

The LOLIPOP trial
Protocol Version 5.0
2nd April 2024
UK V3.0

On behalf of the Australian and New Zealand College of Anaesthetists Clinical Trials Network (ANZCA CTN)

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Date: 2nd April 2024
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Sponsor: Monash University, Melbourne and University Hospital Southampton NHS Foundation Trust, UK
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1. PROTOCOL AGREEMENT

This document is confidential. The Investigators declare that they have read the final study protocol and any amendments. The Investigators will conduct the study according to the procedures specified in the study protocol, and in accordance with ICH GCP notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and the Australian NHMRC National Statement on Ethical Conduct in Research Involving Humans or national equivalent.

LOLIPOP Trial Protocol version 5.0 dated 2nd April 2024

UK V3.0

Site Investigator Name_____

Investigator Signature: _____ Date: _____

Please scan and email back to LOLIPOP project manager (Monash University) or Bristol Trials Centre (For UK sites only)

2. TRIAL SUMMARY

The LOLIPOP Trial is a large (n=4,300 patients) pragmatic, international, multicentre, prospective, randomised, double blind, placebo-controlled, parallel assessment, safety and effectiveness superiority study. Its purpose is to evaluate the effectiveness of lidocaine infusions commenced during surgery and extending up to 24 hours postoperatively, on the incidence of ***moderate or severe*** chronic post-surgical pain (CPSP) detected one year following surgery in female patients undergoing elective breast cancer surgery. Analysis will include adjustment for the stratification variables of surgery type [breast conserving surgery (BCS) (unilateral or bilateral) or mastectomy (M) (unilateral or bilateral)], and the presence of preoperative chronic pain at a site other than the surgical site. The trial has 90% power to detect a clinically meaningful (25%) reduction in the incidence of the primary outcome. Secondary outcomes include safety events, analgesic efficacy (pain scores and opioid consumption), neuropathic characteristics of CPSP, and psychological and quality of life outcomes.

Title	**LOLIPOP (Long term Outcomes of Lidocaine Infusions for Post-Operative Pain)** **A pragmatic, international, multicentre, prospective, randomised, double blind, placebo-controlled, parallel assessment, safety and effectiveness superiority study.**
Overall Trial Chief Investigator	**Professor Tomás Corcoran**
UK Chief Investigator	**Associate Professor Mark Edwards**
Hypothesis	**The administration of lidocaine by infusion during the intraoperative period and up to 24 hours following surgery will decrease the incidence of *moderate or severe* Chronic Post-Surgical Pain (CPSP) detected at one year in patients undergoing elective primary surgical procedures for breast cancer.**
Trial size	**4,300 patients**
Primary endpoint	**The incidence of moderate or severe CPSP at 1 year after surgery, as reported (numerical rating scale ≥4 out of 10 for worst pain in the last week) by the patient at follow-up review. See Appendix 2 for full definition.**
Secondary endpoints	• **The severity of acute postoperative pain at rest in the first 24 hours postoperatively (maximum pain score, Numerical rating scale (NRS) 0-10)** • **The severity of acute postoperative pain on movement in the first 24 hours (maximum pain score, NRS 0-10)** • **Postoperative opioid (Morphine Equivalent (MEQ)) consumption on day 1** • **The incidence of severe CPSP at 1 year after surgery as reported by the patient at follow-up review and defined by NRS for the worst pain in the last week of ≥7.** • **The incidence of mild or greater CPSP at 1 year after surgery as reported by the patient at follow-up review and defined by NRS for the worst pain in the last week of ≥1.** • **Postoperative opioid (MEQ) consumption at 3 months (last 24 hours)** • **The incidence of moderate to severe CPSP at 1 year after surgery, with a significant contribution from radiation therapy** • **The incidence of moderate to severe CPSP at 1 year after surgery, with a significant contribution from repeat surgery** • **The incidence of discomfort or altered sensation at the site of surgery (not reported as pain) at 1 year after surgery.** • **Severity of CPSP (assessed using "average" and "worst" NRS pain score in the last week, obtained from the adapted mBPI-SF) at 1 year after surgery (See Appendix 8).**

	• Incidence of neuropathic symptoms at 1 year (incidence examined as a binary outcome using the Short form of Douleur Neuropathique 4 (S-DN4) questionnaire (see Appendix 8). • Postoperative opioid (MEQ) consumption at 1 year (last 24 hours) • Physical functioning at 1 year using interference component of mBPI-SF • Changes in quality of life metrics EuroQol 5 Dimension 5 Level (EQ-5D-5L) at 1 year after surgery compared to baseline (See Appendix 6). • Changes in psychological wellbeing using Kessler Psychological Distress Scale (K-10) at 1 year after surgery compared to baseline (Appendix 7). • The incidence of mortality at 1 year • Estimation of the cost-effectiveness of perioperative lidocaine infusions in this setting (UK/NHS Sites only)
Study Drug Related Safety Endpoints	• Incidence of treated bradycardia intraoperatively • Incidence of treated hypotension intraoperatively • Incidence of treated bradycardia in PACU • Incidence of treated hypotension in PACU • Incidence of intraoperative infusion stopping events • Incidence of PACU infusion stopping events • Incidence of post-operative infusion stopping events on the ward • Incidence of suspected lidocaine toxicity events • Incidence of suspected SEVERE local anaesthetic toxicity events (generalised seizure, sudden unexplained loss of consciousness, life-threatening arrhythmia, cardiac arrest) • Incidence of Medical Emergency Team (MET) activation • Incidence of unplanned ICU, HDU or CCU admission • Incidence of study drug unblinding events • Incidence of subcutaneous catheter site events
Inclusion criteria	• Consenting adult female patients (≥18 years) undergoing mastectomy (unilateral or bilateral) or breast conserving surgery (unilateral or bilateral) for the primary excision of confirmed or suspected breast cancer under general anaesthesia (including those with simultaneous insertion of tissue expanders or implants). • American Society of Anaesthesiologist (ASA) physical scale 1-3
Exclusion criteria	• Pre-existing pain at site of surgery, axilla, ipsilateral side of chest wall or the ipsilateral upper arm • Re-excision procedures where the margins at the index surgery have been deemed insufficient • When immediate autologous reconstruction surgery is planned • Where delayed autologous reconstruction surgery on the operative breast within 1 year is planned • Planned use of regional analgesia infusions • Impaired cognition • Pregnant or lactating females • Transgender patients • Known metastatic disease • History of anaphylaxis, sensitivity or known contraindication to lidocaine (or other amide local anaesthetic agents), including patients with known porphyria or methaemoglobinaemia • History of epilepsy • Baseline heart rate <50 bpm or systolic blood pressure <100mmHg • Acute coronary event in the last 3 months

Exclusion Criteria (continued)	• Cardiac conduction abnormalities, including: Atrial fibrillation, Heart block (all degrees), Bundle Branch Block or Fascicular block, Prolonged QT interval, Wolf Parkinson White syndrome, channelopathy such as Brugada syndrome. A preoperative Electrocardiogram (ECG) is not mandatory unless clinically indicated. • Abnormal serum potassium concentration (based upon site laboratory reference ranges) • Abnormal serum sodium concentration (based upon site laboratory reference ranges) • Active liver disease • Medications within the last 7 days which are known/suspected to slow lidocaine metabolism (amiodarone, beta blockers, cimetidine, fluoroquinolones, fluvoxamine, imidazole's, macrolides, verapamil, HIV drugs) • Cardiac Failure • Severe Renal Failure (Creatinine Clearance of less than 30ml/min or dialysis dependent) • Co-administration of lidocaine within 24 hours prior to surgery for other reasons (e.g. lidocaine patches)
Trial Intervention	Intraoperative: • A bolus of the study drug, 0.125 ml/kg of lean body weight (LBW) of 2% lidocaine (2.5 mg/kg (LBW) or matched placebo) to be administered after anaesthetic induction, but prior to surgical incision, followed by an intraoperative intravenous infusion, 0.1665 ml/kg (LBW)/h of 2% lidocaine (3.33 mg/kg (LBW)/h or matched placebo). Postoperative: • A subcutaneous infusion of study drug, 0.0222 ml/kg (LBW)/h of 10% lidocaine (2.22 mg/kg (LBW)/h or matched placebo) to be administered for up to 24 hours. Dosage will be capped at a maximum lean body weight of 68kg.
Follow-up	Patients will be followed up during their hospitalisation on day 1, and with telephone and/or electronic contact at 3 months and 1 year postoperatively to assess clinical and economic (UK/NHS sites only) endpoints. There will be a further economic follow up at 6 months (UK/NHS sites only)
Trial Duration	6 years (5 years recruitment July 2022 to July 2027, 1 year follow up)
Trial registration	ClinicalTrials.gov Identifier: NCT05072314
Funding	• The Australian National Health and Medical Research Council, Medical Research Future Fund (APP1200994) Funding initiative: Rare Cancers, Rare Disease and Unmet Need Neurological Disorders 2020 • National Institute for Health and Care Research UK (NIHR159174) Health Technology Assessment (HTA) Programme

3. TRIAL FLOW DIAGRAM

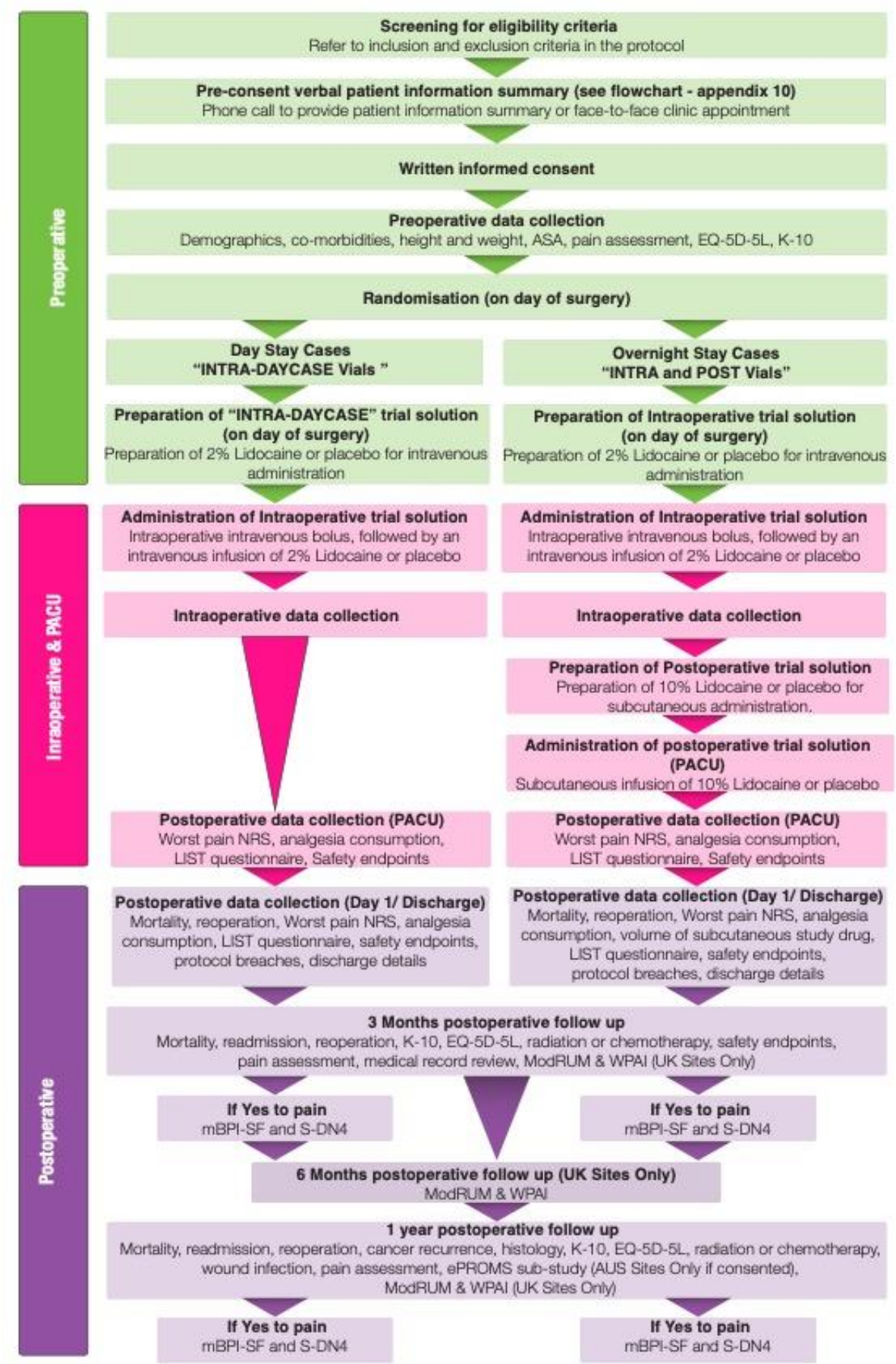


Figure 1: Trial flow diagram

4. INVESTIGATOR LIST

4.1 Principal Chief Investigator

Professor Tomás B. Corcoran, MB, BCh, BAO, MRCPI, FCARCSI, MD (Res), FCICM
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Clinical Professor | School of Medicine and Pharmacology, University of Western Australia
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Associate Professor Andrew Toner, BA, MA, MBBCh, FRCA, FANZCA MD(Res)
Specialist Anaesthetist | Department of Anaesthesia and Pain Medicine, Royal Perth Hospital
Clinical Associate Professor | School of Medicine and Pharmacology, University of Western Australia

Professor Paul S Myles, MBBS, MPH, MD, DSc, FCAI, FANZCA, FRCA, FAHMS
Director, Department of Anaesthesiology and Perioperative Medicine, Alfred Hospital and Monash University Melbourne, Australia

Professor Christobel Saunders MB, BS (Lond.), FRCS, FRACS, FAAHMS, AO
James Stewart Chair of Surgery, Department of Surgery, Melbourne Medical School and Royal Melbourne Hospital

Professor Andrew Forbes, MSc, PhD
Head, Biostatistics Unit and Division of Biostatistics, Analytics, Modelling and Health Economics, School of Public, Health and Preventive Medicine, Monash University

Professor Philip J. Peyton, MD, PhD, MBBS, FANZCA
Staff Anaesthetist and Head of Research, Department of Anaesthesia, Austin Health
Professor, Department of Critical Care, Melbourne Medical School, The University of Melbourne

Professor Kate Leslie, MBBS, MD, MEpid, MHlthServMt, HonDMedSci, FANZCA, AO, FAHMS
Specialist Anaesthetist and Head of Research, Department of Anaesthesia and Pain Management, Royal Melbourne Hospital
Honorary Professorial Fellow in Department of Critical Care, Melbourne Medical School, and Department of Pharmacology, University of Melbourne
Honorary Adjunct Professor, Central Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University

Professor Stephan Schug, DM, MD, FANZCA, FFPMANZCA
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Honorary Senior Research Fellow, Anaesthesiology and Pain Medicine, School of Medicine, University of Western Australia

Professor David Story, MBBS, MD, BMedSci, FANZCA
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Head of the Department of Critical Care, Melbourne Medical School, The University of Melbourne

Professor David A Scott, MB, BS, PhD, FANZCA, FFPMANZCA
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Professorial Fellow, Department of Critical Care, University of Melbourne

Professor Matthew Chan, MBBS, MMed, PhD,FHKCA, FANZCA, FHKAM
Specialist Anaesthetist, Department of Anaesthesia and Intensive Care, Prince of Wales Hospital
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Associate Professor Mark Edwards, BMedSci, BMBS, MRCP, FRCA, MD(Res)
Consultant in Anaesthesia and Perioperative Medicine, Department of Anaesthesia, University Hospital Southampton NHS Foundation Trust, UK.

Professor Shelley Potter, BSc (Hons), M.B.Ch.B.(Hons), PhD, FHEA, FRCS
Professor of Surgical Oncology, Bristol Medical School and North Bristol NHS Trust, UK.

UK Team

UK Chief Investigator
Associate Professor Mark Edwards, BMedSci, BMBS, MRCP, FRCA, MD(Res)
UK Surgical Lead

UK Co-Lead
Professor Shelley Potter, BSc (Hons), MB.ChB.(Hons), PhD, FHEA, FRCS

Associate Professor Andrew Toner, BA, MA, MBBCh, FRCA, FANZCA MD(Res)

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Trial Manager
Chloe Beard, BSc (Hons)

Bristol Trials Centre, 1-5 Whiteladies Road, Clifton, BS8 1BN
Patient and Public Representative
Ms Patricia Fairbrother
Independent Cancer Patients' Voice (ICPV)

5. PERSONNEL, SUBCOMMITTEES AND RESPONSIBILITIES

The interplay of trial sub-committees and personnel is outlined in Figure 2 - *Committee Organisational Chart.*

5.1 Steering Committee (SC)

The SC will be responsible for all aspects of the trial. It will meet at least biannually, or more frequently as required.

Chair: Tomás Corcoran
Deputy Chair: Andrew Toner

Members:
Paul Myles, Christobel Saunders, Andrew Forbes (trial statistician), Philip Peyton, Kate Leslie, Stephan Schug, David Story, David Scott, Matthew Chan, Gill Ormond (LOLIPOP Project Manager), Ms Julie Mews (Consumer Representative), Mark Edwards (UK Lead), Shelley Potter

In attendance (by invitation):
Natalie Hird (Clinical Support Manager)
Karen Goulding (CTN Manager)
Paige Druce (CTN Coordinator)
Chloe Beard (UK Trial Manager)
Rachel Brierley (UK Trial Portfolio Lead)

5.2 Operations Committee (OC)

The OC will be responsible for the day-to-day running of the trial, and will be the initial point of contact for administrative considerations (e.g. protocol modification, proposed sub-studies, proposed media engagement in relation to the study etc.). The OC will be responsible for enacting decisions taken by the SC, but will also be expected to present administrative issues for consideration by the SC. The UK team will have their own Operations Team (See Figure 2). Members of the UK Operations Team will meet once a quarter with the OC.

The UK team will have their own Operations Team (See Figure 2). Members of the UK Operations Team will meet once a quarter with the OC.

Chair: Tomás Corcoran
Deputy Chair: Andrew Toner

Members:
Gill Ormond, Natalie Hird and once a quarter members of the UK Operations Team

UK Operations Team

The UK study arm will be managed by the UK Chief Investigator and co-lead, BTC senior staff, co-applicants, PPI lead and the trial manager, and fully supported by the wider BTC. The co-lead is Deputy Chief Investigator for the overall trial and will be a key day-to-day link to the central Australian trial group.

The Trial Management Group (TMG) will comprise of the UK Chief Investigator and co-lead, trial manager, BTC team members plus all other co-applicants. The TMG is expected to meet at least every 4-6 months. The TMG will monitor all aspects of the conduct and progress of the trial in the UK, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial. The TMG will receive regular input from the LOLIPOP PAG.

The CI and surgical co-applicant will also attend the whole trial 6 monthly Steering Committee (equivalent to a UK TEG) meetings chaired by the Australian group. The TEG will be responsible for enacting decisions taken by the OC and by the SC and will also be expected to present administrative issues for consideration by the OC, and the SC. Meetings will be held with use of video/teleconference facilities to reduce environmental impact where appropriate.

5.3 Writing Committee [Main Paper]

Chair: Tomás Corcoran

Members:
Andrew Toner, Paul Myles, Andrew Forbes (On behalf of the LOLIPOP investigators and the ANZCA Clinical Trials Network)

5.4 Independent Endpoint Adjudication Committee (IEAC)

The SC will decide on the definitions of outcomes. The IEAC will evaluate individual patient events and determine primary outcomes at the direction of the SC. The process of adjudication is described in the Endpoint Adjudication Manual. The IEAC will receive de-identified data and be blinded as to treatment allocation.

Chair:
Dr Donald Johnson *FANZCA, FFPMANZCA, FRCA*
Consultant, Anaesthesia and Pain Management, Royal Perth Hospital
Head of Department of Pain Medicine, Royal Perth Bentley Group

Members:
Dr Chui Chong MBBS, FANZCA, FFPMANZCA
Specialist Anaesthetist and Pain Medicine Specialist, Royal Perth Bentley Group
Independent 3rd party
Dr Aston Wan MBBCh, MA GDMM, MClEpid, MPainMed, MHeadacheMed, FRACGP, FFPMANZCA
Specialist Pain Medicine Physician, Barbara Walker Centre for Pain Management Clinical Director

5.5 Data Safety Monitoring Committee (DSMC)

Chair

Professor Chris Frampton BSc(Hons) PhD(Cant)
Department of Statistics, Christchurch Clinical School of Medicine, University of Otago, New Zealand

Members

Associate Prof Bridin Murnion, MBChB, FRACP, FFPMANZCA, FAChAM
Head of Department, Drug & Alcohol Services, Central Coast Local Health District
Conjoint Associate Professor, School of Medicine and Public Health, University of Newcastle
Dr Yi-Ching Lee, FFPMANZCA, FCICM, PGCerCU, MMed (Pain Mgt), MBBS, BSc
Pain Specialist, Pain Management Centre, Royal Prince Alfred Hospital
Pain Specialist, Pain Management Service, Chris O'Brien Lifehouse
Clinical Lecturer, Central Clinical School, Faculty of Medicine and Health, University of Sydney
Prof Lesley A Colvin
Professor of Pain Medicine/ Hon Consultant in Anaesthesia & Pain Medicine
Division of Population Health and Genomics, University of Dundee, United Kingdom
Professor Richard Riley MBBS, FANZCA, DABA, FSSH
Emeritus, Department of Anaesthesia and Pain Medicine, Royal Perth Hospital,
Clinical Associate Professor, University of Western Australia
Senior Lecturer, University of Notre Dame University

The responsibilities of the DSMC are outlined in the DSMC Charter and Terms of Reference documents.

They include:

- **A.** Safeguarding the interests of the study participants
- **B.** Responsibility for monitoring the conduct of the trial and assessing the safety of the trial
- **C.** Meeting at least every year to assess the safety and conduct of the trial
- **D.** Evaluating the effectiveness and safety data after one interim analysis has been performed; this will occur after 2150 patients have completed their 1 year follow up.

The DSMC may provide recommendations concerning the conduct of the trial and if there are significant safety concerns the committee may consider stopping the trial. Members will review Serious Adverse Events (SAE), Suspected Unexpected Serious Adverse Reactions (SUSAR) and Safety Endpoint data and where necessary make a determination as to likely causation or relationship to study drug. They will also review the lidocaine concentration data from the pharmacokinetic cohort, and consider any necessary dose adjustments as suggested under "Dose adjustments authorised by the DSMC". In the event that there are serious safety concerns, they will take a vote on whether to recommend continuing the trial or modifying the protocol to address any relevant safety concerns. A majority vote to stop will be recommended to the SC at the LOLIPOP Trial Project Office.

UK Oversight Committees

The international DSMC will monitor the safety of the trial in the UK. A standalone UK DSMC is unlikely to be able to detect a safety signal examining UK safety data only. Therefore there will be no UK-specific DSMC. Safety data from UK sites will be entered into the international trial database and UK safety reports will be passed to the international DSMC as required. The international DSMC will make recommendations to a UK-specific independent Trial Steering Committee (TSC) that will function in accordance with NIHR guidance in the UK. The NIHR have agreed to this approach and international DMSC names will be provided to the funder for communication purposes.

The independent UK TSC will oversee study progress in the UK and make recommendations about any issues identified specific to the UK arm. This includes participant recruitment and retention rates, and data quality. They will review UK safety/toxicity data in the context of the international safety data. To facilitate this, they will receive reports of UK specific and whole trial data summaries.

The international SC has primary responsibility for making decisions about the overall trial, including those that will impact the trial in the UK. In the event of a major decision by the international SC (whether or not in response to a recommendation by the DMSC) affecting trial conduct or continuation in the UK, input from the UK TSC, UK sponsor +/- UK funder will be sought. In the event of a disagreement, the final decision will rest with the international SC and international sponsor.

5.6 Data Quality Committee (DQC)

The LOLIPOP Trial Data Quality Committee reports on the data quality and integrity of the case report forms and the study database.

Chair: Andrew Toner
Deputy Chair: Tomás Corcoran

Members:
Andrew Forbes (Trial Statistician), Gill Ormond, Natalie Hird. Mr Adam Meehan (Database Technical Manager, Research Path Pty Ltd.) will attend when necessary on invitation. Mark Edwards will also attend on invitation The DQC roles are described in its terms of reference document. They are related primarily to ensuring that the trial data is of high quality, to identify any errors in data collection through central monitoring, and to ensure that site monitoring is performed.

5.7 Trial Statistician

Professor Andrew Forbes

5.8 Independent Trial Statistician

Dr Catherine Martin

5.9 Consumer Representative

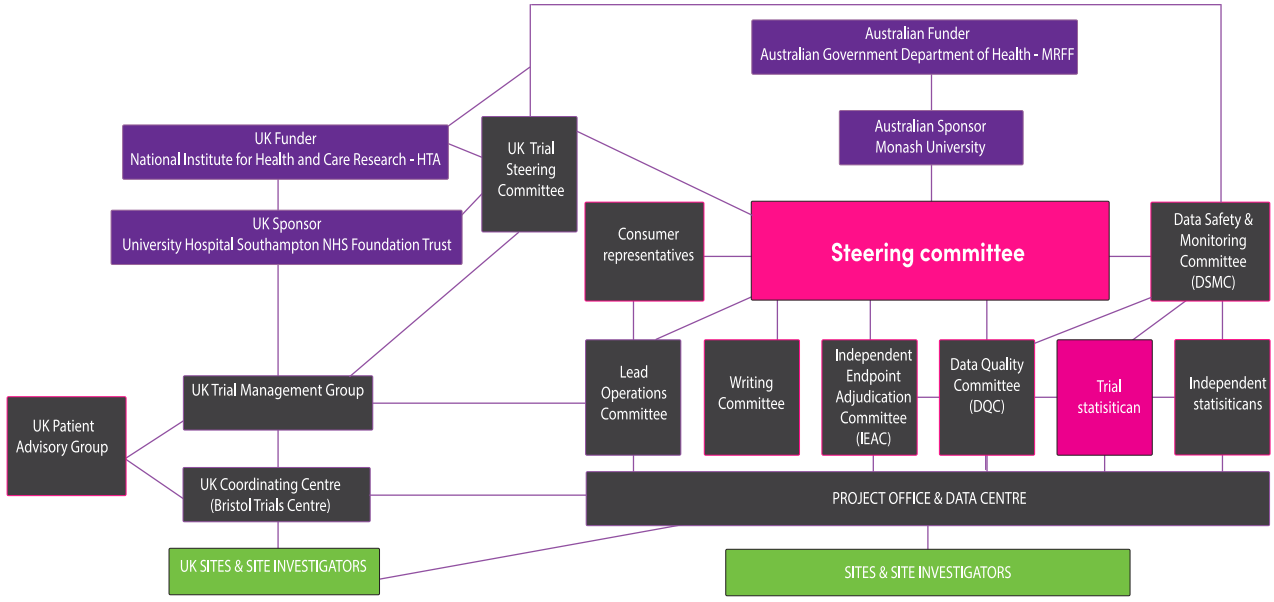
Ms Julie Mews

UK Patient and Public Involvement

The international team developed the trial processes with continuous input from individuals with a lived experience of breast cancer and national patient groups. In the UK, a LOLIPOP Patient Advisory Group (PAG) will be formed to guide how best to do the trial in the UK. This will be led by an experienced individual who became a breast cancer advocate after developing the disease in 2000 and is a trustee of Independent Cancer Patients' Voice. There will be PPI representatives on both the TMG and UK oversight committee.

Throughout the trial, participants will be kept up to date with study progress through newsletters, prepared in collaboration with the LOLIPOP-UK-PAG. We will work with the LOLIPOP-UK-PAG to develop publicly accessible information which will be disseminated through press releases, web-based resources (e.g., blogs, social media) and other appropriate outlets (e.g. advocacy groups). We are also engaged with the Communication & PPI Officer at University Hospital Southampton NHS Foundation Trust and the Press Offices at the University of Bristol to facilitate dissemination to the public. We will work with our stakeholders with high profile on social media (e.g. X @POMCTN ~2k followers) to enhance the visibility of any outputs.

5.10 Committee Organisational Chart



Note: All Relationships in the Organisational Chart are two way

Figure 2: Committee Organisational Chart

5.11 Role of Investigators

Principal Chief Investigator: Professor Tomás Corcoran provides overall leadership of the study. His roles include leading the design of the study protocol, data management and analysis and authorship of the main paper.

Deputy and Western Australia Chief Investigator: Associate Professor Andrew Toner will deputise in the absence of Professor Corcoran

New Zealand and Hong Kong Principal Investigators and United Kingdom Chief Investigator: Dr Nani Le Tagaloa (New Zealand), Prof Matthew Chan (Hong Kong) and Associate Professor Mark Edwards (United Kingdom) will oversee the application for grant funds in these countries and lead the recruitment, initiation and ongoing performance of study sites.

Site investigators: The responsibilities of site investigators will include

- submitting the study protocol to the local ethics committee (if they are a non-Australian site or not part of the National Mutual Acceptance (NMA)) and research governance office and obtaining approval before commencing the study
- ensuring that all staff conducting the trial are qualified to do so
- ensuring that all staff involved in the study are fully instructed on the study procedures and are given access to the study protocol and other information relating to the study
- ensuring that the study is conducted in accordance with the current protocol and ICH GCP notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and the Australian National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Research Involving Humans (or relevant regulatory approvals for non-Australian sites)
- ensuring that written informed consent is obtained from each patient prior to entering the study (see Appendix 10)
- ensuring that the paper and web-based Case Report Forms (CRFs) are complete and accurate on completion of the study
- ensuring that the quality control procedures are performed on both the CRFs and the database
- ensuring the relevant sections of the LOLIPOP COVID-19 Contingency plan (Appendix 9) is followed when required

UK: In the UK, the UK Sponsor will be responsible for submitting the study protocol to the Research Ethics Committee and Medicines and Healthcare products Regulatory Agency (MHRA).

6. ABBREVIATIONS

AE	Adverse event
ANZCA	Australian and New Zealand College of Anaesthetists
ANZCA CTN	Australian and New Zealand College of Anaesthetists Clinical Trials Network
AR	Adverse Reaction
ASA	American Society of Anesthesiologists
BCS	Breast Conserving Surgery
BMI	Body Mass Index
CCU	Critical Care Unit
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CPSP	Chronic Post-Surgical Pain
CRF	Case Report Form
DSMC	Data Safety and Monitoring Committee
DQC	Data Quality Committee
EQ-5D-5L	EuroQol 5 Dimension 5 Level
ePROMS	Electronic Patient Reported Outcome Measures
GCP	Good Clinical Practice
HDU	High Dependency Unit
HREC	Human Research Ethics Committee
ICD-11	International Classification of Diseases – 11
ICU	Intensive Care Unit
IEAC	Independent Endpoints Adjudication Committee
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IORT	Intraoperative Radiotherapy
IQR	Interquartile Range
IV	Intravenous
K-10	Kessler Psychological Distress Scale
LAST	Local Anaesthetic Systemic Toxicity
LBW	Lean Body Weight
LIST	Lidocaine Infusion Surveillance Tool
M	Mastectomy
mBPI-SF	Modified brief pain inventory – Short Form
mITT	Modified Intention to Treat
MET	Medical Emergency Team
ModRUM	Modular Resource-Use Measure
NMA	National Mutual Acceptance
NMDA	N-Methyl-D- aspartate
NHMRC	Australian National Health and Medical Research Council
NNT	Numbers needed to treat
NRS	Numerical rating scale
OC	Operations Committee
OR	Operating Room
PACU	Post Anaesthetic Care Unit (UK equivalent: Theatre Recovery)
PICF	Patient Information and Consent Form
PONV	Postoperative nausea and vomiting
PP	Per Protocol

S-DN4	Short form of Douleur Neuropathique 4 Questions
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SC	Steering Committee (UK equivalent: Trial Management Group)
SD	Standard Deviation
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Australian Therapeutic Goods Administration
WPAI	Work Productivity and Activity Impairment

UK equivalents to Australian abbreviations

[1] MET Medical Emergency team – UK equivalent: rapid/urgent review by critical care team, defined by inclusion of intensivist or anaesthetist

[2] OR Operating Room - UK equivalent: Operating Theatre

[3] SC Steering Committee - UK equivalent: Trial Management Group (TMG)

UK specific Abbreviations:

DMSC	Data Monitoring and Safety Committee
MHRA	Medicines and Healthcare products Regulatory Agency
PAG	Patient Advisory Group
REC	Research Ethics Committee

UK Definitions (where they differ from those used in the Master Protocol):

Trial Steering Committee	The role of the TSC is to provide overall supervision for a study on behalf of the Sponsor and Funder and to ensure that the study is conducted to the rigorous standards set out in Good Clinical Practice. It does not handle the day to day management of the study. Its main focus is the progress of the study, adherence to the protocol, participant safety and the consideration of any new relevant information.
Chief Investigator	The authorised professional, usually appointed by the sponsor of the research study, whether he/she is an Investigator at any site, who takes primary responsibility for the conduct and reporting of that study.
Principal Investigator	The person at a participating research site responsible for conducting the research to required standards at that site. The Chief Investigator may also be the PI at the site where he/she is based.

