Prevention of Phantom Limb Pain After Transtibial Amputation (PLATA)

Randomized, double-blind, controlled, multi-center trial comparing Optimized intravenous pain control vs Optimized intravenous pain control plus Regional anesthesia

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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>AR</td>
<td>Adverse Reaction</td>
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<td>ASA</td>
<td>American Society of Anesthesiologists</td>
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<td>CRPS</td>
<td>Complex Regional Pain Syndrome</td>
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<td>CV</td>
<td>Curriculum Vitae</td>
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<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
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<td>EudraCT</td>
<td>European Drug Regulatory Affairs for Clinical Trials</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>ICH</td>
<td>International Conference on Harmonization</td>
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<td>IMP</td>
<td>Investigational Medicinal Product (Appendix 3)</td>
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<td>IMPD</td>
<td>Investigational Medicinal Product Dossier</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<td>sf MPQ</td>
<td>Short Form McGill Pain Questionnaire (Appendix 3A)</td>
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<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
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<td>NRS</td>
<td>Numerical Rating Scale for pain (scale from 0 = no pain to 10 = worst pain)</td>
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<td>OBAS</td>
<td>Overall Benefit of Analgesia Score (Appendix 3B)</td>
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<td>PCA</td>
<td>Patient Controlled Anesthesia</td>
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<td>PLP</td>
<td>Phantom Limb Pain</td>
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<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<td>SF-12</td>
<td>Short-Form 12 questionnaire assessing quality of life (Appendix 3C)</td>
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<td>SNP</td>
<td>Single Nucleotide Polymorphism</td>
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<td>SIGAM</td>
<td>Special Interest Group in Amputation Medicine (score for disability)</td>
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<td>Sponsor</td>
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<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
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<td>WMO</td>
<td>Wet Medisch Onderzoek (Dutch law on clinical research)</td>
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SUMMARY

Rationale:
Phantom limb pain following amputation is a major clinical problem. Current evidence on how to best prevent phantom limb pain is equivocal because previous trials have included small numbers of patients, and tested heterogeneous patient collectives. There is some evidence that optimized perioperative pain control is effective in preventing phantom limb pain, but the potential added role of regional anesthesia has not been defined.

Objective:
The aim of this study is to test the hypothesis that a combination of optimized intravenous pain therapy and continuous sciatic nerve block decreases the point prevalence of phantom limb pain 12 months after transtibial amputation for peripheral vascular disease when compared to optimized intravenous pain therapy alone.

Study design:
Interventional, randomized, prospective, triple-blind (patient, physician, statistician) clinical trial.

Study population:
Patients with ASA status II to IV undergoing elective transtibial amputation for peripheral vascular disease at one of the participating centers.

Main study parameter/endpoint:
Point prevalence of chronic phantom limb pain after 12 months.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
All patients, regardless of group allocation, will receive optimized intravenous pain treatment. The aim of this study is to assess whether additional regional anesthesia (ultrasound-guided sciatic nerve block) can further decrease the incidence of phantom limb pain.
The administration of both optimized intravenous pain treatment and peripheral nerve blockade is routine clinical practice for many procedures on the lower leg, including amputation. The risk of this intervention can be described as very low.
1. INTRODUCTION AND RATIONALE

The collective of patients featuring critical limb ischemia is large and growing. For the population aged 60-90 years, the prevalence is estimated at 1% and growing. Current literature suggests that about 25% of these patients will need to undergo amputation. Even with the increased use of interventional treatments for vascular disease, amputation remains a frequently performed surgery with a frequency of approx. 190 / 100.000 / year, and for the United States alone, current projections estimate that the number of patients living with loss of a limb due to vascular disease will rise from the current 850.000 to 2.200.000 by the year 2050.

The prevalence of phantom pain following surgical amputation is high. A recent study confined to patients undergoing lower limb amputation for peripheral vascular disease reported phantom limb pain in 79% of patients. Other survey data describes figures around 75%. For amputations incurred during wartime, reports from the U.S. Department of Veteran Affairs cite similar numbers (72-76%).

Despite the growing importance of phantom limb pain following amputation, there is no consensus or robust evidence-base how to best minimize risk of chronic post-amputation pain. Several recent publications have implicated preamputation pain and acute postsurgical pain in the development of chronic phantom limb pain, but no direct prospective randomized investigations sufficiently powered have been carried out.

1.1. Anesthesia

Several studies have addressed the potential of analgesic interventions to reduce the incidence of chronic phantom pain. However, these have been hampered by small numbers of patients, and heterogeneous patient collectives. A recent systematic review by Ypsilantis et al. (2010) concluded that robust evidence to support a positive impact of anesthetic interventions in the prevention of phantom limb pain is, to date, lacking.

Many of the national and local protocols and guidelines (e.g. the Dutch National Guidelines for Perioperative care for Amputation) are based upon case series, observational studies, and small randomized controlled trials, most of them recruiting not more than 10-20 patients per treatment group. Moreover, many of these studies included heterogeneous patient collectives, i.e. undergoing different types of amputation. The difficulties encountered are maybe best exemplified by a recent randomized controlled trial conducted Karanikolas et al. Here, it was suggested that strict perioperative pain control using fixed regimens of non-opioid agents and patient-controlled anesthesia reduced the incidence of phantom limb pain from 75% to 53%. However, the small number of patients (n=12 to 13 in each group) makes extrapolation problematic, and renders it impossible to analyze whether the addition of epidural anesthesia would be of added benefit.
1.1.1. Neuraxial anesthesia

The concept that regional anesthesia would protect against the development of phantom limb pain stem from a landmark study in which Bach et al. included 25 patients in a non-blinded observational study. The authors found that in those 11 patients arbitrarily receiving epidural anesthesia, incidence of phantom limb pain was almost zero, while a third of patients in the group receiving standard intravenous and oral medication continued to experience pain after 6 and 12 months. In a small and non-blinded trial testing epidural diamorphine, bupivacaine and clonidine (n=13) versus on-demand analgesia (n=11), the incidence of phantom pain was decreased from 81 to 7%. Two other small trials conducted by the group of Nikolajsen studies with randomized design testing epidural anesthesia failed to confirm these promising findings. In a small non-blinded trial, Lambert and co-authors failed to demonstrate a difference in phantom limb pain after 12 months whether epidural anesthesia, or a perineural catheter placed intraoperatively infusion was used for pain control. Therefore, the efficacy of epidural anesthesia to protect against chronic phantom limb pain remains controversial. Moreover, vascular surgery patients are frequently medicated with inhibitors of platelet aggregation or plasmatic hemostasis. This necessitates judicious use of epidural catheters in these patients to avoid the complication of epidural hematoma.

