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PERINEURAL LOCAL ANAESTHETIC CATHETER AFTER MAJOR LOWER LIMB AMPUTATION TRIAL (PLACEMENT)

A phase III clinical trial examining the use of perineural catheters after major lower limb amputation in adults with critical limb ischaemia

CLINICAL TRIAL PROTOCOL

VERSION: 2.0

DATE: 22.01.2024

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

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Director:			
Name **Dr David Gillespie**	**Signature** **Approved by email**	**Date** **19th Feb 2024**	
Chief Investigator:			
Name **Mr David Bosanquet**	**Signature** **Approved by email**	**Date** **19th Feb 2024**	

General Information This protocol describes the PLACEMENT clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

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Trial Co-ordination:

The PLACEMENT trial is being coordinated by the Centre for Trials Research (CTR) Cardiff University, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the PLACEMENT Trial Management Group (TMG).

For **all queries,** please contact the PLACEMENT team through the main trial email address. Any clinical queries will be directed through the Trial Manager (TM) to either the Chief Investigator (CI) or a co-Investigators.

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Randomisation

To randomise a participant visit the PLACEMENT trial database (www.placement2.ctr.cardiff.ac.uk)

or call 02920 687418 from Monday to Friday between 9am-5pm.

(See Section 9.5 for more details).

Clinical queries

placement-trial@cardiff.ac.uk

All clinical queries will be directed to the most appropriate clinical person.

SAE reporting

Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to the Centre for Trials Research Safety Team within 24 hours of becoming aware of the event (See Section 13 for more details).

Contact details: CTR-Safety@Cardiff.ac.uk

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Glossary of abbreviations

AE	Adverse Event
AKA	Above Knee Amputation
AR	Adverse Reaction
BKA	Below Knee Amputation
CA	Competent Authority
CDC	Centres for Disease Control and Prevention
CHI	Community Health Index
CI	Chief Investigator
COVID-19	Coronavirus
CRF	Case Report Form
CRO	Contract Research Organisation
CSRI	Client Service Receipt Inventory
CTA	Clinical Trials Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
DAOH-90	Days alive and out of hospital at 90 days
DH	Department of Health
DM	Data Manager
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EQ-5D-5L	EuroQol-5 Dimension-5 level descriptive system and visual analogue scale

EudraCT	European Clinical Trials Database
GA	General Anaesthetic
GCP	Good Clinical Practice
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HADS	Hospital Anxiety and Depression Scale
HCP	Healthcare Professional
HE	Health Economics
HRA	Health Research Authority
HSCIC	Health and Social Care Information Centre
HTA	Health Technology Assessment
IB	Investigator Brochure
IC	Informed Consent
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IFU	Instructions For Use
IMP	Investigational Medicinal Product
INMB	Incremental net monetary benefit
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IV	Intravenous

MA	Marketing Authorisation
MHRA	Medicine and Healthcare products Regulatory Agency
MLLA	Major Lower Limb Amputation
MRC	Medical Research Council
NCT	National Clinical Trial
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NRS	Numeric Rating Scale
OR	Odds Ratio
PAD	Peripheral Vascular Disease
PI	Principal Investigator
PIL	Participant Information Leaflet
PNC	Perineural Catheter
PPI	Patient and Public Involvement
PRO	Patient Reported Outcome
PWC	Peripheral Wound Catheter
QALY	Quality-adjusted Life Years
QoL	Quality of Life
QRF	Questionnaire Report Form
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SIGAM	Special Interest Group in Amputee Medicine
SMD	Standardised Mean Difference
SmPC	Summary Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA	Trial Administrator
TKA	Through Knee Amputation
TL	Trial Lead
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TS	Trial Statistician
TSF	Trial Site File
TSC	Trial Steering Committee
UK	United Kingdom
USM	Urgent Safety Measures

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No. *(substantial/non-substantial)*	**Protocol version no.**	**Date issued**	**Summary of changes made since previous version**
N/A			First version
1	1.1	14/07/2023	The following amendments have been made in response to MHRA feedback: - The exclusion criteria have been updated to include breastfeeding (pages 16, 30) - The Clinical Trial Facilitation Group definition of childbearing potential has been added (page 30) - The inclusion criteria have been updated to include "(For male participants with female sexual partners who are considered to be of childbearing potential) Willing to agree to use a condom or abstain from sexual intercourse for seven days after MLLA" (page 16, 30) - Review of a pre-operative pregnancy test result has been added to definitely rule out pregnancy (pages 46, 51) - Liver and renal function tests have been added to the "Pre-operative routinely collected blood results" to detect patients with hepatic impairment for whom IMP dose modification may be required (pages 46, 50) - Review of a pre-operative resting 12-lead ECG has been added to establish any undiagnosed heart block and/or cardiac conduction abnormalities in patients for whom IMP dose modification may be required (pages 46, 51) The following amendments have been made in response to REC feedback:

			- Details of HCP consent procedure for optional qualitative interviews added (page 37, 62) - Site staff to check participants' vital status before follow up contacts attempts are made added (page 62) - Section 16.4 (Data collection, use sharing, security and integrity) added (page 79 - 80) The following administrative changes have been made: - REC number added (page 1) - CTR staff details updated (pages 3 – 4) - Wording of 'Up to 5 days' changed to 'First 5 postoperative days' (pages 18, 24, 27 – 29) - Wording of 'by the 5th postoperative day' changed to 'on the 5th postoperative day, unless earlier removal is required (page 25) - 'Returned copy of the Self-Evident correction log signed by the PI' removed (page 29) - Withdrawal of consent options expanded (page 37-38) - Typo corrected ('avoid' changed to 'advise') (page 42) - Recording elastomeric ball pump make and model and volume of drug in ball prior to commencement of infusion if participant in intervention arm removed (page 46, 54) - 'Cigarette use' changed to 'Smoking History'; 'BMI' changed to 'weight' and 'Postoperative 5 days' changed to 'First 5 postoperative days' (Table 2 – page 49) - Secondary outcomes clarified at 3 and 6-month follow-up (page 57, Table 2 – page 49 and Table 8 – page 73) - Table 6 updated with correct CTCAE terminology (page 64 – 65) - Link to CTCAE V5.0 added (page 67)

			- 'CTR will code events using MedDRA Version 26.0' added (page 67) - Details of yellow card scheme for reporting AEs (if applicable) added (page 69) - Figure 1 Adverse event reporting flow chart added (page 74) - Details added to Qualitative analysis (section 15.2, page 76) - 'Site staff will only have access to their own participants and not see other sites' participants' added to page 78 - 'or if research staff are unavailable e.g. over the weekend' added (page 78) - 'and update the necessary data within the database' added (page 79) - 'PLACEMENT Trial Database guidance and PLACEMENT Trial Manual' changed to 'PLACEMENT Site Manual' (page 79) - 'Optional' and 'gender, date of birth' added to collection of NHS number (section 21.3, page 83)
2	2.0	04/01/2024	- Inclusion criteria have been expanded to include participants undergoing MLLA for acute or chronic infection - Exclusion criteria have been clarified to allow participants undergoing guillotine amputation - Participant Information Sheet (PIS) changed to Participant Information Leaflet (PIL) - Eighth lead site (Cambridge) added to internal pilot - Section 7: 'A copy of the most recent Pregnancy Information Leaflet(s) and Consent Form(s) on host care organisation headed paper' added to document list - Section 9.2: Updated to include clarification about patients undergoing a Guillotine amputation - Section 11.4 Minimum dose/range removed from IMP

			- Section 11.7: Clarification added to prohibited medications and interaction with other drugs - Section 13.8.1: Clarification of pregnancy information relating to levobupivacaine, ropivacaine and bupivacaine hydrochloride - Section 26: Addition of PrinciPIL study within a trial (SWAT) 89 Appendices 1 - 3: Updated SmPcs for IMPs

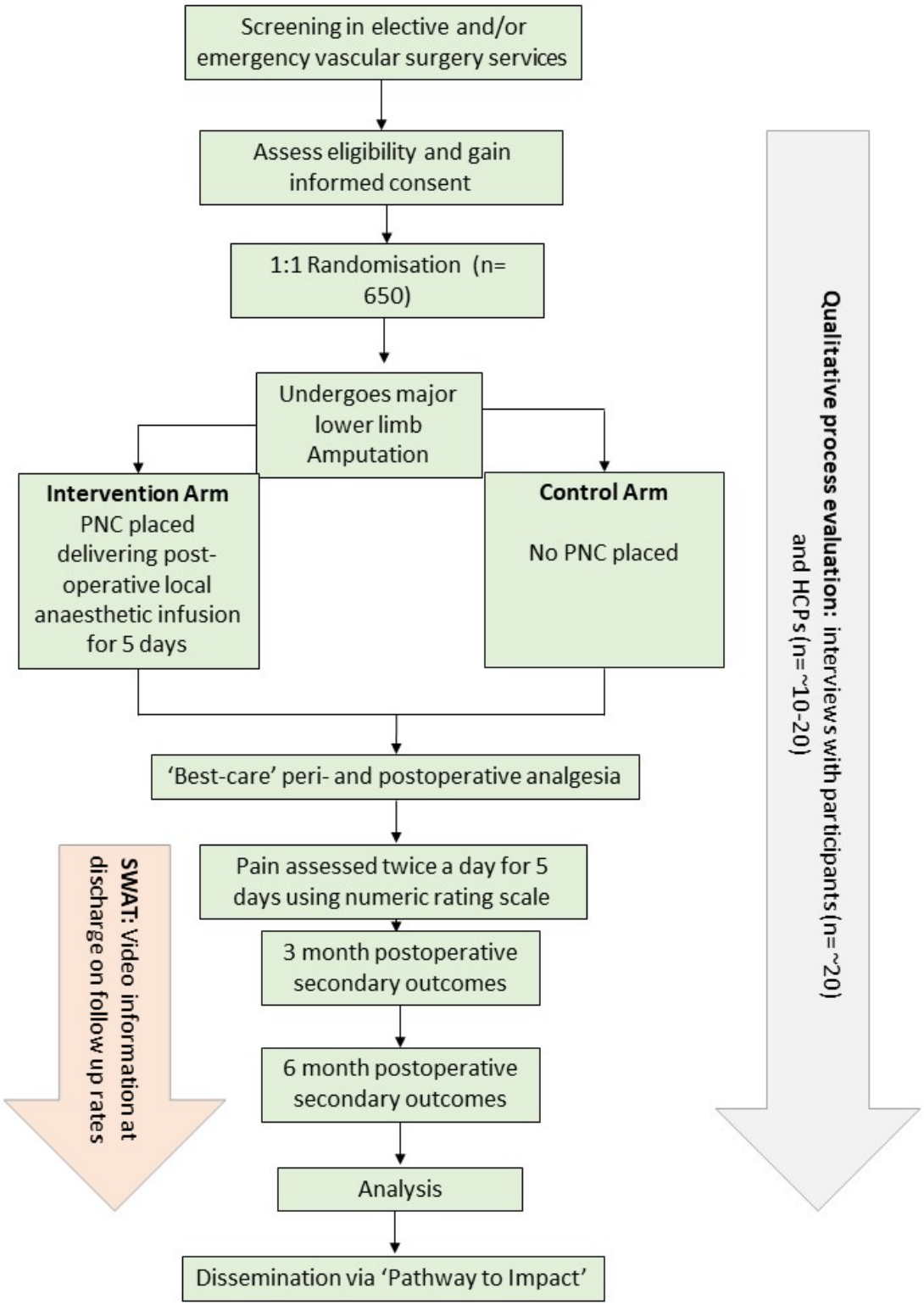
2 Synopsis

Short title	Perineural Local Anaesthetic Catheter aftEr Major lowEr limb amputatioN Trial
Acronym	PLACEMENT
Internal ref. no.	965
Clinical phase	III
Funder and ref.	NIHR HTA Programme (134746)
Trial design	Pragmatic, open-label two-arm individually randomised controlled trial (RCT)
Trial participants	Adults undergoing major lower limb amputation (MLLA) [above knee amputation (AKA), through knee amputation (TKA) or below knee amputation (BKA)] for complications of peripheral arterial disease (PAD) and/or diabetes
Planned sample size	650
Planned number of sites	~14 (internal pilot undertaken in eight centres)
Inclusion criteria	1. Aged 18 years or older 2. Undergoing elective or emergency MLLA (BKA, TKA, or AKA) for complications of PAD, diabetes and/or acute or chronic infection 3. Able to assess pain using NRS 4. Life expectancy of greater than two weeks 5. (For people of childbearing potential) Willing to undergo a preoperative pregnancy test and agree to either use a highly effective method of contraception or abstain from sexual intercourse for seven days after MLLA 6. (For male participants with female sexual partners who are considered to be of childbearing potential) Willing to agree to use a condom or abstain from sexual intercourse for seven days after MLLA
Exclusion criteria	1 Undergoing MLLA for trauma or cancer 2 Undergoing digital, metatarsal, tarsal amputation, disarticulation of the hip or hindquarter amputation 3 Undergoing simultaneous bilateral amputations 4 Undergoing MLLA revision (excluding previous guillotine amputation) 5 Allergy or intolerance to the perineural catheter (PNC) or local anaesthetic agents, or chronically taking class 1B antiarrhythmic agents or local anaesthetic agents, for example in the form of transdermal patches 6 Expected to be sedated for more than 24 hours postoperatively 7 Unable to provide consent due to incapacity (as defined by the Mental Capacity Act 2005) 8 Vulnerable or protected adults 9 Persons who are currently pregnant or breastfeeding 10 Previously enrolled in PLACEMENT (excluding Feasibility trial) for a prior MLLA
Treatment duration	Up to five days
Follow-up duration	Six months
Planned trial period	1st September 2022 to 31st March 2026

Primary objective	To compare pain in participants undergoing MLLA randomised to PNC placement with participants not randomised to PNC placement, captured by twice daily pain scores for the first five postoperative days following MLLA.
Secondary objectives	To evaluate the effect of PNC use on opioid usage and complications, and longer-term outcomes on pain, Health-Related Quality of Life (QoL), cost and ambulation rates.
Primary outcomes	'Freedom from pain,' defined as the proportion of time points with self-reported pain ≤3 on a 0-10 numeric rating scale (NRS), assessed twice a day for the first 5 postoperative days.
Secondary outcomes	(First 5 postoperative days) • Participant satisfaction of pain management (0 – 4 NRS) • Total opioid use, converted to morphine equivalents • Opioid side effects (Frequency and severity of symptoms) (At discharge) • Postoperative complications rate and severity (Clavien-Dindo grading) (At 30 days) • Surgical site infection (At 90 days) • Hospital stays, including re-admissions after discharge, used to calculate Days Alive and Out of Hospital at 90 days (DAOH-90) (At 3 to 6 months) • Phantom limb pain at 6 months (NRS) • Chronic stump pain at 6 months (NRS) • Residual limb surgery (revision or debridement) • Delayed wound healing (absence of complete epithelialisation of the wound) • Health-Related QoL (EQ-5D-5L) • Depression (Hospital Anxiety and Depression Scale (HADS) • Time to achieve prosthesis fitting (if applicable) • Level of independence (SIGAM) • MLLA of contralateral limb (for unilateral amputees) • Healthcare resource use at 6 months • Cost effectiveness • Mortality at 6 months
Investigational medicinal products	Levobupivacaine hydrochloride Ropivacaine hydrochloride Bupivacaine hydrochloride
Form	Solution
Dose	Levobupivacaine hydrochloride (maximum 400mg per 24 hours) Ropivacaine hydrochloride (maximum 800mg per 24 hours) Bupivacaine hydrochloride (maximum 400mg per 24 hours)
Route	Local anaesthetic delivered to the perineural space by a PNC placed at the time of amputation

3 Trial Summary and Schema

3.1 Trial Schema and Participant Flow Diagram



3.2 Trial Lay Summary

THE PROBLEM: Having a leg amputation is a life changing event. About 10,000 leg amputations are performed in the UK every year. Leg amputations are often very painful, both straight after surgery and in the longer term. For example, pain can be felt both in the stump and in the foot which is no longer there. This pain is called 'phantom pain' and may interfere with fitting and using an artificial leg. The pain associated with leg amputations may delay recovery and limit what people can do for the rest of their lives. Morphine is often used to help with this pain. However, morphine has major side effects, including sickness, confusion, and breathing problems.

