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Study protocol for the TRUSt trial: a pragmatic randomised controlled trial comparing the standard of care with a Transitional Pain Service for patients at Risk of chronic postsurgical pain Undergoing Surgery

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ABSTRACT

Introduction: Patients with either surgery- or patient-related risk factors are at an increased risk of acute and chronic postsurgical pain (CPSP) and long-term opioid use. To improve recovery, prevent CPSP and decrease opioid use, we need to identify these patients before surgery and provide a multidisciplinary pain management strategy throughout hospital admission and follow up in the post discharge period. We hypothesise that a multidisciplinary transitional pain service (TPS) improves quality of recovery and reduce the incidence of CPSP and opioid consumption.

Methods and analysis: We aim to investigate the effectiveness of implementation of a TPS for patients at risk of developing CPSP. The trial design is a pragmatic, open label, randomised controlled trial (RCT). After stratification for sex, patients are randomly assigned to the TPS or standard of care (SOC) group. Our primary outcome is the between group difference in quality of recovery, measured at the morning of the 3rd postoperative day, employing the quality of recovery (QoR)-15 questionnaire. Secondary outcomes are the incidence of CPSP, opioid consumption and patient-reported outcome measures (PROMs) at three and six months postoperatively. To allow a detection of the minimal clinical important difference of 8 points on the QoR-15 score, we need to enroll 180 patients.

Ethics and dissemination: Ethics approval was obtained by the accredited medical research ethics committee of the Academic Medical Center (AMC) in Amsterdam (2020_211) on 15-10-2020. Protocol version 3.2 was approved on 25-01-2020.

Trial registration

Trialregister.nl, NL9115. Registered on 2020-12-11.

STRENGTHS AND LIMITATIONS OF THE STUDY

Strengths

- This study is the first RCT comparing a TPS with standard of care for patients at risk of CPSP.
- This is a pragmatic RCT and will therefore provide real world evidence on the use of TPS.
- The primary outcome is a patient reported outcome measure, which takes into account all aspects of quality of recovery, including pain, mobility and patient satisfaction.

Limitations

- TPS team and patients cannot be blinded due to the nature of the study.
- The standard of care group might also benefit from implementation of TPS due to an increased awareness for CPSP among health care givers (Hawthorne effect).

INTRODUCTION

Globally, over 320 million people undergo major surgery each year, of which approximately 10% will develop chronic postsurgical pain (CPSP). [1, 2] CPSP is often underdiagnosed and poorly managed, thereby placing a major burden on patient's daily life resulting in significant health problems. In addition, patients with CPSP often take high dosages of opioids due to inappropriate opiate prescribing.[3] Major risk factors for CPSP include chronic pain before surgery, preoperative opioid exposure and the intensity of acute postoperative pain.[4] Key is to identify these patients before surgery and provide multidisciplinary pain management throughout hospital admission, a so called Transitional Pain Service (TPS). Studies on the effectiveness of TPS are scarce, but some studies do support further research into implementation of TPS. Tiippana et al. retrospectively collected data from medical records and determined whether referral of surgical patients to an Acute Pain Service Out-Patient Clinic (APS-OPC) was effective in reducing opioid use in the immediate postoperative period at home.[5] At discharge, 54% of the patients were using weak opioids and 32% strong opioids. This was reduced to 20% and 6% after implementation of the APS-OPC. Also, the Toronto General Hospital launched the first prospective study on TPS in 2014.[6] Patients at high risk of developing CPSP were referred to TPS to manage pain, maintain musculoskeletal function and to lower opioid consumption. Six months postoperatively, opioid-naïve and opioid-experienced patients reduced opioid use by 69% and 44% respectively. Thus, these studies justify further prospective randomised studies on the effectiveness of TPS.

The aim of our study is therefore to investigate the effectiveness of implementation of a multidisciplinary TPS team for patients at risk of developing CPSP, as measured by the quality of recovery, the incidence of CPSP and the postoperative opioid consumption. We hypothesise that a multidisciplinary transitional pain service (TPS) improves quality of recovery and reduce the incidence of CPSP and opioid consumption.

METHODS

For the content of this protocol we used the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and the SPIRIT patient-reported outcome (PRO) extension guidelines. Besides that, this trial implements the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[7-10] The trial is registered with the Netherlands Trial Register; NL9115.

Study design

The TRUSt study is a randomised single-center, parallel grouping, two-armed, superiority trial with a 1:1 allocation ratio. The study will be conducted in an urban tertiary referral teaching hospital in the Netherlands. Approximately 12,000 patients undergo surgery in the Amsterdam UMC, location AMC, each year.

Eligibility criteria

Patients will be eligible for inclusion if they fulfil the following criteria:

- 18 years and older, Dutch-speaking and reading
- Willing and able to provide informed consent
- Undergoing a surgical procedure with an increased risk of CPSP (amputation, spinal surgery, thoracotomy, mastectomy, herniotomy, hysterectomy and arthroplasty).[11]

Or, any surgery and meeting one or more of the following criteria*:*

- Diagnosed with chronic pain, defined according to the ICD-11 as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Chronic pain is pain that persists or recurs for longer than 3 months”.[12]
- Chronic opioid use, defined as > 20 mg daily morphine equivalent (MME) consumption for more than 3 months in the last 3 months
- Allergy to opioids
- The usage of pain medication as methadone, buprenorphine, anticonvulsants, antidepressants or medicinal cannabis for chronic pain for more than 3 months in the last three months
- Psychosocial comorbidities like anxiety, depression, pain catastrophising if documented in the electronic medical record.

Exclusion criteria:

- Patients who undergo emergency surgery are excluded to ensure sufficient time for the informed consent process.
- Patients undergoing implementation of pain device implants, such as intrathecal pain pump, spinal cord stimulators or peripheral nerve stimulator.

- Patients who undergo surgery that most likely leads to prolonged sedation and for that reason cannot fill in the QoR-15 questionnaire at day three postoperative.

Recruitment strategies

Patients are recruited at the anaesthesiology outpatient preoperative evaluation (OPE) clinic, due to COVID-19 mostly by phone. Trained study personnel will inform the patient about the study. If the patient gives permission, a member of the research team calls and informs the patient about the purpose, nature, and duration of this study. Besides that the risks and benefits will be fully explained. Due to logistics because of SARS-CoV-2, randomisation will be performed after verbal informed consent is provided. Patients will sign on the day of admission, before surgery, and are blinded for randomisation until they have signed the consent form.

Study outline

Patient enrollment has started on 18-01-2021 and the study is expect to end in December 2022. After informed consent is provided, patient characteristics will be recorded (table 1) and the patient is randomised. Study duration, including follow-up, is six months. During the study, patients will complete different questionnaires, at six different time points (figure 1).

Table 1. The patient characteristics

Age
Sex
Education level
Gainful employment
Lifestyle
Comorbidities
Pain history
Pre-existent medication

Randomisation and blinding

Patients will be randomly assigned to TPS or standard of care (SOC) in a 1:1 ratio. Treatment assignments will be performed centrally using a computer-generated random schedule in permuted blocks of 4, 6 or 8 with stratification for sex.

The study is not blinded for patients or study staff. The outcome assessor will be blinded to treatment allocation by receiving the raw dataset coded and without having access to information about the

allocation. Figure 2 is the CONSORT flow diagram and includes estimates for eligible, screened, enrolled and analysed patients.

Study treatment

Control (SOC) group:

Patients in the SOC group (figure 3A) will receive standard of care. This includes pre-assessment at the OPE-clinic, during which medical screening is performed, the perioperative anaesthetic and analgesic strategy is discussed and perioperative pain management is planned. For perioperative analgesia the practice guidelines for Acute Pain management in the perioperative setting are adhered to.[13] After surgery, on the ward, nurses, supervised by surgeons, hold a great deal of responsibility for pain management. In addition, the consultative service of the acute pain team (APS) can be requested. The APS is indicated for patients in pain after recent surgery or trauma. Commonly used modalities for pain treatment by the APS include epidural analgesia, peripheral nerve catheter or patient controlled analgesia (PCA). A specialised APS nurse (supervised by an anesthesiologist) visits each patient once or twice per day. The APS is available 24 hours a day, seven days a week. Postsurgical opioids are prescribed by the surgeon. From that moment on, both the surgeon and the general practitioner could approve a series of repeat prescriptions. In The Netherlands, ninety-nine percent of the population is insured for health expenses. The health insurance, consists of care provided by a general practitioner, who they can refer themselves to when needed.

Intervention (TPS) group:

For patients randomised to the intervention group (figure 3B), the TPS focuses on patient-centered continuity of care. This starts preoperatively and continues until six months after discharge. The TPS team is led by three anaesthetists who are specialised in acute and/or chronic pain management and consists of nurse practitioners, a pain psychologist, a physiotherapist, a social worker and a PhD-researcher. After preoperative screening, patients will receive a folder with a brief and simple explanation about pain and patient empowerment to facilitate coping with their condition.[14] Preoperatively, the patient is discussed in the TPS team according to a standard format (appendix 1). Here, an individualised perioperative pharmacological and/or interventional pain management strategy will be agreed on. The multimodal pain approach according to the guidelines produced by the American Society of Anaesthetists is leading.[13] During this multidisciplinary meeting, the need for referral to a pain psychologist, physiotherapist or social worker will be discussed and initiated when deemed necessary. Afterwards, one of the TPS members will call the patient to explain the perioperative analgesic strategy. Then, to enhance patient autonomy, decisions about care and

treatment are made collaboratively between the patient and the healthcare professional (shared decision making).

After discharge, follow up occurs every two weeks for two months and then every month for the remaining four months, or till adequate pain control is achieved and opioids are weaned off completely. The definition of follow-up is a telephone call or an appointment at the outpatient clinic. At this follow-up consultation, progress of the patient and the pain treatment plan are evaluated. When possible, opioids are tapered or discontinued. In the post-discharge period, the patient's General Practitioner will be called by a member of the TPS team and provided with information on the further pain treatment strategy. In this post-discharge period, additional consultation of the TPS team is possible if the treatment goals are not achieved. If the patient develops CPSP within six months after surgery or did not wean off opioids completely, we will refer the patient to our chronic pain team.

Outcomes

Primary outcome

Our primary outcome is the between group difference in quality of recovery, measured at the morning of the 3rd postoperative day. The quality of recovery (QoR)-15 questionnaire will be used to measure this primary outcome. For constructs such as pain or satisfaction, the patient's perception is the only source of information and therefore Patient Reported Outcome Measures (PROMs) should be considered the gold-standard evaluation. A well validated patient outcome questionnaire is an objective evaluation that quantifies the patients pain, recovery as perceived by the patient.[15] The QoR-15 questionnaire is a validated, reliable and objective PROM as described in several studies.[16] By taking the questionnaire on the morning of the third postoperative day, we effectively assess the second postoperative day.

Secondary outcomes

Secondary outcomes include postoperative long-term follow up data:

1. CPSP diagnosis (after three and six months) defined according to the IASP.[11]

2. Opioid consumption (preoperative, postoperative day three, after three and six months): calculated as morphine milligram equivalent (MMEs) per day (both orally and intravenously).

3. Patient reported health outcome measurements:

- *The WHO Disability Assessment Schedule* (WHODAS) *2.0*, 12-items: brief assessments that covers six domains of functioning including cognition, mobility, self-care, getting along, life activities and participation.[17] Scoring has three steps; summing of recorded item scores within each domain, summing of all six domain scores and lastly converting the summary score into a metric ranging from 0 to 100 (where 0 = no disability; 100 = full disability).[18] We will analyse the difference across groups

at baseline and after three and six months postoperative. We will also analyse a change in the score over time for each group. A change in score of 5% or more after surgery is consistent with a clinically important change in disability.[19]

- *EuroQol-5D-5 level version* (EQ-5D-5L): reflecting generic health status: a 5-item summary measure of overall health status. The descriptive system comprises the dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[20] We will summarise the EQ-5D-5L health state by an index value which reflects how good or bad a health state is according to the preferences of the general population of a country/region.[21] A value set is established that represent the views of the Dutch population.[22] At a minimum, we will analyse the change in index over time within groups (preoperative to three and six months postoperatively) and between groups. The dimension pain/discomfort will be analysed separately as well.

- *Patient-reported outcomes measurement information system* (PROMIS)-*29:* a generic health-related quality of life survey, assesses each of the seven PROMIS domains (anxiety; physical function; pain interference; fatigue; sleep disturbance an disability to participate in social roles an activities), with four questions. The questions are ranked on a 5-point Likert Scale. There is also one eleven-point rating scale for pain intensity.[23] Norm-based scores have been calculated for each domain, so that a score of 50 represents the mean of the reference population with a standard deviation of 10. At a minimum, we will analyse the change in index over time within groups (preoperative to three and six months postoperatively) and between groups. The dimension pain/discomfort will be analysed separately as well.

- *QoR-15* comparing changes in time (baseline, day one, two and three postoperatively) within groups. The QoR-15 scores range from 0 (extremely poor) to 150 (excellent quality of recovery). Interventions that result in a change of 8.0 reflect a clinically minimally important difference.[24]

4. Satisfaction staff of the implementation of a TPS, rated on a five point Likert scale from 1 (extremely dissatisfied) to 5 (extremely satisfied).[25]

5. The frequency the perioperative plan (like type of anesthetic), changed after evaluation of the patient by the TPS team, instead of the earlier discussed method during preoperative assessment.

Other outcomes:

- *Intraoperative data:* type of anaesthesia, doses of opioids, duration of surgery, duration of recovery room stay, etc. (table 2).
- *Postoperative data:* length of hospital stay, method of pain control, dose of opioids etc. (table 3).
- *Long term follow-up data:* number of contacts with TPS, number of referrals etc. (table 4).

Table 2. Intraoperative variables

Type of surgery
Type of anaesthetic
Duration of surgery
Duration at Post Anesthesia Care Unit
Medication use

Table 3. Postoperative variables

Postoperative pain
Locoregional techniques
Medication use
Postoperative complications
Length of hospital stay
Dose of opioids at discharge (average per day in MMQ)
Readmissions
Complications

Table 4. Long term follow-up data

Development of CPSP
Use and dosage of pain medication
Incidence of referrals
Number of contacts with TPS

Sample size and drop-out

Using nQuery Advisor version 8.5.1, sample size is driven by the analysis for superiority of TPS compared to standard care employing the QoR-15 questionnaire score. Assuming a standard deviation of 18 points on postoperative day three and being able to detect a QoR-15 score difference of at least 8 (based on the minimal clinically important difference and standard deviation found by Myles et al [24]), randomisation ratio 1:1, a total sample size of 160 patients is required (80 patients per group) to detect this difference with a statistical power of 80% and a significance level of (alpha) 0.05. Patients can leave the study at any time for any reason if they wish to do so without any consequences. Patients will not be replaced in case of withdrawal. To account for a possible drop-out rate of 10% we will include 90 patients per arm, thus a total of 178.

Protocol deviation

Protocol deviations or violations could occur in this study and will be reported. An example of a protocol deviation is a follow up visit at a slightly different time frame than required by protocol, e.g. because of the participant's schedule. Furthermore, an anaesthesia technique provided diverging from the one agreed on at the OPE. Besides, a patient allocated to the SOC group who is in severe pain could be discussed in the TPS team because of Good Clinical Practice. Patients with protocol deviations will be included in the intention to treat analysis. All protocol violations, except canceled surgery, will be included in intention to treat analysis but will lead to exclusion from analysis per protocol. When a patients surgery is cancelled this patient will be excluded from all analysis. There are no safety risks associated with protocol violations in this trial.