1.1.2. Peripheral nerve block

Another alternative way to provide pain relief which is less prone to cause bleeding complications is peripheral nerve blockade. In a pilot case series, Fisher and Meller applied perineural catheters to 11 patients undergoing amputation, and found that none of them had phantom pain after 12 months. Another case series, Borghi and coworkers reported their experience in 71 patients undergoing lower extremity amputation. Here, using an elastomeric infusion system connected to a sciatic catheter in place for a median duration of one month, the incidence of phantom limb pain was 15%, and phantom limb sensations were present in 39% after 12 months. However, the incidence of severe phantom limb pain was only 3%. In a small randomized trial, Pinzur and coworkers compared the application of a peripheral nerve block in 11 patients versus sham in 10 patients, and found no beneficial effect of peripheral nerve blockade. However, this trial was hampered by a very small number of patients in each treatment arm, no standardization in perioperative protocols, and a drop-out rate of 33%. This very scarce evidence-base (two case series and one weak randomized trial) is in contrast to the clinical reality that many institutions have implemented protocols which stipulate the use of regional anesthesia for amputation surgery. This is, however, not supported by the available literature. Provocatively, it could be stated that peripheral nerve
blocks are common practice, but not substantiated by any solid evidence, a very undesirable combination in the age of evidence-based medicine. Therefore, this trial seeks to define the role of regional anesthesia in the perioperative management of patients presenting for amputation. The PLATA trial, when completed, will allow for the first time a risk-benefit analysis of peripheral nerve blocks for this specific type of surgery, including the immediate postoperative pain, and effects on the long-term development of chronic phantom limb pain.

1.1.3. NMDA antagonists

Other authors have attempted to prevent chronic phantom limb pain by administering antagonists of the n-methyl-d-aspartate (NMDA) receptor, ketamine or memantine. However, also in this case, studies are frequently unblinded, and enrolled few patients. The first case study described the successful treatment of three patients with existing phantom limb pain using ketamine infusion. In a prospective observational study with historical controls (n=14 each), Dertwinkel et al. reported a decrease in severe phantom limb pain from 71 to 9%. Haynes et al. randomized 45 patients to receive standard morphine PCA with or without perioperative ketamine continued 72 hours postoperatively. Despite finding a reduction in phantom limb pain from 71 to 47%, this was non-significant due to the small number of included patients (Type II error). Later small studies failed to confirm positive effects of NMDA antagonists. For example, Wilson et al. did not find a difference whether epidural bupivacaine was combined with ketamine, or not. Results concerning memantine are equivocal, as well. On one hand Maier et al. failed to demonstrate a benefit when memantine was administered to patients with chronic phantom limb pain. On the other hand, a small RCT comparing 9 patients receiving plexus blockade plus memantine to 10 patients receiving plexus blockade only found lower rates or phantom limb pain when both modalities were combined.

1.1.4. Anticonvulsants

Nikolajsen et al. investigated the benefits of oral gabapentin, frequently used to treat phantom limb pain once it has occurred, during the first postoperative month, and failed to detect benefits on postamputation pain.

1.1.5. Initiation of treatment

Finally, the optimal timepoint to start perioperative pain treatment remains unclear, as well. In a small observational study, Bach et al. postulated benefits of starting perioperative analgesic regimen one day before surgery, but later randomized controlled trials found evidence for or against starting analgesic protection ahead of amputation.
In summary, the efficacy of all perioperative interventions remains equivocal. The trials reporting the least incidence of chronic phantom limb pain had instituted strict perioperative pain control, but the numbers of enrolled patients are by far too small to draw evidence-based conclusions, and many of these studies were observational in nature and not blinded. The hypothesis that may cautiously be formed is that optimized perioperative analgesia possibly confers significant protection against phantom limb pain, perhaps with an added advantage when combined with regional anesthesia.\textsuperscript{12}

1.2. Surgery

Limited evidence exists to support use of some interventions during transtibial amputation. Wolthuis et al. found that employing a tourniquet led to a decreased incidence in revision and postoperative bleeding complications.\textsuperscript{29} Furthermore, limited evidence suggests a distance of 10-15 cm below the knee joint to be the optimal site of amputation.\textsuperscript{30} Finally, a two-stage technique combining guillotine amputation at the ankle joint with a long posterior flap seems to ameliorate primary wound healing without affecting long-term outcome.\textsuperscript{30} The wide variety of surgical techniques used to handle nerves intraoperatively\textsuperscript{31} may similarly impact ultimate outcome, but no study has documented surgical factors.

1.3. Genetics

Why certain patients develop ongoing pain and in others the pain resolves is unknown and is the reason for this study. Part of this risk is likely genetic. Acute pain thresholds, in contrast to chronic pain levels, are less genetically determined (with estimated heritability scores of 22-55\%).\textsuperscript{32} In contrast, mono- versus di-zygotic twins studies show a heritable component to the risk of developing persistent pain of 55-68\%.\textsuperscript{32} \textsuperscript{33} Such data clearly suggest a genetic predisposition for those who develop chronic pain following a precipitating incident, such as limb amputation and attendant nerve damage. The aim of the present study is to advance in defining these genetic factors.

Previous work within this collaborative framework has focused on several genes including GCH1 and KCNS1 because these genes have been found to be important mechanistic drivers in pre-clinical animal models of chronic neuropathic pain.\textsuperscript{34}\textsuperscript{35} As well as establishing their relevance in this lab setting, data has been confirmed in human populations. For instance, the incidence of phantom pain, post limb amputation in Israeli war veterans ranges from 56\% to 78\%, depending on the genotype of the patient at one single nucleotide polymorphism (SNP) in KCNS1 (\textit{rs734784}, \textit{p}=0.0001). In addition the haplotype of KCNS1 identified by this SNP was also associated with pain outcome in five out of six human populations tested (overall \textit{p} value of association with higher pain risk = 1.14 E-08).\textsuperscript{34} Analysis of one of the cohorts identified multiple pain risk genes such as GCH1, KCNS1,
CACNA2D3 and Nav1.7 across the genome.\textsuperscript{34} \textsuperscript{35} \textsuperscript{36} \textsuperscript{37} SNPs from previously published acute to chronic neuropathic pain risk genes (GCH1, KCNS1, Nav1.7 and P2X7R) will be analyzed to define genes important for the transition from acute to chronic pain following amputation.

1.5. Conclusions and Aim

Current literature is plagued by small numbers of enrolled patients,\textsuperscript{13} and frequent mixing of patient populations. This study is designed to compare two interventions thought to contribute to decreased incidence of phantom limb pain (\textit{strict intravenous pain control} versus \textit{strict intravenous pain control plus peripheral nerve block}).