Terms used in Master Protocol that are different in UK:

Master PICF – a non-localised copy of the combined participant information leaflet and consent form

7. LIDOCAINE

LIDOCAINE [2-(diethylamino)-N-(2, 6-dimethylphenyl)acetamide]

7.1 Pharmacology

Structurally, lidocaine is an amide derivative of diethylamino acetic acid [2-diethylaminoaceto-2',6'-xylidide ($C_{14}H2_2N_2O$)], and, like other amide-type local anaesthetics, it consists of a lipophilic aromatic ring attached by an amide linkage to a hydrophilic amino group.[1] Lidocaine has a molecular weight of 234. Lidocaine is a weak base with a pKa of 7.9. Thus, at a physiological pH of 7.4, about 65% of lidocaine is in the charged cationic form and 35% in the uncharged base form. Because the uncharged form is primarily responsible for diffusion across the nerve sheath and membrane, the onset of action of lidocaine is fast compared with other local anaesthetics. It is also a Class 1b antiarrhythmic agent and binds to open sodium channels during phase 0 of the action potential, therefore blocking many of the channels when the action potential peaks.

7.1.1 Action as a local anaesthetic agent

Similar to other local anaesthetics, the mechanism of action of Lidocaine for local or regional anaesthesia is by reversible blockade of nerve fibre impulse propagation. Some local anaesthetic is removed by tissue binding and circulation when Lidocaine is infiltrated near a nerve. The remaining anaesthetic enters the nerve cells by diffusion through membranes. Lidocaine then binds to sodium channels, causing a conformational change that prevents the transient influx of sodium, therefore depolarisation. All potentially excitable membranes are affected, however sensory fibres are blocked preferentially because they are thinner, unmyelinated and more easily penetrated. Lidocaine's onset of action is rapid, and blockade, whilst dependent of dose given, concentration used, nerves blocked and status of the patient, may last for up to 5 h when administered as a peripheral nerve block. The traditional explanation for lidocaine's analgesic effect is related to its ability to block voltage-gated sodium channels. These structurally consist of a single alpha subunit forming an ion pore and varying auxiliary beta subunits. Local anaesthetics dose-dependently decrease peak sodium current by selectively binding intracellularly to and stabilizing these alpha subunits in their inactivated state (inactivated block). They can also bind within the ion channel pore to prevent ion flux (open state block). Both of these actions rely on the channel being activated and therefore, with repeated depolarisation, there is an incremental decrease in Na+ current. This is termed a use-dependent or phasic inhibition.[2] Given that this is a dose dependent effect, and with intravenous administration the concentrations at the nociceptive neuronal membranes are likely to be extremely low in comparison, this theory cannot entirely explain systemic lidocaine's promising clinical effects in the context of pain. It also fails to explain the findings of a review by Barreveld et al., who concluded that lidocaine is a useful preventative analgesic agent. Ten of the 13 clinical trials demonstrated the effect of lidocaine lasting longer than eight and a half hours (which is five and a half times the half-life of Intravenous (IV) lidocaine).[3]

7.2 Pharmacokinetics and pharmacodynamics

7.2.1 Intravenous administration

When Lidocaine is given intravenously to normal subjects, the volume of distribution is 0.6-4.5 L/kg. The plasma binding of Lidocaine is inversely proportional to the drug concentration. It is 60% to 80% protein-bound at concentrations of between 1 and 4 mcg/mL. Binding fraction also depends on the plasma levels of the acute phase reactant alpha-1-glycoprotein. Lidocaine may exist in ionised or unionized form depending on the pH of the environment. As a weak basic drug, Lidocaine tends to be more unionised and able to cross cell membranes in basic media.

7.2.2 Metabolism and elimination

Lidocaine is dealkylated in the liver by the cytochrome P450 system forming numerous metabolites. Monoethylglycine xylidide [MEGX], glycine xylidide [GX] and xylidide [X] are the key active metabolites, all of which have reduced potency but have comparable pharmacologic activity to Lidocaine.[4] After the intravenous administration of Lidocaine, monoethylglycine, xylidide and glycine xylidide concentration equate to approximate 11% to 36%, and 5% to 11%, respectively, of the total plasma Lidocaine concentrations. Hepatic blood flow appears to be a limiting factor in Lidocaine's metabolism. The rate of metabolism is slower reduced in patients with congestive cardiac failure, chronic liver disease and hepatic insufficiency, and after acute myocardial infarction. Lidocaine and its metabolites are predominantly renally excreted. Less than 10% of Lidocaine is excreted without being metabolised. The total body plasma clearance of Lidocaine in healthy volunteers has been reported to be approximately 10-20 mL/min per kilogram.[5] The majority of Lidocaine elimination occurs in the liver, and since the total body plasma clearance of Lidocaine is about 800 mL/min and hepatic blood flow is about 1.38 L/min, up to 60% of an oral dose is metabolised before entry into the systemic circulation. This accounts for the low plasma Lidocaine concentrations observed following the oral administration of 500 mg Lidocaine hydrochloride. Elimination half-life is defined as the rate at which a local anaesthetic is removed from the blood. Therefore, the time necessary for 50% reduction in Lidocaine blood level is one half-life; two half-lives equates to a 75% reduction, three half-lives to an 87.5% reduction, four half-lives to a 94% reduction, five half-lives to a 97% reduction and six half-lives to a 98.5% reduction. The half-life of Lidocaine has been shown to be approximately 100 min following either an23nfuseon lasting less than 12 h or a bolus injection. In this setting Lidocaine demonstrates linear pharmacokinetics. However, following an intravenous infusion greater than 12 h, Lidocaine exhibits nonlinear, or time-dependent pharmacokinetics. Patients who received prolonged Lidocaine infusions following a myocardial infarction were found to have Lidocaine concentrations that continued to rise for approximately 48 h, with the half-life extending up to 4 h.

Polymorphisms in the cytochrome P450 system, particularly CY1A2 and 3A4 are known to influence the rate of metabolism of lidocaine, and we will examine this concept in a pharmacogenomic analysis of the LOLIPOP cohort. [6,7]

7.2.3 Toxicity

Generally, Lidocaine toxicity can result when either the correct dose of Lidocaine is inadvertently administered or delivered via the intravascular route, or when doses, even if given by the correct route, are excessive. There are a number of factors that influence or directly affect the severity of Lidocaine toxicity. These include the vascularity of the site of injection, speed of the injection, acid base status, and underlying hepatic or renal impairment. Lidocaine is metabolised by the liver,

therefore severe hepatic dysfunction will significantly increase both the risk and severity of toxicity. In addition, given that Lidocaine is protein bound, severe hypoalbuminemia may also predispose to toxicity risk. Acidosis increases the risk of toxicity due to Lidocaine dissociating from plasma proteins. Lidocaine's pharmacokinetics and antiarrhythmic effects may be potentiated or altered by beta-blockers, ciprofloxacin, cimetidine, clonidine, and phenytoin. Beta-blockers such as propranolol and metoprolol can reduce Lidocaine's metabolism, whilst cimetidine and amiodarone reduce its clearance. Lidocaine's interactions with phenytoin and ciprofloxacin are through their effects on the liver's cytochrome system. Adverse effects of Lidocaine and other amide local anaesthetic agents are similar in nature. Low plasma concentrations of Lidocaine (less than 5 mcg/mL) are used in the clinical setting to suppress cardiac ventricular arrhythmias and status seizures, but seizure activity may be induced at higher concentrations. Seizures result from selective depression of central nervous system inhibitory tracts. As plasma Lidocaine levels increase all pathways are suppressed, resulting in respiratory arrest, cardiovascular collapse and coma. Lidocaine toxicity may commence at concentrations greater than 5 mcg/mL, although convulsive seizures most often occur at concentrations greater than 10 mcg/mL.

7.2.4 Chronic Postsurgical Pain (CPSP)

CPSP – A neurological condition with limited therapeutic options

Chronic pain (pain that recurs or persists for more than three months) is a neurological disorder in which alterations in neural networks affect multiple aspects of brain function, structure and chemistry.[8] Chronic Pain has recently been incorporated into the 11th edition of the **International Classification of Diseases** (ICD-11, released by the World Health Organisation in June 2018). [9] Chronic postsurgical pain (CPSP) is one of the 7 unique subsets of this condition.[10] It defines CPSP as pain developing or increasing in intensity after a surgical procedure, in the area of the surgery, persisting beyond the healing process (at least 3 months) and not better explained by another cause such as infection, malignancy, or a pre-existing pain condition. CPSP is due to a predictable (and planned) inciting stimulus.[11] It is frustrating that although we can predict this condition, there are ***no proven interventions*** which can prevent it.[12] Neuropathic characteristics are prominent, rendering the condition distressing and very difficult to treat. [13] The use of opioids to treat this resistant condition are likely contributing to the global opioid crisis. [14]

7.2.5 Pathophysiology of CPSP

The factors influencing the transition from acute to chronic postsurgical pain are complex and incompletely understood.[15] Current understanding implicates peripheral neuronal hypersensitivity, the establishment and maintenance of central sensitisation in dorsal horn nociceptive neurons, and neuroinflammation as key pathological processes.[16] This neuronal plasticity (the ability of the nervous system to change structurally and functionally in response to various stimuli) becomes maladaptive when prolonged, and if these changes fail to resolve they become embedded and very difficult to reverse.[15] Hence the paradigm that prevention is preferable to treatment.[11]

Central sensitisation is a long-term maladaptive neuroplasticity resulting in a form of "pain memory".[11,17] In the dorsal horn of the spinal cord, increased spontaneous activity, reduced depolarisation thresholds, enlargement of receptive fields and temporal summation all amplify nociceptive signalling and contribute to the pain state.[18] This process is triggered by intense repetitive activation of peripheral pain neurons, is maintained by glial cell mediated neuroinflammation, and culminates in the experience of increased pain due to painful stimuli (hyperalgesia) and pain even with non-painful stimuli (allodynia). Importantly, peripheral nerve

injury can maintain already established central sensitisation due to ongoing low-grade spontaneous neural activity. [19] The N-Methyl-D-aspartate (NMDA) and glycinergic signalling pathways are active in the initiation of hyperalgesia and wind-up in chronic pain conditions, whilst calcium channel inhibition is believed to reduce hyperexcitability and spontaneous depolarisations – key components of ***peripheral sensitisation***. Transcriptional and post-translational changes in sodium channels that induce hyperexcitability, lead to permanent peripheral sensitisation and spontaneous ectopic discharges,[20] and the sort of sustained peripheral input required to both initiate and maintain central sensitisation.[21] Prolonged central sensitisation is also evident in some individuals that recover pain-free after injury but have compensated with upregulated endogenous opioid pathways – a phenomenon that can be unmasked by naloxone.[22] Thus, cancer patients receiving adjuvant therapies after surgery may be particularly vulnerable to CPSP, as they undergo repeated and multi-modal injury in areas where pain pathways are already sensitised. Hence, if neuronal and central nervous system vulnerability following surgery can be reduced, then the impact of chemo- or radio-therapy will likely be diminished.

7.2.6 The role of the NMDA receptor and voltage gated sodium (Nav) channels in CPSP

The two most promising target receptors to emerge as candidates in the pathophysiology of CPSP are the NMDA receptor and the voltage gated sodium (Nav) channel.[23]

7.2.7 Voltage gated sodium (Nav) channels

The voltage gated sodium channel has numerous subtypes which differ in the structure of their homologous alpha subunit. Of the subtypes NaV1.7, NaV1.8 and NaV1.9 are thought to be expressed exclusively in peripheral neurons and play an essential part in nociceptive transmission[24]. The presence of individuals with an overexpression of NaV1.7 are known to have a decreased sensitivity to local anaesthetics[25] and a strong predisposition to certain pain syndromes such as erythromyalgia and paroxysmal extreme pain disorder[26]. In contrast, loss of function mutations of NaV1.7 (also referred to as SCN9A channelopathy) are reported in humans with an inability to experience pain[27]. Of particular interest, a recent study by Minett et al. in both humans and mice with such loss of function mutations, showed that the administration of naloxone led to profound loss of congenital analgesia in these subjects. This suggests that the absence of NaV1.7 function led to alterations in gene expression resulting in endogenous opioids contributing to the congenital analgesia. This is supported by the findings that specific NaV1.7 channel blockers do not replicate the analgesic phenotype of those with loss of function mutations[28]. Nav channel number, distribution and function are radically altered in nerve injury and CPSP, and play a critical role in the primary nociception that occurs during surgical incision and subsequent acute inflammation.[29] These are in turn important drivers of central sensitisation. There is speculation amongst pain researchers that specific NaV1.7 channel blockers in combination with opioids, dosed well below the current perceived therapeutic window, will potentially lead to side effect free analgesia[28,30].

7.2.8 The NMDA receptor

NMDA receptors are involved in both the peripheral and central sensitisation process, but mainly centrally. [31] They may alter synaptic transmission and long-term potentiation,[31,32] such that semipermanent changes can become fixed (embedded) through the activity of this receptor. [11]

7.2.9 Pharmacological interventions to prevent chronic post-surgical pain

A number of small trials have examined the efficacy of NMDA receptor antagonists, gabapentinoids, corticosteroids, and non-steroidal anti-inflammatory drugs in attenuating CPSP. A Cochrane systematic review and meta-analysis reported that, beside techniques of regional anaesthesia, the only systemic drug with encouraging albeit limited evidence to support a reduced incidence of CPSP at six months was intravenous ketamine.[33] ***Lidocaine infusions were not examined in that metanalysis.***

7.2.10 How important is Chronic Postsurgical Pain (CPSP)?

CPSP is increasingly recognised as a common, and sometimes catastrophic, complication of surgery,[11] and is one of the most important research priorities in perioperative medicine.[33] It can complicate up to 70% of surgical procedures, with patients undergoing limb amputation, thoracotomy, and breast cancer surgery having the highest risk.[11] Estimates have varied due to the lack of a standardised definition, but CPSP is now represented as a separate disease entity, with clear diagnostic criteria, in the ICD-11 manual.[10] In our mixed surgical population in Evaluation of Nitrous Oxide in the Gas mixture for Anaesthesia (ENIGMA) trials, we established a CPSP incidence of 12% up to 3 years after surgery, with 4% of patients rating their pain as severe.[34] This is consistent with recent European data.[35] Conservative estimates of new cases of any CPSP occurring in the USA annually vary from 394,000 to 1.5 million.[13] However, more liberal estimates put the incidence of ***severe*** CPSP at between 960,000 and 4.8 million in the USA annually.[15]

7.2.11 CPSP in Australia

Using the figures from our ENIGMA trials, the estimates from the Australian Institute of Health and Welfare regarding surgical volumes, and by extrapolating from epidemiological data, we estimate that 264,000 Australian patients experienced CPSP in 2016-17 (12% of the 2.2 million elective surgical episodes) and approximately 90,000 of those would be as severe. CPSP is associated with decreased quality of life and impaired function in virtually every domain in which it has been examined.[35,36] The economic cost of chronic pain (including CPSP) in Australia has been estimated at $73.2 billion dollars each year including $48.3 billion in lost productivity.[37] As a direct consequence of the impact of CPSP on quality of life, the additional cost to our community is estimated at $66.1 billion every year. Surgery is the most important preventable cause of chronic pain; CPSP accounts for up to 25% of the one in five Australian adults suffering chronic pain conditions.[38]

7.2.12 Clinical features

Epidemiological studies have identified those most “at-risk” for CPSP.[11,39,40] Whilst CPSP is clearly a maladaptive response, it is considered a continuation of acute postoperative pain in certain circumstances, with clinical factors enabling prediction in up to 70% of cases.[41] These factors include but are not limited to;[15] age, sex, psychosocial factors, the presence and severity of preoperative pain, surgical procedure type, intraoperative nerve injury and the severity and speed of resolution of acute postoperative pain. “Emotional numbing” and “catastrophizing” are the psychological factors which feature most strongly in the risk of CPSP.[42] Neuropathic characteristics are prominent, rendering the condition distressing and very difficult to treat. [13]

7.2.13 The role of genetic predisposition in the development of CPSP

There is a growing body of work suggesting that differences in genetic predisposition may significantly influence the risk of development of chronic pain after injury, including CPSP. [43,44] Establishment of biobanks in large clinical trials for subsequent analysis is now considered the ideal approach to providing opportunity from clinical trials to examine genetic factors that influence the development of disease or the influence of drug therapy. Subsequent analyses may then be performed, either as large GWAS (genome wide association studies), the examination of single-nucleotide polymorphisms (SNPs), or the examination of pharmacogenomic factors influencing drug metabolism and effectiveness. Assessment of SNP variants in candidate genes important in neurotransmitter systems (COMT), voltage-gated ion channel activity (KCNJ6), tetrahydrofolate biosynthesis (GCH1), oestrogen receptor (ESR1) and mu opioid receptor (OPRM1) have demonstrated associations with the development of CPSP in small studies.[45] Furthermore, there is growing interest in the dopamine neurotransmission pathway as a target involved with chronic postsurgical pain.[44] Hence, we propose to expand the panel of candidate genes that may be examined from our biobank to include SNPs in dopamine receptor-2 (DRD2) and Calcium Voltage-Gated Channel Auxiliary Subunit Gamma 2 (CACNG2), in addition to COMT, voltage-gated ion channel activity (KCNJ6), tetrahydrofolate biosynthesis (GCH1), oestrogen receptor (ESR1) and mu opioid receptor (OPRM1). Pharmacogenomic factors such as polymorphisms in the genes coding for hepatic cytochrome enzyme systems which are responsible for the metabolism of lidocaine, may also be important in explaining the interindividual differences in the efficacy of the same dose of the same drug. The hepatic enzymes, cytochromes P450 (CYP450), are a major source of variability in drug pharmacokinetics and response, and several interindividual genetic variations may result in altered plasma concentrations of, and hence therapeutic response to, different drugs.[46] The *CYP3A4*22* polymorphism has gained recent prominence due to its association with considerably reduced CYP3A4 protein expression and function, that could in turn translate into slower lidocaine metabolism[47]. In the event of a beneficial effect of lidocaine on the incidence of CPSP being identified in the LOLIPOP trial, as an advantage of biobanking our genetic material, we may then examine whether polymorphisms in the CYP genes may account for some of this observed effect. This may be a first step towards “precise and individualised” perioperative medicine.

7.2.14 Why study breast cancer surgery patients?

Chronic pain as a result of cancer and cancer treatments (including chemotherapy) is well identified. Women undergoing breast surgery and cancer treatment are a particularly high risk group for development of CPSP; chronic pain after breast surgery is a listed specific syndrome in the ICD-11 manual.[10] The indication and type of breast surgery are important predictors.[12,48] The incidence in simple breast reduction surgery is 22% compared to 49% amongst patients undergoing mastectomy with reconstruction.[48] This is consistent with the theory that the presence of depression, psychological vulnerability, and anxiety in cancer surgery patients may render patients more likely to develop CPSP.[42] Gärtner identified a prevalence of CPSP in breast cancer surgery patients of 47%, of which 52% had moderate or severe pain (24.4% of total).[49] Pain was predominantly neuropathic in nature, and although breast conserving surgery conferred no clear pain risk advantage over mastectomy, CPSP was more frequently classified as severe in the mastectomy group despite many of these patients not undergoing radiotherapy. More conservative estimates are lower at around 13.5%.[39] This is such a consistent and important finding across studies, that direct and indirect pain related outcomes have been incorporated into the recently published International Consortium for Health Outcomes Measurement Initiative value-based patient-centred outcomes for breast cancer.[50]

Relevance to the Australian Population: In 2018 there were 18,235 cases of breast cancer diagnosed in Australia (the commonest of all cancers).[51] These patients are young (mean age = 62 years) and overwhelmingly female with a five-year survival rate of 91%. Hence, these patients have high survival rates and long post-treatment survival times and carry a substantial and prolonged personal burden of chronic pain along with a proportional economic cost to the healthcare system.

7.2.15 The biological plausibility of a lidocaine role to prevent CPSP

Lidocaine is a commonly used amide local anaesthetic and a Class 1b antiarrhythmic agent which has actions at many receptors that play a role in CPSP.[52] It is most commonly used by injection into or around wounds or nerves, where the high local concentration, through an effect on Nav channels, produces profound reversible blockade of conduction in the sensory nerves transmitting pain sensation. We are proposing to administer the drug systemically (either intravenously or by subcutaneous infusion), achieving higher systemic concentrations than are seen when nerve blocks are performed, and over a more sustained period of time. Lidocaine decreases peripheral nociceptive input, not only by blockade of Nav channels, but also via antagonism of other receptor systems that modulate peripheral signal transduction; including at low-doses the glycinergic system, some potassium channels and Gαq-coupled protein receptors, and at higher doses calcium channels and NMDA receptors.[52] The NMDA and glycinergic signalling effects are necessary to reduce hyperalgesia and wind-up in chronic pain conditions, whilst calcium channel inhibition is believed to reduce hyperexcitability and spontaneous depolarisations – key components of peripheral sensitisation. Thus, intravenous lidocaine may modify central sensitisation by reducing the initial barrage of nociceptive inputs through sodium channel blockade and, in a similar fashion to the theory regarding ketamine, by antagonizing the NMDA receptor.[53] Lidocaine also has potent and wide-ranging anti-inflammatory effects that stand to attenuate both peripheral and central sensitisation.[54] The acute analgesic effect may also result in opioid sparing, and potentially decrease opioid induced hyperalgesia. Lidocaine therefore may attenuate the initiation of central sensitisation and the inputs which appear necessary to maintain it.

7.2.16 Indirect clinical evidence for perioperative lidocaine infusions

Systemic lidocaine has been successfully used for the treatment of acute pain after surgery, which itself is strongly associated with CPSP, [55] demonstrating a modest reduction of surgical pain severity in the first four postoperative hours[56] with higher dose (≥ 2 mg/kg/h) infusion regimens. A systematic review identified that 13 out of 16 perioperative lidocaine studies[3] reported a preventive analgesic effect during the inpatient period, defined as analgesia outlasting five and a half times the lidocaine plasma half-life. Lidocaine infusions are also established as a treatment for mixed aetiology chronic pain patients, with effective analgesia occurring at plasma concentrations around 1.5-3 mcg/ml[57] which again often outlasts the systemic presence of lidocaine by days and weeks.[58]

7.2.17 Direct clinical evidence for perioperative lidocaine infusions:

In our recent systematic review and meta-analysis of the efficacy and safety of perioperative lidocaine infusions in relation to CPSP, [59] the primary outcome was the presence or absence of any procedure-related pain at three months or longer after surgery. Perioperative lidocaine infusions significantly reduced the primary outcome (odds ratio [OR], 0.29; 95% CI, 0.18 to 0.48). In a pre-

specified secondary analysis of patients undergoing breast surgery, the primary outcome was also similarly reduced (OR, 0.32; 95% CI, 0.18 to 0.58). In each of the six studies included, authors explicitly stated that there were no complications attributable to lidocaine infusions. Overall, the primary outcome findings of our meta-analysis (number needed to treat = 5) exceed the results observed in the ketamine meta-analysis (number needed to treat = 6.7).[60]

Limitations of the direct clinical evidence: The findings of our systematic review and meta-analysis must be interpreted with caution as sources of bias were highly apparent, as were limitations in trial design and safety surveillance. The funnel plot was indicative of a marked publication bias towards small, highly positive trials.[61] Four out of six trials used pain outcomes at three months, with only two trials assessing pain outcomes at six months.

7.2.18 Literature review and pilot data

1. We have completed and published the **Long-term Outcomes of Lidocaine Infusions for PostOperative Pain (LOLIPOP) Pilot Study** pilot study (ACTRN12618000463279) which has been endorsed by the ANZCA CTN. It has demonstrated both the effectiveness of drug delivery systems (median plasma lidocaine concentration; Post Anaesthetic Care Unit (PACU) = 1.8 mcg/ml; WARD = 1.6 mcg/ml) and safety. [62]
2. In our recent meta-analysis, we observed a 71% reduction of the odds of CPSP, with a number-needed-to-treat (NNT) of approximately 5 for lidocaine infusions (**Figure 3**) – a finding that remained consistent in a planned sub-group analysis limited to breast surgery.[59] The primary purpose of a meta-analysis is in hypothesis generation, and hence, this very substantial reduction in the odds of CPSP must be tested in a properly conducted large trial.
3. In our recent survey of ANZCA Fellows, 52% of respondents reported the incorporation of perioperative lidocaine into their practice, with the principal aim to reduce acute surgical pain and opioid use. These findings confirm that there is equipoise regarding lidocaine as a perioperative intervention. [63]

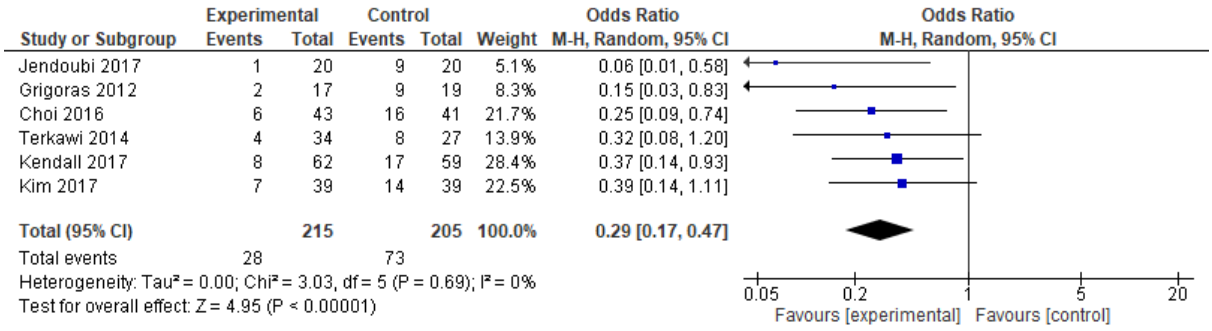


Figure 3: Random effects metanalysis of the effect of perioperative lidocaine infusions compared to placebo on CPSP in all surgery types.

Safety Issues: A safety evaluation in the meta-analysis of lidocaine for acute surgical pain (45 trials, n=2802) found no evidence that intravenous lidocaine was associated with an increased risk of adverse events such as death, arrhythmias, other heart rate disorders or lidocaine toxicity[56]. Safety surveillance is a key component of this trial protocol, and the safety data from our pilot trial of 150 patients failed to identify any safety concerns.

Dose selection: The trials examined in our meta-analysis employed a range of bolus doses (1.5 to 2 mg/kg) and infusion rates (1 to 3 mg/kg/h). In healthy volunteers, lidocaine infusions reduce experimentally induced hyperalgesia[64]. The mechanisms by which lidocaine may modify the pathophysiology of CPSP point towards greater efficacy with prolonged exposure, and many acute pain trials extend infusions up to 24 hours postoperatively and beyond.[56] Data from our pilot study has indicated that our selected dosing regimen achieves plasma concentrations both in the PACU and postoperatively on the ward, that are in the likely therapeutic range whilst well below toxic concentrations. [62] Our dosing regimen is based upon this data to ensure safe and appropriate plasma concentrations (see "Dose justification").

7.2.19 Conclusion

CPSP is a common, debilitating and at times incapacitating complication of major surgery, with as yet few completely effective therapeutic options. Once established, it is difficult to treat. Primary prevention of CPSP is now seen as the "Holy Grail" of anesthesiology.[65] It represents substantial long-term costs to the economy and to the patients' quality of life. This is particularly true for women undergoing ablative and, in the majority of cases, curative surgery. Lidocaine is inexpensive, safe, and widely accessible. There is substantial biological plausibility, and preliminary clinical evidence supporting its role to prevent CPSP. A pharmacogenomic analysis will further refine this intervention and, if successful, represent a truly personalised patient-specific regimen. This trial may alter routine anaesthesia care worldwide for breast cancer surgery, and most importantly, it would provide real benefit for the millions of women around the world who develop this dreaded complication, with inestimable economic and humanitarian benefits.

8. RESEARCH PLAN

8.1 HYPOTHESIS AND DESIGN

Hypothesis: The administration of lidocaine by infusion during the intraoperative period and up to 24 hours following surgery will decrease the incidence of ***moderate or severe*** CPSP which has been present on most days, on most weeks, for the last 3 months detected at 1 year in patients undergoing elective primary surgical procedures for breast cancer.

Study Design: International, multicentre, prospective, randomised, double blind, placebo-control, parallel assessment, effectiveness and safety superiority study.

8.2 OUTCOMES/ENDPOINTS

8.2.1 Primary Outcome /Endpoint

The incidence of moderate or severe CPSP at 1 year after surgery, as reported by the patient at follow-up review, meeting the criteria outlined below.

8.2.2 Primary Outcome Definition

In order to meet the criteria for moderate or severe CPSP at 1 year, the reported pain:

- **a.** Must be reported to be completely or partly caused by the breast surgery undertaken 1 year ago
- **b.** Must have been present for at least 3 months
- **c.** Must be reported as of "worst" intensity ≥4 out of 10 in the last week on the Modified brief pain inventory short form (mBPI-SF) (See Appendix 8).
- **d.** Be in the area of the breast surgery performed 1 year ago or in one of the following related areas: axilla, ipsilateral side of chest wall or ipsilateral upper arm
- **e.** Must not be clearly and exclusively attributable to another cause such as:
    a. Radiation therapy at or near the pain location
    b. Repeat Surgery at or near the pain location
    c. Musculoskeletal injury at or near the pain location
    d. Infection at or near the pain location
    e. Recurrence of cancer at or near the pain location

8.2.3 Secondary Endpoints

1. The severity of acute postoperative pain at rest in the first 24 hours postoperatively (maximum pain score, Numerical rating scale (NRS) 0-10)
2. The severity of acute postoperative pain on movement in the first 24 hours (maximum pain score, NRS 0-10)
3. Postoperative opioid (Morphine Equivalent; MEQ) consumption on day 1
4. Postoperative opioid (MEQ) consumption at 3 months (last 24 hours)
5. The incidence of moderate to severe CPSP at 1 year after surgery, with a significant contribution from radiation therapy

6. The incidence of moderate to severe CPSP at 1 year after surgery, with a significant contribution from repeat surgery
7. The incidence of severe CPSP at 1 year after surgery as reported by the patient at follow-up review and defined by NRS for the worst pain in the last week of ≥7)
8. The incidence of mild or greater CPSP at 1 year after surgery as reported by the patient at follow-up review and defined by NRS for the worst pain in the last week of ≥1.
9. The incidence of discomfort or altered sensation at the site of surgery (not reported as pain) at 1 year after surgery.
10. Severity of CPSP (assessed using "average" and "worst" NRS pain score in the last week, obtained from the adapted mBPI-SF) at 1 year after surgery.
11. Incidence of neuropathic symptoms at 1 year (incidence examined as a binary outcome using the Short Form of Douleur Neuropathique 4 Questions; (S-DN4) see Appendix 8).
12. Postoperative opioid (MEQ) consumption at 1 year (last 24 hours)
13. Physical functioning at 1 year (using interference component of mBPI-SF)
14. Changes in quality of life metrics EuroQol 5 Dimension 5 Level (EQ-5D-5L) at 1 year after surgery compared to baseline (Appendix 6).
15. Changes in psychological wellbeing using Kessler Psychological Distress Scale (K-10) at 1 year after surgery compared to baseline (Appendix 7).
16. The incidence of mortality at 1 year.
17. UK NHS costs of care over 1 year following surgery. (UK/NHS sites only)
18. Productivity costs over 1 year following surgery. (UK/NHS sites only)
19. Quality-adjusted life years (QALYs) over 1 year following surgery. (UK/NHS sites only)
20. Cost-effectiveness of perioperative lidocaine infusions compared to usual care, from a primary UK NHS perspective and broader perspective including productivity, at 1 year. (UK/NHS sites only)

8.2.4 Study drug related Safety Endpoints

1. Incidence of treated bradycardia intraoperatively
2. Incidence of treated hypotension intraoperatively
3. Incidence of treated bradycardia in PACU
4. Incidence of treated hypotension in PACU
5. Incidence of intraoperative infusion stopping events (*See Section **8.9.1.1**: Study drug infusion stopping criteria*)
6. Incidence of PACU infusion stopping events
7. Incidence of infusion stopping events on the ward
8. Incidence of suspected lidocaine toxicity events
9. Incidence of suspected **SEVERE** lidocaine toxicity **events** (generalised seizure, sudden unexplained loss of consciousness, life-threatening arrhythmia, cardiac/circulatory arrest)
10. Incidence of Medical Emergency Team (MET) activation
11. Incidence of unplanned ICU, HDU or CCU admission
12. Incidence of study drug unblinding events
13. Incidence of subcutaneous catheter site events (up until Day 30, collected at 3 months)

SAE's and severity of Adverse Events (AEs) (mild, moderate, severe), will be collected and classified by organ system and captured in the CRF. See Appendix 3 for definitions of Safety Endpoints.