RESEARCH IMPORTANCE: A group of patients and clinicians from the UK discussed the most important research topics for amputation surgery. Reducing pain after amputation was the fourth most important topic. A UK-wide review (published 2014) showed that only one out of every three patients had the 'best' pain relief after amputation. High quality research looking at how we can reduce pain after leg amputation is urgently needed.

AIMS: This research will test a method for reducing pain after leg amputation. It involves the surgeon placing a tiny tube, called a 'perineural catheter,' next to the main nerve which is cut during surgery. Local anaesthetic is slowly pumped into the tube for five days. Putting the tube in and taking it out are easy and problems are rare. The tube can replace some (or all) of the morphine often needed. The tube may also reduce phantom pain. The research will be a 'randomised' trial. This means patients will be randomly chosen to either have surgery with, or without, the tube. Everything else will be the same. The amount of pain will then be compared between those who did and those who did not have the tube.

WHAT WE HAVE ALREADY DONE: We have already done a small 'feasibility' trial. In this, 49 patients were 'randomised' to either receive the tube, or not. Patients were happy to take part, and the tube was safe and easy to use. Interviews with those taking part helped us design this research. However, that trial was not designed to fully test the use of the tube or if it represents value for money.

WHAT WE ARE PLANNING: This trial called PLACEMENT, will take place in 14 NHS hospitals. 650 patients having an amputation because of blocked arteries and/or diabetes will take part. Half will be randomly chosen by a computer to receive the tube, whilst the other half will not. All will have the

best anaesthetic and pain control medication. The amount of pain, morphine used, painkiller side effects, and surgery complications will be recorded. We will ask about pain and if they are walking on an artificial leg at three and six months after their surgery.

PATIENT AND PUBLIC INVOLVEMENT (PPI): Two members of the public are a central part of our research team. One has had two amputations, one with and one without a tube. Our other member lost her father after an amputation. Both helped us plan and run our 'feasibility' trial and plan this larger trial. We also held a discussion group with amputees. They helped us design this trial by telling us what is important to them about amputation pain. Our PPI group will work with us throughout the trial and prepare a summary of the results.

DISSEMINATION: The findings will be presented at medical conferences, published in free to access medical journals, and shared with people who write amputation surgery guidelines and policies. We will share results via the national press, amputation charities and social media.

4. Background

4.1 Major Lower Limb Amputation and Post Amputation Pain

The number of adults with age-related chronic diseases, including diabetes and peripheral arterial disease (PAD), is increasing globally in the context of an ageing population (1, 2). Similarly, the number of adults who undergo major lower limb amputation (MLLA) due to PAD and/or diabetes in the UK each year is rising (3,4). Between 2017 and 2019, 10,022 cases were submitted to the National Vascular Registry (3), compared with 8,866 between 2014 and 2016 (5). Public Health England data show a similar increase (4). MLLA can be very painful, which significantly impacts on postamputation recovery, ambulation, satisfaction, and QoL (6,7). Therefore, good management of pain relief following MLLA is imperative for favourable short- and long-term patient outcomes, including satisfaction with care, rehabilitation potential, and QoL (8).

Amputees may experience different types of pain, including immediate postoperative pain, chronic stump pain (pain localised to the residual portion of the limb) and phantom limb pain (experienced where the limb was prior to amputation). Postoperative pain is one of three leading contributors to patient dissatisfaction (9), causes significant anxiety (10), and is the main barrier to rehabilitation (11,12). Poorly controlled acute pain post-MLLA is associated with chronic pain (13), exposing patients to the side effects of long-term analgesic use (14,15). These patients are less likely to use a prosthetic limb (16), or if they can, they ambulate shorter distances than those without chronic pain (17). They report a lower QoL, which is inversely correlated to pain severity (18,19). Healthcare resource utilisation is doubled for chronic pain sufferers (19), who require more than double the outpatient and inpatient care compared to those without chronic pain (20). Therefore, the management of postamputation pain is essential for both the short-term recovery and ongoing rehabilitation of amputees. However, determining how to best manage both acute and chronic pain post-amputation pain is not clear, despite numerous studies (21).

Immediate postoperative pain management commonly involves epidural or intravenous (IV) patient-controlled analgesia, which relies on opioid based agents. A recent UK wide National Confidential Enquiry into Patient outcome and Deaths review into lower limb amputations found that strong opioids were the most frequently used type of postoperative analgesia (22). While opioids provide excellent pain relief, they also have many associated side effects, including nausea and vomiting (23), constipation (24), sedation and pruritus (25). Morphine is normally self-administered via a pump, and

therefore the patient experiences pain before self-treating. Tolerance, dependence, and addiction to opioids can occur with prolonged use (26,27). The pharmacokinetics of opioids are altered with increasing age, deteriorating renal function and polypharmacy, all of which are common in people with PAD and/or diabetes, leading to unpredictable adverse drug effects and interactions (28). Furthermore, opioid related side effects are problematic, increasing in-hospital costs by 7 to16% and overall length of stay by approximately 10% (29,30). Acute postoperative opioid use costs £23/day/patient (31).

Given the marked side effects of opioids, the American Society of Anaesthesiologists suggest using multimodal analgesic strategies for managing postoperative pain (32). These include the use of opioid sparing agents (such as nonsteroidal anti-inflammatory drugs, paracetamol, or anticonvulsants) which have been shown to reduce overall inpatient costs compared to opioid analgesia (33). The use of peripheral wound catheters (PWCs) with local anaesthetic infusion is also suggested, where possible. PWCs are thin catheters (epidural catheters are commonly used) that may be placed under direct vision at the time of surgery by the operating surgeon (surgical PWCs), or percutaneously under radiological guidance either pre- or postoperatively (radiological PWCs). Perineural catheters (PNCs) are a specific type of PWC placed adjacent to major nerves, allowing a constant infusion of local anaesthetic directly to the perineural (juxta-neural) space, in addition to the wound locally. Therefore, PNCs may reduce postoperative pain and opioid use (34). In a meta-analysis of randomised controlled trials (RCTs, n = 44, 2141 patients) examining surgical PWCs placed during a variety of surgical procedures, PWC use was associated with a reduction in postoperative pain scores at rest and movement, opioid usage, nausea and vomiting and length of hospital stay, and with an increase in patient satisfaction (35). In general, the risks of PWC use appear low (36) with very low rates of side effects, including infection, occurring with PNC use specifically (37).

4.2 Perineural Catheter use for Amputees

A PNC can be inserted at the time of lower limb amputation. As the tissues are divided, the sciatic nerve (for AKAs) or tibial nerve (for BKAs or TKAs) is identified. An epidural catheter is placed in the perineural space so that its tip lies as far as possible cranially from the amputated end. The catheter end is then removed through the skin away from the wound edge and secured. The overall process takes 5 to 10 minutes (38). It is then attached to a local anaesthetic infusion device which provides continuous infusion of local anaesthetic for the first 5 postoperative days. The PNC is removed on the

ward on the 5th postoperative day, unless earlier removal is required. The process of PNC placement and removal is almost identical to the placement and removal of surgical drains, which are often placed within the wound at the time of an amputation at the discretion of the operating surgeon.

The first use of a PNC for amputees was first described more than three decades ago (38). Malwer et al. (1991) demonstrated PNC usage to be associated with a significant reduction in postoperative opioid use in a series of case studies of upper and lower limb amputations (38). Our 2015 systematic review showed that no high-quality evidence exists regarding PNCs and pain relief in MLLA (39). We published an updated (2021) systematic review, including data from our feasibility trial (40). Ten studies (731 participants) were included; 350 participants receiving a PNC delivering local anaesthetic and 381 receiving no PNC or a PNC with placebo. We also searched ClinicalTrials.gov and the International Clinical Trials Registry Platform, finding no trials currently recruiting participants to a trial evaluating surgically placed PNC in MLLA (last search 10/08/21). Ongoing/future research that will complement PLACEMENT are trials evaluating ultrasound-guided peripheral nerve catheters/blocks preoperatively (41-43).

Our systematic review showed the following:

Acute pain

Meta-analysis of data from four studies; two RCTs (one of which was our feasibility trial) and two observational studies, including 462 participants, demonstrated that PNC use was associated with reduced acute pain (SMD: -0.30, 95% CI: -0.58 to -0.01). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality of evidence was low.

Opioid use

Meta-analysis of data from eight studies; three RCTs (one of which was our feasibility trial) and five observational studies, including 526 participants, demonstrated that PNC use was associated with reduced postoperative morphine use (SMD: -0.63, 95% CI: -1.03 to -0.23). This effect was lost when looking at RCTs only. GRADE quality of evidence was moderate.

In-hospital mortality, phantom pain, and chronic stump pain

In-hospital mortality analysis included 403 participants from four studies, phantom limb pain analysis included 355 participants from five studies, and chronic stump pain analysis included 190 participants from three studies. No difference between PNC use and control was noted on meta-analysis. GRADE quality of evidence was low.

Limitations of the existing evidence

1. Most studies were observational, and only four studies were RCTS, including our feasibility (50)
2. Of the four RCTs, some studies may have been underpowered due to their small sample size (n = 91) and no reported sample size calculation (39)
3. The GRADE assessments for quality of evidence for the reported outcomes were low, except for opioid use (moderate)
4. There is a low volume and poor quality of long-term phantom limb and chronic stump pain outcome data
5. There are no robust data on QoL following PNC use compared to control
6. No RCTs selected outcomes outlined in the Amputation Core Outcome Set (44)
7. No studies examined the cost-effectiveness of PNC usage

The use of PNCs without fully understanding its long-term effects is not without risk. PNCs may theoretically increase the risks of chronic and/or phantom limb pain (45), by direct peripheral nerve injury (including damaging the perineurium and neural vascular supply) (46,47), local anaesthetic toxicity leading to Schwann cell apoptosis and myelin damage (47, 48), and/or increased intraneural pressure leading to neural ischaemia (48). Furthermore, PNC usage involves the time taken to place the catheter, the associated consumables, the local anaesthetic and infusion device, and the additional healthcare professional (HCP) time required to monitor, refill, and remove the PNC. Widespread adoption based on poor quality meta-analysed data is therefore not appropriate and an adequately powered RCT is therefore timely and essential. PNC use varies across the UK, and most HCPs recently surveyed felt they had equipoise to randomise participants to a trial of PNC use (49). Our randomised feasibility trial of PNCs in MLLA, completed ahead of schedule, suggested that using a PNC could be an easy and efficient way to reduce pain, with few side effects (50,51). Furthermore, we found that a full trial is both acceptable to stakeholders and is feasible. However, the clinical and cost-effectiveness of PNCs is unknown (50). We now need to test the clinical and cost-effectiveness of PNCs in an appropriately powered multi-centre randomised trial.

4.3 Rationale for Current Trial/Justification of Treatment Options

The management of pain following amputation is a significant problem for both people undergoing MLLA and HCPs. Pain management following MLLA has been identified as a priority research topic by

patients, carers, and HCPs. In 2015, the 'Anaesthesia and Perioperative Care James Lind Alliance' identified 'What can we do to stop patients developing chronic pain after surgery?' as a top ten research priority (52). In January 2021, 30 patients, carers and HCPs completed a James Lind Alliance Priority Setting process with The Vascular Society Amputation Surgery Special Interest Group (53). Three of the four highest ranking priorities will be addressed by PLACEMENT, including: 'What are the best ways to prevent or treat pain (including phantom pain) after MLLA?;' 'How can we improve clinical outcomes for patients following MLLA?;' and 'What are the best ways to support rehabilitation following MLLA?.'

5 Trial Objectives/Endpoints and Outcome Measures

PLACEMENT aims to evaluate the clinical and cost-effectiveness of a PNC with continuous local anaesthetic infusion, inserted at the time of MLLA, compared to no PNC. The primary aim of PLACEMENT is to evaluate if the use of a PNC with continuous local anaesthetic infusion, inserted at the time of MLLA, impacts on the amount of pain participants experience, compared to no PNC.

5.1 Primary Objectives

Our primary objective is to compare 'freedom from pain' in participants undergoing MLLA randomised to receive PNC placement, with participants undergoing MLLA who are randomised not to receive PNC placement, defined as the proportion of time points with self-reported pain ≤3 on a 0-10 NRS, assessed twice daily for the first five postoperative days.

5.2 Secondary Objectives

Secondary objectives include assessing the effect of PNC use on:

(First 5 postoperative days)

- Participant satisfaction of pain management (4-point Likert scale)
- Total opioid use, converted to morphine equivalents
- Opioid side effects (frequency and severity of symptoms)

(At discharge)

- Postoperative complications rate and severity (Clavien-Dindo grading)

(At 30 days)

- Surgical site infection (Centres for Disease Control and Prevention [CDC] criteria)

(At 90 days)

- Hospital stays, including re-admissions after discharge, used to calculate DAOH-90

(At 3 to 6 months)

- Phantom limb pain (NRS)
- Chronic stump pain (NRS)
- Residual limb surgery (revision or debridement)
- Delayed wound healing (absence of complete epithelialisation of the wound)
- Health-Related QoL (EQ-5D-5L)
- Depression (Hospital Anxiety and Depression Scale (HADS)
- Time to achieve prosthesis fitting (if applicable)
- Level of independence (SIGAM)
- MLLA of contralateral limb (for unilateral amputees)
- Healthcare resource use
- Cost effectiveness
- Mortality

5.3 Primary Outcome Measure

Our primary outcome will be 'freedom from pain' defined as the proportion of time points with self-reported pain ≤3 on a 0-10 NRS, assessed twice daily (am and pm, separated by > 4 hours) for the first five postoperative days.

5.4 Secondary Outcomes measures

Secondary outcome measures:

(First 5 postoperative days)

- Participant satisfaction related to pain management during the preceding 24 h, assessed pre-operatively and once daily postoperatively for up to five days using a 4-point Likert scale
- Opioid use assessed once daily postoperatively for five days, converted to morphine equivalents using the University of Alberta Multidisciplinary Pain Centre Opioid Conversion Guide (54)
- Opioid side effects (frequency and severity of symptoms) assessed once daily postoperatively for five days

(At discharge)

- Morbidity, assessed using Clavien-Dindo grading at discharge
- Length of hospital stay

(At 30 days)

- Surgical site infection rates classified as per the 2008 CDC/NHSN document assessed at 30 days (55)

(At 90 days)

- Days alive and out of hospital assessed at 90 days (DAOH-90)

(At 3 to 6 months)

- Chronic residual limb pain assessed at 3 and 6 months
- Phantom limb pain assessed at 3 and 6 months
- Length of hospital stay assessed at 3 and 6 months
- Residual limb surgery assessed at 30 days, 3 months, and 6 months
- Health-related QoL assessed using EQ-5D-5L at 3 months and 6 months
- Participant reported anxiety and depression assessed using HADS at 3 months and 6 months
- Prosthesis fitting assessed as rate and time to fitting using SIGAM at 3 and 6 months
- Assessment of health care resource usage during the first 6 months postoperatively
- Mortality assessed at 6 months.

