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Journal of Clinical Trials

Research Article

Low Pressure Pneumoperitoneum and Deep Neuromuscular Block Versus Standard Laparoscopy during Robot Assisted Radical Prostatectomy to Improve the Quality of Recovery and Immune Homeostasis: Study Protocol for a Randomized Controlled Study

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ABSTRACT

Background: A pneumoperitoneum with Carbon Dioxide (CO_2) is required to obtain an adequate surgical field for laparoscopic surgery, including Robot Assisted Radical Prostatectomy (RARP). Nevertheless, the use of an increased Intra-Abdominal Pressure (IAP) may have a negative impact on the quality of recovery after surgery. IAP causes a temporary decrease in the perfusion of surrounding tissues leading to ischemia-reperfusion injury with oxidative stress and release of Danger Associated Molecular Patterns (DAMPs). Thereby contributing to pain and inflammation which has a negative impact on the quality of recovery. With accumulating evidence demonstrating the safety and advantages of low-pressure IAP (6-8 mmHg), such as reduction in postoperative pain, opioid consumption, improved bowel function recovery, a reduced inflammatory response and preserving innate immune function, this study is designed to unravel the link between the degree of IAP, parietal peritoneal perfusion, innate immune function, and the quality of recovery after RARP.

Methods: This is a blinded randomized controlled trial comparing 'standard laparoscopy', consisting of standard IAP (14 mmHg) with moderate Neuromuscular Blockade (NMB) and low IAP (8 mmHg) with deep NMB. All patients will receive surveys focused on recovery on three time points. For inflammatory response and innate immune function blood samples and biopsies will be taken and for imaging of the peritoneal perfusion, indocyanine green injection will be given after which a recording will be collected for further analysis.

Discussion: There is increasing evidence of the benefits of low IAP, although there is limited evidence on low pressure RARP. Studies indicate that mainly prolonged, high intra-abdominal pressures lead to ischemia-reperfusion injury and oxidative stress. Recent studies with low-pressure RARP reported a shorter length of hospital stay and less readmission within 30 days. Furthermore, it is important to maintain an adequate neuromuscular block during laparoscopic procedures at low pressure, as insufficient surgical conditions may hamper patient safety. Deep NMB itself may also contribute to improved postoperative outcomes with lower postoperative pain scores and analgesic requirement. Therefore, we hypothesize that 'low impact laparoscopy', defined as the combination of low IAP (<10 mmHg) facilitated with deep NMB, could be beneficial to improve the quality of postoperative recovery after RARP.

Trial registration: Clinicaltrials.gov (NCT04250883 (RECOVER2)).

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Received date: 16-Nov-2021, Manuscript No. JCTR-21-14433; **Editor assigned:** 18-Nov-2021, PreQC No. JCTR-21-14433(PQ); **Reviewed:** 01-Dec-2021, QC No. JCTR-21-14433; **Revised:** 06-Dec-2021, Manuscript No. JCTR-21-14433 (R); **Published:** 13-Dec-2021, DOI: 10.35248/2167-0870.22.S15.001.

Citation: Reijnders-Boerboom GTJA, Van Basten JP, Jacobs LMC, Brouwer M, Van Dijck M, Albers KI, et al. (2022) Low Pressure Pneumoperitoneum and Deep Neuromuscular Block Versus Standard Laparoscopy during Robot Assisted Radical Prostatectomy to Improve the Quality of Recovery and Immune Homeostasis: Study Protocol for a Randomized Controlled Study. J Clin Trials. S15:001.

Keywords: Intra-abdominal pressure; Neuromuscular block; Robot assisted laparoscopic prostatectomy; Immune function; Quality of recovery; Perfusion

Abbreviations: IAP: Intra-Abdominal Pressure; NMB: Neuro Muscular Block; RARP: Robot Assisted Radical Prostatectomy; EAES: European Association for Endoscopic Surgery; DAMP: Danger Associated Molecular Patterns; SIRS: Systemic Inflammatory Response Syndrome; QoR-40: Quality of Recovery-40 questionnaire; SF-36: Short Form health survey-36 questionnaire; L-SRS: Leiden Surgical Rating Scale.