The five most decisive innovative aspects of our proposed study are:

- the inclusion of \textit{larger numbers of patients} (n=400) out of a relatively \textit{homogeneous patient collective} (transtibial amputation for peripheral vascular disease),
- the administration of \textit{strict perioperative (“optimized”) analgesia} to every patient,
- ultrasound-guided peripheral nerve blocks as \textit{“state of the art” control intervention} added in the intervention group,
- the documentation of \textit{surgical technique}, and
- the prospective determination of individual patient “pain” \textit{genotype}.

2. OBJECTIVES

General Aim:

The aim of this study is to test the hypothesis that a combination of optimized intravenous pain therapy and continuous sciatic nerve block decreases the point prevalence of phantom limb pain 12 months after transtibial amputation for peripheral vascular disease when compared to optimized intravenous pain therapy alone.

Primary Outcome:

Point prevalence of chronic phantom limb pain at 12 months postoperatively (for definition refer to section 7.1.1).

Secondary Outcomes (for a full list see 7.1.2.):

- Incidence of phantom limb pain at 7 days, 1, and 6 months.
- McGill Pain Questionnaire (short form MPQ) preoperatively, and postoperatively at Day 7, and 1, 6, and 12 months postoperatively.\textsuperscript{38}
- SF-12 quality of life score
- Overall Benefit of Analgesia Score during the first postoperative week (OBAS)\textsuperscript{39}
- Recording of surgical handling of nerves / surgical technique. \textsuperscript{31}
- Genotype of patients assessed preoperatively. Gene haplotype will be assayed for association with acute to chronic pain conversion using SNPs from known risk factor genes including GCH1, KCNS1, Nav1.7 and P2X7R.\textsuperscript{34-37}
3. STUDY DESIGN

**Design:** This present study is an interventional, prospective, randomized, and triple-blinded (blinding of patient, physician, and statistician). This necessitates the involvement of two main researchers at each participating institution. One researcher will be responsible for randomization and blinded drug preparation. The second researcher will assess the patient before and after surgery, and at follow-up, and will retrieve source data for inclusion in the electronic CRF.

**Method of randomization:** Online computer-based randomization stratified according to planned anesthetic technique (spinal / general anesthesia).

**Duration:** The research network will encompass a network of hospitals performing approximately 400 transtibial amputations for peripheral vascular disease per year. Assuming 50% inclusion rate and a desired inclusion of 400 patients, the inclusion time is foreseen to take between 2 and 2.5 years, followed by 1 year follow-up. The study is projected to last for an estimated 3.5 years for data collection including follow-up.

**Setting:** The aim is to recruit a total of 20 to 25 centers with assistance of the European Society of Anaesthesiology Clinical Trial Network (see Appendix 8 with list of participating centers).
Flowchart: Study timeline overview.

Inclusion into the study
Randomization (online)

-Multimodal pain therapy
- opiate PCA
- ketamine iv
- non-opiates
- Sciatic nerve catheter

Control group
Sciatic catheter: NaCl 0.9%

Intervention group
Sciatic catheter: bupivacaine

Observation period:

Pain treatment: standardized

Days after surgery
D = 1 - ?

Follow up:
Phantom limb pain
Stump pain
Opiate consumption

Follow up:
Phantom limb pain
Stump pain
Opiate consumption
Rehabilitation score
Quality of life

Follow up
1, 6, 12 months
4. STUDY POPULATION

4.1 Patient population
Surgical patients. Recruitment will be performed during the preoperative evaluation period by an independent investigator (Dutch: onderzoeker), who performs intake interviews independently from the treating physician (surgeon, anesthetist).

4.2 Inclusion criteria
Patients undergoing elective transtibial amputation for peripheral vascular disease, age over 18 years, ASA status II to IV.

American Society of Anaesthesiologists (ASA) status classification
ASA I: healthy patient
ASA II: mild systemic disease
ASA III: severe systemic disease
ASA IV: severe systemic disease which poses a constant threat to life
ASA V: moribund patient expected not to survive without surgery

4.3 Exclusion criteria
- contraindication to peripheral regional anesthesia
- confirmed allergy to local anesthetics
- prior amputation resulting in current phantom limb pain
- severe psychiatric disease
- pregnancy or breastfeeding status
- amputation for tumour surgery
- traumatic amputation and
- inability to give written and informed consent.

4.4 Sample size calculation
Previous outcome studies investigating the effect of optimized perioperative analgesia alone have indicated a prevalence of phantom limb pain one year after amputation of 45%. A meaningful clinical effect will be assumed when the point prevalence of phantom limb pain 12 months after amputation can be reduced from 45% to 30%. For detailed definition of primary endpoint refer to 7.1.1. Taking an alpha level of 0.05 and a power of 80%, the prognosticated sample size per group is 163 patients, assuming a drop-out rate of approximately 18%, this trial will recruit 163/0.8 = 200 patients per treatment group.

Total sample size (in two groups) is 400 patients.
5 TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

All patients will receive "optimized intravenous pain control", a term describing the administration of optimal intravenous and oral analgesia in a stepwise fashion until pain subsides to light levels. The corresponding numeric rating scale (NRS) value for acute postoperative pain frequently used in clinical practice is <4 on a scale of 10. The key components of this regimen are:

- administration of low-dose ketamine given as bolus of 0.25 mg/kg and continuous intravenous infusion titrated to effect starting at 0.125 mg/kg/h,
- patient-controlled analgesia (PCA) using strong opiates (morphine, piritramide, or buprenorphine; 1 mg morphine equivalent, 5 min lockout interval, no background infusion)
- non-opioids: at least one from the following: paracetamol (15 mg / kg max every 6 hours in the absence of contraindications), metamizol (15 mg / kg, upper dose limit 60 mg / kg / 24 hours in the absence of contraindications).

All patients will further receive an ultrasound-guided subgluteal sciatic nerve catheter at the start of treatment (see 7.3.9)

According to randomization, patients then follow one of the two standardized pain therapy regimens:

- Optimized intravenous treatment ("Control", n=200)
- Optimized intravenous treatment plus sciatic nerve block ("Intervention", n=200)

Description of treatment groups (n=200 each):

1. Optimized intravenous treatment ("Control" group)
   This group will receive optimized intravenous treatment from the timepoint of surgery for 7 days postoperatively.
   The sciatic nerve catheter will be started using a bolus injection of 20 mL saline 0.9%, followed by continuous infusion of saline at 10 mL/h postoperatively.
2. Optimized intravenous treatment plus regional anesthesia ("Intervention" group)
   This group will receive optimized intravenous treatment from the timepoint of surgery for 7 days postoperatively.
   The sciatic nerve catheter will be started using a bolus injection of 20 mL bupivacaine 0.25%, followed by continuous infusion of bupivacaine 0.125% at 10 mL/h intra- and postoperatively.

5.2 Use of co-intervention
Patients will receive general or spinal anesthesia at the discretion of the treating physician. Randomization will be stratified according to planned type of anesthesia. Global anesthesia parameters will be recorded (see 7.1.2. and Appendix 1, CRF). Surgical methods are at the discretion of the treating surgeon, and will be recorded (see 7.1.2. and Appendix 1, CRF). The only interventions and standardizations are done with regards to perioperative pain therapy.