6 Trial Design and Setting

6.1 Design

We will conduct a pragmatic, open-label, two-arm RCT with internal pilot trial. The trial will evaluate the clinical and cost-effectiveness of a PNC with local anaesthetic infusion for to the first 5 postoperative days, with 'best care' anaesthetic and analgesia, versus 'best care' anaesthetic and analgesia alone, following MLLA. We plan to enrol 650 participants. This is a Type A Clinical Trial of Investigational Medicinal Product (CTIMP) as both treatment and control arms include only procedures and medications which are already given in routine clinical practice. We expect to reach the enrolment target within 24 months of starting recruitment. The trial will end six months after the date of last data capture. Data collection will involve recording of pain scores and adverse events in the electronic case report form (CRF) as well as questionnaires administered either in person or via telephone.

6.1.1 Setting

Inpatient setting at NHS hospitals providing elective and/or emergency vascular surgery services in the United Kingdom (n=~14 sites). Eight lead centres (Cardiff, Swansea, Bristol, Leicester, London Imperial, Newcastle, Hull and Cambridge) will take part in the internal pilot. Further additional sites will be opened as required. If further sites are needed, those who are interested in participating in the trial will be required to compete a registration form to confirm that they have adequate resources and experience to conduct the trial.

6.2 Risk Assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the Medical Research Council (MRC), Department of Health (DH) and Medicine and Healthcare products Regulatory Agency (MHRA) Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as TYPE A, where the level of risk is no higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the TM. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see Section 23.1).

7 Site and Investigator Selection

This trial will be carried out at participating sites (n = ~14) within the UK. All sites who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial. Before any site can begin recruitment a Principal Investigator (PI) at each site must be identified. The following documents must be in place and copies sent to the PLACEMENT Trial email account (see contact details on page 4):

- Confirmation of Capacity and Capability from Research and Development (R&D) department following sharing of local information pack
- Favourable opinion of host care organisation/PI from Main Ethics committee
- MHRA approval
- A signed Trial Agreement
- Current Curriculum Vitae and Good Clinical Practice (GCP) training certificate of the PI
- Completed Site Delegation Log and Roles and Responsibilities document
- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Leaflet (PIL) and Consent Form (s) on host care organisation headed paper
- A copy of the most recent approved GP letter on host care organisation headed paper
- A copy of the most recent Pregnancy Information Leaflet(s) and Consent Form(s) on host care organisation headed paper.

Upon receipt of all the above documents, the TM will send written confirmation to the PI/lead Research Nurse detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Investigator Site File (ISF). Along with the written confirmation, the site should receive all the documents required to recruit into the trial. Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents. The TMG will apply for the trial to be registered with the Associate PI scheme run by NIHR, and will encourage the PI at each site to recruit a HCP early in their research career to consider registering with the scheme. Site initiation will be in person or by teleconference.

8 Participant Selection

Participants are eligible for the trial if they meet all the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the PLACEMENT TM before randomisation/registration using the PLACEMENT email address.

8.1 Inclusion Criteria

The following participants are suitable for inclusion into the trial:

1. Aged 18 years or older
2. Undergoing elective or emergency MLLA (BKA, TKA, or AKA) for complications of PAD, diabetes and/or acute or chronic infection
3. Able to assess pain using NRS
4. Life expectancy of greater than two weeks
5. (For people of childbearing potential)* Willing to undergo a preoperative pregnancy test and agree to either use a highly effective method of contraception or abstain from sexual intercourse for 7 days after MLLA.
6. (For male participants with female sexual partners who are considered to be of childbearing potential)* Willing to agree to use a condom or abstain from sexual intercourse for seven days after MLLA

*A person is considered to be of childbearing potential i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.

- Permanent sterilisation includes hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

8.2 Exclusion Criteria

The following participants are not suitable for inclusion into the trial:

1. Undergoing MLLA for trauma or cancer
2. Undergoing digital, metatarsal, tarsal amputation, disarticulation of the hip or hindquarter amputation
3. Undergoing simultaneous bilateral amputations
4. Undergoing MLLA revision (excluding previous guillotine amputation)

5. Allergy or intolerance to the PNC or local anaesthetic agents, or chronically taking class 1B anti-arrhythmic agents or local anaesthetic agents, for example in the form of transdermal patches.
6. Expected to be sedated for more than 24 hours postoperatively
7. Unable to provide consent due to incapacity (as defined by the Mental Capacity Act 2005)
8. Vulnerable or protected adults.
9. People who are currently pregnant or breastfeeding
10. Previously enrolled in PLACEMENT (excluding PLACEMENT feasibility trial) for a prior MLLA

Patients who met the inclusion criteria but who subsequently would not be suitable include:

1. Patients where a planned MLLA was not performed (due to patient choice, anaesthetic, or surgical events)
2. Patients where a MLLA was performed but the appropriate nerve was not identified
3. Patients who, due to instability in the intra-operative period, require admission to the ICU postoperatively and are most likely to be sedated for more than 24 hours
4. Patients who, due to instability in the intra-operative period, are not expected to survive more than two weeks.

9 Recruitment, Screening and Registration

9.1 Internal Pilot

An internal pilot is planned in the eight lead sites where the CI and PI co-applicants are based. It will assess participant recruitment rates and proportion of participants providing primary outcome data.

9.1.1 Recruitment Rates

Our recruitment estimates for the internal pilot have considered published reviews and recommendations (56), and that recruitment rates are slower when centres initially open. Our overall projected recruitment rates are based on our feasibility data. Pooled data of NIHR funded studies show internal pilots typically recruit 15% of their participants within 33% of the total recruiting period (56). These figures have been used to calculate the number of participants expected to be recruited (n = 98; 15% of 650) by 8 months (33% of the total 24 month recruiting window). This 8-month window will start when the first site is open to recruitment. We plan for the eight lead sites to open during this

8-month window. The average recruitment rate would be 2.03 participants/site/month, which accounts for slower recruitment as sites open. The remaining recruitment time after the internal pilot is completed (16 months) would need to average 2.49 participants/site/month. This rate is exactly what was achieved in the feasibility trial (not including setup time). Of note, the feasibility was undertaken in two hospitals, one of which (the lead site) was a District General Hospital serving a population of 600,000. This lead site has moved, due to the centralisation of vascular services in Wales, to a larger hospital with double the patient population served. PI co-applicants come from hospitals serving similar large populations (≥1 million). We therefore predict rates achieved in the feasibility should be readily achievable in the full trial.

9.1.2 Progression to Full Trial

Included in the progression criteria is the proportion of participants providing primary outcome data. Our sample size calculations are based on our feasibility, in which 92% of participants provided primary outcome data. Rates below this (80-91%) will prompt a review of the process of capturing primary outcome data. To progress from the internal pilot to the full trial, we would be looking to use the following criteria in Table 1.

Table 1 Progression Criteria

Progression criteria	Red	Amber	Green
Expected recruitment % complete	≤60%	61-99%	≥ 100%
Total number of participants recruited	≤59	60-97	≥98
Recruitment rate/site/month	≤1.02	1.03-2.02	≥2.03
Number of sites opened	<4	4-6	8
Participants providing primary outcome data	≤79%	80-91%	≥92%

The progression criteria have been designed to allow for mitigating strategies to be discussed (when a criterion is in the amber range) to allow for some adaptation to recruitment and/or follow-up processes.

We have built in a planned review of the internal pilot at 8 months. At this time we will also review PPI impact, the early feedback from qualitative interviews regarding participant understanding of the consent process, and HCP interviews about trial processes. Results of this review will be discussed with the trial steering committee (TSC) and fed back to the NIHR HTA Programme for permission to proceed.

9.2 Participant Identification

Patients listed for MLLA will be screened by members of the clinical care team against the above inclusion/exclusion criteria. Those who are considered potentially suitable for inclusion will be approached and provided with a PIL. The site PI, or suitably qualified medical practitioner who has been delegated the role, will confirm eligibility prior to consent.

Non-English language translation of participant facing documentation (e.g., PIL and consent form (s), questionnaires), subtitles to the infographic videos/animations, and interpretation services such as 'Language Line' will be used where available, to ensure language is not a barrier to being considered for the trial.

In certain circumstances, patients with lower limb tissue loss may be listed for exploration of their wound in theatre, with the possibility of proceeding to a MLLA. In this instance, patients will be approached and if willing consented for inclusion in the trial. However, they will only be randomised if a major amputation is due to be performed.

Patients may undergo a BKA or TKA, only to require a subsequent TKA or AKA in the future. It is also possible for patients to have revisions of AKAs, where the femur is shortened, and the residual limb is refashioned. Patients undergoing ipsilateral MLLA revision are excluded from the trial. If a participant was included in PLACEMENT for their first MLLA, and requires a revision operation, the decision to place a PNC at the time of revision is at the operating surgeon's discretion, and the participant's

previous randomisation allocation (to PNC or not) should not impact this decision. Participants who have subsequent ipsilateral amputations will be followed up per protocol to examine for long term outcomes but will be excluded from certain subgroup analysis.

If a patient undergoes a 'Guillotine' amputation (i.e. amputation at the level of the malleoli, typically for urgent removal of a septic foot, prior to definitive MLLA), they may be eligible for PLACEMENT when they undergo their definitive procedure (AKA, BKA or TKA). The definitive procedure is not considered a 'MLLA revision'.

Occasionally patients who are already amputees undergo subsequent amputation of their contralateral limb. These patients are suitable for PLACEMENT, unless previously enrolled in the PLACEMENT trial (excluding the feasibility trial) for their previous amputation. If a patient undergoes bilateral amputation simultaneously this is considered an exclusion criterion, due to the difficulty of obtaining individual pain scores for two amputation sites.

MLLA may be performed following other vascular surgery, such as revascularisation of the affected limb. To be pragmatic such patients can be included, even though they may still experience pain from their preceding surgery. We will however capture this information on the appropriate CRF.

9.3 Screening Logs

A screening log of all 'ineligible' and 'eligible but not consented/not approached' patients will be kept at each site so that any biases from differential recruitment will be detected. When at site, logs may contain identifiable information, but this **must** be redacted prior to being sent to the CTR. Paper copies of the screening log should be sent to the PLACEMENT-trial@cardiff.ac.uk every month or an electronic copy may be completed directly on the database (see Section 23 for further detail on data monitoring/quality assurance).

9.4 Informed Consent

Patients will be approached after the decision has been made to proceed with a MLLA. Before any trial related procedures are undertaken, the participant's written informed consent must be obtained using the PLACEMENT consent form, which follows the PIL. Please note, only when written informed

consent has been obtained from the patient and they have been registered into the trial can they be considered a trial participant.

The patient's consent to participate in the trial should be obtained by those delegated to do so (usually the PI or a qualified member of staff who has been delegated this role on the PLACEMENT delegation log) after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. All patients must be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which they may be exposed. They will be informed of the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.

Patient's consent will be sought to notify their GP of their involvement in the trial. Patient's consent will also be requested to collect NHS Numbers to utilise NHS data for future research. Patients may also opt to consent to participate in the Follow-up Study Within a Trial (SWAT) (see Section 17). Patients may also opt to consent to participate in qualitative interviews (see Section 12.3). If patients provide their (optional) written consent on the PLACEMENT consent form to be contacted by the research team for further information about the interviews, a consent to contact form will be sent from the site to the research team. Similarly, HCPs who are interested in participating in the interviews will complete a separate consent to contact form which will be sent from the site to the research team. The research team will then contact 20 to 30 of these participants and 10 to 20 of these HCPs and go through a separate information sheet with them before obtaining their verbal consent to proceed with the interview. Participants will be reimbursed for their time with a £20 gift voucher for taking part in the qualitative interviews.

Patients should be given as long as they require after being given the trial PIL to consider and discuss participation in the trial with friends and family. A contact number for someone at the site should be given to the patient should they wish to discuss any aspect of the trial. Following this, the investigator should determine that the patient is fully informed of the trial and their participation, is in accordance with the principles of GCP. Patients should always be asked to sign a consent form. One copy should be given to the participant but the original copy should be kept in the investigator site file and a further copy should be kept with participant's hospital notes. In instances where a patient wishes to participate and does not have the physical capacity to sign a consent form, an independent witness

(e.g., a member of the healthcare team not involved in the trial) may record in writing on the consent form that they have witnessed the participant giving verbal consent.

Both urgent and elective cases will be suitable for inclusion, so long as there is sufficient time to obtain informed consent. National Vascular Registry (a prospectively collected and maintained UK database of all major vascular operations undertaken) data shows that even for patients admitted as an emergency, the median time from vascular assessment to amputation was 7 days (3). Experience from our feasibility shows that it is rare for there to be insufficient time for patients to be approached, informed of the trial, given sufficient time to consider participation, and give informed consent, before MLLA.

Sites are required to send consent forms to the PLACEMENT Trial Team at the CTR by secure file transfer or encrypted email within 24 hours (or the next working day) of consent being taken. Patient consent will be obtained for this. In instances where the original copy of the consent form cannot be obtained straight away, for example due to restrictions on paperwork leaving the bedspace because of confirmed or suspected COVID-19, the consent form may be sent to the research delivery staff later when able to leave the bedspace.

The right of the participant to refuse to participate in the trial without giving reasons will be respected. After the participant has entered the trial, the treating clinical team will remain free to give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant will remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing their further treatment (see Section 10 for further details).

9.5 Registration and Randomisation

9.5.1 Registration

Eligible participants scheduled for MLLA for complications of PAD, diabetes +/- acute or chronic infection who have consented to take part in the trial will be registered in the trial pre-operatively. Key information will be collected, including planned level of amputation, past medical, surgical and

drug history. The database will generate a unique trial number which will be the primary identifier for all participants in the trial.

9.5.2 Randomisation

Participants will be randomised intraoperatively (preferably) or pre-operatively if required. If randomisation occurs prior to the participant entering the theatre, the surgical and anaesthetic teams should not be informed of the allocation until the participant is in theatre and the nerve has been identified.

Randomisation will be 1:1 ratio using minimisation to either active treatment (placement of a PNC with a postoperative infusion of local anaesthetic in addition to standard anaesthetic and postoperative analgesia) or control (standard anaesthetic and postoperative analgesia alone).

Computerised web-based remote randomisation (available 24 hours a day) will be used. The TM will also be notified that a participant has been randomised via an automated e-mail alert mechanism to the PLACEMENT email inbox. If the online system does not work or the site has problems accessing the online website, a telephone back up managed by the CTR Trial team will be available for use during office hours Monday to Friday:

For online randomisation: Participants will be randomised to either placement of a PNC or no PNC.

For Telephone randomisation: A randomisation form must be completed before telephoning the randomisation line. Participants will be randomised to either placement of a PNC or no PNC.

