

RESEARCH PROTOCOL

The effectiveness of deep *versus*
moderate neuromuscular blockade
during laparoscopic donor nephrectomy
in enhancing postoperative recovery.

A blinded, randomized controlled study

RELAX study

PROTOCOL TITLE

The effectiveness of deep versus moderate neuromuscular blockade during laparoscopic donor nephrectomy in enhancing postoperative recovery.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
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
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
LDN	Laparoscopic Donor Nephrectomy
LUMC	Leids Universitair Medisch Centrum
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
NMB	Neuromuscular Block
PNP	Pneumoperitoneum
POD	Post Operative Day
PTC	Post Tetanic Count
QOR	Quality of Recovery
RCT	Randomized Controlled Trial
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)
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.

SRS **Surgical Rating Scale**

SUSAR **Suspected Unexpected Serious Adverse Reaction**

TOF **Train of Four (measurement)**

Wbp **Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)**

WMO **Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)**

SUMMARY

Rationale: As both patients with end-stage kidney disease as society benefit tremendously from living kidney donors, their safety and well-being are highly important objectives in living kidney donation. In this randomized controlled clinical trial we will compare the use of deep neuromuscular blockade versus moderate neuromuscular blockade – with standard pressure pneumoperitoneum – during laparoscopic donor nephrectomy.

Objective: To establish the relationship between the use of deep neuromuscular blockade (NMB) during laparoscopic donor nephrectomy (LDN) - with standard pressure pneumoperitoneum (PNP) - and the early quality of recovery.

Study design: A multi-center, blinded, randomized controlled clinical trial.

Study population: Adult individuals who are scheduled for living kidney donation are eligible for this study. All types of donors, including related, unrelated, anonymous and donors who participate in the “cross-over” exchange program are eligible.

Intervention: 2 treatment groups:

- deep neuromuscular blockade and standard pressure pneumoperitoneum
- moderate neuromuscular blockade and standard pressure pneumoperitoneum

Main study endpoint: Quality of recovery score (QOR-40 questionnaire) at 24 hours after extubation.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

The burden for participants in this study is mainly related to the evaluation of the endpoints during the early postoperative phase. Assessment of the differential pain scores and the QOR-40 questionnaire will take approximately 10 minutes per time-point (-18h, 1h, 6h, 24h and 48h after detubation). As the use of a deep NMB with a standard insufflations pressure improves the quality of the surgical field, there are no risks related to the surgery. A deep neuromuscular block can be achieved by higher doses of rocuronium as compared to the routine intubation dose. A higher dose of rocuronium in living kidney donors is safe, as renal function is only slightly reduced which does not have a clinically relevant impact on the clearance of rocuronium.

To overcome the extended effects of deep neuromuscular blockade that may lead to airway obstruction, hypoxia, pneumonia and/or atelectasis, sugammadex is administered to antagonize the effects of rocuronium. Sugammadex is a rapid antagonist of neuromuscular blockade by rocuronium that is given immediately after surgery. Randomized controlled trials have shown that sugammadex can be safely administered in patients, without dose adjustments for young, elderly or obese patients and that it can also be safely administered in patients with suboptimal renal function.

A recent study performed by Martini *et al.* has shown that deep neuromuscular blockade improves surgical conditions with reduced postoperative pain scores after laparoscopic surgery (1). Moreover, preliminary data of our recently performed Leopard-3 study, show that the mean SRS (surgical rating scale) was significantly better during deep NMB with less opiate consumption (2). Altogether, we expect that the use of deep NMB during LDN reduces postoperative pain scores and/or analgesia consumption. This may improve the early quality of recovery of living kidney donors.

1. INTRODUCTION AND RATIONALE

In our previous pilot study (*acronym: Leopard-1 study*) low-pressure pneumoperitoneum during LDN reduced postoperative pain scores as compared to standard pressure pneumoperitoneum (3). This finding is in line with our recent meta-analysis which shows that the use of low-pressure pneumoperitoneum (7 mmHg) provides a clinically relevant reduction in postoperative pain scores after laparoscopic surgery (4). Despite this evidence and the fact that international consensus guidelines state that the lowest possible intra-abdominal pressure should be used during laparoscopic procedures (5, 6), almost all laparoscopic surgeons use a fixed standard insufflation pressure (10-15 mmHg) instead of the lowest possible pressure (<10 mmHg). In our view, the main reason for this is that low-pressure PNP may compromise the quality of the surgical field.

Staeher-Rye *et al.* showed that the use of a deep NMB improves surgical conditions during low-pressure PNP laparoscopy as compared to a moderate NMB (7). To investigate whether the use of low-pressure PNP facilitated by profound muscle relaxation not only improves postoperative pain but also the early quality of recovery, we performed a blinded RCT in patients undergoing LDN (*Leopard-2 study; NCT02146417*) (8, 9). Results from this study show that live kidney donors allocated to the low-pressure group mobilized earlier and were sooner physically independent. This led to a remarkably shorter length of hospital stay. In the low-pressure group, 45% of live kidney donors went home at postoperative day 2 as compared to 20% in the standard-pressure group. However, patients in the low-pressure group did not have lower overall pain scores, nor reduced analgesia consumption (9).

