Quality of Recovery after day care surgery with app controlled Remote Monitoring: a randomized controlled trial

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De kwaliteit van herstel na een dagbehandeling operatie met thuismonitoring via een smartphone app

PROTOCOL TITLE: ***Quality of Recovery after day care surgery with app controlled Remote Monitoring: a randomized controlled trial***

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
ACWO	**Advies Commissie Wetenschap en Onderzoek**
AE	**Adverse Event**
App	**(smartphone) Application**
AR	**Adverse Reaction**
ASA	**American Society of Anaesthesiologists**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IC	**Informed Consent**
NRS	**Numerical Rating Scale (for pain)**
NVA	**Nederlandse vereniging voor Anesthesiologie**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
PDNV	**Post Discharge Nausea and Vomiting**
PDMS	**Patient Data and Management System**
POP	**Post Operative Pain**
(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.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: To date the majority of surgical interventions is performed in day care and patients are being discharged soon after the first critical postoperative period. At home, patients have limited options to contact the hospital in case of severe pain and nausea. We have provided day care surgical patients with a smartphone application for remote monitoring that is configured to self-record postoperative pain and nausea after being discharged from hospital. Furthermore, it provides a messaging service to contact the hospital in case of (severe) pain or nausea. Despite the promising initial patient experiences of such an application, we do not know whether remote monitoring with a smartphone application improves the patient's experience during the recovery period.

Objective: To evaluate the experienced quality of recovery after day care surgery between patients provided with a smartphone application for remote monitoring and patients receiving standard of care (no remote monitoring).

Study design: (Non-blinded) randomized controlled trial with mixed methods design

Study population: Adult patients (aged 18 years or older) scheduled for day care surgery

Intervention (if applicable): The intervention group receives the smartphone application for remote monitoring during weekdays from 8 am to 17 pm up to 7 days after surgery. With this application, patients are able to record experienced pain and nausea. In addition, they can send messages to the hospital. Daily monitoring is performed by an anaesthesia professional who will contact the patient in case severe pain or nausea is reported in the app. The control group receives standard of care (with post-discharge verbal and paper instructions).

Main study parameters/endpoints: The main study endpoint is the difference between patients using remote monitoring and patients not using remote monitoring in perceived quality of recovery measured with the QoR-15 questionnaire on the 7th day after day care surgery. Secondary endpoints are 1) the overall score on the Quality of Recovery-15 at day 1, 4 and 7 post discharge, 2) the perceived quality of hospital aftercare and 3) experienced psychological effects of remote monitoring during postoperative recovery from day care surgery.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participating in this study does not pose any additional risks either for patients allocated to the intervention group with remote monitoring or for patients allocated to the standard of care group. Patients in the remote monitoring group are being asked to use a smartphone application to record pain and nausea daily for up to 7 days post discharge. Recording pain and nausea will take 2 minutes daily. Patients from both groups are being asked to fill in the validated QoR-15 questionnaire one day before admission and on the 1st, 4th and 7th day post discharge and this will take 2.5 minutes. No extra hospital visits, physical examinations or tests are required. Patients in the remote monitoring group could benefit

from participating in the study because they are monitored daily by a healthcare professional. Therefore, severe pain, nausea and possibly other complications can be noticed and managed earlier.

1. INTRODUCTION AND RATIONALE

To date the majority of patients receiving minor or intermediate surgical interventions are being discharged as soon as the critical post-operative phase is passed and vital signs and physical wellbeing have been stabilized. In general patients will leave the hospital within 4 to 5 hours after the intervention usually without further monitoring (1). Most hospitals provide their patients with verbal and paper instructions on what to do in case of severe pain, nausea and alleged surgical complications. The usual advice is to contact the surgical or anesthesia outpatient department during office hours and if not available, patients are advised to contact their general practitioner or the hospitals' emergency department. For patients whilst being in pain, nauseous or worried about physical wellbeing, contacting the hospital can be a challenging task. Answering machines and gatekeepers (e.g., secretaries who may or may not connect you with the doctor) stand between the patient and their healthcare professional in order to prevent for improper contact. In addition, doctors and nurses have ongoing clinical obligations, which makes it unrealistic to expect that they are available on-demand.