10 Withdrawal & Lost to Follow-Up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants' care will not be affected at any time by declining to participate or withdrawing from the trial.

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

1. Withdrawal from randomisation to receive either a perineural nerve catheter or not as part of the trial (pre-operatively)
2. Withdrawal from continuing to receive local anaesthetic via the perineural nerve catheter for (up to) the first 5 postoperative days as part of the trial (post-operatively)
3. Withdrawal from using routinely collected clinical data for the trial (no permission for the research team to look in medical notes to collect health and medications information)
4. Withdrawal from 3-month follow-up (no permission to be contacted by a member of the research team to ask questions about health at 3 months)
5. Withdrawal from 6-month follow-up (no permission to be contacted by a member of the research team to ask questions about health at 6 months)
6. Withdrawal from contacting alternative contact for 3-month follow-up (no permission to be contacted by a member of the research team to ask questions about health at 3 months)
7. Withdrawal from contacting alternative contact for 6-month follow-up (no permission to be contacted by a member of the research team to ask questions about health at 6 months)
8. Withdrawal from the research team communicating with their GP
9. (If applicable) Withdrawal from the optional use of information collected by NHS digital and other NHS central bodies for longer term follow up
10. (If applicable) Withdrawal from the optional Follow-Up Study Within A Trial (SWAT) (to be shown an additional video)
11. (If applicable) Withdrawal from the optional qualitative interview (interview about health and experiences in the trial)
12. Withdrawal of use of data already collected. (Does the participant wish us to destroy trial data collected prior to their withdrawal?)
13. Withdrawal of consent to all of the above

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal. Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. There is specific guidance on this contained in the PIL but briefly: If a participant wishes to stop taking part in the trial completely, they will need to be seen one last time for an assessment

and tests. If the participant is suffering a serious reaction to the trial treatment when they decide to stop, collection of information about them will need to continue for as long as the reaction lasts.

A participant may withdraw or be withdrawn from trial treatment for the following reasons:

- Intolerance to trial medication
- Serious toxicity
- Withdrawal of consent for treatment by the participant
- Any alteration in the participant's condition which justifies the discontinuation of the treatment in the Investigator's opinion

In all instances participants who consent and subsequently withdraw should complete a withdrawal of consent form (see Withdrawal Form in trial pack) or the withdrawal form should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant. This withdrawal form should be sent to the PLACEMENT TM. Any queries relating to potential withdrawal of a participant should be forwarded to the PLACEMENT TM.

10.2 Lost to Follow-Up

Participants will be identified as lost to follow-up if it is not possible to contact them directly or designated additional contact person for 3- and 6-month follow-up. At enrolment, participants will be asked to provide details of an alternative contact person (e.g. close friend, relative or carer) who they are happy for members of the research team to contact for follow-up if the participant themselves cannot be contacted. Participants will also consent to the research team communicating with their GP if required. All outcome data will be collected, and the primary analysis will be performed on an intention to treat basis for protocol non-adherers.

11 Trial Intervention

11.1 Treatment(s)

In participants randomised to the intervention arm, a PNC is inserted adjacent to the cut end of the major nerve (either sciatic nerve for AKAs, or tibial nerve for BKA/TKAs) and tunnelled externally before being connected to a local anaesthetic infusion device delivering local anaesthetic via an elastomeric or electronic pump for up to five days. Participants randomised to the control arm will not have a PNC inserted during their MLLA.

The placement of the PNC is rapid to learn for surgeons who are not already trained in the technique. All surgeons involved in placing a PNC will undergo training according to the Standard Operating Procedure (SOP) for insertion of the perineural catheter and management of local anaesthetic infusion, to ensure the technique used is as homogenous as possible. An accompanying training presentation will illustrate the intervention. The important points are covered in Section 11.1.1 below.

All participants in both arms will receive 'best care' personalised pre-, intra-, and postoperative analgesia at the discretion of the treating medical teams. This may include patient-controlled, IV, and/or oral analgesia. Ultrasound-guided nerve blocks and catheters (e.g., to the femoral nerve), and injections of local anaesthetic directly into/around the nerve at the time of surgery, are permitted in either arm.

11.1.1 Placement of the Perineural Catheter

Placement of a PNC takes 5-10 minutes (38) and requires no further dissection over and above what is already undertaken for lower limb amputations. Intra-operatively, the sciatic nerve (for AKA) or tibial nerve (for BKA/TKA) is identified and divided long. An epidural catheter (typically 20G, 0.85mm diameter) is used as the PNC and placed in the perineural space after the limb has been removed. Epidural catheter packs come with a Tuohy needle; a non-coring needle with a slight curve at its tip which causes a catheter passed through the needle to exit at approximately 45 degrees which is used to place the catheter in the correct location. The Tuohy needle is first placed in the appropriate space, either in the extraneural space (i.e., perineural space), or (if the epineurium is deliberately entered with the needle) in the intraneural space. The fenestrated end of the epidural catheter is advanced along the needle so to lie approximately 10 cm cranial from the cut end, and the needle withdrawn leaving the catheter in place. A suitable exit site for the catheter on the lateral aspect of the amputation stump is selected, and the Tuohy needle passed through the skin (external to internal) at this point. The free end of the epidural catheter is then passed through the needle, which is then withdrawn to leave the catheter exiting the wound. The nerve is transected sharply under gentle tension, to allow the cut end of the nerve to retract away from the wound to reduce the incidence of neuroma formation, as is standard surgical practice (57). The amputation is completed, and the epidural catheter secured to the skin with a silk suture or dressing. The epidural infusion system is then connected to the end of the catheter, is typically flushed with a local anaesthetic bolus, and is

then ready for connection to the local anaesthetic infusion device. The PLACEMENT Trial SOP for insertion of the PNC should be followed for trial participants randomised to the Intervention arm.

11.1.2 Local Anaesthetic Infusion Devices

Two different local anaesthetic infusion devices may be used: an electronic infusion pump or elastomeric reservoir ball. These are both licensed for administration of peripheral local anaesthetic infusions.

11.1.2.1 Electronic Infusion Pumps

Electronic infusion pumps, similar to epidural infusion pumps, provide a continuous infusion of fluid to the PNC. Nursing staff are familiar with the machines used and the type of records such pumps require in nursing notes (volume given and remaining, infusion rate). The infusion is typically stored in a 250 ml bag, and both are mounted on a 'drip stand' or equivalent by the patient's bed. Any breaks in infusion of <60 minutes will be considered as continuous to allow for changeover of bags. The rate will be variable as described below in Section 11.4. Additional boluses of local anaesthetic may be used, but the total dose in 24 hours must be kept below the amount recommended in the SmPCs.

11.1.2.2 Elastomeric Reservoir Ball System

Elastomeric reservoir balls provide an automated continuous controlled infusion of local anaesthetic for use with the PNC in the postoperative period. They are widely used in a range of surgical settings. Pressure is generated by the force of the stretched elastomer, which has been shown to result in constant infusion rates within a 15% tolerance (58).

Once attached to the PNC, the elastomeric reservoir balls require no input to undertake their function. The infusion device has markings which can be used to ascertain how much volume has been infused, and thereby check the infusion rate. During the trial, the amount (and concentration) of drug infused will be recorded daily to ensure consistent infusion rates. Additional boluses of local anaesthetic may be used, but the total dose in 24 hours must be kept below the amount recommended in the SmPCs.

11.2 Treatment Supply and Storage

The IMPs are typically available and stored in the theatre department. They are stored at room temperature/below 25°C, in clearly labelled bags similar to other infusion fluid bags. They are stable

with a long shelf life under standard conditions (room temperature/below 25°C) therefore IMP storage temperature will not be monitored in this trial consistent with Type A clinical trials.

11.3 Treatment Prescribing and Dispensing

For participants randomised to the treatment arm, local procedures will be followed e.g. local anaesthetic infusions prescribed on a specific prescription chart designed for PNCs and dispensed either from the store kept in the theatre complex or directly from the pharmacy department.

11.4 Dosing Schedule

When devices allowing varying infusion rates are used, infusions will be commenced in theatre and titrated as appropriate by anaesthetists, specialist pain nurses or another appropriate HCPs. Participants will only be permitted to have a single type of IMP for the duration of the trial; use of multiple agents for a single patient is very unusual in clinical practice and would only be required due to supply issues. The choice of IMP is down to the treating clinical team.

The total dose and rates of the IMPs not to be exceeded are:

- Levobupivacaine hydrochloride, maximum dose over 24 hours should not exceed 400 mg.
- Ropivacaine hydrochloride, maximum dose over 24 hours should not exceed 800 mg.
- Bupivacaine hydrochloride, maximum dose over 24 hours should not exceed 400 mg.

The maximum doses should be reduced for patients who are acutely ill, elderly, debilitated or weigh <60kg. Note that the 24-hour dose must be calculated to include one-off injections at the time of anaesthesia/surgery, and bolused local anaesthetic doses.

11.5 Dose Modification to Avoid Toxicity

To avoid the risk of toxicity in obese participants, dose calculations that include weight should be calculated using the participant's ideal weight, rather than actual weight. Manufacturers advise caution in using Bupivacaine and Ropivacaine in the presence of significant renal impairment. Manufacturers advise caution in using Levobupivacaine, Bupivacaine, and Ropivacaine in the presence of significant hepatic impairment, cardiovascular disease, complete heart block, epilepsy, hypovolaemia, impaired cardiac conduction, impaired respiratory function, myasthenia gravis, and

shock. Manufacturers advise to consider a reduction in the dose of Levobupivacaine, Bupivacaine, and Ropivacaine in debilitated and/or elderly patients.

11.6 Management of Toxicity and Hypersensitivity Reactions

Patients are typically assessed by both the ward nursing staff and by specialist pain nurses for signs of local anaesthetic hypersensitivity or systemic toxicity. Signs/symptoms of hypersensitivity may include new rash, facial swelling, nasal congestion, shortness of breath, coughing, wheezing, vomiting and diarrhoea, dizziness, hypotension, seizure, loss of consciousness, respiratory arrest. Signs/symptoms of local anaesthetic systemic toxicity include agitation, acute delirium, dizziness, drowsiness, tinnitus, perioral hypoaesthesia, metallic taste, dysarthria, seizures, arrhythmia, hypotension, respiratory arrest, cardiac arrest.

If local anaesthetic hypersensitivity or systemic toxicity is suspected, the infusion must be stopped immediately, and the on-call anaesthetic team contacted. If the participant is in cardiac arrest, cardiopulmonary resuscitation must commence. Alternatively, if the participant has a cardiac output, 100% oxygen should be administered, and the airway secured, as necessary. IV access needs to be confirmed or established. Seizures should be addressed quickly, and treatment options include propofol. Cardiovascular system effects, such as arrhythmias, conduction block, and progressive hypotension and bradycardia, should be managed by conventional Advanced Life Support protocols.

Local anaesthetic toxicity would be considered a SAR and would be reported within 24 hours (see Section 13 on Pharmacovigilance).

11.7 Prohibited Medications and Interaction with Other Drugs

Caution must be used in the administration of other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g., certain antiarrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive. While patients already taking these medications at time of enrolment will be excluded, use of them postoperatively must be undertaken with caution but is not specifically prohibited. Full information is available from the SmPC for Levobupivacaine, Ropivacaine and Bupivacaine which are attached as an appendix to this protocol.

Caution must be used in the concomitant administration of local anaesthetic(s) to ensure that local anaesthetic toxicity does not occur. This is especially important when local anaesthetic is being delivered via different routes, or concurrently alongside the PNC infusions Specifically, caution must be used for in the following scenarios:

i. epidural anaesthesia at time of MLLA

ii. use of IV lidocaine within the first 5 post-operative days

iii. use of liposomal bupivacaine within the first 5 post-operative days

The maximum doses should be reduced for patients who are acutely ill, elderly, debilitated or <60kg.

11.8 Accountability Procedures

No medications or associated equipment or consumables are being provided to sites as part of the trial, and therefore, sites are expected to use their own stock. No CTR accountability, recall and disposal procedures are required as described in the PLACEMENT IMP Management Plan. Sites should follow local governance for the off-license use of Levobupivacaine, Ropivacaine and Bupivacaine (i.e., via PNC). The PLACEMENT Trial SOP for insertion of the PNC should also be followed.

Local anaesthetic will be infused for up to five days postoperatively, and therefore, continuation of the IMP after completion of the trial is not applicable. Once participation in the trial has ended, any additional care is not expected to differ from what is normally expected for patients who have undergone MLLA for PAD +/- diabetes.

11.9 Compliance

Pls and other medically qualified staff who are deemed experienced and competent at inserting PNCs by the PI and have been delegated this responsibility as per the PLACEMENT delegation log, are required to watch the Training presentation and read the PLACEMENT Trial SOP for the insertion of PNCs. This training must be documented on the PLACEMENT Training log. The PLACEMENT Delegation and Training logs will be monitored by the CTR.

12 Trial Procedures

All participants will be enrolled in the trial for approximately six months, from pre-operative screening to 6-month postoperative follow-up. During the inpatient phase there is a pre-operative baseline

assessment and daily postoperative assessments up to five days following the operation. If a member of the research team is unable to collect patient reported outcomes (PROs) (e.g., over the weekend), a member of the clinical team may be permitted to collect this data. If a member of the clinical team is unable to collect PROs, these may be retrospectively captured from information in the clinical notes. Should pain scores be routinely captured, but not using an 11-point scale, we will permit conversion of clinical pain scores (with a range of none (0) – severe (3)) as per published conversion methods (18). During follow-up there are two assessments, which may be conducted either via telephone, email, post or in person at 3 months and 6 months post randomisation.

12.1 Assessments

12.1.1 Baseline

The baseline assessment consists of collecting the following information:

- Preoperative pain assessed by the NRS
- Participant satisfaction of pain management during the preceding 24 h, assessed using a 4-point Likert scale
- Preoperative opioid and analgesic use
- Health-Related QoL assessed using EQ-5D-5L (59)
- Depression measured by the Hospital Anxiety and Depression Scale (HADS) (60)
- Past surgical and medical history, including cigarette use and type of diabetes mellitus
- Health services contact
- Results from the routinely collected pre-operative blood tests, including liver and renal function tests
- Planned level of amputation
- Body weight
- Residential status on admission
- Review of pre-operative resting 12-lead ECG
- (For participants of child-bearing potential) Review of pre-operative pregnancy test result

12.1.2 At Operation

Operative assessment includes recording the following information:

- Method of anaesthesia

- Whether a pre-operative regional nerve block was performed, and if so, what this was and what drugs were used
- Whether the nerve was successfully identified
- Method used to cut the nerve and whether it was tied
- Level of amputation
- Fidelity of nerve catheter placement, specifically assessing successful placement of the nerve catheter at the time of surgery.

Providing that the nerve is successfully identified, the participant is either randomised at this point, or if randomisation has already been performed, allocation is revealed to the treating team, and the nerve catheter is placed if randomisation is to the treatment arm. If the nerve is not successfully identified, randomisation cannot take place and the participant's enrolment in the trial is terminated. Baseline and intra-operative data will be retained for analysis (providing the participant does not withdraw consent), but no further assessments will be performed.

