BMJ Open

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

Jessica Lee ,[1,2] David Currow,[3] Melanie Lovell,[4,5] Jane L Phillips,[1,6] Andrew McLachlan,[7] Megan Ritchie,[2] Linda Brown,[1] Belinda Fazekas,[1] Rajesh Aggarwal,[8] Davinia Seah,[9] Caitlin Sheehan,[10] Richard Chye,[9] Beverly Noble,[1] Nikki McCaffrey ,[11] Ghauri Aggarwal,[2] Rachel George,[12] Marian Kow,[12] Chadi Ayoub,[13] Anthony Linton,[14] Christine Sanderson,[15] Dipti Mittal,[2] Angela Rao,[1,10] Grace Prael,[1] Katalin Urban,[16] Priyanka Vandersman,[17] Meera Agar[1,18]

To cite: Lee J, Currow D, Lovell M, *et al*. Lidocaine for Neuropathic Cancer Pain (LiCPain): study protocol for a mixed-methods pilot study. *BMJ Open* 2023;**13**:e066125. doi:10.1136/bmjopen-2022-066125

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-066125).

Received 05 August 2022
Accepted 04 February 2023

For numbered affiliations see end of article.

Correspondence to
Dr Jessica Lee;
Jessica.Lee1@health.nsw.gov.au

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.

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 CI 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.

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.

Trial registration number ANZCTR ACTRN12617000747325.

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 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.[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 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-analysis[9] 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 trial[21] 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 regimenn
- 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 IMPACCT trials coordination centre. 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

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.[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 30 mg/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 amitriptyline 37.5 mg, duloxetine 30 mg, gabapentin 900 mg, pregabalin 150 mg,venlafaxine 60 mg 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.	► 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 4 weeks prior to study entry at a dose greater than or equal to 1 mg/kg/hour intravenous or subcutaneous ► Liver failure (Child class B or C, likely due to hepatic impairment) ► Renal failure (estimated glomerular filtration rate <15 mL/min/1.73 m^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 10 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 min at rest while awake – Systolic blood pressure less than 100 mm Hg or greater than 160 mm Hg sitting – Unstable angina or myocardial ischaemia – Atrial or supraventricular tachycardia greater than 100 beats per min 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[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 4 weeks prior to study entry ► Pregnant or breast feeding

Box 1 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 w/v (3000 mg/30 mL).
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 30 mL or 50 mL syringe. The syringe holds 30 mL 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 100 mg.

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

The patient will be assessed for efficacy and toxicity on days 2 and 3 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 0.5 mg/kg/hour every 24 hours to a maximum of 2 mg/kg/hour or 120 mg/hour (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.

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 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.[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 *et al*[21] who evaluated 10 mg/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/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%.[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 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.[38]

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.[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 3–8 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.[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 10–48 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 1.3–3.3 µg/mL. Schwartzman *et al*[41] 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*[17] of intravenous lidocaine at a dose of 1–2 mg/kg bolus, 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[42] 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[16] 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*[43] reported 23 hospice patients with a median subcutaneous lidocaine dose of 0.65 mg/kg/hour. Thomas *et al*[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 *et al*[44] 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*[45] 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*[23] 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.[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 2 shows the primary and secondary outcomes.

Table 3 provides an overview of the data collection tools used in this study. Figure 1[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 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[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 have been collected to inform a future phase III study. The null hypothesis that the true response rate is 0.6 will be

Table 2 Primary and secondary outcomes

Primary outcome and measure
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.
Secondary outcomes

Feasibility

- The no of eligible participants who are consented and randomised within the first 18 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 with 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 (substudy)
- Impacts of the intervention relevant to participants and carers (substudy)
- Time taken to complete study measures at the assessment prior to dose change

Preliminary toxicity

- Prospectively sought adverse events with the likelihood of relationship to intervention

Pathophysiology

- The median dose at study completion
- The relationship between serum lidocaine (lignocaine) level at steady state and continuous subcutaneous infusion dose (substudy)
- Preliminary relationship between serum lidocaine (lignocaine) level and efficacy and toxicity (substudy)

Preliminary quality of life and health services utilisation

- 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 4 of 7, of the total items have been completed on a given administration.
- Total RUG-ADL score on day 4 compared with baseline
- Lidocaine (lignocaine) and analgesic medication costs
- Management of adverse effects, for example, investigations, additional clinician review, medications
- Inpatient stays (length of stay, AR-DRG), excluding pharmacy costs

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 point 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
  - No 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 point 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 personalised 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 days 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 days 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 versus 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.