We recently completed a randomized controlled study (*Leopard-3 study*) in which low-pressure PNP was used and the intra-abdominal pressure was increased step-wise in case of insufficient surgical conditions during LDN (2). Preliminary data show that the use of a deep NMB led to a mean intra-abdominal pressure of 7.5 mmHg, whereas a mean pressure of 9 mmHg was required to achieve sufficient conditions with a moderate NMB (paper in preparation). Moreover, the mean SRS score was significantly better in during deep NMB. In our view this shows that a step-wise approach combined with deep NMB enables the use of low-pressure PNP without compromising the quality of the surgical field during laparoscopic procedures. Interestingly, we also observed a reduced cumulative opiate consumption during the first 24 hours after surgery in the deep NMB group. In our view, this finding could not be attributed to the slight difference in mean intra-abdominal pressure (7.5 *versus* 9 mmHg). Therefore, this observation appears to contradict the results from the Leopard-2 study in which no difference was found between low- and standard pressure PNP with regard to

postoperative pain and analgesia use (please see table 1). However, results from both studies could be brought in line if the use of deep NMB independently reduces postoperative pain after laparoscopy. Therefore we hypothesize that the use of a deep NMB during LDN with standard pressure PNP (12 mmHg) reduces postoperative pain scores and/or analgesia consumption which leads to an improved early quality of recovery.

2. OBJECTIVES

Primary Objective:

To establish the relationship between the use of deep neuromuscular blockade (NMB) during laparoscopic donor nephrectomy (LDN) -with standard pressure pneumoperitoneum of 12 mmHg- and the early quality of recovery.

Secondary Objective:

To study whether deep NMB during LDN influences postoperative pain and/or analgesia consumption.

3. STUDY DESIGN

Study design and duration:

A multi-center, blinded, randomized controlled clinical trial.

A multicenter design was chosen to optimize generalizability and to guarantee patient enrollment within 12 months.

Participating centers:

- Radboudumc, Nijmegen (M.C. Warlé, surgeon and G.J. Scheffer, anesthesiologist)
- LUMC, Leiden (A.E. Braat, surgeon and A. Dahan, anesthesiologist)

4. STUDY POPULATION

4.1 Population

Adult individuals who are scheduled for live kidney donation are eligible for this study. All types of donors, including related, unrelated, anonymous and donors who participate in the “cross-over” exchange program are eligible.

4.2 Inclusion criteria

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

- obtained informed consent
- age over 18 years

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- insufficient control of the Dutch language to read the patient information and to fill out the questionnaires
- chronic use of analgesics or psychotropic drugs
- use of NSAIDs shorter than 5 days before surgery
- known or suspect allergy to rocuronium or sugammadex
- neuromuscular disease
- indication for rapid sequence induction
- deficiency of vitamin K-dependent clotting factors, coagulopathy or use of coumarin derivatives.
- Peri-operative use of fusidic acid or flucloxacillin
- Severe renal impairment (creatinine clearance <30ml/min)
- Morbid obesity (BMI >35 kg/m²)

4.4 Sample size calculation

A sample size of 48 patients per group is needed to provide 90% power to detect a 10-point difference in the quality of recovery score at 1 day after extubation (alpha 5%). A 10-point difference represents a minimal relevant difference (8). Based upon our previous study, the standard deviation is 15 points (9).

At the Radboudumc and LUMC, respectively 90 and 45 laparoscopic donor nephrectomies are performed annually. All eligible donors will be screened. With an inclusion rate of approximately 80%, we expect that the screening (and inclusion period) will be 11 months.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

The patient will be randomly assigned to one of the two treatment groups (1:1):

- Deep neuromuscular block/group A
- Moderate neuromuscular block/group B

Intra-operative protocol

- induction with remifentanyl, propofol and rocuronium (intubation dose 0.6 mg/kg). Anesthesia is aimed at a bispectral index score between 45-55. Tracheal intubation is performed 2 minutes after administration of 0.6 mg/kg rocuronium in both groups. In case of a BMI > 30 kg/m² the dose rocuronium will be adjusted taking into account ideal body weight. In group A (deep NMB), an infusion of rocuronium (0.3 to 0.4 mg/kg) is started and titrated towards PTC 0-1. In group B (moderate NMB), no additional rocuronium is administered after tracheal intubation and the neuromuscular function was allowed to recover spontaneously. PTC and TOF measurements every 5 minutes.
- in case of insufficient surgical conditions due to (severe) muscle contractions (SRS 1-2), the protocol allows a 0.6 mg/kg bolus of rocuronium. In case of insufficient surgical conditions (SRS 1 or 2), the surgeon only decides to convert to an open- or hand-assisted procedure if the safety of the patient is compromised.
- pressure-regulated volume-controlled ventilation through an endotracheal tube with a mixture of oxygen in air with 5 cmH₂O PEEP and tidal volume between 6 and 8 ml/kg is used. Minute ventilation is adjusted to main end-tidal carbon dioxide between 31 and 43 mmHg by changing respiratory rate during surgery.
- neuromuscular function will be monitored in a standardized fashion by an acceleromyograph at the wrist (TOF-watch-SX, MIPM GmbH).
- blood loss will be compensated with colloid solution; for 100 ml blood loss, 120 ml colloid solution is given.
- after induction and intubation, patient is positioned in lateral decubitus position
- nasogastric tube for gastric decompression; removed before the end of surgery
- core temperature is measured continuously, aiming at 36-37 C
- no local infiltration of surgical wounds
- the use of drains is avoided
- One hour before the end of the procedure, a loading dose morphine of 0.2mg/kg will be administered.

