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Lidocaine for Neuropathic Cancer Pain (LiCPain): study protocol for a mixed-methods feasibility pilot study.

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Lidocaine for Neuropathic Cancer Pain (LiCPain): study protocol for a mixed-methods feasibility pilot study.

ABSTRACT

Introduction: Many patients experience unrelieved neuropathic cancer-related pain. Most current analgesic therapies have psychoactive side effects, lack of efficacy data for this indication, and potential medication-related harms. The local anaesthetic lidocaine (lignocaine) has the potential to safely and effectively manage neuropathic cancer-related pain when administered as an extended, continuous subcutaneous infusion. Data supports lidocaine as a promising, safe agent in this setting, warranting further evaluation in robust, randomised controlled trials. This protocol describes the design of a pilot study to evaluate this intervention and explains the efficacy, adverse effects and pharmacokinetic evidence informing the intervention.

Methods and analysis: A mixed-methods pilot study will determine the feasibility of an international first, definitive phase three trial to evaluate the efficacy and safety of an extended continuous subcutaneous infusion of lidocaine for neuropathic cancer-related pain. This study will comprise: a phase II double-blind randomised controlled parallel-group feasibility pilot of subcutaneous infusion of lidocaine hydrochloride 10%w/v (3000mg/30ml) or placebo (sodium chloride 0.9%) over 72 hours for neuropathic cancer-related pain, a pharmacokinetic sub-study and a qualitative sub-study of the patient and carer experiences. The pilot study will provide important safety data and help inform the methodology of a definitive trial, including testing proposed outcome measures, recruitment strategy, randomisation process and patients' acceptability of the methodology, as well as providing a signal of whether this area should be further investigated.

Ethics and dissemination: Participant safety is paramount and standardised assessments for adverse effects are built into the trial protocol. Findings will be published in a peer-reviewed journal and presented at conferences. This study will be considered suitable to progress to a phase III study if there is a completion rate where the confidence interval includes 80% and excludes 60%.

Trial registration: Australian New Zealand Clinical trials Registry on 22 May 2017, registration number ACTRN12617000747325.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first randomised controlled trial to our knowledge of extended continuous subcutaneous infusion of lidocaine for neuropathic cancer-related pain
- This trial has been robustly designed following CONSORT guidelines to achieve the aims and objectives
- Feasibility criteria are appropriately chosen as primary outcomes to provide crucial data informing a phase III study

- Mixed methodology provides greater depth and understanding of the intervention and factors which will impact implementation
- Stringent exclusion criteria required for safety may be a limitation, slowing recruitment

INTRODUCTION

Unrelieved cancer-related pain remains a pressing problem, with current treatments being unsatisfactory[1]. Patients with neuropathic cancer-related pain are significantly more likely to receive strong opioids and adjuvant analgesia, have a reduced performance status and report worse physical, cognitive and social functioning.[2]

Neuropathic cancer-related pain is thought to require multi-modal pharmacological therapy, with adjuvant analgesics such as anticonvulsants and antidepressants together with opioids. However, level I evidence for adjuvants in cancer-related pain is limited.[3] The efficacy seen in clinical practice is variable[4 5] and treatment is often associated with harms.[6] Both opioids and gabapentinoids carry risk of misuse, abuse and diversion which is increasingly recognized to impact people with cancer.[7 8] There is currently no 'gold standard' medication to manage neuropathic cancer-related pain.

Lidocaine offers an innovative approach to manage this challenging clinical problem.[9] This medication aims to provide analgesic benefit without significant psychoactive side effects, unlike alternatives in this setting. Lidocaine's mechanism of action is biologically plausible and targets pathways not previously investigated in this patient population.[10-13]
Systemic lidocaine can be administered as an intravenous or subcutaneous bolus, short or extended infusion. We define an extended infusion as lasting greater than 24 hours. Lidocaine is also likely to be cost-effective, as better cancer-related pain management is likely to reduce health system costs due to reduced unplanned hospital readmissions, hospitalisations, emergency department and medical attendances and shorter inpatient stays.[14 15] Moreover, subcutaneous lidocaine offers a therapeutic option for people with cancer who cannot swallow or tolerate the side effects of other anti-neuropathic medications.

Data support lidocaine as a promising, safe agent in this setting, warranting further evaluation in robust, randomised controlled trials. Three observational studies have found 67% to 87% response to continuous subcutaneous or intravenous lidocaine infusion in cancer pain or palliative care patients.[16-18] A 2015 Cochrane review found that lidocaine as a bolus dose or a short infusion is safe and more effective than placebo in treating chronic, non-cancer neuropathic pain,[19] as well as better than placebo for early post-operative pain.[20] A meta-analysis[9] of bolus intravenous lidocaine 4-5mg/kg over 30-80 minutes versus placebo in cancer pain showed a significant benefit for >50% reduction in cancer pain but not other outcomes. A single phase III randomised controlled trial[21] of subcutaneous lidocaine in cancer pain has evaluated the infusion of 10mg/kg lidocaine over 5.5 hours and found no effect on pain, which may have been related to the sub-therapeutic serum concentration in all but two participants out of 33 randomised. Studies have shown lidocaine may have an effect beyond the duration of infusion.[22 23]

Despite the use of extended, continuous subcutaneous infusion of lidocaine over days in clinical practice,[24] there are no randomised controlled trials evaluating subcutaneous lidocaine infusions of greater than six hours duration for the treatment of unrelieved neuropathic cancer-related pain.

The aim of this mixed-methods pilot study is to determine the feasibility of an international-first definitive phase three randomised double-blind parallel-arm trial that would evaluate the efficacy and safety of a continuous subcutaneous infusion of lidocaine for neuropathic cancer-related pain. The pilot will provide important safety data and help inform the methodology of a definitive trial, including testing proposed outcome measures, recruitment strategy, randomisation process and patient acceptability of the methodology to ultimately provide a signal of whether this treatment should be further investigated.

This paper complies with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations for protocol reporting,[25] and the study will report against Consolidated Standards of Reporting Trials guidelines.[26]

Objectives

The primary objective of this study is to determine the percentage of participants who complete the study intervention. This will be calculated by the number of participants in both arms who complete the study medication and procedures from day 1 to 4 as a percentage of the total number of participants randomised.

The secondary objectives are to evaluate other aspects of feasibility; preliminary efficacy, harms, health outcomes, and health service utilisation; and the pathophysiology of subcutaneous lidocaine infusion. Specific aims and objectives can be found in the protocol on the Australian New Zealand Clinical trials Registry (ANZCTR).[27]

METHODS AND ANALYSIS

Trial design

We propose a mixed-methods pilot study to determine the feasibility of a definitive phase III trial which would evaluate the efficacy and safety of a continuous subcutaneous infusion of lidocaine for neuropathic cancer-related pain.

This feasibility study will comprise:

- A phase II double-blind randomised controlled parallel-group feasibility pilot of subcutaneous infusion of lidocaine versus placebo over 72 hours for neuropathic cancer-related pain
  Descriptive quantitative data will provide important feasibility data about trial procedures, recruitment, preliminary efficacy, safety and health service use.
- A pharmacokinetic sub-study of subcutaneous lidocaine
  Pharmacokinetic data will inform the definitive study and confirm extrapolation from existing data to this subcutaneous infusion regimenn
- A descriptive qualitative sub-study of patient experience of the intervention
  Semi-structured interview data will inform the design of a definitive trial
- A descriptive qualitative sub-study of informal carer experience of the intervention
  Semi-structured interviews will generate understanding of the experience of the intervention and caring for a person with cancer-related neuropathic pain. The perspective

of informal carers is essential to inform the provision of holistic care and is likely to impact recruitment to a definitive study.

The three sub-studies will be undertaken in a subset of consenting patients. Methods and analysis plans for these will be fully reported together with publication of the results in accordance with relevant reporting guidelines.

Patient and Public Involvement

The investigator team includes a consumer who has been involved in study design and drafting of participant materials. She will be involved in analysis and interpretation of data obtained.

Setting

Data will be gathered from five palliative care inpatient units in Sydney, Australia. Participants must be inpatient for the 72 hours of the study. The study is sponsored by the University of Technology Sydney. The study will be coordinated by the IMPACCT trials coordination centre (ITCC). Scientific endorsement was provided by Cancer Symptom Trials.[28]

Study population

Inclusion and exclusion criteria are listed in Table 1.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion Criteria

• Age 18 years or more
• Capacity to provide informed consent
• Ability to complete study assessments and comply with the study procedures
• Participant is willing to be an inpatient for the duration of the trial
• Pain related to cancer or its treatment with an worst pain score of 4 or greater on an 11-point (0-10) numerical rating scale in the past 24 hours
• Patient's cancer may be solid tumour or haematological
• Neuropathic component to pain which the clinician assesses to meet the International Association for the Study of Pain criteria for neuropathic pain which is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system"[48] OR has a score of 12 or greater on the Leeds Assessment of
	• Previous adverse reaction to lidocaine (lignocaine) or other amide-type local anaesthetics such as prilocaine, mepivacaine or bupivacaine
	• Use of systemic lidocaine (lignocaine) infusion for analgesia within the four weeks prior to study entry at a dose greater than or equal to 1mg/kg/h intravenous or subcutaneous
	• Liver failure (Child class B or C, likely due to hepatic impairment)
	• Renal failure (eGFR <15ml/min/1.73m^2)
	• Cardiac comorbidity deemed a contraindication by the treating clinician including
	  ○ Symptomatic cardiac failure (New York Heart Association class II or greater[51] within the past year
	  ○ heart block (first, second or third degree) at any time in the