INTRODUCTION

Background and rationale

A pneumoperitoneum with Carbon Dioxide (CO_2) is required to obtain an adequate surgical field for laparoscopic and robotic surgery, which is important to avoid intra-operative adverse events related to a limited workspace and view on critical anatomical structures. Nevertheless, the side-effects of using an increased Intra-Abdominal Pressure (IAP) include for example increased postoperative pain, inflammation and opioid requirement which may have a negative impact on the quality of recovery after surgery. Low pressure pneumoperitoneum (IAP<10 mmHg) may therefore be beneficial and is recommended by the European Association for Endoscopic Surgery (EAES) [1]. To ensure the safety of low IAP, deep NMB facilitates a sufficient surgical field. Several studies show a significant reduction of 3-4 mmHg in IAP with deep NMB compared to moderate-NMB, without compromising surgical conditions during laparoscopic surgery [2-9].

Introducing Robot Assistance for Radical Prostatectomy (RARP) improved the perioperative outcomes with less blood loss and transfusion rates, less surgical complications and significant reduction in length of hospital stay compared to open radical prostatectomy. Moreover, RARP contributes to earlier sexual recovery and urinary continence in high volume surgical centers [10]. The use of low intra-abdominal pressure during RARP is feasible and may contribute to a further shortening the length of hospital stay and reduction of readmission rate within 30 days after surgery [11,12].

Standard IAP (usually 12-15 mmHg) causes a temporary decrease in the perfusion of surrounding tissues leading to ischemia-reperfusion injury with oxidative stress and release of Danger Associated Molecular Patterns (DAMPs) [13-18]. These DAMPs e.g. Nuclear DNA, Heat Shock Protein-70, mitochondrial DNA, are released and elicit an immune response of innate immune cells. The release of DAMPs results in a Systemic Inflammatory Response Syndrome (SIRS) followed by a compensatory anti-inflammatory reaction [19]. This response causes sensitization of nociceptors enhancing postoperative pain and the anti-inflammatory reaction is related to fatigue and leads to a higher susceptibility for postoperative infections [20-22]. Maca et al. shows the relation between the degree of surgical trauma, and predicted morbidity and mortality and DAMPs after elective major abdominal surgery [23,24]. Fragidiakis et al. described a strong correlation between immune status and recovery from surgery. Particularly signaling responses downstream in monocytes correlate with recovery outcomes including pain and fatigue [25,26].

A limited number of studies investigated the immune response after low pressure laparoscopy. It was found that low intra-abdominal pressure was associated with reduced serum levels of pro-inflammatory cytokines like IL-6 and TNF-alpha and with lower levels of anti-inflammatory IL-10 as compared to standard IAP [3-5,6]. Moreover, Schietroma et al. also described a better preservation of monocyte function as reflected by higher levels of HLA-DR expression on monocytes [3]. Altogether this provides indirect evidence that lower intra-abdominal pressures may contribute to recovery by a reduced stress response and subsequently a better preservation of innate immune function as compared to laparoscopy with high IAP (Figure 1).

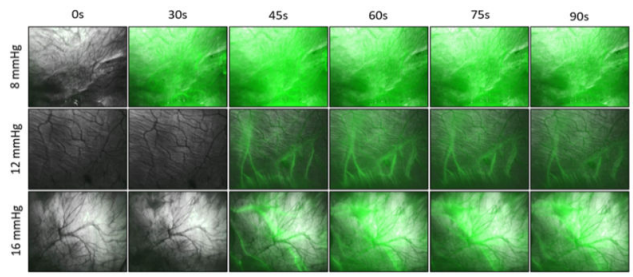

Figure 1: Recording of peritoneum after indocyanine green injection at different intra-abdominal pressure levels [27].

The evidence of better perfusion of intra-abdominal tissues with low-pressure laparoscopy was reported by Albers et al. with fluorescence of the parietal peritoneum at different intra-abdominal pressures. This study showed the time to maximum fluorescent intensity was significantly lower in patients allocated to 8 mmHg [27]. Also, the maximal fluorescent intensity was significantly higher at 8 mmHg as compared to 12 and 16 mmHg (Figure 1). These data indicate that perfusion of intra-abdominal organs and tissues are better below 12 mmHg. Moreover, accumulating evidence shows the safety and advantages of low-pressure IAP (6-8 mmHg), reduction in postoperative pain [28,29], cumulative opioid consumption [30] and improved bowel function [2,29]. Furthermore, it reduces the inflammatory response upon surgery as reflected by reduced effect on pro-inflammatory mediators IL-6, IL-10, TNF-alfa, and it preserves innate immune function as reflected by monocytic HLA-DR expression [3-6].