5.3 Escape medication
For ethical reasons, a true "conventional" pain control group as described in previous trials (opiates administered intramuscularly or subcutaneously as needed, no strict control of pain scores and therapy) will not be included in the present study because these groups have featured excessive pain scores and a very high probability of chronic phantom limb pain.\textsuperscript{12,13} Therefore, all patients receive the maximum intravenous standard treatment regimen. In case of breakthrough pain, titration of opiates in addition to PCA, and titration of the ketamine infusion dosing will take place.
6 INVESTIGATIONAL MEDICINAL PRODUCT

As mentioned in the accompanying letter, the present study does not seek to address the efficacy or comparative efficacy of bupivacaine for sciatic nerve block, as the respective evidence supporting bupivacaine as the standard long-acting local anesthetic for nerve block is substantial. Rather, the aim of this study is to investigate the effect of peripheral nerve block on the prevalence of chronic phantom limb pain. Therefore, even though an investigational medical product is used, the focus of this application is not on the drug bupivacaine, but on the intervention “sciatic nerve block”.

The medicinal product used for intervention (sciatic nerve block) in the present study is used in authorized form. Bupivacaine 0.125%-0.5% is licensed in The Netherlands for wound infiltration and nerve block under register no. RVG 08029 by Astra Zeneca BV by the College ter Beoordeling van Geneesmiddelen – CBG). Bupivacaine is used daily in clinical routine to perform regional anesthesia worldwide, and is part of routine clinical protocols. Based upon the regular and routine clinical use, we will perform drug accountability via the local Hospital pharmacy (in this application: AMC), which will create a drug preparation protocol conform to ICH-GCP, oversee purchase and storage of drugs, and perform drug accountability for drugs given out to researchers. Also, the local pharmacy will prepare a concluding drug accountability report and store the documentation for 15 years according to ICH-GCP. Study drugs will prepared at the point of care by two certified and competent health care professionals according to the Pharmacy protocol.

Name and description of investigational medicinal product(s)
The name of the investigational medicinal product is bupivacaine, a classic long-acting local anesthetic used for wound infiltration or nerve conduction block.

Summary of findings from non-clinical studies
Since this investigational medicinal product has long been registered and in clinical use, and is used as authorized, refer to the IMPD Bupivacaine. In the attached IMPD for Bupivacaine in The Netherlands (Appendix 5A), refer to chapter 5 (pages 12-14 in IMPD).

Summary of findings from clinical studies
In the attached IMPD for Bupivacaine, refer to chapter 4 (pages 1-12 in IMPD). Bupivacaine has been in routine clinical use for more than 40 years for wound infiltration and regional anesthesia.
Summary of known and potential risks and benefits
In the attached IMPD for Bupivacaine, we refer to chapter 4.3-4.9 (pages 5-12 in IMPD). The risks for participants taking part in either control or nerve block group can be described as extremely low.

Description and justification of route of administration and dosage
Ultrasound-guided sciatic nerve block allows for maximum reduction in dose, and allows for direct visualization of the sciatic nerve. Performance of sciatic nerve block for lower extremity surgery is a common procedure.

Dosages, dosage modifications and method of administration
The initial bolus will be 20 mL of 0.25% bupivacaine, followed by continuous administration of 10 mL / hour of 0.125% bupivacaine via catheter.

6.1 Preparation and labelling of Investigational Medicinal Product

All patients receive optimized intravenous analgesia (patient-controlled analgesia, ketamine). The designation intervention or control treatment pertains to the drug administered via the sciatic nerve catheter.

- All drugs are prepared for administration by two trained professionals (physicians, nurses) in analogy to a protocol outlined by the Hospital Pharmacy, Academic Medical Center, University of Amsterdam, The Netherlands.

For patients in the intervention group, two investigators will prepare:
- 20 mL bupivacaine 0.25% for the initial bolus injection
- bupivacaine 0.125% for continuous administration at 10 mL/hour for one week of drug administration

For patients in the control group, the hospital pharmacy will provide:
- 20 mL saline 0.9% for the initial bolus injection
- saline 0.9% for continuous administration at 10 mL/hour for one week of drug administration

All syringes are labelled after preparation with uniform labels containing information on patient identification, study name, and the remark “Contains NaCl 0.9% or Bupivacaine 0.125%”. For an exemplary label see Appendix 5C.
7 METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

Point prevalence of phantom limb pain 12 months postoperatively defined (yes/no) as:

1) Pain in the amputated area of the limb with a corresponding NRS score of ≥ 2 during the preceding 4 weeks (constant or at least three episodes)

AND / OR

2) Ingestion of drugs administered specifically to treat phantom limb pain during the preceding 4 weeks (classified as none, non-opiate, weak opiate, strong opiate, antidepressant, anticonvulsant, other).

*This endpoint will also be assessed at 1 week, and 1 and 6 months postop. by interview.*

The NRS score of 2 or higher is chosen because this is considered the lowest NRS score associated with pain. In accordance to previous studies, testing will be for pain at the moment of testing, or during the four preceding weeks. This pain can be constant, or paroxysmal, with at least three episodes over a period of four weeks defined as constituting phantom limb pain. Weak opiates are tramadol and codeine, strong opiates are morphine, morphine derivatives, buprenorphine, piritramide, sufentanil, and fentanyl.

7.1.2 Secondary study parameters/endpoints (see Appendix 1, CRF)

General secondary endpoints
- Subjective classification of chronic phantom limb pain by patient in the preceding 4 weeks (classified on a NRS, see 7.3.7) and a questionnaire on impact of pain on daily activities (see 7.3.1)
- SF-12v2 Short form 12 quality of life assessment (see 7.3.2)
- McGill short Pain Questionnaire (see 7.3.3.)
- Employment status (yes/no)
- Incidence of stump pain (differentiated into somatic, CRPS-like, neuroma (see 7.3.4.)
- Incidence of pre-amputation pain: duration (days, weeks, months, years), frequency of pain (daily, weekly, monthly, constant pain), duration of pain attacks (seconds, minutes, hours)
- Vascular preoperative status (occlusion of 1) aortoiliacal 2) femoropopliteal 3) combination of both arteries, see 7.3.5)
- SIGAM mobility scale (see 7.3.6)
- Inventarization of rehabilitation methods applied during follow-up (behavioural therapy, physiotherapy, mirror therapy)
- Inventarization of drugs used to treat phantom limb pain (none, non-opioid analgesics, weak opioids, strong opioids, antidepressants, antiepileptics, if strong opioids give daily morphine equivalent)
- Incidence of reamputation and surgical complications (bleeding, infection of surgical site)