8.2.5 Trial endpoints

The trial study endpoints must be entered into the CRF. The trial database contains an endpoint module where information regarding positive primary endpoints must be entered. Please see the reporting section of the Standard Operating Procedures (SOP) manual and Appendix 2 – *primary endpoint diagnostic criteria.*

UK internal Pilot

Within the UK, an internal pilot phase will be conducted across 10 diverse NHS sites during the first 12 months of UK recruitment. The UK internal pilot will monitor:
1) recruitment rates (randomised participants per site per month);
2) adherence to the allocated treatment and
3) primary outcome data completeness.

Any shortfalls will prompt strategies to tackle identified barriers. Criteria for progression from phase 1 to phase 2 are outlined in Table 1. These targets allow for staggered site opening. If all criteria are green, we will proceed to a full trial with the same protocol; if one or more criteria are amber, we will propose adaptions to address the short fall; if one or more criteria are red, we will discuss with the trial steering committee and funder whether the full UK arm is feasible. The results from the internal pilot will be central to an Investigators' meeting held after the first year to share best recruiting practices.

Criterion	Target	Red	Amber	Green
Participant Recruitment	220	<110	110-219	≥220
Randomisation rate / centre / month	2.6	<1.3	1.3-2.5	≥2.6
Centres open	10	<5	5-9	10
Adherence to allocated intervention	95%	<90%	90-94%	≥95%
Primary outcome data available	95%	<90%	90-94%	≥95%

Table 1. Progression Criteria (after 12 months of active recruitment)

Site Selection

At least 10 UK sites will participate in LOLIPOP. Essential criteria for site selection include an appropriate research infrastructure and an adequate volume of breast cancer surgery, defined as 2 or more 4-hour theatre sessions per week. Desirable criteria include experience with interventional drug trials. Expressions of interest will be sought via multiple networks, for example: the UK Perioperative Medicine Clinical Trials Network, the Association of Breast Surgery and NIHR Clinical Research Network.

Overall UK recruitment target

The UK will aim to recruit 1000 participants over the full duration of the UK arm of the trial.

8.3 Study Population

8.3.1 Inclusion Criteria

- Consenting adult female patients (≥18 years) undergoing mastectomy (M) (unilateral or bilateral) or breast conserving surgery (BCS) (unilateral or bilateral) for the ***primary*** excision of confirmed or suspected breast cancer under general anaesthesia (including those with simultaneous insertion of tissue expanders or implants).
- American Society of Anaesthesiologist (ASA) physical scale 1-3

8.3.2 Exclusion Criteria

- Pre-existing pain at site of surgery, axilla, ipsilateral side of chest wall ***or*** the ipsilateral upper arm (at diagnosis prior to any tumour locating procedures)
- Re-excision procedures where the margins at the index surgery have been deemed insufficient
- Transgender patients
- When immediate autologous reconstruction surgery is planned
- Where delayed autologous reconstruction surgery on the operative breast within one year is planned
- Planned use of regional analgesia infusions
- Impaired cognition
- Pregnant or lactating females
- Known metastatic disease
- History of anaphylaxis, sensitivity or known contraindication to lidocaine (or other amide local anaesthetic agents*), including patients with known porphyria or methaemoglobinaemia
- History of epilepsy
- Baseline heart rate < 50 bpm or systolic blood pressure < 100mmHg
- Acute coronary event in the last 3 months
- Cardiac conduction abnormalities, including; Atrial Fibrillation, Heart block (all degrees), Bundle Branch Block or Fascicular block, Prolonged QT interval, Wolf Parkinson White syndrome, channelopathy such as Brugada syndrome. A preoperative Electrocardiogram (ECG) is not mandatory (see explanatory note**).
- Abnormal serum potassium concentration (based upon site laboratory reference ranges) ***
- Abnormal serum sodium concentration (based upon site laboratory reference ranges) ***
- Active liver disease****
- Medications within the last 7 days which are known / suspected to slow lidocaine metabolism (amiodarone, beta blockers, cimetidine, fluoroquinolones, fluvoxamine, imidazole's, macrolides, verapamil, HIV drugs)
- Cardiac Failure (any documented heart failure at preoperative assessment or GP records)
- Severe Renal Failure (Creatinine Clearance of less than 30ml/min or dialysis dependent)

- Co-administration of lidocaine within 24 hours prior to surgery for other reasons (e.g. lidocaine patches)

*Other amide local anaesthetic agents: ropivacaine, bupivacaine, mepivacaine, prilocaine, etidocaine
- An electrocardiogram does not need to be performed purely for the purpose of enrolment into the trial. An electrocardiogram should be performed ***ONLY* if there are clear clinical indications.
*** Check results if ordered by attending preoperative team, do not order for trial purposes only
**** Active liver disease – e.g. viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, haemochromatosis, cirrhosis, sclerosing cholangitis, liver cancer, other rarer causes)

8.4 TRIAL INTERVENTIONS

An overview of the trial processes, and study drug preparation and administration timepoints are outlined in Figure 1 –*Trial flowchart.*
Upon randomisation, patients will be classified as "Confirmed day-case surgery" or "Possible overnight stay" surgery. This is important as these patients are treated almost identically EXCEPT that the day-cases will not receive the postoperative ward infusion (see below).

8.4.1 Blinding

All trial participants, research coordinators, members of the anaesthesia and surgical teams, pharmacists, theatre and ward staff and all individuals performing patient follow up will be blinded to the patient's treatment allocation. All of the trial committees associated with the study will be blinded, with the exception of the DSMC, who will receive unblinded (open) reports from the independent statistician. Unblinding of the patient's treatment allocation will be possible in exceptional circumstances, and a process will be in place to facilitate unblinding requests (*see Section 8.9 – Bias Control and Safety Mechanisms*).

8.4.2 Randomisation

Following written informed consent from the patient, and liaison with the surgical **and** anaesthesia teams, the patient will be randomised by the research staff at the site via an online password-protected portal on the day of surgery. Patients will be randomised as either "Day-case" or "overnight stay" surgery. A computer-generated list, accessed by a web-based randomisation service (which we use for our other trials), will allocate the patient (1:1) to either the **L**idocaine or **C**ontrol groups, using permuted blocks of 10, and a unique study identifier will be assigned. This will be stratified according to study centre and by "day-case" or "overnight stay".

8.4.3 Preparation and delivery of study drug

For patients with an overnight stay, the study drug for infusion will be provided in two 50 mL vials, clearly labelled as "For use INTRAOPERATIVELY" and "For use POSTOPERATIVELY". For patients that are confirmed day-cases the study drug for infusion will be provided in a 50mL vial clearly labelled as "For use INTRAOPERATIVELY FOR DAYCASE".

Overnight stay cases:
Each patient will be first allocated a vial code using the INTRA-1XXXX format from the drug dispensing module on the database matching a vial from the "INTRAOPERATIVE" study drug box. Once commencement of the intraoperative infusion is confirmed in the drug dispensing module,

a second distinct vial code using the POST-2XXXX format matching a vial from the "POSTOPERATIVE" study drug box will be allocated as a separate drug dispensing episode. **It is critical that these two vials are not inadvertently switched.**

The research coordinators (or delegated members of the research team) will prepare two drug syringes as below. The "*Intraoperative solution*" syringe is prepared, labelled, inserted into the Alaris Pk infusion pump and commenced ***BEFORE*** the *"Postoperative solution"* is dispensed and the syringe is prepared. This is a key safety process to ensure that the two solutions do not get swapped in the event of confusion. A lock out period of 15 minutes will apply to the database and the infusion start time for the intraoperative solution will need to be entered in the database to allow allocation of the postoperative solution.

1. ***Intraoperative solution*** – 50 ml vial of 2% lidocaine or placebo will be prepared in a 50 ml syringe that is compatible with the Alaris PK infusion pump. This syringe contains the solution for an intraoperative pre-programmed bolus followed by a continuous infusion, to be delivered by a dedicated Alaris PK infusion pump.
2. ***Postoperative solution***- 50 ml vial of 10% lidocaine or placebo will be prepared into a 50/60 Terumo syringe to leave a residual volume of 38 mL after priming the infusion line. This will be delivered via a Bodyguard T (BD) pump programmed for a specific infusion rate and volume to be infused for each individual patient (the maximum volume to be infused is 36 mL). The Bodyguard T pump will be placed in a tamper proof, locked box, which will then be placed in a wearable pouch, thus not hindering the patients' early mobilisation.

Confirmed day-cases:
Patients that are confirmed day-cases will be allocated a single vial code using the INTRA-DAYCASE-3XXXX format matching a vial from the INTRAOPERATIVE FOR DAYCASE box. This vial will be prepared and administered as for the "intraoperative solution" as above.

UK:

<u>Manufacture of IMP</u>

Lidocaine in 50ml vials of either 2% or 10% solution and matched placebo (0.9% sodium chloride solution) will be produced centrally in Australia by Sypharma and imported to the UK by Eramol (Eramol Unit 11, Gatwick Metro Centre, Horley, RH6 9GA, UK and Unit 9, North Downs Business Park, Lime Pit Lane, Sevenoaks, TN13 2TL, UK), an MHRA licensed wholesale distributer of human medicinal products.

<u>Packaging, labelling, storage and shipping of IMP</u>

The IMP and matched placebo will be labelled in Australia by Sypharma before shipment to the UK. Upon arrival in the UK, the labelling will be checked by Eramol (Eramol Unit 11, Gatwick Metro Centre, Horley, RH6 9GA, UK and Unit 9, North Downs Business Park, Lime Pit Lane, Sevenoaks, TN13 2TL, UK) to ensure that it is compliant with MHRA requirements. If necessary they will re-label the vials before distribution. Eramol will store and distribute the trial IMPs, providing identical vials of lidocaine and placebo for intra-operative and post-

operative infusions (labelling will indicate whether the vials are for inter or post-operative infusion.

Details about the drug supply chain will be included in the trial specific pharmacy manual

8.4.4 Study Drug Administration

All patients: The intraoperative study drug is delivered **a)** as a bolus following anaesthesia induction, **b)** an intravenous infusion intraoperatively following bolus administration. The intraoperative study drug loaded in the Alaris PK pump is to be available in the operating theatre prior to induction of anaesthesia. Intravenous access is to be established as per routine for anaesthesia – if the participant has provided additional consent for the *biobanking sub-study (See Section 8.4.13.2 Biobanking Sub-study),* the blood sample for this purpose will be taken at this time. A delegated member of the research team should ensure that the pump has been attached correctly to the IV line. The study drug infusion line is to be connected via a 3-way splitting device. After induction of anaesthesia and airway securement, but prior to surgical incision, the Alaris PK pump is commenced with a single button press. The LOLIPOP program installed on the pump delivers the pre-programmed bolus, followed immediately by the pre-programmed infusion. The infusion is then continued during surgery, emergence and transfer to PACU.

UK:

The delegated prescriber will be qualified, registered and named on the delegation log. A clinician on the delegation log will review eligibility of potential participants before consent. The study drug will be prescribed using local processes (e.g. electronic hospital drug chart).

Note – no blood samples will be taken for UK patients.

The intraoperative infusion pumps use a bespoke infusion protocol that will be pre-programmed into the supplied pumps to maximise patient safety and protocol compliance. IMP/placebo may be stored in pharmacy, operating theatres, suitable wards (or a combination) in lockable cupboards. Pumps for LOLIPOP should also be stored in locked cupboards when not in use.

Confirmed daycase surgery: Patients with a clear plan for discharge on the day of surgery will only receive the intraoperative solution as per a) and b) above. This infusion will continue until PACU discharge criteria are met, with a maximum PACU infusion duration of 1 hour. Thereafter no further study drug is administered and the Lidocaine Infusion Surveillance Tool will cease. Even if these cases have an unanticipated need for an overnight stay post-randomisation, they will still be treated **ONLY** as per the daycase group.

Planned overnight admission: Patients that are in the planned overnight stay group will have trial solution administered through a subcutaneous cannula for up to 24 hours postoperatively. This is started on admission to PACU prior to discontinuing the intraoperative infusion. The BD SAF-T Intima subcutaneous cannula (or equivalent) is inserted at an abdominal site under aseptic conditions and secured in place. Process for connection of the postoperative subcutaneous infusion:

- The postoperative study drug loaded in the Bodyguard T pump is to be connected to the patient on arrival in PACU via the subcutaneous cannula, with an appropriate "Subcutaneous" label fixed to the infusion line close to the point of connection.

- The connection and commencement of the postoperative subcutaneous infusion must be a two person check, with one person a member of the research team. This individual must be listed on the trial delegation log for that site.

- A hospital-specific subcutaneous infusion chart should be initiated prior to the onset of the subcutaneous infusion, including a doctor's prescription and two countersignatures confirming appropriate dosing and connection. This chart is then subsequently used by attending nurses to check the subcutaneous cannula site and infusion progression at the required intervals.

- If a hospital does not have a specific subcutaneous infusion chart, the LOLIPOP Trial subcutaneous infusion chart should be used.

If the participant has provided additional consent for the *lidocaine concentration sub-study (See Section 8.4.13.1 Lidocaine Concentration Study)* up to two blood samples for this purpose will be taken at 6-12 hours and 12-24 hours if the infusion is still running. The intraoperative study drug infusion is then discontinued and disconnected from the intravenous cannula. Patients meeting discharge criteria before the 24-hour postoperative infusion is complete will have the study drug ceased, and a minimum period of 1 hour (2 hours if next day discharge) of observation thereafter must elapse free of all symptoms or signs on the Lidocaine Infusion Surveillance Tool (LIST; Appendix 4) prior to discharge.

UK: No blood samples will be taken for UK participants.

8.4.5 Drug dosing calculations

In order to ensure the correct dose of study drug is administered, the database contains a drug calculation module which **MUST** be used to calculate the correct dose to be administered for each patient. Because these are blinded solutions, each dose is calculated as a volume of 2% lidocaine solution, 10% lidocaine solution or placebo. Our drug dosing strategy will employ ***a lean body weight model***.[66] The patient's height and weight will be entered at randomisation into the drug dosing module, and the module will provide three values.

A. The first value is the volume of "intraoperative solution" (2% lidocaine or placebo) that is to be delivered as a bolus post induction over 5 minutes.
B. The second value provided is the rate of infusion of the "intraoperative solution" (in mls per hour) to be commenced after the administration of the bolus and continued into PACU

C. The third value provided is the rate of infusion of the "postoperative solution" via the subcutaneous cannula (overnight stay only). This infusion will commence on admission to PACU and then continued for up to 24 hours or until just before discharge from hospital, whichever comes first.

8.4.6 Study drug (Lidocaine or Placebo) doses

BOLUS: 0.125 ml/kg(LBW) of 2% lidocaine (2.5 mg/kg(LBW)) or placebo

Intraoperative intravenous infusion: 0.1665 ml/kg(LBW)/h of 2% lidocaine (3.33 mg/kg(LBW)/h) or placebo

The maximum permissible intraoperative dose of lidocaine is 1g. If surgery extends beyond the end of the intraoperative infusion, then the infusion is taken down, and no further lidocaine (or placebo) is administered until the postoperative infusion commences.

Postoperative subcutaneous infusion: 0.0222 ml/kg(LBW)/h of 10% lidocaine (2.22 mg/kg(LBW)/h).

Patients allocated to the placebo arm will receive the same volumes and rates of placebo infusion. Dosing will be based on lean body weight formula.

8.4.7 Lean body weight dosing model

Lean body weight = (9270 x weight)/ (8780 + (244 x BMI))

where BMI = body mass index = W/H^2

W = total body weight in kilograms

H = height in metres

We have capped maximum lean body weight at 68kg, such that the *maximum permissible postoperative dose of lidocaine is 3.6g over 24 hours. This is a safety consideration and based upon data from our pilot study, where the maximum lean body weight was 57 Kg.*

The values entered into the Alaris PK pump program **MUST** be double checked against the printout from the drug dosing module by the research coordinator with the attending anaesthetist.

8.4.8 Dose justification

The above dosing regimen is the equivalent of the dosing used in the pilot study, albeit modified to use lean body weight (Janmahasatian formula) rather than total body weight capped at 100 kg. In the pilot study, median (IQR) [range] serum lidocaine concentrations were observed in PACU (2.16 (1.74-2.83) [1.12-6.06]) and during the postoperative infusion on the ward (1.52 (1.28-1.83) [0.64-2.85]) that were safe and potentially therapeutic. During the postoperative infusion, patients with higher total body weights had higher serum lidocaine concentrations (Panel A in Figure 4) and effectively received a higher dose per kg of lean body weight (Panel D in Figure 4). Modifying the dosing regimen according to lean body weight is therefore anticipated to

reduce the inter-individual variability in serum lidocaine concentrations and avoid overshoot in obese patients. [67]

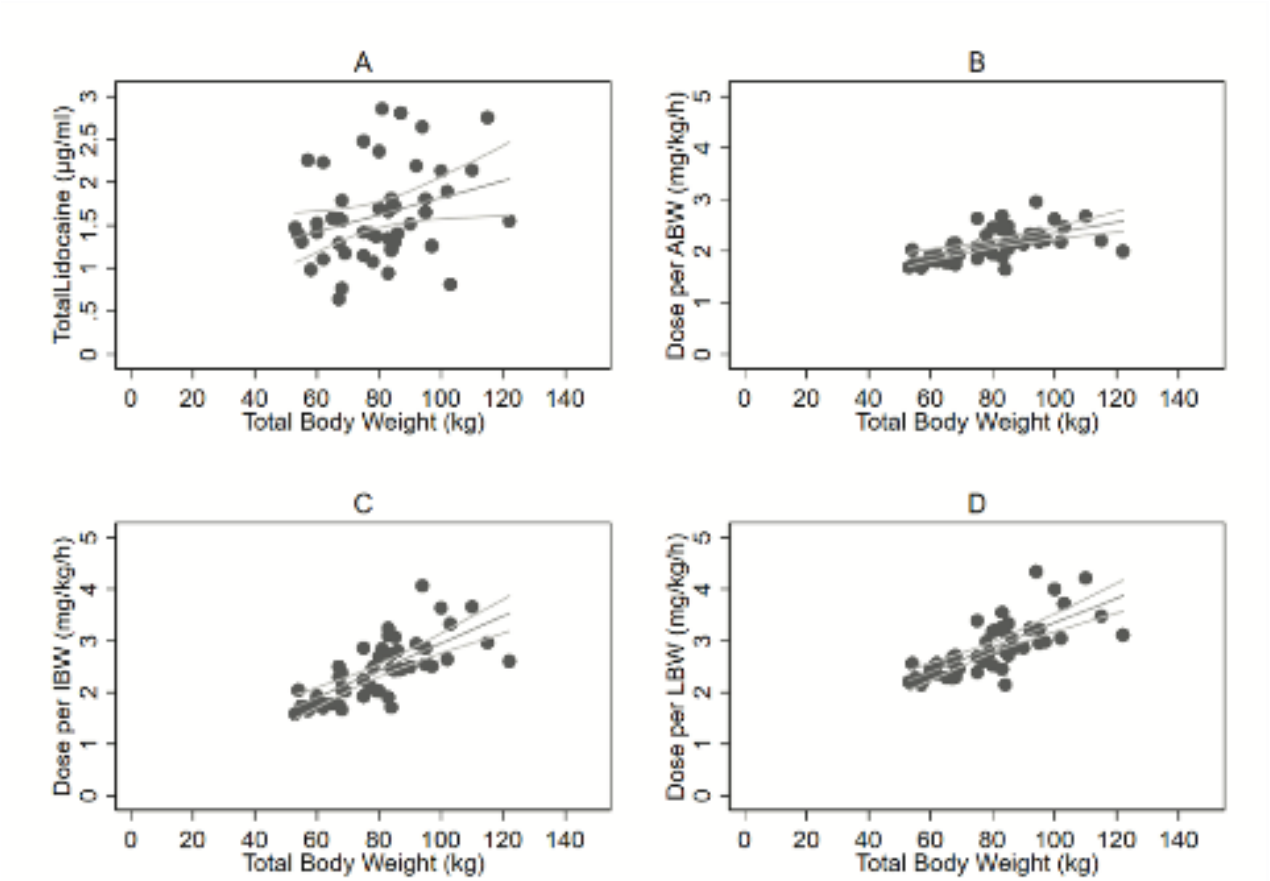


Figure 4. Serum Lidocaine Concentration versus Body Weight

8.4.9 Parallel regional anaesthesia techniques

Anaesthesia type and modality is at the discretion of the attending anaesthetist. Paravertebral blocks, PECs I or II blocks, and surgical infiltration are permitted according to the dose limits below (and doses are to be collected in the CRF). *Regional anaesthesia infusions (paravertebral catheters or wound catheters)* ***are not*** *permitted.* The addition of lidocaine to propofol to minimise pain on injections is permitted up to a dose of 40mg. There are no other stipulations regarding the perioperative management of trial participants. Anaesthesia care will not otherwise be influenced.

8.4.10 Total dose limits for any combination of paravertebral, PECS I/II block and surgical infiltration:

- Bupivacaine (or Levobupivacaine) 1mg / kg *(without adrenaline. Maximum dose 100 mg.)*

OR

- Bupivacaine (or Levobupivacaine) 1.5mg / kg *(with adrenaline. Maximum dose 100 mg.)*

AND/OR

- Ropivacaine 2mg / kg *(with or without adrenaline. Maximum dose 150 mg)*

The body weight used for this dosing calculation is the recorded total body weight of the patient, ***NOT*** the calculated LBW. The total dose that can be administered to the patient will be available on the printed dosing sheet. If both Bupivacaine (or Levobupivacaine) and Ropivacaine are administered to the same patient, the sum of the percentage of the maximum dose delivered of each drug should not exceed 100%. Our dose calculations have erred on the side of caution to avoid excessively high concentrations, but it is still a possibility that patients may develop some toxicity during the intraoperative period, in the PACU or on the ward. Study drug infusion should be ceased if any of the stopping criteria are met. The criteria for stopping the study drug infusion and the treatment of possible Local Anaesthetic Systemic Toxicity (LAST) are detailed under Section 8.9 "Bias control and safety mechanisms." If the permitted additional doses of lidocaine, bupivacaine (or Levobupivacaine) or ropivacaine are inadvertently exceeded by 25% or more, the study drug infusion should be permanently ceased.

8.4.11 Surveillance for local anaesthetic toxicity

The **L**idocaine **I**nfusion **S**urveillance **T**ool (LIST) questionnaire (5 symptom questions answered as Yes / No, and 7 clinical signs sought – see Section 8.9 "Bias control and safety mechanisms" and Appendix 4) is to be commenced in the PACU for all patients when it is deemed patients can answer the questions.

Confirmed day-cases: will complete the LIST tool once they reach PACU, and another prior to discharge. Answering 'yes' to *two or more* LIST questions at any given time, or the presence of *one or more* LIST clinical signs, is an indication to permanently cease the study drug infusion and delay PACU discharge until these criteria are no longer met. If the study drug is stopped due to meeting LIST criteria, the LIST should be completed at hourly intervals until these criteria are no longer met.

Overnight stay cases: will commence the LIST in PACU and continue the LIST questionnaire for the full duration of the infusion (maximum 24h). Upon arrival to the ward, with their first set of observations, overnight stay participants will be asked to complete the LIST tool. This tool is administered every four hours while patients are on their study drug subcutaneous infusions. Answering 'yes' to *two or more* questions at any given time is an indication to permanently cease the study drug infusion. The presence of *one or more* clinical signs at any time consistent with local anaesthetic toxicity or surgical complications are also indications to permanently cease the study drug. If the study drug is stopped due to meeting LIST criteria, the LIST should be completed at hourly intervals until these criteria are no longer met.

8.4.11.1 Re-siting the subcutaneous cannula

In the event that the patient reports a subcutaneous cannula site event on the ward (local irritation or erythema) then the subcutaneous cannula should be re-sited to the opposite side of the abdomen in the first instance (if resources allow). Should the subcutaneous cannula site event reoccur in the new position, the subcutaneous infusion should be discontinued.

8.4.12 Managing interruptions to the Intraoperative infusion

Interruption of the intraoperative infusion may occur due to technical problems that can be easily remedied, whilst maintaining sterility, such as intravenous cannula misplacement (re-site

cannula), occlusion alarms (check bungs and clamps), pump power supply failure (attach mains supply) and disconnection (prime new line). In these circumstances, the intraoperative maintenance infusion rate should be confirmed on the drug dispensing sheet (2-person check) and re-started using the standard ml/hr function (NOT the LOLIPOP program) on the Alaris PK pump*, as per the instructional video hosted on the database. No attempts should be made to compensate for an incomplete or absent bolus dose. Overnight stay patients should still switch to the subcutaneous postoperative drug delivery in PACU as per Section 8.4.4. A breach form is required to acknowledge that an interruption has occurred and the full intended intraoperative dose has not been delivered.

*In the event of a complete failure of the trial pump, any Alaris PK pump in clinical use can deliver the standard ml/hr function.

8.4.13. Managing interruptions to the Postoperative infusion

Interruption to the postoperative infusion may occur due to technical problems that can be easily remedied, whilst maintaining sterility, such as a subcutaneous cannula site event (re-site cannula), occlusion alarm (check clamps, re-site cannula), syringe misplacement alarm (adjust syringe insertion points) or loss of power (replace battery). In these circumstances, the "Resume" option should be selected on the Bodyguard T pump to resume the infusion rate initially programmed by the research team. A breach form should still be completed to acknowledge an interruption has occurred and the full intended postoperative dose has not been delivered. If for whatever reason the initial infusion rate cannot be resumed following an interruption, the postoperative infusion should cease.

UK:

Drug accountability

A full reconciliation is not required. Drug accountability records will be maintained throughout the course of the trial using the IMP track system, by the in house-Eramol central pharmacy and each participating site. Sites will communicate with BTC regarding need for more drug supply and BTC will initiate supply from Eramol. Designated pharmacy staff will document the date and quantity of IMP as it is received and dispensed to study participants. Temperature monitoring and deviations will also be documented.

Drug accountability activity and who is responsible:

Activity	**Responsibility**
Supply of IMP (active and matched placebo)	Sypharma
Provision and QP of IMP	Eramol
Package and labelling of IMP	Eramol
QP release IMP to trial pharmacy	Eramol
Dispense IMP in line with prescription to participant	Hospital pharmacy or delegated member of the research team
Maintain dispensing log	Hospital pharmacy or delegated member of the research team
Report stock levels at site	Hospital pharmacy or delegated member of the research team

Destruction of unused trial medicines after sponsor approval with destruction log completed	Hospital pharmacy
Emergency unblinding	Site PI

Return and destruction of IMP

Any remaining unused lidocaine/placebo from the infusions for each participant should be disposed into sharps bins by the research team as per local hospital procedures.

Any unused IMP should be returned to the local pharmacy. Any unused IMP held by the trial pharmacy at the end of the study will be destroyed (when authorised by the Sponsor) in line with the central pharmacy trial specific instructions on disposal of IMP. An IMP destruction log will be completed.

8.4.14 Blood sampling

UK:
No blood samples to be collected.

8.4.14.1 Lidocaine concentration sub-study

Where resources allow, in a nested cohort of patients, up to two blood samples will be taken during the postoperative study drug infusion for serum extraction, storage and analysis of lidocaine concentrations. Blood sample one will be obtained within a time-window 6-12 hours after the onset of the intraoperative study drug. Blood sample two will be obtained within a time-window 12-24 hours after the onset of the intraoperative study drug, at least 2 hours after blood sample one. Samples are only to be taken while the infusion is still underway. If the subcutaneous infusion has ceased at the proposed time of 12-24-hour sampling, then no blood sample is to be taken. Since only a minority of trial sites have 24-hour access to spin and store facilities, it is anticipated that pharmacokinetic data will be available in a maximum of 300 patients (7% of total participants). The target recruitment for the lidocaine sub-study is 300 patients (150 of whom will have received lidocaine). Furthermore, where possible blood sampling and serum storage for analysis of lidocaine concentrations will occur during any unblinding events or suspected toxicity reactions. Serum will be processed in batches through the laboratory of our collaborators in Queensland. The data from these samples will be made available to the DSMC in an unblinded fashion. The DSMC will take these values into account when considering the overall conduct and safety of the trial, and in particular when examining the details of any unblinding events or suspected toxicity reactions.

8.4.14.2 Biobanking sub-study

In patients who have provided consent to participate in the biobanking sub-study (including pharmacogenomics), a blood sample will be drawn at the time of cannula insertion and stored for further processing at the end of the trial.

UK:
Patients will not be included in either sub study detailed in section 8.4.14 Blood sampling.

8.5 DATA COLLECTION

An overview of the trial and data collection processes is outlined in Figure 1 –*Trial flowchart* and Appendix 1 – *Trial Schematic.*

8.5.1 General Principles

Patients may be recruited from preoperative patient assessment clinics, on hospital wards, in surgical outpatients and in surgeon's private rooms. Information about the trial will be provided to patients including verbal discussions using either the master PICF with or without sub-studies, and initial telephone discussions using the pre-consent verbal patient information summary. If patients have not received a copy of the master PICF already, they will be given the option to receive the master PICF by downloading it from the trial website, email or post. A member of the research team will discuss the master PICFs in person with the patient at the earliest convenient time, to enable participants to make a fully informed decision to participate. This process is outlined in Appendix 10: Approaching patients for participation in the LOLIPOP Trial.

To adapt to trial processes in light of COVID-19, the LOLIPOP COVID-19 Contingency plan (Appendix 9) should also be followed when applicable. The protocol for collection of data on CPSP will meet the 6 core domain requirements set out by the recommendations of the IMMPACT. [68,69] These are 1) pain assessment; 2) physical functioning; 3) emotional functioning; 4) participant ratings of improvement and satisfaction with treatment; 5) symptoms and AEs; and 6) participant disposition.

UK: Staff involved in the identification and approach of current patients will be members of the patient's clinical care team or authorised Trust employed personnel.

8.5.2 Screening Logs

Sites will need to maintain current patient screening and refusal logs which are to be uploaded to the database monthly. A pro-forma screening log will be provided in the SOP manual.

8.5.3 Process

Data collection will be on paper CRFs at participating sites or obtained from the sites electronic medical record, then uploaded onto a central electronic database via a secure online portal, which will incorporate rapid response to incomplete data or data queries, to maximize compliance in data completeness, as we have successfully used in our previous large studies.

Operational definitions: All endpoints will be clearly described by operational definitions. The mBPI-SF, K10, and S-DN4 questionnaires (Appendices 7 & 8) are in use in our other ANZCA CTN trials and have been well validated in our context.[61] All reported primary endpoints (moderate or severe CPSP at 1 year) will be adjudicated by the IEAC. In the event of a reported pain episode not being clearly attributable to the index surgery, then the independent endpoints adjudication committee will arbitrate these potentially contentious outcomes.

Chronic pain preoperatively is defined as pain at a site ***other than the operative site*** and which is persistent for most days of most weeks in the past 3 months. This data is collected at baseline.

Protocol adherence is defined to have occurred when the randomised treatment is received with the intraoperative bolus and infusion, and the postoperative infusion being delivered without interruption due to "Inappropriate Cessation", and without open label lidocaine being administered systemically in excess of the prespecified limit of 40mg. It is recognised that some anaesthetists routinely mix lidocaine with propofol for administration at induction, hence our acceptance of a 40mg dose limit for systemic administration. It is also recognised that the postoperative subcutaneous infusion will be ceased either due to the entire infusion having been delivered, or due to the requirement for cessation for a fixed period of time prior to discharge from hospital. In the latter case, if this is before the scheduled time at which the entire postoperative infusion is expected to be complete, this is still considered complete adherence with the trial protocol. The term "Stopping" refers to the interruption of either the intraoperative bolus, intraoperative infusion or postoperative infusion due to the patient meeting the stopping criteria (see Section 8.9 *Bias Control and Safety Mechanisms*), and this is considered to be adherent to the protocol. "Inappropriate Cessation" occurs when the study drug is ceased / interrupted when the patient's clinical condition does not meet the stopping criteria, and this is considered a breach of protocol and a protocol breach form will need to be completed.

8.5.4 Preoperative Data

8.5.4.1 Baseline data

Data considered relevant to risk of CPSP including demographics, ASA physical status, major co-morbidities, preoperative medications and other preoperative data, will be collected.
Height and weight will be collected to facilitate exact calculation of study drug dosing.
Previous treatments, including neoadjuvant (chemotherapy/Targeted therapies, radiotherapy, hormone and immune) therapies will be recorded.

Participants will complete the EQ-5D-5L and the K-10 scale (Appendices 6-7).
A screening pain assessment question will be asked to determine the presence of pre-existing chronic pain at a site other than the proposed surgical site and to provide a measure of its severity.

UK: All baseline questionnaires should be entered onto the main LOLIPOP trial database.

8.5.5 Intraoperative Data

Anaesthesia related: In a subset of participants who have agreed to biobanking, a blood sample will be collected for pharmacogenomic typing at the time of cannula insertion. Anaesthesia type and agents, lidocaine injection with propofol, analgesic and antiemetic agents. Details regarding the use of paravertebral block or PECS blocks including the bolus doses of drug used will be collected.