Statistical analysis

Final data will be screened for typos, missing values, outliers and distribution. All data analyses will be carried out according to a pre-established analyses plan. We are planning for complete case analyses and multiple imputations for missing data.

Baseline characteristics, as mentioned in table 1, will be summarized with the use of the appropriate descriptive statistics.

Primary outcome analysis

All randomised patients will be analysed as the primary population for the analysis according the intention-to treat principle. As mentioned above, canceled surgery is the only protocol violation that will lead to exclusion from analysis. The primary outcome, the between group difference in QoR-15 scores will be analysed. Because of the small interval between the intervention and the primary endpoint, we do not expect a significant amount of missing data on the QoR-15 survey. However, patients who are sedated or experiencing a delirium and patients who are discharged before day three, could cause missing data. Therefore, we will compare responders (patients who returned a completely filled-in QoR-15 questionnaire) and non-responders for differences in patient characteristics, perioperative surgical and anesthetic factors, to examine non-response bias on age, sex and item-response.

Depending on the distribution of the data, we will test the raw between group difference using an unpaired-t-test or Mann-Whitney U test. Statistical uncertainties will be quantified with two-sided 95% confidence intervals. A two-sided p-value < 0,05 will be considered statistically significant. Because of our randomization stratification for sex, we will additionally report effects adjusted for sex.

As part of our secondary analyses, we will perform a per protocol analysis including all randomised patients completing the whole study period on the between group difference in QoR-15 scores as described above.

Secondary outcome analysis

Between group difference in the proportion of patients having the diagnosis CPSP after three and six months will be compared using the Chi-square test. We expect the change in opioid consumption to be bimodal distributed, some patients will not change their opioid consumption while other will reduce their consumption completely. The between group difference in change in opioid consumption (MMEs) (postoperative day three, after three and six months) will be compared using a generalized linear mixed model, with treatment as fixed effect and preoperative opioid consumption, time and the interaction between treatment and time as covariates and subject as random factor.

Only if time, or interaction between treatment and time differs significantly between groups, we will perform post-hoc analysis. We will use the Benjamini-Hochberg procedure to correct for multiple testing. [26] Non normal distribution is expected in WHODAS 2.0, EQ-5D-5L, PROMIS-29 scores and therefore we will analyse the between group differences at 1 point using a Mann-Witney U test. and a generalized mixed model. We will use a generalized mixed model to correct for time and to test multiple measurements at the same time. For missing item scores, multiple imputation will be applied. After the study period, staff satisfaction will be measured on implementation of a TPS, using a Mann-Whitney U test and the proportion of perioperative plan changes after evaluation of the TPS team, will be compared using a Chi-square test. Finally, an exploratory analyses will be performed by studying differences in treatment effect in subgroups other than sex; different risk factors of CPSP, baseline characteristics and on perioperative treatment. For the exploratory analyses, correction for multiple testing will be applied using the Benjamini-Hochberg method. R studio (Affero General Public License V3) will be used for the analyses.

Data collection and management

Paper and online surveys will be used to collect PROMs. Only Dutch translated surveys will be used. A automatically reminder will be sent by mail after three days (as an exception the QoR-15 survey at day three postoperatively, this reminder will be sent after one day). If the patient did not complete the survey after 6 days a manual survey invite will sent and in case of no response after another three days a phone call will be made to the patient who did not complete the survey.

For collecting long term data at three and six months, the researcher calls the patients and evaluates if symptoms of CPSP develop and gathers data on the amount of pain medication. At this phone call the researcher will also remind the patient on the survey Specify PRO data collection and management strategies for minimizing avoidable missing data.

The data of each patient will be recorded on an individual electronic case report form (eCRF) using Castor EDC (Ciwit B.V. the Netherlands, version 1.5, a GCP compliant database). Data will be coded using a unique numerical code. The key to this code is only available to the research team and is stored

in the trial master file (TMF) in accordance with the European Union regulation act (GDPR; General Data Protection Regulation) and GCP. All patient data will be handled confidential. The correctness of entries will be verified for 15% of the data, by a second investigator. All recorded data, including CRFs, TMF, investigator site file and ICFs will be stored for 15 years after completion of the study. Study data will always be stored securely, in a locked cabinet or on password secured computers, only accessible for study team members.

Monitoring

The study will be monitored, based on a low-risk study design, by a monitor from the Clinical Monitoring Center at the Amsterdam UMC. This is a qualified, independent team that is put in place to monitor according to the monitor plan. The principal investigator and all investigators will permit and facilitate study-related monitoring or regulatory inspection by providing direct access to study files and source data/documents. After each monitoring visit, a site report will be issued by the monitor to the principal investigator and a copy will be provided to the local investigators. Due to the minimal risk nature of the study, there will be no external data and safety monitoring board.

ETHICS AND DISSEMINATION

Ethics approval (2020_211) was obtained on 15 October 2020, in the Netherlands at the Medical Research Ethics Committee location Academic Medical Center (Amsterdam, The Netherlands). The trial will be conducted in compliance with this study protocol, the Declaration of Helsinki and Good Clinical Practice (GCP). Protocol amendments will be subjected to the Medical Ethics Committee for approval and thereafter communicated to all investigators an trial registries. There are no publication disclosures.

Data availability statement

The results of the current study will be disseminated to healthcare providers, policy-makers and patients via presentations at local and national meetings, as well as by open access publication in a peer-reviewed journal. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

Authors' contributions

MWH, JH, HH, CW, SM, MR, HW, VW and MA were involved in conception and trial design. SM, HW, MR, VW helped with implementation. MA and SM will be responsible for the PRO content of the trial. JH, HH, and MA were involved in drafting the article. MWH, SM, HW, MR and CW were involved in critical revision of the article. All the authors contributed to refinement of the study protocol and final approval of the article.

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The TRUSt study is investigator initiated and there is no external funding.

Competing interest statement

None declared.

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FIGURES

Figure 1: The study assessment flow diagram

Figure 2: Consolidated Standards of Reporting Trials flow diagram estimating patient screening, enrolment and response rate.

Figure 3 Perioperative pathway for patients

3A: Patients allocated to standard of care

[1] The APS team is nurse based and anesthetist supervised. A clinical pain nurse visits each patient on the APS service at least once a day, mostly when pain treatment modalities like intravenous or epidural patient controlled analgesia (PCA), with or without peripheral nerve catheter, are used. The team is in-house 24 hours a day, seven days a week. When pain medication is switched to oral medication only, the patient is usually discharged from services of the APS.

3B: Patients allocated to TPS

[1] The TPS team consists of three anaesthetists who are specialized in acute and/or chronic pain, pain nurse practitioners, a psychologist, a physiotherapist, a social worker and a PhD-student.

[2] Non-pharmacological interventions include:

- An information folder regarding pain and empowerment
- Shared decision-making about care and treatment to promote patient autonomy during the study.

[3] The TPS team can refer the patient to a psychologist, a social worker or a physiotherapist.

[4] Follow-up after discharge occurs every two weeks with a telephone call until his/her pain is under control or medication is weaned off completely.

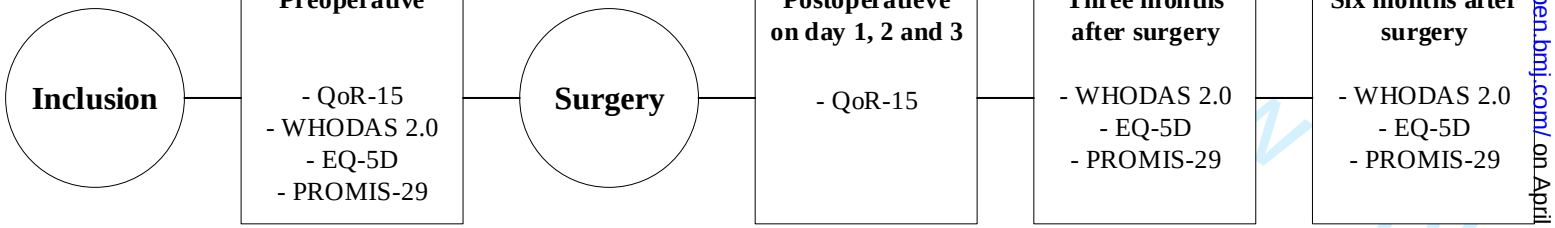
Appendix 1: Standard format treatment TPS patient

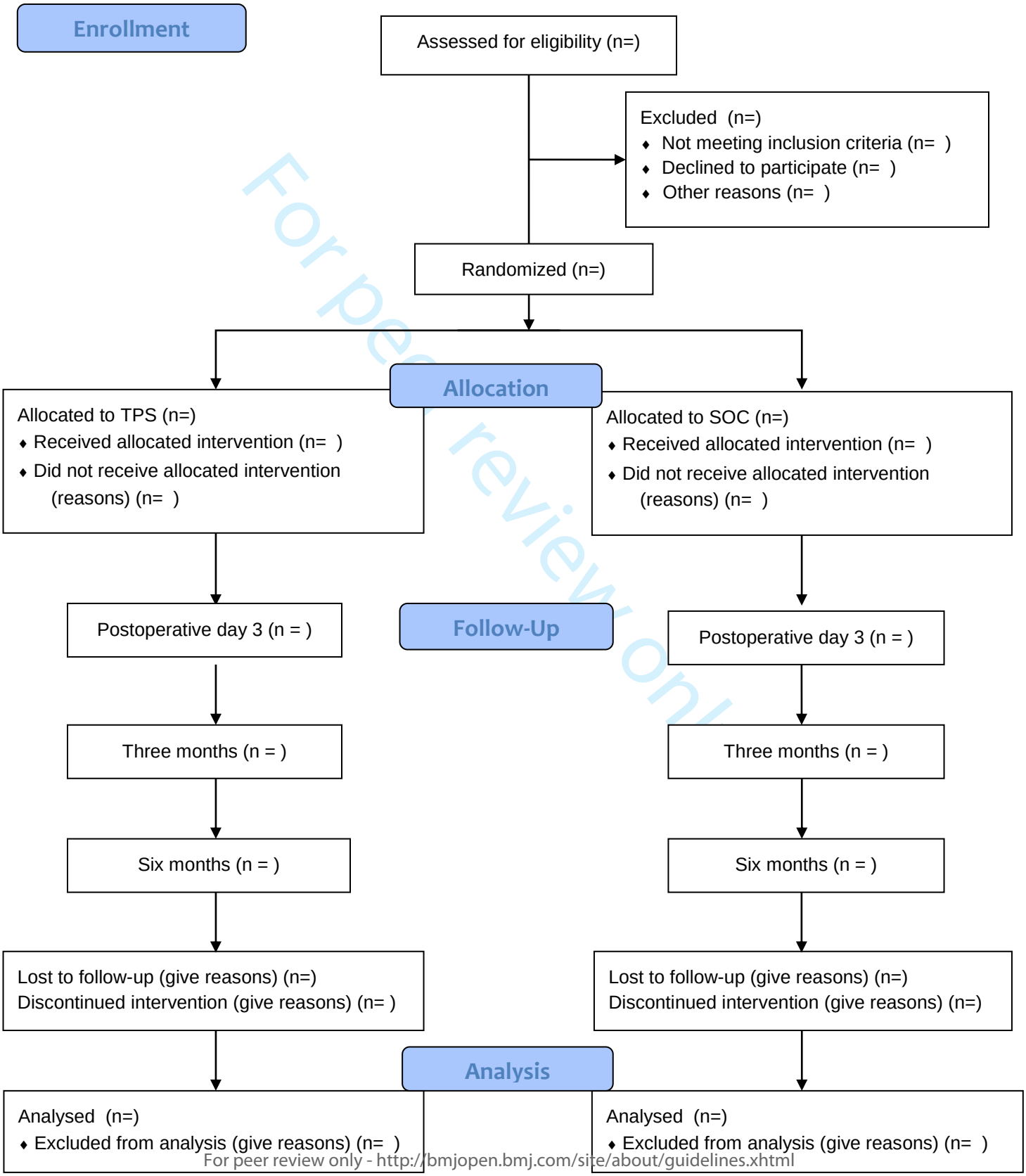
Appendix 2: Reporting checklist for protocol of a clinical trial.
Based on the SPIRIT guidelines.

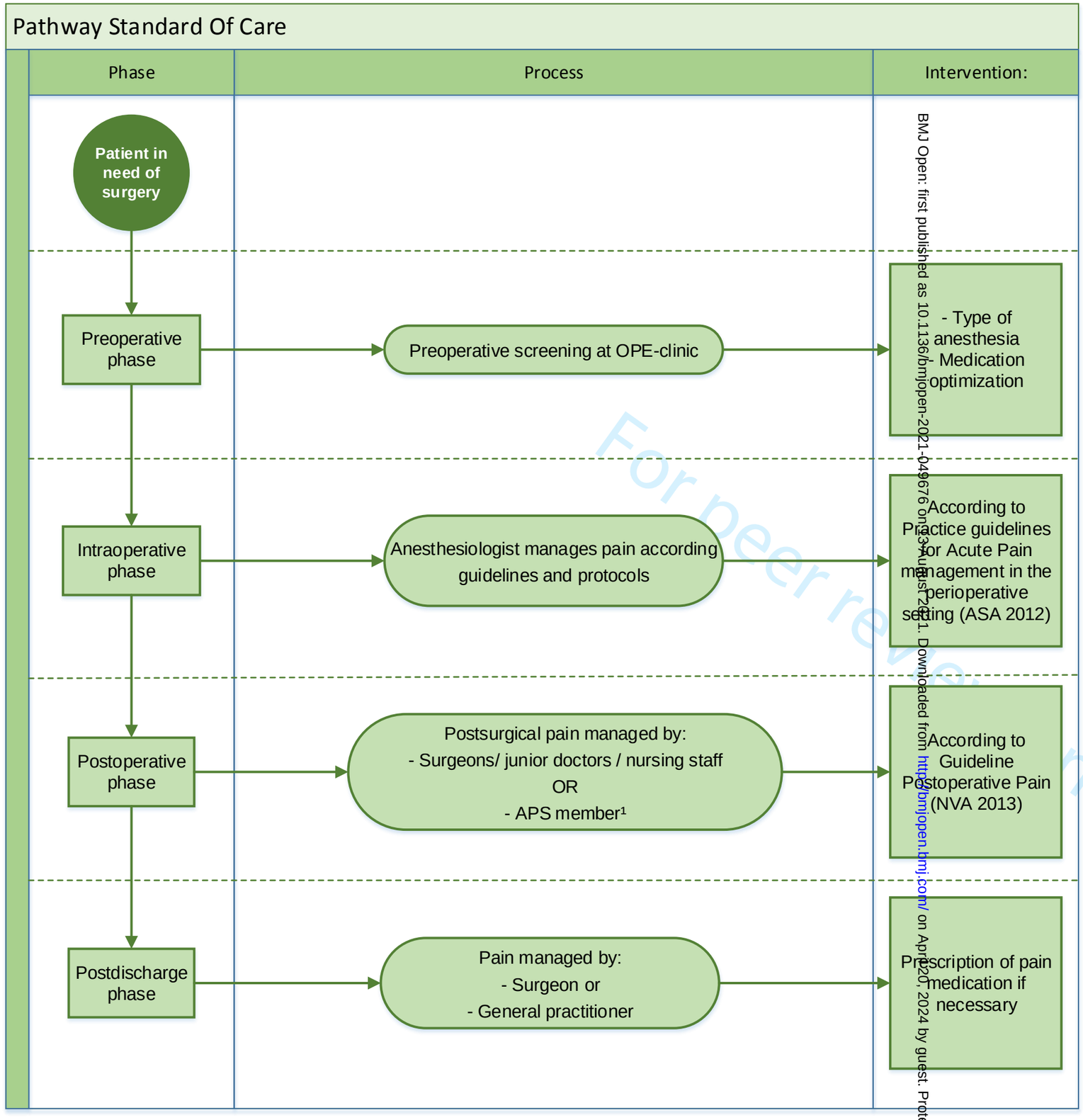
Appendix 3: Trial registration: data set