**Perioperative secondary endpoints**
- Intensity of postoperative pain and phantom limb pain assessed using the NRS scale twice daily at 08:00 and 20:00 during the first 7 days postoperatively (see 7.3.7.)
- Overall Benefit of Analgesia Score (OBAS), determined daily at 20:00 from the day preceding surgery, until 7 days postoperatively (see 7.3.7.)
- Global anesthesia variables (type and duration of anesthesia, opiates used perioperatively classified as morphine, (su)fentanyl, remifentanil)
- Recording of surgical handling of nerves / surgical technique modified from Rasmussen and Kehlet (2007):31
  - Duration of surgery (min)
  - Traction on nerve (yes/no)
  - Tourniquet (yes/no)
  - Ligation on nerve (yes/no)
  - Closure of epineurium (yes/no)
  - Two-step surgery (first step: guillotine surgery; second step: definitive closure) (yes/no/duration between steps)
- Time to discharge from hospital
- Blood for analysis of candidate genes linked to development of chronic pain is drawn preoperatively (see 7.3.8)

### 7.1.3 Other study parameters

Data assessed preoperatively: age, gender, height, weight, smoking status, diabetes.
### 7.1.4 Timetable of assessment for primary and secondary endpoints

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Follow up is performed at one and six months within a time window of +/- 1 week, and the follow up at one year within a time window of +/- 1 month.

### 7.2 Randomisation, blinding and treatment allocation

Randomization stratified to anesthetic technique (spinal / general anesthesia) and stratified to center will be performed using a dedicated interface linked to from the study website [www.plata-study.net](http://www.plata-study.net) and constructed by the Clinical Research Unit, AMC, Amsterdam. The code of randomization consists of the prefix “P” designating the PLATA study, a two-letter code for the participating center, and a three-letter code for all eligible patients. Each coordinating center will need to provide two trained researchers. One of them is unblended. He randomizes the patient and prepares the study medications for the patient. The second researcher conducts the
perioperative and postoperative data acquisition, and follow-up. The code of randomization should not be broken during the study. The procedures contained in this protocol are all part of routine clinical practice worldwide. In the case of a SAE, the code of randomization may be broken by logging into the online randomization module. Reasons for breaking of code must be thoroughly documented.

7.3 Study procedures in detail

7.3.1. Impact of Phantom pain on daily life

The impact of phantom pain on the activities of daily life will be assessed using a questionnaire consisting of a numerical rating scale for the pain and interference, followed by detailed assessment of impact upon key areas of life (work, social activities, walking) and rehabilitation (prosthesis use). The latter is significant since about 50% of patients undergoing amputations are prescribed a lower limb prosthesis.

7.3.2. SF-12 quality of life questionnaire

The Short-Form-12 (version 2) questionnaire will be purchased from QualityMetric® and used to determine quality of life after amputation, and will be performed with the patient before surgery, and postoperatively after 1, 6, and 12 months. Completion of the test as text questionnaire will take approximately 3 minutes. This is a validated and extensively used scoring instrument to determine quality of life. The SF-12v2 survey will be completed on paper form with the patient, and data will be transcribed into the electronic database by the local investigator in raw format. Calculation of physical and mental composite health scores will be done using the official licensed computing software for SF-12v2.

7.3.3. McGill short Pain Questionnaire

The short-form McGill Pain Questionnaire (sf MPQ) will be performed with the patient before surgery, and postoperatively at Day 7, and after 1, 6, and 12 months. The relevance of sf MPQ in the description of phantom limb pain has repeatedly been stressed.

7.3.4. Differentiation of stump pain

It will be sought to further distinguish stump pain, if present, according to the criteria proposed by Lindsay et al. into somatic pain (sharp wound pain), CRPS-like pain (continuous burning pain) and neuroma pain (paroxysmal electrifying pain attacks).
This will be done by interview, and will include a NRS value assigned to stump pain, and inventarisation of drugs taken to specifically treat stump pain.

### 7.3.5. Preoperative vascular status

Chart review will be performed to assess the status of aortoiliacal and/or femoropopliteal occlusion (determined by conventional angiography, MRA, CTA or duplex scanning or sonography according to local center protocols).

### 7.3.6. SIGAM mobility score

The score devised by the Special Interest Group on Amputation Medicine (SIGAM) is an algorithm-based scoring system used to determine progress in rehabilitation specifically in lower-limb amputees. It has been validated in English \(^46\) and Dutch \(^43\) in this specific patient collective and consists of a series of questions to assign the patient to any of the following 6 stages of rehabilitation:

- **Class A**: Wears no prosthesis, or prosthesis used for cosmetic purposes
- **Class B**: Wears prosthesis only to assist nursing or therapy
- **Class C**: Walks on level ground (subgroups used to designate walking aids) but not more than 50m
- **Class D**: Walks more than 50m (subgroups used to designate walking aids)
- **Class E**: Walks more than 50m, mostly without walking aids
- **Class F**: Full rehabilitation, normal or near normal walking pattern.

A process for validation of translation in other languages will be organized for participating centers using other languages by the European Society of Anaesthesiology.

### 7.3.7. Overall benefit of analgesia score (OBAS) and NRS score

The OBAS score is a multi-dimensional quality assessment instrument which goes beyond simple measurement of Numerical Rating Scale (NRS) ciphers to assess the relationship and balance between efficacy of pain treatment, side-effects, and patient satisfaction. The OBAS score ranges from “0” (indicating a satisfied patient with minimal pain and no side-effects) to “24” (indicating a patient in severe pain with maximum side-effects and dissatisfaction). In analogy to the NRS system, a reduction in OBAS (corresponding to improvement of symptoms) by 20% will be considered clinically relevant.\(^39\) Multi-dimensional assessment of pain will significantly increase in use and relevance.\(^39\)
Conventional pain scores assessed by NRS will be taken twice daily in rest and motion, at 08:00 and 20:00.

7.3.8. Genetic analysis
Before surgery, at preoperative lab testing, 10 mL of whole blood will be drawn for genetic analysis. Blood must be stored in a -80°C freezer at the participating center. Blood samples will be labeled with the study name (PLATA) and study patient I.D., and no direct patient details such as name or date of birth will be kept on the blood samples. After study enrollment is finished, all samples will be shipped by the local sites to the Chief Investigator in Amsterdam in one single shipment. The Chief Investigator will ship all samples to the Children's Hospital Boston (Research Core) for analysis. Analysis takes place only after conclusion of the trial, no information regarding outcome of testing is reported to patients or to individual investigating sites, and all remaining materials are immediately discarded after analysis.