Maintaining and improving high quality and cost-effective healthcare for outpatients is a hospital priority. The volume and complexity of outpatient surgical procedures continues to increase, with a wider range of patients now considered suitable for day care surgery (2). In-addition, recent drives to reduce the length of hospital stay because of the Covid-19 pandemic emphasize that day care surgery is fundamental to modern patientcare. For example, in the Netherlands in 2012, 54% of the patients are treated via day care surgery versus 25% in 1993 (3), considering 1.4 million surgical procedures annually (4). To realize the aims of improving recovery after outpatient surgery, it is especially important to optimize management of postoperative pain (POP) and post discharge nausea and vomiting (PDNV). Even today, 40% to 75% of the patients experience moderate-to-severe POP (5, 6) and 28% to 57% experience PDNV (7-10).

eHealth interventions are currently broadly applied in perioperative care (e.g. remote monitoring, educational websites and tele-rehabilitation) (11, 12). In a similar way, we configured an existing and already applied remote monitoring application to enable follow up of patients after day care surgery with the objective to improve the efficiency and quality of postoperative recovery. In order to do so, we have provided patients a smartphone application to record postoperative pain and nausea and to be in contact with a healthcare professional when worried about their physical well-being after day-care surgery. Despite the promising first results from a proof of concept study with a similar application amongst

clinically admitted patients we do not know to what extend it improves the patient's recovery after day care surgery (13). A recent systematic review showed that the overall primary purpose of 'pain related' apps is education and pain self-management and to the lesser extend remote monitoring . More importantly, many applications lacked a direct feedback loop between the patient and their healthcare professionals (14, 15).

We hypothesized that the realization of being monitored remotely and receiving feedback from healthcare professionals during the postoperative recovery period will improve patient experienced recovery. In a non-blinded randomized controlled trial with mixed methods design, we propose to answer the following research question: *What is the difference in experienced quality of recovery between patients provided with a smartphone app-based remote monitoring tool and patients without remote monitoring (standard care) after day care surgery?*

2. OBJECTIVES

a. Primary Objective

b. Primary outcome is to assess the difference between patients using remote monitoring and patients not using remote monitoring in perceived quality of recovery measured with the QoR-15 questionnaire on the 7th day after day care surgey.

c. Secondary Objective(s)

To assess the experienced postoperative pain (POP) between patients provided with a smartphone application for remote monitoring and patients receiving standard of care (no remote monitoring) after day care surgery.

To assess the experienced post discharge nausea and vomiting (PDNV) between patients provided with a smartphone application for remote monitoring and patients receiving standard of care (no remote monitoring) after day care surgery.

To assess the difference in the number of surgical complications rated with the Clavien Dindo classification of surgical complication between patients provided with a smartphone application for remote monitoring and patients receiving standard of care (no remote monitoring) after day care surgery.

To assess the difference in the number of re-admissions between patients provided with a smartphone application for remote monitoring and patients receiving standard of care (no remote monitoring) after day care surgery.

To assess the difference in the number of hospital contacts / general practitioner between patients provided with a smartphone application for remote monitoring and patients receiving standard of care (no remote monitoring) after day care surgery.

To assess the difference in experienced quality of communication with the hospital staff between patients provided with a smartphone application for remote monitoring and patients receiving standard of care (no remote monitoring) after day care surgery.