Neuropathic Symptoms and Signs Pain Scale (LANSS). [49] Mixed neuropathic/nociceptive pains are included as well as cancer induced bone pain which is considered to have a neuropathic component.[50] • An adequate trial of opioid medication defined as titration to the maximum tolerated dose as limited by adverse effects or titration to at least a dose of 30mg/day oral morphine equivalent, for at least 24 hours *or* inability to tolerate opioids (eg due to allergy) • An adequate trial of at least ONE adjuvant analgesic defined as titration to the maximum tolerated dose as limited by adverse effects or titration to at least a dose of Amitryptilline 37.5mg, Duloxetine 30mg, Gabapentin 900mg, Pregabalin 150mg, Venlafaxine 60mg or equivalent, for at least 24 hours *or* inability to tolerate any adjuvant analgesic listed above (eg. due to comorbidity, medication interaction or previous adverse effects) *or* inability to take oral medications (as determined by the treating clinician eg due to dysphagia) *or* expected poor absorption of oral medications (as determined by the treating clinician, eg due to vomiting) • Stable regular adjuvant analgesics, opioids, cannabinoids, antidepressants, anticonvulsants, benzodiazepines, paracetamol, non-steroidal anti-inflammatory drugs and steroids for 24 hours. Transdermal opioids must have had stable dosing for 48 hours due to the extended time to reach steady state. Short acting breakthrough opioid may be used as required.	past ten years. Participants managed with a permanent pacemaker are not excluded. ○ Stokes-Adams syndrome • Cardiac abnormalities at time of screening ○ bradycardia less than 60 beats per minute at rest whilst awake ○ systolic blood pressure less than 100mmHg or greater than 160mmHg sitting ○ unstable angina or myocardial ischemia ○ atrial or supraventricular tachycardia greater than 100 beats per minute at rest • Seizure episode within the past 4 weeks • Fluctuating level of consciousness or delirium as determined by the treating team • Acute porphyria • Current use of medications which may interact with lidocaine or impact its metabolism:[52] propranolol, phenytoin, amiodarone, metoprolol, nadolol, St John's Wort, donepezil, cimetidine, flecainide, fluvoxamine, dihydroergotamine, vernakalant, saquinavir, dronedarone, amprenavir, lopinavir, propofol, arbutamine, atazanavir, succinylcholine, dasabuvir, paritaprevir, cobicistat, hyaluronidase, delavirdine, fosamprenavir, etravirine, ombitasvir, quinidine, disopyramide, procainamide, tocainide, mexiletine, propafenone, encainide, moricizine, bupropion, telaprevir, penbutolol, rapacuronium, nevirapine, nitrous oxide, cisatracurium, indinavir, ritonavir • Participants who have participated in a clinical study of a new chemical entity within the four weeks prior to study entry • Pregnant or breastfeeding

Study population

The intervention is described in Table 2.

Table 2: Intervention

Intervention

Participants will be randomised to receive the intervention or placebo, with both treatment arms receiving best practice standard of care.

1. **Lidocaine Hydrochloride 10%w/v (3000mg/30ml)**
2. **Placebo: Sodium chloride 0.9%**

The appropriate dose of interventional product or identical volume of placebo will be diluted in sodium chloride 0.9% to the volume of the syringe driver(s). All study drugs will be prescribed as a continuous subcutaneous infusion to be changed every 24 hours of the intervention period. There will be up to two dose modifications during the treatment period, at 24 hours and 48 hours, unless toxicity requires a dose reduction. All doses will be rounded to the nearest 100mg.

The continuous subcutaneous infusion of lidocaine/placebo will commence on day 1 at 1mg/kg/h (maximum 120mg/h).

The patient will be assessed for efficacy and toxicity on days two and three between 0.5 and 4 hours prior to the infusion change time. The dose for the next 24 hours will be charted according to the following algorithm:

- The dose will be increased by 0.5mg/kg/h every 24 hours to a maximum of 2mg/kg/h or 120mg/h (whichever is lower).

Exceptions:

- If the patient's average and worst pain score in the last 24 hours is ≤3/10, the dose will remain the same
- If there is any new or increased toxicity, this will be managed according to the protocol, which may include treatment of the symptom, dose reduction or cessation of infusion

After 72 hours (on day 4), the infusion will be ceased.

All medications will be charted on the standard inpatient medication chart and will be signed off by nursing staff according to local protocol.

Concomitant care

Best practice standard of care will include continuation of prescribed analgesic or potentially analgesic medications (without further dose change) in both arms of the study, and additional opioid use as required by the patient for breakthrough pain. Due to the fluctuating nature of neuropathic cancer-related pain, and the high psychosocial distress that accompanies a diagnosis of cancer, it would be unethical to deny this population access to breakthrough medication (typically an opioid). If a participant becomes unable to tolerate medications, equivalent substitutions may be made.

Rationale for dose schedule

The intervention schedule has been devised to maximise the likelihood of benefit while minimising the risk of adverse events. The commencing dose, dose increments, and maximum doses are within the doses where efficacy has been seen in other settings, and where reported toxicity is infrequent as outlined below.

Weight-based dosing will be used as lidocaine pharmacokinetics are influenced by body size.[29]

The effect of lidocaine is dose-dependent.[30 31] Therefore, it is proposed to increase the dose if optimal analgesic benefit has not been obtained. Adverse effects are also likely to be dose-related, and severe reactions are often preceded by somnolence and paresthesia.[32]

Selection of starting dose (mg/kg), increments, and maximal doses of lidocaine are limited by the fact that there are no prospective interventional trials evaluating an extended continuous infusion of lidocaine for pain. The longest randomised controlled trials were by Hawley[21] who evaluated 10mg/kg subcutaneous lidocaine over 5.5 hours and found no effect on cancer pain and Tremont-Lukats[30] who randomized 32 patients with neuropathic pain to placebo, 1, 3 or 5 mg/kg/h intravenous infusion of lidocaine over six hours and found a benefit of lidocaine 5mg/kg/h after four hours, which lasted a further six hours. Blood pressure, heart rate, ECG readings as well as adverse effects were monitored throughout both trials. No serious adverse events were reported.

Available pharmacokinetic data have also been considered in deciding the optimum dose schedule, although lidocaine serum concentrations do not always correlate with toxicity, as cases of toxicity are found at serum concentrations within the presumed 'therapeutic range'. Most of the pharmacokinetic data for lidocaine is from intravenous studies in which bioavailability is 100%.[33] The bioavailability of subcutaneous lidocaine, the route being used in this study, is dependent on the vascularity of the site, and is likely to be less than intravenous administration. In a horse model, when compared to administration of an equivalent intravenous lidocaine dose, a subcutaneous lidocaine dose may take ten times longer to reach a maximum concentration which is nearly three times lower.[34]

Physical signs of toxicity are more likely seen at lidocaine serum concentrations above 6 to 10 µg/ml, and serious adverse effects are rare below 5µg/ml.[33] Adverse effects typically follow a progression with mild adverse effects such as numbness, tinnitus, lightheadedness, dizziness, confusion and visual disturbance at lidocaine serum concentrations around 3-8µg/ml, nausea and vomiting, severe dizziness, decreased hearing, tremors and changes in blood pressure and pulse at serum concentrations 8-12 µg/ml and drowsiness, confusion, muscle twitching, convulsions, loss of consciousness, cardiac arrhythmias and cardiac arrest at serum concentrations greater than 12µg/ml.[35]

Pharmacokinetic data are available from a study by Ferrini[36] who reported a case series of six patients with cancer pain. Infusions were continued until death, for up to 240 days. Two patients were given intravenous lidocaine at 10-48mg/h intravenously and returned concentrations from 2-9.3µg/ml. Four patients were given lidocaine 32-80mg/h subcutaneously, and lidocaine serum concentrations were 1.3-3.3µg/ml. Schwartzman[37] found that when intravenous lidocaine infusion was given for chronic regional pain syndrome at 88mg/h, plasma

concentrations were between 1.1-4.4µg/ml, but at 120mg/h, 3 out of 49 patients had plasma concentrations between 5.1-6.1µg/ml. Mild self-limiting adverse effects were found at 120 to 144 mg/h. Serum lidocaine concentrations were obtained in a subset of the study by Thomas[17] of intravenous lidocaine at a dose of 1-2mg/kg bolus followed by 1mg/kg/h, which found a mean lidocaine serum concentration of 5.1µg/ml and standard deviation of 2.9µg/ml.

Several case series describe other lidocaine dose ranges used in clinical practice for analgesia. Brose[38] gave three patients with cancer pain randomised boluses of lidocaine 4mg/kg, fentanyl or normal saline. This was followed by a subcutaneous infusion of lidocaine 100-160mg/h for 3 weeks to 6 months with good analgesia and no attributable adverse effects. Blood concentrations ranged from 1.3µg/ml to 5µg/ml. In two patients, recurrent pain was associated with lidocaine blood concentrations under 2µg/ml. Amikura[16] gave 32 patients with neuropathic cancer pain lidocaine with an average maintenance dose of 38mg/h (range: 8-60mg/h) for 5 to 158 days, and 87.5% experienced significant pain relief. Seah[39] reported 23 hospice patients with a median subcutaneous lidocaine dose of 0.65mg/kg/h. Thomas[17] conducted a retrospective chart review of 82 consecutive hospice patients as above which found 82% had a major response and 8% had a partial response of their pain.