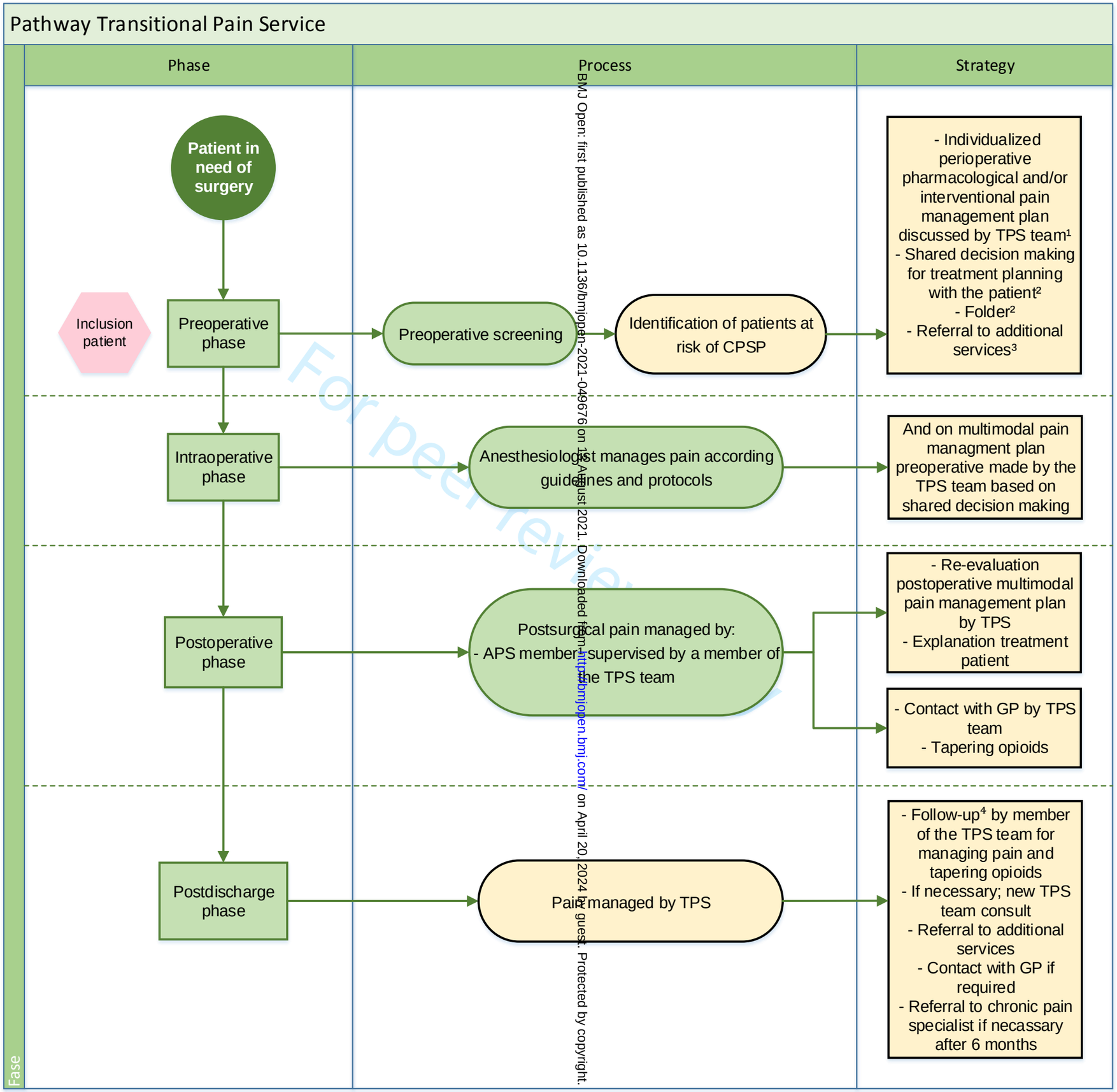
Appendix 4: Protocol date and version identifier

Appendix 5: Informed consent material









Checklist Transitional Pain Service (TPS)

Multidisciplinary meeting (preoperative)

Patient data	
Patient number	
Type of surgery	
Date of preoperative screening	
Date of surgery	
Date of Multidisciplinary Team Meeting TPS	

Pre-existent pain medication

Intraoperative phase	
Anesthetic	
○ General ○ Local	
Multimodal pain management	
Intravenous medication	
Regional techniques	
Local techniques	

Postoperative phase	
Pharmacological pain management, algorithm 1	
Non-pharmacological	
If necessary, referral to psychologist, social worker or physiotherapist	

Checklist Transitional Pain Service (TPS)

Additional information about this patient/treatment

Checkboxes:

- ☐ After the multidisciplinary meeting one of the members of the TPS group will call the patient and explain the intraoperative multimodal pain treatment (informed consent and psychoeducation
- ☐ One of the members sends the information folder towards the address

Checklist postoperative period

APS or CPS

- ☐ Is there adequate pain control?

*If not, supervision about treatment by TPS anesthetist**

- ☐ Cease medication that is deemed unnecessary (taper opioids)
- ☐ Give adequate education about the individual multimodal pain management plan and the process of weaning from opioids

TPS member

- ☐ Contact surgeon; propose and discuss discharge pain medication, *algorithm 2*
- ☐ Discusses post discharge medication with the patient
- ☐ Contact general practitioner; inform about the study

Checklist Transitional Pain Service (TPS)

Checklist post-discharge period

After discharge, follow up occurs:
- After three months and after six months for every patient, or extra;

For a patient that is not completely weaned of pain medication or still experiences pain in the surgical area (until adequate pain control is achieved and medication is weaned of):
- For the first two months: every two weeks
- For the last four months: every four weeks

* The definition of follow-up is a telephone call or an appointment at the outpatient clinic.

TPS member

	Pain in surgical area	Use of pain medication	Opioids and dose in MME?	Other pain med?	Switch? Tapering? Referral?	Healthcare consumption?
15th day						
30th day						
45th day						
60th day						
90th day						
120th day						
150th day						
180th day						

☐ At day 90th day remember patient of questionnaires

☐ At 180th day remember patient of questionnaires

☐ If CPSP developed after six months > referral to chronic pain specialist

Additional information about this patient/treatment

Checklist Transitional Pain Service (TPS)

Appendix

Algorithm 1: pharmacological multimodal postoperative pain management

1. Paracetamol + NSAID (preferably metamizole)
2. Regional analgesia (epidural or peripheral nerve block)
3. Continuous Wound infiltration or Continuous surgical site analgesia
4. Adjuvants
    a. NMDA antagonist (S-ketamine)
    b. Alfa2 agonist (clonidine)
5. Opioids
    a. Oral administered
    b. Transdermal, nasal, sublingual
    c. Patient controlled analgesia (PCA) infusion pomp (morphine, buprenorphine, piritramide).

Algorithm 2: Out of hospital pharmacological pain management

1. Paracetamol + NSAID
2. Medication for neuropathic pain
    a. Anticonvulsants (pregabalin)
    b. Tricyclic antidepressant (amitriptyline)
3. Tapering opioids
4. Opioid substitute therapy
    a. Methadone
    b. Buprenorphine

*** List of members TPS team supervisors:**
- Hans Wartenberg 29588
- Martin Rutten 28657
- Soe Meinsma 27636 (specialized pain nurse)
- Vivian Ward- van der Stam 27350
- Marcus Hollmann 23932

In case above members not available:
- Jeroen Hermanides 28319
- Henning Hermanns 27426

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	appendix 3
Protocol version	#3	Date and version identifier	1 en appendix 4
Funding	#4	Sources and types of financial, material, and other support	13

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants,			

interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6,7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/a.
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8,9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5 and figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	9

		clinical and statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate	11

		measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10,11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10,11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10,11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	12

		interim results and make the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 5
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

Notes:

- 3: 1 en appendix 4
- 13: 5 and figure 1 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 29. January 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

Acronym
TRUSt study
Title
Transitional Pain Service for patients at Risk of chronic postsurgical pain Undergoing Surgery
Scientific title
Transitional Pain Service for patients at Risk of chronic postsurgical pain Undergoing Surgery
Summary
Patients with either surgery or patient-related risk factors (e.g. pre-existing chronic pain or preoperative opioid consumption) are at an increased risk of acute and chronic postsurgical pain (CPSP) and long-term opioid use. To improve recovery, prevent CPSP and decrease opioid use, we need to identify these patients before surgery and provide a multidisciplinary pain management strategy throughout hospital admission and follow up in the post discharge period. Randomized trials assessing the impact of a multidisciplinary transitional pain service (TPS) on quality of recovery, incidence of CPSP and opioid consumption have not been conducted yet and is the purpose of this study.
Status
Open for patient inclusion
Study type
Interventional
Control group
Active
Grouping
Parallel
Arms
2 or more arms, randomized
Masking
None
Target size
180
Inclusion criteria
Patients aged 18 years or older 2. Willing and able to provide informed consent 3. Undergoing a surgical procedure with an increased risk of CPSP (amputation, spinal surgery, thoracotomy, breast surgery, herniotomy, hysterectomy and after arthroplasty) (9). Or; Any surgical procedure and one of the following: - Diagnosed chronic pain, defined according to the ICD-11 as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Chronic pain is pain that persists or recurs for longer than 3 months (3)” - Chronic opioid use, defined as > 20 mg daily morphine equivalent (MME) consumption for more than 3 months in the last 3 months - Allergy to opioid agents - Patients with pain device implants, such as intrathecal pain pump, spinal cord stimulation or peripheral nerve stimulator - The usage of pain medication as methadone, buprenorphine, anticonvulsants, antidepressants or medicinal cannabis for chronic pain for more than 3 months in the last three months Psychosocial comorbidities like anxiety, depression, pain catastrophizing if documented in the electronic medical record
Exclusion criteria
- Not willing or able to provide written informed consent - Emergency surgery
Start date
2021-01-01
Stop date
2022-12-31
Diseases
Chronic postoperative pain
Hypothesis
The aim of our study is to investigate the effect of the implementation of a multidisciplinary TPS team for patients at risk of developing CPSP, on the quality of recovery, the incidence of CPSP and the opioid consumption. We hypothesize that the effect of implementation of a TPS team is superior to standard of care for outcomes as previously mentioned.
Interventions
Patients will be randomized to the TPS group or standard of care group. Patients allocated to the standard of care group will receive a pre-assessment at the outpatient preoperative evaluation (OPE) clinic. Postoperative pain will be managed by the Acute Pain Service (APS) for patients with an epidural, or peripheral nerve catheter or those with patient controlled analgesia (PCA). When the APS is not involved, postoperative pain will be managed by the

surgeon and/or nurses on the ward. In the TPS intervention group, the multidisciplinary TPS team, consisting of anesthesiologists and nurses who are specialized in pain, will make an individualized perioperative pain management plan. If necessary, referrals to a psychologist, physiotherapist or social worker will be made. Education of the patient will take place. After surgery, the APS, supervised by a member of the TPS team, will perform daily visits to monitor the effectiveness of pain treatment and to cease any medication that is deemed unnecessary. Following discharge from the hospital, the General Practitioner will be provided with information on the further pain treatment strategy for a better transition of care. Patients will be scheduled for follow-up appointments at the TPS outpatient clinic, or receive follow-up telephone calls to re-evaluate the pain treatment plan, taper opioids and if CPSP is diagnosed, referred to a pain specialist after six months.

Primary outcome

The primary outcome is the between group difference in Quality of Recovery (QoR)-15 questionnaire score at day three after surgery.

Secondary outcome

- Postsurgical chronic pain (CPSP) at three and six months after surgery, defined according to the IASP (as mentioned in chapter 1), and/or taking pain medication to treat CPSP as described above. - Opioid consumption per day, calculated as morphine equivalent dose (MEDs) at day three after surgery, prescription at discharge, and at three and six months after discharge. - Patient-reported outcome as measured by the WHODAS 2.0 (15), PROMIS-29 (16) and EQ-5D-5L (17) preoperatively and at three and six months after discharge.

Sponsors

Amsterdam University Medical Center, location Meibergdreef (AMC)

Time points

Baseline, 3 days postoperatively, 3 and 6 months postoperatively.

MEC approved

Yes

Multicenter

Randomised

Yes

Plan to share IPD

Undecided

IPD plan description

The results of the current study will be disseminated to healthcare providers, policy-makers and patients via presentations at local and national meetings, as well as by open access publication in a peer-reviewed journal. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Publications

N/A

Issueing body

METC AMC

Source ID

METC2020_211

Funding sources

No external funding

Old NTR ID

N/A

Date registered

2020-12-11

URL

N/A

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Phone: 0682346824

Amsterdam UMC, locatie Meibergdreef

Issue date: 25 Januari 2021

Protocol amendment number: 3.2

Revision chronology:

- Protocol version 3.2, 25-01-2021: approved.
  At postoperative day one and two patients have to fill in the QoR-15 questionnaire.
- Protocol version 3.1, 26-11-202: approved.
  Different informed consent procedure necessary due to COVID-19.
- Protocol version 2.0, 15-10-2020**:** Ethics approval was obtained by the accredited medical research ethics committee of the Academic Medical Center (AMC) in Amsterdam (2020_211)
  All the proposals and recommendations put forward by the ethics committee have been followed and integrated into the amended version of the protocol.
- Protocol version 1.0, 04-09-2020 sent to medical research ethics committee of the Academic Medical Center (AMC) in Amsterdam.

Proefpersoneninformatie voor deelname aan medisch-wetenschappelijk onderzoek

Beter herstel na een operatie met een Transitionele Pijn Service

Een Transitionele Pijn Service rondom een operatie voor patiënten met een hoger risico op langdurige postoperatieve chronische pijn

Inleiding

Geachte heer/mevrouw,

Met deze informatiebrief willen we u vragen of u wilt meedoen aan medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig. U krijgt deze brief omdat u binnenkort een chirurgische ingreep ondergaat of recentelijk ondergaan heeft.
U leest hier om wat voor onderzoek het gaat, wat het voor u betekent, en wat de voordelen en nadelen zijn. Het is veel informatie. Wilt u de informatie doorlezen en beslissen of u wilt meedoen?

Stel uw vragen

U kunt uw beslissing nemen met de informatie die u in deze informatiebrief vindt. Daarnaast raden we u aan om dit te doen:
- Stel vragen aan de onderzoeker die u deze informatie geeft.
- Praat met uw partner, familie of vrienden over dit onderzoek.
- Stel vragen aan de onafhankelijk deskundige, dr. M.F. Stevens
- Lees de informatie op www.rijksoverheid.nl/mensenonderzoek.

