesthesiologist. There are implications for the individual patient, for the practice of anesthesia, and for the community (such as safe return to work or to driving). If providing deep neuromuscular block does lead to improved quality outcomes, then it is essential to use sugammadex to reverse the block. There may be benefits (such as cognitive recovery) that may be worsened by drugs such as neostigmine and avoidance of neostigmine may be a mechanism of improving recovery. The coupling of drugs with similar offset times may further lead to improved quality of recovery.
2.3 Study Design	**Study design** Parallel randomized trial with allocation ration 1:1. The trial will be registered prior to commencement and will conform too CONSORT guidelines. **Study environment** The study will be conducted in a secondary or tertiary hospitals, which have an active laparoscopic surgery unit for gynecology or abdominal surgery. It is anticipated that a 24-month study period will be required. The combined institutions conduct more than 40 elective operative laparoscopies per week, making an average of 8 patients per week recruitment very feasible to achieve. Additional study sites will be added to increase recruitment if required. **Eligibility criteria** Inclusion: 1. Adult participants undergoing operative gynecological or abdominal surgery under general anesthesia of at least 1 hour duration Exclusion: 1. Participants, who are not fluent in English will be excluded, as they may be unable to answer the recovery questionnaire adequately. 2. Participants undergoing diagnostic laparoscopy only 3. Participants <18 years of age 4. Current pregnancy 5. Known allergy to rocuronium, neostigmine or sugammadex, or desflurane

2.4 Study Flowchart



2.5 Study Procedures

Interventions

Common management will include the following

1. Pre-medication other than oral analgesic (such as paracetamol) will not be used.

2. Induction will be with intravenous propofol, including co-induction consisting of fentanyl 0.5-3.0 mcg/kg, or equivalent short acting opiate including remifentanil.

3. Analgesia will consist of multimodal analgesia as determined by the anesthesiologist to treat the degree of pain, but in principle to avoid long acting opiates, e.g. use intraoperative short acting opiates, 1 g acetaminophen qid, NSAID's including Cox II inhibitors (such as paracoxib 40mg i.v.), or oxycontin 10-20mg 6 hourly.

4. Dual antiemetic therapy as per hospital guidelines

5. The maintenance anesthetic will be desflurane, and will be titrated to effect by the attending anesthesiologist

6. Rocuronium administration: for moderate neuromuscular block an initial dose of 0.6 mg/kg, with repeat doses of 0.15mg/kg given if the TOF >2 twitches. After completion of the majority of surgical resection, the level of block may be reduced to at least 3 twitches in preparation for the end of surgery.

For DNB, the initial dose will be 1.2 mg/kg and repeat doses of 0.15 mg/kg until PTC ≤ 2. TOF counts may be checked as frequently as every 15 seconds, but the PTC count interval must be at least 2 minutes (26).

7. If vecuronium (a similar steroidal muscle relaxant) is used instead of Rocuronium, then the dose is reduced to 10% of the dose of rocuronium, and titrated to achieve the same TOF endpoints.

8. Reversal of neuromuscular block

a. Neostigmine 50 micrograms/kg coupled with atropine 20 micrograms/kg or glycopyrrolate 5 micrograms/kg, to a maximum dose of neostigmine of 5.0 mg. The neostigmine should not be administered until the TOF has at least 3 twitches present.

b. Sugammadex dosage will be adjusted to body weight and PTC/TOF count at the time of reversal, and not administered until PTC at least 1. Dosage will be 4mg/kg if TOF = 0 and PTC ≥ 1; and 2 mg/kg if TOF ≥1.

9. Extubation for all groups will occur when the TOF has 4 twitches with no visible fade, (or a TOF ratio > 0.7 for institutions using a TOF ratio measurement device) adequate respiration and degree of alertness as determined by the anesthesiologist

as safe for extubation. Patients should not leave the operation room until TOF has 4 twitches with no visible fade, or for institutions using a TOF ratio measurement device, a TOF ratio > 0.9.

Intervention –groups

1. ModNB - participants will receive moderate neuromuscular blockade with rocuronium aiming for TOF 0-2 twitches, with neostigmine reversal when the TOF at least 3 twitches. After completion of the majority of surgical resection, the levl of block may be reduced to at least 3 twitches in preparation for the end of surgery.