Because of limited prospective data for extended continuous infusions of lidocaine in cancer-related pain or neuropathic pain populations, the following data from randomised controlled trials evaluating perioperative pain was also considered. Swenson[40] found that, with a dosing regimen of intravenous lidocaine 2mg/minute for patients under 70kg and 3mg/minute for patients over 70kg, several patients had potentially toxic plasma concentrations. This regimen was changed to 60mg/h and 120mg/h, respectively. Herroeder[41] found that an intravenous infusion of 120mg/h did not produce any plasma concentrations above 5µg/ml. These patients were monitored, and no adverse effects were observed. Kuo[23] found 3 patients in the intravenous lidocaine group developed intermittent bradycardia at doses of 3mg/kg/h.

After considering the above data, a starting lidocaine dose of 1 mg/kg/h was chosen. This dose is unlikely to cause serious adverse effects given experience in previous trials. In addition, the infusion will be delivered subcutaneously, which is likely to have less bioavailability and systemic absorption than the intravenous infusions used for cardiac stability. Nonetheless, rigorous monitoring (including vital signs, ECG readings and structured symptom assessment for adverse effects) will occur to detect and manage potential adverse events as soon as possible. Lidocaine dose titration up to 2mg/kg/h will allow for individual response, with patients remaining on the minimal dose required for adequate analgesia. Although appearing to have better efficacy and lower risks of serious adverse events in a non-cancer population, higher doses would need to be used with caution in the cancer population, who may have a higher rate of frailty and comorbidity. Therefore, a maximum dose of 120mg/h (regardless of the calculated weight-based dose) will be imposed to limit the risks from higher dose infusions[37 40].

Outcomes and data collection

The primary outcome is the rate of completion of study procedures and medication use from day 1 to day 4. A completion rate of 80% or more of randomised patients will be considered feasible, while a completion rate of 60% or less will be considered unacceptable.

The secondary feasibility outcomes are the number of eligible participants who are consented to and randomised within the first 18 months from the lead site opening, recruitment:screening

ratio, completion:screening ratio, rate of complete data sets, and time taken to complete the study measures at the main daily assessment. Other secondary outcomes measure preliminary efficacy, toxicity, health outcomes and health service utilisation associated with the intervention, and the relationship between lidocaine serum concentration and dose/efficacy/toxicity.

Table 3 provides an overview of the data collection tools used in this study. SPIRIT **Error! Reference source not found.** [25] describes the tools and data collected at each study time point. The systematic adverse effects screening assessment is shown in Table 4. Participants will be reviewed face-to-face daily from baseline to day 4 in the four hours before intervention dose change, then by telephone during follow up.
In the pharmacokinetic sub-study, timed blood sample collection will occur daily, 20 to 24 hours after commencing of the lidocaine infusion. Samples will be analysed using a validated HPLC assay[42] to estimate lidocaine and metabolite concentrations.

Table 3: Overview of study instruments

Instrument	Details
Eligibility and demographic	
Leeds assessment of neuropathic symptoms and signs (LANSS)	Seven item scale including sensory description and examination. Score of 12 or greater has 85% sensitivity that neuropathic mechanisms likely contribute to the patient's pain[49]
Charlson Comorbidity Index (CCI)	Score composed of major comorbidities weighted to reflect risk of death[53]
Non-pharmacological management	Use of patient education, pain diary, physiotherapist, occupational therapist, psychologist, music therapist or other complementary therapy to improve pain management collected from medical record or participant recollection. Recommended by guidelines[47]
Efficacy assessments	
Brief Pain Inventory – Short Form (BPI-SF)	Validated 9-item tool based primarily on 0-10 numeric rating scale assessing pain intensity and impact.[54] Question 7 omitted to reduce participant burden as medication information collected by study staff
Worst pain	Numeric rating scale from 0 to 10 of worst pain in the last 24 hours
Average pain	Numeric rating scale from 0 to 10 of average pain in the last 24 hours
Neuropathic Pain Symptom Inventory (NPSI)	12 item questionnaire covering the domains of superficial and deep spontaneous pain, paroxysmal pain, evoked pain and paresthesia/dysaesthesia. Validated to assess neuropathic pain[55] and may detect treatment effect[48]
Personalised pain goal	Patients asked to describe on a 0-10 scale the level/intensity of pain that will allow the to

	achieve comfort in physical, functional, and psychosocial domains[56]
Medications	Regular opioid and adjuvant analgesics recorded Breakthrough medication formulation, route of administration, frequency prescribed, number taken during the prior 24-hour period
Health and service use outcomes	
EQ-5D-5L	Validated tool measuring five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) of health-related quality of life with relevant population norms[57-59]
Global impression of change	Seven-point scale regarding participant perception of change in overall status since study commencement; graded from 'very much worse' to 'very much improved'
Australia-modified Karnofsky Performance Status (AKPS)	Validated scale measuring performance status from 100 (normal) to 0 (dead)[60]
Resource Utilisation Group Activities Daily Living (RUG-ADL)	Four-item scale measuring patient motor function for activities of daily living including bed mobility, toileting, transfers and eating[61], of most value when AKPS is less than 60[62]
Australian Refined Diagnosis Related Group (AR-DRG)	Groups inpatient stays into clinically meaningful categories of complexity that consume similar amounts of resources[63]
Toxicity	
Adverse effects	Documented using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0[64] terminology with indication of severity, likely causality, and action taken. Vital signs, electrocardiogram (ECG), and structured toxicity assessment will aid this. These will be measured in a full assessment daily. An additional focused toxicity screen will occur three hours after dose changes to improve safety.

Table 4: Adverse effect screening assessment

	Yes	No
Fatigue, somnolence, lethargy, depressed level of consciousness, delirium, hallucinations		
Paraesthesia, circumoral paraesthesia		
Seizure, tremor		
Light headedness, dizziness, presyncope, syncope, headache, blurred vision, throat tightness		

tinnitus		
Ataxia, dysarthria		
Depression, anxiety, euphoria		
Palpitations		
Chest pain		
Cardiac failure, pedal edema		
Review vital signs: bradycardia less than 60 beats per minute at rest, awake systolic blood pressure less than 100mmHg or greater than 160mmHg tachycardia greater than 100 beats per minute at rest oxygen saturation less than 88% on room air respiratory rate less than 8 breaths per minute		
Review ECG: arrhythmia, conduction disorder		
Dyspnoea, cough, wheezing		
Anaphylaxis		
Injection site reaction (check site)		
Nausea, vomiting, constipation		
Pruritis		

Sample size and Recruitment

Based on an acceptable completion rate of 80% and an unacceptable completion rate of 60% the sample size is 36 participants. Participants will be invited to participate on admission to the palliative care unit and during regular screening at each site. Regular promotion of this study to clinicians at this site will aim to improve recruitment. Advertising posters may be placed in clinical areas.

Allocation

At each centre, potential participants will be sequentially allocated an ID number. The REDCap (Research Electronic Data Capture) randomisation tool will be used to facilitate randomisation. REDCap is a secure web application for building and managing online surveys and databases.[43] Random allocation tables will be created by the trial statistician and uploaded into the REDCap project. Treatment for each participant will be allocated according to a block randomisation schedule in a 1:1 ratio. The site investigator or delegate will enrol participants. To maintain the blind, the site pharmacist will consult the online REDCap tool to randomise.

Blinding

Treatment allocation will not be disclosed to participants, study staff or, treating clinicians. All investigators except the collaborative national manager and statistician will be blinded. The study medication and placebo will be packed into identical syringes and labelled by an accredited pharmaceutical packaging facility holding a license to manufacture therapeutic goods for clinical trials. All medicine packs will be prepared by the unblinded site clinical trial pharmacist according to the randomisation schedule. The ward nurse or study nurse will load the syringe driver from the dispensed study medications. A nursing record of administration will document study medication administered and discarded. Used syringes will be disposed on the ward.

Unblinding will only be done in cases of emergencies where knowledge of the code will have consequences for clinical decision making.

Data management

Deidentified study data will be collected on paper worksheets and then entered onto and managed on REDCap database. All identifiable data (master list, consent forms, pathology reports, copies of medical record) will be filed separately to the worksheets and stored securely as set out in Good Clinical Practice guidelines.[44] Data will be stored for 15 years, then destroyed.

Statistical and data analysis methods

The study completion rate will be calculated by the number of participants in both arms who complete the study medication and procedures from day 1 to 4 as a percentage of the total number of participants randomised. A rate that has a confidence interval including 80% and excluding 60% will be considered feasible.

The number of eligible participants who are consented and randomised within the first eighteen months from the lead site opening will be documented. Thirty-six patients will be considered satisfactory. Study chronology will be adjusted if the study requires a break for operational reasons. The number of patients randomised as a percentage of the patients screened will be calculated. The data completion rate will be calculated. A rate of greater than 80% of patients with a complete data set will be considered satisfactory. The mean and range of time taken to complete study measures will be calculated for the major assessment point prior to dose adjustment.

Descriptive statistics will be used to calculate the proportion of participants with improvements in preliminary efficacy measures. A cumulative responder graph for all changes in the worst pain score on BPI-SF on day 4 will be plotted. Sub-group analysis will be performed to evaluate potential biomarkers or responses. Missing data will be imputed where possible by carrying forward the last available measurement. The rate of adverse effects will be tabulated. A preliminary economic analysis will describe the direct cost of treatment, health services use and health-related quality of life measured using the EQ-5D-5L. A comparison of the interference of the subscale on BPI-SF and RUG-ADL between arms will also be conducted.