Study Drug related:
Trial safety events will be recorded. Study drug stopping or inappropriate cessation to be recorded. Any AE/ SAE/ SUSAR related to trial drug infusion to be recorded.

Surgery related: Surgery duration, local anaesthetic infiltration (type and total amount), details of surgical approach (+/- axillary surgery) to be recorded in the CRF. Intraoperative radiotherapy (IORT) to be recorded.

Safety endpoints, AEs, incomplete infusion events and protocol breaches to be recorded.

8.5.6 PACU

Worst pain NRS (at rest and on movement), total analgesics administered, and toxicity questionnaire data to be collected (see Appendix 4: LIST questionnaire). Confirmation of commencement of subcutaneous infusion and rate. Confirmation of intraoperative bolus dose and infusion total volumes. Safety endpoints, AEs, protocol breaches, study drug stopping or inappropriate cessation to be recorded.

8.5.7 Postoperative day 1 (this is from the end of PACU up to 24 hours post op)

Worst pain NRS (at rest and on movement) and total analgesia administered in-hospital in the first 24 hours after discharge from PACU. Confirmation of total volume of subcutaneous infusion administered. Day of surgery discharge. LIST questionnaire (see Appendix 4) values to be recorded on the CRF. Safety endpoints, SAEs, AEs, protocol breaches and study drug stopping or inappropriate cessation to be recorded. Time of cessation of infusion and total volume of study drug administered to be recorded. Catheter related events to be recorded. Blood samples for lidocaine concentration study to be collected – time of collection to be noted in the CRF (at participating centres where resources allow). Reoperation information and mortality to be collected.

8.5.8 Three months (to be performed +/- two weeks of the three-month anniversary of surgery):

Medical record review and telephone contact and/or electronic contact. Patient mortality, details regarding hospital readmission, reoperation, reconstruction and wound infection to be collected. K-10 and EQ-5D-5L to be completed (Appendices 6-7). Catheter site related events and AE's up to 30 days post operatively, post-operative radiation and chemotherapy treatment to be recorded. ModRUM and WPAI questionnaires to be completed by UK/NHS Sites only.

Pain assessment to comprise:
Yes / No to pain in wound or related area. If yes to pain, then mBPI-SF and S-DN4 to be collected (see Appendix 8). Analgesic consumption to be collected. Review of hospital/ medical notes should also be undertaken to ensure all events are captured and documented.

UK: Three month follow-up will be completed by medical record review and questionnaire completion. Most questionnaires will be sent directly to the participant using an email link. Reminders will also be sent to the participant e.g by email, text message and/or telephone contact. Three month questionnaires will be entered onto a standalone UK database.

8.5.9 Six months (to be performed +/- two weeks of the six-month anniversary of surgery):

ModRUM and WPAI questionnaires to be completed by UK/NHS Sites only.

UK: Six month follow-up will be completed by questionnaire completion. Most questionnaires will be sent directly to the participant using an email link. Reminders will also be sent to the participant e.g by email, text message and/or telephone contact. Six month questionnaires will be entered onto a standalone UK database.

8.5.10 One Year (to be performed up to one week before/- four weeks after the one-year anniversary of surgery):

Medical record review and telephone and/or electronic contact (AUS sites – if consented to ePROMS substudy)*. Patient mortality to be collected. Details regarding hospital readmission, reoperation, and reconstruction to be collected. Tumour histology and cancer recurrence data to be collected. Confirm whether autologous reconstruction has been performed since the index ablative surgical procedure. Details regarding chemotherapy and radiotherapy to be collected. K-10 and EQ-5D-5L questionnaires to be completed (Appendices 6-7). ModRUM and WPAI questionnaires to be completed by UK/NHS Sites only.

Pain assessment to comprise:
Yes / No to pain in wound or related area. If yes to pain, then mBPI-SF and S-DN4 to be collected (see Appendix 8). Analgesic consumption to be collected. Review of hospital/ medical notes should also be undertaken to ensure all events are captured and documented.

*Patient reported outcomes required to adjudicate the primary endpoint will be sought by both electronic questionnaire and telephone contact – a single source is sufficient to adjudicate a primary endpoint. Where both sources of data are obtained and outcomes reported electronically differ to those obtained by telephone contact, only the latter will be used for endpoint adjudication. Information pertaining to the patient experience of electronic questionnaire completion and future preferences will be collected.

UK: One year follow-up will be completed by medical record review and questionnaire completion. Most questionnaires will be sent directly to the participant using an email link. Reminders will also be sent to the participant e.g by email, text message and/or telephone contact. One year questionnaires will be entered onto a standalone UK database.

8.5.11 Withdrawal of Participants:

Each participant has the right to withdraw from all aspects of the study at anytime. It is only the patient that can withdraw themselves from the study. If a participant withdraws, all data collected up to that point will be included in the analysis, in accordance with the regulatory guidance. Patients will not be contacted for further follow up. Patients will need to let a member of the research team know that they wish to withdraw from the trial and a withdrawal form must be completed. For all other events where the patient meets exclusion from the modified intention to treat (mITT) population(Section 8.6.1), then no further follow up will be pursued. If a

patient meets an exclusion from the mITT population but has received study drug, then they must undergo follow up to identify AEs/ SAEs/ and SUSARS until 30 day postoperatively.

8.5.12 End of the trial:

The end of the trial is the date when all patients have completed the one year follow up, or are considered lost to follow-up, the database has been locked and all the data queries have been resolved. The end of the trial for an individual patient is defined as completion of the one year follow up or they are considered lost to follow up. Note: Patients can only be considered lost to follow-up if attempts have been made to contact patients for the one year assessment and this has been unsuccessful.

8.6 STATISTICAL CONSIDERATIONS

(i) Analysis populations are as follows

8.6.1 Modified Intention-To-Treat population (mITT)

The "mITT" population will consist of all randomised patients who undergo eligible surgery. Eligible surgery is primary unilateral or bilateral mastectomy or breast conserving surgery for the treatment of confirmed or suspected breast cancer, performed under general anaesthesia. The only exclusions will be for:

a) patients who withdraw consent prior to surgery
b) clinician refusal to comply with the protocol at the time of surgery
c) screening failures
d) study drug not available at the time of surgery
e) where surgery is abandoned
f) when surgery is cancelled and the patient is not re-enrolled

8.6.2 Per protocol population (PP)

The PP population will be those patients who completed the treatment to which they were originally allocated, meaning **ONLY** those patients who received the study drug or placebo according to their original randomised allocation. This analysis specifically ***excludes*** patients who were not given their randomised study drug during or in the first 24 hours after surgery, any patient data collected following emergency allocation unblinding, and those who had their treatment interrupted due to "Inappropriate cessation". This also excludes patients randomised to lidocaine whose randomisation was overridden and received open-label lidocaine during surgery. The term 'protocol non-adherence' will be used henceforth as an abbreviation to describe these exclusions.

8.6.3 Sample size

Based on population data, an incidence of moderate or severe CPSP of approximately 13.5% in the placebo arm is expected.[34,40] Assuming that a 25% reduction in the incidence of moderate or severe CPSP (i.e. from 13.5% to 10.13%, a RR of 0.75) by lidocaine is considered clinically significant and using a two-sided type I error of 4.9% with power of 90%, 1931 patients per treatment arm will be required. This takes into account a 1% increase in sample size and correction to the Type I error for including one planned interim analysis at 50% of recruitment that allows stopping for efficacy early in case of an unexpected strong efficacy outcome using the

O'Brien-Fleming stopping boundary (see 8.6.7 Section Interim Analysis). Allowing for a 10% loss to follow-up rate this leads to a sample size of 2146 patients per treatment arm, or 4292 patients in total. We therefore propose to recruit 4300 patients in total, with one interim analysis upon completion of follow up of 2150 randomised patients.

8.6.4 Statistical analysis

The analysis and reporting of the results will follow the Consolidated Standards of Reporting Trials (**CONSORT)** guidelines,[70] and recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (**IMMPACT**).[69] Descriptive statistics for key baseline variables will be tabulated by randomised treatment as mean (SD), median (IQR) or number (proportion) as appropriate.

a) Primary outcome

The principal research question for this trial is the effect of randomised treatment on moderate/severe CPSP at 1 year after surgery at 1 year in the mITT population, i.e. a treatment policy estimand. It will be estimated in the mITT population using log-binomial regression to estimate risk ratios directly with confidence intervals accounting for the interim analysis, and with adjustment for the stratification variables of presence of preoperative pain and surgery type. Should model nonconvergence occur, a modified Poisson regression model will be used with robust standard errors. Additional analyses will include adjustment for study site.

Missing CPSP outcome data at 1 year will be multiply imputed under a missing-at-random assumption using chained equations separately within each treatment arm, employing baseline and post-baseline variables in the imputation modelling that are predictive of the CPSP outcome being missing, or are predictive of CPSP itself.

The primary outcome will also be assessed in the PP population to assess the effect of randomised treatment in the hypothetical case of complete treatment adherence. This will use the same analysis methods as in the mITT population, but with the addition of regression adjustment for baseline and intraoperative variables predictive of protocol non-adherence or of CPSP at 1 year in order to control for potential selection bias arising from the patient exclusions from the mITT population. This regression adjustment is valid if the adjustment variables are sufficient to make plausible the assumption that treatment non-adherence is 'at random' conditional on randomised treatment arm and these adjustment variables.

b) Secondary outcomes

Analysis of secondary outcomes will be performed in the mITT population only. Binary secondary outcomes will be analysed using log-binomial regression with adjustment for the stratification variables of preoperative pain and surgery type. Continuous or semi-continuous secondary outcomes will use a linear regression model with robust standard errors and the same adjustment variables.

Adverse events and medication use will be summarised.

8.6.5 Subgroup Analyses

Planned sub-group analyses will assess consistency of differences between lidocaine and placebo arms with respect to the primary outcome for the primary estimand only. These will be assessed using regression models with subgroup-by-randomised arm interaction terms:

- Preoperative chronic pain at another site stratum
- Surgical approach stratum (BCS versus M)
- Admission type (daycase versus overnight stay)
- Axillary operation (none, sentinel node biopsy, axillary lymph node clearance)
- Age (quartiles)
- Country of enrolment
- Receipt of radiotherapy during the 1 year follow-up period[+]
- Receipt of chemotherapy during the 1 year follow-up period[+]
- Reoperation or reconstructive procedures within the 1 year follow-up period[+]
- BMI (quintiles)*
- Ethnicity
- EQ-5D-5L (quartiles)
- K10 (quartiles)
- Total duration of drug infusion (<6h, 6-12h, 12-18h, 18-24h)[#]

[+] Although reoperation and receipt of radiotherapy or chemotherapy are post-randomisation events, they are unrelated to the treatment received (lidocaine/placebo) or its consequences. Therefore, analyses in these subgroups are valid estimates of the effect of randomised treatment in patients who would (or would not) undergo reoperation or radiotherapy/chemotherapy during the follow-up period. These effects are known as principal stratum effects (estimands).

*BMI categories (underweight [BMI<18.5], normal [18.5 to <25], overweight [25 to <30], obese [30 to <40], super obese [40+])

[#]The regression model for with interaction terms of randomised treatment with duration of infusion will include additional regression adjustment for baseline and intraoperative variables predictive of infusion duration or of CPSP at 1 year in order to control for potential selection bias within each duration of infusion category.

Full details of statistical analyses, including multiple imputation modelling for missing data, procedures for selection of covariates for regression adjustment where necessary, and details of any sensitivity analyses will be provided in a Statistical Analysis Plan (SAP). The SAP will be made available on the trial's website, and will be finalised prior to database lock and unblinding of treatment arms.

8.6.6 Serious adverse events (SAEs) and adverse events (AEs)

The SAE and AE rates for non-outcome variables will be summarised for each randomised group as percentage of patients and as frequencies (number of occurrences) and classified according to organ system and severity.

8.6.7 Details of Interim Analysis Monitoring Boundaries

Interim analyses for assessment of efficacy and harm of the primary outcome will be performed after 2150 randomised patients (50% of total recruitment) have completed their planned 1 year follow-up period. The principal analysis will be of the primary endpoint for the primary estimand in the mITT population defined above and using a symmetric O'Brien-Fleming spending function.

The pooled event rate of the primary endpoint will be reviewed at the interim analysis for assessment of the planned sample size and the impact on the power analysis for the trial. The total required sample size will then be adjusted, if required.

The boundaries will be adjusted according to the actual number of patients randomised and included in the interim analysis. Should an interim analysis result cross a designated boundary, consideration will be given by the DSMC to recommend terminating the trial if the committee believes the interim results are sufficiently compelling to change practice around the world. No assessment of futility will be performed.

The analyses will be performed by the Independent Statistician, and results will be provided to the DSMC members, together with secondary endpoints, summary statistics of the recruitment, eligibility violations, completeness of follow-up and compliance with the protocol and summaries of adverse events and safety events. The Chair of the DSMC will report the recommendation of the DSMC to continue, modify or terminate the trial based on superiority, safety or ethical considerations.

UK: Health Economics

The aim of the economic evaluation is to estimate the cost-effectiveness of the lidocaine intervention. The primary analysis will be a within-trial cost-utility analysis from a UK NHS perspective, as recommended in the National Institute of Health and Care Excellence[1] (NICE) reference case for health technology assessment. Data will be included over a 12-month time horizon and include participants recruited in the UK only. A broader perspective will be considered in a secondary analysis including productivity.

Health-related quality of life will be measured using the EQ-5D-5L at baseline, and 3 and 12 months postoperatively. Utilities will be estimated from responses to the EQ-5D-5L using the approach recommended by NICE at the time of analysis. Quality-adjusted life years (QALYs) will be estimated using EQ-5D-5L utility values and the area under the curve approach, controlling for baseline utility[2].

Data collected will include the initial hospital admission, including intervention anaesthetic, and time spent in the operating theatre, PACU and on a ward. Secondary care data on inpatient stays, day cases, accident and emergency visits, and outpatient appointments will also be collected. Secondary care received at the initial treating hospital will be collected from hospital medical records and recorded on case report forms post initial admission and at 3 and 12 months postoperatively, where available. Data on all other secondary care, primary care, community care, prescribed medications and productivity will be collected via patient self-report at 3-, 6- and 12-months follow-up. Self-report healthcare utilisation data will be collected using ModRUM[3] and data on productivity will be collected via the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem[4].

Resource-use data from the intraoperative and post-operative stages of the initial admission, will be valued using unit costs sought from hospital finance departments, and will include staff time, overheads, consumables, and medications. Intervention lidocaine will be valued using national unit costs (e.g. from the British National Formulary), where available. Resource utilisation following the initial admission will be valued using the latest unit costs from UK sources at the time of analysis, including the Unit Costs for Health and Social Care for primary care data[5], the national schedule of NHS costs for secondary care data[6], the prescription cost analysis for prescribed medications[7], and the Office for National Statistics Annual Survey of Hours and Earnings for time off paid employment[8]. Discounting will not be required as follow-up does not extend beyond one year.

Data will be assessed for missingness and handled appropriately[9]. Cost and QALY data will be combined in the primary analysis to estimate the incremental cost-effectiveness ratio and the incremental net monetary benefit statistic at a willingness to pay threshold of £20,000 per gain in QALY. Uncertainty will be addressed using bootstrapping, plotting cost-effectiveness acceptability curves and in sensitivity analyses. A health economic analysis plan including subgroup analyses will be finalised prior to database lock and unblinding of treatment arms.

References:

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2 Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost effectiveness analysis: the importance of controlling for baseline utility. *Health Economics* 2005; **14**: 487-96.

3 Garfield K, Husbands S, Thorn JC, Noble S, Hollingworth W. Development of a brief, generic, modular resource-use measure (ModRUM): cognitive interviews with patients. *BMC Health Services Research* 2021; **21**.

4 Reilly M, Zbrozek A, Dukes E. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics* 1993; **4**: 353-65.

5 Curtis LA, Burns A. *Unit Costs of Health & Social Care 2020*. University of Kent: PSSRU, 2020

6 NHS England and NHS Improvement. National Schedule of NHS Costs 2018/19. 2020. Available from https://www.england.nhs.uk/national-cost-collection/] (accessed 12th June 2021

7 NHS Business Services Authority. *Prescription Cost Analysis - England 2019.* 2020

8 Office for National Statistics. Annual Survey of Hours and Earnings (ASHE). 2021

9 Faria R, Gomes M, Epstein D, White I. A guide to handling missing data in costeffectiveness analysis conducted within randomised controlled trials. *PharmacoEconomics* 2014; **32**: 1157-70.

8.7 DATA LOGISTICS

8.7.1 Case Report Forms

For each paper-based form on which information is entered, the patient's centre number, study ID, date of the visit and person completing the form will be entered in the appropriate space. Errors will be corrected by drawing a single line through the incorrect entry and writing in the new value positioned as close to the original as possible. The correction will then be initialled and dated by the authorised individual making the change. Authorised individuals will not obliterate, write over, or erase the original entry when making a correction. CRFs will be opened as soon as possible following the start of screening and will be kept up to date as the patient continues in the study. The CRF will be completed as soon as possible after the end of each patient's participation in the study. All centres will store the paper based CRFs according to ICH/GCP guidelines.

Real time data entry using iPad or tablet is acceptable however sites must ensure all supporting evidence must be scanned and filed in accordance with ICH/GCP guidelines.

UK:
Real time data entry is not permitted at UK sites. Paper CRFs must be used in the first instance and transcribed into the database at the earliest opportunity.

The primary data source will be the participant's medical notes. Where information is collected on the CRFs and not the medical notes, the CRFs may also be source data. Completed questionnaires will also be primary source data for the follow-up timepoints.

All trial documentation should be retained in a secure location during the conduct of the trial and for 15 years after the end of the trial, when all patient identifiable paper records will be destroyed by confidential means. Where trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial (or equivalent for electronic medical records).

8.7.2 Web-based data entry

Following completion of each section of the paper-based CRF, data will be entered by research staff into the database through a web-based data entry system. Further information can be found in the SOP Manual. The system will audit the timeliness of data entry and reports will be generated and supplied to the DQC regularly.

8.7.3 Database establishment and web-based data entry

The study database will be established, verified and tested prior to going live for online randomisation and data entry. All study personnel will have 24-hour access to the LOLIPOP Trial Project Office to resolve any questions that arise. Scheduled "outages'' will be communicated in advance and regular feedback will be provided to sites. Further information can be found in the SOP manual.

UK:

For UK participants, follow-up questionnaire completion will be completed electronically onto a REDCap questionnaire database. This database will be established, verified and tested prior to going live.

All other trial data will be entered onto the main LOLIPOP trial database.

8.8 ADVERSE EVENTS REPORTING

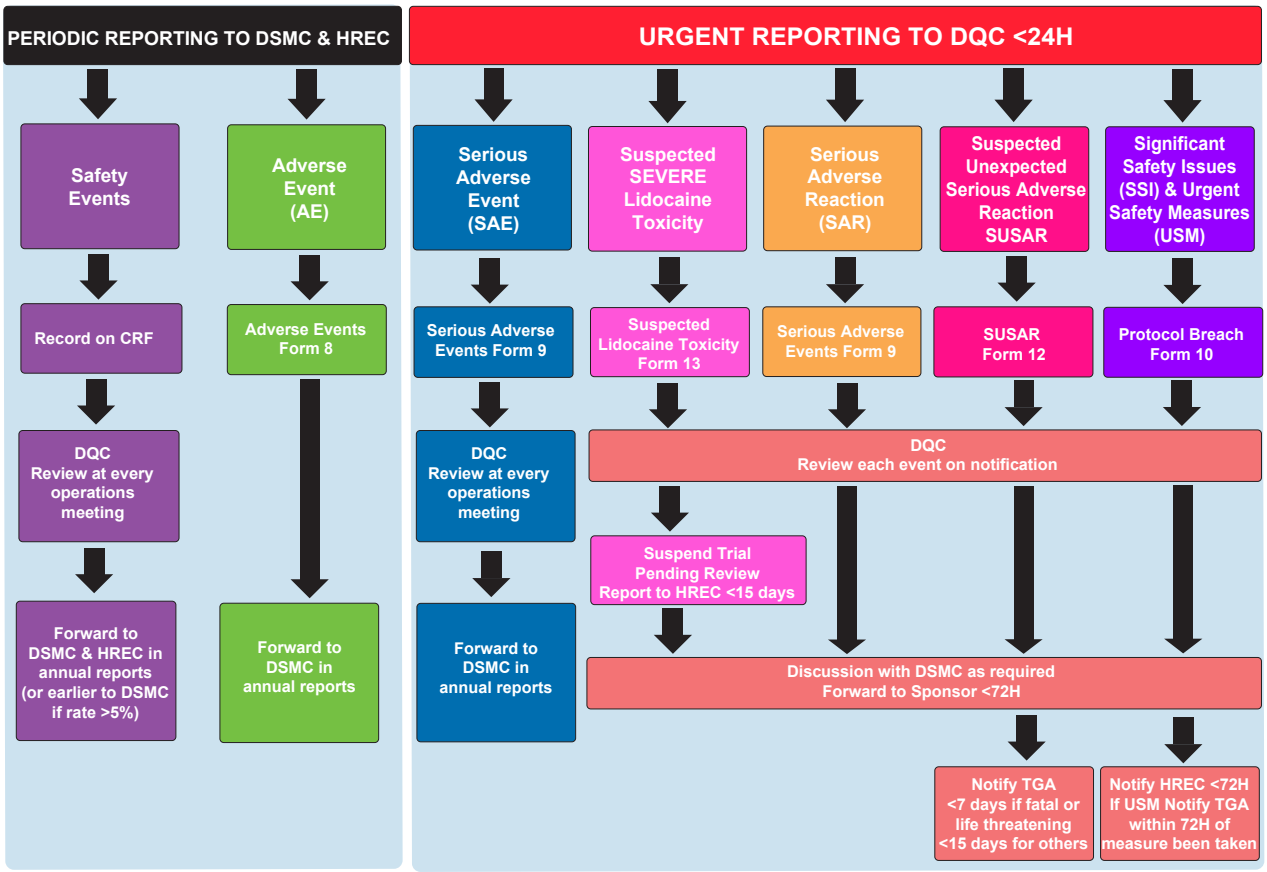


Figure 5: Adverse Events Reporting

UK:

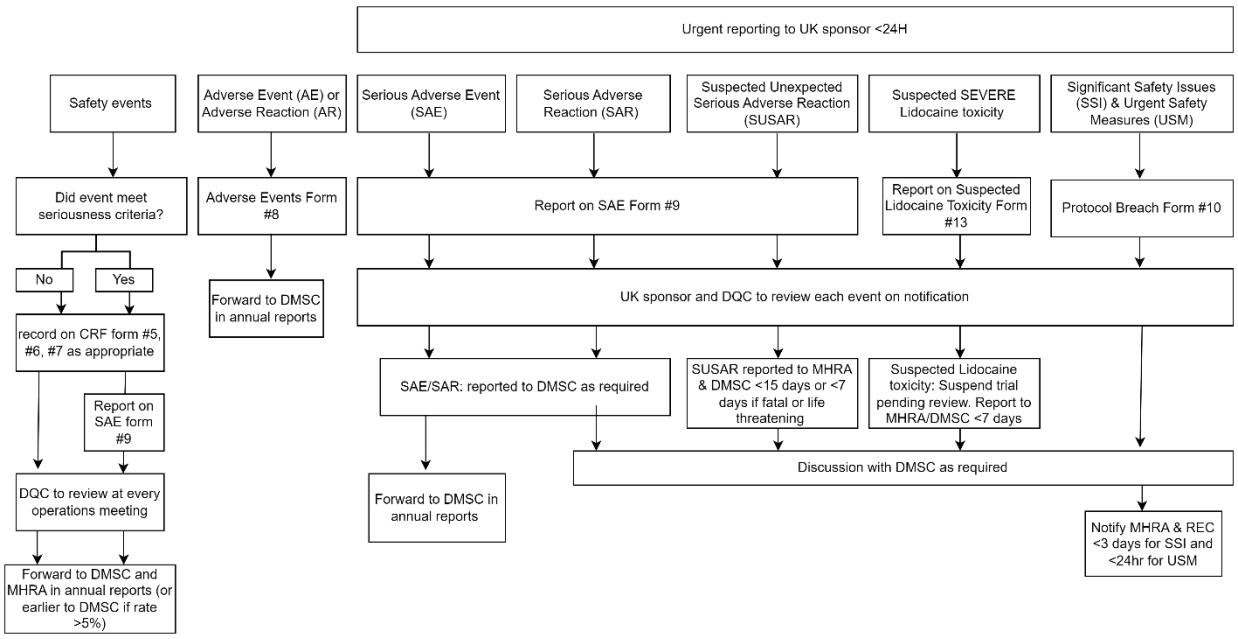


Figure 6 UK Adverse Events Reporting

8.8.1 Summary of reporting and documentation requirements for sites

Sites must report the following five event types to the Trial Office within 24 hours of knowledge of their occurrence (See Figure 5 and Table 1).

Table 1 Adverse Events Reporting and Notification

Event Type	Trial Office/ DQC Response
Serious Adverse Event (SAE)	• DQC review at Operations Meeting • Forward to DSMC in annual reports
Suspected SEVERE lidocaine toxicity	• DQC review each event on notification • Suspend trial pending investigation • Discussion with DSMC as required • Notify Sponsor<72h • Notify HREC of trial suspension <15 days
Serious adverse reaction (SAR)	• DQC review each event on notification • Discussion with DSMC as required • Notify Sponsor<72h
Suspected unexpected serious adverse reaction (SUSAR)	• DQC review each event on notification • Discussion with DSMC as required • Notify Sponsor<72h • Notify TGA within 7 days if fatal or life threatening /15 days for all others
Significant Safety Issues (SSI) and Urgent Safety Measures (USM)	• SSIs to be reported to HREC within 72 hours

	• USMs to be reported to HREC within 72 hours, TGA must also be notified within 72 hours

Serious adverse reactions that are not listed in the TGA product information leaflet for 2 % Lidocaine (Xylocaine 2%)(Appendix 13) and 10% Lidocaine (Xylocard 10%)(Appendix 14) will be classified as a SUSAR.

The reporting of all other AEs will occur as per the guidelines above (see Figure 5). It is imperative that all sites only report events that are not captured as part of the CRF (i.e. not trial or safety endpoints). The CRF has been designed to capture safety endpoints to enable the DSMC to review data in a meaningful way, by independent experts, with blinded separation of treatment groups enabling useful comparisons for the whole dataset. This then will enable the generation of a concise and relevant safety report for dissemination and review by all participating regulatory bodies at all participating centres. [71]

All immediate and follow-up reports should be identified by the participant randomisation number assigned to the trial participants rather than by the participants name, personal identification number, and/or addresses.

- Study endpoints do not need to be reported as AEs or SAEs, as they will be separately recorded in the CRF.
- Safety endpoints will be recorded in the CRF.
- AEs and ARs need to be documented in the CRF.
- The decision as to whether a SAR qualifies to be a SUSAR will generally be taken at the level of the DQC via the LOLIPOP Trial Project Office. Further actions including reporting to the DSMC and regulatory reporting requirements will be taken upon adjudication.
- Protocol breaches must be reported to the LOLIPOP Trial Project Office and in the CRF.
- Unblinding events must be reported on the appropriate forms (See SOP Appendices) to the DQC in the first instance who will escalate to the DSMC.
- AEs and SAEs will be collected from the time of administration of study drug to Day 30 postoperatively.

See Figure 5 for Adverse endpoint reporting flowchart.

Reporting events to the HREC will be based on the latest HREC guidelines available at that time.

UK:

For UK specific variations in safety reporting, see below.

Definitions
Safety reporting definitions can be found in Table 2 (Section 8.8.6), in addition to the following:

Adverse reaction (AR) is any undesirable experience that has happened to a subject while taking a drug that is suspected to be caused by the drug or drugs.

Overview

All safety events will be recorded and reported in accordance with GCP guidelines and the relevant UK Sponsor SOP. Safety events are defined as all events (including safety endpoints and lidocaine toxicity events) meeting the definitions of adverse event (AE), serious adverse event (SAE), AR and suspected unexpected serious adverse reaction (SUSAR).

Data on safety events will be collected from time of administration of study drug up to 30 days from day of surgery using the relevant CRFs. The Principal Investigator, or delegated individual, must review all AE and SAE reports to assess causality. SAE reports must be reported to the UK sponsor by entry into the database within 24hrs of the site becoming aware of the event..

Suspected lidocaine toxicity events are recorded on CRF form #13 and sites should expedite report these to the UK sponsor within 24 hours of event occurrence.

All confirmed SUSARs will be reported to the MHRA in accordance with regulatory requirements.

UK Table i: UK Adverse Events Reporting and Notification

Event Type	BTC/Sponsor/DQC response
Serious Adverse Event (SAE)	• Site to notify BTC/sponsor <24 hr • Sponsor to review upon notification • DQC review at Operations Meeting • Forward to DMSC in annual reports
Serious adverse reaction (SAR)	• Site to notify BTC/sponsor <24 hr • Sponsor & DQC to review upon notification • Discussion with DMSC as required
Suspected unexpected serious adverse reaction (SUSAR)	• Site to notify BTC/sponsor <24 hr • Sponsor & DQC to review upon notification • Report to REC/MHRA/DMSC
Suspected SEVERE lidocaine toxicity	• Site to notify BTC/sponsor <24 hr • Sponsor & DQC to review upon notification • Report to REC/MHRA/DMSC <7 days
Deaths	• Site to notify BTC/sponsor <24 hr • Sponsor & DQC to review upon notification

8.8.2 Safety and reporting for LOLIPOP

LOLIPOP is a phase IV trial of a drug in widespread use across the world, and although it is not licensed for prevention of CPSP, it is licensed for use in anaesthesia. There is a substantial body of literature to support its administration in this capacity.

UK:

For UK specific variations in safety reporting, see below.

Expected adverse reactions associated with the study medication

The current Australian Product Information for 2% Lidocaine (Xylocaine 2%)(Appendix 13) and 10% Lidocaine (Xylocard 10%)(Appendix 14) forms the reference safety information (RSI) and will be referred to as the Summary of Medicinal Product Characteristics (SmPC). Safety end points are also listed in sections 8.2.4/8.8.3 and appendix 3. These listed events will be considered expected reactions and do not require expedited reporting to the study sponsor unless the nature and severity of any event is inconsistent with the information about the IMP in the RSI. Sites should report all adverse reactions as detailed below.

Reporting of AEs

All AEs and ARs that do not meet the serious criteria (Table 2) should be recorded on the Adverse Event form. The Principal Investigator (or delegated individual) must review the form and determine causality. Completed AE forms should be entered onto the database as soon as possible.

If any AE or AR meets the definition of serious (Table 2), an SAE form should be completed instead of the AE form.

Reporting of SAEs, SARs and SUSARs

All SAEs, SARs and SUSARs (including those resulting in death) should be recorded on the SAE form**.** The Principal Investigator (or delegated individual) must review the form and determine causality within 24hrs of the site becoming aware of the event.

The UK sponsor and BTC must also be notified within 24hrs of the site becoming aware of the event, by entry of the SAE form into the LOLIPOP database. Entry will notify the BTC/Sponsor that the SAE requires review. If for any reason this database is unavailable, the completed paper SAE form should be emailed to researchsafety@uhs.nhs.uk (cc lolipop-trial@bristol.ac.uk). The Sponsor is responsible for onward reporting of safety events according to the regulatory requirements.

For deaths, de-identified death certificates will need to be forwarded to the UK sponsor for review by both the UK sponsor and Australian trial team. These should be emailed to researchsafety@uhs.nhs.uk (cc lolipop-trial@bristol.ac.uk).

For ongoing events, follow-up SAE forms will need to be competed and entered into the LOLIPOP database within 5 days of the initial report. All SAEs will be followed up until the event has resolved, a final outcome has been reached, or it has been agreed with the UK sponsor that reporting can stop.

Suspected lidocaine toxicity events

All suspected lidocaine toxicity events should be recorded on the suspected lidocaine toxicity form and sites should report to the UK sponsor at the earliest opportunity and within 24 hours of becoming aware of the event by entry of the suspected lidocaine toxicity form into the LOLIPOP database. Entry will notify the BTC/Sponsor that the toxicity event requires attention. If for any reason this database is unavailable, the completed paper toxicity form should be emailed to researchsafety@uhs.nhs.uk (cc lolipop-trial@bristol.ac.uk).The Sponsor is responsible for onward reporting of safety events according to the regulatory requirements.

8.8.3 Safety Endpoints

All relevant safety endpoints for the trial are pre-specified outcomes and are collected via the CRF. These events are considered by the trial SC as requiring specific reporting to the DQC and/or DSMC in order to detect unanticipated or unexpected safety issues in the trial. Safety Endpoints will be collected from the time of administration of study drug to the end of safety endpoint assessment (30 days postoperatively; with the exception of Point 13 below). The trial SC may request the chair of the DSMC to convene an out of session meeting of the DSMC to consider these safety endpoints.