To assess the experienced psychological effects remote monitoring in patients recovering from day care surgery

3. STUDY DESIGN

A two-arm multicenter non-blinded randomized controlled trial with mixed methods design will be conducted at the day care nursing wards of OLVG Hospital (Locations Oosterpark and Jan Tooropstraat), Amsterdam, the Netherlands, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands and Maasstad Hospital, Rotterdam, the Netherlands. Surgical specialisms involved are gynecology, eye-nose and throat, oral and maxillofacial, orthopedics, general and vascular, trauma and urology. Surgical day care patients will be randomly assigned to one of the two study arms, remote monitoring with a smartphone application (intervention) or standard of care (no remote monitoring) after hospital discharge. Study period is expected to run from 1st of February 2022 up to the 31st December 2022.**STUDY POPULATION**

a. Population (base)

For this study, we will enrol 230 consecutive patients admitted to OLVG Hospital, Canisius Wilhelmina Hospital or Maasstad Hospital who are scheduled to undergo a surgical intervention in day care. In 2020 under the pressure of the covid-19 pandemic over 8000 day care surgical interventions were performed therefore, it is likely that the inclusion will be achieved within the intended study period.

b. Inclusion criteria

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

- Age: older than or equal to 18 years
- Pre-anaesthesia conclusion: ASA I to III
- Scheduled for day care surgery for one of the following surgical specialties: gynaecology, eye-nose and throat, oral and maxillofacial, orthopaedics, general and vascular, trauma and urology
    -
- In possession of a smartphone

c. Exclusion criteria

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

- Not able to speak or understand the Dutch language
- Mentally impaired (e.g. dementia, retardation)

During study:

- Patients who experience a unexpected post-operative complication or prolonged recovery with the result that discharge on the same day of the surgical intervention is not possible will be excluded

d. Sample size calculation

An 8.0 difference in the overall score in the QoR-15 questionnaire on postoperative day 7 is considered a minimal clinically relevant difference (16) with standard deviation of 19.1 (17). Group sample sizes of 91 patients achieve 80% power to detect a difference of -8.0 with a significance level (alpha) of 0,05 using a two-sided two-sample t-test. *Sample Size calculation is performed with PASS 2021 Power Analysis and Sample Size Software (2021). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.* We plan to include 20% extra patients to adjust for dropout or incomplete data. Total sample will be 230 subjects divided into two groups.

4. TREATMENT OF PATIENTS

a. Investigational product/treatment

Patients scheduled for day care surgery within 3 weeks after their pre-anaesthesia workup who fit the inclusion criteria and are willing to participate in this study are allocated to either remote monitoring with a smartphone application after discharge (the intervention) or the standard of care without remote monitoring (control). Both groups will have a pre-anaesthesia workup (e.g. online-assessment, telephone assessment or an assessment during a physical visit to the anaesthesia outpatient department) according to the standards of the Dutch association of Anaesthesiologist and Federation of Medical Specialists (18).

During the pre-anaesthesia workup, patients are being notified about the study by an anaesthesiologist, physician assistant or medical assistant. If interested they will receive the study information and a consent letter. Two days before admission a researcher will explain the study during a telephone call and will ask for informed consent. Moreover, participating patients are asked to complete the first online QoR-15 questionnaire. Patients allocated to the intervention group also receive an invitation e-mail with instructions from Thuismeten (Luscii) © to download and install the remote monitoring application. This invitation is sent by a healthcare professional through a secured connection via the hospitals' patient data management system (e.g. EPIC ©). During the admission patients from both groups receive perioperative anaesthesia care according to standards based on the Guidelines for treatment of the Dutch association of anaesthesiologists (18, 19).

Patients are regularly asked about their postoperative pain and nausea by either nurses or doctors, at least once per perioperative phase (e.g. recovery and day care ward). In case of severe pain, the patient is administered paracetamol, NSAID's, tramadol or opioids. In case of nausea, the patient is administered metoclopramide or granisteron. Both, pain- and nausea treatment is executed by nurses with the aim of making the patient feel comfortable. Postoperative medication is ordered and supervised by the attending anaesthetist.

Before discharge, patients from both groups receive verbal and paper (APPENDIX I: example discharge information OLVG, in Dutch) care- and recovery instructions from a day care ward nurse. In addition, they receive a medication box containing paracetamol,

non-steroid inflammatory drug (NSAID), metoclopramide, pantoprazole and if they underwent a surgical procedure with intermediate risk for complications, they also receive tramadol or opioids.