In the pharmacokinetic sub-study concentration-time data will be used to estimate the steady-state concentration (Css) of lidocaine the maximum observed concentration (Cmax) and the time to the Cmax. Css will be correlated with pharmacological effects of lidocaine.

Monitoring

Adverse events and serious adverse events will be reported using a secure online reporting system to enable study wide reporting and reviewed by an independent medical monitor. The role of the medical monitor[45] is to provide oversight and review of safety reports. Serious adverse events will also be reported to the relevant human research ethics committee.

ETHICS AND DISSEMINATION

Participant safety is paramount and will be carefully monitored. Standardised assessments for

adverse effects are built into the trial protocol. The trial will be conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice Guidelines.[46]

Obtaining consent for this study will be a process of information exchange between the study staff, the potential participant and any other person the potential participant believes should be included in the discussion. The participant information sheet will be used as a basis for the discussion, which will cover all procedures, benefits, burdens and side effects expected or possible during the study.

Findings will be published in peer-reviewed journals and presented at local, national, and international conferences. This study will be considered suitable to progress to a phase III study if there is a completion rate where the confidence interval includes 80% and excludes 60%. Quantitative and qualitative data will be synthesised in an iterative process with the investigator team. Recommendations generated from the data synthesis will inform the design of a subsequent phase III study..

Trial status

The current study protocol is version 3.0 dated 1 June 2022 Recruitment commenced 13th May 2019 and is expected to be completed by January 2023. Recruitment and trial operation have been impacted by Covid-19.

DISCUSSION

This project provides crucial feasibility data for a program of work that aims to improve the management of unrelieved neuropathic cancer-related pain and influence clinical practice. Unrelieved neuropathic cancer-related pain is highly prevalent, with a significant impact on the patient, carer, healthcare system, and society.[2] Continuous subcutaneous infusion of lidocaine for cancer-related pain is a promising intervention that has been prospectively investigated only rarely and inconclusively in small-scale randomised controlled trials with a short infusion duration. Lidocaine is currently used variably in clinical practice with a scant evidence base. Data generated by this work will directly lead to a recommendation to clinicians in the Australian Cancer Pain guideline recommendations[47] and support clinicians to provide the best evidenced-based neuropathic cancer-related pain management.

DECLARATIONS

Ethics approval and consent to participate

The protocol and Patient Information and Consent Form have been approved by Sydney Local Health District (Concord) Human Research Ethics Committee 2019/ETH07984 and University of Technology Sydney ETH17-1820. Protocol amendments are communicated by email and regular trial site meetings and trial investigator meetings after approval by the relevant ethics and governance committees.

Consent for publication

Not applicable

Availability of data and materials

The deidentified trial dataset will be available on request. All investigators will have access to the full re-identifiable data.

Competing interests

This is an investigator initiated study. The study sponsor and funders do not have authority over this study.

AL has received honoraria for lectures and educational material from BMS and Astra Zeneca. DS is funded by the Sydney Partnership for Health, Education, Research and Enterprise as a translational research fellow. AM is a member of the clinical advisory board for Bod Australia, has received honoraria for conference presentations from Bayer, is a member of the DSMB of the CannabisCINV study and is a member of the advisory board for the Lambert Cannabinoid Therapeutics Initiative. CS is a member of the executive committee of ANZSPM and of the executive of PCNT.

Funding

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Author contributions

JL, MA, ML, JP and CS conceived this work. All authors provided substantial contributions to the design of the work. JL, MA and GP wrote the first draft of this work and all authors revised it critically for important intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Acknowledgements

Not applicable

Abbreviations

Abbreviations are listed in Table 5.

Table 5: List of abbreviations

>	Greater than
<	Less than
AKPS	Australia-modified Karnofsky Performance Status
AR-DRG	Australian Refined Diagnosis Related Group
BPI-SF	Brief Pain Inventory – Short Form
CCI	Charlson Comorbidity Index
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0
ECG	electrocardiogram
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	EuroQual-5 Domains-Five Level
ICH GCP	International Conference on Harmonisation, Good Clinical Practice
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
NPSI	Neuropathic pain symptom inventory
NRS	Numeric Rating Scale
PaCCSC	Palliative Care Clinical Studies Collaborative
PGI-C	Patient Global Impressions scale - Change
PK	Pharmacokinetic - serum lidocaine (lignocaine) level
PRO	Patient Reported Outcome
RUG-ADL	Resource Utilisation Group – Activities of Daily Living

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Figure 1: SPIRIT figure of study assessments and schedule

	Eligibility	**Baseline Day 1**	**Day 2-3**	**Day 4**	**Follow up days 8, 15, 29**	**Early cessation of infusion**
Investigations						
Liver function test, potassium, creatinine, INR	*					
PK sub-study (if applicable)		*	*	*		
Medical file review						
Demographics	*					
Diagnosis	*					
AKPS		*		*		
RUG-ADL		*		*		
Charlson Comorbidity Index (CCI)		*				
Selected medications		*			*	
Breakthrough medications		*	*	*	*	
Non-pharmacological management		*				
Admission/discharge date, AR-DRG		*			*	
Patient assessed (PRO assessments)						
BPI-SF		*		*		*
Worst pain	*		*		*	
Average pain			*		*	
NPSI		*		*		*
EQ-5D-5L		*		*		
Global impression of change				*		*
Interview sub-study (if applicable)				*		
Clinician assessed						
Medical assessment	*					
LANSS	*					
Personalised pain goal		*				
Weight and estimated height		*				
Heart rate, Pulse oximetry, Blood pressure, Respiratory rate four times a day	*	*	*	*		*
12 lead ECG	*		*			
Toxicity assessment		*	*	*	*	*
Focused toxicity safety screen		*	*			
Adverse effects		*	*	*	*	*

AKPS: Australia-modified Karnofsky Performance Status; AR-DRG: Australian Refined Diagnosis Related Group; BPI-SF:Brief Pain Inventory – Short Form; CCI: Charlson Comorbidity Index; EQ-5D-5L: EuroQual-5 Domains-Five Level; ECG: echocardiogram; INR: International Normalised Ratio; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs ; NPSI: Neuropathic Pain Symtom Inventory; PRO: patient-reported outcomes; RUG-ADL: Resource Utilisation Group Activities Daily Living. Additional assessments may be performed if required due to adverse effects as clinically indicated.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	In ANZCTR
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Separate file
	5b	Name and contact information for the trial sponsor	4/ contact information on request
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
	6b	Explanation for choice of comparators	2
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Figure 1
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9, ANZCTR
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Table 2
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	supplement
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Lidocaine for Neuropathic Cancer Pain (LiCPain): study protocol for a mixed-methods pilot study.

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Lidocaine for Neuropathic Cancer Pain (LiCPain): study protocol for a mixed-methods pilot study.

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Lidocaine for Neuropathic Cancer Pain (LiCPain): study protocol for a mixed-methods pilot study.

ABSTRACT

Introduction: Many patients experience unrelieved neuropathic cancer-related pain. Most current analgesic therapies have psychoactive side effects, lack efficacy data for this indication, and have potential medication-related harms. The local anaesthetic lidocaine (lignocaine) has the potential to help manage neuropathic cancer-related pain when administered as an extended, continuous subcutaneous infusion. Data support lidocaine as a promising, safe agent in this setting, warranting further evaluation in robust, randomised controlled trials. This protocol describes the design of a pilot study to evaluate this intervention and explains the pharmacokinetic, efficacy and adverse effects evidence informing the design.

Methods and analysis: A mixed-methods pilot study will determine the feasibility of an international first, definitive phase three trial to evaluate the efficacy and safety of an extended continuous subcutaneous infusion of lidocaine for neuropathic cancer-related pain. This study will comprise: a phase II double-blind randomised controlled parallel-group pilot of subcutaneous infusion of lidocaine hydrochloride 10%w/v (3000mg/30ml) or placebo (sodium chloride 0.9%) over 72 hours for neuropathic cancer-related pain, a pharmacokinetic sub-study and a qualitative sub-study of patients' and carers' experiences. The pilot study will provide important safety data and help inform the methodology of a definitive trial, including testing proposed recruitment strategy, randomisation, outcome measures, and patients' acceptability of the methodology, as well as providing a signal of whether this area should be further investigated.

Ethics and dissemination: Participant safety is paramount and standardised assessments for adverse effects are built into the trial protocol. Findings will be published in a peer-reviewed journal and presented at conferences. This study will be considered suitable to progress to a phase III study if there is a completion rate where the confidence interval includes 80% and excludes 60%. The protocol and Patient Information and Consent Form have been approved by Sydney Local Health District (Concord) Human Research Ethics Committee 2019/ETH07984 and University of Technology Sydney ETH17-1820.

Trial registration: Australian New Zealand Clinical Trials Registry on 22 May 2017, registration number ACTRN12617000747325.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first randomised controlled trial to our knowledge of extended continuous subcutaneous infusion of lidocaine for neuropathic cancer-related pain
- This trial has been robustly designed following CONSORT guidelines to achieve the aims and objectives
- Feasibility criteria are appropriately chosen as primary outcomes to provide crucial data informing a phase III study
- Mixed methodology provides greater depth and understanding of the intervention and factors which will impact implementation

- Stringent exclusion criteria required for safety may be a limitation, slowing recruitment

INTRODUCTION

Unrelieved cancer-related pain remains a pressing problem, with current treatments being unsatisfactory[1]. Patients with neuropathic cancer-related pain are significantly more likely to receive strong opioids and adjuvant analgesia, have a reduced performance status and report worse physical, cognitive and social functioning.[2]

Neuropathic cancer-related pain is thought to require multi-modal pharmacological therapy, with adjuvant analgesics such as anticonvulsants and antidepressants together with opioids. However, level I evidence for adjuvants in cancer-related pain is limited.[3] The efficacy seen in clinical practice is variable[4 5] and treatment is often associated with harms.[6] Both opioids and gabapentinoids carry risk of misuse, abuse and diversion which is increasingly recognized to impact people with cancer.[7 8] There is currently no 'gold standard' medication to manage neuropathic cancer-related pain.