1. Algemene informatie

Amsterdam Universitair Medisch Centrum, locatie AMC heeft dit onderzoek opgezet. Hieronder noemen we Amsterdam Universitair Medisch Centrum, locatie AMC steeds de 'opdrachtgever'. Onderzoekers, dit kunnen artsen/onderzoeksverpleegkundigen/ onderzoekers zijn voeren dit onderzoek uit. Voor dit onderzoek zijn 180 proefpersonen nodig. De medische-ethische toetsingscommissie AMC heeft dit onderzoek goedgekeurd.

2. Wat is het doel van het onderzoek?

Met de oprichting van een Transitionele Pijn Service (TPS) willen wij onderzoeken of patiënten hierdoor sneller herstellen van een operatie, minder vaak chronisch postoperatieve pijn ontwikkelen en daarnaast minder opiaten gebruiken (een voorbeeld van een opiaat is morfine). Het is de bedoeling de resultaten te publiceren en op deze manier betere zorg te kunnen leveren.

3. Wat is de achtergrond van het onderzoek?

Chronisch postoperatieve pijn is een complicatie die ongeveer na 10% van de operaties optreedt. Helaas wordt de kwaliteit van leven door deze aandoening vaak negatief beïnvloedt. Daarnaast is deze aandoening ook moeilijk te behandelen.

Tevens is het opiaatgebruik in Nederland de laatste jaren toegenomen. Dit heeft vele negatieve gevolgen zoals een toename in opiaatafhankelijkheid, meer ziekenhuisopnames en een hogere sterftekans.

Chronisch pijn patiënten gebruiken vaak een hogere dosis opiaten, dan patiënten zonder chronisch pijn, met alle negatieve gevolgen van dien. Wij willen een TPS oprichten, die patiënten met een verhoogd risico op postoperatieve pijn opspoort en intensief begeleidt rondom en na de operatie. Wij denken dat er hierdoor minder chronische postoperatieve pijn ontstaat en er ook minder opiaatgebruik na de operatie zal zijn. In Canada is dit recent gedaan en daarbij zijn goede resultaten zijn behaald.

4. Hoe verloopt het onderzoek?

Duur onderzoek:

Als u meedoet, duurt dat totaal ongeveer 6 maanden voor u.

Voor de studie maken wij 2 groepen (Een Transitionele Pijn Service groep en een standaard zorg groep), met ieder 90 patiënten.

De behandeling:

Nadat u heeft besloten mee te doen wordt er geloot tussen de behandeling van een TPS team of de normale zorg in de controle groep. Deze loting vindt plaats met behulp van een computer programma en de onderzoekers weten vooraf niet welke groep u zult komen.

De patiënten in de controle groep krijgen de standaard zorg rondom een operatie.

De patiënten in de Transitionele Pijn Service groep krijgen ook de standaard zorg, maar daarbij extra behandeling van het Transitionele Pijn Service-team. Het Transitionele Pijn Service-team bestaat uit diverse pijn-gespecialiseerde anesthesisten, -verpleegkundigen, psychologen en fysiotherapeuten die samen een individueel pijnbeleid omtrent de operatie zullen maken.

Vragenlijsten:

Van alle proefpersonen wordt gevraagd diverse vragenlijsten in te vullen. Dit zal indien mogelijk, vooraf aan de operatie zijn, net als op dag 1, 2 en 3 na de operatie en na 3 en 6 maanden. Dit kan zowel digitaal, of als u dit liever hebt per post. U hoeft hiervoor niet extra naar het ziekenhuis te komen. De vragen gaan over herstel na de operatie, eventuele pijn en psychische klachten.

De onderzoeker zal deze gegevens verzamelen. Daarnaast zal de onderzoeker gegevens verzamelen uit uw medisch dossier over uw gezondheidstoestand.

5. Welke afspraken maken we met u?

Om het onderzoek goed te laten verlopen, is het belangrijk dat u zich aan de volgende afspraken houdt.

De afspraken zijn dat u:

- afspraken voor bezoeken nakomt.

Het is belangrijk dat u contact opneemt met de onderzoeker:

- voordat u andere geneesmiddelen gaat gebruiken. Ook als dat homeopathische geneesmiddelen, natuurgeneesmiddelen, vitaminen en/of geneesmiddelen van de drogist zijn.
- als u in een ziekenhuis wordt opgenomen of behandeld.
- als u plotseling gezondheidsklachten krijgt.
- als u niet meer wilt meedoen aan het onderzoek.
- als uw contactgegevens wijzigen.

6. Van welke bijwerkingen, nadelige effecten of ongemakken kunt u last krijgen?

Behandeling van het Transitionele Pijn Service-team heeft geen nadelige effecten.

7. Wat zijn de voordelen en de nadelen als u meedoet aan het onderzoek?

Het is belangrijk dat u de mogelijke voor- en nadelen goed afweegt voordat u besluit mee te doen. Als u in de in de groep wordt geplaatst waarbij het Transitionele Pijn Service-team u begeleidt kan dit mogelijk leiden tot een beter herstel na de operatie en minder opiatengebruik. Daarnaast draagt u bij aan meer kennis over de behandeling van pijn. Een nadeel van dit onderzoek kan zijn dat u extra tijd kwijt bent aan het invullen van vragenlijsten en afspraken waaraan u zich moet houden.

Voor deze studie zijn er geen extra bezoeken naar het AMC nodig en dus zullen reiskosten ook niet worden vergoedt.

8. Wanneer stopt het onderzoek?

De onderzoeker laat het u weten als er nieuwe informatie over het onderzoek komt die belangrijk voor u is. De onderzoeker vraagt u daarna of u blijft meedoen.

In deze situaties stopt voor u het onderzoek:

- Er 6 maanden na de operatie contact met u is opgenomen / de laatste vragenlijsten zijn ingevuld
- U wilt zelf stoppen met het onderzoek. Dat mag op ieder moment. Meld dit dan meteen bij de onderzoeker. U hoeft er niet bij te vertellen waarom u stopt. U krijgt dan weer de gewone behandeling rondom een operatie.

- De onderzoeker vindt het beter voor u om te stoppen. De onderzoeker zal u nog wel uitnodigen voor een nacontrole.
- het Amsterdam UMC, de overheid of de beoordelende medisch-ethische toetsingscommissie, besluit om het onderzoek te stoppen.

Wat gebeurt er als u stopt met het onderzoek?
De onderzoekers gebruiken de data die tot het moment van stoppen zijn verzameld. Geef dit door aan de onderzoeker.

Het hele onderzoek is afgelopen als alle deelnemers klaar zijn.

9. Wat gebeurt er na het onderzoek?

Indien u na het onderzoek klachten van chronische pijn blijft houden of een andere indicatie heeft, kunt u verwezen worden naar een chronisch pijnspecialist voor verdere behandeling.
De onderzoeker bespreekt dit met u.

Krijgt u de resultaten van het onderzoek?
Ongeveer een tot drie jaar na uw deelname laat de onderzoeker u weten wat de belangrijkste uitkomsten zijn van het onderzoek. Deze informatie krijgt u per email toegezonden. Wilt u dit niet weten? Zeg dat dan tegen de onderzoeker. Hij zal het u dan niet vertellen.

10. Wat doen we met uw gegevens

Doet u mee met het onderzoek? Dan geeft u ook toestemming om uw gegevens te verzamelen, gebruiken en bewaren.

Welke gegevens bewaren we?
We bewaren deze gegevens:
uw naam
- Uw emailadres
- uw geslacht
- uw geboortedatum
- gegevens over uw gezondheid
- (medische) gegevens die we tijdens het onderzoek verzamelen

Waarom verzamelen, gebruiken en bewaren we uw gegevens?
We verzamelen, gebruiken en bewaren uw gegevens om de vragen van dit onderzoek te kunnen beantwoorden. En om de resultaten te kunnen publiceren.

Hoe beschermen we uw privacy?
Om uw privacy te beschermen geven wij uw gegevens een code. Op al uw gegevens zetten we alleen deze code. De sleutel van de code bewaren we op een beveiligde plek in het

ziekenhuis. Als we uw gegevens verwerken, gebruiken we steeds alleen die code. Ook in rapporten en publicaties over het onderzoek kan niemand terughalen dat het over u ging.

Wie kunnen uw gegevens zien?
Sommige personen kunnen wel uw naam en andere persoonlijke gegevens zonder code inzien. Dit zijn mensen die controleren of de onderzoekers het onderzoek goed en betrouwbaar uitvoeren. Deze personen kunnen bij uw gegevens komen:

- Een monitor die voor de opdrachtgever werkt.
- Inspectie Gezondheiszorg en Jeugd

Deze personen houden uw gegevens geheim. Wij vragen u voor deze inzage toestemming te geven.

Hoelang bewaren we uw gegevens?
We bewaren uw gegevens 15 jaar in het ziekenhuis.

Kunt u uw toestemming voor het gebruik van uw gegevens weer intrekken?
U kunt uw toestemming voor het gebruik van uw gegevens op ieder moment intrekken. Maar let op: trekt u uw toestemming in, en hebben onderzoekers dan al gegevens verzameld voor een onderzoek? Dan mogen zij deze gegevens nog wel gebruiken.

Wilt u meer weten over uw privacy?

- Wilt u meer weten over uw rechten bij de verwerking van persoonsgegevens? Kijk dan op www.autoriteitpersoonsgegevens.nl.
- Heeft u vragen over uw rechten? Of heeft u een klacht over de verwerking van uw persoonsgegevens? Neem dan contact op met degene die verantwoordelijk is voor de verwerking van uw persoonsgegevens. Zie bijlage A voor contactgegevens, en website.
- Het AMC is verantwoordelijk voor de verwerking van de persoonsgegevens. Als u klachten heeft over de verwerking van uw persoonsgegevens, raden we u aan om deze eerst te bespreken met het onderzoeksteam. U kunt ook naar de Functionaris Gegevensbescherming van het AMC gaan (paragraaf 13). Of u dient een klacht in bij de Autoriteit Persoonsgegevens.

Waar vindt u meer informatie over het onderzoek?
Op de volgende website(s) vindt u meer informatie over het onderzoek. www.trialregister.nl
Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek tonen. U vindt het onderzoek door te zoeken op TRUSt.

11. Krijgt u een vergoeding als u meedoet aan het onderzoek?

De behandeling tijdens het onderzoek kost u niets. U krijgt ook geen vergoeding als u meedoet aan dit onderzoek.

12. Bent u verzekerd tijdens het onderzoek?

U bent niet extra verzekerd voor dit onderzoek. Want als u meedoet aan het onderzoek, heeft u dezelfde risico's als bij de gewone behandeling van uw aandoening. Daarom hoeft de onderzoeker van de Medisch Ethische Toetsingscommissie AMC geen extra verzekering af te sluiten.

13. We informeren uw huisarts en behandelend specialist.

Wij stellen altijd uw behandelende specialisten (de chirurg en anesthesioloog) op de hoogte van uw deelname aan het onderzoek. Ook zal uw huisarts worden geïnformeerd over uw deelname en indien u in de TPS groep bent geloot, zal er ook overleg over uw behandeling gedurende het onderzoek met de huisarts en of behandelend specialist kunnen plaatsvinden.

14. Heeft u vragen?

Vragen over het onderzoek kunt u stellen aan het onderzoeksteam. Wilt u advies van iemand die er geen belang bij heeft? Ga dan naar dr. M.F. Stevens. Hij weet veel over het onderzoek, maar werkt niet mee aan dit onderzoek.
Heeft u een klacht? Bespreek dit dan met de onderzoeker of de arts die u behandelt. Wilt u dit liever niet? Ga dan naar de klachtencommissie van het Amsterdam UMC. In bijlage A staat waar u die kunt vinden.

15. Hoe geeft u toestemming voor het onderzoek?

U kunt eerst rustig nadenken over dit onderzoek. Daarna vertelt u de onderzoeker of u de informatie begrijpt en of u wel of niet wilt meedoen. Wilt u meedoen? Dan vult u het toestemmingsformulier in dat u bij deze informatiebrief vindt. U en de onderzoeker krijgen allebei een getekende versie van deze toestemmingsverklaring.

Dank voor uw tijd.

16. Bijlagen bij deze informatie

A. Contactgegevens Amsterdam UMC, locatie AMC

Bijlage A: contactgegevens voor Amsterdam UMC Locatie AMC

Uitvoerend onderzoeker:

M. Admiraal

Amsterdam UMC, Universiteit van Amsterdam

Meibergdreef 9, 1105 AZ Amsterdam

020-5669111 / toestel 29370

m.admiraal1@amsterdamumc.nl

Hoofdonderzoekers:

Prof. dr. dr. Markus W. Hollmann, Anesthesioloog

Afdeling Anesthesiologie, Amsterdam UMC locatie AMC

Meibergdreef 9, H1-132

1105AZ Amsterdam, The Netherlands

Tel. 020 566 3630

Onafhankelijk arts:

Dr. M.F. Stevens, anesthesioloog

Amsterdam UMC, Universiteit van Amsterdam

Meibergdreef 9, 1105 AZ Amsterdam

020-5665815 / toestel 29452

m.f.stevens@amsterdamumc.nl

Klachten: Klachtenfunctionaris Amsterdam UMC locatie AMC

Tel. 020 566 3355

Bereikbaarheid: werkdagen, 9.00 tot 15.30 uur

Functionaris voor de Gegevensbescherming van de instelling:

Mw. M. Inge

Amsterdam UMC, Universiteit van Amsterdam

Meibergdreef 9, 1105 AZ Amsterdam

Tel. 020 566 2015

fg@amc.nl

Bereikbaarheid: ma t/m do, 8.55 tot 17.00 uur

Bijlage B: toestemmingsformulier proefpersoon

Behorende bij
Een Transitionele Pijn Service voor patiënten met een groot risico op postoperatief chronische pijn die een operatie ondergaan

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn huisarts en behandelend specialist te laten weten dat ik meedoe aan dit onderzoek.
- Ik geef de onderzoeker toestemming om informatie op te vragen bij mijn huisarts/specialist(en) die mij behandelen over mijn voorgeschiedenis.
- Ik geef de onderzoekers toestemming om mijn gegevens te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksvraag van dit onderzoek te beantwoorden.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.
- Ik wil meedoen aan dit onderzoek.

Mijn naam is (proefpersoon): ……..

Handtekening: …… Datum : __ / __ / __

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Wordt er tijdens het onderzoek informatie bekend die die de toestemming van de proefpersoon kan beïnvloeden? Dan laat ik dit op tijd weten aan deze proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger):…….
Handtekening:…… Datum: __ / __ / __

De proefpersoon krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.

BMJ Open

Study protocol for the TRUSt trial: a pragmatic randomised controlled trial comparing the standard of care with a Transitional Pain Service for patients at Risk of chronic postsurgical pain Undergoing Surgery

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Study protocol for the TRUSt trial: a pragmatic randomised controlled trial comparing the standard of care with a Transitional Pain Service for patients at Risk of chronic postsurgical pain Undergoing Surgery

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ABSTRACT

Introduction: Patients with either surgery- or patient-related risk factors are at an increased risk of acute and chronic postsurgical pain (CPSP) and long-term opioid use. To improve recovery, prevent CPSP and decrease opioid use, we need to identify these patients before surgery and provide a multidisciplinary pain management strategy throughout hospital admission and follow up in the post discharge period. We hypothesise that a multidisciplinary transitional pain service (TPS) improves quality of recovery and reduce the incidence of CPSP and opioid consumption.