Individual SNP analysis
Individual SNPs are genotyped using the 50 nuclease method, and SNP identities assigned relative to the National Center for Biotechnology Information SNP database. The polymerase chain reaction mixture consists of 2.5 mL Master Mixture (Applied Biosystems, Carlsbad, CA, USA), 100 nM detection probe for each allele, 900 nM forward and 900 nM reverse amplification primers, and 20 ng genomic DNA in a total reaction volume of 25 mL. Amplification and detection are performed with an ABI Prism 7700 Sequence Detection System (Applied Biosystems). Allele-specific signals are distinguished by measuring end point 6-FAM (carboxyfluorescein) or VIC (4,7,20-trichloro-70-phenyl-6-carboxyfluorescein) fluorescence intensities at 508 and 560 nm, respectively; and genotypes are generated using Sequence Detection System Software, version 1.7 (Applied Biosystems). The genotyping error rate using these methods has been determined directly by re-genotyping 25% of the samples, randomly chosen. The overall error rate was previously determined to be less than 0.5%.

Analysis of blood samples will take place after the last patient has been enrolled and all samples received. The following four genes involved in the transition from acute to chronic pain will be analyzed:
- GCH1 (GTP cyclohydroxylase I)
- Na\textsubscript{v}1.7 (sodium channel alpha subunit)
- KCNS1 (voltage-gated potassium channel)
- P2RX7 (purinergic ionotropic receptor)

The field of genetics with regards to chronic pain is rapidly evolving. To this list will be added haplotypes or expression analysis of genes that will have been found to be strongly linked to the transition from acute to chronic pain when enrollment is finished (i.e. in 2 to 2.5 years). Any specimens or fractions thereof not used for analysis will be immediately discarded after testing. Genes unrelated to the transition from acute to chronic pain will not be analyzed, and gene-wide analysis will not be done.

7.3.9. Ultrasound-guided sciatic nerve block

The sciatic nerve is visualized at the thigh, between the gluteal crease and the popliteal fossa according to local protocol. Correct localization of the nerve is confirmed by spread of 5 mL of solution around the nerve, or visualization of the ultrasound catheter if applicable. The catheter is inserted 3 - 5 cm beyond skin-nerve distance. The catheter is checked daily for dislocation and signs of infection daily, and left in place for one week postoperatively. Verification of catheter position is done by ultrasound and can be direct in case of echogenic catheters, or indirect by demonstrating fluid spread next to the sciatic nerve when saline solution is injected via the catheter under sterile conditions. If the catheter is found to be dislodged it is the preference to reinsert and document this in the eCRF. Ultrasound pictures of the catheter near the sciatic nerve are taken at insertion, and on postoperative day 3 and 7. An entry in the eCRF will assess whether the catheter was found to be in the correct position. If possible, these pictures are sent to the Study Steering Committee and later assessed in a blinded manner by two experienced ultrasound users (M.F. Stevens, J.T. Wegener, AMC Amsterdam) to validate correct catheter position. This information will also be forwarded to the DSMB.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

7.5 Replacement of individual subjects after withdrawal

The protocol followed is intention-to-treat. A drop-out of 18 % is anticipated. Data of patients is recorded until drop out.
7.6 Follow-up of subjects withdrawn from treatment

The reasons for withdrawal will be accurately documented in the case report forms. If serious adverse events occur or other adverse events lead to withdrawal, the volunteer will be treated according to good medical practice and will be closely monitored until recovery.

7.7 Premature termination of study

Interim analysis will be done after 200 patients have been included (equally distributed across treatment groups by block randomization) in the perioperative phase (one week postoperatively). Data from 200 patients will be extracted from the database for formal interim analysis. AE and SAE will be determined, and DSMB is requested to judge data quality and patient safety. Data monitoring will be instituted and results of this monitoring will be forwarded to the DSMB. If a risk endangering patients is found study will be terminated prematurely.
8. SAFETY REPORTING

8.1 Obligation to report
Referring to section 10, subsection 1, of the WMO, the Chief Investigator will inform the subjects and the reviewing accredited IRB should it become obvious that the risks of participation were greater than foreseen in the research proposal. In this case, the study will be suspended pending further review by the accredited IRB. The Chief investigator will distribute information to all relevant subjects, and to all local investigators.

8.2 Adverse and serious adverse events
Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. Uniform reporting of SAE's / SUSAR's will be via ToetsingOnline.

A serious adverse event is any untoward medical occurrence or effect that at any dose:
- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported to the approving IRB, and to the Sponsor.

8.2.1. Suspected Unexpected Serious Adverse Reactions (SUSAR)
Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.
Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator’s Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).
The sponsor (Chief Investigator on behalf of the Academic Medical Center, University of Amsterdam, The Netherlands) will report SUSARs immediately to the IRB.

The SUSARs are collected by the Chief Investigator and DSMB and recorded in an overview list (line-listing) that will be supplied to all local investigators once every half year for submission to their respective IRB. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

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

It is the obligation of every local investigator to report serious adverse events directly to the Study Chief Investigator, who will act as Serious Adverse Events (SAE) manager. All adverse events must be reported from individual centers to the Chief Investigator within 7 days. Reports need to be filed in written form using the form included in the Case Report Form.

8.2.2. Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will provide his IRB and all local investigators, once a year following first patient enrolment until last patient visit for follow-up, with a safety report to be submitted to the local accredited IRB.

This safety report consists of:

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

8.3. Follow-up of adverse events

All adverse events will be followed until they have resolved, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
8.4. Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board will be implemented, for details see enclosed DSMB charter (Appendix 6).

The DSMB will be composed of three persons: Dr. Marcel Dijkgraaf (methodologist), Drs. Fabian Kooij (clinician), and Dr. Jan Vrancken (clinician). Dr. Fabian Kooij will be designated as contact person / chairman. The DSMB will meet once before enrolment of patients to become familiarized with protocols and procedures. After enrolment has been started, it will meet first for the safety evaluation after 50 patients have been included in the study (expected after approximately 4-6 months). Subsequently, the DSMB will meet every 6 months. All AE reported will be forwarded to the DSMB for evaluation. All reports of SAE will be forwarded to the DSMB contact person / chairman. All unexpected and possibly related events will be reported to the DSMB. This may include, but is not limited to, side-effects of regional blockade such as neuropathy, and accidental intravascular injection of local anesthetic known from routine clinical practice.

Randomization will be performed in two blocks of 200 patients. Due to the long follow-up, of one year, only acute perioperative outcome variables will be analyzed (perioperative pain scores, adverse events) during interim analysis. The justifications for a recommendation to terminate the study due to clear harm will be based on data showing a notably increase of (serious) adverse events in the intervention group. The justifications for a recommendation to terminate the study due to clear benefit will be based on pre-specified stopping boundaries for the primary endpoint of the study. Specifically, if clinical practice suggests clear benefit of one treatment over the other treatment, the DSMB may decide to consider early termination of the trial as soon as the follow-up of at least one-third of all patients has been completed. If such decision is made, the Haybittle-Peto stopping rule (see 9. Statistical analysis) will be applied. All investigational medicinal products eligible to be used in the present study (local anesthetics such as bupivacaine, levobupivacaine, ropivacaine) have been in clinical use for decades, and are not suspected of causing harm to study patients in the dose proposed in the protocol. The intervention (sciatic nerve block) has similarly been standard of anesthetic care for decades and is considered routine clinical care, even though its efficacy in preventing chronic pain after amputation has not been studied appropriately. Study recruitment will last for approximately 2 years, with follow-up time-points after 1 and 6 months and 1 year.