AR-DRG, Australian Refined Diagnosis Related Group; BPI-SF, Brief Pain Inventory-Short Form; EQ-5D-5L, EuroQual-5 Domains-Five Level; RUG-ADL, Resource Utilisation Group Activities Daily Living.

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

Instrument	Details
Eligibility and demographic	
Leeds assessment of neuropathic symptoms and signs	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	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	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	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	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	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	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 V.4.0[69] 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.

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.[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 licence to manufacture therapeutic goods for clinical trials. All medicine packs

	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		*	*	*	*	*

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; NPSI, Neuropathic Pain Symtom Inventory; PRO, patient-reported outcomes; RUG-ADL, Resource Utilisation Group Activities Daily Living; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

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 CI including 80% and excluding 60% will be considered feasible.

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 oedema		
Review vital signs: bradycardia less than 60 beats per min at rest, awake systolic blood pressure less than 100 mm Hg or greater than 160 mm Hg tachycardia greater than 100 beats per min at rest oxygen saturation less than 88% on room air respiratory rate less than 8 breaths per min		
Review ECG: arrhythmia, conduction disorder		
Dyspnoea, cough, wheezing		
Anaphylaxis		
Injection site reaction (check site)		
Nausea, vomiting, constipation		
Pruritus		

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 (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 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.[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.

Author affiliations
[1]IMPACCT (Improving Palliative, Aged and Chronic Care through Clinical Research and Translation), University of Technology Sydney Faculty of Health, Broadway, New South Wales, Australia
[2]Concord Centre for Palliative Care, Concord Repatriation General Hospital, Concord, New South Wales, Australia
[3]University of Wollongong Faculty of Science Medicine and Health, Wollongong, New South Wales, Australia
[4]Greenwich Palliative and Supportive Care Services, HammondCare, Sydney, New South Wales, Australia
[5]Northern Clinical School, The University of Sydney, St Leonards, New South Wales, Australia
[6]School of Nursing, Faculty of Health, Queensland University of Technology, Brisbane, Queensland, Australia
[7]Sydney Pharmacy School, The University of Sydney, Sydney, New South Wales, Australia
[8]Palliative Care, Bankstown Hospital, Bankstown, New South Wales, Australia
[9]Palliative Care, St Vincent's Health Australia Ltd, Sydney, New South Wales, Australia
[10]Palliative Care, Calvary Health Care, Kogarah, New South Wales, Australia
[11]Deakin Health Economics, Deakin University School of Health and Social Development, Burwood, Victoria, Australia
[12]Pharmacy, Concord Repatriation General Hospital, Concord, New South Wales, Australia
[13]Cardiology, Mayo Clinic Scottsdale, Scottsdale, Arizona, USA
[14]Concord Cancer Centre, Concord Repatriation General Hospital, Concord, New South Wales, Australia
[15]Territory Palliative Care, Alice Springs, Northern Territory, Australia
[16]Palliative Care, Northern New South Wales Local Health Network, Lismore, New South Wales, Australia
[17]Research Centre for Palliative Care Death & Dying, Flinders University, Adelaide, South Australia, Australia
[18]Palliative Care, Sydney South West Area Health Service, Liverpool, New South Wales, Australia

Twitter Jessica Lee @jestics

Contributors JL, MA, ML, JLP and CS conceived this work. All authors (JL, DC, ML, JLP, AM, MR, LB, BF, RA, DS, CS, RC, BN, NM, GA, RG, MK, CA, AL, CS, DM, AR, GP, KU, PV and 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.

Funding This work is supported by funding from the Australian National Palliative Care Clinical Studies Collaborative and IMPACCT: NSW, a joint scholarship from NSW health, University of Technology Sydney and Sydney Local Health District. There are no grant numbers for these fundings. Protocol design was supported by a scholarship to the ACORD workshop. In-kind support has been provided by Concord Centre for Palliative Care, Sacred Heart Hospice, South West Sydney Local Health District, Calvary Healthcare Kogarah, Northern Sydney Local Health District, Hammondcare, IMPACCT Trials Coordination Centre and all investigators.