They are:

1. Incidence of treated bradycardia intraoperatively
2. Incidence of treated hypotension intraoperatively
3. Incidence of treated bradycardia in PACU
4. Incidence of treated hypotension in PACU
5. Incidence of intraoperative infusion stopping events (*See Section **8.9.1.1**: Study drug infusion stopping criteria*)
6. Incidence of PACU infusion stopping events
7. Incidence of post operative infusion stopping events on the ward
8. Incidence of suspected lidocaine toxicity events
9. Incidence of suspected **SEVERE** local anaesthetic toxicity **events** (generalised seizure, sudden unexplained loss of consciousness**,** life-threatening arrhythmia, cardiac arrest)
10. Incidence of Medical Emergency Team (MET) activation
11. Incidence of unplanned ICU, HDU or CCU admission
12. Incidence of study drug unblinding events
13. Incidence of subcutaneous catheter site events (collected up until Day 30)

The Safety Endpoints definitions are defined in Appendix 3. These must be collected in the CRF.

UK:

Reporting for the listed safety endpoints

Where any of the safety endpoints listed above are met, these should be recorded using the AE form, unless an event meets the definition of serious when the SAE form must be completed and entered into the database. If lidocaine toxicity is suspected, a suspected lidocaine toxicity form will also need to be completed and entered into the database.

Reporting should follow the UK requirements outlined under section 8.8.2

8.8.4 Minimum Reporting Requirements for SUSARs

Information on the final description and evaluation of an AR report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits set out by the Australian Therapeutic Goods Administration (TGA). The sponsor liaising with the DQC and DSMC is responsible for ensuring that all relevant follow-up information is requested and submitted to competent authorities and ethics committees as appropriate.

The DSMC is the final arbitrator as to the necessity for safety reporting to the regulatory authorities.

UK: The site must make the Sponsor and the BTC aware of all safety events within 24 hours of becoming aware of the event. Where required, additional information may follow as a follow-up report. The sponsor is the final arbitrator as to the necessity for safety reporting to the regulatory authorities.

8.8.5 Protocol Breaches

8.8.5.1 Definitions for LOLIPOP

A protocol breach is a deviation from the protocol that is likely to effect to a significant degree:
a) The safety or physical or mental integrity of the trial participant
b) The scientific value of the trial
For example, administration of incorrect drug concentration, or failure to administer study drug.

We will collect data on Protocol Breaches only. These are to be reported by investigators on a reporting form in the database within 72 hours. These forms must be supplied to the DQC (see SOP - Reporting forms). The DQC will initially adjudicate as to the safety issues surrounding the breaches. Where there exists concern relating to breach events, then this information will be reported to the DSMC, who may deliberate over specific issues.
Serious protocol breaches will be reported to the HREC within 7 calendar days of the event. All Protocol Breaches will be supplied to sites at least annually. Any recommendations relating to the protocol or any safety recommendations made by the DSMC will be communicated to sites.

UK: The Investigator agrees to comply with the requirements of the Protocol and Good Clinical Practice. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the UK Chief Investigator, UK Sponsor and BTC immediately.

Deviations from the protocol, which are found to frequently recur, are not acceptable and will require immediate action by the Sponsor. Frequent non-compliances could potentially be classified as a serious breach.

8.8.5.2 Protocol breaches

Data relating to safety events will be collected as safety endpoints (Defined in Appendix 3). A protocol breach form will need to be completed for each of the following events:

Infusion related events:

- Inappropriate cessation of the infusion in the Operating Theatre or PACU (stopping criteria not met)
- Inappropriate cessation (or omission) of the infusion on the ward (stopping criteria not met)
- Incorrect dosing of study drug e.g. using patients body weight instead of lean body weight
- Failure to cease trial infusion prior to return to theatre for reoperation

Non-infusion related events:

- Open label administration of lidocaine in excess of permitted amounts (during surgery or up to 24 hours after surgery)
- Excessive dose of other local anaesthetic agents administered (during surgery or up to 24 hours after surgery) e.g. bupivacaine, ropivacaine
- Additional information not known at time of randomisation subsequently discovered that impacts patient eligibility for trial (collected up to 3 months)

8.8.6 Annual Safety Reports

Annual safety reports will be sent by the DQC to the LOLIPOP Trial Project Office. The report will be submitted to the HREC and when approved, circulated to the individual sites to be sent to their HRECs/Research and Governance Offices. This safety report will be compiled in consultation with the DSMC. The aim of the annual safety report is to describe concisely all new safety information **relevant to lidocaine** (See Table 2)**.**

The safety report will contain:

- Safety information obtained by the DSMC during the reporting period
- Analyses of any new information
- Changes to the safety profile of lidocaine and any change in the benefit-risk ratio

UK:

For annual safety reporting, see below.

The UK statistician will generate the development safety update report (DSUR) every 12 months until the end of trial notification has been submitted to the UK regulatory authorities

Table 2 Annual Safety Reporting

8.8.6.1 Adverse Event (AE) and Adverse Reaction (AR) ***Collected up to Day 30 (Recorded at 3-month follow up)***	**An AE is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.** **An AR is any untoward and unintended response to an investigational medicinal product related to any dose administered. All AEs judged by the reporting investigator as having a reasonable possibility (Possibly related, probably related or definitely related) of a causal relationship to an investigational medicinal product would qualify as an AR.** **Intensity of an AE** ● **Mild - an adverse event which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.** ● **Moderate - an adverse event which is sufficiently discomforting to interfere with normal everyday activities.** ● **Severe - an adverse event which is incapacitating and prevents normal everyday activities and/or requires therapeutic intervention (i.e. use of a prescription drug), but is not usually life-threatening**
8.8.6.2 Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR) ***Collected up to Day 30 (Recorded at 3-month follow up)***	**Any AE/AR that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.** ***Note: Life-threatening in the definition of a SAE or SAR refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe*.** ***Note: Medical and scientific judgement should be exercised in deciding whether an AE/ AR should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.***
8.8.6.3 Suspected Unexpected Serious Adverse Reactions (SUSARs) ***Collected up to Day 30 (Recorded at 3-month follow up)***	**A SAE with a possible relationship to the study drug, should be considered unexpected or unanticipated if the nature, severity or frequency of that event is not consistent with the information on the Investigator's Brochure or in the current Australian Product Information (See Appendices 12-13)**

8.8.6.4 Suspected SEVERE lidocaine toxicity ***Collected up to 24 hours***	• **Incidence of suspected SEVERE local anaesthetic toxicity events (generalised seizure, sudden unexplained loss of consciousness, life-threatening arrhythmia or asystole, cardiac / circulatory arrest)**
8.8.6.5 Significant Safety Issue (SSI) ***Collected up to 24 hours***	**A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.**
8.8.6.6 Urgent Safety Measure ***Collected up to 24 hours***	**A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.**
8.8.6.7 Other Infusion related Safety Endpoints ***Collected on Day 1***	• **Incidence of treated bradycardia intraoperatively** • **Incidence of treated hypotension intraoperatively** • **Incidence of treated bradycardia in PACU** • **Incidence of treated hypotension in PACU** • **Incidence of intraoperative infusion stopping events (*See Section 8.9.1.1*: *Study drug infusion stopping criteria*)** • **Incidence of PACU infusion stopping events** • **Incidence of infusion stopping events on the ward** • **Incidence of suspected lidocaine toxicity events** • **Incidence of Medical Emergency Team (MET) activation** • **Incidence of unplanned ICU, HDU or CCU admission** • **Incidence of study drug unblinding events** • **Incidence of subcutaneous catheter site events (up until Day 30, collected at three months)**
8.8.6.8 Protocol Breaches ***Collected up to 24 hours/3 months***	**Infusion related:** • **Inappropriate cessation of the infusion in the Operating Theatre or PACU (stopping criteria not met; collected up to 24 hours)** • **Inappropriate cessation (or omission) of the infusion on the ward (stopping criteria not met; collected up to 24 hours)** • **Failure to cease trial infusion prior to return to theatre for reoperation (collected up to 24 hours)** • **Incorrect dosing of study drug e.g. using patient's body weight instead of lean body weight (collected up to 24 hours)** **Non-infusion-related events:** • **Open label administration of lidocaine in excess of permitted amounts (during surgery or up to 24 hours after surgery)** • **Excessive dose of other local anaesthetic agents administered (during surgery or up to 24 hours after surgery) e.g. bupivacaine, ropivacaine** • **Additional information not known at time of randomisation subsequently discovered that impacts patient eligibility for trial (collected up to 3 months)**

8.8.6.9 Data collection points ***Collected up to 1 year***	• **Mortality** • **Re-operation** • **Radiotherapy** • **Chemotherapy** • **Wound infection** • **Tumour Histology** • **Cancer Recurrence**

8.9 BIAS CONTROL AND SAFETY MECHANISMS

Bias Control: Study drug (lidocaine or placebo) will be delivered to participating sites following site initiation. Details of drug handling will be available in the SOP manual. The study drug (both lidocaine and placebo) will be presented, prepared and administered as detailed under Sections 8.4.3 *Preparation and delivery of study drug* and Section 8.4.4 *Study drug Administration*. Patients, anaesthetists, surgeons and observers will be blinded to group assignment. All decisions about discharge will be made by the surgical team concerned who, as already mentioned, will have been blinded to group assignment. Outcomes are clearly defined in the protocol. All events will be determined by the **IEAC** who will remain blinded to the treatment group.

8.9.1 SAFETY MECHANISMS

LIDOCAINE TOXICITY AND STUDY DRUG CESSATION

The term "Stopping" refers to the interruption or premature cessation of either the intraoperative bolus, intraoperative infusion or postoperative infusion due to the patient meeting the stopping criteria (as defined in Section 8.9.1.1 *Study drug infusion stopping criteria*).

Local anaesthetic toxicity can be a very serious and even life-threatening event. It is important to detect it early and if suspected, then the study drug infusion must be ceased as early as possible. In the event of a patient developing suspected SEVERE lidocaine toxicity, then the patient needs to be appropriately resuscitated, treated and transferred to a high acuity environment. In the event of an episode of suspected severe lidocaine toxicity occurring, then we recommend following the management guidelines in Appendix 5.

In order to assist early detection of lidocaine toxicity which is in evolution, we have developed the Lidocaine Infusion Surveillance Tool (LIST; Appendix 4**)**. This tool is intended as a rapid aid to identify clinical signs OR symptoms which may indicate that the patient is starting to develop lidocaine toxicity, and which will lead to cessation of the study drug infusion. It also facilitates prompt cessation of the study drug infusion in the event of a patient developing significant surgical bleeding or being required to return to theatre urgently.

Table 3 is a summary of the criteria used to define the need to cease the study drug infusion, to identify suspected lidocaine toxicity and to also identify suspected severe lidocaine toxicity.

8.9.1.1 Study drug infusion stopping criteria

Table 3 LOLIPOP Cessation and Toxicity criteria

	INTRAOPERATIVE	**PACU** *(Apply +30 minutes after arrival when LIST tool is first delivered, intraoperative criteria apply prior)*	**POSTOPERATIVE**
Infusion Cessation Criteria	1. Seizure activity 2. Unresponsive bradycardia 3. Unresponsive hypotension 4. Significant arrhythmia 5. Other cause for concern (free text- such as excessive bleeding causing haemodynamic instability)	1. LIST Symptoms 2. LIST Signs a. Unexplained altered mental state* b. Tremor/Twitches/ Seizures c. Slurred speech d. RR<10 e. SBP<90 f. HR<50 g. HR>130 3. LIST complications a. Active bleeding b. Urgent return to theatre c. Persistent subcutaneous site event	**1.** LIST Symptoms **2.** LIST Signs a. Unexplained altered mental state* b. Tremor/Twitches/ Seizures c. Slurred speech d. RR<10 e. SBP<90 f. HR<50 g. HR>130 **3.** LIST complications a. Active bleeding b. Urgent return to theatre c. Persistent subcutaneous site event
Suspected Lidocaine Toxicity Criteria	1.Unexplained altered mental state* 2. Seizure activity 3. Unresponsive bradycardia 4. Unresponsive hypotension 5. Significant arrhythmia	1. Unexplained altered mental state* 2. Seizure activity 3. Unresponsive bradycardia 4. Unresponsive hypotension 5. Significant arrhythmia	1. Unexplained altered mental state* 2. Seizure activity 3. Unresponsive bradycardia 4. Unresponsive hypotension 5. Significant arrhythmia
Suspected severe lidocaine toxicity	Suspected Lidocaine Toxicity AND life-threatening features (tonic-clonic seizures, sudden unexplained loss of consciousness, cardiac arrest, life-threatening arrhythmia*)	Suspected Lidocaine Toxicity ***AND / OR*** life-threatening features (tonic-clonic seizures, sudden unexplained loss of consciousness, cardiac arrest, life-threatening arrhythmia*)	Suspected Lidocaine Toxicity ***AND / OR*** life-threatening features (tonic-clonic seizures, sudden unexplained loss of consciousness, cardiac arrest, life-threatening arrhythmia*)

*- Unexplained altered mental state: this include delayed emergence from anaesthesia (> 20 minutes), excessive sedation, confusion, delirium or severe agitation.
-Life-threatening arrhythmia = any episode of ventricular fibrillation, ventricular tachycardia, asystole **OR significant arrhythmia + haemodynamic compromise or resistance to treatment.
Please note, any suspected episodes of lidocaine toxicity may lead to a request for unblinding if there is a deteriorating clinical situation, or if there are features of a suspected ***SEVERE*** lidocaine toxicity.

i). Criteria to cease intraoperative study drug infusion

Because many of the conventional early signs of ***impending*** lidocaine toxicity cannot be detected under general anaesthesia, we need to have a lower threshold at which we consider cessation of the study drug infusion. We therefore recommend cessation of the lidocaine infusion in the event of:

- Seizure activity
- Unresponsive bradycardia
  - *Defined as a heart rate < 50 bpm despite treatment with glycopyrrolate, atropine, ephedrine, isoprenaline or adrenaline*
- Unresponsive hypotension
  - *Defined as SBP < 80 mmHg despite ephedrine (up to 30 mg bolus), phenylephrine, fluid resuscitation (500 mls bolus of crystalloid) and metaraminol (max 5 mg /hr), noradrenaline or adrenaline*
- Significant arrhythmia
- Other cause for concern (such as excessive bleeding causing haemodynamic instability)
- Other reasons to strongly suspect lidocaine toxicity: see Appendix 5 *Guidelines for the Management of a suspected case of severe local anaesthetic toxicity*

ii). Criteria to cease study drug infusion in PACU

When a patient returns to PACU, they will generally not have recovered consciousness, and hence the criteria for cessation are the same as above for the intraoperative period. Once the patient has recovered consciousness, the participants will be asked to complete the LIST tool (5 questions answered as Yes / No, 7 clinical signs and three surgical complications sought). Hence, the LIST tool criteria are then used. Once the LIST tool is in use in PACU, in the presence of two or more of the LIST symptoms, any LIST sign, or the occurrence of a LIST surgical complication, the study drug infusion should be discontinued.

LIST Symptoms:

- Perioral or periocular paraesthesia
- Ringing in the ears (tinnitus)
- Troubling dizziness
- Visual disturbances (such as aura, halo or floaters)
- Metallic taste

LIST Signs:

- Unexplained altered mental state*
- The presence of Tremor/Twitches/Seizures
- Slurred speech
- Respiratory Rate <10 bpm
- Systolic Blood Pressure <90mmHg
- Heart Rate <50bpm
- Heart Rate >130bpm

*- Unexplained altered mental state: this includes delayed emergence from anaesthesia (> 20 minutes after the end of anaesthesia), excessive sedation, confusion, delirium or severe agitation.

LIST Complications:

- Active bleeding
- Urgent return to theatre
- Persistent catheter site event

i) Criteria to cease study drug infusion on the ward

The criteria to cease the postoperative subcutaneous infusion on the ward are the same as in the PACU once the LIST tool is used.

Upon arrival to the ward, with their first set of observations, the participants will be asked to complete the LIST tool (5 questions answered as Yes / No, and 7 clinical signs, 3 complications sought). This tool is administered every four hours while patients are on the study drug subcutaneous infusion. Answering 'yes' to *two or more* questions at any given time is an indication to cease the study drug infusion.

The presence of *one or more* clinical signs at any time potentially consistent with local anaesthetic toxicity is also an indication to cease study drug. Should complications arise or the patient must return to theatre, this is also an indication to cease the study drug infusion along with persistent catheter site events despite re-siting of the subcutaneous catheter.

ii) Criteria to cease study drug infusion at any point (intraoperative, PACU, ward)

The infusion should also be ceased at any time if suspected ***severe*** lidocaine toxicity is suggested by:

- Tonic-clonic seizures
- Life-threatening arrhythmia or asystole
- Sudden unexplained loss of consciousness
- Cardiac / circulatory arrest

iii) Cessation of infusion due to reoperation or bleeding

If an intravenous (in PACU) or subcutaneous (on the ward) study drug infusion is running then it must be ceased in the PACU/ward prior to transfer to theatre for reoperation, or in the event of the participant experiencing significant bleeding. These two events form the LIST "Surgical Complications" criteria.

iv) Cessation of infusion due to persistent subcutaneous catheter site events

In the event that the patient reports a subcutaneous catheter site event on the ward (local irritation or erythema) then the subcutaneous cannula should be re-sited to the opposite side of the abdomen in the first instance. Should the subcutaneous catheter site event reoccur in the new position, the subcutaneous infusion should be discontinued.

8.9.1.2 Procedures to follow upon stopping study drug infusion

If the study drug has been stopped then the actions to be taken are determined by the nature of the symptoms and signs. The LIST has a low threshold for cessation as the symptoms/signs may

occur early as lidocaine toxicity is developing. If study drug has been ceased due to the LIST stopping criteria being met, then in many cases a period of observation will be required. This period will involve repeated assessments and escalation of care if necessary. If lidocaine toxicity is suspected, then resuscitative measures may be needed, in addition to transfer to a higher care environment and an escalation of the level of monitoring of vital signs. If ***SEVERE*** lidocaine toxicity is suspected, then resuscitative and other measures, including treatment with Intralipid, should be followed, as detailed in **Appendix 5** *Guidelines for the Management of a suspected case of severe local anaesthetic toxicity*. If the study drug infusion is ceased for this reason, then the patient must receive full cardiorespiratory support and neurological monitoring. Please note that **SEVERE** lidocaine toxicity must be treated promptly. Treatment should not be withheld pending unblinding to determine whether the patient was in the lidocaine arm.

8.9.1.3 Serum sampling upon stopping study drug infusion

Where possible, in the event of a patient being treated for suspected severe lidocaine toxicity, or if study drug infusion is ceased due to symptoms or signs of suspected early lidocaine toxicity (LIST stopping criteria met), then the research coordinators at sites should endeavour to obtain a serum sample from any blood samples that are taken from the patient at the time of the suspected event. The sample should be processed at the local laboratory. The trial management team will make appropriate arrangements to have the sample sent to the trial team in Monash University where it will be processed and sent for serum local anaesthetic concentration measurement.

UK: UK sites are not required to do toxicity serum sampling.

8.9.1.4 Reporting requirements for stopping study drug infusion

Where the study drug infusion is prematurely ceased on clinical grounds, this event will be captured in the CRF. If the relevant stopping criteria were not met, a protocol breach form will also need to be reported to provide further details surrounding the event.

8.9.1.5 DSMC composition and function

The DSMC will comprise experienced perioperative clinical researchers (with expertise in pharmacology, pain medicine and anaesthesia) and will be chaired by an epidemiologist/ statistician. One planned interim analysis will be performed by the DSMC at recruitment of 2150 patients (50% of total recruitment). Interim results will be discussed and a consensus decision to recommend to continue the trial, or to abandon for efficacy or safety reasons (according to predetermined stopping rules (see Section 8.6.7 *Details of Interim Analysis Monitoring Boundaries)* will be communicated through to the Principal Chief Investigator and the Chair of the SC in the first instance. **The DSMC is the final arbitrator as to the necessity for safety reporting to the regulatory authorities and / or individual sites.** The DSMC will also convene to consider the results of the plasma concentrations of lidocaine collected in a cohort of trial participants (see Section 8.9.1.6 *Dose adjustments authorised by the DSMC*). In the event that any new safety issues arise which require a change to the protocol or which require communication to sites, this role will be performed by the DSMC through the DQC. In general, the decision to unblind data will be performed by the DSMC on a case-by-case basis if a safety concern arises. This decision will be communicated to the individual site involved by the data quality committee. The terms of reference of the DSMC are contained in the SOP and the functions of the DSMC are contained within its charter.

8.9.1.6 Dose adjustments authorised by the DSMC

Where possible, patients will be recruited to the lidocaine concentration sub-study, and will have blood sampling and serum extraction/storage for batch lidocaine assay at two time-points during the lidocaine infusion; 6-12 hours and 12-24 hours after the initial bolus. Batch assay will take place after approximately 100 patients (50 receiving lidocaine) have been recruited to the sub-study. The results of these analyses will be made available to the DSMC at the first interim analysis, to give consideration as to whether a dose increase or reduction needs to be instituted for the remaining patients to be recruited. In the event that the results are not available until after the first interim analysis, then the data will be provided to the chair of the DSMC who may convene an extra DSMC meeting to consider these values. The DSMC may authorise:

1. A 25% dose reduction of the postoperative subcutaneous infusion if the following conditions are met:
    a. Any concentration > 6 mcg mL^{-1}
    b. Any concentration > 5 mcg mL^{-1} **AND** stopping criteria met
    c. At the 12-24h time-point: ≥5% concentrations > 5 mcg mL^{-1}

2. A 25% dose increase of the postoperative subcutaneous infusion if the following conditions are met:
    a. At the 12-24h time-point: median concentration < 1.5 mcg mL^{-1} **AND** no values exceed 3.5 mcg mL^{-1}

UK: The UK will not be recruiting into the lidocaine concentration sub-study or taking any blood samples.

8.9.2 EMERGENCY UNBLINDING OF STUDY DRUG

If there is concern at a study site that the study drug has had a detrimental influence on the patient and that unblinding of treatment allocation will assist in the delivery of appropriate care to that patient, then the site staff will be able to unblind the patient's treatment allocation through the trial database. Such unblinding episodes, including the reasons for the unblinding, will need to be reported to the DSMC via the trial management centre. An "unblinding form" will need to be completed.

8.9.2.1 Provision for emergency unblinding of study group allocation

Protection of the safety of trial participants is of paramount importance.

The principal circumstances in which emergency unblinding of study drug will occur is where there are grave clinical grounds that the patient may be experiencing a condition that is directly related to lidocaine. In the event that the patient is suspected to be experiencing an episode of severe lidocaine anaesthetic toxicity, then the guidelines for the management of such a reaction (**Appendix 5**: *Guidelines for the management of a suspected case of severe local anaesthetic toxicity)* should be followed. This involves the cessation of infusion (the administration of intralipid is only indicated as per Appendix 5: *Guidelines for the management of a suspected case of severe local anaesthetic toxicity*).

We recommend that all emergency unblinding applications be made through the process available on the LOLIPOP Trial database (see details in the SOP and in Section 8.9.2 *Emergency Unblinding of Study Drug*). If the local Principal Investigator believes emergency unblinding is essential for the patient's management then it can be undertaken through the LOLIPOP Trial database, with an unblinding breach form being completed and forwarded to the LOLIPOP Trial Project Office. The principal investigator at the site from which the unblinding application emanates should approve the request for unblinding wherever possible. The treatment allocation group will be made known to the medical staff investigating and treating such an occurrence, and to the Principal Investigator for that site.

9. ADMINISTRATIVE GUIDELINES

9.1 Amendments to the protocol

Amendments to the protocol must be approved by a majority vote of the SC. This will only occur with the approval of the HREC when applicable. All modifications will be written and filed as amendments, maintaining the original section identification. Any modifications will be applied to all subsequent patients.

UK: All amendments to the Australian protocol for LOLIPOP will be reviewed by the UK TMG. Where changes are also required for the UK protocol, if possible these will be amended in parallel through the UK regulatory authorities. Otherwise the UK process will follow that detailed above

9.2 Early termination or extension of the study

The SC, with HREC approval may discontinue or extend the study at any time.

9.3 Confidentiality and publication of study results

Interim and preliminary results will not be discussed or presented outside the trial group unless authorised by the SC. The investigators plan to publish the results in a peer-reviewed journal.

9.4 Retention of records

All CRFs and all other documents associated with the study must be archived for at least 15 years following the completion of the trial, in accordance with local ethics committee requirements for storage and TGA guidelines.

UK: All records will be archived for at least 15 years following completion of the trial. Archiving must comply with the UK Sponsor SOP.

9.5 Screening Logs

All sites will be requested to submit monthly screening logs to the LOLIPOP trial project office. These logs should detail as a minimum the number of eligible patients that are recruited in addition to any reasons for refusal by eligible patients.

9.6 Audits

This study is performed in accordance with GCP. The SC reserves the right to audit a sample of patients at all sites at any time. We will audit as many sites as is feasible. For the purpose of compliance with ICH GCP notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95), it may be necessary for a regulatory agency to conduct a site audit. The IEAC may also request to randomly audit outcomes as indicated in the IEAC charter.

UK: This trial will be monitored and may be participant to monitoring and audit by University Hospital Southampton NHS Foundation Trust, under their remit as sponsor and other regulatory bodies to ensure adherence to ICH GCP, UK Policy Framework for Health and Social Care

Research, applicable contracts/agreements and national regulations. All trial related documents will be made available on request for monitoring and audit by UHS, the relevant REC or other licensing bodies.

9.7 Compliance checks

Random monitoring of centres will be undertaken, to assess the accuracy and legitimacy of the trial data. Statistical monitoring of the data completeness, data variance and risk-appropriate endpoint rates will be done for all patient data.

9.8 Sub-studies

All sub-studies will be approved by the SC. A formal scientific background and protocol will be required for consideration by the SC.

9.9 Authorship List

Individuals may be invited to join the authorship list based upon a voting majority of the SC.

9.10 Media relating to the trial

The SC must be made aware, in advance, of any significant media in relation to the trial and its findings by a member of the SC or another investigator.

9.11 Ethics Processes

The trial will be performed in accordance with ICH GCP notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

UK:
The trial will be performed in accordance with GCP, the study protocol and UK regulatory framework.

9.12 Site Payments

Sites in Australia, New Zealand and Hong Kong will be eligible for payment at two timepoints. The first payment will be $350 which will be paid after submitting all clean data on a patient up to the three-months follow up point. The second payment will be $150 which will be paid after submitting complete clean one year follow up data.

UK:
Sites will be paid as per the arrangements detailed in the site agreement.

10. AUTHORSHIP PLAN

Target Journal: New England Journal of Medicine, the Lancet, BMJ or JAMA.
Planned Authorship: On behalf of the LOLIPOP investigators and the ANZCA CTN.

The planned authorship may be extended or altered according to a majority vote of the trial SC. Following acceptance for publication, all co-investigators and site investigators at each centre may plan secondary analyses for follow-up publication or presentation. A separate protocol will be developed and will require approval by the SC before the presentation or submission for publication.

11. SUBSTUDIES

a. Genetic Biobanking sub-study (section 8.4.13.1)
b. Lidocaine concentration sub-study (section 8.4.13.2)
c. Epigenetics sub-study- Dr Daniel Chiang, Auckland
d. Lead-time sub-study – Ms Gillian Ormond
e. The prevalence and risk factors of distress in newly diagnosed breast cancer patients – Ms Natalie Hird
f. Electronic Patient reported outcome measures (ePROMs) feasibility sub-study - Ms Allison Kearney
g. Bayesian sub-study – Prof Tomás Corcoran

UK: The UK will not be participating in any of the above sub-studies.

12. CO-ENROLMENT WITH OTHER STUDIES

Co-enrolment with other trials will be permitted in principle. A formal process of consideration of the protocol of the "other" trial will need to occur before approval is definitive. The LOLIPOP project office will forward the trial protocol to the members of the OC who will consider the trial and reach agreement as to whether co-enrolment will be permitted. The LOLIPOP project office will maintain a list of patients who are co-enrolled in other studies.

13. APPENDICES

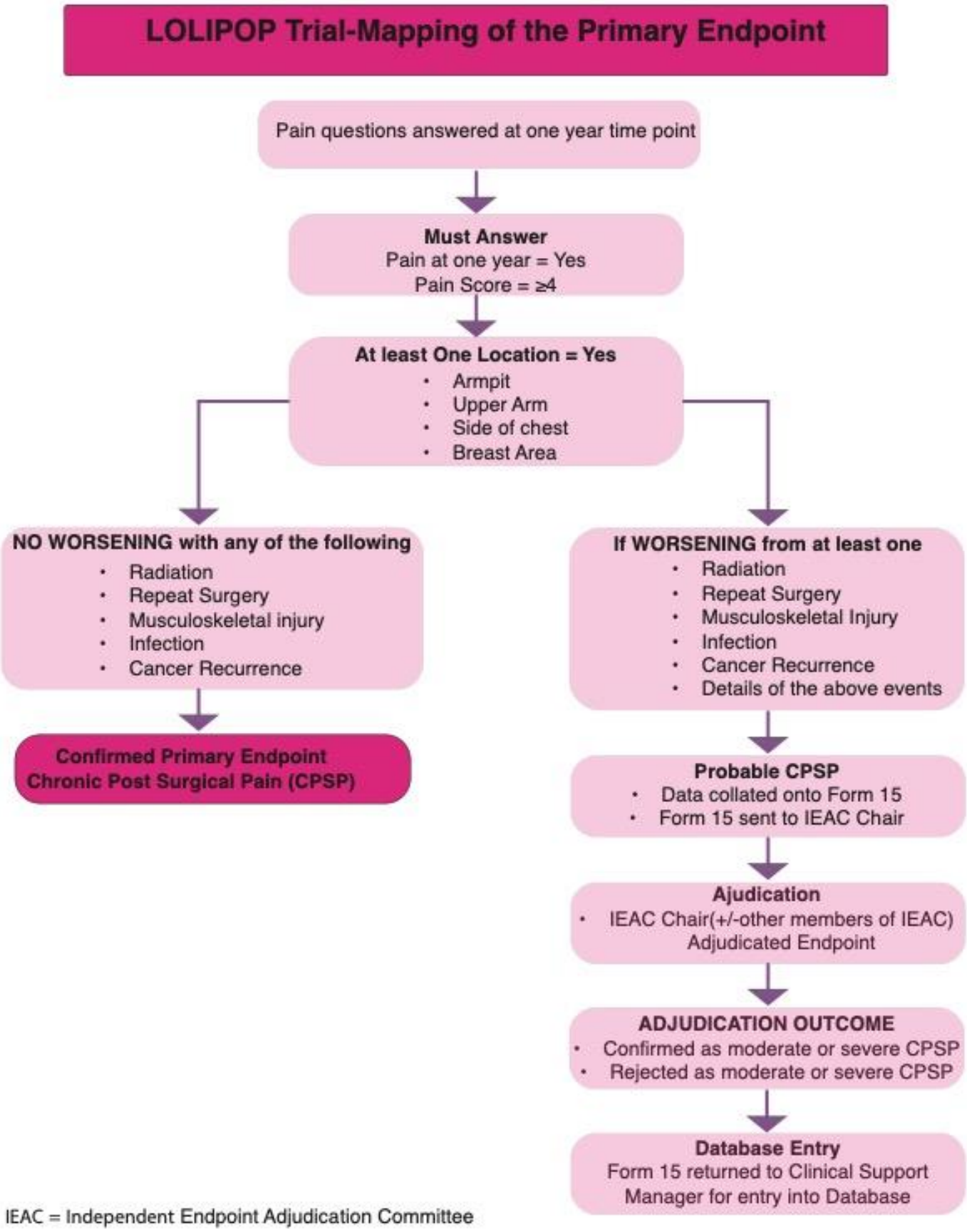
Appendix 1: Schematic

	Pre Op	Intra Op	PACU	6 to 12 hours	Day One	Three months	Six Months	One Year
Screening, Eligibility criteria, Pre-consent Informed Consent, contact details and randomisation	**x**							
Demographics	**x**							
Pain Assessment	**x**					**x**		**x**
mBPI-SF, S-DN4						**x** (if yes to pain)		**x** (if yes to pain)
EQ-5D-5L and Kessler K-10	**x**					**x**		**x**
Biobank and PK blood samples		**Biobank** (at induction)		**PK** (6-12 hour)	**PK** (12 to 24 hours)			
Intra-operative information		**x**						
Trial solution calculations and data	**x**	**x**	**x**	**x** (during infusion)	**x** (during infusion)			
PACU data			**x**					
LIST questionnaire			**x**	**x** (during infusion)	**x** (during infusion)			
Acute pain NRS			**x**		**x**			
Analgesia data (MEQ, other analgesics)			**x**		**x**	**x**		**x**
Safety Data Collection (endpoints and AEs)		**x**	**x**		**x**	x (up to 30 days)		
Protocol Breach data	**x**	**x**	**x**	**x**	**x**	**x**		**x**
Mortality					**x**	**x**		**x**
Reoperation data					**x**	x		x
Readmission						x		x
Radiotherapy and chemotherapy	**x**	x				x		x
Wound infections						**x**		
Tumour histology								x
Cancer Recurrence								**x**
ePROMS substudy (AUS Sites Only)								x
ModRUM & WPAI (UK Sites Only)						**x**	x	**x**

Appendix 2: Primary endpoint diagnostic criteria

In order to meet the criteria for moderate or severe CPSP at one year, the reported pain:

1. **Must be reported to be completely or partly caused by the breast surgery undertaken 1 year ago.**
2. Must have been present for at least three months
3. Must be reported as of "worst" intensity ≥4 out of 10 in the last week on the Modified brief pain inventory short form (mBPI-SF) (See Appendix 8).
4. Be in the area of the breast surgery performed one year ago or in one of the following related areas: axilla, ipsilateral side of chest wall or ipsilateral upper arm
5. Must not be clearly and exclusively attributable to another cause such as:
    a. Radiation therapy at or near the pain location
    b. Repeat Surgery at or near the pain location
    c. Musculoskeletal injury at or near the pain location
    d. Infection at or near the pain location
    e. Recurrence of cancer at or near the pain location



IEAC = Independent Endpoint Adjudication Committee

Appendix 3: Safety Endpoint Definitions

a. **Treated bradycardia**- bradycardia (HR<50bpm) requiring intervention during the period from the commencement of the bolus in theatre to cessation of the subcutaneous infusion. Treatments may comprise the administration of atropine, glycopyrrolate, ephedrine or adrenaline. This may be defined according to when it is observed to occur, as intraoperatively, in PACU or on the ward.
b. **Treated hypotension**- hypotension requiring intervention during the period from the commencement of the bolus in theatre to cessation of the subcutaneous infusion. Treatments may comprise the administration of fluid boluses, metaraminol, phenylephrine, ephedrine or adrenaline. This may be defined according to when it is observed to occur, as intraoperatively, in PACU or on the ward. The threshold systolic blood pressure (SBP) for defining hypotension is less than 90 mmHg, except during the intraoperative period, where the threshold is 80 mmHg.
c. **Significant arrhythmia**- this includes supraventricular tachycardia, atrial fibrillation or flutter, and second or third-degree heart block.
d. **Life-threatening arrhythmia-** this includes any significant arrhythmia (defined above) which is resistant to treatment or associated with significant haemodynamic compromise. It also includes ventricular tachycardia or ventricular fibrillation.
e. **Medical Emergency Team (MET) activation**- activation of the MET team (or rapid/urgent review by critical care team, defined by inclusion of intensivist or anaesthetist) for escalation of patient care up to the end of the subcutaneous infusion
f. **Unplanned ICU, High Dependency Unit (HDU) or Critical Care Unit (CCU) admission**- admission to the ICU, HDU or CCU which was not planned prior to surgery
g. **Intraoperative infusion stopping events**- cessation of the study drug infusion in the intraoperative period where clinically indicated and appropriate (i.e. Stopping criteria have been met)
h. **PACU infusion stopping events -** cessation of the study drug infusion in the PACU where clinically indicated and appropriate (i.e. Stopping criteria have been met)
i. **Postoperative infusion stopping events -** cessation of the study drug infusion following discharge from the PACU where clinically indicated and appropriate (i.e. Stopping criteria have been met)
j. **Episodes of suspected lidocaine toxicity-** when the patient develops symptoms or signs suggestive of lidocaine toxicity, including unexplained altered mental state, seizure activity, unresponsive bradycardia, unresponsive hypotension or significant arrhythmia
k. **Episodes of suspected *SEVERE* lidocaine toxicity**- features of suspected lidocaine toxicity with additional findings suggesting imminent neurological or cardiovascular collapse, including tonic-clonic seizures, sudden unexplained loss of consciousness, cardiac arrest or life-threatening arrhythmia.
l. **Study drug unblinding events**- where treatment group allocation is unblinded for clinical reasons
m. **Subcutaneous catheter site events**- these includes episode of catheter dislodgement, kinking or other technical failure. Also includes episodes of inflammation or infection at

the catheter site, assessed up to 30 days postoperatively but recorded at three-month follow up.