Lidocaine offers an innovative approach to manage this challenging clinical problem.[9] This medication aims to provide analgesic benefit without significant psychoactive side effects, unlike alternatives such as opioids where this may limit dose escalation. Lidocaine's mechanism of action is biologically plausible and targets pathways not previously investigated in this patient population.[10-13]
Systemic lidocaine can be administered as an intravenous or subcutaneous bolus, short or extended infusion. We define an extended infusion as lasting greater than 24 hours. Lidocaine is also likely to be cost-effective, as better cancer-related pain management is likely to reduce health system costs due to reduced unplanned hospital readmissions, hospitalisations, emergency department and medical attendances and shorter inpatient stays.[14 15] Moreover, subcutaneous lidocaine offers a therapeutic option for people with cancer who cannot swallow or tolerate the side effects of other anti-neuropathic medications.

Data support lidocaine as a promising, safe agent in this setting, warranting further evaluation in robust, randomised controlled trials. Three observational studies have found 67% to 87% response to continuous subcutaneous or intravenous lidocaine infusion in cancer pain or palliative care patients.[16-18] A 2015 Cochrane review found that lidocaine as a bolus dose or a short infusion is safe and more effective than placebo in treating chronic, non-cancer neuropathic pain,[19] as well as better than placebo for early post-operative pain.[20] A meta-analysis[9] of bolus intravenous lidocaine 4-5mg/kg over 30-80 minutes versus placebo in cancer pain showed a significant benefit for >50% reduction in cancer pain but not other outcomes. A single phase III randomised controlled trial[21] of subcutaneous lidocaine in cancer pain has evaluated the infusion of 10mg/kg lidocaine over 5.5 hours and found no effect on pain, which may have been related to the sub-therapeutic serum concentration in all but two participants out of 33 randomised. Studies have shown lidocaine may have an effect beyond the duration of infusion.[22 23]

Despite the use of extended, continuous subcutaneous infusion of lidocaine over days in clinical practice,[24] there are no randomised controlled trials evaluating subcutaneous lidocaine infusions of greater than six hours duration for the treatment of unrelieved neuropathic cancer-related pain.

This mixed-methods pilot aims to determine the feasibility of undertaking an international-first

definitive phase three randomised double-blind parallel-arm trial to evaluate the efficacy and safety of a continuous subcutaneous infusion of lidocaine for neuropathic cancer-related pain. The pilot will provide important safety data and help inform the methodology of a definitive trial, including testing proposed outcome measures, recruitment strategy, randomisation process and patient acceptability of the methodology to ultimately provide a signal of whether this treatment should be further investigated.

This paper complies with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations for protocol reporting,[25] and the study will report against Consolidated Standards of Reporting Trials guidelines.[26]

Objectives

The primary objective is to determine the percentage of participants who complete the study intervention. This will be calculated by the number of participants in both arms who complete the study medication and procedures from day 1 to 4 as a percentage of the total number of participants randomised.

The secondary objectives are to evaluate other aspects of feasibility; preliminary efficacy, harms, health outcomes, and health service utilisation; and the pathophysiology of subcutaneous lidocaine infusion. Specific aims and objectives can be found in the protocol on the Australian New Zealand Clinical trials Registry (ANZCTR).[27]

METHODS AND ANALYSIS

Trial design

We propose a mixed-methods pilot study to determine the feasibility of a definitive phase III trial which would evaluate the efficacy and safety of a continuous subcutaneous infusion of lidocaine for neuropathic cancer-related pain.

This feasibility study will comprise:

- A phase II double-blind randomised controlled parallel-group pilot of subcutaneous infusion of lidocaine versus placebo over 72 hours for neuropathic cancer-related pain
  Descriptive quantitative data will provide important feasibility data about trial procedures, recruitment, preliminary efficacy, safety and health service use.
- A pharmacokinetic sub-study of subcutaneous lidocaine
  Pharmacokinetic data will inform the definitive study and confirm extrapolation from existing data to this subcutaneous infusion regimenn
- A descriptive qualitative sub-study of patient experience of the intervention
  Semi-structured interview data will inform the design of a definitive trial
- A descriptive qualitative sub-study of informal carer experience of the intervention
  Semi-structured interviews will generate understanding of the experience of the intervention and caring for a person with cancer-related neuropathic pain. The perspective of informal carers is essential to inform the provision of holistic care and is likely to impact recruitment to a definitive study.

The three sub-studies will be undertaken in a subset of consenting patients. Methods and analysis plans for these will be fully reported together with publication of the results in accordance with relevant reporting guidelines.

Patient and Public Involvement

The investigator team includes a consumer (BN) with lived experience both as a person with cancer as well as carer, who has been involved in study design and drafting of participant materials. The consumer will be involved in analysis and interpretation of data obtained.

Setting

Data will be gathered from five palliative care inpatient units in Sydney, Australia. Participants must be inpatient for the 72 hours of the study. The study is sponsored by the University of Technology Sydney. The study will be coordinated by the IMPACCT trials coordination centre (ITCC). Scientific endorsement was provided by Cancer Symptom Trials.[28]

Study population

Inclusion and exclusion criteria are listed in Table 1.

Inclusion and exclusion criteria were chosen with safety as first priority, aiming to limit participation by patients with unpredictable lidocaine pharmacology while still reflecting the diversity of the population who may benefit from this intervention. Participants are required to have a trial of opioid and non-lidocaine adjuvant analgesia unless otherwise contraindicated as the existing evidence for these therapies, while limited, is stronger than for the intervention. Minimum doses for inclusion were chosen based on studies by Reis-Pina et al,[29] Caraceni et al,[30] Mercadante et al;[31] with a 25% threshold of total daily maximum dose of adjuvant agents as defined by Dworkin et al.[32]

Study intervention

The intervention is described in Table 2.

Rationale for dose schedule

The intervention schedule has been devised to maximise the likelihood of benefit while minimising the risk of adverse events. The commencing dose, dose increments, and maximum doses are within the doses where efficacy has been seen in other settings, and where reported toxicity is infrequent as outlined below.

Weight-based dosing will be used as lidocaine pharmacokinetics are influenced by body size.[33]

The effect of lidocaine is dose-dependent.[34 35] Therefore, it is proposed to increase the dose if optimal analgesic benefit has not been obtained. Adverse effects are also likely to be dose-related, and severe reactions are often preceded by somnolence and paresthesia.[36]

Selection of starting dose (mg/kg), increments, and maximal doses of lidocaine are limited by the fact that there are no prospective interventional trials evaluating an extended continuous infusion of lidocaine for pain. The longest randomised controlled trials were by Hawley[21] who evaluated 10mg/kg subcutaneous lidocaine over 5.5 hours and found no effect on cancer pain

and Tremont-Lukats[34] who randomised 32 patients with neuropathic pain to placebo, 1, 3 or 5 mg/kg/h intravenous infusion of lidocaine over six hours and found a benefit of lidocaine 5mg/kg/h after four hours, which lasted a further six hours. Blood pressure, heart rate, ECG readings as well as adverse effects were monitored throughout both trials. No serious adverse events were reported.

Available pharmacokinetic data have also been considered in deciding the optimum dose schedule, although lidocaine serum concentrations do not always correlate with toxicity, as cases of toxicity are found at serum concentrations within the presumed 'therapeutic range'. Most of the pharmacokinetic data for lidocaine is from intravenous studies in which bioavailability is 100%.[37] The bioavailability of subcutaneous lidocaine, the route being used in this study, is dependent on the vascularity of the site, and is likely to be less than intravenous administration. In a horse model, when compared to administration of an equivalent intravenous lidocaine dose, a subcutaneous lidocaine dose may take ten times longer to reach a maximum concentration which is nearly three times lower.[38]

Physical signs of toxicity are more likely seen at lidocaine serum concentrations above 6 to 10 µg/ml, and serious adverse effects are rare below 5µg/ml.[37] Adverse effects typically follow a progression with mild adverse effects such as numbness, tinnitus, lightheadedness, dizziness, confusion and visual disturbance at lidocaine serum concentrations around 3-8µg/ml, nausea and vomiting, severe dizziness, decreased hearing, tremors and changes in blood pressure and pulse at serum concentrations 8-12 µg/ml and drowsiness, confusion, muscle twitching, convulsions, loss of consciousness, cardiac arrhythmias and cardiac arrest at serum concentrations greater than 12µg/ml.[39]

Pharmacokinetic data are available from a study by Ferrini[40] who reported a case series of six patients with cancer pain. Infusions were continued until death, for up to 240 days. Two patients were given intravenous lidocaine at 10-48mg/h intravenously and returned concentrations from 2-9.3µg/ml. Four patients were given lidocaine 32-80mg/h subcutaneously, and lidocaine serum concentrations were 1.3-3.3µg/ml. Schwartzman[41] found that when intravenous lidocaine infusion was given for complex regional pain syndrome at 88mg/h, plasma concentrations were between 1.1-4.4µg/ml, but at 120mg/h, 3 out of 49 patients had plasma concentrations between 5.1-6.1µg/ml. Mild self-limiting adverse effects were found at 120 to 144 mg/h. Serum lidocaine concentrations were obtained in a subset of the study by Thomas[17] of intravenous lidocaine at a dose of 1-2mg/kg bolus followed by 1mg/kg/h, which found a mean lidocaine serum concentration of 5.1µg/ml and standard deviation of 2.9µg/ml.