12.1.3 Daily Postoperative Assessment

For the first five postoperative days, routine assessments will consist of:

- Pain scores, assessed twice daily (am and pm, separated by ≥4 hours), using NRS
- Participant satisfaction related to pain management during the preceding 24 h, assessed once daily using a 4-point Likert scale (with am pain score for amputations completed in the morning and pm pain score for amputations completed in the afternoon)
- Total opioid use, converted to morphine equivalents (54)
- Frequency and severity of opioid side effects (61)
- Duration PNC remains in place
- Duration of delivery of local anaesthetic
- Analgesic use, including opioid, paracetamol, non-steroidal and neuropathic pain agent (gabapentin, pregabalin, amitriptyline) use. For participants in the treatment arm, amount of local anaesthetic infused will also be recorded.

12.1.4 Discharge

At discharge, assessments will include:

- Postoperative complications rate and severity assessed by Clavien-Dindo grading (62)

Upon discharge, participants will be given information packs which will include:

- Information on the trial follow ups via leaflet (and watch a short animation video if randomised to the intervention arm of the Follow-up SWAT – see Section 17)
- Information on the Limbless Association's Volunteer Visitor Scheme, that links patients who have recently undergone MLLA with someone who has lived experience of MLLA and is willing to provide peer-to-peer support.

Many participants will also be supported on discharge by the local 'limb fitting' team, which often includes a psychologist. Some hospitals also have access to inpatient psychologists who can support these participants.

12.1.5 Outcomes Collected at 30 Days

- **Surgical site infection**, as defined by CDC 2021 (55)
- Delayed **wound healing** of the surgical wound (defined as absence of complete epithelialisation of the wound)
- **Residual limb surgery (revision or debridement)**

Table 2 Schedule of enrolment, interventions, and assessments

Data Type		Source Data	Data type	Screening	Baseline/ Pre-operative assessment	At Operation	First 5 Post-operative days	30 days	At discharge	3 Month FU	6 Month FU	Frequency	By whom
1	Informed Consent	Consent form, documented in medical notes	-	X								Once	Qualified practitioner with delegated responsibility
2	Eligibility Assessment	Eligibility form	-	X								Once	Qualified practitioner with delegated responsibility
3	Registration	Registration form	-		X							Once	Site research team
4	Demographics	CRF			X							Once	Site research team

Data Type		Source Data	Data type	Screening	Baseline/ Pre-operative assessment	At Operation	First 5 Post-operative days	30 days	At discharge	3 Month FU	6 Month FU	Frequency	By whom
5	Past surgical and medical history	Medical notes and CRF	(inc. smoking history, weight, and type of diabetes mellitus)		X							Once	Site research team
6	Pre-operative pain	CRF	11-point NRS		X							Once	Participant reported
7	Pre-operative opioid and analgesic use	Medical notes			X							Once	Site Research team
8	Pre-operative blood results, including liver & renal function tests	Medical notes	Routine blood tests		X							Once	Site Research team

Data Type		Source Data	Data type	Screening	Baseline/ Pre-operative assessment	At Operation	First 5 Post-operative days	30 days	At discharge	3 Month FU	6 Month FU	Frequency	By whom
9	Review of pre-operative resting 12-lead ECG	Medical notes	ECG		X							Once	Site Research team
10	(For participants of child-bearing potential) Review of pre-operative pregnancy test result	Medical notes	Pregnancy test result		X							Once	Site Research team
11	Planned level of amputation	Medical notes			X							Once	Site Research team
12	Health services contact in previous 3 months	QRF	Client Service Receipt Inventory (CSRI)		X					X	X	Once	Participant reported / Site Research team

Data Type		Source Data	Data type	Screening	Baseline/ Pre-operative assessment	At Operation	First 5 Post-operative days	30 days	At discharge	3 Month FU	6 Month FU	Frequency	By whom
13	Health-related Quality of Life	QRF	EQ-5D-5L and HADS		X					X	X	Once	Participant reported
14	Randomisation	CRF	-			X						Once	Site Research team
15	Method of anaesthesia	Medical notes and CRF	Surgery CRF			X						Once	Site Research team
16	Pre-operative regional nerve block performed, and drugs used	Medical notes and CRF	Surgery CRF			X						Once	Site Research team
17	Intraoperative nerve management	CRF, documented in surgical notes	Surgery CRF- Successful identification of nerve, method			X						Once	Site Research team

Data Type		Source Data	Data type	Screening	Baseline/ Pre-operative assessment	At Operation	First 5 Post-operative days	30 days	At discharge	3 Month FU	6 Month FU	Frequency	By whom
			used to cut nerve and whether it was tied.										
18	Actual level of amputation	Medical notes and CRF	Surgery CRF			X						Once	Site Research team
19	Postoperative pain	CRF	11-point NRS				X					Twice daily	Participant reported
20	Overall satisfaction with analgesia	CRF	5-point scale (0 to 4)		X		X					Once daily	Participant reported
21	Total opioid use (converted to morphine equivalents)	Medical notes					X					Daily	Site Research team

Data Type		Source Data	Data type	Screening	Baseline/ Pre-operative assessment	At Operation	First 5 Post-operative days	30 days	At discharge	3 Month FU	6 Month FU	Frequency	By whom
22	Opioid side effects	CRF	Frequency & severity of symptoms				X					Daily	Participant reported
23	**(Intervention arm only)** Fidelity of nerve catheter usage, specifically duration it remains in place, and duration of delivery of local anaesthetic	CRF	Catheter monitoring CRF				X					Daily	Site Research team
24	Surgical site infection	Medical Notes						X				Once	Site Research team

Data Type		Source Data	Data type	Screening	Baseline/ Pre-operative assessment	At Operation	First 5 Post-operative days	30 days	At discharge	3 Month FU	6 Month FU	Frequency	By whom
25	Delayed wound healing	Medical Notes						X			X	Once	Site Research team
26	Residual limb surgery	Medical Notes						X			X	Once	Site Research team
27	Residential status upon discharge	CRF	Discharge form						X			Once	Site Research team
28	Resource use: Additional equipment and home adaptions	CRF	Discharge form						X			Once	Site Research team
29	Inpatient analgesic use	Medical notes							X			Once	Site Research team
30	Postoperative complications	Medical notes/ CRF	Clavien-Dindo grading						X			Once	Site Research team

Data Type		Source Data	Data type	Screening	Baseline/ Pre-operative assessment	At Operation	First 5 Post-operative days	30 days	At discharge	3 Month FU	6 Month FU	Frequency	By whom
31	Phantom limb pain		11-point NRS							X	X	Once	Participant reported
32	Chronic stump pain		11-point NRS							X	X	Once	Participant reported
33	Prosthesis fitting (inc. Time to achieve fitting)		SIGAM							X	X	Once	Participant reported
34	Level of independence		SIGAM grading							X	X	Once	Participant reported
35	Resource Use (additional operations, consultations)	QRF						X		X	X	Once	Participant reported
36	Length of hospital stay	Medical notes							X		X	Once	Site Research team

Data Type		Source Data	Data type	Screening	Baseline/ Pre-operative assessment	At Operation	First 5 Post-operative days	30 days	At discharge	3 Month FU	6 Month FU	Frequency	By whom
37	Hospital re-admissions										X	Once	Site Research team
38	MLLA of contralateral limb										X	Once	Site Research team
39	Mortality (Time, Cause)	Medical notes									X	Once	Site Research team
40	Adverse effects	Medical notes /CRF					----------As Required----------						Site Research team
41	SAEs / SARs	Medical notes /CRF	SAE form				----------As Required----------						Site Research team
42	Withdrawals	Withdrawal form	-				----------As Required----------						Site Research team and CTR

12.2 Follow-up

Follow-up assessments will be carried out at 3 months (+/- 1 month window) and 6 months (+/- 2-month window) by either telephone or email, with both used where possible to maximise response. Alternatively, if participants are unwilling or unable to complete their follow up over the telephone or by email, they will be asked if they would be willing to fill out the follow up questionnaires sent to them in the post. A freepost self-addressed envelope will be provided. Around 3 attempts will be made to contact the participant at each follow-up. If it is not possible to contact participants, a relative/carer may be contacted as an alternative. If all contact attempts are unsuccessful, a questionnaire booklet may be posted to the participant for them to complete and return. If a routine in-person outpatient visit is scheduled for clinical reasons within the follow-up visit windows, the follow up questionnaires may be completed in-person, and/or clinical information collected at this visit may be used for follow-up assessments. Site staff will ensure, to the best of their knowledge, that participants are still alive before any contact attempts are made, by checking all local patient management systems available to them e.g. Spine data (England), Welsh Clinical Portal (Wales).

12.2.1 Three-month Follow-up

Participant reported outcomes will be assessed:

- NRS to assess phantom limb pain and chronic stump pain
- Health-related QoL, measured by EQ-5D-5L (59)
- Hospital Anxiety and Depression Scale (HADS) (60)
- Healthcare resource use questionnaire (including subsequent amputations and hospital readmissions, drug administration, number of physiotherapy or occupational therapy consultations and additional procedures performed)
- Prosthesis fitting rate (using a prosthesis for standing, transferring, or walking; SIGAM ‘B’ or greater), and (if applicable) time to achieve prosthesis fitting and level of independence assessed by SIGAM (63)

12.2.2 Six-month Follow-up

At the 6 month follow up, all the PROs will be collected as per the 3 month follow up, and a medical note review will collect:

- Mortality, including cause of mortality

- Delayed wound healing of the surgical wound (defined as absence of complete epithelialisation of the wound)
- Residual limb surgery (revision or debridement)
- (For unilateral amputees) MLLA of contralateral limb
- Length of hospital stay (censored at 6 months in the unlikely event that the participant remains in hospital at 6-month follow-up), including re-admissions after discharge, used to calculate DAOH-90 and time spent in level 2 or 3 care.

12.2.3 Longer-term Follow-up

Participants will be asked to consent to routine data-linked longer-term follow-up. Should our results indicate longer-term follow-up is desirable (for example, to further explore the impact of PNC usage on chronic pain), we will apply for further funding for this.

12.3 Qualitative Process Evaluation

Although a small-scale process evaluation was conducted as part of the PLACEMENT feasibility trial, Medical Research Council guidance recommends that this should be repeated at full trial stage, as new issues are likely to be identified when testing the intervention in a larger and more diverse group of participants (64). A qualitative process evaluation can help interpret trial findings and aid the implementation of successful interventions in practice (65). Therefore, we will conduct a qualitative evaluation of PNC implementation, comprising semi-structured interviews with approximately 20 to 30 trial participants and/or relatives/carers and approximately 10 to 20 HCPs across different sites (around three to six sites, total: 30 to 50 interviews). Trial participants and HCPs will be sampled purposively to encourage diversity.

More specifically this qualitative evaluation will aim:

- to explore how delivery of the intervention was achieved and what was delivered (qualitative measure of fidelity); how the intervention components and delivery processes worked in the real healthcare setting (covering feasibility, implementation, practicality of intervention), and acceptability of the trial to participants and intervention deliverers (e.g. how did the consent models work, how was randomisation understood, was trial information understood, to what extent was there equipoise amongst stakeholders).

- To explore the experiences and understanding of participants in the PLACEMENT trial about the participant's condition and MLLA (where appropriate), and experience of decisions around care and participation in the trial.

12.3.1 Semi-structured Interviews

We will use semi-structured qualitative interviews to encourage participants to initiate and elaborate on topics most important to them which we may not have pre-empted if using survey type closed questions. Semi-structured interviews will be conducted with HCPs and trial participants. Interviews may be undertaken remotely (via telephone or teleconference) or in-person. The length of the interviews will vary, but we expect them to take about 30 to 60 minutes. Brief demographic details will be taken by the interviewer (interviewee age, gender etc.) and used to describe the interviewee sample. Field notes may be made by the interviewer following the interview which will include reflections on the interview process, overall observations, and any relevant contextual details.

Trial Participant Interviews

Interviews with participants will explore understanding of the trial (e.g., the randomisation process). They will also explore experiences and acceptability of the PNC, experiences of undertaking follow-up, and further explore/develop themes identified in the feasibility trial and in our focus group, including rehabilitation experiences, information needs following MLLA, and participant anxieties and satisfaction related to pain management. For example, we found considerable uncertainty amongst participants regarding the rehabilitation process, unrealistic expectations regarding future mobility and anxiety associated with patient-controlled analgesia. As these are issues identified in our previous research as important to patients, gathering more robust data will lead to recommendations for changes to patient care which have the potential to impact on QoL.

Healthcare Professional Interviews

Interviews with HCPs will explore how the intervention was delivered, how the intervention and components worked in a real healthcare setting, acceptability of the intervention, decision making around care of patients, and views on the trial processes. Findings from early HCP and participant interviews (specifically regarding understanding of the trial, the randomisation process and follow-up) will be fed back to the TMG during the trial pilot phase. Separate consent to contact forms will be used to identify healthcare professionals from the clinical care team. Completed consent to contact forms

will be sent from the site to the research team. The research team will contact 10 to 20 of HCPs and go through a separate information sheet with them before obtaining their verbal consent to proceed with the interview. Written copies of this information sheet will be available at sites for HCPs to read after filling in a consent to contact form.

Topic Guide

The semi-structured interview topic guide will be developed from a review of previous research with input from the multi-disciplinary research team to avoid bias in wording of questions. The topic guide will be refined, as necessary. The direction of questions may be led by the participants themselves and therefore the interview topic guide will remain flexible, in keeping with the method of semi-structured interviewing. Interviews will be recorded and transcribed verbatim. Transcripts to be used for analysis will be de-identified with personal details such as name, address, and date of birth removed.

12.3.2 Sample Size

A purposive sample of HCPs who are involved in delivering the PLACEMENT Trial will be identified from the sites. The sample strategy will be developed to address representation from around three to six different sites and encourage variation in HCP role (e.g., ward nurse, consultant, research nurse etc.) We anticipate that interviews with around 10 to 20 professionals based on saturation and breadth of views expressed should be sufficient.

A purposive sample of PLACEMENT trial participants will be identified. We anticipate that a sample size of around 20 to 30 participants will be sufficient. The sample strategy will be developed to include participants from both the intervention and control arm, and inclusion of different sites. By sampling along these lines, we envisage there will be a range in terms of age, gender, ethnicity, and level of amputation to encourage maximum variation.

With regards to the sample size for both HCPs and trial participants, the qualitative researcher(s) will make pragmatic decisions along with the research team regarding when enough is known about certain themes (i.e., data saturation has occurred).

13 Pharmacovigilance

The PI is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR PV and Safety Specialist unless the SAE is specified as not requiring immediate reporting (see Section 13.2). This includes SAEs related to IMPs.

13.1 Definitions

Table 3 Definitions of Adverse and Serious Adverse Events and Reactions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an investigational medicinal product which is related to any dose administered to that participant
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is **related** to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event, or it is suspected that used or continued used of the product would result in the subject's death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g., for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

13.2 Trial Specific SAE Reporting requirements

In addition to the SAE reporting requirements defined in Table 3, for the purposes of this trial the following events will also be considered SAEs and must be captured on the SAE form and reported to the CTR with 24 hours of knowledge of the event:

- Infection around PNC exit site
- Local anaesthetic toxicity reactions (see Section 11.6)

For the purposes of this trial the following events will **not** require reporting as SAEs:

- AEs as a result of surgical complications of CTCAE grades 1 and 2 as listed in the protocol (Table 6, page 64 - 65)

These should be completed in the participant's notes and on the relevant CRF page and forwarded to the CTR in the normal timeframes for CRFs.