Methods and analysis: We aim to investigate the effectiveness of implementation of a TPS for patients at risk of developing CPSP. The trial design is a pragmatic, open label, randomised controlled trial (RCT). After stratification for sex, patients are randomly assigned to the TPS or standard of care (SOC) group. Our primary outcome is the quality of recovery, measured at the morning of the 3rd postoperative day, employing the quality of recovery (QoR)-15 questionnaire. Secondary outcomes are the incidence of CPSP, opioid consumption and patient-reported outcome measures (PROMs) at three and six months postoperatively. To allow a detection of the minimal clinical important difference of 8 points on the QoR-15 score, we need to enrol 176 patients.

Ethics and dissemination: Ethics approval was obtained by the accredited medical research ethics committee of the Academic Medical Center in Amsterdam (2020_211) on 15-10-2020. Protocol version 3.2 was approved on 25-01-2020. The trial is registered with the Netherlands Trial Register; NL9115. The results will be disseminated by open access publication in a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THE STUDY

Strengths

- This study is the first RCT comparing a TPS with standard of care for patients at risk of CPSP.
- This is a pragmatic RCT and will therefore provide real world evidence on the use of TPS.
- The primary outcome is a patient reported outcome measure, which takes into account all aspects of quality of recovery, including pain, physical comfort and independence, psychological support and emotional state.

Limitations

- TPS team and patients cannot be blinded due to the nature of the study.
- The standard of care group might also benefit from implementation of TPS due to an increased awareness for CPSP among health care givers (Hawthorne effect).

INTRODUCTION

Globally, over 320 million people undergo major surgery each year, of which approximately 10% will develop chronic postsurgical pain (CPSP). [1, 2] CPSP is often underdiagnosed and poorly managed, thereby placing a major burden on patient's daily life resulting in significant health problems. In addition, patients with CPSP often take high dosages of opioids due to inappropriate opiate prescribing.[3] Major risk factors for CPSP include chronic pain before surgery, preoperative opioid exposure and the intensity of acute postoperative pain.[4] Key is to identify these patients before surgery and provide multidisciplinary pain management throughout hospital admission, a so called Transitional Pain Service (TPS). Studies on the effectiveness of TPS are scarce, but some studies do support further research into implementation of TPS. Tiippana et al. retrospectively collected data from medical records and determined whether referral of surgical patients to an Acute Pain Service Out-Patient Clinic (APS-OPC) was effective in reducing opioid use in the immediate postoperative period at home.[5] At discharge, 54% of the patients were using weak opioids and 32% strong opioids. This was reduced to 20% and 6% after implementation of the APS-OPC. Also, the Toronto General Hospital launched the first prospective study on TPS in 2014.[6] Patients at high risk of developing CPSP were referred to TPS to manage pain, maintain musculoskeletal function and to lower opioid consumption. Six months postoperatively, opioid-naïve and opioid-experienced patients reduced opioid use by 69% and 44% respectively. Thus, these studies justify further prospective randomised studies on the effectiveness of TPS.

The aim of our study is therefore to investigate the effectiveness of implementation of a multidisciplinary TPS team for patients at risk of developing CPSP, as measured by the quality of recovery, the incidence of CPSP and the postoperative opioid consumption. We hypothesise that a multidisciplinary transitional pain service (TPS) improves quality of recovery and reduce the incidence of CPSP and opioid consumption.

METHODS

For the content of this protocol we used the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and the SPIRIT patient-reported outcome (PRO) extension guidelines. Besides that, this trial implements the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[7-10] The trial is registered with the Netherlands Trial Register; NL9115 (appendix 1).

Study design

The TRUSt study is a randomised single-centre, parallel grouping, two-armed, superiority trial with a 1:1 allocation ratio. The study is being conducted in an urban tertiary referral teaching hospital in the Netherlands. Approximately 12,000 patients undergo surgery in the Amsterdam UMC, location AMC, each year.

Eligibility criteria

Patients are eligible for inclusion if they fulfil the following criteria:

- 18 years and older, Dutch-speaking and reading
- Willing and able to provide informed consent
- Undergoing a surgical procedure with an increased risk of CPSP (amputation, spinal surgery, thoracotomy, mastectomy, herniotomy, hysterectomy and arthroplasty).[11]

Or, any surgery and meeting one or more of the following criteria*:*

- Diagnosed with chronic pain, defined according to the ICD-11 as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Chronic pain is pain that persists or recurs for longer than 3 months”.[12]
- Patients with pain device implants, such as intrathecal pain pump, spinal cord stimulation or peripheral nerve stimulator.
- Chronic opioid use, defined as consumption of more than 20 morphine milligram equivalents (MME) per day for more than three months in the last three months (appendix 2).
- Allergy to opioids
- The usage of pain medication as methadone, buprenorphine, anticonvulsants, antidepressants or medicinal cannabis for chronic pain for more than 3 months in the last three months
- Psychosocial comorbidities like anxiety, depression, pain catastrophizing if documented in the electronic medical record.

Exclusion criteria:

- Patients who undergo emergency surgery are excluded to ensure sufficient time for the informed consent process.

- Patients undergoing implementation of pain device implants, such as intrathecal pain pump, spinal cord stimulators or peripheral nerve stimulator.
- Patients who undergo surgery that most likely leads to prolonged sedation and for that reason cannot fill in the QoR-15 questionnaire at day three postoperative.

Recruitment strategies

Patients are recruited at the anaesthesiology outpatient preoperative evaluation (OPE) clinic, due to COVID-19 mostly by phone. Trained study personnel informs the patient about the study. If the patient gives permission, a member of the research team calls and informs the patient about the purpose, nature, and duration of this study. Besides that the risks and benefits are fully explained. Due to logistics because of SARS-CoV-2, randomisation is performed after verbal informed consent is provided. Patients sign on the day of admission, before surgery, and are blinded for randomisation until they have signed the consent form (appendix 3).

Study outline

Patient enrolment has started on 18-01-2021 and the study is expect to end in December 2022. After informed consent is provided, patient characteristics are be recorded (table 1) and the patient is randomised. Study duration, including follow-up, is six months. During the study, patients will complete different questionnaires, at six different time points (figure 1).

Table 1. The patient characteristics

Age
Sex
Education level
Paid employment
Lifestyle (smoking, alcohol-, drug use)
Comorbidities
Pain history
Pre-existent medication

Randomisation and blinding

Patients are randomly assigned to TPS or standard of care (SOC) in a 1:1 ratio. Treatment assignments are performed centrally using a computer-generated random schedule in permuted blocks of 4, 6 or 8 with stratification for sex.

The study is not blinded for patients or study staff. The outcome assessor will be blinded to treatment allocation by receiving the raw dataset coded and without having access to information about the allocation. Figure 2 is the CONSORT flow diagram and includes estimates for eligible, screened, enrolled and analysed patients.

Study treatment

Control (SOC) group:

Patients in the SOC group (figure 3) will receive standard of care. This includes pre-assessment at the OPE-clinic, during which medical screening is performed, the perioperative anaesthetic and analgesic strategy is discussed and perioperative pain management is planned. For perioperative analgesia the practice guidelines for Acute Pain management in the perioperative setting are adhered to.[13] After surgery, on the ward, nurses, supervised by surgeons, hold a great deal of responsibility for pain management. In addition, the consultative service of the acute pain team (APS) can be requested. The APS is indicated for patients in pain after recent surgery or trauma. Commonly used modalities for pain treatment by the APS include epidural analgesia, peripheral nerve catheter or patient controlled analgesia (PCA). A specialised APS nurse (supervised by an anaesthesist) visits each patient once or twice per day. The APS is available 24 hours a day, seven days a week. Postsurgical opioids are prescribed by the surgeon. From that moment on, both the surgeon and the general practitioner could approve a series of repeat prescriptions. In The Netherlands, ninety-nine percent of the population is insured for health expenses. The health insurance, consists of care provided by a general practitioner, who they can refer themselves to when needed.

Intervention (TPS) group:

For patients randomised to the intervention group (figure 4), the TPS focuses on patient-centred continuity of care. This starts preoperatively and continues until six months after discharge. The TPS team is led by three anaesthesist who are specialised in acute and/or chronic pain management and consists of nurse practitioners, a pain psychologist, a physiotherapist, a social worker and a PhD-researcher. After preoperative screening, patients receive a folder with a brief and simple explanation about pain and patient empowerment to facilitate coping with their condition.[14] Preoperatively, the patient is discussed in the TPS team according to a standard format (appendix 4). Here, an individualised perioperative pharmacological and/or interventional pain management strategy is agreed on. The multimodal pain approach according to the guidelines produced by the American Society of Anesthesiologists is leading.[13] During this multidisciplinary meeting, the need for referral to a pain psychologist, physiotherapist or social worker will be discussed and initiated when deemed necessary. Afterwards, one of the TPS members calls the patient to explain the perioperative

analgesic strategy. Then, to enhance patient autonomy, decisions about care and treatment are made collaboratively between the patient and the healthcare professional (shared decision making).

After discharge, follow up occurs every two weeks for two months and then every month for the remaining four months, or till adequate pain control is achieved and opioids are weaned off completely. The definition of follow-up is a telephone call or an appointment at the outpatient clinic. At this follow-up consultation, progress of the patient and the pain treatment plan are evaluated. When possible, opioids are tapered or discontinued. In the post-discharge period, the patient's General Practitioner is called by a member of the TPS team and provided with information on the further pain treatment strategy. In this post-discharge period, additional consultation of the TPS team is possible if the treatment goals are not achieved. If the patient develops CPSP within six months after surgery or did not wean off opioids completely, we refer the patient to our chronic pain team.

Outcomes

Primary outcome

Our primary outcome is the quality of recovery, using the quality of recovery (QoR)-15 questionnaire, measured at the morning of the 3rd postoperative day[15]. The transition from acute to chronic pain is a very complex, not fully elucidated process. However, in patients undergoing surgery, CPSP typically begins as acute pain after surgery, that often is difficult to manage. We hope that by the implementation of a TPS, pain in this primary phase is better controlled and thus results in less transition phase to CPSP. The QoR-15 questionnaire evaluates the patients' initial recovery post-surgery.

For constructs such as pain, comfort or emotional state, the patient's perception is the only source of information and therefore Patient Reported Outcome Measures (PROMs) should be considered the gold-standard evaluation. A well validated patient outcome questionnaire is an objective evaluation that quantifies the patients pain, recovery as perceived by the patient.[16] The QoR-15 questionnaire is a validated, reliable and objective PROM as described in several studies.[17] By taking the questionnaire on the morning of the third postoperative day, we effectively assess the second postoperative day.

Secondary outcomes

A TPS is not only targeting this acute postoperative phase and therefore we evaluate long-term outcomes in this study as well. Secondary outcomes include postoperative long-term follow up data:

1. CPSP diagnosis (after three and six months) defined according to the IASP.[11]
2. Opioid consumption (preoperative, postoperative day three, after three and six months): calculated as MME per day.
3. Patient reported health outcome measurements:

- *The WHO Disability Assessment Schedule* (WHODAS) *2.0*, 12-items: brief assessments that covers six domains of functioning including cognition, mobility, self-care, getting along, life activities and participation.[18] Scoring has three steps; summing of recorded item scores within each domain, summing of all six domain scores and lastly converting the summary score into a metric ranging from 0 to 100 (where 0 = no disability; 100 = full disability).[19] We will analyse the difference across groups at baseline and after three and six months postoperative. We will also analyse a change in the score over time for each group. A change in score of 5% or more after surgery is consistent with a clinically important change in disability.[20]

- *EuroQol-5D-5 level version* (EQ-5D-5L): reflecting generic health status: a 5-item summary measure of overall health status. The descriptive system comprises the dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[21] We will summarise the EQ-5D-5L health state by an index value which reflects how good or bad a health state is according to the preferences of the general population of a country/region.[22] A value set is established that represent the views of the Dutch population.[23] At a minimum, we will analyse the change in index over time within groups (preoperative to three and six months postoperatively) and between groups. The dimension pain/discomfort will be analysed separately as well.

- *Patient-reported outcomes measurement information system* (PROMIS)-*29:* a generic health-related quality of life survey, assesses each of the seven PROMIS domains (anxiety; physical function; pain interference; fatigue; sleep disturbance an disability to participate in social roles an activities), with four questions. The questions are ranked on a 5-point Likert Scale. There is also one eleven-point rating scale for pain intensity.[24] Norm-based scores have been calculated for each domain, so that a score of 50 represents the mean of the reference population with a standard deviation of 10. At a minimum, we will analyse the change in index over time within groups (preoperative to three and six months postoperatively) and between groups. The dimension pain/discomfort will be analysed separately as well.

- *QoR-15* comparing changes in time (baseline, day one, two and three postoperatively) within groups. The QoR-15 scores range from 0 (extremely poor) to 150 (excellent quality of recovery). Interventions that result in a change of 8.0 reflect a clinically minimally important difference.[25]

4. Satisfaction staff of the implementation of a TPS, rated on a five point Likert scale from 1 (extremely dissatisfied) to 5 (extremely satisfied).[26]

5. The frequency the perioperative plan (like type of anaesthetic), changed after evaluation of the patient by the TPS team, instead of the earlier discussed method during preoperative assessment.

Other measurements:

- *Intraoperative data:* type of anaesthesia, doses of opioids, duration of surgery, duration of recovery room stay, etc.
- *Postoperative data:* length of hospital stay, method of pain control, dose of opioids etc.
- *Long term follow-up data:* number of contacts with TPS, number of referrals etc.

Sample size and drop-out

Using nQuery Advisor version 8.5.1, sample size is driven by the analysis for superiority of TPS compared to standard care employing the QoR-15 questionnaire score. Assuming a standard deviation of 18 points on postoperative day three and being able to detect a QoR-15 score difference of at least 8 (based on the minimal clinically important difference and standard deviation found by Myles et al [25]), randomisation ratio 1:1, a total sample size of 160 patients is required (80 patients per group) to detect this difference with a statistical power of 80% and a significance level of (alpha) 0.05. Patients can leave the study at any time for any reason if they wish to do so without any consequences. Patients will not be replaced in case of withdrawal. To account for a possible drop-out rate of 10% we will include 88 patients per arm, thus a total of 176.

Protocol deviation

Protocol deviations or violations could occur in this study and will be reported. An example of a protocol deviation is a follow up visit at a slightly different time frame than required by protocol, e.g. because of the participant's schedule. Furthermore, an anaesthesia technique provided diverging from the one agreed on at the OPE. Besides, a patient allocated to the SOC group who is in severe pain could be discussed in the TPS team because of Good Clinical Practice. Patients with protocol deviations will be included in the intention to treat analysis. All protocol violations, except cancelled surgery, will be included in intention to treat analysis but will lead to exclusion from analysis per protocol. When a patients surgery is cancelled this patient will be excluded from all analysis. There are no safety risks associated with protocol violations in this trial.

Statistical analysis

Final data will be screened for typos, missing values, outliers and distribution. All data analyses will be carried out according to a pre-established analyses plan. We are planning for complete case analyses and multiple imputations for missing data.

Baseline characteristics, as mentioned in table 1, will be summarized with the use of the appropriate descriptive statistics.

Primary outcome analysis

All randomised patients will be analysed as the primary population for the analysis according the intention-to treat principle. As mentioned above, cancelled surgery is the only protocol violation that will lead to exclusion from analysis. The primary outcome, the between group difference in QoR-15 scores will be analysed. Because of the small interval between the intervention and the primary endpoint, we do not expect a significant amount of missing data on the QoR-15 survey. However, patients who are sedated or experiencing a delirium and patients who are discharged before day three, could cause missing data. Therefore, we will compare responders (patients who returned a completely filled-in QoR-15 questionnaire) and non-responders for differences in patient characteristics, perioperative surgical and anaesthetic factors, to examine non-response bias on age, sex and item-response.