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 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.

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.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Jessica Lee http://orcid.org/0000-0003-1570-066X
Nikki McCaffrey http://orcid.org/0000-0003-3684-3723

REFERENCES

1 Breivik H, Cherny N, Collett B, *et al*. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. *Ann Oncol* 2009;20:1420–33.
2 Rayment C, Hjermstad MJ, Aass N, *et al*. Neuropathic cancer pain: prevalence, severity, analgesics and impact from the European palliative care research collaborative-computerised symptom assessment study. *Palliat Med* 2013;27:714–21.
3 Jongen JLM, Huijsman ML, Jessurun J, *et al*. The evidence for pharmacologic treatment of neuropathic cancer pain: beneficial and adverse effects. *J Pain Symptom Manage* 2013;46:581–90.
4 Sanderson C, Quinn SJ, Agar M, *et al*. Pharmacovigilance in hospice/palliative care: net effect of pregabalin for neuropathic pain. *BMJ Support Palliat Care* 2016;6:323–30.
5 Sanderson C, Quinn SJ, Agar M, *et al*. Pharmacovigilance in hospice/palliative care: net effect of gabapentin for neuropathic pain. *BMJ Support Palliat Care* 2015;5:273–80.
6 Bennett MI. Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review. *Palliat Med* 2011;25:553–9.
7 Evoy KE, Sadrameli S, Contreras J, *et al*. Abuse and misuse of pregabalin and gabapentin: a systematic review update. *Drugs* 2021;81:125–56.
8 Dalal S, Bruera E. Pain management for patients with advanced cancer in the opioid epidemic era. *Am Soc Clin Oncol Educ Book* 2019;2019:24–35.
9 Lee JT, Sanderson CR, Xuan W, *et al*. Lidocaine for cancer pain in adults: a systematic review and meta-analysis. *J Palliat Med* 2019;22:326–34.
10 Catterall WA, Mackie K, *et al*. Local anesthetics. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill, 2011.
11 Zhang JM, Li H, Munir MA. Decreasing sympathetic sprouting in pathologic sensory ganglia: a new mechanism for treating neuropathic pain using lidocaine. *Pain* 2004;109:143–9.
12 Joo JD, Choi JW, In JH, *et al*. Lidocaine suppresses the increased extracellular signal-regulated kinase/cyclic AMP response element-binding protein pathway and pro-inflammatory cytokines in a neuropathic pain model of rats. *Eur J Anaesthesiol* 2011;28:106–11.
13 Hahnenkamp K, Durieux ME, Hahnenkamp A, *et al*. Local anaesthetics inhibit signalling of human NMDA receptors recombinantly expressed in Xenopus laevis oocytes: role of protein kinase C. *Br J Anaesth* 2006;96:77–87.
14 Meads DM, O'Dwyer JL, Hulme CT, *et al*. Cost-effectiveness of pain management strategies in advanced cancer. *Int J Technol Assess Health Care* 2019;35:141–9.
15 Fortner BV, Demarco G, Irving G, *et al*. Description and predictors of direct and indirect costs of pain reported by cancer patients. *J Pain Symptom Manage* 2003;25:9–18.