Several case series describe other lidocaine dose ranges used in clinical practice for analgesia. Brose[42] gave three patients with cancer pain randomised boluses of lidocaine 4mg/kg, fentanyl or normal saline. This was followed by a subcutaneous infusion of lidocaine 100-160mg/h for 3 weeks to 6 months with good analgesia and no attributable adverse effects. Blood concentrations ranged from 1.3µg/ml to 5µg/ml. In two patients, recurrent pain was associated with lidocaine blood concentrations under 2µg/ml. Amikura[16] gave 32 patients with neuropathic cancer pain lidocaine with an average maintenance dose of 38mg/h (range: 8-60mg/h) for 5 to 158 days, and 87.5% experienced significant pain relief. Seah[43] reported 23 hospice patients with a median subcutaneous lidocaine dose of 0.65mg/kg/h. Thomas[17] conducted a retrospective chart review of 82 consecutive hospice patients as above which found 82% had a major response and 8% had a partial response of their pain.

Because of limited prospective data for extended continuous infusions of lidocaine in cancer-related pain or neuropathic pain populations, the following data from randomised controlled trials evaluating perioperative pain was also considered. Swenson[44] found that, with a dosing regimen of intravenous lidocaine 2mg/minute for patients under 70kg and 3mg/minute for patients over 70kg, several patients had potentially toxic plasma concentrations. This regimen was changed to 60mg/h and 120mg/h, respectively. Herroeder[45] found that an intravenous infusion of 120mg/h did not produce any plasma concentrations above 5µg/ml. These patients were monitored, and no adverse effects were observed. Kuo[23] found 3 patients in the intravenous lidocaine group developed intermittent bradycardia at doses of 3mg/kg/h.

After considering the above data, a starting lidocaine dose of 1 mg/kg/h was chosen. This dose is unlikely to cause serious adverse effects given experience in previous trials. In addition, the infusion will be delivered subcutaneously, which is likely to have less bioavailability and systemic absorption than the intravenous infusions used for cardiac stability. Nonetheless, rigorous monitoring (including vital signs, ECG readings and structured symptom assessment for adverse effects) will occur to detect and manage potential adverse events as soon as possible. Lidocaine dose titration up to 2mg/kg/h will allow for individual response, with patients remaining on the minimal dose required for adequate analgesia. Although appearing to have better efficacy and lower risks of serious adverse events in a non-cancer population, higher doses would need to be used with caution in the cancer population, who may have a higher rate of frailty and comorbidity. Therefore, a maximum dose of 120mg/h (regardless of the calculated weight-based dose) will be imposed to limit the risks from higher dose infusions[41 44].

Outcomes and data collection

The primary outcome is the rate of completion of study procedures and medication use from day 1 to day 4. A completion rate of 80% or more of randomised patients will be considered feasible, while a completion rate of 60% or less will be considered unacceptable.

The secondary feasibility outcomes are the number of eligible participants who are consented to and randomised within the first 18 months from the lead site opening, recruitment:screening ratio, completion:screening ratio, rate of complete data sets, and time taken to complete the study measures at the main daily assessment. Other secondary outcomes measure preliminary efficacy, toxicity, health outcomes and health service utilisation associated with the intervention, and the relationship between lidocaine serum concentration and dose/efficacy/toxicity.

Table 3 shows the primary and secondary outcomes.
Table 4 provides an overview of the data collection tools used in this study. SPIRIT **Error! Reference source not found.** [25] describes the tools and data collected at each study time point. The systematic adverse effects screening assessment is shown in Table 5. Participants will be reviewed face-to-face daily from baseline to day 4 in the four hours before intervention dose change, then by telephone during follow up. The protocol provides specific guidance for management of drug specific side effects including dose reduction, cessation and increased frequency of review depending on the severity and risk of the symptom.

In the pharmacokinetic sub-study, timed blood sample collection will occur daily, 20 to 24 hours after commencing of the lidocaine infusion. Samples will be analysed using a validated HPLC assay[46] to estimate lidocaine and metabolite concentrations.

Sample size and Recruitment

Based on an acceptable completion rate of 80% and an unacceptable completion rate of 60% the sample size is 36 participants. Fleming's two-stage design[47] will be used. This calculation generates a range of values. A mid value has been selected taking into consideration is whether sufficient feasibility data has been collected to inform a future phase III study. The null hypothesis that the true response rate is 0.6 will be tested against a one-sided alternative. In the first stage, 17 patients will be accrued. If there are 10 or fewer responses in these 17 patients, the study will be stopped for futility. If there are 15 or more responses in 17 patients, the study will be stopped and the null hypothesis rejected. Otherwise, 19 additional patients will be accrued for a total of 36. The null hypothesis will be rejected if 25 or more responses are observed in 36 patients. This design yields a type I error rate of 0.05 and power of 0.8 when the true response rate is 0.8. A maximum of twelve participants will be recruited to the pharmacokinetic substudy.
Participants will be invited to participate on admission to the palliative care unit and during regular screening at each site. Regular promotion of this study to clinicians at this site is designed to improve recruitment. Advertising posters may be placed in clinical areas.

Allocation

At each centre, potential participants will be sequentially allocated an ID number. The REDCap (Research Electronic Data Capture) randomisation tool will be used to facilitate randomisation. REDCap is a secure web application for building and managing online surveys and databases.[48] Random allocation tables will be created by the trial statistician and uploaded into the REDCap project. Treatment for each participant will be allocated according to a block randomisation schedule in a 1:1 ratio. The site investigator or delegate will enrol participants. To maintain the blind, the site pharmacist will consult the online REDCap tool to randomise.

Blinding

Treatment allocation will not be disclosed to participants, study staff or, treating clinicians. All investigators except the collaborative national manager and statistician will be blinded. The study medication and placebo will be packed into identical syringes and labelled by an accredited pharmaceutical packaging facility holding a license to manufacture therapeutic goods for clinical trials. All medicine packs will be prepared by the unblinded site clinical trial pharmacist according to the randomisation schedule. The ward nurse or study nurse will load the syringe driver from the dispensed study medications. A nursing record of administration will document study medication administered and discarded. Used syringes will be disposed on the ward.

Unblinding will only be done in cases of emergencies where knowledge of the code will have consequences for clinical decision making.

Data management

Deidentified study data will be collected on paper worksheets and then entered onto and managed on REDCap database. All identifiable data (master list, consent forms, pathology

reports, copies of medical record) will be filed separately to the worksheets and stored securely as set out in Good Clinical Practice guidelines.[49] Data will be stored for 15 years, then destroyed.

Statistical and data analysis methods

The study completion rate will be calculated by the number of participants in both arms who complete the study medication and procedures from day 1 to 4 as a percentage of the total number of participants randomised. A rate that has a confidence interval including 80% and excluding 60% will be considered feasible.

The number of eligible participants who are consented and randomised within the first eighteen months from the lead site opening will be documented. Thirty-six patients will be considered satisfactory. Study chronology will be adjusted if the study requires a break for operational reasons. The number of patients randomised as a percentage of the patients screened will be calculated. The data completion rate will be calculated. A rate of greater than 80% of patients with a complete data set will be considered satisfactory. The mean and range of time taken to complete study measures will be calculated for the major assessment point prior to dose adjustment.

Descriptive statistics will be used to calculate the proportion of participants with improvements in preliminary efficacy measures. A cumulative responder graph for all changes in the worst pain score on BPI-SF on day 4 will be plotted. Sub-group analysis will be performed to evaluate potential biomarkers or responses. Missing data will be imputed where possible by carrying forward the last available measurement. The rate of adverse effects will be tabulated. A preliminary economic analysis will describe the direct cost of treatment, health services use and health-related quality of life measured using the EQ-5D-5L. A comparison of the interference of the subscale on BPI-SF and RUG-ADL between arms will also be conducted.

In the pharmacokinetic sub-study concentration-time data will be used to estimate the steady-state concentration (Css) of lidocaine the maximum observed concentration (Cmax) and the time to the Cmax. Css will be correlated with pharmacological effects of lidocaine.

Monitoring

Adverse events and serious adverse events will be reported using a secure online reporting system to enable study wide reporting and reviewed by an independent medical monitor. The role of the medical monitor[50] is to provide oversight and review of safety reports. Serious adverse events will also be reported to the relevant human research ethics committee.

ETHICS AND DISSEMINATION

Participant safety is paramount and will be carefully monitored. Standardised assessments for adverse effects are built into the trial protocol. The trial will be conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice Guidelines.[51]

Obtaining consent for this study will be a process of information exchange between the study staff, the potential participant and any other person the potential participant believes should be included in the discussion. The participant information sheet will be used as a basis for the

discussion, which will cover all procedures, benefits, burdens and side effects expected or possible during the study. No compensation is provided to participants.

Findings will be published in peer-reviewed journals and presented at local, national, and international conferences. This study will be considered suitable to progress to a phase III study if there is a completion rate where the confidence interval includes 80% and excludes 60%. Quantitative and qualitative data will be synthesised in an iterative process with the investigator team. Recommendations generated from the data synthesis will inform the design of a subsequent phase III study.

The protocol and Patient Information and Consent Form have been approved by Sydney Local Health District (Concord) Human Research Ethics Committee 2019/ETH07984 and University of Technology Sydney ETH17-1820.

Trial status

The current study protocol is version 3.0 dated 1 June 2022 Recruitment commenced 13th May 2019 and is expected to be completed by June 2023. Recruitment and trial operation have been impacted by Covid-19.

DISCUSSION

This project provides crucial feasibility data for a program of work that aims to improve the management of unrelieved neuropathic cancer-related pain and influence clinical practice. Unrelieved neuropathic cancer-related pain is highly prevalent, with a significant impact on the patient, carer, healthcare system, and society.[2] Continuous subcutaneous infusion of lidocaine for cancer-related pain is a promising intervention that has been prospectively investigated only rarely and inconclusively in small-scale randomised controlled trials with a short infusion duration. Lidocaine is currently used variably in clinical practice with a scant evidence base. Data generated by this work will directly lead to a recommendation to clinicians in the Australian Cancer Pain guideline recommendations[52] and support clinicians to provide the best evidenced-based neuropathic cancer-related pain management.

DECLARATIONS

Ethics approval and consent to participate

The protocol and Patient Information and Consent Form have been approved by Sydney Local Health District (Concord) Human Research Ethics Committee 2019/ETH07984 and University of Technology Sydney ETH17-1820. Protocol amendments are communicated by email and regular trial site meetings and trial investigator meetings after approval by the relevant ethics and governance committees.

Consent for publication

Not applicable

Availability of data and materials

The deidentified trial dataset will be available on request. All investigators will have access to the full re-identifiable data.

Competing interests

This is an investigator initiated study. The study sponsor and funders do not have authority over this study.

AL has received honoraria for lectures and educational material from BMS and Astra Zeneca. DS is funded by the Sydney Partnership for Health, Education, Research and Enterprise as a translational research fellow. AM is a member of the clinical advisory board for Bod Australia, has received honoraria for conference presentations from Bayer, is a member of the DSMB of the CannabisCINV study and is a member of the advisory board for the Lambert Cannabinoid Therapeutics Initiative. CS is a member of the executive committee of ANZSPM and of the executive of PCNT.

Funding

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Author contributions

JL, MA, ML, JP and CS conceived this work. All authors (JL, DC, ML, JP, AM, MR, LB, BF, RA, DS, CS, RC, BN, NM, GA, RG, MK, CA, AL, CS, DM, AR, GP, KU, PV, MA) provided substantial contributions to the design of the work. JL, MA and GP wrote the first draft of this work and all authors revised it critically for important intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Acknowledgements

Not applicable

Figures

Figure 1: SPIRIT figure of study assessments and schedule

Table 1: Inclusion and exclusion criteria

Inclusion criteria	**Exclusion Criteria**
• Age 18 years or more • Capacity to provide informed consent • Ability to complete study assessments and comply with the study procedures • Participant is willing to be an inpatient for the duration of the trial • Pain related to cancer or its treatment with an worst pain score of 4 or greater on an 11-point (0-10) numerical rating scale in the past 24 hours • Patient's cancer may be solid tumour or haematological • Neuropathic component to pain which the clinician assesses to meet the International Association for the Study of Pain criteria for neuropathic pain which is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system"[53] OR has a score of 12 or greater on the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS). [54] Mixed neuropathic/nociceptive pains are included as well as cancer induced bone pain which is considered to have a neuropathic component.[55] • An adequate trial of opioid medication defined as titration to the maximum tolerated dose as limited by adverse effects or titration to at least a dose of 30mg/day oral morphine equivalent, for at least 24 hours *or* inability to tolerate opioids (eg due to allergy) • An adequate trial of at least ONE adjuvant analgesic defined as titration	• Previous adverse reaction to lidocaine (lignocaine) or other amide-type local anaesthetics such as prilocaine, mepivacaine or bupivacaine • Use of systemic lidocaine (lignocaine) infusion for analgesia within the four weeks prior to study entry at a dose greater than or equal to 1mg/kg/h intravenous or subcutaneous • Liver failure (Child class B or C, likely due to hepatic impairment) • Renal failure (estimated Glomerular Filtration Rate <15ml/min/1.73m^2) • Cardiac comorbidity deemed a contraindication by the treating clinician including ○ Symptomatic cardiac failure (New York Heart Association class II or greater[56] within the past year ○ heart block (first, second or third degree) at any time in the past ten years. Participants managed with a permanent pacemaker are not excluded. ○ Stokes-Adams syndrome • Cardiac abnormalities at time of screening ○ bradycardia less than 60 beats per minute at rest whilst awake ○ systolic blood pressure less than 100mmHg or greater than 160mmHg sitting ○ unstable angina or myocardial ischemia ○ atrial or supraventricular tachycardia greater than 100 beats per minute at rest

to the maximum tolerated dose as limited by adverse effects or titration to at least a dose of Amitriptyline 37.5mg, Duloxetine 30mg, Gabapentin 900mg, Pregabalin 150mg, Venlafaxine 60mg or equivalent, for at least 24 hours *or* inability to tolerate any adjuvant analgesic listed above (eg. due to comorbidity, medication interaction or previous adverse effects) *or* inability to take oral medications (as determined by the treating clinician eg due to dysphagia) *or* expected poor absorption of oral medications (as determined by the treating clinician, eg due to vomiting) • Stable regular adjuvant analgesics, opioids, cannabinoids, antidepressants, anticonvulsants, benzodiazepines, paracetamol, non-steroidal anti-inflammatory drugs and steroids for 24 hours. Transdermal opioids must have had stable dosing for 48 hours due to the extended time to reach steady state. Short acting breakthrough opioid may be used as required.	• Seizure episode within the past 4 weeks • Fluctuating level of consciousness or delirium as determined by the treating team • Acute porphyria • Current use of medications which may interact with lidocaine or impact its metabolism:[57] propranolol, phenytoin, amiodarone, metoprolol, nadolol, St John's Wort, donepezil, cimetidine, flecainide, fluvoxamine, dihydroergotamine, vernakalant, saquinavir, dronedarone, amprenavir, lopinavir, propofol, arbutamine, atazanavir, succinylcholine, dasabuvir, paritaprevir, cobicistat, hyaluronidase, delavirdine, fosamprenavir, etravirine, ombitasvir, quinidine, disopyramide, procainamide, tocainide, mexiletine, propafenone, encainide, moricizine, bupropion, telaprevir, penbutolol, rapacuronium, nevirapine, nitrous oxide, cisatracurium, indinavir, ritonavir • Participants who have participated in a clinical study of a new chemical entity within the four weeks prior to study entry • Pregnant or breastfeeding

Table 2: Intervention

Intervention

Participants will be randomised to receive the intervention or placebo, with both treatment arms receiving best practice standard of care.

1. **Lidocaine Hydrochloride 10%w/v (3000mg/30ml)**
2. **Placebo: Sodium chloride 0.9%**

The appropriate dose of interventional product or identical volume of placebo will be diluted in sodium chloride 0.9% to the volume of the syringe driver(s). Sites use existing Niki T34 syringe drivers which allow a maximum of either a 30mL or 50mL syringe. The syringe holds 30mL of interventional product, however the maximum syringe driver capacity is less than this. If required, two syringe drives may be used. All study drugs will be prescribed as a continuous subcutaneous infusion to be changed every 24 hours of the intervention period. There will be up to two dose modifications

during the treatment period, at 24 hours and 48 hours, unless toxicity requires a dose reduction. All doses will be rounded to the nearest 100mg.

The continuous subcutaneous infusion of lidocaine/placebo will commence on day 1 at 1mg/kg/h (maximum 120mg/h).

The patient will be assessed for efficacy and toxicity on days two and three between 0.5 and 4 hours prior to the infusion change time. The dose for the next 24 hours will be charted according to the following algorithm:

- The dose will be increased by 0.5mg/kg/h every 24 hours to a maximum of 2mg/kg/h or 120mg/h (whichever is lower).

Exceptions:

- If the patient's average and worst pain score in the last 24 hours is ≤3/10, the dose will remain the same
- If there is any new or increased toxicity, this will be managed according to the protocol, which may include treatment of the symptom, dose reduction or cessation of infusion

After 72 hours (on day 4), the infusion will be ceased.

All medications will be charted on the standard inpatient medication chart and will be signed off by nursing staff according to local protocol.

Concomitant care

Best practice standard of care will include continuation of prescribed analgesic or potentially analgesic medications (without further dose change) in both arms of the study, and additional opioid use as required by the patient for breakthrough pain. Due to the fluctuating nature of neuropathic cancer-related pain, and the high psychosocial distress that accompanies a diagnosis of cancer, it would be unethical to deny this population access to breakthrough medication (typically an opioid). If a participant becomes unable to tolerate medications, equivalent substitutions may be made.

Table 3: Primary and Secondary Outcomes

<table>
<tr><td colspan="2">Primary outcome and measure</td></tr>
<tr><td colspan="2">The primary outcome is the completion rate of the study medication and procedures from day 1 to day 4. A completion rate of 80% or more of randomised patients is considered feasible and a completion rate of 60% or less is considered unacceptable.</td></tr>
<tr><td colspan="2">Secondary outcomes</td></tr>
<tr><td>Feasibility
• The number of eligible participants who are consented and randomised within the first eighteen months from the lead site opening.
• Recruitment to screening ratio.
• Completion to screening ratio. The ratio of participants who complete all study medication and procedures from day 1 to day 4 compared to number of patients screened.
• Completion of data. A rate of greater than 80% of randomised participants with complete data set is considered feasible
• Acceptability of subcutaneous lidocaine (lignocaine) or placebo infusion and study design to participants and carers (sub-study)
• Impacts of the intervention relevant to participants and carers (sub-study)
• Time taken to complete study measures at the assessment prior to dose change</td><td rowspan="4">Preliminary Efficacy
Exploratory efficacy outcomes will include the following.
• The proportion of participants who have an improvement from baseline to day 4 in:
- Average pain of 1 points or more on the BPI-SF
- Worst pain of 2 point or more on the BPI-SF (moderate clinically important difference)
- Average pain of 2 point or more on the BPI-SF
- Worst pain of 4 points or more on the BPI-SF (major clinically important difference)
- Average pain of 4 points or more on the BPI-SF
- Worst pain to be reduced to ≤3 on the BPI-SF
- Average pain to be reduced to ≤3 on the BPI-SF
- Arithmetic mean of worst, least, average and now pain of 1 point or more on the BPI-SF
- Number of breakthrough pain medications used
- Burning (superficial) spontaneous pain of 1 points or more on the Neuropathic pain symptom inventory (NPSI)
- Pressing (deep) spontaneous pain of 1 points or more on the NPSI
- Paroxysmal pain of 1 points or more on the NPSI
- Evoked pain of 1 points or more on the NPSI
- Parasthesia/Dysesthesia of 1 points or more on the NPSI

• Global impression of change measured on a 7 point scale
• Mean change in worst pain on BPI-SF
• Mean change in average pain on BPI-SF
• Proportion of participants who achieve their personalized pain goal
• Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 OR those who have unchanged pain but a reduction in number of breakthrough medications used in the last 24 hours
• Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 AND breakthrough medication use which is unchanged or reduced in the last 24 hours
• Cumulative responders for all changes in worst pain score on BPI-SF on day 4
• Cumulative responders for the proportion of participants who have a reduction in worst pain score of 1 point or more on day 2, 3 and 4
• The proportion of responders, defined by a 1-point reduction in worst pain at day 4, who have a continued response at day 9, 15 and 29 will be calculated for each group.

Subgroup analysis will be performed to evaluate the following for potential as biomarkers of response to lignocaine
1. patients who have not vs patients who have been on the adjuvant doses listed in table 1.
2. patients who are on minimal, moderate and large doses of morphine (<60, 60-200, >200 mg/day)
3. patients who have severe pain (≥7/10) and moderate pain (4-6/10)
4. patients with allodynia</td></tr>
<tr><td>Preliminary Toxicity
• Prospectively sought adverse events with the likelihood of relationship to intervention</td></tr>
<tr><td>Pathophysiology
• The median dose at study completion
• The relationship between serum lidocaine (lignocaine) level at steady state and continuous subcutaneous infusion dose (sub-study)
• Preliminary relationship between serum lidocaine (lignocaine) level and efficacy and toxicity (sub-study)</td></tr>
<tr><td>Preliminary Quality Of Life And Health Services Utilization
• Completion rate of EQ-5D-5L(generic)
• Arithmetic mean of the seven items assessing interference on the BPI-SF on day 4 compared with baseline. This mean can be used if more than 50%, or four of seven, of the total items have been completed on a given administration.
• Total RUG-ADL score on day 4 compared to baseline
• Lidocaine (lignocaine) and analgesic medication costs
• Management of adverse effects, e.g. investigations, additional clinician review, medications
• Inpatient stays (length of stay, AR-DRG), excluding pharmacy costs</td></tr>
</table>

Table 4: Overview of study instruments

Instrument	Details
Eligibility and demographic	
Leeds assessment of neuropathic symptoms and signs (LANSS)	Seven item scale including sensory description and examination. Score of 12 or greater has

	85% sensitivity that neuropathic mechanisms likely contribute to the patient's pain[54]
Charlson Comorbidity Index (CCI)	Score composed of major comorbidities weighted to reflect risk of death[58]
Non-pharmacological management	Use of patient education, pain diary, physiotherapist, occupational therapist, psychologist, music therapist or other complementary therapy to improve pain management collected from medical record or participant recollection. Recommended by guidelines[52]
Efficacy assessments	
Brief Pain Inventory – Short Form (BPI-SF)	Validated 9-item tool based primarily on 0-10 numeric rating scale assessing pain intensity and impact.[59] Question 7 omitted to reduce participant burden as medication information collected by study staff
Worst pain	Numeric rating scale from 0 to 10 of worst pain in the last 24 hours
Average pain	Numeric rating scale from 0 to 10 of average pain in the last 24 hours
Neuropathic Pain Symptom Inventory (NPSI)	12 item questionnaire covering the domains of superficial and deep spontaneous pain, paroxysmal pain, evoked pain and paresthesia/dysaesthesia. Validated to assess neuropathic pain[60] and may detect treatment effect[53]
Personalised pain goal	Patients asked to describe on a 0-10 scale the level/intensity of pain that will allow the to achieve comfort in physical, functional, and psychosocial domains[61]
Medications	Regular opioid and adjuvant analgesics recorded Breakthrough medication formulation, route of administration, frequency prescribed, number taken during the prior 24-hour period
Health and service use outcomes	
EuroQual-5 Domains-Five Level (EQ-5D-5L)	Validated tool measuring five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) of health-related quality of life with relevant population norms[62-64]
Global impression of change	Seven-point scale regarding participant perception of change in overall status since study commencement; graded from 'very much worse' to 'very much improved'
Australia-modified Karnofsky Performance Status (AKPS)	Validated scale measuring performance status from 100 (normal) to 0 (dead)[65]

Resource Utilisation Group Activities Daily Living (RUG-ADL)	Four-item scale measuring patient motor function for activities of daily living including bed mobility, toileting, transfers and eating[66], of most value when AKPS is less than 60[67]
Australian Refined Diagnosis Related Group (AR-DRG)	Groups inpatient stays into clinically meaningful categories of complexity that consume similar amounts of resources[68]
Toxicity	
Adverse effects	Documented using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0[69] terminology with indication of severity, likely causality, and action taken. Vital signs, electrocardiogram (ECG), and structured toxicity assessment will aid this. These will be measured in a full assessment daily. An additional focused toxicity screen will occur three hours after dose changes to improve safety.

Table 5: Adverse effect screening assessment

	Yes	No
Fatigue, somnolence, lethargy, depressed level of consciousness, delirium, hallucinations		
Paraesthesia, circumoral paraesthesia		
Seizure, tremor		
Light headedness, dizziness, presyncope, syncope, headache, blurred vision, throat tightness		
tinnitus		
Ataxia, dysarthria		
Depression, anxiety, euphoria		
Palpitations		
Chest pain		
Cardiac failure, pedal edema		
Review vital signs: bradycardia less than 60 beats per minute at rest, awake systolic blood pressure less than 100mmHg or greater than 160mmHg tachycardia greater than 100 beats per minute at rest oxygen saturation less than 88% on room air respiratory rate less than 8 breaths per minute		
Review ECG: arrhythmia, conduction disorder		
Dyspnoea, cough, wheezing		
Anaphylaxis		
Injection site reaction (check site)		
Nausea, vomiting, constipation		
Pruritis		

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Figure 1: SPIRIT figure of study assessments and schedule

	Eligibility	**Baseline Day 1**	**Day 2-3**	**Day 4**	**Follow up days 8, 15, 29**	**Early cessation of infusion**
Investigations						
Liver function test, potassium, creatinine, INR	*					
PK sub-study (if applicable)		*	*	*		
Medical file review						
Demographics	*					
Diagnosis	*					
AKPS		*		*		
RUG-ADL		*		*		
Charlson Comorbidity Index (CCI)		*				
Selected medications		*			*	
Breakthrough medications		*	*	*	*	
Non-pharmacological management		*				
Admission/discharge date, AR-DRG		*			*	
Patient assessed (PRO assessments)						
BPI-SF		*		*		*
Worst pain	*		*		*	
Average pain			*		*	
NPSI		*		*		*
EQ-5D-5L		*		*		
Global impression of change				*		*
Interview sub-study (if applicable)				*		
Clinician assessed						
Medical assessment	*					
LANSS	*					
Personalised pain goal		*				
Weight and estimated height		*				
Heart rate, Pulse oximetry, Blood pressure, Respiratory rate four times a day	*	*	*	*		*
12 lead ECG	*		*			
Toxicity assessment		*	*	*	*	*
Focused toxicity safety screen		*	*			
Adverse effects		*	*	*	*	*

AKPS: Australia-modified Karnofsky Performance Status; AR-DRG: Australian Refined Diagnosis Related Group; BPI-SF:Brief Pain Inventory – Short Form; CCI: Charlson Comorbidity Index; EQ-5D-5L: EuroQual-5 Domains-Five Level; ECG: echocardiogram; INR: International Normalised Ratio; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs ; NPSI: Neuropathic Pain Symtom Inventory; PRO: patient-reported outcomes; RUG-ADL: Resource Utilisation Group Activities Daily Living. Additional assessments may be performed if required due to adverse effects as clinically indicated.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	In ANZCTR
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Separate file
	5b	Name and contact information for the trial sponsor	4/ contact information on request
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
	6b	Explanation for choice of comparators	2
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Figure 1
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9, ANZCTR
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Table 2
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	supplement
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.