- In group A, the rocuronium perfusor will be stopped after removal of the trocars.
- After skin closure, the NMB is reversed with sugammadex using 4 mg/kg in group A and 2mg/kg in group B. When the patients have a stable TOF ratio of more than 0.9 for 2 minutes and were fully awake, extubation is performed.

Post-operative protocol equal for all patients

- postoperative pain management: patient-controlled analgesia (morphine, 1 mg morphine per bolus, lock-out 6 minutes) and acetaminophen. On day 1 PCA morphine will be replaced by oral analgesics.
- ondansetron 4 mg intravenous (maximum 12 mg/day) or, second choice, metoclopramide (10 mg p.o.) is administered in case of nausea and/or vomiting
- removal of urine catheter on day 1
- immediate start of normal diet
- immediate mobilization

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

a) Rocuronium 10 mg/ml solution for infusion

Rocuronium bromide is indicated as an adjunct to general anaesthesia to facilitate tracheal intubation during routine sequence induction and to provide skeletal muscle relaxation during surgery.

b) Sugammadex (Bridion®) 100 mg/mL solution for injection

Bridion reverses neuromuscular blockade induced by rocuronium or vecuronium in adults, by selective binding with the relaxant agent.

6.2 Summary of findings from non-clinical studies

a) Rocuronium:

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and development. Carcinogenicity studies have not been performed with rocuronium bromide (11).

b) Sugammadex:

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity potential, and toxicity to reproduction, local tolerance or compatibility with blood.

Sugammadex is rapidly cleared in preclinical species, although residual sugammadex was observed in bone and teeth of juvenile rats. Preclinical studies in young adult and mature rats demonstrate that sugammadex does not adversely affect tooth colour or bone quality, bone structure, or bone metabolism. Sugammadex has no effects on fracture repair and remodelling of bone (12).

6.3 Summary of findings from clinical studies

a) Rocuronium:

The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine anaesthesia is 0.6 mg/kg rocuronium bromide. Regardless of the anaesthetic technique used, the recommended infusion rate is 0.3-0.4 mg/kg/h. For children and adolescents the recommended intubation dose during routine anaesthesia and maintenance dose are similar to those

in adults. When used in overweight or obese patients (defined as patients with a body weight of 30% or more above ideal body weight) doses should be reduced taking into account ideal body weight. The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Rocuronium: hepatic and/or biliary tract disease and renal failure, prolonged circulation time, neuromuscular disease, hypothermia, obesity, burns, hypokalaemia, hypermagnesaemia, hypocalcaemia, hypoproteinaemia, dehydration, acidosis, hypercapnia and cachexia (11).

b) Sugammadex:

The use of sugammadex in patients with severe renal impairment (including patients requiring dialysis ($\text{CrCl} < 30 \text{ mL/min}$)) is not recommended (see section 4.4).

Studies in patients with severe renal impairment do not provide sufficient safety information to support the use of sugammadex in these patients (see also section 5.1).

For mild and moderate renal impairment (creatinine clearance ≥ 30 and $< 80 \text{ mL/min}$): the dose recommendations are the same as for adults without renal impairment.

Even though the recovery times in elderly tend to be slower, the same dose recommendation as for adults should be followed.

In obese patients, the dose of sugammadex should be based on actual body weight. The same dose recommendations as for adults should be followed. For mild to moderate hepatic impairment are no dose adjustments required, as sugammadex is mainly excreted renally (12).

6.4 Summary of known and potential risks and benefits.

a) Rocuronium:

The most commonly occurring adverse drug reactions include injection site pain/reaction, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse drug reactions during post-marketing surveillance is 'anaphylactic and anaphylactoid reactions' and associated symptoms (11).

b) Sugammadex:

Sugammadex is administered concomitantly with neuromuscular blocking agents and anaesthetics in surgical patients. The causality of adverse events is therefore difficult to assess. The most commonly reported adverse reactions in surgical patients were cough, airway complication of anaesthesia, anaesthetic complications, procedural hypotension and procedural complication (Common ($\geq 1/100$ to $< 1/10$)).

The following adverse reactions were reported in placebo controlled trials where subjects received anaesthesia and/or neuromuscular blocking agents (1,078 subject exposures to sugammadex versus 544 to placebo) (12):

[Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$)]

System organ class	Frequencies	Adverse reactions (Preferred terms)
Immune system disorders	Uncommon	Drug hypersensitivity reactions (see section 4.4)
Respiratory, thoracic and mediastinal disorders	Common	Cough
Injury, poisoning and procedural complications	Common	Airway complication of anaesthesia Anaesthetic complication (see section 4.4) Procedural hypotension Procedural complication

6.5 Description and justification of route of administration and dosage

a) Rocuronium:

Rocuronium bromide is administered intravenously (i.v.) either as a bolus injection or as a continuous infusion.