This study is designed to unravel the link between the degree of IAP (low versus standard IAP), parietal peritoneal perfusion,

innate immune function, and the quality of recovery after RARP.

Objectives

The primary objective is to study the relationship between the use of low IAP facilitated by deep NMB, innate immune function, and the quality of recovery after robot assisted radical prostatectomy. The secondary objective is to study the effect of low IAP on the perfusion of the parietal peritoneum.

Trial design

This is a blinded, randomized controlled trial including 96 participants divided in two groups (Figure 2). The experimental group will get "Low impact laparoscopy"; consisting of low IAP (8 mmHg) facilitated by deep NMB. The control group receives "standard laparoscopy"; consisting of standard IAP (14 mmHg) with moderate NMB. Computer-generated randomization will be used in a 1:1 manner with stratification for additional pelvic lymph dissection in RARP. To ensure a balanced distribution, we will use block randomization. The surgical team and postoperative care nurses will be blinded. All study endpoints will be arbitrated by a blinded researcher. Also, the perfusion index is extracted from video registration by a researcher blinded to the level of pressure and NMB depth.

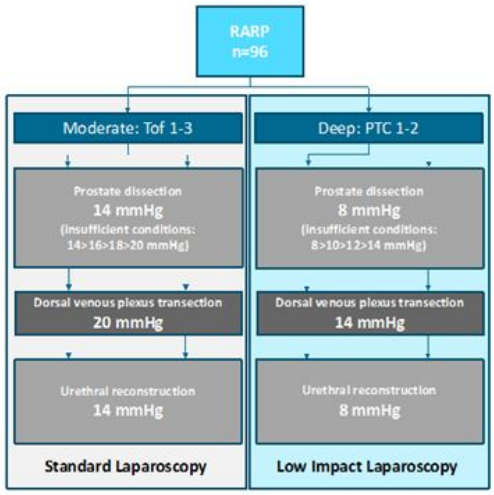

Figure 2: Trial design with control group (standard) and experimental group (low impact).

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

This trial includes patients operated in the Canisius Wilhelmina Hospital in Nijmegen, where approximately 450 Robot Assisted Radical Prostatectomy (RARP) procedures are performed annually in the prosper prostate cancer network. The prosper network includes patients from Radboudumc, Canisius Wilhelmina Hospital in Nijmegen and Catharina Hospital in Eindhoven.

Eligibility criteria

To participate in this trial, a participant must meet the following criteria, 18 years or older, undergoing elective RARP and given informed consent. A patient will be excluded from participation when there is insufficient control of Dutch language, (chronic) use of immunosuppressive medication or medication which interacts with indocyanine green, neuromuscular disease, hyperthyroidism, indication for rapid sequence induction, BMI >35 kg/m^2 or suspected hypersensitivity to study medication.

Consent of assent

The main practitioner will give a patient information folder and ask consent so the researcher can contact the patient. The researcher will contact after consent is provided and answer any questions about the trial to ensure the patient is fully informed. Informed consent is obtained at least one week after providing written information about the study. Thereafter an informed consent is asked by the researcher for participation. When consent is given, all biological samples are included.

Interventions

All interventions and measurements are summarized in Figure 2 and Table 1. Each patient will receive a survey (QoR-40, SF-36) and blood samples will be collected before entering the operation theatre. Randomization will be done right before entering the operation theatre. General anesthesia will be performed with a standardized protocol using total intravenous anesthesia, supplemented with multimodal analgesia, propofol, remifentanil, ketamine and lidocaine. Insufflation and placing trocars will be done with an intra-abdominal pressure of 14 mmHg to ensure safe entering of the abdomen. Directly afterwards IAP will be set as randomized to 8 or 14 mmHg. Neuromuscular block will be strived to as randomized at TOF 1-2 or PTC 1-2 with rocuronium perfusion.