8.5. Monitoring

Monitoring of this study will be performed.

Monitoring is proposed based on a low-risk study design. All PLATA interventions are part of routine practice and we include only centers where these procedures
have been implemented into standardized care of patients undergoing amputations.

Monitoring will include one visit before study initiation at each participating center, and one visit per year for the duration of the study, followed by one closing visit. The amount of data checked will be in analogy with Dutch GCP regulations, including on-site source data verification (see Appendix 7). All investigators will permit and facilitate trial-related monitoring, audit 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 DSMB and the Chief Investigator and copy will be provided to the local investigators.

The Chief Investigator, the Steering Committee, and all local investigators commit themselves to facilitating any inspections and monitoring, including Monitors, Auditors, IRB review, and Regulatory review.
9. STATISTICAL ANALYSIS

This is a randomized, triple-blind, controlled, multi-center trial comparing optimized pain control versus optimized pain control plus nerve block. Patients will be randomized into two treatment groups (n=200 each):

1. Optimized intravenous treatment (control group)
   This group will receive optimized intravenous treatment from the timepoint of surgery until one week postoperatively.
   The sciatic nerve block will be placed on the day of surgery, and started using 20 mL saline 0.9%, followed by continuous infusion of saline at 10 mL/h preoperatively.

2. Optimized intravenous treatment plus regional anesthesia (experimental group)
   This group will receive optimized intravenous treatment from the timepoint of surgery until one week postoperatively.
   The sciatic nerve block will be placed on the day of surgery, and started with 20 mL bupivacaine 0.25%, followed by continuous infusion of bupivacaine 0.125% at 10 mL/h intra- and postoperatively.

9.1. Analysis Populations
Statistical analysis for efficacy and safety will be performed according to the intention-to-treat principle (ITT). The ITT population consists of all randomised patients who received at least one dose of study medication in either the control or experimental group. Additional secondary analyses will be performed on a per protocol basis. The per-protocol (PP) population consists of all patients who have a valid assessment of the primary endpoint of the study that is the point prevalence of chronic phantom limb pain at 12 months.

9.2. Efficacy Analysis
The primary efficacy variable is the point prevalence of chronic phantom limb pain at 12 months. This variable is categorical (yes/no) and will be presented for both treatment groups as proportions (π) together with 95% confidence intervals. A two sided Pearson’s chi-square test will be applied to test the following hypothesis:

Null hypothesis $H_0$: $\pi_{\text{experimental group}} = \pi_{\text{control group}}$

Alternative hypothesis $H_1$: $\pi_{\text{experimental group}} \neq \pi_{\text{control group}}$

Logistic regression analyses will be performed to assess the effect of potential influential variables such as SNP polymorphisms, pre-amputation pain, and surgical technique.
9.3. Safety and secondary analysis

All secondary and safety parameters will be summarised using descriptive statistics, i.e. number (%) of patients for categorical variables and mean, SD (standard deviation), median, minimum/maximum for continuous variables. Descriptive statistics will be produced by treatment group. No formal hypothesis testing will be performed. Appropriate statistical tests will be applied in an explorative manner only.

Analysis of variance or Kruskal-Wallis test will be used to analyse variables such as postoperative pain scores (static and dynamic) or OBAS score. The Kaplan-Meier method will be used to analyse variables such as total analgesic consumption, or time to discharge from hospital. Kappa statistics will be calculated for comparison between the two investigators assessing ultrasound pictures verifying correct catheter position.

If clinical practice suggests clear benefit of one treatment over the other treatment, the DSMB may decide to consider early termination of the trial as soon as the follow-up of at least one-third of all patients has been completed. If such decision is made, the Haybittle-Peto stopping rule will be applied; meaning the termination of the trial will be performed when the \( P \) at interim analysis is < 0.001. Final analysis will still be performed using a \( P \) cutoff value of < 0.05.

9.4. Statistical and Analytical Issues

Handling of Missing Data

Last observation carried forward (LOCF) procedure will be applied in case of withdrawals. For the ITT analysis, incidence of phantom limb pain at 7 days, 1, and 6 months will be carried forward to 1 year in case the (1-year) observation is missing.

Analysis

Formal interim analysis will be performed after 200 patients have completed the perioperative phase (1 week postoperatively). The statistical analysis will be performed after termination of the clinical trial and will be discussed in the clinical trial report. Any deviations from the original statistical plan will be reported in end reports and / or publications. Interim analyses of the acute postoperative phase will be performed for the DSMB to assess safety of the study after the first 50 patients have been followed through the first week after amputation, and every six months thereafter.
9.5. Methods to reduce bias
To reduce bias, patients will be randomized into two experimental groups. Randomization is performed using a separate online randomization portal (ALEA, https://nl.tenalea.net/amc/ALEA), accessible via the Trial website (www.plata-study.net). All patients will receive a two-digit institution code followed by a three-digit patient ID number. All eligible patients screened will be registered, as will all patients fulfilling inclusion and exclusion criteria to meet CONSORT requirements. Further, the anesthesiologist performing peripheral nerve block will be blinded, and all investigators assessing the patient after the intervention to group allocation.

9.6. Source data
There are certain data which are entered directly into the CRF, and which are considered source data. These are the data obtained in the peri- and postoperative questionnaires and described in paragraphs 7.1.1. and 7.1.2. with the exception of the visual analogue scale pain score (if regularly recorded on the ward). Demographic variables are sourced in the original patient file, as are details of surgical and anesthetic procedure, and times of surgery, anesthesia, and discharge.
10. ETHICAL CONSIDERATIONS

10.1. Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki in the current version of Seoul, Korea (2008), and in analogy with the Dutch Medical Research Involving Human Subjects Act. Data collection and analysis will be done according to ICH–GCP guidelines. This protocol must be approved by the respective Regulatory Authorities and Ethics Committees of the participating Clinical Trial Network Site prior to the start of inclusion of patients. Respective documents have to be forwarded to the Research Department at the European Society of Anaesthesiology prior to recruitment of the first patient.