Pre-existing conditions should only be reported if they met the definitions for an SAE and if the condition worsens by at least one CTCAE grade.

13.3 Causality

Causal relationship will be assessed for IMPs and procedures:

Table 4 IMP

IMP: Levobupivacaine hydrochloride, Ropivacaine hydrochloride, Bupivacaine hydrochloride **Procedure:** Placement of perineural catheter during surgery (MLLA)

The PI (or another delegated medically qualified doctor from the trial team) and CI (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship:

Table 5 Definition of Relationship with IMP

Relationship	Description	Reasonable possibility that the SAE may have been caused by the IMP?

Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g., the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g., because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the PI (or delegate) cannot be downgraded by the CI (or delegate), and in the case of disagreement both opinions will be provided.

13.4 Expectedness

The CI (or another delegated appropriately qualified individual) will assess each SAR to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the current Reference Safety Information (RSI) for each IMP. Expectedness decisions must be based purely on whether the event is listed in the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease. SARs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. Fatal and life-threatening SARs should not be considered expected (unless explicitly stated in the RSI and approved by the NCA). For example, an event more specific or more severe than that described in the RSI is considered unexpected.

The table below lists the expected events in relation to surgery and this should be used as the RSI when assessing the expectedness of AEs causally related to surgery. Anticipated treatment related AEs of grade ≤2 are not subject to expedited reporting. These should be completed in the participant's notes and on the relevant toxicities CRF (if applicable) and submitted to the CTR in the normal timeframes for CRFs.

Table 6 Expected Events in Relation to MLLA (CTCAE v5.0)

Blood and lymphatic system disorders • Anaemia • Postoperative hemorrhage • Hematoma	Renal and urinary disorders • Acute kidney injury • Haematuria • Urinary retention	Nervous system disorders • Dizziness • Dysarthria • Headache • Paraestheis • Presyncope • Seizure/convulsions • Spasticity • Stroke • Transient ischemic attacks (TIAs) • Tremor • Phantom pain
Ear and labyrinth disorders • Tinnitus	Immune system disorders • Allergic reaction (If related to infusion, use 'Infusion related reaction' - do not report both)	Psychiatric disorders • Agitation • Anxiety • Confusion • Delirium • Delusions • Hallucinations • Psychosis
Cardiac disorders • Chest pain – cardiac (includes angina) • Sinus bradycardia • Sinus tachycardia • Heart failure • Myocardial infarction	Infections and infestations • Phlebitis infective • Urinary tract infection (UTI) • Wound infection • Enterocolitis infectious (includes clostridium difficile)	Respiratory, thoracic and mediastinal disorders • Atelectasis • Dysponea • Pleural effusion Lung infection (including pneumonia)

Gastrointestinal disorders • Constipation • Ileus • Bowel obstruction • Diarrhea • Nausea • Vomiting	Injury, poisoning and procedural complications • Fall • Fracture • Infusion site extravasation • Infusion related reaction • Wound dehiscence	Surgical • Need for revision amputation • Retained foreign body (including unable to remove PNC)
General disorders • Chills • Fever • Hypothermia	Eye disorders • Visual disturbances (includes blurred vision, flashing lights)	Musculoskeletal • Back pain
Metabolism and nutrition disorders • Acidosis • Dehydration	Skin and subcutaneous tissue disorders • Skin ulceration (includes pressure ulcers)	Vascular disorders • Hypertension • Hypotension • Thromboembolic event • Phlebitis

The table below lists the RSI's that should be referenced:

Table 7 Reference Safety Information

IMP	RSI to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Levobupivacaine	SmPC for Levobupivacaine 0.125% w/v Solution for Infusion (Altan Pharma Ltd; Fresenius Kabi Ltd)	Section 4.8 of SmPC
Ropivacaine hydrochloride	SmPC for Ropivacaine hydrochloride 2 mg/ml solution for infusion (Altan Pharma Ltd; Fresenius Kabi Ltd; Sintetica Ltd)	Section 4.8 of SmPC
Bupivacaine Hydrochloride	SmPC for Bupivacaine Hydrochloride 0.125%w/v Solution for Infusion (Sintetica Ltd)	Section 4.8 of SmPC

Placement of perineural catheter	IFU Portex Epidural Minipacks, IFU for pump	Warnings sections of Instructions for use (IFU)

Reference Safety Information (RSI) on any CTR trial will be reviewed regularly according to CTR procedures.

13.5 Reporting Procedures

13.5.1 Participating Site Responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice. A completed SAE form for all events requiring immediate reporting should be submitted via email (or fax if email unavailable) to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether the events had the same date of onset. The participant will be identified only by trial number, month and year of birth, or year of birth and initials. The participant's name (or any other personal identifiers) should not be used on any correspondence. It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR companies may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

Serious Adverse Event (SAE) Fax number (Only use if email unavailable:

0203 0432 376

SAEs should be reported from time the participant goes into theatre, throughout the treatment period up to, and including seven postoperative days. SARs (such as long-term side effects of trial treatment under investigation) should continue to be reported until the end of follow up as defined in the protocol (page 77). SAEs should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

(https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf). CTR will code events using MedDRA Version 26.0.

An SAE form should contain at least the minimum information:

- Full participant trial number
- An AE/AR
- IMP or trial intervention
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log)

If any of these details are missing, the site will be contacted, and the information must be provided by the site to the CTR within 24 hours. All other AEs should be reported on the CRF following the CRF procedure described in Section 13. If applicable, the PI should report any AE/SAE involving a device deficiency or occurring with a CE-marked device using the yellow card scheme (https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/.

13.5.2 The CTR Responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. The most recent form can be updated with new information. Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the CI (or their delegate) for an assessment of expectedness. Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the MHRA, Main Ethics Committee.

13.6 SUSAR Reporting

Cardiff University is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the regulatory authorities (NCAs and relevant ethics committees) as follows:

- SUSARs which are fatal or life-threatening must be reported to the MHRA and REC within 7 calendar days of receipt at the CTR

- SUSARs that are not fatal or life-threatening must be reported to the MHRA and REC within 15 days of receipt at the CTR. If report is incomplete, then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report.

13.7 Safety Reports

A list of all SARs (expected and unexpected) will be reported annually to the MHRA REC and trial sponsor in the form of a Development Safety Update Report (DSUR). This report must be submitted within 60 days of the anniversary of the MHRA CTA approval date. The CTR will report a list of all SARs (expected and unexpected) and any other safety recommendations to all PIs annually throughout the course of the trial. This frequency may be reviewed and amended, as necessary. This reporting will be done via the Investigator safety report (ISR).

13.8 Contraception and Pregnancy

13.8.1 Contraception

In accordance with the National Safety Standards for Invasive Procedures (NatSSIPs 2) (https://cpoc.org.uk/guidelines-resources-guidelines/national-safety-standards-invasive-procedures-natssips) and the National Institute for Health and Care Excellence (NICE) guideline 45 (NG45) (https://www.nice.org.uk/guidance/ng45/chapter/Recommendations) for Routine preoperative tests for elective surgery, pregnancy status should be confirmed in all participants of childbearing potential before undergoing surgery. Participants who are currently pregnant are not eligible for inclusion into the trial as per the exclusion criteria. All discussions about pregnancy testing should be documented in the patient's notes (NG45). All participants of childbearing potential should be made aware of the risks of becoming pregnant during local anaesthetic administration as summarised below (BNF (British National Formulary) | NICE):

- Ropivacaine hydrochloride is not known to be harmful in human pregnancy
- No safety information for Bupivacaine hydrochloride in early human pregnancy is available
- Levobupivacaine hydrochloride has a demonstrated or suspected fetotoxicity in animal studies, and therefore, administration of Levobupivacaine hydrochloride should be avoided in the first trimester of human pregnancy if possible.

People of childbearing potential entering this trial must therefore agree to use a highly effective method of contraception preferably with low user dependency for at least one week

postoperatively. A highly effective method of contraception is considered as having a failure rate of less than 1%. Some acceptable contraception methods are listed below:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable*
- intrauterine device (IUD)*
- intrauterine hormone-releasing system (IUS)*
- bilateral tubal occlusion*
- vasectomised partner*
- sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments.

N.B. periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

**These contraception methods are considered to be low user dependency.*

13.8.2 Pregnancy Reporting while Participating in the Trial

Pregnancy, or the pregnancy of a partner occurring while participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g., termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, termination of pregnancy or other outcome . Without follow-up of the pregnancy, it would not be possible for the CTR to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the IMP. Information on a pregnancy in a trial participant will be captured on the CTR Pregnancy Report Form supplied to sites by the CTR.

Sites should report pregnancy occurring within SAE reporting periods stipulated in the trial protocol. Congenital anomalies or birth defects are considered an SAE and so these events must also be reported to the CTR on a trial-specific SAE form. Congenital anomalies or birth defects related to the IMP and unexpected with respect to the IMP Reference Safety Information (RSI) must be submitted by the CTR within expedited SUSAR time frames (7 or 15 days) to the MHRA, relevant REC and the drug manufacturer of the IMP (to comply with any contractual agreement).

13.9 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, CI or PI may carry out to protect the subjects of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial must be notified to the MHRA and Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

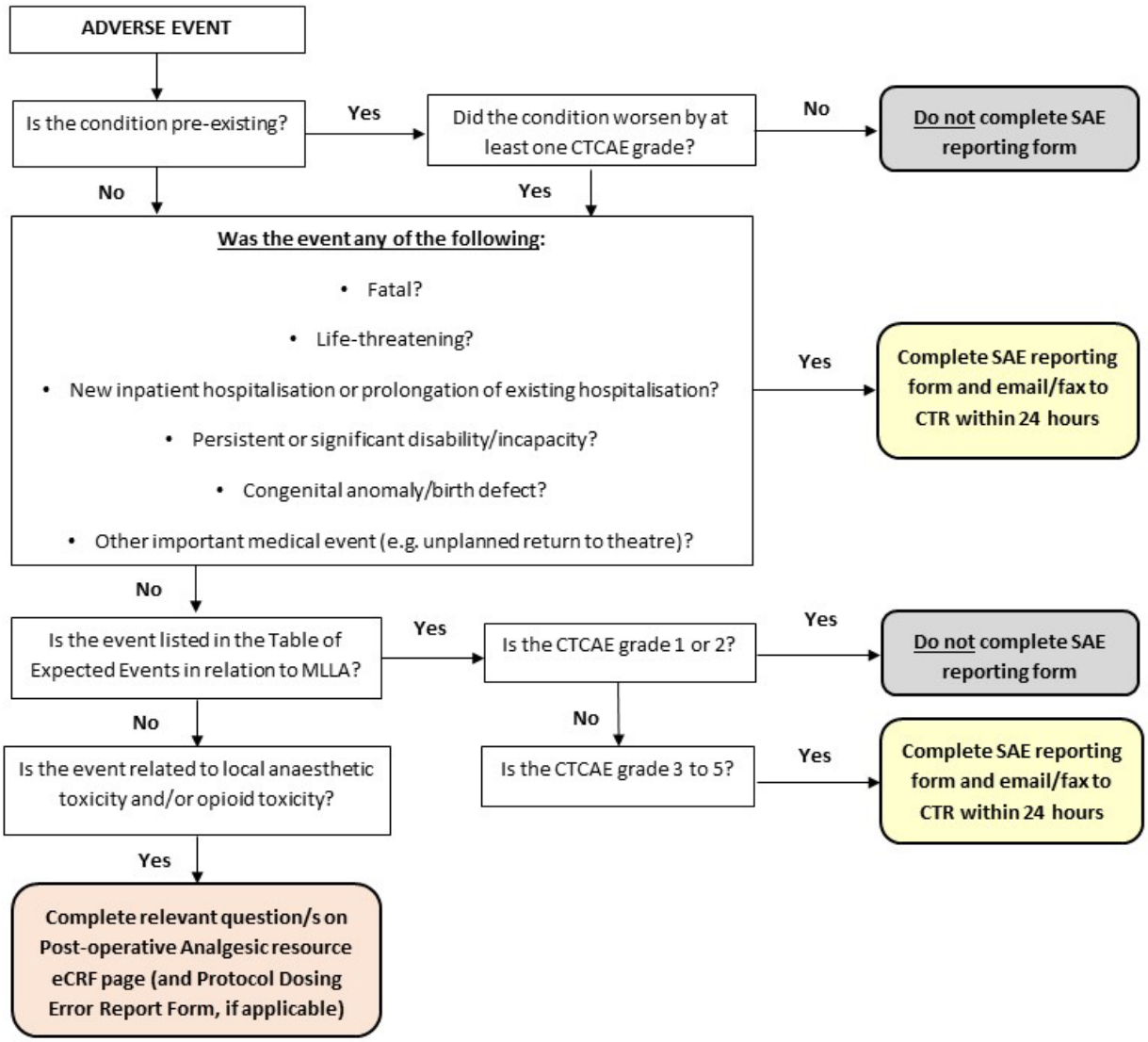


Figure 1 Adverse event reporting flow chart

14. Statistical considerations

14.1 Randomisation

Participants will be allocated via covariate minimisation on the planned level of amputation (BKA vs. TKA vs. AKA), type of anaesthesia (general vs. neuraxial), preoperative pain score, and recruitment site. Allocation will be in a 1:1 ratio to either active treatment (placement of a PNC with a postoperative infusion of local anaesthetic in addition to standard anaesthetic and postoperative analgesia) or control (standard anaesthetic and postoperative analgesia alone). A random element will be added to the (otherwise strictly deterministic) minimisation algorithm to reduce predictability [REF: www.bmj.com/content/330/7495/843].

Computerised web-based remote randomisation (available 24 hours a day) will be used. A 9am-5pm telephone back up will be available for use if the online system does not work or the site has problems accessing the online website. A detailed randomisation plan will be finalised and signed off prior to any participant being randomised.

14.2 Blinding

The PLACEMENT trial does not use blinding.

14.3 Sample size

'Good' pain control is defined as ≤3 on a 0-10 NRS (66). Feasibility trial participants in the control arm reported 'freedom from pain' (defined as NRS ≤3, or pain ≤'mild' on a 4-point Verbal Rating Scale) 61.7% of the time in the first 5 postoperative days. Treatment arm participants reported 'freedom from pain' 76.8% of the time, a relative improvement of 24.5%. Using a more conservative (but still clinically important) relative improvement of 20% between arms results in a sample size of 299 participants per arm for 90% power when using a two-sample test for proportions with two-sided 5% alpha. In our feasibility trial, 45 of the 49 participants (92%) provided primary outcome data (defined as a participant providing outcome data for pain in >50% of possible timepoints). To account for this, a sample size of 650 is required.

14.4 Missing, Unused and Spurious Data

Complete case analysis will be used for the primary analysis. We will employ multiple imputation of missing outcome data as a sensitivity analysis and report the impact on the treatment effect alongside the complete case analysis. Further detail will be provided in the Statistical Analysis Plan (SAP).

14.5 Procedures for Reporting Deviation(s) from the Original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

14.6 Termination of the Trial

Progression criteria for the internal pilot phase are described in Section 9.12. There is the potential for the trial to terminate early if our funder assesses the trial as not being feasible following assessment of progress against our targets at the end of the internal pilot with input from our TSC and IDMC.

14.7 Inclusion in Analysis

All randomised participants will be included in the primary intention-to-treat analysis. As part of sensitivity analyses, ineligible/unevaluable participants will be excluded from the analysis population.