2. **DNB**– participants will receive DNB aiming for a post tetanic count of 1-2, which will be maintained until removal of the laparoscopic ports, with reversal using sugammadex.

Study assessments protocol

Quality of recovery will be assessed using the Postoperative Quality of Recovery Scale (PostopQRS) see www.postopqrs.com. The survey takes around 5-6 minutes on each occasion to administer and is conducted either face-to-face whilst the participant is in hospital or via the telephone when discharged. Five recovery domains are assessed (physiological, nociceptive, emotive, function (ADL) and cognitive, and an additional overall patient perspective domain is recorded including satisfaction.

The scale will be conducted prior to surgery (baseline) and at 15 mins, 40 mins, 1 and 3 days, 1 and 2 weeks, 1 and 3 months after surgery to track recovery from the immediate to long-term.

Outcome measurements

Primary outcome

The most sensitive recovery domain of the Postoperative Quality of Recovery Scale to the effects of short acting drugs and avoidance of neostigmine is cognition. The primary outcome will be the cognitive domain at 1 week after surgery, when it is expected that most of the acute inflammation will have resolved, and analgesia requirements minimal.

Secondary outcomes

1. Recovery for all domains and within domains at the other time points of measurement (15 minutes, 40 minutes 1 day, 3 days, 1 and 2 weeks, and 3 months following cessation of anesthesia). The domains of recovery are physiological, nociceptive, emotive activities of daily living, cognitive and overall patient perspective.

2. Compliance with protocol to ensure deep block or light/moderate block, and correctly assigned anesthetic.

3. Anesthesia, surgical (first incision to last stitch), operating room, and PACU times, and hospital length of stay

4. Incidence of persistent neuromuscular block (TOF < 4 twitches or visible fade, or TOF ratio < 0.9) upon arrival in the PACU.

5. Surgical operating conditions measured by maximal inflation pressure required for surgery, and number of times that organ movement occurred (due to diaphragmatic movement or abdominal wall tone), and overall surgical satisfaction using a 1-5 Likert scale (1 = very unacceptable, 2 = unacceptable, 3 = acceptable, 4 = good, 5 = excellent).

Ethical issues

This study will be reviewed by the Melbourne Health HREC. All patients will receive a written plain language statement and will provide informed written consent.

Both neuromuscular reversal drugs are commonly used in Australia. If the participating anesthesiologist believes that the anesthetic regimen is inappropriate, then the patient will not be recruited into the study. The concept of deep neuromuscular block is relatively new in laparoscopic surgery as it can only be safely performed if reversal can be reliably achieved in an acceptable time frame. Accordingly, the deep neuromuscular block group will receive sugammadex using dosage guidelines according to body weight and degree of neuromuscular block at the time of reversal. Each PostopQRS measurement takes approximately 5-10 minutes, and is not onerous or stressful to the patient. However, if the patient does not wish to participate further, then they may withdraw from the study. Measurements performed after discharge from hospital are conducted via telephone interviews and do not require the patient to return to the hospital or other location. The interviews are arranged between the researcher and patient at a time of mutual convenience.

2.6 Study Duration

Anticipated time-line

The aim is to recruit an average of 4-6 patients per week (at least 4 hospitals to participate, with potential to add more hospitals). That timeline for the study schedule is listed below, though could advance earlier if recruitment is faster than anticipated.

Objective	**3 months**	**3-12 months**	**12 -21 months**	**21-24 months**
Ethics	XXXXXXXX			
Recruit 40%		XXXXXXXXX		
Recruit 100%			XXXXXXXXX	
Complete 3 month follow up				XXXX
Analysis and manuscript				

2.7 Statistical Analysis and Sample Size Justification

The team statistician is Dr. Sandy Clarke, Statistical Consulting Centre, Department of Mathematics, The University of Melbourne, who will oversee the statistical analysis.