In addition to standard care as delineated above, patients in the intervention group (remote monitoring after discharge) will have the monitoring application installed on their personal smartphone. Once they are back home, they can start recording pain and nausea and may ask questions about their recovery within the application. Once a day patients receive a push notification to record pain and nausea. The application is operational up to 7 days post discharge. After this period the application is disconnected from the Thuismeten (Luscii) © server.

In case of recording unbearable pain and nausea or asking a question and being in need for help or assistance, an anaesthesia medical assistant will contact these patients during office hours from 08:00 to 16:30 by using the applications' messaging service or by telephone. First the medical assistant will perform an initial triage of the patients in need, subsequently pain and nausea reports and additional questions that appear as an alert in the electronic back office systems of Thuismeten (Luscii) © will be addressed. The alerts are set to the in-app question 'do you want something to be done about your pain or nausea?' or an increase of 3 points numerical rating scale (NRS) for pain and additional questions asked in the apps messaging service. During triage, the medical assistant will follow a protocolled workflow to assess actions to be taken (APPENDIX II triage workflow, in Dutch). If contacting the patient by telephone is necessary, the medical assistant will use a call script to assess patients' pain, nausea and physical status (APPENDIX III, call script, in Dutch). The medical assistant will often give appropriate feedback or advice via message or telephone. In case of a possible medical alert or a necessary medication adjustment, the medical assistant will consult the anaesthetist, trainee nurse specialist or physician assistant responsible for remote postoperative pain care.

b. Use of co-intervention (if applicable)

Not applicable

c. Escape medication (if applicable)

Not applicable

5. INVESTIGATIONAL PRODUCT (Not applicable)

a. Name and description of investigational product(s)

Not applicable

b. Summary of findings from non-clinical studies

Not applicable

c. Summary of findings from clinical studies

Not applicable

d. Summary of known and potential risks and benefits

Not applicable

e. Description and justification of route of administration and dosage

Not applicable

f. Dosages, dosage modifications and method of administration

Not applicable

g. Preparation and labelling of Investigational Medicinal Product

Not applicable

h. Drug accountability

Not applicable

6. NON-INVESTIGATIONAL PRODUCT

a. Name and description of non-investigational product(s)

The remote monitoring application for day care patients is a configuration of an already existing and applied monitoring platform by Luscii Healthtech B.V. The configuration for postoperative monitoring was commissioned by OLVG hospital. In this study app versions 2.43.0 or higher are being used. The application is CE IIa certified. For more information about Luscii technical, privacy and security specifications, we refer to https://www.notion.so/Security-and-privacy-at-Luscii-fc51e66e21ae4a87a51499a52d4c8db2. Information on intended use is available at https://www.notion.so/luscii/Luscii-vitals-Instructions-for-Use-for-Patients-and-Clinicians-3d5050d94f6f40f9aa6af2e9aa77084d both the triage protocol and the call script are developed by the OLVG hospital department of anaesthesia (APPENDIX II and III).

b. Summary of findings from non-clinical studies

Not applicable

c. Summary of findings from clinical studies

The Luscii tele-monitoring platform is currently being used in the care for patients with acute and chronic diseases such as hypertension during pregnancy, hearth failure, COPD and COVID-19. The different telemonitoring modules are based on a direct feedback loop between patients and health care providers and alarming combinations of patient recorded results (20, 21). Results show a significant reduction of hospital admissions, days spent in hospital and healthcare costs (22, 23).

d. Summary of known and potential risks and benefits

No potential risk or harm is to be expected from using the Luscii application and remote monitoring. Patients using the application and remote monitoring could benefit from being monitored daily by an anaesthesia medical assistant as formulated in the study objectives. It is expected that in patients receiving remote monitoring the quality of recovery be improved.

e. Description and justification of route of administration and dosage

Not applicable

f. Dosages, dosage modifications and method of administration

Not applicable

g. Preparation and labelling of Non Investigational Medicinal Product

Not applicable

h. Drug accountability

Not applicable

7. METHODS

a. Study parameters/endpoints

i. Main study parameter/endpoint

Quality of recovery measured with the Quality of Recovery questionnaire-15 (QoR-15) (16, 24) at day 7post discharge between patients with remote monitoring (intervention group) and patients without remote monitoring (non-intervention group) after day care surgery.

ii. Secondary study parameters/endpoints (if applicable)

Quality of recovery measured with the quality of recovery questionnaire-15 (QoR-15) (16, 24) at post discharge day at post discharge day 1, 4 and 7.