15 Analysis

15.1 Main Analysis

For the statistical analysis of the primary outcome (proportion of 'successes' and 'failures' of pain control in the first 5 postoperative days for each participant, as defined in Section 14.3), we will use the intention-to-treat population and fit a multilevel logistic regression model, with the minimisation variables and condition (PAD or diabetes) as fixed-effect covariates and with random centre effects, to test for a difference between treatment arms at a 5% two-sided alpha level. Secondary outcomes will be analysed using similar multilevel regression models depending on the type of outcome (see Table 8) with the same covariate adjustments using the intention-to-treat principle. We will account for possible 'truncation by death' in sensitivity analyses. Additional secondary analyses considering the level of intervention fidelity will also be undertaken, including successful placement of the PNC, the PNC remaining in place for 5 days, and the local anaesthetic being infused (not exceeding the

maximum daily dose specified in the protocol) for 5 days. All treatment effects will be reported as point estimates with 95% confidence intervals and p-values.

Table 8 Summary of Analysis for Secondary Outcomes

Outcome	Measure	Time frame	Analysis
Average pain	NRS	5d	Linear regression of median or mean (adjusted for baseline)
Overall satisfaction with analgesia	Likert scale	5d	Linear regression of transformed measure (if appropriate)
Total opioid use	Morphine equivalents	5d	Linear regression (adjusted for baseline)
Opioid side effects	Frequency and severity of symptoms	5d	Linear regression of transformed measure (if appropriate)
Surgical site infection	Proportion of people with infection	30d	Logistic regression
Delayed wound healing	Proportion of people with delay	30d, 6m	Logistic regression
Residual limb surgery	Proportion of people with surgery	30d, 6m	Logistic regression
Phantom limb pain	NRS	3m, 6m	Linear regression
Chronic stump pain	NRS	3m, 6m	Linear regression
Health utility/QoL	EQ-5D-5L	3m, 6m	Linear regression of transformed measure (adjusted for baseline)
Depression	HADS	3m, 6m	Linear regression of transformed measure (adjusted for baseline)
Prosthesis fitting	Proportion of people using prosthesis Time to achieve fitting	3m, 6m	Logistic regression Cox regression

Level of independence	SIGAM grading	3m, 6m	(Ordered) logistic regression, tabulation
Mortality	Proportion of people dead Time to death Cause of death	6m	Logistic regression Cox regression Tabulation
Hospital stay	Time to discharge	6m	Cox regression
Hospital re-admissions	Proportion of people re-admitted	6m	Logistic regression
DOAH-90	Days alive and out of hospital	90d	Linear regression of transformed measure (if appropriate)
Postoperative complications	Clavien-Dindo grading	At discharge	(Ordered) logistic regression, tabulation
MLLA of contralateral limb	Proportion of people who were a unilateral amputee who subsequently underwent contralateral MLLA.	6m	Logistic regression

A comprehensive SAP will be finalised prior to database lock by the trial statistician, with support from the TMG, and agreed by the TSC.

15.1.1Sub-group and Interim Analysis

No interim analysis is planned. Sub-group analyses may be performed for sex, history of diabetes mellitus, anaesthetic given, type of infusion device used and level of amputation. Any planned sub-group analyses will be agreed by the TMG and pre-specified in the SAP.

15.2 Qualitative Analysis

Qualitative interviews will be audio recorded, transcribed and de-identified for analysis; transcripts will be analysed using a thematic approach (67). We will use thematic analysis to identify key patterns in the interview transcript data (67). This will consist of a series of steps: familiarisation with data,

generating initial codes, and searching, reviewing, and defining themes. We will identify themes that relate to the objectives of the research but analysis will also allow new themes generated by interviewees to be identified. Contradictory data will be identified as points of contrast as well as similarities in order to understand views on PNC. References to identifiable personal details such as name, address, and date of birth, will be removed from the transcript. Vital measures will be put into place to ensure validity and reliability. Interview transcripts will be managed and coded using the qualitative coding software NVivo. The qualitative component of this study has been designed using the principles of the Critical Appraisal Skills Programme qualitative checklist, to ensure the quality of qualitative research (CASP 2006). More than one person will be involved in the analysis, and double coding will be carried out until consensus is reached.

15.3 Cost Effectiveness Analysis

A within-trial economic evaluation will assess:

1. Resource use and costs associated with the use of PNC compared to no PNC in the postoperative period.
2. Resource use and associated costs from baseline to six months post-amputation for PNC compared to no PNC.
3. Cost-effectiveness measured in terms of a) the incremental cost for percentage increase in freedom from pain at five days and b) the incremental cost per quality adjusted life year (QALY) gain at six months, with trial outcomes reported in a cost consequence analysis.

The primary health economic analysis will adopt a UK NHS perspective at six months. A partial societal perspective considering participant costs and lost work, will also be considered. A health economic analysis plan will be developed with the evaluation reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (68).

Delivery costs associated with PNC (compared to no PNC) will be calculated from trial records (e.g., device costs, drugs). Using a current understanding of costing surgical trials (69), and data from our feasibility trial, a process map/pathway of care for the intervention and control group will be produced with the trial team, targeting efficiency of costing on key resource drivers (e.g., replacement equipment and staff time). Participant-level resource use for both PNC and no PNC groups will be collected using an adapted Client Service Receipt Inventory (CSRI) developed to capture subsequent

resources to the NHS, patient and society based on good practice (70), and other surgical trial contexts (71). Data collected from trial report forms alongside expert clinical and participant opinion will be used to calculate resource use with relevant published unit costs or local records/literature sources used to value resource use in pound sterling. A comprehensive summary of costs to UK NHS will be produced.

The primary economic outcome will be QALY gain/lost at six months derived from participant reported Health-Related QoL. Utility scores will be obtained using the EQ-5D-5L instrument. EQ-5D-5L will be administered at baseline, and 3-month and 6-month follow-ups within the CSRI. No discounting will be undertaken as the trial horizon does not exceed 12 months.

Cost-utility analyses will be used to estimate the incremental cost per QALY gained at 6-months using the area under the curve approach and linear interpolation. An incremental cost-effectiveness analysis will be undertaken, based on primary clinical outcome analysis to assess costs relative to the primary clinical benefit achieved by using PNC in MLLA. The pattern of missing data (e.g., missing at random) will be examined and accounted for by suitable methods such as multiple imputation for missing observations of cost (resource category level) and EQ-5D-5L measure. Incremental net monetary benefit (INMB) for the PNC compared to no PNC will be calculated. The INMB will be presented at National Institute for Health and Care Excellence (NICE) specified cost-effectiveness threshold(s). To capture the full extent of the trial outcomes, other secondary outcomes will be presented in a cost-consequence analysis. A range of sensitivity analyses will test the robustness of results in different scenarios such as one-way analysis to investigate the impact of parameter variation.
Analyses will be adjusted using appropriate regression models. All analyses will be conducted on an intention to treat basis. A separate health economic analysis plan will be written alongside the SAP. The findings will be reported according to the Consolidated Standards of Reporting Trials statement (72).

16 Data Management

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents."* There is only one set of

source data at any time for any data element, as defined in the site source data agreement. The source data for PLACEMENT will be from a variety of sources as described in Table 2.

16.1 Data Collection

Data will be collected using an electronic CRF system with paper CRF back up for PROs. Training for completion of trial CRFs will be provided to the appropriate trial staff prior to trial commencement at site initiation.

16.2 Completion of Case Report Forms

All data collection will be completed using web based CRFs, held on a secure encrypted system hosted by Cardiff University. It is accessed by username and password and complies with General Data Protection Regulation 2016. If the web-based system is not accessible, the data will be inputted by local site staff once it is accessible. A full Data Management Plan for the PLACEMENT trial will accompany this protocol and will be stored in the TMF.

16.2.1 Electronic Case Report Forms

The system can be accessed on:

www.placement2.ctr.cardiff.ac.uk

A user password will be supplied to investigators upon completion of all processes required prior to site opening. Site staff will only have access to their own participants and not see other sites' participants. Web-based data collection forms should be completed as described in the PLACEMENT Site Manual.

16.2.2 Paper Case Report Forms

Paper CRFs will be used for PROs if the electronic database is not available, or if research staff are unavailable e.g. over the weekend. Data will then be entered on to the database by site staff at a later point. In accordance with the principles of GCP, the PI is responsible for ensuring accuracy, completeness, legibility, and timeliness of the data reported to the CTR in the CRFs. CRF pages and data received by the CTR from participating trial sites will be checked for missing, illegible, or unusual values (range checks) and consistency over time.

If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant participating site. The site shall be requested to respond to the data query on the data clarification form and update the necessary data within the database. All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant participating site. The completed data clarification form should be returned to the CTR, and a copy retained at the site along with the participant's CRFs. The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in a timely manner. Further details of data management procedures can be found in the PLACEMENT Data Management Plan.

16.3 Qualitative Data Management

All information, including any personal information (e.g., name), will be kept completely confidential. Recordings will not be labelled with participant name. Written quotes of what the participant says in the interview may be used word for word, but quotes will be anonymised. Participant names will not appear on any publications. All trial related records will be stored for 25 years. The results are likely to be published in medical journals over the next few years. The participants will not be personally identified in any report or publication. Full details of qualitative data management will be specified in the PLACEMENT Trial Qualitative Data Management Plan.

16.4 Data collection, use sharing, security and integrity

The personal data (including name, address, email address and telephone number) of participants will be stored on a dedicated study database. The data will be entered onto a password protected main database on secure Cardiff University maintained servers. Patients' identifiable data will be kept separately from clinical data. Participants will consent to clinical members of the research team viewing their records in order to gain baseline data and healthcare resource usage data during the six-month follow-up period. If participants consent to be contacted about the results of the trial, their contact details will be stored in encrypted files and will only be accessible by delegated members of the study team for purposes specified in the PIL. Participants will be asked to express their preferred method of contact (e.g. email or postal address) for this purpose and this question will be asked explicitly on the consent form.

A unique participant identification number (PID) will be assigned sequentially by site to each participant as they are allocated to a treatment arm. The PID will be used for the purpose of participant identification and data collection throughout the study.

Clinically trained members of the research team (research doctors and/or nurses) will have access to hospital and GP records for collection of resource usage data. This is described in the PIL and ICF. Members of the research team will also have access to trial specific data, and consent for this will be sought. Qualified Quantitative researchers, Statisticians and Data Managers at the Centre for Trials Research, Cardiff University will be responsible for data analysis.

Personal data will be stored or accessed for 3 to 6 months after the study has ended. Electronic files will be stored securely on a Cardiff University research drive with restricted access. Paper files will be stored in a locked cupboard for up to 5 years after database lock and then archived onsite for 25 years.

17 Study Within A Trial (SWAT): Video information given at the point of discharge to improve participant follow-up rates

17.1 Background

Attrition in the PLACEMENT feasibility trial was high; less than 40% of alive participants provided outcome data at six months (50). Research on how to improve follow-up, particularly in this cohort of participants, is essential given the importance the PPI focus group, and the team who developed the amputation Core Outcome Set (44), placed on long-term outcomes. Assessing tools aimed at improving follow-up aligns with the Prioritising Recruitment in Randomised Trials study (PrioRiTy II) priorities (73), including research question number 4: “what are the best ways to encourage trial participants to complete the tasks (e.g., attend follow-up visits, complete questionnaires) required by the trial?”.

We will conduct a study within a trial (SWAT) which will assess the presentation of video information at the point of discharge on follow up rates. This will include information about how the follow-up is organised and undertaken, and prompt discussion around its practicalities. This will be shown to the participant alongside a follow up information leaflet.

17.2 Methods

At the time of randomisation (to PNC no PNC), participants will be also randomised (1:1) to the SWAT. Every alive participant will be reviewed by the research team at day 7 (+/-2 days) to confirm capacity to consent, and those randomised to participate in the SWAT will be shown a short video, created by the TMG, about what the follow-up will entail, when it will be, and how long it will take. The video will also be shown to those participants randomised to the SWAT on the day of discharge, if possible.

All participants will be given a leaflet regarding their follow-up, and a chance to ask any questions regarding it. The video will contain the same information as the follow up information leaflet. Our primary hypothesis is that those shown the video will engage better with follow-up than those only given the information leaflet alone.

17.3 Results

The primary outcome of the SWAT will be successful completion of 6-month follow-up data capture. Completion rates will be presented as point estimates of the difference in rates alongside 95% confidence intervals.

17.4 Dissemination

The SWAT will be registered on the Northern Ireland MRC Trials Hub for Methodology Research SWAT registry. Dissemination of the results will be in line with NIHR guidance, and published open-access once results are available, without delaying for the results from the main trial.

18 Protocol/GCP Non-compliance

The PI should report any non-compliance to the trial protocol or the conditions and principles of GCP to the CTR in writing as soon as they become aware of it. The CTR will assess the nature and severity of any issues of non-compliance in accordance with their SOP.

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g., consent process or administration of trial intervention) or from GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in a non-compliance form and filed in the PLACEMENT TMF.

A CTR SOP is in place describing the procedure for identifying non-compliances, escalation to the central safety team and assessment of whether a non-compliance/deviation may be a potential Serious Breach.

19 End of Trial Definition

The treatment phase will be followed by a 6-month follow-up period, which will end 6-months after the last participant completes protocol treatment. The end of trial is defined as the date of final data capture of the last participant to meet the trial endpoints. Database lock, defined as the final lock of the database when no further locks are required, will be requested when all cleaning and validation of the data in the database is complete (within 6 months of the end of trial). Sponsor must notify the MHRA and main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

20 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 25 years. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The PI is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

21 Regulatory Considerations

21.1 CTA

This trial has Clinical Trials Authorisation (CTA) from the UK Competent Authority (CA): MHRA. Classification of whether any changes to the protocol is defined as a substantial amendment or not will be based on HRA guidance and sponsor assessment. All amendments will be reviewed by the TMG, and if necessary, sponsor representative, for approval prior to being submitted, via IRAS and email, to REC, HRA, and if necessary, the MHRA. The central trial team will alert all site trial teams and R&D departments once approval has been received for the amendment. The amendment history will be listed in the protocol and in the amendment log which is filed in the PLACEMENT TMF.

21.2 Ethical and Governance Approval

This protocol has approval from a Research Ethics Committee (REC) that is legally “recognised” by the United Kingdom Ethics Committee Authority for review and approval. This trial protocol will be

submitted through the relevant permission system for global governance review dependant on the location of the lead site i.e., Health and Care Research Wales for Wales-led trial. The trial will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1996, and later revisions.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation. All substantial protocol amendments must be approved by the REC responsible for the trial, in addition to approval by NHS R&D. Minor amendments will not require prior approval by the REC.

If the trial is stopped due to serious adverse events or an urgent safety measure it will not be recommenced without reference to the REC responsible for the trial. A summary of the results will be submitted to the REC responsible for the trial within one year of completion of trial closure.

21.3 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016. The data custodian and the translational sample custodian for this trial is the CI. This includes the optional collection of NHS number (or equivalent – e.g., CHI number in Scotland), name, date of birth, gender and postcode to register and trace participants with the HSCIC, and the collection of NHS number (or equivalent), to use NHS data for future research through NHS Digital.

