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 III 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 (3000 mg/30 mL) or placebo (sodium chloride 0.9\%) over 72 hours for neuropathic cancer-related pain, a pharmacokinetic substudy and a qualitative substudy 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.

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 Consolidated Standards of Reporting Trials 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. 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.

Neuropathic cancer-related pain is thought to require multimodal 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. The efficacy seen in clinical practice is variable and treatment is often associated with harms.

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For numbered affiliations see end of article.

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carry risk of misuse, abuse and diversion which is increasingly recognised 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 antineuropathic 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%–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 postoperative pain.20 A meta-analysis9 of bolus intravenous lidocaine 4–5 mg/kg over 30–80 min 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 trial21 of subcutaneous lidocaine in cancer pain has evaluated the infusion of 10 mg/kg lidocaine over 5.5 hours and found no effect on pain, which may have been related to the subtherapeutic 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 6 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 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.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 substudy of subcutaneous lidocaine.
Pharmacokinetic data will inform the definitive study and confirm extrapolation from existing data to this subcutaneous infusion regimen
► A descriptive qualitative substudy of patient experience of the intervention
Semistructured interview data will inform the design of a definitive trial.
► A descriptive qualitative substudy of informal carer experience of the intervention
Semistructured 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 substudies 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 IMPACT trials coordination centre. Scientific endorsement was provided by Cancer Symptom Trials.

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

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18 years or more</td>
<td>Previous adverse reaction to lidocaine ( lignocaine) or other amide-type local anaesthetics such as prilocaine, mepivacaine or bupivacaine</td>
</tr>
<tr>
<td>Capacity to provide informed consent</td>
<td>Use of systemic lidocaine ( lignocaine) infusion for analgesia within the 4 weeks prior to study entry at a dose greater than or equal to 1 mg/kg/hour intravenous or subcutaneous injection</td>
</tr>
<tr>
<td>Ability to complete study assessments and comply with the study procedures</td>
<td>Liver failure (Child class B or C, likely due to hepatic impairment)</td>
</tr>
<tr>
<td>Participant is willing to be an inpatient for the duration of the trial</td>
<td>Renal failure (estimated glomerular filtration rate &lt; 15 mL/min/1.73 m²)</td>
</tr>
<tr>
<td>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</td>
<td>Cardiac comorbidity deemed a contraindication by the treating clinician including</td>
</tr>
<tr>
<td>Patient’s cancer may be solid tumour or haematological</td>
<td>– Symptomatic cardiac failure (New York Heart Association class II or greater) within the past year</td>
</tr>
<tr>
<td>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’ OR has a score of 12 or greater on the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale. Mixed neuropathic/ nociceptive pains are included as well as cancer induced bone pain which is considered to have a neuropathic component.</td>
<td>– Heart block (first, second or third degree) at any time in the past 10 years. Participants managed with a permanent pacemaker are not excluded.</td>
</tr>
<tr>
<td>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 30 mg/day oral morphine equivalent, for at least 24 hours</td>
<td>– Stokes-Adams syndrome</td>
</tr>
<tr>
<td>or inability to tolerate opioids (eg, due to allergy)</td>
<td>Cardiac abnormalities at time of screening</td>
</tr>
<tr>
<td>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 amitriptyline 37.5 mg, duloxetine 30 mg, gabapentin 900 mg, pregabalin 150 mg, venlafaxine 60 mg or equivalent, for at least 24 hours</td>
<td>– Bradycardia less than 60 beats per min at rest while awake</td>
</tr>
<tr>
<td>or inability to tolerate any adjuvant analgesic listed above (eg, due to comorbidity, medication interaction or previous adverse effects)</td>
<td>– Systolic blood pressure less than 100 mm Hg or greater than 160 mm Hg sitting</td>
</tr>
<tr>
<td>or inability to take oral medications (as determined by the treating clinician, eg, due to dysphagia)</td>
<td>– Unstable angina or myocardial ischaemia</td>
</tr>
<tr>
<td>or expected poor absorption of oral medications (as determined by the treating clinician, eg, due to vomiting)</td>
<td>– Atrial or supraventricular tachycardia greater than 100 beats per min at rest</td>
</tr>
<tr>
<td>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.</td>
<td>Seizure episode within the past 4 weeks</td>
</tr>
<tr>
<td>Participants who have participated in a clinical study of a new chemical entity within the 4 weeks prior to study entry</td>
<td>Fluctuating level of consciousness or delirium as determined by the treating team</td>
</tr>
<tr>
<td>Pregnant or breast feeding</td>
<td>Acute porphyria</td>
</tr>
<tr>
<td>Current use of medications which may interact with lidocaine or impact its metabolism: propranolol, phentoyin, amiodarone, metoprolol, nadolol, St John’s Wort, donepezil, cimetidine, flecainide, fluvaxamine, dihydroergotamine, vernakalant, saquinavir, dronedarone, amprenavir, lopinavir, propofol, arbutamine, atazanavir, succinylcholine, dabasuvir, paritaprevir, cobicistat, hyaluronidase, delavirdine, fosamprenavir, etravirine, ombitasvir, quinidine, disopyramide, procainamide, tocainide, mexiletine, propafenone, enacainide, moricizine, bupropion, telaprevir, penbutolol, rapacuronium, nevirapine, nitrous oxide, cisatracurium, indinavir, ritonavir</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Inclusion and exclusion criteria


3
Study intervention
The intervention is described in box 1.

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. The effect of lidocaine is dose-dependent. 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.

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 et al who evaluated 10 mg/kg subcutaneous lidocaine over 5.5 hours and found no effect on cancer pain and Tremont-Lukats who randomised 32 patients with neuropathic pain to placebo, 1, 3 or 5 mg/kg/hour intravenous infusion of lidocaine over 6 hours and found a benefit of lidocaine 5 mg/kg/hour after 4 hours, which lasted a further 6 hours. Blood pressure, heart rate, ECG readings and 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%.

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 with administration of an equivalent intravenous lidocaine dose, a subcutaneous lidocaine dose may take 10 times longer to reach a maximum concentration, which is nearly 3 times lower.

Physical signs of toxicity are more likely seen at lidocaine serum concentrations above 6–10 µg/mL, and serious adverse effects are rare below 5 µg/mL. 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 3–8 µg/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 12 µg/mL.

Pharmacokinetic data are available from a study by Ferrini 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 10–48 mg/hour intravenously and returned
concentrations from 2 to 9.3 µg/mL. Four patients were given lidocaine 32–80 mg/hour subcutaneously, and lidocaine serum concentrations were 1.5–3.3 µg/mL. Schwartzman et al. found that when intravenous lidocaine infusion was given for complex regional pain syndrome at 88 mg/hour, plasma concentrations were between 1.1 and 4.4 µg/mL, but at 120 mg/hour, 3 out of 49 patients had plasma concentrations between 5.1 and 6.1 µg/mL. Mild self-limiting adverse effects were found at 120–144 mg/hour. Serum lidocaine concentrations were obtained in a subset of the study by Thomas et al. of intravenous lidocaine at a dose of 1–2 mg/kg/hour, followed by 1 mg/kg/hour, which found a mean lidocaine serum concentration of 5.1 µg/mL and SD of 2.9 µg/mL.

Several case series describe other lidocaine dose ranges used in clinical practice for analgesia. Brose and Cousins gave three patients with cancer pain randomised boluses of lidocaine 4 mg/kg, fentanyl or normal saline. This was followed by a subcutaneous infusion of lidocaine 100–160 mg/hour for 3 weeks to 6 months with good analgesia and no attributable adverse effects. Blood concentrations ranged from 1.3 µg/mL to 5 µg/mL. In two patients, recurrent pain was associated with lidocaine blood concentrations under 2 µg/mL. Amikura gave 32 patients with neuropathic cancer pain lidocaine with an average maintenance dose of 38 mg/hour (range: 8–60 mg/hour) for 5–158 days, and 87.5% experienced significant pain relief. Seah et al. reported 23 hospice patients with a median subcutaneous lidocaine dose of 0.65 mg/kg/hour. Thomas et al. 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 et al. found that, with a dosing regimen of intravenous lidocaine 2 mg/min for patients under 70 kg and 3 mg/min for patients over 70 kg, several patients had potentially toxic plasma concentrations. This regimen was changed to 60 mg/hour and 120 mg/hour, respectively. Herroeder et al. found that an intravenous infusion of 120 mg/hour did not produce any plasma concentrations above 5 µg/mL. These patients were monitored, and no adverse effects were observed. Kuo et al. found three patients in the intravenous lidocaine group developed intermittent bradycardia at doses of 3 mg/kg/hour.

After considering the above data, a starting lidocaine dose of 1 mg/kg/hour 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 2 mg/kg/hour 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 120 mg/hour (regardless of the calculated weight-based dose) will be imposed to limit the risks from higher dose infusions.

### 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 2 shows the primary and secondary outcomes.

Table 3 provides an overview of the data collection tools used in this study. Figure 1 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 4 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 substudy, timed blood sample collection will occur daily, 20–24 hours after commencing of the lidocaine infusion. Samples will be analysed using a validated High-performance liquid chromatography assay 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 will be used. This calculation generates a range of values. A mid-value has been selected taking into consideration is whether sufficient feasibility data have 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 12 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.
Table 3  Overview of study instruments

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility and demographic</td>
<td></td>
</tr>
<tr>
<td>Leeds assessment of neuropathic symptoms and signs</td>
<td>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.74</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>Score composed of major comorbidities weighted to reflect risk of death.58</td>
</tr>
<tr>
<td>Non-pharmacological management</td>
<td>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</td>
</tr>
<tr>
<td>Efficacy assessments</td>
<td></td>
</tr>
<tr>
<td>Brief Pain Inventory-Short Form</td>
<td>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.</td>
</tr>
<tr>
<td>Worst pain</td>
<td>Numeric Rating Scale from 0 to 10 of worst pain in the last 24 hours.</td>
</tr>
<tr>
<td>Average pain</td>
<td>Numeric Rating Scale from 0 to 10 of average pain in the last 24 hours.</td>
</tr>
<tr>
<td>Neuropathic Pain Symptom Inventory</td>
<td>12-item questionnaire covering the domains of superficial and deep spontaneous pain, paroxysmal pain, evoked pain and paresthesia/aesthesia. Validated to assess neuropathic pain and may detect treatment effect.53</td>
</tr>
<tr>
<td>Personalised pain goal</td>
<td>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</td>
</tr>
<tr>
<td>Medications</td>
<td>Regular opioid and adjuvant analgesics recorded</td>
</tr>
<tr>
<td></td>
<td>Breakthrough medication formulation, route of administration, frequency prescribed, number taken during the prior 24-hour period.</td>
</tr>
<tr>
<td>Health and service use outcomes</td>
<td></td>
</tr>
<tr>
<td>EuroQual-5 Domains-Five Level</td>
<td>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</td>
</tr>
<tr>
<td>Global impression of change</td>
<td>Seven-point scale regarding participant perception of change in overall status since study commencement; graded from ‘very much worse’ to ‘very much improved’.</td>
</tr>
<tr>
<td>Australia-modified Karnofsky Performance Status (AKPS)</td>
<td>Validated scale measuring performance status from 100 (normal) to 0 (dead).65</td>
</tr>
<tr>
<td>Resource Utilisation Group Activities Daily Living</td>
<td>Four-item scale measuring patient motor function for activities of daily living including bed mobility, toileting, transfers and eating, of most value when AKPS is less than 60.67</td>
</tr>
<tr>
<td>Australian Refined Diagnosis Related Group</td>
<td>Groups inpatient stays into clinically meaningful categories of complexity that consume similar amounts of resources.68</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Documented using the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.0 terminology with indication of severity, likely causality and action taken. Vital signs, ECG and structured toxicity assessment will aid this. These will be measured in a full assessment daily. An additional focused toxicity screen will occur 3 hours after dose changes to improve safety.</td>
</tr>
</tbody>
</table>

Allocation
At each centre, potential participants will be sequentially allocated an ID number. The Research Electronic Data Capture (REDCap) randomisation tool will be used to facilitate randomisation. REDCap is a secure web application for building and managing online surveys and databases.58 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 licence to manufacture therapeutic goods for clinical trials. All medicine packs
will be prepared by the unblinded site clinical trial phar-
macist 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 adminis-
tration 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 work-
sheets 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. 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 medi-
cation and procedures from day 1 to 4 as a percentage of
the total number of participants randomised. A rate that
has a CI including 80% and excluding 60% will be consid-
ered feasible.

<table>
<thead>
<tr>
<th>Investigatiosns</th>
<th>Eligibility</th>
<th>Baseline Day 1</th>
<th>Day 2-3</th>
<th>Day 4</th>
<th>Follow up days 8, 15, 29</th>
<th>Early cessation of infusion</th>
</tr>
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<tbody>
<tr>
<td>Liver function test, potassium, creatinine, INR</td>
<td>*</td>
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<tr>
<td>PK sub-study (if applicable)</td>
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</tbody>
</table>

**Medical file review**

- Demographics: *
- Diagnosis: *
- AKPS: *
- RUG-ADL: *
- Charlson Comorbidity Index (CCI): *
- Selected medications: *
- Breakthrough medications: *
- Non-pharmacological management: *
- Admission/discharge date: *

**Patient assessed (PRO assessments)**

- BPI-SF: *
- Worst pain: *
- Average pain: *
- NPNI: *
- 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: *

**Figure 1** SPIRIT figure of study assessments and schedule. Additional assessments may be performed if required due to adverse effects as clinically indicated. AKPS, Australia-modified Karnofsky Performance Status; AR-DRG, Australian Refined Diagnosis Related Group; BPISF, Brief Pain Inventory-Short Form; CCI, Charlson Comorbidity Index; EQ-5D-5L, EuroQual-5 Domains-Five Level; INR, International Normalised Ratio; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; NPNI, Neuropathic Pain Symtom Inventory; PRO, patient-reported outcomes; RUG-ADL, Resource Utilisation Group Activities Daily Living; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.
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 Brief Pain Inventory-Short Form (BPI-SF) on day 4 will be plotted. Subgroup 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 EuroQual-5 Domains-Five Level. A comparison of the interference of the subscale on BPI-SF and Resource Utilisation Group Activities Daily Living between arms will also be conducted.

In the pharmacokinetic substudy, concentration-time data will be used to estimate the steady-state concentration (C(S)) of lidocaine the maximum observed concentration (C(max)) and the time to the C(max). 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 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.

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 CI 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 on 13 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 programme 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. 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 and support clinicians to provide the best evidenced-based neuropathic cancer-related pain management.

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Competing interests This is an investigator-initiated 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 OSMR 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 PONT.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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