Postoperative Pain: Experienced postoperative pain (POP) measured with (in-app) NRS for Pain (25) (combined with 11 faces scale) measured at day 1, 4 and 7 post discharge.

Post discharge nausea and vomiting: Experienced post discharge nausea and vomiting (PDNV) measured with the Myles' PDNV assessment scale (21) between intervention and non-intervention group. Measured at day 1, 4 and 7 post discharge.

Medication Dosage and Use: the total dosage of administered analgesics will be assessed during hospital stay and recorded in the medical record. The total dosage of administered analgesics at home after discharge will assessed by asking patients to indicate which pain medication they have been using. Measured at day 1, 4 and 7 post discharge.

The number of contacts with the hospital, general practitioner or emergency department. All types of contacts (e.g. physically, e-mail, telephone) will be assessed by reviewing the PDMS for registered contacts and by asking the patients to indicate the number of contacts. Measured at day 1, 4 and 7 post discharge.

The number of surgical complications assessed according to the Clavien Dindo classification of surgical complications (26, 27) will be assessed by reviewing the PDMS and by asking the patients to indicate the number of complications. Measured at day 1, 4 and 7 post discharge.

The number of readmissions. A readmission is defined as an admission to hospital or emergency department for medical care or observation regarding their surgical intervention. Readmissions will be assessed by reviewing the PDMS and by asking the patient to indicate the number of readmissions. Measured at day 1, 4 and 7 post discharge.

Satisfaction: Patients' satisfaction with the provided care will be assesses using a 1-item self-created VAS scale ('not at all to very much', 0-10 range). Satisfaction will be measured at day 1, 4 and 7 post discharge.

General evaluations regarding provided care after discharge: Patients' evaluations of their experienced care during the 7 day discharge period are measured using two items. i) How likely is it that the patient would recommend this hospital to other day care surgery patients (using an adapted item from the CQ index (0-10 'would definitely not recommend' to 'would definitely recommend') (28, 29). Ii) Their overall rating of the quality of care provided by the hospital during the 7 day discharge period, using an item from the CQ index (0-10 scale, 'very poor care' to extremely good care') (28, 29). Both items will be measured at discharge day 1, 4 and 7.

The quality, experiences and communication regarding remote monitoring with this application will be assed in one by one semi structured interviews. The perceptions of 20 participants are considered satisfactory or when data saturation is reached (REF). Prior to the interview, participants receive general information concerning the topics and informed consent was requested from the interviewee to allow for audio recording of the interview. See for interview topics (f1_Interview Topics_version_1_11_2021¬).Furthermore, interviews are conducted by telephone or online through Skype, Zoom or FaceTime due to COVID-19 measures.

iii. Other study parameters (if applicable)

The following patient baseline characteristics are collected: age, sex, smoking status, body mass index, ASA classification, PONV score, preoperative NRS, PONV prophylaxis, previous surgical or anaesthesia related complications, history of (chronic) pain, history of motion sickness, surgical specialism, surgical procedure and classification (e.g. laparoscopic cholecystectomy, minor), anaesthesiology technique (i.e. general or spinal anaesthesia), surgery duration, intraoperative medication, PONV and NRS for pain at recovery ward, PONV and NRS for pain at day care ward, duration of admission

b. Randomisation, blinding and treatment allocation

Patients will be allocated oto the intervention (remote monitoring) or standard of care group (no remote monitoring). To adjust for practice variation between the participating hospitals Eligible patients will be randomly assigned to receive remote monitoring with the application or the standard of care without remote monitoring. Treatment assignments were performed

centrally according to a computer-generated random schedule (Castor EDC) in permuted blocks of four within strata of participating hospitals (OLVG Hospital, Maasstad Hospital and Canisius Wilhelmina Hospital). The allocation will be computer-generated with Castor© web application (http://castoredc.com/ and https://castorcrf.com, Castor Services are operated by Ciwit B.V. and located in the Netherlands).

c. Study procedures

Patients are recruited to participate in this study during their appointment for anaesthesia pre-assessment (e.g. online assessment, telephone assessment or during visiting the anaesthesia outpatient department). An anaesthesiologist, trainee nurse specialist, physician assistant or medical assistant will verbally explain the study. If interested, they receive an information-letter about the study, and an informed consent form (PIF_IC_e1_e2_QuReMo_Versie1_14_7_2021).

Patients who are not informed during the preoperative assessment will be contacted afterwards by one of the researchers to explain the study and to ask them to consider participation. If interested, they receive an information-letter about the study, and an informed consent form (PIF_IC_e1_e2_QuReMo_Versie1_14_7_2021).

The patients are given a reflection period of at least 48 hours, after that a researcher or medical assistant will contact the patient if they agree to participate. Patients who have been asked to participate are earmarked in the PDMS (e.g. EPIC). A patient who wishes to participate is asked to sign the consent form and bring it on the day of admission. Patients who, forget to bring their consent form are provided a copy, which is then to be signed on the day of admission. Accordingly, both researchers and patients receive a wet ink copy of the consent form.

After receiving informed consent, the researchers will record the baseline characteristics to the Castor EDC database and perform the randomisation procedure. Moreover, no data is recorded that could trace back the identity of the patients. By randomizing, an anonymous study identification number is allocated to the patients. The researchers from the participating hospitals will keep a secured database in which patient hospital number corresponds with the study identification number, stored locally at their own hospital server. Two days before admission patients in the remote monitoring group (intervention group) receive an invitation e-mail from Luscii © sent by a medical assistant from the anaesthesia outpatient department with instructions to download and install the remote monitoring application. Perioperative patients from both the intervention group and the standard of care group receive anaesthesia

care according to the standards of the Dutch association of anaesthesiologist (18, 19). Intra- and postoperative characteristics and variables will be recorded in Castor EDC by the researchers. Before discharge, patients from both groups receive verbal and paper care and recovery instructions from a day ward nurse. In addition patients receive a medication box with instructions for use, containing paracetamol, naproxen or diclofenac and in case of an intermediate surgical risk for complications also tramadol or an opioid. Once at home, patients in the intervention group can start using the smartphone application for recording pain and nausea and ask additional questions about their recovery. Subsequently an anaesthesia medical assistant will respond appropriately to patients in need following triage and assessment protocol. At day 1, 4 and 7 post discharge patients from both groups receive an online questionnaire (QoR-15). In case patients do not respond, a researcher or a medical assistant will contact the patients from both study arms by telephone to assess the study endpoint questionnaire (f1_vragenlijst_QuReMo_English_version_1_16_7_2021). Thereafter, endpoint data will be recorded in Castor EDC by one of the researchers.

In addition, patients from the remote monitoring group who have given permission for an interview to assess the quality of communication with app receive a telephone appointment at day 7 postoperative for a 30 minutes semi structured interview with one of the researchers.

d. 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.

e. Specific criteria for withdrawal (if applicable)

f. Replacement of individual subjects after withdrawal

In our power calculation, we anticipated for 20% dropout. If data collection is still in progress, new subjects will be recruited.

g. Follow-up of subjects withdrawn from treatment

There will be no follow up on withdrawn subjects.

h. Premature termination of the study

Not applicable

8. SAFETY REPORTING

a. Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO (30), the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise 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.

b. AEs, SAEs and SUSARs

i. 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 investigational intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

ii. Serious adverse events (SAEs)

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

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

An elective hospital admission will not be considered as a serious adverse event. The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs: The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Seen the nature of our intervention, i.e. remote monitoring on top of routine postoperative care, no adverse or serious adverse events are expected.

iii. Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

c. Annual safety report

Not applicable.

d. Follow-up of adverse events

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

e. [Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable

9. STATISTICAL ANALYSIS

All statistical analyses will be conducted according to the intention–to–treat principle (31, 32) considering all patients in the treatment groups to which they were randomly assigned, excluding cases lost to follow-up due to withdrawal of consent or cancellation of surgery. Continuous distribution of the data will be assessed by visual inspection of histograms and normality tests. For both study arms, the baseline characteristics will be reported for the intervention and control group and expressed as counts and percentages, means and standard deviations (SD), or medians and interquartile ranges (IQR) whenever appropriate. Baseline characteristics of patients with and without complete follow up will be compared to examine whether selective dropout occurred. Analyses will be performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

a. Primary study parameter(s)

The primary outcome, QoR-15 at day 1, 4 and 7, will be compared among patients randomized to either the intervention and control group, using Student's t-test or a nonparametric Mann Whitney U test.

Mixed effects linear regression models will be conducted to investigate the effect of the smartphone app on QoR-15 over the first week post discharge as a function of the randomization assignment (i.e. intervention vs control), time (i.e. measurements before surgery, and at day 1, 4 and 7 post discharge), and their interaction term. Random effects, i.e. random intercept, will be fitted per individual to account for clustering effects. To adjust for practice variation between the participating hospitals, the factor hospital will be added as fixed effect to the mixed model. In addition, we will perform a sensitivity analysis if the results of the mixed model analysis indicate for bias.

b. Secondary study parameter(s)

Postoperative pain on post discharge day 1, 4 and 7: Mean, Standard Deviation, Mixed effects linear regression models will be conducted to investigate the effect of the smartphone app on postoperative pain over the first week post discharge as a function of the randomization assignment (i.e. intervention vs control), time (i.e. measurements before surgery, and at day 1, 4 and 7 post discharge), and their interaction term. Random effects, i.e. random intercept, will be fitted per individual to account for clustering effects

Post discharge Nausea and Vomiting (PDNV) on post discharge day 1, 4 and 7: Mean, Standard Deviation and Mixed effects linear regression models will be conducted to investigate the effect of the smartphone app on PDNV over the first week post discharge as a function of the randomization assignment (i.e. intervention vs control), time (i.e. measurements before surgery, and at day 1, 4 and 7 post discharge), and their interaction

term. Random effects, i.e. random intercept, will be fitted per individual to account for clustering effects
Medication Dosage and usage measured in morfine equivalents on post discharge day 1, 4 and 7: Mean, Standard Deviation and Mixed effects linear regression models will be conducted to investigate the effect of the smartphone app on medication dosage and usage over the first week post discharge as a function of the randomization assignment (i.e. intervention vs control), time (i.e. measurements before surgery, and at day 1, 4 and 7 post discharge), and their interaction term. Random effects, i.e. random intercept, will be fitted per individual to account for clustering effects

Difference in the number contacts with the hospital, general practitioner or emergency department (on day 7 post discharge): Mean and Standard Deviation and two sample-t-test (in case of non-normally distributed data we will report on medians and interquartile ranges and differences will be tested using the Mann-Whitney U test)

Difference in the number of surgical complications assessed according to the Clavien Dindo classification of surgical complications (on day 7 post discharge): Mean, Standard Deviation and two sample-t-test (in case of not normally distributed data we will use the Mann-Whitney U test)

Difference in the number of readmissions emergency department (on day 7 post discharge): Mean, Standard Deviation and two sample-t-test (in case of not normally distributed data we will use the Mann-Whitney U test)

Satisfaction (on day 7 post discharge): Median, Interquartile Range and $\chi 2$ tests for equal proportion.

General evaluations regarding provided care after discharge (on day 7 post discharge): Median, Interquartile Range and $\chi 2$ tests for equal proportion.

Experienced quality of communication: Data collection and analysis progression were discussed during regular meetings with researchers. A thematic framework will be used to analyze the qualitative data. First, the audio recordings of the interviews will be transcribed verbatim in Dutch. After familiarization with the data, the transcripts are coded. After coding, overarching themes and patterns are identified and labelled within each concept.

c. Cleaning and locking of the database

The database will be locked as soon as all data are entered, and all discrepant or missing data are resolved – or if all efforts are employed and we consider that, the remaining issues cannot be fixed. At this step, the data will be reviewed before database locking. After that, the study database will be locked and exported for statistical analysis. At this stage, permission for access to the database will be removed for all investigators, and the database will be archived.

d. Missing data

No or minimal losses to follow–up for the primary and secondary outcomes are anticipated. Missing data will be accounted for with multiple imputation techniques.

e. Interim analysis (if applicable)

Not applicable

10. ETHICAL CONSIDERATIONS

a. Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki as stated in the current version of Fortaleza, Brazil 2013, in accordance with the Medical Research Involving Human Subjects Act (WMO) and comply with Good Clinical Practice (GCP) Guidelines and all applicable national (for example WMO for the Netherlands) and international regulatory requirements and general data protection regulations (GDPR).

b. Recruitment and consent

Patients will be recruited at the anaesthesiology outpatient clinic. Patients will be informed verbally by local researchers and by a patient information letter. The patient will be given sufficient time to consider their decision and to discuss the decision with their relatives or the independent expert.

c. Objection by minors or incapacitated subjects (if applicable)

Not applicable

d. Benefits and risks assessment, group relatedness

Patient burden is considered minimal

e. Compensation for injury

There is no injury expected caused by study participation. Insurance exemption has been requested.

f. Incentives (if applicable)

Not applicable

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

a. Handling and storage of data and documents

All participating hospitals have signed a data processing agreement with Luscii healthtech B.C. that complies with the general data protection regulations (GDPR) and national regulations (e.g. Algemene Verordening Gegevensbescherming (AVG)) that apply in the Netherlands. Moreover, all of the patients directly identifying personal data (e.g., name, address, etc.) will be separated from the research data (e.g., measurement data, etc.) and replaced by an assigned code. The directly identifying data will be only used to contact the patients and is only available to the investigators. The handling of personal data complies with the general data protection regulations (GDPR) and applicable national regulations (e.g. Algemene Verordening Gegevensbescherming (AVG)). For data collection and validation, an eCRF, including validation checks and appropriate user access rights, will be set up in CASTOR© (www.castoredc.nl). CASTOR© is a GCP compliant and meets the standard for information security management. All data will be stored in a secure place for 15 years after study end at OLVG Hospital. Electronic files will be archived on the OLVG 'SharePoint wetenschap anesthesiologie' server in a secure and controlled environment to maintain confidentiality. Electronic documents will be controlled with password protection according to best practices. Any data leaks that might occur regardless of these safety precautions will be reported to all parties within 1 working day after discovery of the leak.

b. Monitoring and Quality Assurance

All medical specialists, nurses and other hospital personnel involved in perioperative care for surgical day care patients receive information an instruction about the study procedures either by an information letter (APPENDIX). The conduct of the study will be performed according to BROK/GCP standards and follow guidelines on improving and standardizing evaluations reports of web-based and mobile health interventions (33). Furthermore a clinical data management plan will be used with the objective of the clinical data management plan is to provide high–quality data by adopting standardized procedures to minimize the number of errors and missing data, and consequently, to generate an accurate database for analysis (APPENDIX). Accuracy and consistency checks will be carried out by way of validation, pre-specified and ad hoc checking by the researchers. A qualified monitor will be installed to perform study monitoring according to the monitoring plan. Monitoring will be performed to signal early aberrant patterns, issues with consistency, credibility, and other anomalies.

c. Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable 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

d. Annual progress report

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

e. Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last follow-up. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

f. Public disclosure and publication policy

The study protocol will be registered before inclusion of the first patient on www.clinicaltrials.gov. The results of the study will find their way into (inter–) national scientific journals and guidelines. We will submit analyses to scientific journals in the field of anaesthesiology. A lay summary of the results will be published as well and send to the participants if they are interested.

12. STRUCTURED RISK ANALYSIS

Not applicable

a. Potential issues of concern

Not applicable

b. Synthesis

Not applicable

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