21.4 Indemnity

- Non-negligent harm: This trial is an academic, investigator-led, and designed trial, coordinated by the CTR. The CI, local PIs and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The Association of the British Pharmaceutical Industry guidelines will not apply.
- Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a participant being treated within the hospital, whether the participant is participating

in this trial or not. Cardiff University does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

21.5 Trial Sponsorship

Cardiff University will act as Sponsor for trial with responsibilities delegated to the CTR. The CTR shall be responsible for ensuring that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments
- Conditions and principles of GCP
- Declaration of Helsinki (1996)
- UK Policy Framework for Health and Social Care Research
- The General Data Protection Regulation 2016
- The Human Tissue Act 2004
- Other regulatory requirements as appropriate.

Delegated responsibilities will be assigned to the sites taking part in this trial. The Sponsor has/will be delegating certain responsibilities to Cardiff University (CTR), the CI, PI, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and trial type.

21.6 Funding

This trial is funded by the NIHR HTA Programme (NIHR 134746).

22 Trial Management

22.1 Project Team

The project team will meet at least fortnightly and will include the CI, TL, TM, DMs, TS, TA, and other research staff directly employed to the trial. The project team will discuss all day-to-day management issues and will refer any key management decisions to the TMG.

22.2 Trial Management Group (TMG)

The TMG will consist of the CIs, Co-Applicants, Collaborators, TM, DM, TS, and TA. The role of the TMG will be to help set up the trial by providing specialist advice, input to and comment on trial procedures and documents (information sheets, Protocol, etc.). They will also advise on the promotion and running of the trial and deal with any issues that arise. The group will normally meet monthly throughout the course of the trial. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter which will be filed in the TMF.

22.3 Trial Steering Committee (TSC)

A TSC, consisting of an independent chair, and two/three other independent members including a patient representative, will meet at least annually. The first meeting will be before the trial commences to review the Protocol and arrange the timelines for the subsequent meetings. If necessary, additional/more frequent meetings may occur. The TM and TS will attend as observers. The TSC will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

22.4 Independent Data Monitoring Committee (IDMC)

To monitor accumulating data on safety and any trial intervention benefit, an IDMC will be established. The Committee will consist of an independent chair and two/three other independent members. The first meeting will take place before the trial commences to review the Protocol. The main role of the IDMC is to review the data periodically and make recommendations to the TSC. IDMC members will be required to sign up to the remit and conditions as set out in the IDMC Charter which will be filed in the TMF.

23 Quality Control and Assurance

23.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the PLACEMENT trial. Low monitoring levels will be employed and are fully documented in the trial monitoring plan. Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. All consent forms will be monitored centrally. Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI, and local R&D.

23.2 Audits and Inspections

The trial is participant to inspection by MHRA as the regulatory body. The trial may also be participant to inspection and audit by Cardiff University under their remit as Sponsor. The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/IRB review, and regulatory inspection(s), providing direct access to source data/documents. The site must inform the CTR of any MHRA inspections.

24 Publication Policy

All publications and presentations relating to the trial will be authorised by the TMG and will be in accordance with the trial's publication policy. In addition to the requirements of the NIHR HTA Programme publication model, we will publish the main trial results in international, high impact, peer-reviewed journals and present at surgical and anaesthetic conferences. With the assistance of our collaborators and lay representatives we will disseminate the trial findings to a wide NHS and general audience and vigorously promote uptake of the trial results into clinical care. This will include presentations at meetings and written executive summaries for key stakeholder groups.

At a local level we will interact with and promote research findings through wider NHS Trusts (Health Boards in Wales) and the NIHR Clinical Research Networks. Nationally, we will engage with NICE, the Vascular Society of Great Britain and Ireland, the European Society of Vascular Surgeons, the Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland, as well as relevant patient groups/charities such as Douglas Bader Foundation and the Limbless Association. We

anticipate the results directly impacting clinical amputation guidelines, which to date do not include recommendations regarding PNC usage.

25 Milestones

The PLACEMENT trial is a three-and-a-half-year trial with the following project timetable:

- Month 1-6: Trial set-up, contracts, regulatory approvals.
- Month 7-14: Internal pilot, site set-up (n=8, staffed by PI Co-applicants) and recruitment (n=98). Average recruitment rate: 2.03 participants/site/month.
- Month 15: Review of internal pilot, including early qualitative interview data of participants and HCPs, and PPI impact. Results reported to TSC and NIHR.
- Month 15-30: Complete site set-up (n=14) and recruitment. Average recruitment rate: 2.49 participants/site/month.
- Month 36: Last participant last follow-up.
- Month 37-42: Data cleaning, statistical analysis, prepare report, draft papers, stakeholder event.

26 PrinciPIL Study within a Trial

PLACEMENT will collaborate as a 'host' trial with the Medical Research Council funded PrinciPIL study: Developing Core Principles for Sharing Information about Potential Intervention Benefits and Harms in Patient Information Leaflets (REC reference 22/PR/0063, IRAS 305945) to embed the PrinciPIL 'Study Within a Trial' (SWAT) sub-study. The SWAT is being delivered by The Centre for Trials Research at Cardiff University.

This SWAT has been designed to determine the effects on reported adverse events (AEs), recruitment, and retention rates of a stakeholder-informed way of sharing information about potential trial intervention benefits and harms in patient information leaflets (PILs).

SWATs are cost-effective methods to resolve uncertainties about clinical trial processes, including different methods for obtaining consent. They use the same evaluation methods and techniques used in clinical trials but apply them to evaluations of trial process alternatives that are embedded within a host clinical trial. There are no additional assessments or procedures specific to the PrinciPIL SWAT and the SWAT will only collect data already collected as part of the host trial.

Background

Recent qualitative analysis of 33 PILs used in UK placebo-controlled trials registered between 2016 and 2019 revealed wide variability in the way information about potential trial intervention benefits and harms are shared in PILs (74). Roughly a third (10/33) did not contain any information about potential intervention benefits; by contrast, all (33/33) contained information about potential harms. The relative lack of information about potential benefits could cause information-induced AEs ('nocebo effects'). Supporting this hypothesis, a systematic review found that 49.1% (interquartile range 25.7%- 64.4%) of trial participants in placebo groups reported at least one AE. One in 20 (5%, interquartile range 2.3%-8.4%) dropped out due to a reported AE (75). The information-induced AEs could also affect recruitment and retention.

Possible ethical concerns also arise from the way information about potential trial benefits and harms are shared. Guidance regarding how to balance the presentation of potential trial intervention benefits and harms does not exist. Currently, every PI must negotiate their own method for presenting balanced information about benefits and harms within PILs. If information about potential harms can be presented honestly, while reducing information-induced AEs, then it could be an ethical requirement (based on the principle of non-maleficence) to do so (76).

Aims

The PrinciPIL SWAT sub-study aims to test a stakeholder-informed way of sharing information about potential trial benefits and harms in PILs to determine the effects on reported adverse events (AEs), recruitment, and retention rates.

Method

The standard PLACEMENT PIL will be compared with the PLACEMENT PrinciPIL PIL developed with extensive input on benefit and harm presentation from stakeholders (including patients, research ethics committee members, clinicians, senior trial managers).

Intervention 1: Standard PIL (designed by the PLACEMENT trial team)

Comparator 2: PrinciPIL PIL (designed by the PrinciPIL study team)

Method for allocating to intervention groups will be cluster randomisation.

7 - 8 participating NHS hospital sites (~100 patients recruited) will be randomised to either Intervention 1 (Standard PLACEMENT PIL) or the Comparator 2 (PrinciPIL PIL) using an online research randomizer (https://www.randomizer.org/). The randomising process will be performed by the PrinciPIL team and provided to the trial team prior commencing the SWAT.

Primary outcome: difference in reported AEs.

Secondary outcomes: difference in recruitment and retention rates, and differences in specific AEs.

The primary analysis (to be performed by the PrinciPIL study team) will be the comparison of the proportion of participants who report AEs in the different randomised groups. The secondary analysis will be a comparison of recruitment and retention rates. These analyses will be done in the context of a living meta-analysis of 5 PrinciPIL SWATs (embedded within 3 randomized controlled trials including the PLACEMENT trial).

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27 Appendices

Appendix 1 - SmPC for levobupivacaine 0.125%

Levobupivacaine 1.25 mg/ml solution for infusion

Summary of Product Characteristics Updated 24-Apr-2023 | Martindale Pharma, an Ethypharm Group Company

1. Name of the medicinal product

Levobupivacaine 1.25 mg/ml solution for infusion

2. Qualitative and quantitative composition

One ml contains 1.25 mg levobupivacaine (as hydrochloride).

Each 100ml-bag contains 125 mg levobupivacaine (as hydrochloride). Each 200ml-bag contains 250 mg levobupivacaine (as hydrochloride).

Excipients with known effect: 3.5 mg/ml of sodium per bag.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for infusion.

Clear colourless solution.

pH 4.0 – 6.5

Osmolality: 270 – 330 mOsmol/Kg

4. Clinical particulars

4.1 Therapeutic indications

Adults

Pain management

- Continuous epidural infusion for the management of postoperative pain and labour analgesia.

4.2 Posology and method of administration

Levobupivacaine should be administered only by, or under the supervision of, a clinician having the necessary training and experience.

Posology

"Inverted name". 1.25 mg/ml solution for infusion is for epidural use only. It must not be used for intravenous administration

Type of block	Concentration mg/ml	Infusion Rate Per Hour	
		ml	mg
Continuous Infusion:Post operative pain management	1.25	10-15	12.5 -18.75
Lumbar Epidural (analgesia in labour)	1.25	4-10	5-12.5

Careful aspiration before infusion is recommended to prevent intravascular injection. If toxic symptoms occur, the injection should be stopped immediately.

There is limited safety experience with levobupivacaine therapy for periods exceeding 24 hours. In order to minimise the risk for severe neurological complications, the patient and the duration of administration of levobupivacaine should be closely monitored (see section 4.4).

Maximum dose

The maximum dosage must be determined by evaluating the size and physical status of the patient. The maximum recommended dose during a 24 hour period is 400 mg.

For post-operative pain management, the dose should not exceed 18.75 mg/hour, however the accumulated dose for a 24 hour period should not exceed 400 mg. For labour analgesia by epidural infusion, the dose should not exceed 12.5 mg/hour.

Appendix 2 - SmPC for Ropivacaine hydrochloride 2 mg/ml solution for infusion

Ropivacaine hydrochloride 2 mg/ml solution for infusion

Summary of Product Characteristics Updated 08-Nov-2023 | Aspen

1. Name of the medicinal product

Ropivacaine hydrochloride 2 mg/ml solution for infusion

2. Qualitative and quantitative composition

1 ml solution for infusion contains ropivacaine hydrochloride monohydrate equivalent to 2 mg ropivacaine hydrochloride.

1 bag of 100 or 200 ml solution for infusion contains ropivacaine hydrochloride monohydrate equivalent to 200 mg and 400 mg ropivacaine hydrochloride respectively.

Excipients with known effect:

Each 100 ml bag contains 14.8 mmol (338.7 mg) sodium.

Each 200 ml bag contains 29.6 mmol (677.4 mg) sodium.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for infusion.

Clear, colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

Ropivacaine 7.5 mg/ml is indicated in adults and adolescents aged above 12 years of age for:

Surgical anaesthesia:

- Epidural blocks for surgery, including Caesarean section.
- Major nerve blocks.
- Field blocks.

Ropivacaine 10 mg/ml is indicated in adults and adolescents aged above 12 years of age for:

Surgical anaesthesia:

- Epidural blocks for surgery.

Ropivacaine 2 mg/ml is indicated for acute pain management

In adults and adolescents above 12 years of age for:

- Continuous epidural infusion or intermittent bolus administration during postoperative or labour pain.
- Field blocks.
- Continuous peripheral nerve block via a continuous infusion or intermittent bolus injections, e.g. postoperative pain management.

In infants from 1 year and children up to and including 12 years of age (per- and postoperative):

- Single and continuous peripheral nerve block.

In neonates, infants and children up to and including 12 years of age for (per- and postoperative):

- Caudal epidural block.
- Continuous epidural infusion.

4.2 Posology and method of administration

Ropivacaine should only be used by, or under the supervision of, clinicians experienced in regional anaesthesia.

Posology

Adults and adolescents above 12 years of age:

Appendix 3 - SmPC for Bupivacaine hydrochloride 0.125%w/v Solution for Infusion

Bupivacaine Hydrochloride 0.25%w/v Solution for Injection

Summary of Product Characteristics Updated 04-Dec-2023 | ADVANZ Pharma

1. Name of the medicinal product

Bupivacaine Hydrochloride 0.25%w/v Solution for Injection.

2. Qualitative and quantitative composition

Each 1ml solution contains 2.5mg anhydrous bupivacaine hydrochloride.

3. Pharmaceutical form

Solution for injection

4. Clinical particulars

4.1 Therapeutic indications

Local or regional anaesthesia with bupivacaine is indicated for:

- Surgical operations, including obstetric operations such as Caesarean section.
- Acute pain relief, including labour or postoperative pain.
- Diagnosis and treatment of chronic pain, e.g. sympathetic nerve blocks.

Bupivacaine can be used for different anaesthetic techniques including local infiltration, minor and major nerve blocks and epidural blockade.

- Surgical anaesthesia in adults and children above 12 years of age.
- Acute pain management in adults, infants and children above 1 year of age.

4.2 Posology and method of administration

Posology

Care should be taken in order to prevent acute toxic reactions by avoiding intravascular injection. Careful aspiration before and intermittently during the injection is recommended. For epidural anaesthesia, a test dose of 3 - 5ml of bupivacaine containing adrenaline is recommended, since an intravascular injection of an adrenaline-containing solution may be recognised by an increase in heart rate. Verbal contact with the patient and repeated measurements of heart rate (ECG) should be maintained following the test dose. Aspiration should be repeated prior to administration of the main dose. The main dose should be injected slowly in incremental doses of 4 - 5ml while keeping in constant contact with the patient. If toxic symptoms or signs of an intrathecal blockade occur, the injection should be stopped immediately.

Unnecessarily high doses of local anaesthetics are to be avoided. In general, complete blockade of all nerve fibres in large nerves, requires high concentrations of drug. For thinner nerves, or when only a sensory blockade is required (e.g. in the relief of labour pain), the lower concentrations producing less motor blockade are indicated. The volume of drug used will affect the extent of spread of anaesthesia.

For prolongation of the blockade, an indwelling catheter through which local anaesthetic drug can be injected or infused, may be used. This is common for epidural anaesthesia, but can also be used, for example, for brachial plexus anaesthesia and interpleural analgesia.

The following table is a guide to dosage for the more commonly used techniques. The clinician's experience and knowledge of the patient's physical status are of importance in calculating the required dose. When prolonged blocks are used, either by continuous infusion or by repeated bolus administration, the potential problem of increasing systemic concentrations must be addressed. Experience to date indicates that 400mg administered over 24 hours is well tolerated in average adults.

Dosage recommendations for Bupivacaine

The dosages in the table are those considered to be necessary for the production of a successful block and should be regarded as guidelines for use in the average adult. There are wide individual variations in the time to onset and the duration of anaesthesia and it is impossible to be precise. For other regional local anaesthetic techniques consult standard textbooks.

N.B. Risk of systemic effects of adrenaline with large volumes of adrenaline-containing solutions.

Type of block	Conc mg/ml	Dose	Onset (min)	Duration (Hours)	Indication	Comment