When the robot is docked a peritoneum biopsy will be taken and the indocyanine green injection of 0.2 mg/kg will be given and recorded for 2 minutes. The camera trocar is aimed at a standardized point of the peritoneum and the start of ICG infusion is signed in the recording. Besides standard anesthesia monitoring, vital parameters, quality of surgical field measured in L-SRS and interventions will be noted every 15 minutes.

In case of an insufficient surgical field, the surgeon can request an increase of IAP by 2 mmHg. NMB will be corrected with a bolus of rocuronium (10-15 mg) when needed. The transection of the deep dorsal venous plexus can be done at a higher IAP as protocolized because of the bleeding risk at this point of surgery.

At the end of surgery, a second peritoneal biopsy will be taken. Deep NMB will be antagonized by 4 mg/kg sugammadex, and moderate NMB will be antagonized when needed with 2 mg/kg sugammadex. There must be a TOF of 4 with TOFr >0.9 before the end of anesthesia.

At the postoperative care unit routine measurements will be done and noted, such as vital parameters, pain assessment, and nausea and vomiting, given pain medication and Aldrete score.

	Pre-operative	Peroperative		Postoperative					
		After trocar introduction	End of IAP	1 hr	8 hrs	24 hrs	48 hrs	12 days	3 mos
Questionnaires									
- QoR- 40	x					x		x	
- SF-36	x							x	x
- McGill – chronic pain									x
Biological samples									
- Anti-coagulated blood	x					x		x	
- Peritoneal biopsy		x	x						
Video recording									
-ICG injection		x							
Clinical									
-Pain scores, PONV analgesia use				x	x	x	x		
- Complications, Discharge criteria						x	x		x
Length of hospital days									

Note: IAP: Intra-abdominal pressure; QoR-40: Quality of Recovery-40; SF-36: Sort Form health survey-36; ICG: Indocyanine Green; PONV: Postoperative Nausea and Vomiting.

Table 1: Participant timeline with all measurements.

On postoperative day 1 and ± 12, blood samples will be collected and another survey package (QoR-40, SF-36) will be obtained. The last survey after 3 months includes the McGill questionnaire to measure chronic pain.

Each collection of blood samples includes a standard 6 mL lithium/heparin, 10 mL EDTA tube and 2.5 mL Paxgene RNA tube to measure innate immune function and will be combined with routine laboratory assessment as much as possible. Otherwise, blood will be drawn by vena puncture. Peritoneal biopsy will be performed during laparoscopy when peritoneal tissue is directly visible and easily accessible. A small biopsy (0.5-1 × 0.5-1 cm, 2-4 mm deep) will be taken as previously described and performed by Schaefer et al. [31] and Williams et al. [32]. The sample is used to determine HIF1α mRNA

Outcomes

Quality of Recovery score (QoR-40) at postoperative day 1 and IL-6 response upon whole blood LPS stimulation at postoperative day 1 are the primary outcomes.

Secondary will be the perfusion index of the parietal peritoneum as calculated from the slope of ICG fluorescence intensity and time to maximal intensity in seconds (extracted from video registration).

Other outcomes will be general parameters such as age, gender, body mass index and intraoperative routinely measured parameters. Other clinical parameters measured at the postoperative care and ward such as pain score, analgesia use, shoulder pain and PONV. But also, length of hospital stay, complications, the additional questionnaires (SF-36 and McGill), *ex-vivo* immune function on additional time-points and peritoneal HIF-1-alfa messenger RNA expression.

Participant timeline

A schedule of trial enrolment, interventions and outcomes is presented in Table 1 and Figure 2.

Sample size

The sample size for this trial includes 48 patients per study arm. With this, a sufficient power will be generated for the primary and secondary analyses. As calculated for quality of recovery at postoperative day 1 as reflected by the QoR-40 questionnaire a

sample size of 48 patients per group is needed to provide 90% power to detect a 10 point difference in the QoR-40 at postoperative day 1 (alpha 5%) with an estimated standard deviation of 15. For innate immune function as reflected by the *ex vivo* release of IL-6 upon LPS stimulated leukocytes at postoperative day 1. A sample size of 45 patients per group is needed to provide 90% power to detect a 3.000 pg/mL difference in IL-6 release (alpha 2.5%) with an estimated standard deviation of 4.000 pg/mL at postoperative day 1. As IL-10 will also be measured, a Bonferroni correction was used (alpha 2.5%).