Study size

Sample size estimates are based on the primary outcome of cognitive recovery at 1 week after surgery, and a clinically important difference in cognitive recovery at 1 week

	after surgery of 15%. Estimates of cognitive recovery are based on prior PostopQRS research and using multiple ages and surgical cohorts. It is estimated that the cognitive recovery for this cohort and duration of surgery will be 85% if there is good recovery. Using a two tailed estimate and Chi-squared analysis, alpha of 0.05, and power of 90%, with 1:1 allocation ratio; the sample size required to detect an absolute difference of 15% is 161 per group, which will be rounded up to a total sample size of 350 patients to account for potential non-completion of the study **Statistical methods** Variables of “recovery” are dichotomized to "recovered" or "not recovered" based on whether they have achieved baseline values or better at each of the time points when measurement is performed. A tolerance factor is included in the scoring of cognitive recovery to allow for performance variability (5). Statistical analysis for the primary outcome will be with the Chi-squared test. For the secondary outcomes of recovery over time, analysis will be performed using the a general linear mixed model to investigate group differences over time. Continuous data will be analyzed using independent samples t test, or RM ANOVA for repeated measurements. A $P<0.05$ will define statistical significance, and $P<0.01$ will define statistical significance for secondary endpoints to reduce risk of Type I error. Analysis is intention to treat. **Randomization** The randomization sequence will be produced using a computer generated randomization sequence, in unequal blocks and stratified for gynecological and abdominal surgery. Concealment will be by placing the card containing the allocation information in double opaque sealed envelopes, and concealment will be maintained until after recruitment and the patients is admitted to the operating theatre. The treating anesthesiologist will then open the envelopes to reveal the allocation. A non-participant in any process of the study will perform preparation of the envelopes. A copy of the randomization sequence will be stored in a separate databank, which is password protected and not available to the investigators until the study is complete. **Blinding** Due to the nature of the drugs, it is not possible to blind the treating anesthesiologist to the allocation, but the patient and study investigators who collect the PostopQRS data will be blinded to allocation.
2.9 Adverse Experience Reporting	A data monitoring committee will be established and chaired by a senior academic who is not part of the clinical trial conduct. Adverse events will be reported to the HREC.
2.10 References	**References** 1. Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesth Analg. 1970;49(6):924-34. 2. Myles PS, Reeves MD, Anderson H, Weeks AM. Measurement of quality of recovery in 5672 patients after anaesthesia and surgery. Anaesth Intensive Care. 2000;28(3):276-80. 3. Myles PS, Weitkamp B, Jones K, Melick J, Hensen S. Validity and reliability of a postoperative quality of recovery score: the QoR-40. Br J Anaesth. 2000;84(1):11-5.