16 Amikura K, Kobayashi T, Takeshita Y, *et al*. Effect of continuous lidocaine infusion for the management of cancer pain in the patients with terminal gastrointestinal carcinoma [Japanese]. *Jpn J Gastroenterol Surg, Nihon Shokaki Geka Gakkai Zasshi* 2004;37:117–22.
17 Thomas J, Kronenberg R, Cox MC, *et al*. Intravenous lidocaine relieves severe pain: results of an inpatient hospice chart review. *J Palliat Med* 2004;7:660–7.
18 Kiani CS, Hunt RW. Lidocaine continuous subcutaneous infusion for neuropathic pain in hospice patients: safety and efficacy. *J Pain Palliat Care Pharmacother* 2021;35:52–62.
19 Challapalli V, Tremont-Lukats IW, McNicol ED, *et al*. Systemic administration of local anesthetic agents to relieve neuropathic pain. *Cochrane Database Syst Rev* 2005;2005:CD003345.
20 Kranke P, Jokinen J, Pace NL, *et al*. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. *Cochrane Database Syst Rev* 2015;2015:CD009642.
21 Hawley P, Fyles G, Jefferys SG. Subcutaneous lidocaine for cancer-related pain. *J Palliat Med* 2020;23:1357–64.
22 Sharma S, Rajagopal MR, Palat G, *et al*. A phase II pilot study to evaluate use of intravenous lidocaine for opioid-refractory pain in cancer patients. *J Pain Symptom Manage* 2009;37:85–93.
23 Kuo CP, Jao SW, Chen KM, *et al*. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J Anaesth* 2006;97:640–6.
24 Lidocaine. Available: https://www.palliativedrugs.com/doc-library.html?&entryid=125 [Accessed 25 Jun 2022].
25 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
26 Schulz KF, Altman DG, Moher D, *et al*. Consort 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
27 Australian New Zealand Clinical trials Registry. Lidocaine (lignocaine) for neuropathic cancer pain – feasibility study (licpain). n.d. Available: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372930&isReview=true
28 Cancer symptom trials. Available: https://www.uts.edu.au/research-and-teaching/our-research/impacct [Accessed 28 Jun 2022].
29 Reis-Pina P, Acharya A, Lawlor PG. Cancer pain with a neuropathic component: a cross-sectional study of its clinical characteristics, associated psychological distress, treatments, and predictors at referral to a cancer pain clinic. *J Pain Symptom Manage* 2018;55:297–306.
30 Caraceni A, Zecca E, Bonezzi C, *et al*. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the gabapentin cancer pain study group. *J Clin Oncol* 2004;22:2909–17.
31 Mercadante S, Arcuri E, Tirelli W, *et al*. Amitriptyline in neuropathic cancer pain in patients on morphine therapy: a randomized placebo-controlled, double-blind crossover study. *Tumori* 2002;88:239–42.
32 Dworkin RH, O'Connor AB, Backonja M, *et al*. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007;132:237–51.
33 Hsu Y-W, Somma J, Newman MF, *et al*. Population pharmacokinetics of lidocaine administered during and after cardiac surgery. *J Cardiothorac Vasc Anesth* 2011;25:931–6.
34 Tremont-Lukats IW, Hutson PR, Backonja M-M. A randomized, double-masked, placebo-controlled pilot trial of extended IV lidocaine infusion for relief of ongoing neuropathic pain. *Clin J Pain* 2006;22:266–71.
35 Wallace MS, Dyck BJ, Rossi SS, *et al*. Computer-controlled lidocaine infusion for the evaluation of neuropathic pain after peripheral nerve injury. *Pain* 1996;66:69–77.
36 AstraZenica. Xylocard: product information; 2007.
37 Benowitz NL, Meister W. Clinical pharmacokinetics of lignocaine. *Clin Pharmacokinet* 1978;3:177–201.
38 Soma LR, You Y, Robinson MA, *et al*. Pharmacokinetics of intravenous, subcutaneous, and topical administration of lidocaine hydrochloride and metabolites 3-hydroxylidocaine, monoethylglycinexylidide, and 4-hydroxylidocaine in horse. *J Vet Pharmacol Ther* 2018;41:825–37.
39 Pasero C, McCaffery M. *Pain assessment and pharmacologic management*. Missouri: Mosby Elselvier, 2010: 706–7.
40 Ferrini R. Parenteral lidocaine for severe intractable pain in six hospice patients continued at home. *J Palliat Med* 2000;3:193–200.
41 Schwartzman RJ, Patel M, Grothusen JR, *et al*. Efficacy of 5-day continuous lidocaine infusion for the treatment of refractory complex regional pain syndrome. *Pain Med* 2009;10:401–12.
42 Brose WG, Cousins MJ. Subcutaneous lidocaine for treatment of neuropathic cancer pain. *Pain* 1991;45:145–8.