Appendix 4: Lidocaine Infusion Surveillance Tool (LIST) screening tool

Page 1: LIST Tool (double sided; guidelines on reverse)

LOLIPOP
Long-term Outcomes of Lidocaine Infusions for Post-Operative Pain

CRF PAGE 8

Patient Study Number ☐☐☐-☐☐☐☐

FORM 4 Lidocaine Infusion Surveillance Tool (LIST)

4.1 **Subcutaneous Infusion START date and time** ☐☐.☐☐☐.☐☐☐☐ (d d . m m m . y y y y) ☐☐:☐☐ (h h : m m) (24 hr)

4.2 **Subcutaneous Infusion STOP date and time** ☐☐.☐☐☐.☐☐☐☐ (d d . m m m . y y y y) ☐☐:☐☐ (h h : m m) (24 hr)

All data points will be required for entry into the eCRF, please keep the original paper record.

LIST SYMPTOMS (Ask every 4 hours; cease if ≥2 yes)	**LIST SIGNS (Cease infusion if ≥1 at ANY time)**
Q1 Are you experiencing any **Tingling/ Pins** and **needles** (especially) around the **Eyes** and **Mouth?**	☐ Unexplained **altered mental state**
Q2 Do you have **Ringing** in the ears?	☐ **Tremor/ Twitches/ Seizures**
Q3 Do you have **Dizziness** that you are finding troubling?	☐ **Slurred Speech**
Q4 Are you experiencing any obvious **Visual Disturbances** (e.g. seeing **shapes, flashing lights** or **blurriness**)?	☐ **Respiratory Rate (RR) <10** (not opioid induced) *RR Value* ☐☐
Q5 Do you have a **Metallic taste** in your mouth?	☐ **Hypotension** (HT): **SBP <90** *SBP Value* ☐☐
	☐ New **Bradycardia**: Heart Rate **[HR] < 50BPM** *HR Value* ☐☐
	☐ **Unexplained Tachycardia**: Heart Rate **[HR]>130BPM** *HR Value* ☐☐☐
	LIST COMPLICATIONS (Cease infusion if ≥1 at ANY time)
	☐ **Active bleeding**
	☐ **Urgent return to theatre**
	☐ **Recurrent subcutaneous catheter events (>1 events)**

Time point from infusion start (approx)	Time assessed 24 hour clock	4 HOURLY SYMPTOM ASSESSMENT										STOPPING CRITERIA			
		Q1 Tingling		Q2 Ringing		Q3 Dizzy		Q4 Visual		Q5 Metallic		≥2 SYMPTOMS		≥1 LIST SIGN or COMPLICATION	
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes*	No	Yes*	No
4.3 PACU	☐☐:☐☐ (h h : m m)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4.4 Ward arrival	☐☐:☐☐ (h h : m m)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4.5 +4h	☐☐:☐☐ (h h : m m)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4.6 +8h	☐☐:☐☐ (h h : m m)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4.7 +12h	☐☐:☐☐ (h h : m m)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4.8 +16h	☐☐:☐☐ (h h : m m)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4.9 +20h	☐☐:☐☐ (h h : m m)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4.10 +24h	☐☐:☐☐ (h h : m m)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

*If the Patient answers **Yes to 2 of the 5 SYMPTOMS** (at the one time) or **ANY of the SIGNS or COMPLICATIONS** occur please **STOP THE INFUSION BY REMOVING THE SUBCUTANEOUS CANNULA** and **TURN OFF THE PUMP.**
Please contact medical staff to review and monitor for signs of local anaesthetic toxicity and treat appropriately (see AAGBI Safety Guideline attached).
In the event of circulatory arrest **INTRALIPID 20%** should be administered intravenously as per attached.

CRF V 1.0 Completed by ☐☐☐

Page 2: LIST Tool Guidelines Page (double sided; LIST Tool on reverse)

GUIDELINES PAGE 8

FORM 4: THE LIST TOOL

The Lidocaine Infusion Surveillance Tool (List) contains 5 questions about toxic symptoms, 7 Toxic signs and 3 potential complications. **This tool should be used whilst the patient has the postoperative subcutaneous infusion running.**

The nurse should ask the first set of questions to the patient just after commencement in PACU/Recovery, **on arrival to the ward and at 4 hourly intervals until the infusion is ceased**. As well as asking the questions the nurse caring for the patient should observe for and toxic signs and surgical complications.

The 5 questions to check for ***LIST SYMPTOMS*** are:

1. Any **Tingling/Pins and needles** (especially) around the Eyes and Mouth?
2. Do you have **Ringing in the ears**?
3. Do you have **Dizziness** that you are finding troubling?
4. Obvious **Visual Disturbances** (e.g. seeing shapes, flashing lights or blurriness)?
5. Do you have a **Metallic taste** in your mouth?

If the Patient answers YES to 2 or more of the 5 questions (at the same time) CEASE THE INFUSION AND REMOVE THE SUBCUTANEOUS CANNULA.

LIST SIGNS to monitor for at any time whilst the infusion is running are:

- Unexplained altered mental state
- Tremor/twitches/seizures
- Slurred Speech
- Respiratory Rate (RR) <10 per minute (not opioid induced)*
- Hypotension (HT) Recurrent fainting or Systolic Blood Pressure <90mmHg*
- New Bradycardia Heart rate (HR) < 50BPM*
- Unexplained Tachycardia Heart rate (HR) >130BPM*

**** Please record the RR/SBP/HR value that triggered the stopping event (if applicable) in the box provided.***

If the Patient has LIST SIGNS at ANY time, CEASE THE INFUSION AND REMOVE THE SUBCUTANEOUS CANNULA.

LIST COMPLICATIONS

- Active bleeding
- Urgent return to theatre
- Recurrent subcutaneous catheter site events*
  ****Please check the insertion site at each time point. In the first instance of irritation or erythema at the site of the cannual insertion please attempt to re-site the cannula to the opposite side of the abdomen. Should the irritation reoccur please cease the post operative infusion).***

If the Patient has COMPLICATIONS at ANY time, CEASE THE INFUSION AND REMOVE THE SUBCUTANEOUS CANNULA.

SUSPECTED LIDOCAINE TOXICITY CRITERIA

- Unresponsive bradycardia
- Unresponsive hypotension
- Unexplained altered mental state — Delayed emergence from anaesthesia (>20 minutes), excessive sedation, confusion, delirium or severe agitation.
- Significant/ife threatening arrhythmia — Supraventricular tachycardia (SVT), Atrial Flutter/fibrillation, 2nd degree/complete heart block)systole (Cardiac arrest), Ventricular Tachycardia (VT), Ventricular Fibrillation (VF), or a significant arrythmia either with haemodynamic compromise or unresponsive to treatment.

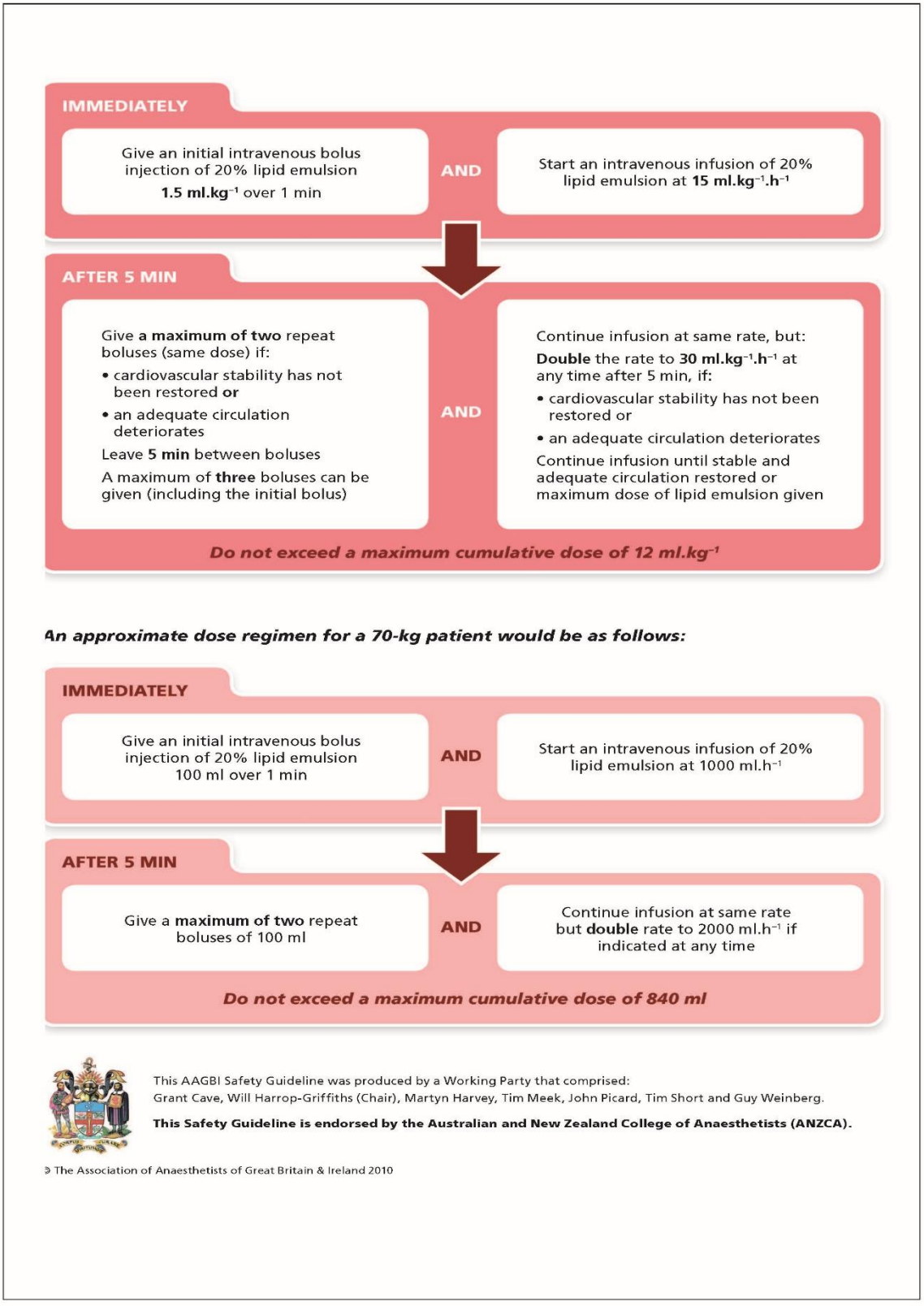
If the Patient meets ANY of the above criteria at ANY time, CEASE THE INFUSION AND REMOVE THE SUBCUTANEOUS CANNULA.

If the infusion is stopped for symptoms or signs of lidocaine toxicity, please contact medical staff to review. Monitor for signs of severe local anaesthetic toxicity and treat appropriately (see AAGBI Safety Guideline). ***In the event of circulatory arrest INTRALIPID 20% should be administered intravenously.*** **Check where the lipid emulsion is stored at your site.**

INTRALIPID 20% DOSING IN SEVERE TOXICITY				
Patient Weight	☐☐☐ kg	**Intralipid 20% location on ward:**		
Bolus Dose over 1 minute (1.5 ml/kg)	1.5 ml x patient weight	1.5 x ☐☐☐ kg	= ☐☐☐☐	ml (BOLUS)
Infusion rate after bolus (15 ml/kg/h)	15 ml x patient weight	15 x ☐☐☐ kg	= ☐☐☐☐	ml/h (INFUSION) (reassess after 5 mins)*
* Refer to attached **AAGBI Safety Guideline** for further dosing details				

Appendix 5: Guidelines for the management of a suspected case of severe local anaesthetic toxicity

Page 1: Intralipid dosing guidelines (double sided)



IMMEDIATELY

Give an initial intravenous bolus injection of 20% lipid emulsion **1.5 ml.kg⁻¹** over 1 min

AND

Start an intravenous infusion of 20% lipid emulsion at **15 ml.kg⁻¹.h⁻¹**

AFTER 5 MIN

Give **a maximum of two** repeat boluses (same dose) if:

- cardiovascular stability has not been restored **or**
- an adequate circulation deteriorates

Leave **5 min** between boluses

A maximum of **three** boluses can be given (including the initial bolus)

AND

Continue infusion at same rate, but:

Double the rate to **30 ml.kg⁻¹.h⁻¹** at any time after 5 min, if:

- cardiovascular stability has not been restored or
- an adequate circulation deteriorates

Continue infusion until stable and adequate circulation restored or maximum dose of lipid emulsion given

Do not exceed a maximum cumulative dose of 12 ml.kg⁻¹

An approximate dose regimen for a 70-kg patient would be as follows:

IMMEDIATELY

Give an initial intravenous bolus injection of 20% lipid emulsion 100 ml over 1 min

AND

Start an intravenous infusion of 20% lipid emulsion at 1000 ml.h⁻¹

AFTER 5 MIN

Give a **maximum of two** repeat boluses of 100 ml

AND

Continue infusion at same rate but **double** rate to 2000 ml.h⁻¹ if indicated at any time

Do not exceed a maximum cumulative dose of 840 ml

This AAGBI Safety Guideline was produced by a Working Party that comprised:
Grant Cave, Will Harrop-Griffiths (Chair), Martyn Harvey, Tim Meek, John Picard, Tim Short and Guy Weinberg.

This Safety Guideline is endorsed by the Australian and New Zealand College of Anaesthetists (ANZCA).

℗ The Association of Anaesthetists of Great Britain & Ireland 2010

Page 2: AAGBI Safety Guideline (double sided)

AAGBI Safety Guideline

Management of Severe Local Anaesthetic Toxicity

1 Recognition

Signs of severe toxicity:

- Sudden alteration in mental status, severe agitation or loss of consciousness, with or without tonic-clonic convulsions
- Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias may all occur
- Local anaesthetic (LA) toxicity may occur some time after an initial injection

2 Immediate management

- Stop injecting the LA
- Call for help
- Maintain the airway and, if necessary, secure it with a tracheal tube
- Give 100% oxygen and ensure adequate lung ventilation (hyperventilation may help by increasing plasma pH in the presence of metabolic acidosis)
- Confirm or establish intravenous access
- Control seizures: give a benzodiazepine, thiopental or propofol in small incremental doses
- Assess cardiovascular status throughout
- Consider drawing blood for analysis, but do not delay definitive treatment to do this

3 Treatment

IN CIRCULATORY ARREST

- Start cardiopulmonary resuscitation (CPR) using standard protocols
- Manage arrhythmias using the same protocols, recognising that arrhythmias may be very refractory to treatment
- Consider the use of cardiopulmonary bypass if available

GIVE INTRAVENOUS LIPID EMULSION
(following the regimen overleaf)

- Continue CPR throughout treatment with lipid emulsion
- Recovery from LA-induced cardiac arrest may take >1 h
- Propofol is not a suitable substitute for lipid emulsion
- Lidocaine should not be used as an anti-arrhythmic therapy

WITHOUT CIRCULATORY ARREST
Use conventional therapies to treat:

- hypotension,
- bradycardia,
- tachyarrhythmia

CONSIDER INTRAVENOUS LIPID EMULSION
(following the regimen overleaf)

- Propofol is not a suitable substitute for lipid emulsion
- Lidocaine should not be used as an anti-arrhythmic therapy

4 Follow-up

- Arrange safe transfer to a clinical area with appropriate equipment and suitable staff until sustained recovery is achieved
- Exclude pancreatitis by regular clinical review, including daily amylase or lipase assays for two days
- Report cases as follows:
  - in the United Kingdom to the National Patient Safety Agency (via **www.npsa.nhs.uk**)
  - in the Republic of Ireland to the Irish Medicines Board (via **www.imb.ie**)

If Lipid has been given, please also report its use to the international registry at **www.lipidregistry.org**. Details may also be posted at **www.lipidrescue.org**

Your nearest bag of Lipid Emulsion is kept.....

This guideline is not a standard of medical care. The ultimate judgement with regard to a particular clinical procedure or treatment plan must be made by the clinician in the light of the clinical data presented and the diagnostic and treatment options available.

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Appendix 6: EQ-5D-5L

LOLIPOP
Long-term Outcomes of Lidocaine Infusions for Post-Operative Pain

CRF PAGE 2

Patient Study Number ☐☐☐-☐☐☐☐

FORM 1 - PRE-OPERATIVE

1.6 EQ-5D-5L - Interviewer administered - ALL PATIENTS MUST COMPLETE THE EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

1.6.1	**MOBILITY**	
	I have no problems in walking around	☐
	I have slight problems in walking around	☐
	I have moderate problems in walking around	☐
	I have severe problems in walking around	☐
	I am unable to walk around	☐
1.6.2	**SELF-CARE**	
	I have no problems with washing or dressing myself	☐
	I have slight problems with washing or dressing myself	☐
	I have moderate problems with washing or dressing myself	☐
	I have severe problems with washing or dressing myself	☐
	I am unable to wash or dress myself	☐
1.6.3	**USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)***	
	I have no problems doing my usual activities	☐
	I have slight problems doing my usual activities	☐
	I have moderate problems doing my usual activities	☐
	I have severe problems doing my usual activities	☐
	I am unable to do my usual activities	☐
1.6.4	**PAIN / DISCOMFORT**	
	I have no pain or discomfort	☐
	I have slight pain or discomfort	☐
	I have moderate pain or discomfort	☐
	I have severe pain or discomfort	☐
	I have extreme pain or discomfort	☐
1.6.5	**ANXIETY / DEPRESSION**	
	I am not anxious or depressed	☐
	I am slightly anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am severely anxious or depressed	☐
	I am extremely anxious or depressed	☐

1.6.6 We would like to know how good or bad your health is TODAY. This scale is numbered from 0 to 100. 100 means the best health you can imagine. 0 means the worst health you can imagine.

Please state a number to indicate how your health is TODAY. ☐☐☐ / 100

CRF V 1.0

Completed by ☐☐☐

Appendix 7: Kessler K-10 Psychological Distress Scale

LOLIPOP
Long-term Outcomes of Lidocaine Infusions for Post-Operative Pain

Patient Study Number ☐☐☐-☐☐☐☐

FORM 1 - PRE-OPERATIVE

1.7 KESSLER K-10 Psychological Distress Scale (ALL PATIENTS MUST COMPLETE)

Please tick the answer that is correct for you:		All of the time (Score 5)	Most of the time (Score 4)	Some of the time (Score 3)	A little the time (Score 2)	None the time (Score 1)
1.7.1	In the past 4 weeks, about how often did you feel tired out for no good reason?	☐	☐	☐	☐	☐
1.7.2	In the past 4 weeks, about how often did you feel nervous?	☐	☐	☐	☐	☐
1.7.3^	^In the past 4 weeks, about how often did you feel so nervous that nothing could calm you down?	☐	☐	☐	☐	☐
1.7.4	In the past 4 weeks, about how often did you feel hopeless?	☐	☐	☐	☐	☐
1.7.5	In the past 4 weeks, about how often did you feel restless or fidgety?	☐	☐	☐	☐	☐
1.7.6^	^In the past 4 weeks, how often did you feel so restless that you could not sit still?	☐	☐	☐	☐	☐
1.7.7	In the past 4 weeks, about how often did you feel depressed?	☐	☐	☐	☐	☐
1.7.8	In the past 4 weeks, about how often did you feel that everything was an effort?	☐	☐	☐	☐	☐
1.7.9	In the past 4 weeks, about how often did you feel so sad that nothing could cheer you up?	☐	☐	☐	☐	☐
1.7.10	In the past 4 weeks, about how often did you feel worthless?	☐	☐	☐	☐	☐

^Questions 1.7.3 and 1.7.6 do not need to be asked if the response to the preceding question was "none of the time". In such cases questions 1.7.3 and 1.7.6 will automatically receive a score of 1.

CRF V 1.0

Completed by ☐☐☐

Appendix 8: Adapted modified Brief Pain Inventory – short form (Adapted mBPI-sf) & Short form of Douleur Neuropathique 4 questionnaire (S-DN4)

LOLIPOP
Long-term Outcomes of Lidocaine Infusions for Post-Operative Pain

CRF PAGE 13

Patient Study Number ☐☐☐-☐☐☐☐

FORM 6 - 3 MONTH FOLLOW UP

6.6 Adapted modified Brief Pain Inventory - short form (Adapted mBPI-sf) - ONLY COMPLETE if Yes to pain

With regard specifically to your pain you have, please rate the severity of your pain, using a number from 0 to 10.
For example, if you have no pain, you would rate it "0". If you have the worst pain imaginable, you would rate it "10".

6.6.1	Please rate your pain with the number that best describes your pain at its WORST in the last 7 days.	☐/10
6.6.2	Please rate your pain with the number that best describes your pain at its LEAST in the last 7 days.	☐/10
6.6.3	Please rate your pain with the number that best describes your pain on the AVERAGE in the last 7 days	☐/10
6.6.4	Please rate your pain with the number that best describes your pain AT REST in the last 7 days.	☐/10
6.6.5	Please rate your pain with the number that best describes your pain WITH MOVEMENT OR ACTIVITY in the last 7 days.	☐/10
6.6.6	Using a number, from 0 to 10, (where 0 = does not interfere, and 10 = interferes completely) describe how, during the past 7 days, pain in the area of, or related to, your operation 3 months ago interferes with your:	
6.6.6.1	General activity	☐/10
6.6.6.2	Mood	☐/10
6.6.6.3	Walking ability	☐/10
6.6.6.4	Normal work (includes both work outside the home and housework)	☐/10
6.6.6.5	Relations with other people	☐/10
6.6.6.6	Sleep	☐/10
6.6.6.7	Enjoyment of life	☐/10

6.7 Short Form of Douleur Neuropathique 4 Questions (S-DN4) - ONLY COMPLETE if Yes to pain

To estimate the probility of neuropathic pain, please answer yes or no for each item of the following questions.

Does the pain have one or more of the following characteristics?			
6.7.1	Burning	☐ Yes	☐ No
6.7.2	Painful Cold	☐ Yes	☐ No
6.7.3	Electric Shocks	☐ Yes	☐ No
Is the pain associated with one or more of the following symptoms in the same area?			
6.7.5	Tingling	☐ Yes	☐ No
6.7.6	Pins and Needles	☐ Yes	☐ No
6.7.7	Numbness	☐ Yes	☐ No
6.7.8	Itching	☐ Yes	☐ No

CRF V 2.0

Completed by ☐☐☐

Appendix 9: COVID-19 Contingency Plan

LOLIPOP

Long-term Outcomes of Lidocaine Infusions for Post-Operative Pain

The LOLIPOP trial will recruit patients that are undergoing Category 1 surgery (primary breast cancer surgery). Since the start of the pandemic, even during elective surgery slow down periods, Category 1 surgeries are allowed to continue due to their time critical nature. This ensures that despite any surges in COVID-19 cases, it is unlikely that this will materially impact trial recruitment from the perspective of available patient cohorts to recruit from.

The LOLIPOP Trial will run at a number of established hospital sites in Australia, New Zealand and Hong Kong that belong to the Australian and New Zealand College of Anaesthetists (ANZCA). The pandemic has uniquely affected hospital sites across the regions and therefore the study team will select sites with a strong track record in running trials, have adequate resources, and site leadership and personnel.

The study team has developed the following contingency plan to ensure the trial can commence and run to budget and on time whilst weighing up the risks of running the trial during the pandemic. All available contingencies to limit risk from face-to-face contact with patients and between trial staff will be explored and incorporated into trial processes.

Throughout the COVID-19 pandemic, a number of ANZCA Clinical Trial Network (CTN) trials have continued to recruit and have adapted processes to ensure the safety of participants and trial teams. Lessons learned from our other recruiting trials have been incorporated into the plan for LOLIPOP as outlined in the table below. Equally, the LOLIPOP trial team will share learnings and resources with other trial teams.

Domain	Adaptations and COVID-19 pandemic contingencies to trial processes	Post-pandemic or non-COVID-19 affected activities
Site selection	Study team to undergo site feasibility assessments to select hospitals sites to participate with the following considerations: Site track record in running clinical trials Adequate patient population at site Adequate resources and personnel at the sites	

	Dedicated research coordinator at the site Electronic medical records where possible Experienced site investigator Financial stability Diverse geographical regions ANZCA CTN sites cover a number of geographical locations, with participating sites in most states and territories in Australia, New Zealand and Hong Kong. Western Australia (WA) sites that are local to the trial team and investigators. Diversity in locations is of benefit as different jurisdictions have so far experienced the pandemic in different ways and with different periods of reduced or increased workload depending on the number of cases in communities.	
Ethics and research governance	Trial team will support sites to prepare ethics and governance paperwork and to address COVID-19 related considerations. Ethics and governance submissions are often prepared remotely and will proceed without alteration in the event of lockdowns or work from home orders. During the pandemic there has been an increasing acceptance of electronic signatures, which has limited the need for physical copies or postage of trial paperwork across regional areas.	
Site commencement	The trial team will support sites to seek hospital guidance and comply with hospital directives around research activity. Approval from the head department and trial sponsor will be provided as part of commencement activities. Seek local research governance office advice and approval addressing COVID-19 related concerns.	
Site research teams, communication, training and site support	Site training will be done online. Regular and clear communications to sites via emails and newsletters. In person site visits will be minimised, unless it is appropriate to do so in line with COVID-19 guidelines. LOLIPOP trial team members work across different time zones allowing for regional coverage and support while minimising the need to travel interstate for many sites. Face-to-face site support may be delivered by experienced research coordinators at sites local to them.	

Site research team resources and clinical redeployment	An increasing number of the ANZCA CTN research coordinator workforce come from a scientific, rather than nursing background. This protects a number of sites from losing key research personnel to clinical workforce redistribution during pandemic surges.	
Site start-up meeting	The LOLIPOP start-up meeting was delivered online at the virtual ANZCA CTN workshop by the trial team. The start-up meeting was recorded and has been made available to sites.	
Site initiations	Site initiations will be delivered using Zoom. Online training videos will be made available on the LOLIPOP website. On-site site initiations can be conducted with one representative from the sponsor in jurisdictions that have a local trial team member, if appropriate.	Site initiations may be delivered face-to-face to sites local to the trial team members
Site monitoring	Centralised monitoring will be utilised Limited travel by the study team to sites and areas not affected by the pandemic. On-site and in-person monitoring suspended at sites affected by COVID-19 Remote access to the electronic medical record (EMR) utilised where possible Training for trial team staff to undertake remote monitoring via videoconferencing Trial team members visiting trial teams on-site will comply with hospital COVID-19 policies and screening procedures	Face-to -face monitoring
Patient recruitment and consent	Consent of the patient will be obtained in person by a member of the research team using a hard copy of the Patient Information and Consent Forms (PICFs). Where possible at sites, patients will receive a copy of the PICF as part of their pre-surgery information pack. A pre-consent verbal patient information summary has been approved by HREC so discussions about the trial can be completed with the patient over the phone to gauge interest about their participation in the trial and answer any questions they may have. During the pre-consent verbal patient information summary discussion, the patient will have the option to receive the PICF by downloading it from the trial website, by post or email if they have not already received it. Discussions about the trial will not	Consent patient in pre-admission clinic

	take place until the patient has received and read a copy of the PICF. PICFs will be provided in a non-editable PDF format via email to participants prior to ve rbal discussion, if this option is to be used at sites. Hard copy PICFs will be available for patients still presenting in person to hospital appointments. If the patient wishes to take part in the trial, fully written informed consent will be sought from the patient at a convenient time at a hospital appointment or on admission to hospital prior to their surgery.	
Patients	LOLIPOP will recruit Category 1 surgical patients undergoing primary cancer surgery. This surgical cohort will proceed as it is classified as critical surgery even during COVID-19 surges. COVID-19 surgical pathways for elective surgeries will be followed as per local hospital guidelines. This will likely involve increased screening for COVID-19 in the perioperative period, along with the potential for quarantine pre-operatively for patients to ensure the safety of both patients and health care workers.	
Trial team leadership, management, communication and training	Team meetings and training will be held online using Zoom. Trial team members affected by the pandemic will have the option to work from home where possible under guidance by their organisation. Trial team to share knowledge and resources with other trial teams Weekly Operations Committee meetings to keep the team engaged and prepare for the trial start-up phase. Daily contact with trial team members over email, Zoom and group phone messaging.	
In-hospital patient follow ups	Site teams will follow individual organisational guidelines around appropriate visitation to patient wards and the use of Personal Protective Equipment (PPE) for clinical areas during the post op follow up periods. Additional options including liaising with ward staff or conducting phone follow ups with patients while still in hospital can be utilised during high risk periods, at the discretion of sites and their governance and clinical guidelines.	