10.2. Recruitment and consent

Volunteers will be recruited at the participating centers after pre-operative visit with the anesthesia department. A physician not related to the treating surgeon will inform at least 24 hours before start of any intervention all volunteers about the nature, relevance and consequences of the study in their own language; volunteers have to give their written informed consent to participate in the study in a form in the patient's own language. Additionally they will receive written study information. Informed consent form and written information must be approved by the respective Ethics Committee. Templates are attached in Appendix 2A (Patient Information Sheet) and 2B (Informed Consent Form).

10.3. Objection by minors or incapacitated subjects

Not applicable. Incapacitated subjects (not able to give written and informed consent) will not be recruited into this study.

10.4. Benefits and risks assessment, group relatedness

For all patients, taking part in this study results in a thorough and continuous evaluation and strict treatment of perioperative pain. This kind of intensive pain therapy is often not offered to patients because of uncertainties in literature over how best to treat patients with phantom limb pain.\textsuperscript{12,13} So, every patient enrolled benefits from receiving the state-of-the-art treatment.

The possible benefit of adding regional anesthesia to optimized pain treatment means that improved perioperative pain treatment, and decreased incidence of Phantom limb pain after 12 months is expected in the intervention group. For patients in the control group, the sciatic catheter poses little risk, as it is inserted under ultrasound guidance.
Even though there is beginning evidence to suggest benefits of this strict pain control, many patients worldwide do not receive this kind of standardized pain treatment. Another consideration is whether retrospective analysis could yield the same information, without subjecting patients to any test protocol. However, the numbers of patients operated upon in a single center is small, and protocols change frequently. Therefore, even if many institutions contributed to a retrospective pooling of patients, this would imply an enormous heterogeneity in treatment protocols, and definitions of outcome. Moreover, many of the parameters which are considered very relevant in modern evidence-based medicine, such as quality of life, are not routinely performed in most institutions. Finally, the evidence-based impact of retrospective trials is far smaller than that of a properly organized and well-controlled randomized trial. This proposed prospective trial devised as a gold-standard RCT has the potential to immediately shape the treatment of patients undergoing amputation surgery for years to come.

Peripheral nerve blockade has come to be accepted as common practice by some and has been integrated in clinical protocols at many sites worldwide, but this has happened despite a lack of evidence. Only two case series\(^ {19} \)\(^ {20} \) have described potential benefits of peripheral nerve block, while one very small randomized study with many methodological weaknesses refuted any benefit.\(^ {21} \) Therefore, the patients in the control group are not withheld an evidence-based intervention, rather they profit from optimized intravenous treatment.

In conclusion, it is conceivable that some aspects of the current trial could be attained in a retrospective study, but the evidence-based impact of a randomized controlled trial is magnitudes higher and has the potential to directly influence patient care. The benefits of this study for all participating patients are a very good and thorough pain evaluation and control using the best available intravenous combination of medications, and, for the patients in the intervention group, the potential of added benefit using a peripheral nerve block.

10.5. Compensation for injury
Pending respective considerations by the applicable local Ethics Review Board, the local investigator is obliged to ensure patient insurance providing cover for damage to research subjects through injury or death caused by the study. Respective documentation needs to be forwarded to the Research Department at the European Society of Anaesthesiology prior to recruitment of the first patient. For the Academic Medical Center as lead Ethics Review Board for The Netherlands, the obligation to provide insurance to participants has been waived on grounds of negligible risk.
10.6. Incentives to patients
Not applicable.

10.7. Incentives to local investigators
There are no personal incentives to local investigators. The Steering Committee will negotiate lump sums to cover GCP hospital pharmacy costs (local protocols on study drug preparation). If necessary, the Sponsor will defray costs for patient insurance upon receipt.
11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1. Handling and storage of data and documents
Data entries will be made on a paper version of the CRF. These are later transferred to an electronic Case Report Forms (eCRF). All changes or addition to the data are tracked by the data management system in the audit trail. Access to data entry system and eCRF is managed by the Research Department of the European Society of Anaesthesiology and protected by a personalized user name and password.

The investigator will be responsible for ensuring that all the questions on the eCRF are answered fully. If certain data are not available, not done or not applicable, this will be marked on the eCRF in appropriate spaces. The 24-hour clock will be used for all time entries (00:00 – 23:59).

The investigators are mandated to enter the data from the paper CRF into the eCRF within one week after patient discharge from the hospital, and directly following each follow up visit.

Correctness of entries will be checked by plausibility testing. The database will be hosted by the European Society of Anaesthesiology.

The local investigator will keep a record of the full names and addresses of the patients, and a copy of the signed informed consent form, which must be able to uniquely identify a volunteer, and the corresponding study subject I.D., as well as forms relating to the GCP-conform preparation of study drugs. The original signed informed consent form and CRF together with GCP documents (drug handling protocol, drug accountability tracking form) are stored behind a lock in each study site for the duration of this trial and according to local laws following the completion of the trial.

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

11.3. Annual progress report
The Chief Investigator on behalf of the Sponsor will submit a yearly summary of the progress of the trial to the accredited IRB of the Academic Medical Center / University of Amsterdam summarizing all participating sites. This report will be made available to all local investigators for submission to their respective IRB. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions,
other problems, and amendments. Reports will be issued on a yearly basis after first visit by first patient, until last follow-up visit by last patient.

11.4. End of study report
The Chief investigator will notify the accredited IRB of the end of the study (last visit of subject for follow-up) within a period of 90 days. The end of the study is defined as the last patient’s last visit. Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited IRB. The summary report will be made available to the local investigators to inform their respective IRB’s.

11.5. Public disclosure and publication policy
Data will be stored using ALEA™ its software system for data collection and data management. This service will be provided by FormsVision B.V. who will liaise with European Society of Anaesthesiology. ESA will communicate the data to the Steering Committee on behalf of the Sponsor (Academic Medical Center, University of Amsterdam, The Netherlands). The Steering Committee has the right to use all pooled data for scientific and other purposes. The Steering Committee and the Sponsor retain intellectual property of stored data. Local investigators contributing to PLATA will have access to pooled data via the Steering Committee upon provision of a detailed research proposal. Proposals of secondary analysis are encouraged and will be administrated via the Steering Committee. After end of the study and statistical report, the results will be forwarded to the ESA Research Committee. The Steering Committee must approve publication of all manuscripts related to the data acquired during the PLATA study. Individual patient data provided by participating centers remain the property of the provider.

The results of this study will be published in a peer-reviewed medical journal. Preparation of the manuscript will be done by the Steering committee on behalf of the PLATA investigators. In the list of investigators, one investigator per center recruiting more than 5 patients will be listed, two for each center recruiting more than 10 patients, and three investigators for each center recruiting more than 20 patients. The ESA will be acknowledged in publications and presentations arising from the published work.
11.6. Logbook

Every study site is mandated to keep up to date a logbook of all persons actively involved in the study, for tasks of randomization, patient assessment, or drug preparation, containing name, training, date of first participation, and signature.
LIST OF APPENDICES
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