Recruitment

At Canisius Wilhelmina Hospital, more than four hundred robot-assisted radical prostatectomy procedures are performed annually. All eligible patients will be screened for participation in the trial. With an inclusion rate of approximately 2 patients per week, we expect that the screening (and inclusion period) will be 12-15 months. We intend to include 96 patients. After informed consent is given the participants will be randomly assigned in a 1:1 fashion to the experimental group or control group.

Assignment of interventions

Allocation: Computer-generated block randomization (supported by our statistician) will be used with stratification for RARP with or without pelvic lymph node dissection. The allocation is only accessible in a password provided database which cannot be seen by anyone except the researcher present in the operating theatre. This researcher will also assign the interventions and keep the surgical team, caregivers, patients and outcome assessors blinded.

Blinding

Blinding of the surgeons to the level of IAP and NMB is ensured by facing monitoring equipment away or covering these under sterile drapes. The level IAP will be set and adjusted by the researcher who is not blinded to the allocation of treatment. Surgical conditions will be assessed after introduction of the trocars, every 15 minutes or when the surgeon indicates inadequate surgical conditions. When L-SRS is ≤ 3 (Table 2), pressure is increased with 2 mmHg to max 14 mmHg in the experimental group or 20 mmHg in the control group. The researcher titrates the dose of rocuronium to the desired level of NMB. The nerve stimulator and computer are placed behind the sterile drapes away from the surgeons. To minimize the risk of observer bias and/or unblinding of the entire team, the following measures will be taken: Surgical adverse events will be registered directly after surgery by the blinded, primary surgeon. Surgeons, scrub nurses, postoperative care nurses, and ward physicians are blinded. Postoperative clinical outcomes are collected by a blinded researcher.

Scale	Short description	Description
1	Extremely poor conditions	The surgeon is unable to work because of coughing or the inability to obtain a visible laproscopic field because of inadequate muscle relaxation.
2	Poor conditions	There is a visible laparoscopic field, but the surgeon is severely hampered by inadequate muscle relaxation with continuous muscle contractions, movements or both with the hazard of tissue damage.
3	Acceptable conditions	There is a wide visible laparoscopic field but muscle contractions, movements or both occur regularly causing some interference with the surgeon's work.
4	Good conditions	There is a wide laparoscopic field with sporadic muscle contractions, movements or both.
5	Optimal conditions	There is a wide visible laparoscopic working field without any movement or contractions.

Table 2: Leiden-surgical rating scale.

RESULTS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

Data collection methods

This trial is registered at Clinicaltrials.gov under number NCT04250883 with the acronym RECOVER 2. Furthermore, this study will be conducted according to the principles of the Declaration of Helsinki (59th version, Seoul, October 2008) and other Dutch guidelines, regulations and Acts. Subjects will be coded by a numeric code (a unique study number will be assigned) in order to create an anonymous dataset. Investigators have access to this code and will store the subject identification code list at a separate location from the dataset. The anonymous dataset will be securely stored in the database of the department of surgery of the Radboudumc accessible to the investigators, in accordance with the Dutch Personal Data Protection Act. Videos are recorded in the operating room on a research restricted hard drive, video files are imported into the database

of the department of surgery of the Radboudumc by the researcher and saved anonymously under the study number. Biopsies taken during surgery are directly after collection coded by study number.

Collection of blood samples is combined with hospital visits to ensure complete follow-up. Questionnaires are sent with Castor EDC at the same time blood samples are collected, a reminder is given a few days after if the questionnaire is not completed.

Data management

Subjects will be coded by a numeric code in order to create and anonymous dataset. A Castor EDC database will be developed and used for data management. This encrypted data management system will be used to minimize errors, to ensure traceability and privacy of the subjects. An independent statistician will provide assistance for data-analysis. The data will be unblended after completion of the follow-up period and identification of protocol violations. Investigators have access and will store the subject identification code list at a separate location from the dataset. Anonymous data will be securely stored in the database of the department of surgery of the Radboudumc accessible to the investigators, in accordance with the Dutch Personal Data Protection Act.