Depending on the distribution of the data, we will test the raw between group difference using an unpaired-t-test or Mann-Whitney U test. Statistical uncertainties will be quantified with two-sided 95% confidence intervals. A two-sided p-value < 0,05 will be considered statistically significant. Because of our randomization stratification for sex, we will additionally report effects adjusted for sex.

As part of our secondary analyses, we will perform a per protocol analysis including all randomised patients completing the whole study period on the between group difference in QoR-15 scores as described above.

Secondary outcome analysis

Between group difference in the proportion of patients having the diagnosis CPSP after three and six months will be compared using the Chi-square test. We expect the change in opioid consumption to be bimodal distributed, some patients will not change their opioid consumption while other will reduce their consumption completely. The between group difference in change in opioid consumption (MMEs) (postoperative day three, after three and six months) will be compared using a generalized linear mixed model, with treatment as fixed effect and preoperative opioid consumption, time and the interaction between treatment and time as covariates and subject as random factor.

Only if time, or interaction between treatment and time differs significantly between groups, we will perform post-hoc analysis. We will use the Benjamini-Hochberg procedure to correct for multiple testing. [27] Non normal distribution is expected in WHODAS 2.0, EQ-5D-5L, PROMIS-29 scores and therefore we will analyse the between group differences at 1 point using a Mann-Witney U test. and a generalized mixed model. We will use a generalized mixed model to correct for time and to test multiple measurements at the same time. For missing item scores, multiple imputation will be applied.

After the study period, staff satisfaction will be measured on implementation of a TPS, using a Mann-Whitney U test and the proportion of perioperative plan changes after evaluation of the TPS team, will be compared using a Chi-square test. Finally, an exploratory analyses will be performed by studying differences in treatment effect in subgroups other than sex; different risk factors of CPSP, baseline

characteristics and on perioperative treatment. For the exploratory analyses, correction for multiple testing will be applied using the Benjamini-Hochberg method. R studio (Affero General Public License V3) will be used for the analyses.

Data collection and management

Paper and online surveys will be used to collect PROMs. Only Dutch translated surveys will be used. A automatically reminder will be sent by mail after three days (as an exception the QoR-15 survey at day three postoperatively, this reminder will be sent after one day). If the patient did not complete the survey after 6 days a manual survey invite will sent and in case of no response after another three days a phone call will be made to the patient who did not complete the survey.

For collecting long term data at three and six months, the researcher calls the patients and evaluates if symptoms of CPSP develop and gathers data on the amount of pain medication. At this phone call the researcher will also remind the patient on the survey Specify PRO data collection and management strategies for minimizing avoidable missing data.

The data of each patient will be recorded on an individual electronic case report form (eCRF) using Castor EDC (Ciwit B.V. the Netherlands, version 1.5, a GCP compliant database). Data will be coded using a unique numerical code. The key to this code is only available to the research team and is stored in the trial master file (TMF) in accordance with the European Union regulation act (GDPR; General Data Protection Regulation) and GCP. All patient data will be handled confidential. The correctness of entries will be verified for 15% of the data, by a second investigator. All recorded data, including CRFs, TMF, investigator site file and ICFs will be stored for 15 years after completion of the study. Study data will always be stored securely, in a locked cabinet or on password secured computers, only accessible for study team members.

Monitoring

The study will be monitored, based on a low-risk study design, by a monitor from the Clinical Monitoring Center at the Amsterdam UMC. This is a qualified, independent team that is put in place to monitor according to the monitor plan. The principal investigator and all investigators will permit and facilitate study-related monitoring or regulatory inspection by providing direct access to study files and source data/documents. After each monitoring visit, a site report will be issued by the monitor to the principal investigator and a copy will be provided to the local investigators. Due to the minimal risk nature of the study, there will be no external data and safety monitoring board.

ETHICS AND DISSEMINATION

Ethics approval (2020_211) was obtained on 15 October 2020, in the Netherlands at the Medical Research Ethics Committee location Academic Medical Center (Amsterdam, The Netherlands). The trial will be conducted in compliance with this study protocol, the Declaration of Helsinki and Good Clinical Practice (GCP). Protocol amendments will be subjected to the Medical Ethics Committee for approval and thereafter communicated to all investigators an trial registries (appendix 5). There are no publication disclosures.

Data availability statement

The results of the current study will be disseminated to healthcare providers, policy-makers and patients via presentations at local and national meetings, as well as by open access publication in a peer-reviewed journal. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

Authors' contributions

MWH, JH, HH, CW, SM, MR, HW, VW and MA were involved in conception and trial design. SM, HW, MR, VW helped with implementation. MA and SM will be responsible for the PRO content of the trial. JH, HH, and MA were involved in drafting the article. MWH, SM, HW, MR and CW were involved in critical revision of the article. All the authors contributed to refinement of the study protocol and final approval of the article.

Funding statement

The TRUSt study is investigator initiated and there is no external funding.

Competing interest statement

None declared.

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FIGURES

Figure 1: The study assessment flow diagram

Figure 2: Consolidated Standards of Reporting Trials flow diagram estimating patient screening, enrolment and response rate.

Figure 3: Perioperative pathway for patients allocated to standard of care

[1] The APS team is nurse based and anesthetist supervised. A clinical pain nurse visits each patient on the APS service at least once a day, mostly when pain treatment modalities like intravenous or epidural patient controlled analgesia (PCA), with or without peripheral nerve catheter, are used. The team is in-house 24 hours a day, seven days a week. When pain medication is switched to oral medication only, the patient is usually discharged from services of the APS.

Figure 4: Perioperative pathway for patients allocated to Transitional Pain Service

[1] The TPS team consists of three anaesthetists who are specialized in acute and/or chronic pain, pain nurse practitioners, a psychologist, a physiotherapist, a social worker and a PhD-student.

[2] Non-pharmacological interventions include:

- An information folder regarding pain and empowerment
- Shared decision-making about care and treatment to promote patient autonomy during the study.

[3] The TPS team can refer the patient to a psychologist, a social worker or a physiotherapist.

[4] Follow-up after discharge occurs every two weeks with a telephone call until his/her pain is under control or medication is weaned off completely.

Appendix

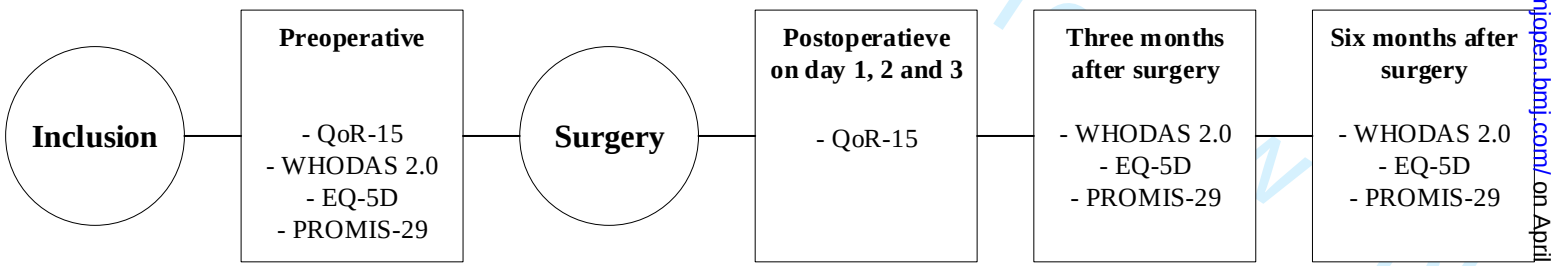
Appendix 1: Trial registration: data set

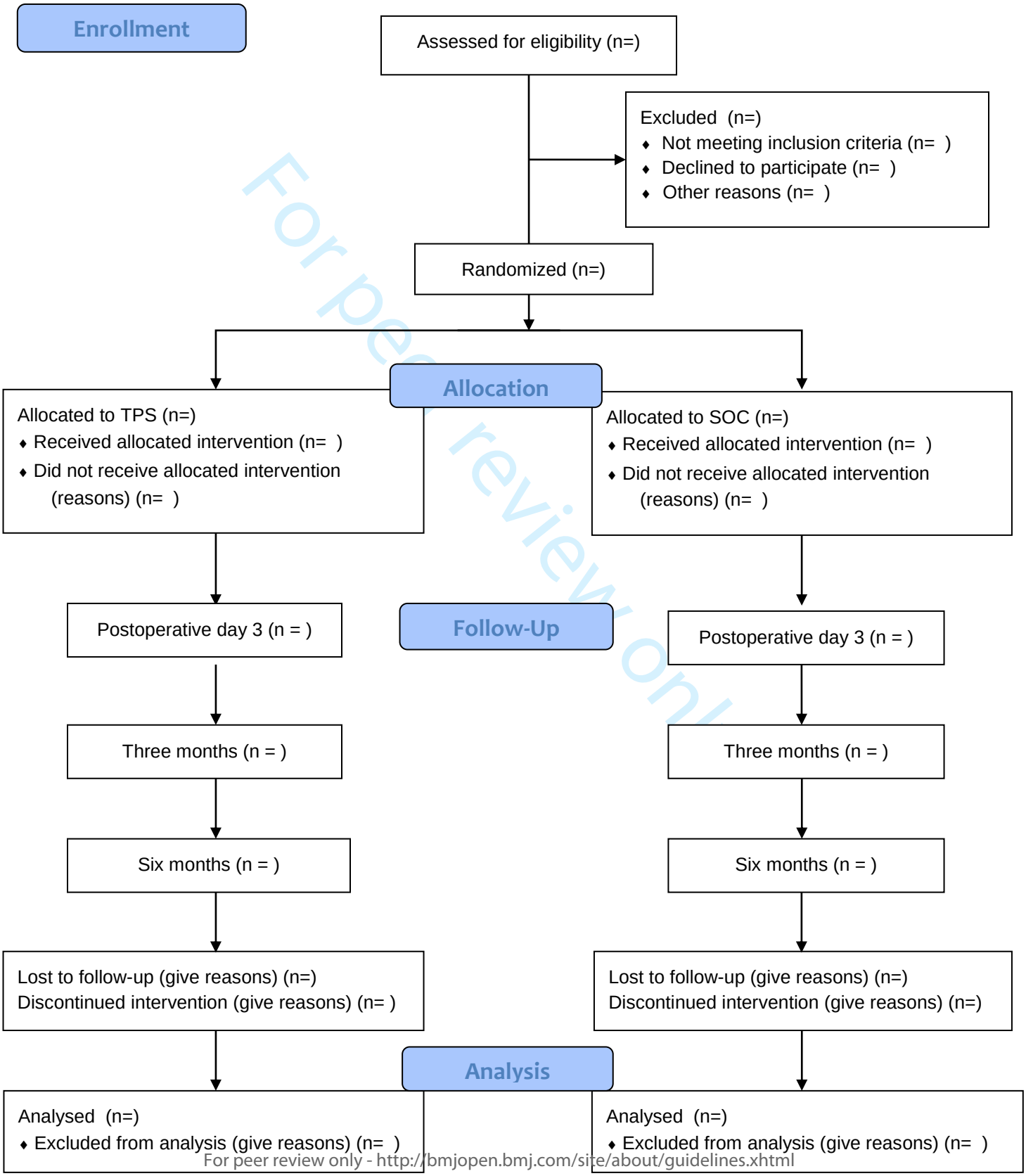
Appendix 2: Opioid oral morphine milligram equivalent conversion table