Patient follow up visits at 3 months and one year	The three month and one year follow-up visits will continue to be managed remotely over the phone. Patients are not required to return to the hospital for any post-operative research follow up or sample collection Trial teams with secure access to hospital records / Electronic Medical Records (EMR) may be able to undertake patient follow ups from home	
Biobank samples	Sites will store biobanking samples onsite until a safe and appropriate time to courier presents	
Data collection and research documentation	Data collection can be done remotely with site personnel who have authorisation and access to the hospital Virtual Private Network (VPN) Remote and secure access to the LOLIPOP Clinical Trial Management System is available over a standard internet connection Sites that have reduced capacity for data entry should prioritise safety and adverse event reporting during busy periods.	
Safety adverse event reporting and reporting of protocol deviations directly related to the impact of the pandemic	Sites to prioritise safety adverse event reporting and report any protocol deviations related to the pandemic to the project office. Normal timelines for the reporting of safety or adverse events and protocol deviations will be required if sites are recruiting to the trial.	
Site investigator meetings and site engagement	Trial and sites teams to meet off-site at the annual ANZCA CTN strategic research workshop or at the ANZCA annual scientific meetings Trial and site teams to meet and network at virtual meetings	Trial team investigators can visit hospital sites to engage with research teams
Risk assessments	Ongoing risk assessments will be conducted for all trial related procedures. Adaptations to trial protocol and ethics.	

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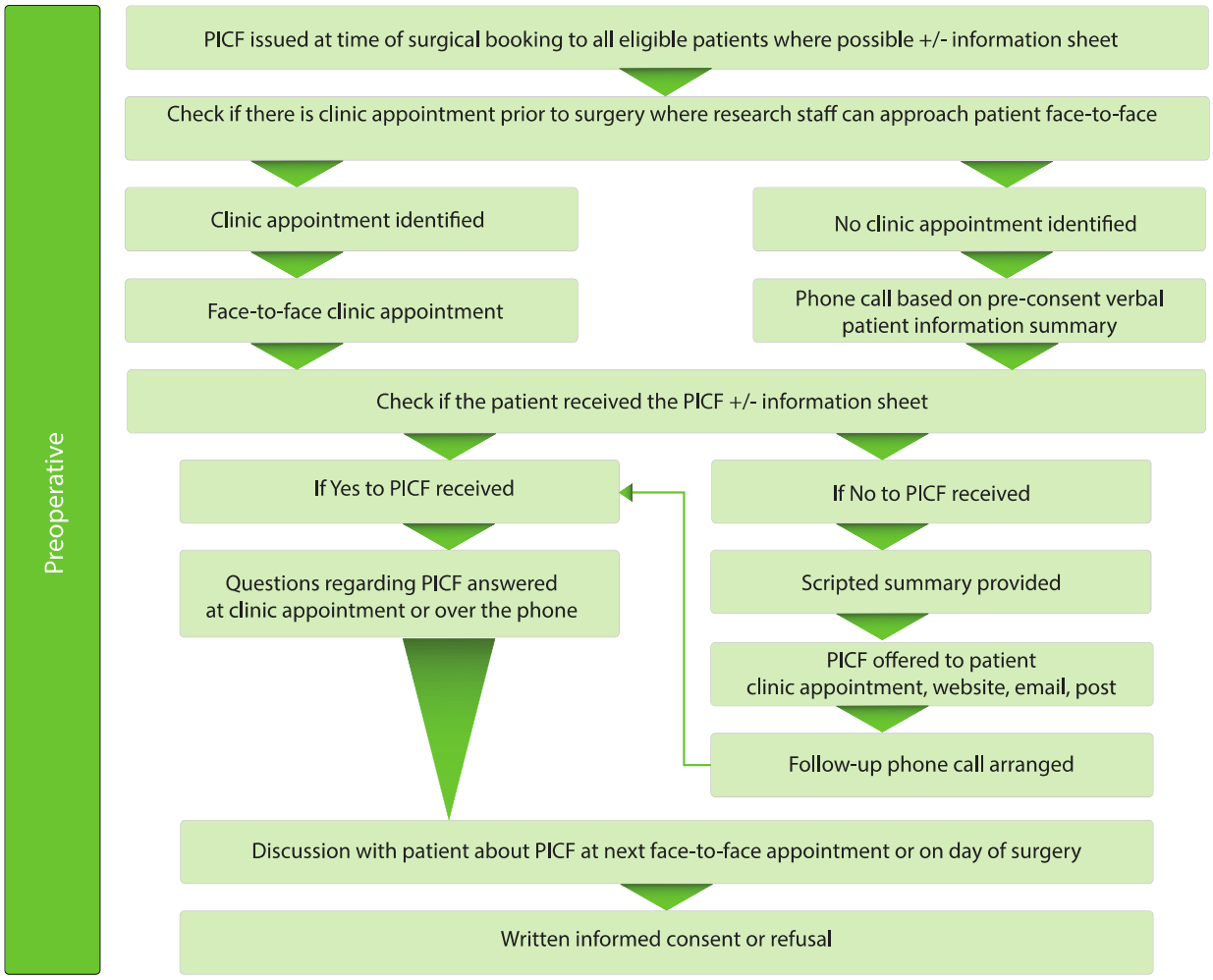
Stephen Jane. Alfred Health Updated Alfred Health COVID19 Guidance on Clinical Trials and Other Research. Nov 2020

Change control register

Version	Authors	Changes	Reviewed by	Date approved

1.0	Allison Kearney, Karen Goulding & Gillian Ormond	Creation	Operations Committee	5/10/2021

Appendix 10: Approaching patients for participation in the LOLIPOP trial



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Appendix 12: Use of Pumps at Hong Kong Sites Only

Hong Kong sites are restricted to using a single type of infusion pump in theatre, the Agilia pump. They do not have technical support for any other intraoperative infusion devices and would be unable to maintain the Alaris PK pumps intraoperatively. Hong Kong sites will therefore use the Agilia pump intraoperatively, applying the following steps:

1. The attending anaesthetist will manually program the LOLIPOP intravenous bolus delivery, entering the bolus volume and duration (5 minutes) directly from the LOLIPOP intraoperative drug dispensing sheet. This will be cross-checked by a member of the research team.
2. After induction of anaesthesia, the attending anaesthetist will commence the programmed bolus.
3. When the bolus is complete, the attending anaesthetist will set the intraoperative infusion rate according to the intraoperative drug dispensing sheet. Again, this will be cross-checked by a member of the research team.
4. Upon completion of the intraoperative intravenous infusion, the review button will be used to view and document the total volume that has been infused.

The Principal Investigator for Hong Kong sites will ensure safety processes using the Agilia pumps are satisfactory.

Sites in Hong Kong will continue to use the Bodyguard T pump to deliver the postoperative subcutaneous infusion as per the protocol.

Appendix 13: 2% Lidocaine Product Information

AUSTRALIAN PRODUCT INFORMATION

XYLOCAINE AND XYLOCAINE WITH ADRENALINE

Lidocaine (lignocaine) hydrochloride
Lidocaine (lignocaine) hydrochloride with adrenaline (epinephrine) acid tartrate

(Injection solutions for the production of local or regional anaesthesia)

1 NAME OF THE MEDICINE

XYLOCAINE: lidocaine (lignocaine) hydrochloride

XYLOCAINE with ADRENALINE: lidocaine (lignocaine) hydrochloride and adrenaline (epinephrine) acid tartrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Plain aqueous solutions are sterile, isotonic and contain lidocaine (lignocaine) hydrochloride, sodium chloride, sodium hydroxide and/or hydrochloric acid for pH adjustment and water for injections.

Lidocaine (lignocaine) hydrochloride with adrenaline (epinephrine) acid tartrate solutions are also sterile and isotonic, and in addition contain adrenaline (epinephrine) acid tartrate and sodium metabisulfite.

Excipients with known effect: XYLOCAINE with ADRENALINE contains sulphites.

XYLOCAINE solutions contain no antimicrobial agent and should be used only once and any residue discarded.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Clear, colourless solution for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

XYLOCAINE solutions are indicated for the production of local or regional anaesthesia by the following techniques:

- infiltration,
- intravenous regional anaesthesia – excluding solutions with adrenaline (epinephrine) acid tartrate,
- peripheral nerve block such as intercostal block,
- major plexus block such as brachial plexus block,
- epidural block,
- subarachnoid block.

4.2 DOSE AND METHOD OF ADMINISTRATION

The lowest dosage and volume that results in effective anaesthesia should be used and should be based on the status of the patient and the type of regional anaesthesia intended. XYLOCAINE solutions contain no antimicrobial agent and should be used only once and any residue discarded.

Lidocaine (lignocaine) should be administered with great caution to patients with impaired cardiovascular function as they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs.

ADULT

Table 1. Recommended dosages for xylocaine plain and xylocaine with adrenaline 1:200,000 (5 micrograms/ml) solutions for various anaesthetic procedures in the average, healthy, 70 kg adult patient.

PROCEDURE	CONCENTRATION	DOSE			
		Plain		With adrenaline	1:200,000
	%	mL	mg	mL	mg
INFILTRATION					
	0.5	40	200	100	500
	1.0	20	200	50	500
	2.0	10	200	25	500
IV REGIONAL ANAESTHESIA*	Bier's Block				
	0.5 (plain only)	40	200	contraindicated	-
BRACHIAL PLEXUS BLOCK					
	1.0	-	-	20 - 40	200 - 400
	1.5	-	-	15 - 30	225 - 450
OTHER NERVE BLOCKS					
Intercostal	1.0	-	-	3 - 5 / segment	30 - 50
Paravertebral	1.0	3 - 5	30 - 50	3 - 5 / segment	30 - 50
Pudendal (each side)	1.0	10	100	10 - 20	100 - 200
Paracervical	1.0 (plain only)	10	100	-	-
STELLATE GANGLION BLOCK					
Cervical	1.0	5	50	5 - 10	50 - 100
Lumbar	1.0	10	100	5 - 20	50 - 200
EPIDURAL ANAESTHESIA**					
Thoracic	1.0	10 - 20	100 - 200	15 - 30	150 - 300
Lumbar	1.5			15 - 30	225 - 450
	2.0	5 - 10	100 - 200	10 - 25	200 - 500
Caudal	1.5			15 - 30	225 - 450
EPIDURAL ANALGESIA					
Lumbar	1.0	10 - 20	100 - 200	15 - 30	150 - 300

2

PROCEDURE	CONCENTRATION	DOSE			
		Plain		With adrenaline	1:200,000
	%	mL	mg	mL	mg
Caudal	1.0	10 - 20	100 - 200	15 - 30	150 - 300

* IV administration of lidocaine (lignocaine) may provoke a hypotensive response and in an overdosage may be precipitous. Therefore, when administering an IV regional dose of 200 mg per single injection, slowly releasing the tourniquet in Bier's block is advocated.

** Dose determined by number of segments to be anaesthetised (2 – 3 mL per segment).

Note:

1. Recommended doses

The above suggested concentrations and volumes serve only as a guide. Toxic doses vary widely between patients and toxic effects may occur after any local anaesthetic procedure.

Careful observation of the patient must therefore be maintained. It is recommended that the dose of lidocaine (lignocaine) at any one time should not exceed 3 mg/kg (plain solutions) or 7 mg/kg (solutions with adrenaline (epinephrine) acid tartrate). However, the dose administered must be tailored to the individual patient and procedure, and the maximum doses here quoted should be used as a guide only.

2. Hypotension

During thoracic, lumbar and caudal epidural anaesthesia, a marked fall in blood pressure and/or intercostal paralysis may be seen, possibly due to the use of excessive doses, improper positioning of the patient or accidental disposition of the anaesthetic within the subarachnoid space. Hypotension and bradycardia may occur as a result of sympathetic blockade.

3. Test dose

For epidural anaesthesia, a 3 - 5 mL test dose of a local anaesthetic solution preferably containing up to 15 micrograms of adrenaline (epinephrine) acid tartrate (e.g. 3 mL of XYLOCAINE 2.0% WITH ADRENALINE 1:200,000) should be administered.

Verbal contact and repeated monitoring of heart rate and blood pressure should be maintained for 5 minutes after the test dose after which, in the absence of signs of subarachnoid or intravascular injection, the main dose may be administered.

Use of a test dose containing adrenaline (epinephrine) acid tartrate may have further advantages in that an intravascular injection of adrenaline (epinephrine) acid tartrate will be quickly recognised by an increase in heart rate, usually within about 40 seconds. To detect this, the heart rate and rhythm should be monitored with an electrocardiogram.

Prior to administration of the total dose, aspiration should be repeated. The main dose should be injected slowly, with continual assessment of the patient. If toxic symptoms or signs occur, the injection should be stopped immediately.

Use in Children
For children, a reduced dosage based on body weight or surface area should be used. The dosage should be calculated for each patient individually and modified in accordance with the physician's experience and knowledge of the patient.

In order to minimise the possibility of toxic effects, the use of XYLOCAINE 0.5% or 1% solutions is recommended for most anaesthetic procedures involving paediatric patients.

In children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

Use in Elderly
A reduction in dosage may be necessary for elderly patients especially those with compromised cardiovascular and/or hepatic function.

In epidural anaesthesia, a smaller dose may provide adequate anaesthesia.

With impaired hepatic function
Although lidocaine (lignocaine) is metabolised by the liver, dosage reduction for local anaesthesia is probably not warranted. However, caution should be exercised with repeated doses.

With impaired renal function
Impairment of renal function is unlikely to affect lidocaine (lignocaine) clearance in the short term (24 hours). However, toxicity due to accumulation may develop with prolonged or repeated administration.

4.3 CONTRAINDICATIONS

1. Allergy or hypersensitivity to amide type local anaesthetics or to any excipients. Allergy or hypersensitivity *to* sodium metabisulfite in solutions with adrenaline (epinephrine) acid tartrate. Detection of suspected hypersensitivity by skin testing is of limited value.

2. Local anaesthetics are contraindicated for epidural and spinal anaesthesia in patients with uncorrected hypotension or coagulation disorders or in patients receiving anti coagulation treatment.

3. Local anaesthetic techniques must not be used when there is inflammation and/or sepsis in the region of the proposed injection and/or in the presence of septicaemia.

4. General contraindications related to epidural anaesthesia, regardless of the local anaesthetic used, should be taken into account.

The following are additional contraindications for solutions with adrenaline (epinephrine) acid tartrate:

5. Adrenaline (epinephrine) acid tartrate is contraindicated in conditions where the production or exacerbation of tachycardia may prove fatal, such as thyrotoxicosis or severe heart disease, or in obstetrics when maternal blood pressure exceeds 130/80 mm Hg.

6. Solutions with adrenaline (epinephrine) acid tartrate must not be used for local analgesia in parts of the body with compromised blood supply or supplied by end arteries, such as fingers, toes, nose, ears or penis. There is a possibility of producing arterial vasoconstriction and subsequent ischaemic gangrene distal to the site of injection.

7. Solutions with adrenaline (epinephrine) acid tartrate must not be used for intravenous regional techniques.

8. Solutions with adrenaline (epinephrine) acid tartrate should not be used in patients with a known sensitivity to sympathomimetic amines.

9. Solutions with adrenaline (epinephrine) acid tartrate should not be used in most patients with cerebral arteriosclerosis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

1. WHEN ANY LOCAL ANAESTHETIC AGENT IS USED, RESUSCITATIVE EQUIPMENT AND DRUGS, INCLUDING OXYGEN, SHOULD BE IMMEDIATELY AVAILABLE IN ORDER TO MANAGE POSSIBLE ADVERSE REACTIONS INVOLVING THE CARDIOVASCULAR, RESPIRATORY OR CENTRAL NERVOUS SYSTEMS. BECAUSE OF THE POSSIBILITY OF HYPOTENSION AND BRADYCARDIA FOLLOWING MAJOR BLOCKS, AN IV CANNULA SHOULD BE INSERTED BEFORE THE LOCAL ANAESTHETIC IS INJECTED. DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDER-VENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND DEATH.

2. INJECTION SHOULD ALWAYS BE MADE SLOWLY WITH FREQUENT ASPIRATIONS TO AVOID INADVERTENT INTRAVASCULAR INJECTION WHICH CAN PRODUCE CEREBRAL SYMPTOMS EVEN AT LOW DOSES.

3. ALTHOUGH INTRA-ARTICULAR CONTINUOUS INFUSIONS OF LOCAL ANAESTHETICS FOLLOWING ARTHROSCOPIC AND OTHER SURGICAL PROCEDURES IS AN UNAPPROVED USE, THERE HAVE BEEN POST-MARKETING REPORTS OF CHONDROLYSIS IN PATIENTS RECEIVING SUCH INFUSIONS. THE MAJORITY OF REPORTED CASES OF CHONDROLYSIS HAVE INVOLVED THE SHOULDER JOINT; CASES OF GLENO-HUMERAL CHONDROLYSIS HAVE BEEN DESCRIBED IN PAEDIATRIC AND ADULT PATIENTS FOLLOWING INTRA-ARTICULAR CONTINUOUS INFUSIONS OF LOCAL ANAESTHETICS WITH AND WITHOUT ADRENALINE (EPINEPHRINE) ACID TARTRATE FOR PERIODS OF 48 TO 72 HOURS. THERE IS INSUFFICIENT INFORMATION TO DETERMINE WHETHER SHORTER INFUSION PERIODS ARE NOT ASSOCIATED WITH THESE FINDINGS. THE TIME OF ONSET OF SYMPTOMS, SUCH AS JOINT PAIN, STIFFNESS AND LOSS OF MOTION CAN BE VARIABLE, BUT MAY BEGIN AS EARLY AS THE 2ND MONTH AFTER SURGERY. CURRENTLY, THERE IS NO EFFECTIVE TREATMENT FOR CHONDROLYSIS; PATIENTS WHO EXPERIENCED CHONDROLYSIS HAVE REQUIRED ADDITIONAL DIAGNOSTIC AND

THERAPEUTIC PROCEDURES AND SOME REQUIRED ARTHROPLASTY OR SHOULDER REPLACEMENT. THEREFORE, XYLOCAINE AND XYLOCAINE WITH ADRENALINE (EPINEPHRINE) ACID TARTRATE SHOULD NOT BE USED FOR POST-OPERATIVE INTRA-ARTICULAR CONTINUOUS INFUSION.

4. Careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness should be accomplished after each local anaesthetic injection. It should be kept in mind that at such times restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of CNS toxicity.

5. LOW MOLECULAR WEIGHT HEPARINS AND HEPARINOIDS (Spinal/Epidural Haematomas) – When neuraxial anaesthesia (epidural / spinal anaesthesia) is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events is increased by the use of indwelling epidural catheters, traumatic or repeated epidural/spinal puncture, and the concomitant use of drugs affecting haemostasis such as NSAID, platelet inhibitors or other anticoagulants. Patients should be frequently monitored for signs and symptoms of neurological impairment.

6. The safety and effectiveness of XYLOCAINE depends on proper dosage, correct technique and adequate precautions. Standard textbooks should be consulted regarding specific techniques and precautions for various regional anaesthetic procedures.

7. The lowest dosage that results in effective anaesthesia should be used (see section 4.2 Dose and method of administration). Repeated injection of XYLOCAINE may cause accumulation of lidocaine (lignocaine) or its metabolites and result in toxic effects.

   Tolerance to elevated blood levels varies with the status of the patient. Elderly, young or debilitated patients, including those with advanced liver disease or severe renal dysfunction, should be given reduced doses commensurate with their age and physical condition.

8. Lidocaine (lignocaine) should be given with great caution to patients with epilepsy, impaired cardiac conduction, bradycardia, severe shock or digitalis intoxication. Lidocaine (lignocaine) should also be administered with great caution to patients with impaired cardiovascular function as they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs. In patients with Stokes-Adams syndrome or Wolff-Parkinson-White syndrome extreme care should be taken to avoid accidental arterio-venous injection.

9. Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia. Epidural anaesthesia should be used with caution in patients with impaired cardiovascular function. Epidural anaesthesia may lead to hypotension and bradycardia. Hypotension should be treated promptly with a sympathomimetic intravenously and repeated as necessary.

10. Local anaesthetics should be given with great caution (if at all) to patients with pre existing abnormal neurological pathology, e.g. myasthenia gravis. Use with extreme caution in epidural, caudal and spinal anaesthesia when there are serious diseases of the CNS or of the spinal cord, e.g. meningitis, spinal fluid block, cranial or spinal haemorrhage, tumours, poliomyelitis, syphilis, tuberculosis or metastatic lesions of the spinal cord.

11. Since lidocaine (lignocaine) is metabolised in the liver and excreted via the kidneys, the possibility of drug accumulation should be considered in patients with hepatic and/or renal impairment (see section 4.2 Dose and method of administration).

12. Inadvertent intravascular or subarachnoid injection of small doses of local anaesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses.

    Clinicians who perform retrobulbar blocks should be aware that there have been reports of cardiovascular collapse and apnoea following the use of local anaesthetic injections for retrobulbar block. Prior to retrobulbar block, necessary equipment, drugs and personnel should be immediately available as with all other regional procedures. Retrobulbar injections may very occasionally reach the subarachnoid space, causing temporary blindness, cardiovascular collapse, apnoea, convulsions etc. These must be diagnosed and treated promptly.

    Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular muscle dysfunction. The primary causes include trauma and/or local toxic effects on muscles or nerves. The severity of such tissue reactions is related to the degree of trauma, the concentration of the local anaesthetic and the duration of exposure of the tissue to the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used. Vasoconstrictors may aggravate tissue reactions and should be used only when indicated.

13. Foetal bradycardia/tachycardia frequently follows paracervical block and may be associated with foetal acidosis and hypoxia. Occasional cases of perinatal morbidity and mortality have been reported. When the recommended dose is exceeded the risk of foetal bradycardia increases. Careful monitoring of the foetal heart rate is necessary.

14. Lidocaine (lignocaine) should be used with caution in patients with known drug sensitivities.

15. Patients being treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be under close surveillance and ECG monitoring since cardiac effects may be additive.

16. Solutions with adrenaline (epinephrine) acid tartrate should be used with extreme caution in patients with severe or untreated hypertension, arteriosclerotic heart disease, cerebral vascular insufficiency, heart block, advanced diabetes, poorly controlled thyrotoxicosis or any other pathological conditions that might be

aggravated by the effects of adrenaline (epinephrine) acid tartrate. Adrenaline (epinephrine) acid tartrate may induce anginal pain in patients suffering from ischaemic heart disease.

17. Solutions containing adrenaline (epinephrine) acid tartrate should be used with caution in patients with ventricular fibrillation, prefibrillatory rhythm, tachycardia, myocardial infarction, phenothiazine induced circulatory collapse and prostatic hypertrophy. (see section 4.3 Contraindications, 4.8 Adverse effects (Undesirable effects) and 4.5 Interactions with other medicines and other forms of interactions).

18. Solutions containing adrenaline (epinephrine) acid tartrate also contain sodium metabisulfite which may cause allergic type reactions including anaphylactic type symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

19. XYLOCAINE PLAIN and XYLOCAINE WITH ADRENALINE solutions for injection are probably porphyrinogenic and should only be prescribed to patients with acute porphyria on strong or urgent indications. Appropriate precautions should be taken for all porphyric patients.

Use in hepatic impairment
See section 4.2 Dose and method of administration.

Use in renal impairment
See section 4.2 Dose and method of administration.

Use in the elderly
See section 4.2 Dose and method of administration.

Paediatric use
See section 4.2 Dose and method of administration.

Effects on laboratory tests

1. Creatinine
Creatinine measurements in patients with therapeutic plasma levels of lidocaine (lignocaine) are about 15 - 35% higher when measured by an enzymatic method versus the Jaffé method. This appears to be due to assay interference from N-ethylglycine, a metabolite of lidocaine (lignocaine).

2. Creatine kinase
The intramuscular injection of lidocaine (lignocaine) may result in an increase in creatine kinase levels for up to 48 hrs. This may interfere with the diagnosis of myocardial infarction.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

1. Anti-arrhythmic drugs
Local anaesthetics of the amide type, such as lidocaine (lignocaine), should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics e.g. certain anti arrhythmic drugs such as disopyramide, procainamide,

mexilitene since potentiation of cardiac effects may occur. Specific interaction studies with lidocaine (lignocaine) and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution should be advised (see section 4.4 Special warnings and precautions for use).

2. Amiodarone

Amiodarone has been reported to reduce the clearance of lidocaine (lignocaine) in two case reports, although a small prospective study of combined therapy on lidocaine (lignocaine) pharmacokinetics found no change in clearance or other pharmacokinetic factor. This combination has been reported to precipitate seizures and to lead to severe sinus bradycardia and a long sinoatrial arrest. Until more experience with concurrent use of lidocaine (lignocaine) and amiodarone becomes available, patients receiving the combination should be monitored carefully.

3. Beta adrenoreceptor antagonists

Propranolol and metoprolol reduce the metabolism of IV administered lidocaine (lignocaine) and the possibility of this effect with other beta adrenergic blockers should be kept in mind. If these drugs are administered concurrently, the patient should be closely observed for signs of lidocaine (lignocaine) toxicity.

4. Cimetidine

Cimetidine reduces the clearance of IV administered lidocaine (lignocaine) and toxic effects due to high serum lidocaine (lignocaine) levels have been reported when these two drugs have been administered concurrently.

5. Anticonvulsive agents

Phenytoin and other antiepileptic drugs such as phenobarbitone, primidone and carbamazepine appear to enhance the metabolism of lidocaine (lignocaine) but the significance of this effect is not known. Phenytoin and lidocaine (lignocaine) have additive cardiac depressant effects.

6. Inhalational anaesthetics

Lidocaine (lignocaine) decreases the minimum effective concentration of inhalational anaesthetics, e.g. nitrous oxide.

7. Skeletal muscle relaxants

Lidocaine (lignocaine) and skeletal muscle relaxants, e.g. suxamethonium, lead to excessive neuromuscular blockade; therefore, this combination must be used with caution.

8. Structurally related local anaesthetics

Lidocaine (lignocaine) should be used with caution in patients receiving agents structurally related to local anaesthetics.

In addition, the following interactions may occur with solutions with adrenaline (epinephrine) acid tartrate:

9. CNS acting drugs

Solutions with adrenaline (epinephrine) acid tartrate should be used with extreme caution in patients receiving monoamine oxidase inhibitors or tricyclic antidepressants as severe sustained hypertension may result. The effects of adrenaline (epinephrine) acid tartrate may be potentiated by some antihistamines and thyroid hormones. (see section 4.4 Special

warnings and precautions for use). Phenothiazines and butyrophenones may reduce or reverse the pressor effects of adrenaline (epinephrine) acid tartrate which may lead to a hypotensive response and tachycardia.

10. Oxytocic drugs of the ergot type
Solutions with adrenaline (epinephrine) acid tartrate should not be used in the presence of oxytocic drugs of the ergot type as they are known to interact to produce severe, persistent hypertension and its subsequent sequelae.

11. Adrenergic neuron blocking agents
Solutions with adrenaline (epinephrine) acid tartrate should be used with extreme caution in the presence of adrenergic neuron blocking agents (e.g. guanethidine, debrisoquine, bethanidine).

12. Inhalation anaesthetics
Serious cardiac arrhythmias and acute pulmonary oedema if hypoxia is present may occur if preparations containing adrenaline (epinephrine) acid tartrate are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other halogenated compounds.

13. Cardiac glycosides
Solutions with adrenaline (epinephrine) acid tartrate may interact with cardiac glycosides resulting in cardiac arrhythmias.

14. Beta blockers
Non-cardioselective beta blockers such as propranolol enhance the pressor effects of adrenaline (epinephrine) acid tartrate which may lead to severe hypertension and bradycardia.

15. Quinidine
Solutions with adrenaline (epinephrine) acid tartrate may interact with quinidine resulting in cardiac arrhythmias.

16. Hypoglycaemics
Adrenaline (epinephrine) acid tartrate-induced hyperglycaemia may lead to loss of blood sugar control in diabetic patients treated with hypoglycaemic agents.

17. Alkaline solutions
The solubility of lidocaine (lignocaine) is limited at pH values above 7.0. This must be taken into consideration if adding an alkaline solution since precipitation might occur at higher pH values.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
See section 5.3 Preclinical safety data.

Use in pregnancy – Pregnancy Category A
The safe use of lidocaine (lignocaine) during pregnancy has not been established. Although lidocaine (lignocaine) has been used extensively for surgical procedures during pregnancy with no reports of ill effects to mother or foetus, there are no adequate or well-controlled studies in pregnant women of the effect of lidocaine (lignocaine) on the developing foetus.

Lidocaine (lignocaine) has been effectively used for obstetrical analgesia and adverse effects on the course of labour or delivery are rare. After epidural administration of lidocaine (lignocaine) to women in labour, lidocaine (lignocaine) crosses the placental barrier. However, concentrations in umbilical veins are lower than those found in the maternal circulation. It has been suggested that blood glucose levels should be checked in newborns after obstetric regional anaesthesia.

Adrenaline (epinephrine) acid tartrate has been given to a large number of pregnant women and women of child-bearing age without any proven increase in the frequency of malformations or other indirect harmful effects on the foetus having been observed.

The addition of adrenaline (epinephrine) acid tartrate may potentially decrease uterine blood flow and contractility, especially after inadvertent injection into maternal blood vessels.

Adrenaline (epinephrine) acid tartrate may delay the second stage of labour by inhibiting uterine contractions.

Adrenaline (epinephrine) acid tartrate free solutions should be used during labour for paracervical or pudendal blocks.

Note: Paracervical blocks may be associated with foetal bradycardia (see section 4.4 Special warnings and precautions for use).

Use in lactation
Lidocaine (lignocaine) passes into breast milk. The amount of lidocaine (lignocaine) appearing in breast milk from a nursing mother receiving parenteral lidocaine (lignocaine) is unlikely to lead to a significant accumulation of the parent drug in the breast fed infant. The remote possibility of an idiosyncratic or allergic reaction in the breast fed infant from lidocaine (lignocaine) remains to be determined.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Depending on dosage, local anaesthetics may have a very mild effect on mental function and may temporarily impair locomotion and coordination.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse experiences following the administration of lidocaine (lignocaine) are similar in nature to those observed with other amide local anaesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage or rapid absorption, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported:

Central nervous system
CNS manifestations are excitatory and/or depressant and may be characterised by light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, hyperacusis, blurred vision, vomiting, sensations of heat, cold or numbness, twitching,

tremors, convulsions, unconsciousness, respiratory depression and/or arrest, agitation, difficulty swallowing, paraesthesia circumoral, numbness of the tongue and slurred speech.

The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest. Drowsiness following administration of lidocaine (lignocaine) is usually an early sign of a high blood level of the drug and may occur as a result of rapid absorption. In unconscious patients, circulatory collapse should be watched for as CNS effects may not be apparent, as an early manifestation of toxicity may in some cases progress to frank convulsions and ultimately lead to respiratory depression and/or arrest. It is crucial to have resuscitative equipment and anticonvulsant drugs available to manage such patients. (see section 4.9 Overdose – Treatment of overdosage)

Cardiovascular
Cardiovascular manifestations are usually depressant and are characterised by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Cardiac arrhythmias and hypertension have also been observed.

Methaemoglobinaemia can occur following IV administration.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as a benzodiazepine or a barbiturate. In rare cases, cardiac arrest has occurred without prodromal CNS effects.

In children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

Haemodynamic
Regional anaesthesia may lead to maternal hypotension.

Allergic
Allergic reactions are characterised by cutaneous lesions, urticaria, oedema or anaphylactoid reactions/shock.

Allergy to amide type local anaesthetics is rare. Sodium metabisulfite (a sulfite), which is included in solutions with adrenaline (epinephrine) acid tartrate, may also cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. If such a reaction occurs, it should be managed by conventional means.

The detection of sensitivity by skin testing is of doubtful value.

Neurologic
The incidences of adverse reactions associated with the use of local anaesthetics may be related to the total dose of local anaesthetic administered and are also dependent on the particular drug used, the route of administration and the physical status of the patient.

Neurological reactions following regional nerve blocks have included persistent numbness, paraethesia and other sensory disturbances.

In a prospective review of 10,440 patients who received lidocaine (lignocaine) for spinal anaesthesia, the incidences were reported to be about 3% each for positional headaches, hypotension and backache; 2% for shivering; and less than 1% each for peripheral nerve symptoms, nausea, respiratory inadequacy and double vision. Many of these observations may be related to local anaesthetic techniques, with or without a contribution from the local anaesthetic.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter may occur. Subsequent adverse effects may depend partially on the amount of drug administered subdurally.

These may include spinal block of varying magnitude (including total spinal block), hypotension secondary to spinal block, loss of bladder and bowel control and loss of perineal sensation and sexual function. Persistent motor, sensory and/or autonomic (sphincter control) deficit of some lower spinal segments with slow recovery (several months) or incomplete recovery have been reported in rare instances when caudal or lumbar epidural block has been attempted. Backache and headache have also been noted following use of these anaesthetic procedures.

Peripheral nerve injury and arachnoiditis have been observed.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms
Acute emergencies associated with the use of local anaesthetics are generally related to high plasma levels or to unintended subarachnoid injection of the local anaesthetic solution (see Section 4.8 Adverse effects (Undesirable effects) and Section 4.4 Special warnings and precautions for use).

With accidental intravascular injections, the toxic effect will be obvious within 1 - 3 min. With overdosage, peak plasma concentrations may not be reached for 20 - 30 min depending on the site of injection and toxic signs will be delayed. Toxic reactions mainly involve the central nervous and cardiovascular systems.

In children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

Symptoms of acute toxicity
Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis and tinnitus. Visual disturbance and muscular tremors are more

serious and precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour.

Unconsciousness and grand mal convulsions may follow. These may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases, apnoea may occur. Acidosis increases the toxic effects of local anaesthetics.

Recovery is due to redistribution of the local anaesthetic drug from the central nervous system and metabolism. Recovery may be rapid unless large amounts of the drug have been injected.

Cardiovascular toxicity indicates a more severe situation. Hypotension, bradycardia, decreased cardiac output, heart block, arrhythmia and even ventricular arrhythmias, ventricular fibrillation and cardiac arrest may occur as a result of huge systemic concentrations of local anaesthetics.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as a benzodiazepine or a barbiturate. In rare cases, cardiac arrest has occurred without prodromal CNS effects.

Treatment of overdosage

If signs of acute systemic toxicity appear injection of the local anaesthetic should be stopped immediately. If convulsions occur then immediate attention is required for the maintenance of a patent airway and assisted or controlled ventilation with oxygen, via a positive airway pressure delivery system mask. Adequacy of the circulation should then be evaluated, bearing in mind that drugs used to treat convulsions depress the circulation when administered intravenously.

Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, appropriate anticonvulsant medication such as an ultra-short acting barbiturate (e.g. thiopentone) or a benzodiazepine (e.g. diazepam) may be administered IV. The clinician should be familiar with these anticonvulsant drugs prior to use of local anaesthetics.

Suxamethonium will stop the muscle convulsions rapidly but will require tracheal intubation and controlled ventilation, and should only be used by those familiar with these procedures.

If ventricular fibrillation or cardiac arrest occurs, effective cardiovascular resuscitation treatment must be instituted and maintained for a prolonged period if necessary. Optimal oxygenation and ventilation, and circulatory support as well as treatment of acidosis are of vital importance.

If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, chronotropic and or inotropic agents should be considered. Children should be given doses commensurate with age and weight.

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine (lignocaine).

To counteract the pressor effects of adrenaline (epinephrine) acid tartrate, use rapidly acting vasodilators, for instance nitrates or α-blocking agents.

For treatment of reactions caused by adrenaline (epinephrine) acid tartrate, consult standard textbooks.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Lidocaine (lignocaine), like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the nerve membrane. Local anaesthetics of the amide type are thought to act within the sodium channels of the nerve membrane.

Local anaesthetic drugs may have similar effects on excitable membranes in the brain and myocardium. If excessive amounts of drug reach the systemic circulation rapidly, symptoms and signs of toxicity will appear, emanating mainly from the central nervous system and cardiovascular systems.

Central nervous system toxicity usually precedes the cardiovascular effects as it occurs at lower plasma concentrations. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

Indirect cardiovascular effects, e.g. hypotension and bradycardia, may occur after epidural or spinal administration depending on the extent of the concomitant sympathetic block.

Adrenaline (epinephrine) acid tartrate acts on both alpha- and beta-adrenergic receptors of tissue innervated by sympathetic nerves, except for the sweat glands and arteries of the face. It is the most important alpha receptor activator. Adrenaline (epinephrine) acid tartrate stimulates the heart to increase output; raises the systolic blood pressure; lowers diastolic blood pressure; relaxes bronchial spasm and mobilises liver glycogen, resulting in hyperglycaemia and possibly glycosuria.

Clinical trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Distribution
Lidocaine (lignocaine) has a rapid onset and a medium duration of action. The onset of action is 1 - 5 minutes following infiltration and 5 - 15 minutes following other types of administration.

The rate of absorption depends upon the dose, the route of administration and the vascularity of the injection site. Intercostal blocks give the highest peak plasma concentrations (approximately 1.5 µg/mL for every 100 mg injected), while abdominal subcutaneous injections give the lowest (approx. 0.5 µg/mL per 100 mg injected). Epidural and major nerve block produce peak plasma levels intermediate between these.

The addition of adrenaline (epinephrine) acid tartrate considerably slows the absorption of lidocaine (lignocaine), although the rate also depends on the site of injection. Peak plasma concentrations are reduced by 50% following subcutaneous injection, by 30% following epidural injection and by 20% following intercostal block if adrenaline (epinephrine) acid tartrate 5 µg/mL is added.

Absorption of lidocaine (lignocaine) from the epidural space occurs in 2 phases; the first phase is in the order of 9 minutes and the second is approximately 82 minutes. The slow absorption is the rate-limiting step in the elimination of lidocaine (lignocaine), which also explains why the apparent elimination half-life following epidural injection is longer than after intravenous administration.

The plasma binding of lidocaine (lignocaine) is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 µg of free base/mL, 60 - 80% of lidocaine (lignocaine) is protein bound. Binding is also dependent on the plasma concentration of the α_1-acid glycoprotein.

Lidocaine (lignocaine) crosses the blood-brain and placental barriers by passive diffusion. Since the degree of plasma protein binding in the foetus is less than in the mother, although free lidocaine (lignocaine) concentrations will be the same, the total plasma concentration will be greater in the mother.

Metabolism and Excretion
Lidocaine (lignocaine) has a total plasma clearance of 0.95 L/min, a volume of distribution at steady state of 91 L, an elimination half-life of 1.6 hr and an estimated hepatic extraction ratio of 0.65. Approximately 90% of a parenteral dose of lidocaine (lignocaine) is rapidly metabolised in the liver by de-ethylation to form monoethylglycinexylidide (MEGX) and glycinexylidide (GX) followed by cleavage of the amide bond to form xylidine and 4-hydroxyxylidine which are excreted in the urine. Less than 10% of a dose is excreted unchanged in the urine.

The principal metabolites, MEGX and GX also possess pharmacological activity. The rate of metabolism of lidocaine (lignocaine) appears to be limited by liver blood flow which may be reduced in patients after acute myocardial infarction and/or congestive heart failure. The rate of lidocaine (lignocaine) metabolism may also be reduced in patients with liver or hepatic tissue necrosis, possibly because of altered perfusion.

The duration of action depends upon the concentration used, the dose given, the nerves to be blocked and the status of the patient. The 2% solution will produce an effect for 1½ - 2 hrs when given epidurally, and up to 5 hrs when given as a peripheral nerve block. When used in a 1% concentration there is less effect on motor nerve fibres and the duration of effect is shorter.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
The genotoxic potential of 2,6-xylidine has been studied with mixed results: Positive results were reported in assays for gene mutations (weakly positive in the Ames test with metabolic activation and in the mouse lymphoma assay) and chromosomal damage (chromosomal aberrations in Chinese hamster ovary cells at concentrations at which the drug precipitated

from solution). No evidence of genotoxicity was found in in vivo assays for chromosomal damage (micronucleus assay) and DNA damage (unscheduled DNA synthesis). Covalent binding studies of DNA from liver and ethmoid turbinates in rats indicate that 2,6-xylidine may be genotoxic under certain conditions in vivo.

Carcinogenicity
A two-year oral toxicity study of 2,6-xylidine, a metabolite of lidocaine (lignocaine), has shown that in both male and female rats, 2-6-xylidine in daily doses of 900 mg/m2 (150 mg/kg) resulted in carcinomas and adenomas of the nasal cavity. No nasal tumours were observed in the low dose (15 mg/kg or control animals). In addition, the compound also caused subcutaneous fibromas and or fibrosarcomas in male and female rats (significant at 150 mg/kg).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

XYLOCAINE: dilute hydrochloric acid, sodium chloride, sodium hydroxide and water for injections.

XYLOCAINE WITH ADRENALINE: hydrochloric acid, sodium chloride, sodium hydroxide, sodium metabisulfite and water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

2 mL and 5 mL Polyamp presentations should be stored below 25°C.
20 mL Polyamp presentations should be stored below 30°C.
XYLOCAINE solutions in glass ampoules should be stored below 30°C.
XYLOCAINE WITH ADRENALINE in glass ampoules should be stored below 25°C.
XYLOCAINE WITH ADRENALINE in single dose vials should be stored below 25°C.

Solutions with adrenaline (epinephrine) acid tartrate should be protected from light.

Local anaesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precautions should be taken to avoid prolonged contact between XYLOCAINE solutions and metal surfaces such as metal bowls, cannulae and syringes with metal parts.

Solutions showing discolouration and unused portions of solutions from ampoules and single dose vials should be discarded. Solutions with adrenaline (epinephrine) acid tartrate should

not be reautoclaved. Surface sterilisation using pure, undiluted isopropyl alcohol (91%) or 70% ethyl alcohol (USP) may be carried out if desired.

6.5 NATURE AND CONTENTS OF CONTAINER

XYLOCAINE 0.5%
[lidocaine (lignocaine) hydrochloride 5 mg/mL
5 mL glass ampoules^
5 mL Polyamp ampoules^

XYLOCAINE 0.5% WITH ADRENALINE 1:200,000
[lidocaine (lignocaine) hydrochloride 5 mg/mL with adrenaline (epinephrine) 5 microgram/mL (as acid tartrate)]
20 mL single dose vials in Sterile Theatre Pack.
20 mL single dose vials.

XYLOCAINE 1.0%
[lidocaine (lignocaine) hydrochloride 10 mg/mL]
5 mL glass ampoules^
2 mL, 5 mL, 20 mL Polyamp ampoules

XYLOCAINE 1.0% WITH ADRENALINE 1:100,000
[lidocaine (lignocaine) hydrochloride 10 mg/mL with adrenaline (epinephrine) 10 microgram/mL (as acid tartrate)]
5 mL glass ampoules

XYLOCAINE 1.0% WITH ADRENALINE 1:200,000
[lidocaine (lignocaine) hydrochloride 10 mg/mL with adrenaline (epinephrine) 5 microgram/mL (as acid tartrate)]
20 mL single dose vials in Sterile Theatre Pack.
20 mL single dose vials.

XYLOCAINE 1.5% WITH ADRENALINE 1:200,000
[lidocaine (lignocaine) hydrochloride 15 mg/mL with adrenaline (epinephrine) 5 microgram/mL(as acid tartrate)]
20 mL single dose Top Hat vials^

XYLOCAINE 2.0%
[lidocaine (lignocaine) hydrochloride 20 mg/mL]
5 mL glass ampoules^
2 mL, 5 mL, 20 mL Polyamp ampoules

XYLOCAINE 2.0% WITH ADRENALINE 1:80,000
[lidocaine (lignocaine) hydrochloride 20 mg/mL with adrenaline (epinephrine) 12.5 micrograms/mL)]
5 mL glass ampoules

XYLOCAINE 2.0% WITH ADRENALINE 1:200,000
[lidocaine (lignocaine) hydrochloride 20 mg/mL with adrenaline (epinephrine) 5 micrograms/mL (as acid tartrate)]
20 mL single dose vials in Sterile Theatre Pack.
20 mL single dose vials.

^ Registered but not marketed.

Note
Solutions with adrenaline (epinephrine) acid tartrate contain the antioxidant sodium metabisulfite, 0.5 mg/mL.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

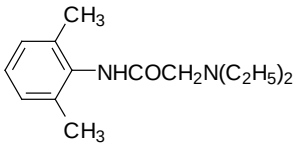
The chemical name for lidocaine (lignocaine) hydrochloride is 2-Diethylaminoaceto-2'6'-xylidide hydrochloride. The Australian Approved Name is lidocaine (lignocaine) hydrochloride.

The chemical name for adrenaline (epinephrine) acid tartrate is (R)-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol. The Australian Approved Name is adrenaline (epinephrine).

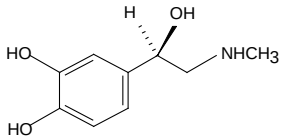
Lidocaine (lignocaine) is classed as a membrane stabilising agent and is a local anaesthetic of the amide type. It is extremely stable and plain solutions can be sterilised by autoclaving, repeated a maximum of two times if necessary. XYLOCAINE solutions are available with or without adrenaline (epinephrine) acid tartrate.

Plain aqueous solutions of lidocaine (lignocaine) hydrochloride have a pH of 5.0 - 7.0 (approx.); lidocaine (lignocaine) hydrochloride with adrenaline (epinephrine) acid tartrate solutions have a pH of 3.3 - 5.5 (approx.). Lidocaine (lignocaine) base has a pKa of 7.85 (25°C), an oil/water coefficient of 2.9 and a molecular weight of 234.3.

Chemical structure
The chemical structure of lidocaine (lignocaine) hydrochloride is:



The chemical structure of adrenaline (epinephrine) acid tartrate is:



CAS number
The CAS number for lidocaine (lignocaine) hydrochloride monohydrate (AAN) is 6108-05-0 and lidocaine (lignocaine) hydrochloride is 73-78-9.

The CAS number for adrenaline (epinephrine) acid tartrate is 51 - 43 - 4.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription only medicine)

8 SPONSOR

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street
St Leonards NSW 2065
Australia
http://www.aspenpharma.com.au

9 DATE OF FIRST APPROVAL

10 October 2008

10 DATE OF REVISION

20 June 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatted PI to the new TGA format
3	Updated to include pharmaceutical form
8	Addition of website to sponsor details
6.5	Addition of details for adrenaline combination product in 20mL vial without theatre pack

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Appendix 14: 10% Lidocaine Product Information

Australian Product Information
XYLOCARD
(Lidocaine Hydrochloride)
Solutions for injection and infusion

1 NAME OF THE MEDICINE

Lidocaine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in XYLOCARD® is lidocaine hydrochloride.

Plain aqueous solutions are sterile, isotonic and contain lidocaine hydrochloride, sodium hydroxide for pH adjustment and Water for Injections.

3 PHARMACEUTICAL FORM

All XYLOCARD solutions are clear and colourless.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Lidocaine is classed as a membrane stabilizing agent; local anaesthetic and antiarrhythmic agent. It is extremely stable and plain solutions can be sterilised by autoclaving, repeated if necessary.

Cardiac arrhythmias
Treatment or prophylaxis of life-threatening ventricular arrhythmias, including those associated with myocardial infarction, general anaesthesia in patients predisposed to ventricular arrhythmias, digitalis intoxication, or following resuscitation from cardiac arrest.

4.2 DOSE AND METHOD OF ADMINISTRATION

XYLOCARD solutions contain no antimicrobial agent and should be used in one patient on one occasion only and any residue discarded.

Cardiac arrhythmias
Dosage is individual. The therapeutic serum concentration range is
5 - 20 micromol/L, 1.5 - 6.0 microgram/mL.

In the treatment of ventricular arrhythmias an intravenous injection should be given first, followed by an intravenous infusion.

Adults

Preinfusion
Intravenous
To obtain therapeutic blood levels rapidly use lidocaine 100 mg/5 mL in a dose of lidocaine 1 mg/kg bodyweight. Inject slowly IV, over a period of 1 to 2 minutes.

The initial effect occurs in 2 to 4 minutes; maximum effect in about 10 minutes; duration 15 to 20 minutes. Infusion should be commenced within 10 minutes.

In the pre-hospital phase 50 - 100 mg doses may be administered at 10 to 20 minute intervals. This dose corresponds to 1 mg/kg body weight per injection. No more than 200 - 300 mg lidocaine should be administered during a one-hour period. Patients with cardiogenic shock may require smaller bolus doses.

Infusion
Use XYLOCARD 500 (100 mg lidocaine /mL ampoules). A drip rate of 2 to 4 mg/min is recommended. For complicating factors see Section 4.4 Special warnings and precautions for use.

In order to maintain therapeutic blood levels in the first few hours of infusion therapy, the initial IV injection may be followed by a further two injections of 50 to 100 mg (lidocaine 100 mg/5 mL) at 15 to 20 minute intervals. This is necessitated by the fairly slow rise to therapeutic concentrations. No more than 200 - 300 mg lidocaine should be administered in a one-hour period.

In certain cases doses higher than 4 mg/min may be needed to achieve antiarrhythmic effect. The risk of side-effects increases with higher doses, however.

The duration of infusion is normally two or more days. It should normally not be discontinued until 24 hours after the last signs of ventricular tachyarrhythmias or serious ventricular ectopic beats.

**The rate of intravenous infusion should be reassessed as soon as the patient's basic cardiac rhythm appears to be stable or at the earliest signs of toxicity. It should rarely be required to continue intravenous infusions of XYLOCARD for prolonged periods.*

Increase in dosage
Before increasing the infusion rate, a slow IV injection of 25 to 100 mg should be given to obtain therapeutic blood levels rapidly.

Preparation of infusion solutions
A concentration of 2 mg lidocaine per mL is normally used. With higher doses, and in cases in which it is desired to limit the administration of fluid, a higher concentration may be used.

XYLOCARD may be diluted with 5.5% glucose, invertose, dextran, physiological saline, Ringer's and sodium bicarbonate solutions.

The addition of medicines to infusion solutions always means an added risk with regard to sterility, stability and incompatibility. As a rule, infusion solutions with approved additives should therefore be used within 12 hours.

Caution
During infusion therapy with XYLOCARD the rate of administration must be carefully checked, preferably by means of a drop counter or the use of a special infusion pump. The total amount of XYLOCARD added to the infusion solution may be lethal if infused too rapidly.

The therapeutic dose regimens described are guides only and because of large intrapatient (with time) and interpatient variability in the response to lidocaine, it is advisable to monitor plasma levels and adjust doses accordingly.
In the case of shock, cardiac or hepatic failure, or the elderly, the dose should be reduced. (See Section 4.4 Special warnings and precautions for use).

4.3 CONTRAINDICATIONS

Stokes-Adams syndrome, or severe degrees of sinoatrial, atrioventricular or intraventricular block. Lidocaine suppresses ventricular pacemaker activity and the result may be ventricular standstill in such patients.

In the treatment of supraventricular arrhythmias.

Known history of allergy or hypersensitivity to lidocaine or other amide-type local anaesthetics such as prilocaine, mepivacaine or bupivacaine. See also Section 4.5 Interactions with other medicines and other forms of interactions.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

1. **RESUSCITATIVE EQUIPMENT AND MEDICINES, INCLUDING OXYGEN, SHOULD BE IMMEDIATELY AVAILABLE WHEN XYLOCARD IS USED, TO MANAGE POSSIBLE LIDOCAINE -INDUCED REACTIONS INVOLVING THE CARDIOVASCULAR, RESPIRATORY OR CENTRAL NERVOUS SYSTEM** (see Section 4.8 Adverse effects (Undesirable effects)).

2. Constant ECG monitoring is essential for the proper IV administration of lidocaine. Signs of excessive depression of cardiac conductivity, such as prolongation of PR interval and QRS complex, should be followed by prompt cessation of the IV infusion.

3. In emergency situations, when a ventricular rhythm disorder is suspected, and ECG equipment is not available, a single dose may be administered when the physician in attendance has determined that the potential benefits outweigh the possible risks.

4. Mortality
   In the Cardiac Arrhythmia Suppression Trial (CAST), a long term, multi-centred, randomised, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmia who had myocardial infarction more than 6 days but less than 2 years previously, an excess mortality and non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730), compared with that seen in patients assigned to matched placebo-treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months. While there are no comparable mortality trial data for other class I antiarrhythmic agents post myocardial infarction or in

other clinical settings, meta-analyses of small scale clinical trials of these agents in similar populations suggests a trend towards increased mortality compared to placebo and no evidence of benefit.

All Class I antiarrhythmic agents share the capacity to produce slowing of conduction velocity which can promote tachycardias via a re-entry mechanism. Indeed, the use of these agents for other than life-threatening arrhythmias or severe symptoms due to arrhythmias is not recommended.

In the light of this information, it is prudent to consider the prophylactic use of Class I antiarrhythmic medicines following myocardial infarction as potentially hazardous.

5. Lidocaine should be given with caution to patients with severe shock, bradycardia, hypovolaemia, cardiac conduction disturbances (see Section 4.3 Contraindications), severe digitalis intoxication. In the case of bradycardia complicated by ventricular tachyarrhythmia, XYLOCARD might be combined with atropine or an atropine-like medicine or pacemaker treatment.

6. Since antiarrhythmic medicines may be ineffective in patients with hypokalaemia, serum potassium levels should be normalised prior to XYLOCARD administration. Hypoxia and acid-base disturbances should also be corrected as these factors may potentiate ventricular arrhythmias.

7. The IV dose of XYLOCARD should not exceed 100 mg in a single injection, and no more than 200 - 300 mg in a one hour period (see Section 4.2 Dose and method of administration) as a hypotensive response is sometimes observed with IV administration of lidocaine.

8. Patients with reduced hepatic blood flow or function, and those on prolonged infusions of lidocaine, have a longer lidocaine half life and lower clearance **resulting in accumulation of lidocaine.* Patients with congestive cardiac failure have a reduced clearance. In patients with renal failure, accumulation **of lidocaine and its metabolites* may develop during prolonged or repeated administration. These patients may therefore require a reduction in dosage.

9. Patients with a chronic elevation in cardiac output or a drug-induced induction of hepatic microsomal enzymes will have a reduced elimination half-life of lidocaine and may therefore require a higher dosage.

10. Debilitated, elderly or acutely ill patients should be given reduced doses commensurate with their age and physical status.

11. Dosage reduction may be required during concomitant use with propranolol, metoprolol or cimetidine as there is a possibility of reduced elimination of lidocaine.

12. Lidocaine should be used with caution in patients with genetic predisposition to malignant hyperthermia as the safety of amide local anaesthetic agents in these patients has not been fully assessed.

13. Blood lidocaine concentrations should be measured in patients in shock who may have markedly reduced lidocaine clearance, on prolonged infusions of greater than 24 hours

duration especially in patients with cardiac or hepatic failure, those who are refractory to the usual dosage given, and in the presence of ambiguous signs and symptoms of lidocaine toxicity. Severe reactions are often preceded by somnolence and paraesthesia, therefore these symptoms should not be dismissed.

14. **Caution should be observed in patients with cardiac decompensation and hypotension or posterior diaphragmal infarction with a tendency towards development of heart block.*

15. **When high doses are used and the patient's myocardial function is impaired, combination with other medicines which reduce the excitability of cardiac muscle requires caution.*

16. **Theoretical evidence suggests that lidocaine may have porphyrogenic properties. The clinical significance of this is unknown. Caution should be exercised if intravenous XYLOCARD is administered to patients with acute porphyria.*

Use in hepatic impairment
Patients with reduced hepatic blood flow or function, and those on prolonged infusions of lidocaine, have a longer lidocaine half-life and lower clearance and may therefore require a reduction in dosage. To lessen the risk of acute toxicity, a regimen with 2 boluses 10 - 30 min apart followed by an infusion is preferable to a single bolus followed by infusion.

Use in renal impairment
Impairment of renal function is unlikely to affect lidocaine clearance in the short term (24 hours). However, toxicity due to accumulation *of lidocaine and its metabolites* may develop with prolonged or repeated administration.

Use in the elderly
A reduction in dosage may be necessary for elderly patients with compromised cardiovascular and/or hepatic function and/or on prolonged infusions.

Paediatric use
The safety of lidocaine in the treatment of arrhythmias in children has not been established. Through their lower enzyme capacity, neonates are at risk of methaemoglobinaemia which can become clinically overt (cyanosis).

Effects on laboratory tests

1. **Creatinine**
   Creatinine measurements in patients with therapeutic plasma levels of lidocaine are about 15 - 35% higher when measured by an enzymatic method versus the Jaffé method. This appears to be due to assay interference from N-ethylglycine, a metabolite of lidocaine.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

1. **Anti-arrhythmic medicines**
   Local anaesthetics of the amide type, such as lidocaine, should be used with caution in patients receiving anti-arrhythmic medicines (e.g. disopyramide, procainamide, mexilitene), since potentiation of cardiac effects may occur.

2. **Amiodarone**
Amiodarone has been reported to reduce the clearance of lidocaine in two case reports, although a small prospective study of combined therapy on lidocaine pharmacokinetics found no change in clearance or other pharmacokinetic factor. This combination has been reported to precipitate seizures and to lead to severe sinus bradycardia and a long sinoatrial arrest. Until more experience with concurrent use of lidocaine and amiodarone becomes available, patients receiving the combination should be monitored carefully.

3. **Beta-adrenoreceptor antagonists**
Propranolol, **nadolol* and metoprolol reduce the metabolism of IV. administered lidocaine and the possibility of this effect with other beta-adrenergic blockers should be kept in mind. If these medicines are administered concurrently, the patient should be closely observed for signs of lidocaine toxicity.

4. **Cimetidine**
Cimetidine reduces the clearance of IV administered lidocaine and toxic effects due to high serum lidocaine levels have been reported when these two medicines have been administered concurrently.

5. **Anticonvulsive agents**
Phenytoin and other antiepileptic medicines such as phenobarbitone, primidone and carbamazepine appear to enhance the metabolism of lidocaine but the significance of this effect is not known. Phenytoin and lidocaine have additive cardiac depressant effects.

6. **Fluvoxamine**
Coadministration of fluvoxamine drastically reduces the elimination of lidocaine.

7. **Inhalational anaesthetics**
Lidocaine decreases the minimum effective concentration of inhalational anaesthetics, e.g. nitrous oxide.

8. **Skeletal muscle relaxants**
Lidocaine and skeletal muscle relaxants, e.g. suxamethonium, lead to excessive neuromuscular blockade; therefore this combination must be used with caution.

9. **Alcohol**
There have been no reports of direct interaction between alcohol and lidocaine. However, acute severe alcohol intoxication can centrally depress the cardiovascular system and may thereby prolong lidocaine elimination half-life.

10. *Potential for influence of lidocaine on the plasma levels/effect of other medicines

Lidocaine is metabolised by CYP1A2 and CYP3A4 and thus has the potential to inhibit the metabolism of medicines metabolised by these isoenzymes, thus increasing their plasma levels, however, this effect has so far not been reported.

11. ***Potential for influence of other medicines on the plasma levels/effect of lidocaine***
Concomitant treatment with medicines that are substrates, inhibitors, or inducers of CYP1A2 or CYP3A4 has the potential to influence the metabolism and hence the plasma levels and effect of lidocaine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
See section 5.3 Preclinical safety data.

Use in pregnancy – Pregnancy Category A
The safe use of lidocaine during pregnancy has not been established. Although lidocaine has been used extensively for surgical procedures during pregnancy with no reports of ill effects to mother or foetus, there are no adequate or well-controlled studies in pregnant women of the effect of lidocaine on the developing foetus.

Use in lactation
Lidocaine passes into breast milk. The amount of lidocaine appearing in breast milk from nursing mother receiving parenteral lidocaine is unlikely to lead a significant accumulation of the parent drug in the breast fed infant. The remote possibility of an idiosyncratic or allergic reaction in the breast fed infant from lidocaine remained to be determined.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reactions to lidocaine hydrochloride are similar in character to those observed with other local anaesthetics.

Adverse experiences are, in general, dose-related and may result from high plasma levels or from a hypersensitivity, idiosyncrasy or diminished tolerance.

Serious adverse events are generally systemic in nature, the following types are those more commonly reported.

Central Nervous System
CNS manifestations are excitatory and/or depressant and may be characterised by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, disorientation, tinnitus, double or blurred vision, vomiting, sensations of heat, cold or numbness, **paraesthesia* twitching, tremors, convulsions, unconsciousness, psychosis, dyspnoea, respiratory depression and/or arrest, agitation, difficulty swallowing and slurred speech.

The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest. Drowsiness following administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a result of rapid absorption. In unconscious patients,

circulatory collapse should be watched for as CNS effects may not be apparent, as an early manifestation of toxicity may in some cases progress to frank convulsions and ultimately lead to respiratory depression and/or arrest. It is crucial to have resuscitative equipment and anticonvulsant medicines available to manage such patients. (see Section 4.9 Overdose-Treatment of Overdosage).

Cardiovascular
Cardiovascular manifestations are usually depressant and are characterised by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest. Methaemoglobinaemia can occur following IV administration, particularly in neonates. Arrhythmias including ventricular tachycardia/ ventricular fibrillation.

Allergic
Allergic reactions are characterised by cutaneous lesions, urticaria, oedema or anaphylactoid reactions. Allergy to amide-type local anaesthetics is very rare.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Toxicity is initially manifested as CNS excitation and may result in a slow onset of nervousness, dizziness, blurred vision and tremors followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest.

**Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with medicines such as a benzodiazepine or a barbiturate.* Toxic cardiovascular reactions are usually depressant in nature, may occur rapidly and with little warning and can lead to peripheral vasodilation, hypotension, myocardial depression and bradycardia. **In rare cases, cardiac arrest has occurred without prodromal CNS effects*

Treatment of Overdosage
Discontinue administration of XYLOCARD. Maintain a patent airway and support ventilation with oxygen and assisted or controlled respiration as required.

Should a convulsion persist despite ventilation therapy, small increments of a benzodiazepine (e.g. diazepam) or an ultra-short-acting barbiturate (e.g. thiopentone) may be given intravenously.

Cardiovascular depression may require circulatory assistance in the form of elevation of legs, intravenous fluids and/or vasopressor agents, volume expanders and, if necessary, cardiac massage.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Lidocaine stabilises all potentially excitable membranes including those of nerve, muscle and secretory cells. Its depression of electrical activity in membranes of such cells is reversible.

In cardiac tissue a therapeutic serum concentration of lidocaine (5 to 20 micromol/L or 1.5 to 6.0 micrograms/mL) has the following effects:

1. Depresses slow spontaneous depolarisation (phase 4), that is, the automaticity of isolated non-depolarized Purkinje fibres, but has little effect on conduction velocity, membrane responsiveness (rate of rise of phase 0) and cardiac output. Automaticity induced by stretch, hypoxia and catecholamines can also be suppressed by lidocaine.

2. Shortens both the action potential period and effective refractory period of Purkinje and ventricular cells. However, the effective refractory period is not reduced to the same extent and the ratio of effective refractory period to action potential duration is increased.

3. In the presence of high extracellular potassium ion concentration, or in myocardial ischaemia where the cells are partially depolarized, depresses the membrane responsiveness (rate of rise of phase 0) and thereby conduction velocity in Purkinje fibres and ventricular myocardium.

Clinical trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Distribution
During the first half hour after an intravenous injection the blood level of lidocaine declines with a half life of 7 - 10 minutes due to the rapid distribution to various tissues, including the heart. After this initial phase the half life is 90 - 120 minutes (metabolism and excretion). During continuous infusion, steady-state is reached after 6 - 8 hours.

Metabolism and Excretion
Lidocaine is metabolised mainly in the liver and excreted via the kidneys. Approximately 90% of administered lidocaine is excreted in the form of various metabolites while less than 10% is excreted unchanged. The principal metabolites, monoethylglycinexylidide and glycinexylidide also possess antiarrhythmic action, but to less extent.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
The genotoxic potential of 2,6-xylidine has been studied with mixed results: Positive results were reported in assays for gene mutations (weakly positive in the Ames test with metabolic activation and in the mouse lymphoma assay) and chromosomal damage (chromosomal aberrations in Chinese hamster ovary cells at concentrations at which the drug precipitated from solution). No

evidence of genotoxicity was found in *in vivo* assays for chromosomal damage (micronucleus assay) and DNA damage (unscheduled DNA synthesis). Covalent binding studies of DNA from liver and ethmoid turbinates in rats indicate that 2,6-xylidine may be genotoxic under certain conditions *in vivo.*

Carcinogenicity
A two-year oral toxicity study of 2,6-xylidine, a metabolite of lidocaine, has shown that in both male and female rats, 2-6-xylidine in daily doses of 900 mg/m^2 (150 mg/kg) resulted in carcinomas and adenomas of the nasal cavity. No nasal tumours were observed in the low dose (15 mg/kg or control animals). In addition, the compound also caused subcutaneous fibromas and or fibrosarcomas in male and female rats (significant at 150 mg/kg).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

XYLOCARD should be stored at 25°C or below.

6.5 NATURE AND CONTENTS OF CONTAINER

All XYLOCARD solutions are available as follows:

Bolus IV solutions for injection
Xylocard® 100 2% (100 mg/5 mL)
5 mL ampoule with disposable syringe [+]

Infusion solutions
Xylocard® 500 10% (500 mg/5 mL)
10 x 5 mL Polyamp Duofit®

Xylocard® 1000 10% (1000 mg/10 mL)
5 x 10 mL ampoules [+]

[+] Not currently marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

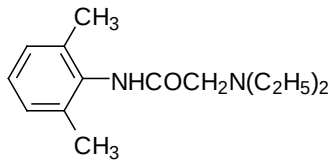
6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name for lidocaine hydrochloride is 2 Diethylaminoaceto 2',6' xylidide hydrochloride.

White crystalline powder which, at 20°C, is soluble in 0.7 parts water; 1.5 parts ethanol (96%); practically insoluble in ether.

Plain aqueous solutions of lidocaine hydrochloride have a pH of 5.0 - 7.0. Lidocaine base has a pKa of 7.85 (25 °C) and a molecular weight of 234.3.

Chemical structure
The chemical structure of lidocaine is:



CAS number
The CAS number for lidocaine hydrochloride is 73-78-9.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

15 August 1996

10 DATE OF REVISION

16 November 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Single ingredient name for lidocaine (lignocaine)

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