4. Royse CF, Newman S, Chung F, Stygall J, McKay RE, Boldt J, et al. Development and feasibility of a scale to assess postoperative recovery: the post-operative quality recovery scale. Anesthesiology. 2010;113(4):892-905.
5. Royse CF, Newman S, Williams Z, Wilkinson DJ. A human volunteer study to identify variability in performance in the cognitive domain of the postoperative quality of recovery scale. Anesthesiology. 2013;119(3):576-81.
6. Newman S, Wilkinson DJ, Royse CF. Assessment of early cognitive recovery after surgery using the Post-operative Quality of Recovery Scale. Acta Anaesthesiol Scand. 2014;58(2):185-91.
7. Royse CF, Williams Z, Ye G, Wilkinson D, De Steiger R, Richardson M, et al. Knee surgery recovery: Post-operative Quality of Recovery Scale comparison of age and complexity of surgery. Acta Anaesthesiol Scand. 2014;58(6):660-7.
8. Royse CF, Williams Z, Purser S, Newman S. Recovery after nasal surgery vs. tonsillectomy: discriminant validation of the Postoperative Quality of Recovery Scale. Acta Anaesthesiol Scand. 2014;58(3):345-51.
9. Abbas AE, Abd Ellatif ME, Noaman N, Negm A, El-Morsy G, Amin M, et al. Patient-perspective quality of life after laparoscopic and open hernia repair: a controlled randomized trial. Surg Endosc. 2012;26(9):2465-70.
10. Abd Ellatif ME, Askar WA, Abbas AE, Noaman N, Negm A, El-Morsy G, et al. Quality-of-life measures after single-access versus conventional laparoscopic cholecystectomy: a prospective randomized study. Surg Endosc. 2013;27(6):1896-906.
11. Bansal VK, Misra MC, Babu D, Victor J, Kumar S, Sagar R, et al. A prospective, randomized comparison of long-term outcomes: chronic groin pain and quality of life following totally extraperitoneal (TEP) and transabdominal preperitoneal (TAPP) laparoscopic inguinal hernia repair. Surg Endosc. 2013;27(7):2373-82.
12. Barkun JS, Wexler MJ, Hinchey EJ, Thibeault D, Meakins JL. Laparoscopic versus open inguinal herniorrhaphy: preliminary results of a randomized controlled trial. Surgery. 1995;118(4):703-9; discussion 9-10.
13. Koo BW, Oh AY, Seo KS, Han JW, Han HS, Yoon YS. Randomized Clinical Trial of Moderate Versus Deep Neuromuscular Block for Low-Pressure Pneumoperitoneum During Laparoscopic Cholecystectomy. World J Surg. 2016.
14. Staehr-Rye AK, Rasmussen LS, Rosenberg J, Juul P, Lindekaer AL, Riber C, et al. Surgical space conditions during low-pressure laparoscopic cholecystectomy with deep versus moderate neuromuscular blockade: a randomized clinical study. Anesth Analg. 2014;119(5):1084-92.
15. Staehr-Rye AK, Rasmussen LS, Rosenberg J, Juul P, Gatke MR. Optimized surgical space during low-pressure laparoscopy with deep neuromuscular blockade. Dan Med J. 2013;60(2):A4579.
16. Madsen MV, Istre O, Staehr-Rye AK, Springborg HH, Rosenberg J, Lund J, et al. Postoperative shoulder pain after laparoscopic hysterectomy with deep neuromuscular blockade and low-pressure pneumoperitoneum: A randomised controlled trial. Eur J Anaesthesiol. 2016;33(5):341-7.
17. Kim MH, Lee KY, Lee KY, Min BS, Yoo YC. Maintaining Optimal Surgical Conditions With Low Insufflation Pressures is Possible With Deep Neuromuscular Blockade During Laparoscopic Colorectal Surgery: A Prospective, Randomized, Double-Blind, Parallel-Group Clinical Trial. Medicine (Baltimore). 2016;95(9):e2920.
18. Kopman AF, Naguib M. Laparoscopic surgery and muscle relaxants: is deep block helpful? Anesth Analg. 2015;120(1):51-8.
19. Abrishami A, Ho J, Wong J, Yin L, Chung F. Cochrane corner: sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. Anesth Analg. 2010;110(4):1239.
20. Carron M, Veronese S, Foletto M, Ori C. Sugammadex allows fast-track bariatric surgery. Obes Surg. 2013;23(10):1558-63.
21. McKay RE, Malhotra A, Cakmakkaya OS, Hall KT, McKay WR, Apfel CC. Effect of increased body mass index and anaesthetic duration on recovery of

	protective airway reflexes after sevoflurane vs desflurane. Br J Anaesth. 2010;104(2):175-82. 22. McKay RE, Bostrom A, Balea MC, McKay WR. Airway responses during desflurane versus sevoflurane administration via a laryngeal mask airway in smokers. Anesth Analg. 2006;103(5):1147-54. 23. McKay RE, Large MJ, Balea MC, McKay WR. Airway reflexes return more rapidly after desflurane anesthesia than after sevoflurane anesthesia. Anesth Analg. 2005;100(3):697-700, table of contents. 24. McKay RE, Hall KT, Hills N. The Effect of Anesthetic Choice (Sevoflurane Versus Desflurane) and Neuromuscular Management on Speed of Airway Reflex Recovery. Anesth Analg. 2016;122(2):393-401. 25. Royse CF, Andrews DT, Newman SN, Stygall J, Williams Z, Pang J, et al. The influence of propofol or desflurane on postoperative cognitive dysfunction in patients undergoing coronary artery bypass surgery. Anaesthesia. 2011;66(6):455-64. 26. Groudine SB, Soto R, Lien C, Drover D, Roberts K. A randomized, dose-finding, phase II study of the selective relaxant binding drug, Sugammadex, capable of safely reversing profound rocuronium-induced neuromuscular block. Anesth Analg. 2007;104(3):555-62.
2.12 Publication Plan	• The main study will be aimed at *Anesthesiology* for the first submission. Presentations will be made at major international anesthesiology meetings