The standard intubating dose during routine anaesthesia is 0.6 mg rocuronium bromide per kg body weight, which results in adequate intubation conditions within 60 seconds in nearly all patients.

If rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6 mg rocuronium bromide per kg body weight and, when the neuromuscular block starts to recover, to start administration by infusion. In adults under intravenous anaesthesia, the infusion rate required to maintain the neuromuscular block ranges from 0.3 - 0.6 mg/kg/h. Under inhalational anaesthesia the infusion rate ranges from 0.3 - 0.4 mg/kg/h (11).

b) Sugammadex:

Sugammadex should be administered intravenously as a single bolus injection.

A dose of 4 mg/kg sugammadex is recommended if recovery has reached at least 1-2 post-tetanic counts (PTC) following rocuronium or vecuronium induced blockade.

A dose of 2 mg/kg sugammadex is recommended, if spontaneous recovery has occurred up to at least the reappearance of T₂ following rocuronium or vecuronium induced blockade (12).

6.6 Dosages, dosage modifications and method of administration

a) Rocuronium:

In group A (deep NMB) and group B (moderate NMB), a bolus of 0.6 mg/kg rocuronium is administered intravenously before tracheal intubation. After tracheal intubation, intravenous infusion of rocuronium (0.3 to 0.4 mg/kg) is started in group A (deep NMB), when PTC is more than 0 and titrated towards PTC 0-1. In group B (moderate NMB), no additional rocuronium is administered after tracheal intubation.

b) Sugammadex:

The NMB is reversed with an intravenous bolus injection of 4 mg/kg in group A and 2 mg/kg in group B.

6.7 Preparation and labelling of Investigational Medicinal Product

Due to limited funding, use of known drugs with known effects and limited risks in this trial, we request a waiver for annex 13 labelling of the IMPs. The IMPs that will be used will be prepared, labelled and administered at the bedside as described in the summary of product characteristics and according to local protocols for routine patient care. The medication will be administered by the anaesthesiologist, who is not blinded. The syringes with the IMPs cannot be directly observed by the blinded researchers as they will be covered by use of the sterile drapes.

6.8 Drug accountability

The IMPs that will be used (Rocuronium and Sugammadex) are dispensed by the clinical trials unit of the pharmacy of the Radboudumc. The anaesthesiologists that prepare and administer the drug will perform drug accountability by logging the administered products and their corresponding batch numbers on patient level. We will store this information in the trial master file.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Quality of recovery score (QOR-40 questionnaire) at 24 hours after extubation (appendix 1).

8.1.2 Secondary study parameters/endpoints

Questionnaires:

- Quality of recovery-40 score at 48 hrs after extubation, (appendix 1)

Medication use:

- Cumulative opiate use
- Cumulative use of other analgesics and anti-emetics

Intra-operative parameters:

- Surgical conditions; the Surgical Rating Scale (please see Table 2) is used to quantify the quality of the surgical field during the pneumoperitoneum phase (after introduction of the Hasson trocar, after introduction of all trocars and then every 15 minutes).
- Intra-operative complications (e.g. major bleeding, spleen or liver injury)
- Operation time, length of pneumoperitoneum, first warm ischemia time
- Estimated blood loss
- Conversion to open donor nephrectomy
- Conversion to hand-assisted donor nephrectomy

Clinical parameters:

- Components of pain scores (NRS 0-10):
 - Superficial wound pain score at 1, 6, 24, 48 hours (after extubation)
 - Deep intra-abdominal pain score at 1, 6, 24, 48 hours
 - Referred shoulder pain score at 1, 6, 24, 48 hours
- Post-operative nausea and/or vomiting (NRS)
- Time to reach discharge criteria*

* discharge criteria are: adequate pain control with oral medication, passage of flatus or defecation, intake of solid food tolerated, patient is mobilized and

independent and patient accepts discharge. Discharge criteria will be evaluated daily. If the donor for social reasons wants to stay longer (e.g. long distance from partner of child who are still hospitalized) the 'virtual' discharge date is listed. A physician who is independent and blinded (ward physician) is responsible for the actual discharge date.

Follow up after 4 weeks:

- 30 day complications
- Pain scores (NRS 0-10)
- Werk en zorg Questionnaire (appendix 2)

8.1.3 Other study parameters

Baseline parameters: age, gender, length, weight, body mass index, comorbidity, side of nephrectomy.

8.2 Randomisation, blinding and treatment allocation

Randomisation:

Computer-generated randomization (supported by our statistician) will be used with stratification for center. To ensure a balanced distribution, we will use block randomization.

Blinding and treatment allocation:

Blinding of the surgeons to the level of NMB is ensured by covering the hand with the neuromuscular monitoring equipment under the sterile drapes and the nerve stimulator and computer are placed behind the sterile drapes away from the surgeons. All study medications are prepared (and labeled 'study medicine') by the anesthesiologist or his/her assistant after opening the envelope containing the allocation of treatment. This will be done in the operating room before the surgeons enter. Surgeons, scrub nurses, postoperative care nurses and the investigator assessing the postoperative endpoints are blinded to group allocation. The attending anesthetic staff in the operating room is not blinded.

8.3 Study procedures

The peri-operative flowchart is shown in figure 1.

With regard to the primary hypothesis the QOR-40 score at pod 1 is the primary variable.

With regard to the secondary hypotheses variables and time-points of interest are shown in Table 3 and Table 4.

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.

8.5 Replacement of individual subjects after withdrawal

Patients withdrawing will be replaced, with a maximum of 10 patients.

8.6 Follow-up of subjects withdrawn from treatment

In case of withdrawal the patient will not be followed.

8.7 Premature termination of the study

Not applicable.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. 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 components of the intervention group (deep neuromuscular block). All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect at any dose:

- Results in death
- If life threatening (at any 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
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the coordinating investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
 - Summary of Product Characteristics (SPC) for an authorised medicinal product;
 - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or *ToetsingOnline* is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

In case of a SUSAR in the participating center LUMC, the responsible investigator of LUMC will inform the Radboudumc within the legal terms and the coordinating investigator of Radboudumc will report the SUSAR to the METC.

In case of a SUSAR the anesthesiologist will uncover the randomization.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

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.

9.5 Data Safety Monitoring Board (DSMB)

The need for a DSMB is assessed taking the EMEA guidelines on data monitoring committees into consideration. We believe that an interim evaluation does not increase patient safety, because safety of the procedure has already been proven. Study conduct and progress will be monitored according a monitor plan. Thus, a DSMB is not beneficial considering the proposed study design and will therefore not be established

10. STATISTICAL ANALYSIS

The principle investigator (MW) has final responsibility with regard to the data; a web-based data management system will be used to minimize errors and to ensure traceability. An independent statistician will provide assistance for data-analysis. The data will be unblinded after completion of the follow-up period and identification of protocol violations.

10.1 Primary study parameter(s) and secondary study parameter(s)

For the primary analysis group A and B will be compared with regard to the primary end-point (QOR-40 score at day 1). Factorial ANOVA will be used to compare groups and to adjust for co-variates *i.e.* age, gender and side of nephrectomy. P-values < 0.05 will be considered statistically significant. All analyses will be performed on an intention-to-treat basis.

Study parameters/endpoints	Presentation of data (quantitative/qualitative)
Quality of recovery	Quantitative
Medication use	Quantitative
Pain	Quantitative
Surgical rating score	Quantitative
Nausea/vomiting	Quantitative
Surgical parameters	Quantitative
Evaluation of post-operative complications	Quantitative

10.2 Interim analysis

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (59th version, Seoul, October 2008) and in accordance with the Medical Research involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

11.2 Recruitment and consent

At the Radboudumc and LUMC, respectively 90 and 45 laparoscopic donor nephrectomies are performed annually. All eligible donors will be screened. With an inclusion rate of approximately 80%, we expect that the screening (and inclusion period) will be 11 months.

Informed consent is obtained at least two weeks after providing written information about the study. During this two-week interval, an independent physician can be consulted for questions. At the day of hospital admission, one day before surgery, informed consent will be obtained. Then, one, unique number will be assigned (study number).

11.3 Objection by minors or incapacitated subjects

Not applicable.

11.4 Benefits and risks assessment, group relatedness

The burden for participants in this study is mainly related to the evaluation of the endpoints during the early postoperative phase. Assessment of the differential pain scores and the QOR-40 questionnaire will take approximately 10 minutes per time-point (-18h, 1h, 4h, 8h, 24h and 48h after detubation). As the use of a deep NMB with a standard insufflations pressure improves the quality of the surgical field, there are no risks related to the surgery. A deep neuromuscular block can be achieved by higher doses of rocuronium as compared to the routine intubation dose.

The participants of this study are approved for live kidney donation. One of the selection criteria is a glomerular infiltration rate above 59-85 ml/min/1.73m² (depending on age) to provide sufficient residual (donor) renal function post donation. According to Li *et al* the early decrease of the glomerular filtration rate after kidney donation is approximately 15-20 ml/min/1.73m² (10). Therefore a higher dose of rocuronium in living kidney donors is safe, as the plasma clearance of rocuronium in patients with moderate to severe renal

dysfunction is only slightly reduced (1ml/kg/min) as compared to patients with normal renal function (rocuronium clearance 3.7 ml/kg/min).

To overcome the extended effects of deep neuromuscular blockade that may lead to airway obstruction, hypoxia, pneumonia and/or atelectasis, sugammadex is administered to antagonize the effects of rocuronium. Sugammadex is a rapid antagonist of neuromuscular blockade by rocuronium that is given immediately after surgery. Randomized controlled trials have shown that sugammadex can be safely administered in patients, without dose adjustments for young, elderly or obese patients and that it can also be safely administered in patients with mild or moderate renal impairment (creatinine clearance ≥ 30 and < 80 mL/min) (12).

Elimination of the rocuronium-sugammadex will take longer in donors, because of the slightly decreased glomerular filtration rate, but since the rocuronium is inactivated by sugammadex, there is no risk at recurrence of neuromuscular blockade.