Confidentiality

All study-related data will be stored in Radboudumc. Participant information will be stored at the study site with password protection or in a locked file in an area with limited access.

Statistical methods

Primary outcomes: The Quality of Recovery score (QoR-40) at postoperative day 1, factorial ANCOVA will be used to compare groups and to adjust for co-variates i.e. age and gender. P-values <0.05 will be considered statistically significant.

For mononuclear cell responsiveness, ANCOVA will be used to compare groups and to adjust for co-variates i.e., age and gender. As the primary endpoint includes changes in both IL-6 and IL-10 release, Bonferroni correction for multiple comparisons will be used. P-values <0.025 will be considered statistically significant.

A perfusion index in peritoneum will be calculated from the slope of ICG fluorescence intensity, and time to maximal intensity in seconds (extracted from video registration). Factorial ANCOVA will be used to compare groups and adjust for covariates i.e. age and gender. P-values <0.05 will be considered statistically significant.

Secondary and other outcomes as noted in section outcomes, paragraph 12, will be presented as quantitative data.

Protocol non-adherence will be assessed on a case-by-case basis by the principal investigator. Missing data are not planned to be imputed. In the event of substantial missing data for ay parameter, a sensitivity analysis could be used.

DISCUSSION

The benefits of low intra-abdominal pressure are supported by an increasing body of evidence. Especially prolonged, high intra-abdominal pressures lead to ischemia-reperfusion injury and oxidative stress [33-35]. Recent studies with low pressure RARP reported benefits in a shorter length of hospital stay and less readmissions within 30 days [11,12].

It is important to also maintain an adequate neuromuscular block during laparoscopic procedures at low pressure, as insufficient surgical conditions may hamper patient safety [28,30]. Some evidence exists indicating that adequate surgical conditions during laparoscopic surgery reduce the rate of intraoperative complications [28]. Moreover, deep NMB itself may also contribute to improved postoperative outcomes with lower postoperative pain scores and analgesic requirement [28-36]. Therefore, we hypothesize that 'low impact laparoscopy', defined as the combination of low IAP (<10 mmHg) facilitated with deep NMB, could be beneficial to improve the quality of postoperative recovery after RARP.

There is limited evidence on low pressure RARP although the evidence is increasing for many other laparoscopic procedures. The strengths of this trial are mainly related to its high internal validity, as this is a single center trial with strict study protocol compliance for all participants. Also, the assessment of a broad spectrum of outcomes will provide further insight in the mechanism behind the hypothesized improvement of the quality of recovery.

Patients, the operating team, ward nurses, and outcome assessors are blinded, however the anesthetic team is not to ensure safety related to the use of deep NMB.

CONCLUSION

A randomized controlled trial (Recover-2 Trial) will be performed to study the impact of low impact versus standard laparoscopy on the quality of recovery after RARP with or without pelvic lymph node dissection. Moreover, the mechanism underlying the possible beneficial influence of low-pressure pneumoperitoneum during RARP will be studied.

Monitoring

Data monitoring: Monitoring will be conducted in accordance with negligible risk monitoring guidelines of the Netherlands Federation of University Medical Centers (NFU), which will be reported in a monitor plan. The data monitoring committee consist of experts in surgery and/or anesthesiology and independent of this trial. They provide recommendations regarding safety and continuation of the trial. No interim analyses are planned.

Harms: 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.

All (serious) adverse events are recorded. In case of a serious adverse even the sponsor will report the SAEs through the web portal Toetsing Online 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.

The product summaries for rocuronium and sugammadex will be used to evaluate whether the adverse event or reaction is expected or unexpected. The following adverse events are inevitable in surgery and will not be recorded, blood loss <500 ml, surgical site infection and wound dehiscence. However, if any of these complications is considered a serious adverse event, they will be recorded.

Auditing: No audits of trial are planned; however, an audit trail is recorded in Castor EDC automatically.

ETHICS AND DISSEMINATION

Research ethics approval and Protocol amendments

Medical ethics committee of Nijmegen gave approval after judging the protocol. All amendments will be notified to the METC that gave a favorable opinion. Non-substantial amendments will not be notified to the accredited METC and the competent authority but will be recorded and filed by the sponsor.

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