43 Seah D, Thakerar A, Tran H, *et al*. Patients receiving subcutaneous lignocaine infusion for pain. In: *MASCC/ISOO Annual meeting on supportive care in cancer*. Adelaide, 2016.
44 Swenson BR, Gottschalk A, Wells LT, *et al*. Intravenous lidocaine is as effective as epidural bupivacaine in reducing ileus duration, hospital stay, and pain after open colon resection: a randomized clinical trial. *Reg Anesth Pain Med* 2010;35:370–6.
45 Herroeder S, Pecher S, Schönherr ME, *et al*. Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. *Ann Surg* 2007;246:192–200.
46 Kakiuchi Y, Fukuda T, Miyabe M, *et al*. Chromatographic determination of free lidocaine and its active metabolites in plasma from patients under epidural anesthesia. *Int J Clin Pharmacol Ther* 2002;40:493–8.
47 Ivanova A. Fleming's two-stage design: UNC lineberger comprehensive cancer center. 2022. Available: http://cancer.unc.edu/biostatistics/program/ivanova/FlemingsTwoStageDesign.aspx [Accessed 26 Sep 2022].
48 REDCap. Available: https://projectredcap.org/ [Accessed 25 Jun 2022].
49 Guideline for good clinical practice ICH harmonised tripartite; 1996.
50 IMPACCT standard operating procedures. Available: https://www.uts.edu.au/research-and-teaching/our-research/IMPACCT/paccsc/researcher-resources/standard-operating-procedures [Accessed 26 Jun 2022].
51 Integrated addendum to ICH E6(R1): guideline for good clinical practice E6(R2); 2016.
52 Lovell M, Boyle F, Luckett T, *et al*. Cancer pain management 2014. 2014. Available: http://wiki.cancer.org.au/australia/Guidelines:Cancer_pain_management/Pharmacological_management#References
53 Haanpää M, Attal N, Backonja M, *et al*. NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011;152:14–27.
54 Bennett M. The LANSS pain scale: the Leeds assessment of neuropathic symptoms and signs. *Pain* 2001;92:147–57.
55 Falk S, Dickenson AH. Pain and nociception: mechanisms of cancer-induced bone pain. *J Clin Oncol* 2014;32:1647–54.
56 Association TCCotNYH. *Nomenclature and criteria for diagnosis of diseases of the heart and great vessels*. 9th ed. Boston: Brown & Co, 1994: 253–6.
57 Chong SF, Bretscher ME, Mailliard JA, *et al*. Pilot study evaluating local anesthetics administered systemically for treatment of pain in patients with advanced cancer. *J Pain Symptom Manage* 1997;13:112–7.
58 Charlson M, Szatrowski TP, Peterson J, *et al*. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245–51.
59 Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, eds. *Advances in Pain Research and Therapy*. New York: Raven Press, 1989: 391–403.
60 Bouhassira D, Attal N, Fermanian J, *et al*. Development and validation of the neuropathic pain symptom inventory. *Pain* 2004;108:248–57.
61 Dalal S, Hui D, Nguyen L, *et al*. Achievement of personalized pain goal in cancer patients referred to a supportive care clinic at a comprehensive cancer center. *Cancer* 2012;118:3869–77.
62 Herdman M, Gudex C, Lloyd A, *et al*. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). quality of life research: an international journal of quality of life aspects of treatment. *Care and Rehabilitation* 2011;20:1727–36.
63 Janssen MF, Pickard AS, Golicki D, *et al*. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013;22:1717–27.
64 McCaffrey N, Kaambwa B, Currow DC, *et al*. Health-related quality of life measured using the EQ-5D-5L: south australian population norms. *Health Qual Life Outcomes* 2016;14:133.
65 Abernethy AP, Shelby-James T, Fazekas BS, *et al*. The Australia-modified Karnofsky performance status (AKPS) scale: a revised scale for contemporary palliative care clinical practice ISRCTN81117481. *BMC Palliat Care* 2005;4:7.
66 Fries BE, Schneider DP, Foley WJ, *et al*. Refining a case-mix measure for nursing homes: resource utilization groups (RUG-III). *Med Care* 1994;32:668–85.
67 Morgan DD, Brown A, Cerdor PA, *et al*. Does resource utilization group-activities of daily living help us better interpret Australian karnofsky-modified performance scale? *J Palliat Med* 2020;23:1153–4.
68 IHPA. Available: https://www.ihpa.gov.au/what-we-do/ar-drg-classification [Accessed 6 Jun 2022].
69 CTCAE. Available: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm [Accessed 25 Jun 2022].