A recent study performed by Martini *et al.* has shown that deep neuromuscular blockade improves surgical conditions with reduced postoperative pain scores after laparoscopic surgery (1). Moreover, preliminary data of our recently performed Leopard-3 study, show that the mean SRS (surgical rating scale) was significantly better during deep NMB with less opiate consumption (2). Altogether, we expect that the use of deep NMB during LDN reduces postoperative pain scores and/or analgesia consumption. This may improve the early quality of recovery of live kidney donors.

11.5 Compensation for injury

The Radboudumc has an insurance in accordance with the legal requirements in the Netherlands (Article WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects though injury or death caused by the study.

1. € 650.000,-- (i.e. sixhundred and fifty thousand Euro) for death or injury for each subject who participates in the Research
2. € 5.000.000,-- (i.e. five million Euro) for death or injury for all subjects who participate in the Research
3. € 7.500.000,-- (i.e. seven million fivehundredthousand Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Not applicable.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Subjects will be coded by a numeric code in order to create an anonymous dataset. A Castor database will be developed and used for data management. Investigators have access to this code and will store the subject identification code list at a separate location from the dataset.

Data will be securely stored in the database of the department of surgery of the Radboud university medical center accessible to the investigators, in accordance with the Dutch Personal Data Protection Act.

12.2 Monitoring and Quality Assurance

In our opinion, this study adds a small chance (“kleine kans”) of mild damage (“lichte schade”) and consequently adds a negligible risk (“verwaarloosbaar risico”) according to the risk classification of the “Nederlandse Federatie van Universitair Medische Centra” (NFU). Monitoring will be conducted in accordance with negligible risk monitoring guidelines of the NFU, which will be reported in a monitorplan.

Risk classification in relation to the chance and severity of damage (Dutch versions)

	Lichte schade	Matige schade	Ernstige schade
Kleine kans	Verwaarloosbaar risico	Verwaarloosbaar risico	Matig risico
Matige kans	Verwaarloosbaar risico	Matig risico	Hoog risico
Grote kans	Matig risico	Hoog risico	Hoog risico

12.3 Amendments

Not applicable.

12.4 Annual progress report

The 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 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 investigator 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 investigator 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/ 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 will be registered at ClinicalTrials.gov. Results will be published in a peer-reviewed international journal.

13. STRUCTURED RISK ANALYSIS

Not applicable.

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 9. Özdemir-van Brunschot DM, Scheffer GJ, van der Jagt MF, Langenhuijsen JF, Dahan A, Mulder JEEA, Willems S, Hilbrands LB, Donders R, van Laarhoven CJHM, D'Ancona FC, Warlé MC. Low pressure pneumoperitoneum facilitated by deep neuromuscular blockade during laparoscopic donor nephrectomy is associated with reduced length of hospital stay. *Submitted.*
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 11. <https://www.medicines.org.uk/emc/medicine/5166>
 12. <https://www.medicines.org.uk/emc/medicine/21299/SPC/Bridion+100+mg+ml+solution+for+injection/>

Table 1.

RCTs	Standard pressure PNP	Low pressure PNP
Moderate NMB	n=10	n=10*
Deep NMB	n=48 [#]	n=17 ^{***}
	n=48	n=17
	n=32	n=32 ^{**}

Diagram illustrating the flow of patients between Standard pressure PNP and Low pressure PNP groups across different NMB levels and studies:

- Moderate NMB:** n=10 (Standard pressure PNP) → 'Leopard-1' → n=10* (Low pressure PNP)
- Deep NMB:**
 - n=48[#] (Standard pressure PNP) → 'this proposal' → n=48 (Standard pressure PNP)
 - n=17^{***} (Low pressure PNP) → 'Leopard-3' → n=17 (Low pressure PNP)
 - n=32 (Standard pressure PNP) → 'Leopard-2' → n=32^{**} (Low pressure PNP)

Overview of RCTs regarding low-pressure PNP and deep NMB in LDN.

* *'Leopard-1 study'*

- design: single center, blinded, randomized controlled pilot study.
- main results: lower pain scores after low-pressure PNP. Longer operation time due to the use of low-pressure PNP.

** *'Leopard-2 study'*

- design: single center, blinded, randomized controlled trial.
- main results: no difference in pain/analgesia consumption. Improved quality of recovery and shorter length of stay after low-pressure PNP.

*** *'Leopard-3 study'*

- design: multi-center, blinded, randomized controlled trial.
- main results: better quality of the surgical field (primary endpoint) and a tendency towards reduced analgesia consumption in the deep NMB group.

This study proposal

- design: multi-center, blinded, randomized controlled trial.
- hypothesis: enhanced quality of recovery by deep NMB.

Table 2.

Assessment of surgical space conditions (SRS) according to Martini *et al.* (8)

<i>Scale</i>		<i>Description</i>
1	Extremely poor conditions	The surgeon is unable to work because of coughing or the inability to obtain a visible laparoscopic 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 3.

Overview of variables and time-points.

	-18h	1h	4h	8h	24h	48h
QOR-40	x				x	x
Components of pain	x	x	x	x	x	x
Analgesia use	x	x	x	x	x	x
Discharge criteria				x	x	x
Evaluation of complications					x	x

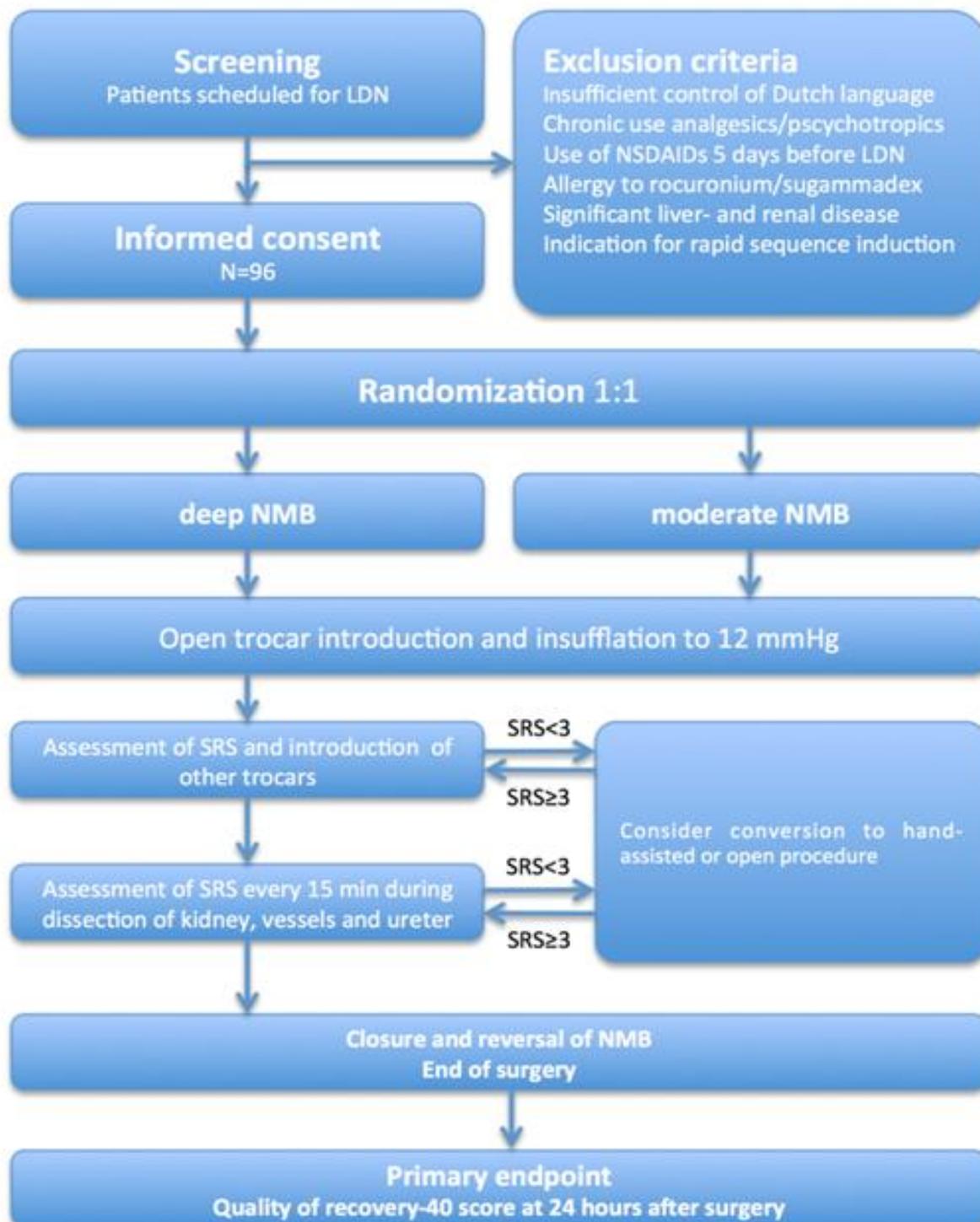
Table 4.

Overview of variables and procedures/techniques.

Study parameters/endpoints	Procedure, technique and/or tests
Quality of recovery	Quality of recovery 40 questionnaire (appendix 1)
Surgical rating score	Peri-operative evaluation (table 2)
Pain	Components of pain
Medication use	Daily evaluation of electronic patient dossier
Nausea/vomiting	Daily evaluation during hospital admission
Surgical parameters	Intra-operative evaluation by the surgeon
Evaluation of post-operative complications	Daily evaluation during hospital admission

Figure 1.

Study Flow Chart



Appendix 1.

QOR-40 questionnaire.

Vragenlijst over kwaliteit van herstel

Om een inzicht te krijgen in het herstel na de operatie die u heeft ondergaan, vragen wij u deze vragenlijst in te vullen.

Geef u daarvoor alstublieft bij elke vraag het antwoord dat het beste weergeeft hoe u zich de laatste 24 uur voelde. Dit gebeurt op een schaal van 1-5. Boven de gevallen staat de betekenis van de getallen.

Welbevinden	<i>Helemaal niet waar</i>			<i>Helemaal waar</i>	
Ik kan gemakkelijk ademen	1	2	3	4	5
Ik heb goed geslapen	1	2	3	4	5
Het eten heeft me gesmaakt	1	2	3	4	5
Ik voel me uitgerust	1	2	3	4	5

Gevoelens	<i>Helemaal niet waar</i>			<i>Helemaal waar</i>	
Ik voel me over het algemeen goed	1	2	3	4	5
Ik heb de situatie/mezelf in de hand	1	2	3	4	5
Ik voel me op mijn gemak	1	2	3	4	5

Zelfredzaamheid	<i>Helemaal niet waar</i>			<i>Helemaal waar</i>	
Ik kan goed een gesprek voeren	1	2	3	4	5
Ik kan mezelf wassen en tanden poetsen	1	2	3	4	5
Ik kan mezelf verzorgen	1	2	3	4	5
Ik kan schrijven	1	2	3	4	5
Ik kan werken/ werkzaamheden thuis verrichten	1	2	3	4	5

Steun	<i>Helemaal niet waar</i>			<i>Helemaal waar</i>	
Het is mogelijk in het ziekenhuis met artsen en verpleegkundigen te spreken	1	2	3	4	5
Het is mogelijk met familie en vrienden te spreken	1	2	3	4	5
Ik wordt gesteund door de artsen in het ziekenhuis	1	2	3	4	5
Ik word gesteund door de verpleegkundigen in het ziekenhuis	1	2	3	4	5
Ik wordt gesteund door familie en vrienden	1	2	3	4	5
Ik begrijp uitleg en adviezen	1	2	3	4	5

PAS OP: HELEMAAL WAAR EN WAAR ZIJN NU OMGEDRAAID!

Welbevinden	<i>Helemaal waar</i>			<i>Helemaal niet waar</i>	
Ik heb last van misselijkheid	1	2	3	4	5
Ik heb overgegeven	1	2	3	4	5
Ik moet kokhalzen	1	2	3	4	5
Ik voel me rusteloos	1	2	3	4	5
Ik heb last van trillen of beven	1	2	3	4	5
Ik heb last van rillerigheid	1	2	3	4	5
Ik heb het te koud	1	2	3	4	5
Ik heb last van duizeligheid	1	2	3	4	5

Gevoelens	<i>Helemaal waar</i>			<i>Helemaal niet waar</i>	
Ik heb naar gedroomd	1	2	3	4	5
Ik voel me angstig	1	2	3	4	5
Ik ben boos	1	2	3	4	5
Ik voel me somber	1	2	3	4	5
Ik voel me alleen	1	2	3	4	5
Ik heb moeite om in slaap te komen	1	2	3	4	5

Steun	<i>Helemaal waar</i>			<i>Helemaal niet waar</i>	
Ik voel me verward	1	2	3	4	5

Pijn en klachten	<i>Helemaal waar</i>			<i>Helemaal niet waar</i>	
Ik heb matige pijn	1	2	3	4	5
Ik heb ernstige pijn	1	2	3	4	5
Ik heb hoofdpijn	1	2	3	4	5
Ik heb spierpijn	1	2	3	4	5
Ik heb rugpijn	1	2	3	4	5
Ik heb een pijnlijke mond	1	2	3	4	5
Ik heb een pijnlijke keel	1	2	3	4	5

Appendix 2.

Vragenlijst over werk en zorg.

Vragenlijst over werk en zorg

In deze vragenlijst wordt u gevraagd in hoeverre u weer in staat bent om te werken en hoeveel extra zorg u de afgelopen week nodig hebt gehad.

1. Heeft u de afgelopen week de huisarts vanwege de operatie bezocht?

0 nee

0 ja, Hoe vaak? _____
—

Waarom? _____

2. Heeft u de afgelopen week een dokter in het ziekenhuis bezocht vanwege de operatie?

0 nee

0 ja, Hoe vaak? _____
—

Waarom? _____

3. Bent u de afgelopen week nogmaals opgenomen in het ziekenhuis vanwege de donor operatie?

0 nee

0 ja, Hoeveel dagen? _____
—

Waarom? _____

4. Heeft u de afgelopen week hulp nodig gehad van familie, vrienden of kennissen?

0 nee

0 ja, Hoeveel uur? _____

5. Heeft u de afgelopen week thuiszorg gehad?

0 nee

0 ja, Hoeveel uur? _____

6. Heeft u de afgelopen week betaalde hulp in de huishouding gehad?

0 nee

0 ja, Hoeveel uur? _____

7. Heeft u de afgelopen week gewerkt?

0 nee, in verband met de operatie *ga verder naar vraag 8*

0 nee, reeds voor de operatie niet (meer) werkzaam *ga verder naar vraag 8*

0 nee, omdat _____ *ga verder naar vraag 8*

0 ja, Op welke datum bent u weer gaan werken? _____

Hoeveel uur heeft u de afgelopen week gewerkt? _____

8. Hoeveel procent van uw dagelijkse bezigheden, die u voor de operatie ook deed, heeft u kunnen uitvoeren deze week? (zoals huishoudelijke werkzaamheden, hobby's en persoonlijke verzorging)

_____ (tussen 0 en 100%)

Dank u wel voor het invullen!