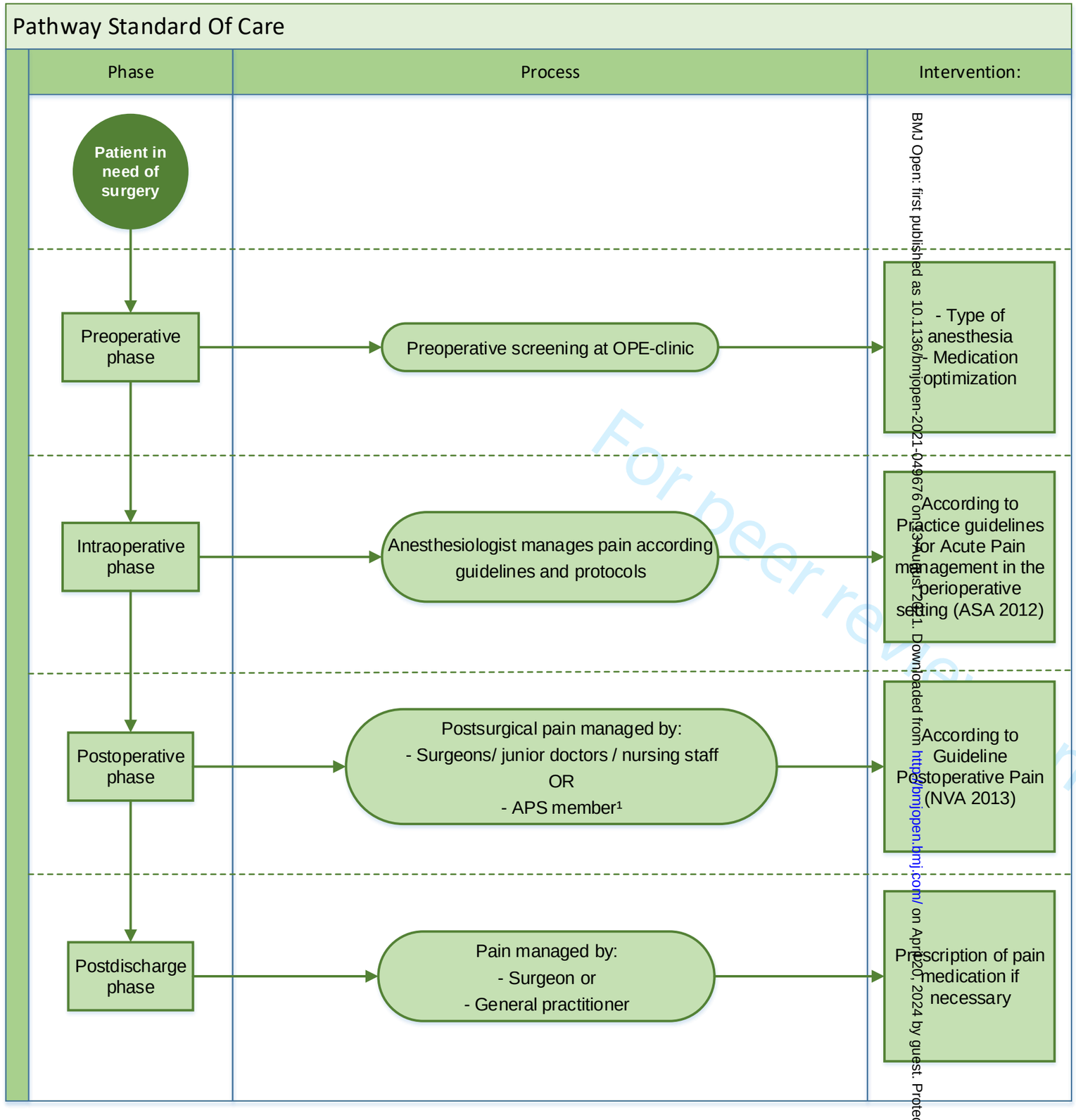
Appendix 3: Informed consent material

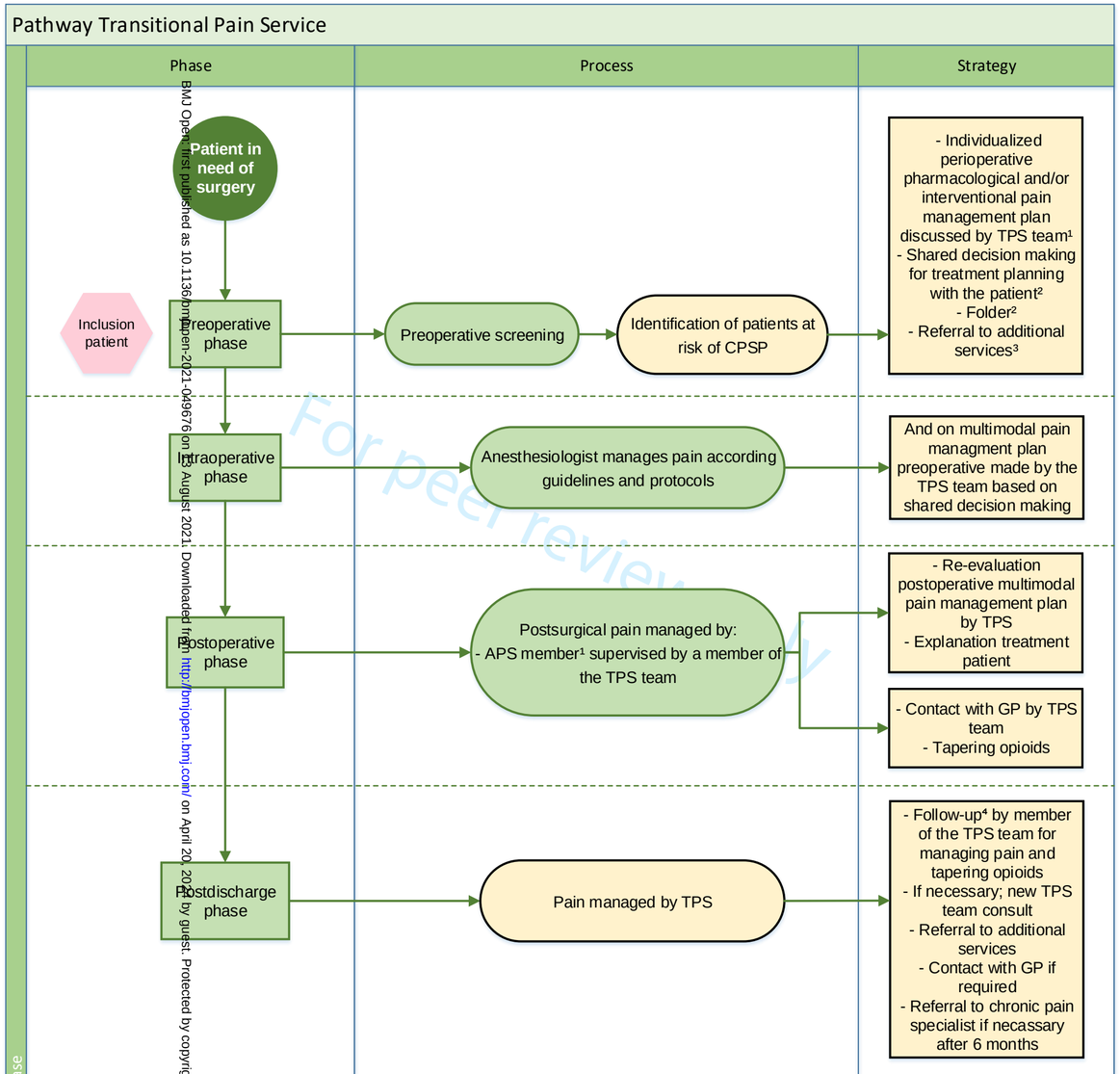
Appendix 4: Standard format treatment TPS patient

Appendix 5: Protocol date and version identifier









Acronym
TRUSt study
Title
Transitional Pain Service for patients at Risk of chronic postsurgical pain Undergoing Surgery
Scientific title
Transitional Pain Service for patients at Risk of chronic postsurgical pain Undergoing Surgery
Summary
Patients with either surgery or patient-related risk factors (e.g. pre-existing chronic pain or preoperative opioid consumption) are at an increased risk of acute and chronic postsurgical pain (CPSP) and long-term opioid use. To improve recovery, prevent CPSP and decrease opioid use, we need to identify these patients before surgery and provide a multidisciplinary pain management strategy throughout hospital admission and follow up in the post discharge period. Randomized trials assessing the impact of a multidisciplinary transitional pain service (TPS) on quality of recovery, incidence of CPSP and opioid consumption have not been conducted yet and is the purpose of this study.
Status
Open for patient inclusion
Study type
Interventional
Control group
Active
Grouping
Parallel
Arms
2 or more arms, randomized
Masking
None
Target size
180
Inclusion criteria
Patients aged 18 years or older 2. Willing and able to provide informed consent 3. Undergoing a surgical procedure with an increased risk of CPSP (amputation, spinal surgery, thoracotomy, breast surgery, herniotomy, hysterectomy and after arthroplasty) (9). Or; Any surgical procedure and one of the following: - Diagnosed chronic pain, defined according to the ICD-11 as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Chronic pain is pain that persists or recurs for longer than 3 months (3)” - Chronic opioid use, defined as > 20 mg daily morphine equivalent (MME) consumption for more than 3 months in the last 3 months - Allergy to opioid agents - Patients with pain device implants, such as intrathecal pain pump, spinal cord stimulation or peripheral nerve stimulator - The usage of pain medication as methadone, buprenorphine, anticonvulsants, antidepressants or medicinal cannabis for chronic pain for more than 3 months in the last three months Psychosocial comorbidities like anxiety, depression, pain catastrophizing if documented in the electronic medical record
Exclusion criteria
- Not willing or able to provide written informed consent - Emergency surgery
Start date
2021-01-01
Stop date
2022-12-31
Diseases
Chronic postoperative pain
Hypothesis
The aim of our study is to investigate the effect of the implementation of a multidisciplinary TPS team for patients at risk of developing CPSP, on the quality of recovery, the incidence of CPSP and the opioid consumption. We hypothesize that the effect of implementation of a TPS team is superior to standard of care for outcomes as previously mentioned.
Interventions
Patients will be randomized to the TPS group or standard of care group. Patients allocated to the standard of care group will receive a pre-assessment at the outpatient preoperative evaluation (OPE) clinic. Postoperative pain will be managed by the Acute Pain Service (APS) for patients with an epidural, or peripheral nerve catheter or those with patient controlled analgesia (PCA). When the APS is not involved, postoperative pain will be managed by the

surgeon and/or nurses on the ward. In the TPS intervention group, the multidisciplinary TPS team, consisting of anesthesiologists and nurses who are specialized in pain, will make an individualized perioperative pain management plan. If necessary, referrals to a psychologist, physiotherapist or social worker will be made. Education of the patient will take place. After surgery, the APS, supervised by a member of the TPS team, will perform daily visits to monitor the effectiveness of pain treatment and to cease any medication that is deemed unnecessary. Following discharge from the hospital, the General Practitioner will be provided with information on the further pain treatment strategy for a better transition of care. Patients will be scheduled for follow-up appointments at the TPS outpatient clinic, or receive follow-up telephone calls to re-evaluate the pain treatment plan, taper opioids and if CPSP is diagnosed, referred to a pain specialist after six months.

Primary outcome

The primary outcome is the between group difference in Quality of Recovery (QoR)-15 questionnaire score at day three after surgery.

Secondary outcome

- Postsurgical chronic pain (CPSP) at three and six months after surgery, defined according to the IASP (as mentioned in chapter 1), and/or taking pain medication to treat CPSP as described above. - Opioid consumption per day, calculated as morphine equivalent dose (MEDs) at day three after surgery, prescription at discharge, and at three and six months after discharge. - Patient-reported outcome as measured by the WHODAS 2.0 (15), PROMIS-29 (16) and EQ-5D-5L (17) preoperatively and at three and six months after discharge.

Sponsors

Amsterdam University Medical Center, location Meibergdreef (AMC)

Time points

Baseline, 3 days postoperatively, 3 and 6 months postoperatively.

MEC approved

Yes

Multicenter

Randomised

Yes

Plan to share IPD

Yes

IPD plan description

Plan to share individual participant data (IPD): Yes

The IPD sharing plan description: Data will be made available on request after an embargo period. After the last manuscript is published, data will be made available, with restricted access. Agreement regarding the following conditions will be needed before data sharing:

- Permission from the participants to send data outside of the EU (if applicable)
- Approval from the Steering Committee and Project Manager for the proposal
- Financial compensation for costs, for example, to obtain data after being archived
- A period of permission to use the dataset will be set
- The format in which the dataset will be made available will need to be discussed
- Approval to couple the dataset to another dataset (privacy) will have to be discussed
- There are provisions with regard to data safety and privacy laws
- Collaboration over use of the dataset, including agreements over publications and authorships
- Agreements regarding methodology

A proposal, in the correct format will be assessed by the Steering Committee. If the research question is deemed relevant, a well-defined analysis plan is available, agreements are made regarding publication, and all other requirements are met, then the Steering Committee will give permission to share the data.

Publications

N/A

Issueing body

METC AMC

Source ID

METC2020_211

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2020-12-11

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N/A
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Amsterdam UMC, locatie Meibergdreef

Appendix 2: Opioid oral morphine milligram equivalent conversion table

	Conversion factor	Dose Equivalent Morphine Sulphate (30 mg)
Morphine		
Oral (= rectal)	1	30 mg
Intravenous	3	10 mg
Epidural	30	1 mg
Intrathecal	300	0,1 mg
Oxycodone	1.5	20 mg
Codeine	0.15	200 mg
Tramadol	0.2	150 mg
Fentanyl		
Transdermal	2.4	12.5 mcg/hour
Intravenous	300	0,1 mg
Sublingual	0.13	230 mcg
Nasal	0.16	190 mcg
Remifentanil (intravenous)	300	0.1mg (= 100 mcg)
Sufentanil (intravenous)	3000	0.01 mg (= 10 mcg)
Buprenorphine		
Sublingual	0.05	600 mcg
Transdermal	2.3	13 mcg/hour
Intravenous	75	0.4 mg
Hydromorphone		
Oral	4	7.5 mg
Intravenous	8	3.75 mg
Piritramide (dipidolor) intravenous	2	15 mg
Tapentadol		
Oral	0.4	7.5
Methadone		
Oral 0-20 mg	4	7.5 mg
21-50 mg	8	3.75 mg
>51 mg	10	3 mg
Intravenous	3	10 mg
Pethidine		
Intramuscular/subcutaneous	0.3	100 mg

Proefpersoneninformatie voor deelname aan medisch-wetenschappelijk onderzoek

Beter herstel na een operatie met een Transitionele Pijn Service

Een Transitionele Pijn Service rondom een operatie voor patiënten met een hoger risico op langdurige postoperatieve chronische pijn

Inleiding

Geachte heer/mevrouw,

Met deze informatiebrief willen we u vragen of u wilt meedoen aan medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig. U krijgt deze brief omdat u binnenkort een chirurgische ingreep ondergaat of recentelijk ondergaan heeft.
U leest hier om wat voor onderzoek het gaat, wat het voor u betekent, en wat de voordelen en nadelen zijn. Het is veel informatie. Wilt u de informatie doorlezen en beslissen of u wilt meedoen?

Stel uw vragen

U kunt uw beslissing nemen met de informatie die u in deze informatiebrief vindt. Daarnaast raden we u aan om dit te doen:
- Stel vragen aan de onderzoeker die u deze informatie geeft.
- Praat met uw partner, familie of vrienden over dit onderzoek.
- Stel vragen aan de onafhankelijk deskundige, dr. M.F. Stevens
- Lees de informatie op www.rijksoverheid.nl/mensenonderzoek.

1. Algemene informatie

Amsterdam Universitair Medisch Centrum, locatie AMC heeft dit onderzoek opgezet. Hieronder noemen we Amsterdam Universitair Medisch Centrum, locatie AMC steeds de ‘opdrachtgever’. Onderzoekers, dit kunnen artsen/onderzoeksverpleegkundigen/ onderzoekers zijn voeren dit onderzoek uit. Voor dit onderzoek zijn 180 proefpersonen nodig. De medische-ethische toetsingscommissie AMC heeft dit onderzoek goedgekeurd.

2. Wat is het doel van het onderzoek?

Met de oprichting van een Transitionele Pijn Service (TPS) willen wij onderzoeken of patiënten hierdoor sneller herstellen van een operatie, minder vaak chronisch postoperatieve pijn ontwikkelen en daarnaast minder opiaten gebruiken (een voorbeeld van een opiaat is morfine). Het is de bedoeling de resultaten te publiceren en op deze manier betere zorg te kunnen leveren.

3. Wat is de achtergrond van het onderzoek?

Chronisch postoperatieve pijn is een complicatie die ongeveer na 10% van de operaties optreedt. Helaas wordt de kwaliteit van leven door deze aandoening vaak negatief beïnvloedt. Daarnaast is deze aandoening ook moeilijk te behandelen.

Tevens is het opiaatgebruik in Nederland de laatste jaren toegenomen. Dit heeft vele negatieve gevolgen zoals een toename in opiaatafhankelijkheid, meer ziekenhuisopnames en een hogere sterftekans.

Chronisch pijn patiënten gebruiken vaak een hogere dosis opiaten, dan patiënten zonder chronisch pijn, met alle negatieve gevolgen van dien. Wij willen een TPS oprichten, die patiënten met een verhoogd risico op postoperatieve pijn opspoort en intensief begeleidt rondom en na de operatie. Wij denken dat er hierdoor minder chronische postoperatieve pijn ontstaat en er ook minder opiaatgebruik na de operatie zal zijn. In Canada is dit recent gedaan en daarbij zijn goede resultaten zijn behaald.

4. Hoe verloopt het onderzoek?

Duur onderzoek:

Als u meedoet, duurt dat totaal ongeveer 6 maanden voor u.

Voor de studie maken wij 2 groepen (Een Transitionele Pijn Service groep en een standaard zorg groep), met ieder 90 patiënten.

De behandeling:

Nadat u heeft besloten mee te doen wordt er geloot tussen de behandeling van een TPS team of de normale zorg in de controle groep. Deze loting vindt plaats met behulp van een computer programma en de onderzoekers weten vooraf niet welke groep u zult komen.

De patiënten in de controle groep krijgen de standaard zorg rondom een operatie.

De patiënten in de Transitionele Pijn Service groep krijgen ook de standaard zorg, maar daarbij extra behandeling van het Transitionele Pijn Service-team. Het Transitionele Pijn Service-team bestaat uit diverse pijn-gespecialiseerde anesthesisten, -verpleegkundigen, psychologen en fysiotherapeuten die samen een individueel pijnbeleid omtrent de operatie zullen maken.

Vragenlijsten:

Van alle proefpersonen wordt gevraagd diverse vragenlijsten in te vullen. Dit zal indien mogelijk, vooraf aan de operatie zijn, net als op dag 1, 2 en 3 na de operatie en na 3 en 6 maanden. Dit kan zowel digitaal, of als u dit liever hebt per post. U hoeft hiervoor niet extra naar het ziekenhuis te komen. De vragen gaan over herstel na de operatie, eventuele pijn en psychische klachten.

De onderzoeker zal deze gegevens verzamelen. Daarnaast zal de onderzoeker gegevens verzamelen uit uw medisch dossier over uw gezondheidstoestand.

5. Welke afspraken maken we met u?

Om het onderzoek goed te laten verlopen, is het belangrijk dat u zich aan de volgende afspraken houdt.

De afspraken zijn dat u:

- afspraken voor bezoeken nakomt.

Het is belangrijk dat u contact opneemt met de onderzoeker:

- voordat u andere geneesmiddelen gaat gebruiken. Ook als dat homeopathische geneesmiddelen, natuurgeneesmiddelen, vitaminen en/of geneesmiddelen van de drogist zijn.
- als u in een ziekenhuis wordt opgenomen of behandeld.
- als u plotseling gezondheidsklachten krijgt.
- als u niet meer wilt meedoen aan het onderzoek.
- als uw contactgegevens wijzigen.

6. Van welke bijwerkingen, nadelige effecten of ongemakken kunt u last krijgen?

Behandeling van het Transitionele Pijn Service-team heeft geen nadelige effecten.

7. Wat zijn de voordelen en de nadelen als u meedoet aan het onderzoek?

Het is belangrijk dat u de mogelijke voor- en nadelen goed afweegt voordat u besluit mee te doen. Als u in de in de groep wordt geplaatst waarbij het Transitionele Pijn Service-team u begeleidt kan dit mogelijk leiden tot een beter herstel na de operatie en minder opiatengebruik. Daarnaast draagt u bij aan meer kennis over de behandeling van pijn. Een nadeel van dit onderzoek kan zijn dat u extra tijd kwijt bent aan het invullen van vragenlijsten en afspraken waaraan u zich moet houden.

Voor deze studie zijn er geen extra bezoeken naar het AMC nodig en dus zullen reiskosten ook niet worden vergoedt.

8. Wanneer stopt het onderzoek?

De onderzoeker laat het u weten als er nieuwe informatie over het onderzoek komt die belangrijk voor u is. De onderzoeker vraagt u daarna of u blijft meedoen.

In deze situaties stopt voor u het onderzoek:

- Er 6 maanden na de operatie contact met u is opgenomen / de laatste vragenlijsten zijn ingevuld
- U wilt zelf stoppen met het onderzoek. Dat mag op ieder moment. Meld dit dan meteen bij de onderzoeker. U hoeft er niet bij te vertellen waarom u stopt. U krijgt dan weer de gewone behandeling rondom een operatie.

- De onderzoeker vindt het beter voor u om te stoppen. De onderzoeker zal u nog wel uitnodigen voor een nacontrole.
- het Amsterdam UMC, de overheid of de beoordelende medisch-ethische toetsingscommissie, besluit om het onderzoek te stoppen.

Wat gebeurt er als u stopt met het onderzoek?
De onderzoekers gebruiken de data die tot het moment van stoppen zijn verzameld. Geef dit door aan de onderzoeker.

Het hele onderzoek is afgelopen als alle deelnemers klaar zijn.

9. Wat gebeurt er na het onderzoek?

Indien u na het onderzoek klachten van chronische pijn blijft houden of een andere indicatie heeft, kunt u verwezen worden naar een chronisch pijnspecialist voor verdere behandeling.
De onderzoeker bespreekt dit met u.

Krijgt u de resultaten van het onderzoek?
Ongeveer een tot drie jaar na uw deelname laat de onderzoeker u weten wat de belangrijkste uitkomsten zijn van het onderzoek. Deze informatie krijgt u per email toegezonden. Wilt u dit niet weten? Zeg dat dan tegen de onderzoeker. Hij zal het u dan niet vertellen.

10. Wat doen we met uw gegevens

Doet u mee met het onderzoek? Dan geeft u ook toestemming om uw gegevens te verzamelen, gebruiken en bewaren.

Welke gegevens bewaren we?
We bewaren deze gegevens:
uw naam
- Uw emailadres
- uw geslacht
- uw geboortedatum
- gegevens over uw gezondheid
- (medische) gegevens die we tijdens het onderzoek verzamelen

Waarom verzamelen, gebruiken en bewaren we uw gegevens?
We verzamelen, gebruiken en bewaren uw gegevens om de vragen van dit onderzoek te kunnen beantwoorden. En om de resultaten te kunnen publiceren.

Hoe beschermen we uw privacy?
Om uw privacy te beschermen geven wij uw gegevens een code. Op al uw gegevens zetten we alleen deze code. De sleutel van de code bewaren we op een beveiligde plek in het

ziekenhuis. Als we uw gegevens verwerken, gebruiken we steeds alleen die code. Ook in rapporten en publicaties over het onderzoek kan niemand terughalen dat het over u ging.

Wie kunnen uw gegevens zien?
Sommige personen kunnen wel uw naam en andere persoonlijke gegevens zonder code inzien. Dit zijn mensen die controleren of de onderzoekers het onderzoek goed en betrouwbaar uitvoeren. Deze personen kunnen bij uw gegevens komen:

- Een monitor die voor de opdrachtgever werkt.
- Inspectie Gezondheiszorg en Jeugd

Deze personen houden uw gegevens geheim. Wij vragen u voor deze inzage toestemming te geven.

Hoelang bewaren we uw gegevens?
We bewaren uw gegevens 15 jaar in het ziekenhuis.

Kunt u uw toestemming voor het gebruik van uw gegevens weer intrekken?
U kunt uw toestemming voor het gebruik van uw gegevens op ieder moment intrekken. Maar let op: trekt u uw toestemming in, en hebben onderzoekers dan al gegevens verzameld voor een onderzoek? Dan mogen zij deze gegevens nog wel gebruiken.

Wilt u meer weten over uw privacy?

- Wilt u meer weten over uw rechten bij de verwerking van persoonsgegevens? Kijk dan op www.autoriteitpersoonsgegevens.nl.
- Heeft u vragen over uw rechten? Of heeft u een klacht over de verwerking van uw persoonsgegevens? Neem dan contact op met degene die verantwoordelijk is voor de verwerking van uw persoonsgegevens. Zie bijlage A voor contactgegevens, en website.
- Het AMC is verantwoordelijk voor de verwerking van de persoonsgegevens. Als u klachten heeft over de verwerking van uw persoonsgegevens, raden we u aan om deze eerst te bespreken met het onderzoeksteam. U kunt ook naar de Functionaris Gegevensbescherming van het AMC gaan (paragraaf 13). Of u dient een klacht in bij de Autoriteit Persoonsgegevens.

Waar vindt u meer informatie over het onderzoek?
Op de volgende website(s) vindt u meer informatie over het onderzoek. www.trialregister.nl
Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek tonen. U vindt het onderzoek door te zoeken op TRUSt.

11. Krijgt u een vergoeding als u meedoet aan het onderzoek?

De behandeling tijdens het onderzoek kost u niets. U krijgt ook geen vergoeding als u meedoet aan dit onderzoek.

12. Bent u verzekerd tijdens het onderzoek?

U bent niet extra verzekerd voor dit onderzoek. Want als u meedoet aan het onderzoek, heeft u dezelfde risico's als bij de gewone behandeling van uw aandoening. Daarom hoeft de onderzoeker van de Medisch Ethische Toetsingscommissie AMC geen extra verzekering af te sluiten.

13. We informeren uw huisarts en behandelend specialist.

Wij stellen altijd uw behandelend anesthesioloog op de hoogte van uw deelname aan het onderzoek. Indien u in de TPS groep bent geloot kan uw huisarts worden geïnformeerd omtrent verdere behandeling/adviezen of overleg.

14. Heeft u vragen?

Vragen over het onderzoek kunt u stellen aan het onderzoeksteam. Wilt u advies van iemand die er geen belang bij heeft? Ga dan naar dr. M.F. Stevens. Hij weet veel over het onderzoek, maar werkt niet mee aan dit onderzoek.
Heeft u een klacht? Bespreek dit dan met de onderzoeker of de arts die u behandelt. Wilt u dit liever niet? Ga dan naar de klachtencommissie van het Amsterdam UMC. In bijlage A staat waar u die kunt vinden.

15. Hoe geeft u toestemming voor het onderzoek?

U kunt eerst rustig nadenken over dit onderzoek. Daarna vertelt u de onderzoeker of u de informatie begrijpt en of u wel of niet wilt meedoen. Wilt u meedoen? Dan vult u het toestemmingsformulier in dat u bij deze informatiebrief vindt. U en de onderzoeker krijgen allebei een getekende versie van deze toestemmingsverklaring.

Dank voor uw tijd.

16. Bijlagen bij deze informatie

A. Contactgegevens Amsterdam UMC, locatie AMC

Bijlage A: contactgegevens voor Amsterdam UMC Locatie AMC

Uitvoerend onderzoeker:

M. Admiraal

Amsterdam UMC, Universiteit van Amsterdam

Meibergdreef 9, 1105 AZ Amsterdam

020-5669111 / toestel 29370

m.admiraal1@amsterdamumc.nl

Hoofdonderzoekers:

Prof. dr. dr. Markus W. Hollmann, Anesthesioloog

Afdeling Anesthesiologie, Amsterdam UMC locatie AMC

Meibergdreef 9, H1-132

1105AZ Amsterdam, The Netherlands

Tel. 020 566 3630

Onafhankelijk arts:

Dr. M.F. Stevens, anesthesioloog

Amsterdam UMC, Universiteit van Amsterdam

Meibergdreef 9, 1105 AZ Amsterdam

020-5665815 / toestel 29452

m.f.stevens@amsterdamumc.nl

Klachten: Klachtenfunctionaris Amsterdam UMC locatie AMC

Tel. 020 566 3355

Bereikbaarheid: werkdagen, 9.00 tot 15.30 uur

Functionaris voor de Gegevensbescherming van de instelling:

Mw. M. Inge

Amsterdam UMC, Universiteit van Amsterdam

Meibergdreef 9, 1105 AZ Amsterdam

Tel. 020 566 2015

fg@amc.nl

Bereikbaarheid: ma t/m do, 8.55 tot 17.00 uur

Bijlage B: toestemmingsformulier proefpersoon

Behorende bij
Een Transitionele Pijn Service voor patiënten met een groot risico op postoperatief chronische pijn die een operatie ondergaan

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn huisarts en behandelend specialist te laten weten dat ik meedoe aan dit onderzoek.
- Ik geef de onderzoeker toestemming om informatie op te vragen bij mijn huisarts/specialist(en) die mij behandelen over mijn voorgeschiedenis.
- Ik geef de onderzoekers toestemming om mijn gegevens te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksvraag van dit onderzoek te beantwoorden.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.
- Ik wil meedoen aan dit onderzoek.

Mijn naam is (proefpersoon): ……..

Handtekening: …… Datum : __ / __ / __

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Wordt er tijdens het onderzoek informatie bekend die die de toestemming van de proefpersoon kan beïnvloeden? Dan laat ik dit op tijd weten aan deze proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger):…….
Handtekening:…… Datum: __ / __ / __

De proefpersoon krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.

Checklist Transitional Pain Service (TPS)

Multidisciplinary meeting (preoperative)

Patient data	
Patient number	
Type of surgery	
Date of preoperative screening	
Date of surgery	
Date of Multidisciplinary Team Meeting TPS	

Pre-existent pain medication

Intraoperative phase	
Anesthetic	
○ General ○ Local	
Multimodal pain management	
Intravenous medication	
Regional techniques	
Local techniques	

Postoperative phase	
Pharmacological pain management, algorithm 1	
Non-pharmacological	
If necessary, referral to psychologist, social worker or physiotherapist	

Checklist Transitional Pain Service (TPS)

Additional information about this patient/treatment

Checkboxes:

- ☐ After the multidisciplinary meeting one of the members of the TPS group will call the patient and explain the intraoperative multimodal pain treatment (informed consent and psychoeducation
- ☐ One of the members sends the information folder towards the address

Checklist postoperative period

APS or CPS

- ☐ Is there adequate pain control?

*If not, supervision about treatment by TPS anesthetist**

- ☐ Cease medication that is deemed unnecessary (taper opioids)
- ☐ Give adequate education about the individual multimodal pain management plan and the process of weaning from opioids

TPS member

- ☐ Contact surgeon; propose and discuss discharge pain medication, *algorithm 2*
- ☐ Discusses post discharge medication with the patient
- ☐ Contact general practitioner; inform about the study

Checklist Transitional Pain Service (TPS)

Checklist post-discharge period

After discharge, follow up occurs:
- After three months and after six months for every patient, or extra;

For a patient that is not completely weaned of pain medication or still experiences pain in the surgical area (until adequate pain control is achieved and medication is weaned of):
- For the first two months: every two weeks
- For the last four months: every four weeks

* The definition of follow-up is a telephone call or an appointment at the outpatient clinic.

TPS member

	Pain in surgical area	Use of pain medication	Opioids and dose in MME?	Other pain med?	Switch? Tapering? Referral?	Healthcare consumption?
15th day						
30th day						
45th day						
60th day						
90th day						
120th day						
150th day						
180th day						

☐ At day 90th day remember patient of questionnaires

☐ At 180th day remember patient of questionnaires

☐ If CPSP developed after six months > referral to chronic pain specialist

Additional information about this patient/treatment

Checklist Transitional Pain Service (TPS)

Appendix

Algorithm 1: pharmacological multimodal postoperative pain management

1. Paracetamol + NSAID (preferably metamizole)
2. Regional analgesia (epidural or peripheral nerve block)
3. Continuous Wound infiltration or Continuous surgical site analgesia
4. Adjuvants
    a. NMDA antagonist (S-ketamine)
    b. Alfa2 agonist (clonidine)
5. Opioids
    a. Oral administered
    b. Transdermal, nasal, sublingual
    c. Patient controlled analgesia (PCA) infusion pomp (morphine, buprenorphine, piritramide).

Algorithm 2: Out of hospital pharmacological pain management

1. Paracetamol + NSAID
2. Medication for neuropathic pain
    a. Anticonvulsants (pregabalin)
    b. Tricyclic antidepressant (amitriptyline)
3. Tapering opioids
4. Opioid substitute therapy
    a. Methadone
    b. Buprenorphine

Appendix 5: Protocol date and version identifier

Issue date: 25 January 2021

Protocol amendment number: 3.2

Revision chronology:

- Protocol version 3.2, 25-01-2021: approved.
  At postoperative day one and two patients have to fill in the QoR-15 questionnaire.
- Protocol version 3.1, 26-11-202: approved.
  Different informed consent procedure necessary due to COVID-19.
- Protocol version 2.0, 15-10-2020**:** Ethics approval was obtained by the accredited medical research ethics committee of the Academic Medical Center (AMC) in Amsterdam (2020_211)
  All the proposals and recommendations put forward by the ethics committee have been followed and integrated into the amended version of the protocol.
- Protocol version 1.0, 04-09-2020 sent to medical research ethics committee of the Academic Medical Center (AMC) in Amsterdam.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	appendix 3
Protocol version	#3	Date and version identifier	1 en appendix 4
Funding	#4	Sources and types of financial, material, and other support	13

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants,			

interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6,7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/a.
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8,9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5 and figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	9

		clinical and statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate	11

		measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10,11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10,11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10,11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	12

		interim results and make the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 5
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

Notes:

- 3: 1 en appendix 4
- 13: 5 and figure 1 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 29. January 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai